Inflammatory Markers in Determining the Severity of Chronic Obstructive Pulmonary Disease in Hospitalized Patients

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ABSTRACT

Aims and background: Chronic obstructive pulmonary disease (COPD) is said to be a heterogeneous lung condition which is characterized by chronic respiratory symptoms that are caused due to abnormalities of the airways and/or alveoli. It is linked with significant mortality and morbidity. The recognition of reliable markers for assessing the severity of acute exacerbations of COPD (AECOPD) is essential for guiding treatment decisions and improving patient outcomes.

Objective: This study investigates the role of inflammatory markers in determining the severity of AECOPD in hospitalized patients.

Methodology: This prospective observational study was conducted among patients admitted to hospitals affiliated with to Bangalore Medical College, Bengaluru, between February 2023 and October 2023. Inflammatory markers such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) were analyzed, and these parameters were correlated with the severity of AECOPD using descriptive statistics, correlations, and area under the curve (AUC) values.

Results: The study included a total of 130 patients with AECOPD. The severity distribution of AECOPD was as follows: mild (10.8%), moderate (20.8%), severe (10.0%), very severe (32.3%), and life-threatening (26.2%). Significant correlations were found between PLR (r = 0.241, p = 0.006), NLR (r = 0.248, p = 0.005), LMR (r = 0.288, p = 0.001), and AECOPD severity. The area under the curve (AUC) values for PLR, NLR, and LMR were 0.639, 0.562, and 0.611, respectively. PLR showed the highest AUC in detecting severe AECOPD.

Conclusion: This study demonstrates a significant correlation between inflammatory markers such as PLR, NLR, and LMR and the severity of AECOPD in hospitalized patients. These markers show potential as adjunctive tools for assessing disease severity and guiding treatment decisions in AECOPD. Further validation studies are warranted to confirm their utility and establish their clinical applicability.

Clinical significance: COPD is a disease associated with high morbidity and mortality during exacerbations. This study aims to utilize hematological indices, which are easily accessible in low-resource settings such as India, to predict the severity of AECOPD. This approach aids in providing early intervention, potentially reducing morbidity and mortality.

Keywords: Acute exacerbations, Chronic obstructive pulmonary disease, Hospitalization, Inflammatory markers, Lymphocyte-to-monocyte ratio, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Severity.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic respiratory symptoms caused by abnormalities of the airways and/or alveoli, leading to persistent and mostly progressive airflow obstruction. It is one of the significant causes of death worldwide, highlighting the substantial burden it places on global health. The disease has varied clinical manifestations, ranging from chronic bronchitis to emphysema, underpinned by heterogeneous pathophysiological processes. Central to these processes is inflammation, driven by chronic inhalation of noxious particles and gases.

The role of inflammation in this disease is complex and multifaceted, involving an array of inflammatory cells, namely neutrophils, macrophages, and T lymphocytes, along with a diverse collection of inflammatory mediators. Understanding the relationship between these inflammatory markers and COPD severity is crucial, as it may allow for improved disease stratification, targeted therapy, and prognosis prediction. In the context of hospitalized patients with COPD exacerbation, the situation becomes even more critical given the associated higher mortality rates.

An acute exacerbation of COPD (AECOPD) is an event described in patients with COPD, characterized by an increase in breathlessness and/or cough and expectoration that worsens in

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<2 weeks. It may be associated with tachypnea and/or tachycardia and is often linked to an increase in local and systemic inflammation caused by infection, pollution, or other insults to the airways. AECOPD is associated with an increased risk of further exacerbations and worsening of coexisting pathological conditions, leading to poor exercise tolerance and physical activity, further resulting in a decrease in respiratory function and, ultimately, death. 7

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Further research into this aspect has shown that many studies have highlighted the role of specific inflammatory markers in COPD, such as C-reactive protein (CRP), fibrinogen, and leukocyte count. These markers, readily available in clinical practice, have been found to be related to disease severity and exacerbation frequency. However, the wide range of inflammation markers, combined with inconsistent results across studies, has created a challenging landscape for clinicians and researchers alike. 10

Emerging research, therefore, focuses on novel biomarkers, such as procalcitonin, tumor necrosis factor-alpha (TNF- α), and interleukins (e.g., IL-6, IL-8), which may provide additional insight into the inflammatory processes in COPD. While these markers are not routinely measured in clinical practice, their potential predictive value for COPD severity and exacerbation is still under active investigation. 12

Various limitations in analyzing the above biomarkers have led to interest in using more readily available parameters to assess disease severity. Hematological markers such as neutrophillymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) have been widely studied globally by various investigators and have proven to be reliable markers. In low-resource settings, the utility of these markers is yet to be established. Hence, this study aims to provide better insight into the use of these readily available parameters as markers for disease severity and mortality in COPD.

This study focuses on analyzing the role of these inflammatory markers (NLR, PLR, and LMR), which can be obtained through routine investigations in low-resource settings, in assessing the severity of COPD in inpatients, evaluating the current evidence, and exploring future directions in this burgeoning field. The easy availability of these parameters can prove vital in low-resource settings for better categorization of patients and providing timely treatment for COPD patients during exacerbations.

AIMS OF THE STUDY

- To correlate the inflammatory markers like NLR, PLR, and LMR with the severity of AECOPD.
- To compare the three inflammatory markers to find the most sensitive marker to predict the severity of AECOPD.

METHODOLOGY

Source of Data

The data for this study were collected from patients admitted to hospitals affiliated with Bangalore Medical College, Bengaluru.

Study Design

Prospective observational study.

Study Period

This study was conducted from February 2023 to October 2023.

Place of Study

The study was conducted in Victoria Hospital, Bengaluru.

Sample Size

According to Daniel et al., the prevalence of COPD is 9.23%. Sample size was calculated by assuming equal variances as

follows: $n = Z^2 pq / d^2$ = (1.96)² (9.23 × 90.77) / 5²

= 128.7 Hence, $n \approx 129$

Where, n, that is, sample size; Z, that is, standard table value for 95% CI; p = prevalence of COPD; q = 100 - p; d = absolute precision. Based on the sample size calculation, it was decided to enroll 130 subjects.

Inclusion Criteria

- Age greater than 45 years.
- Prior diagnosis of COPD based on GOLD guidelines,¹ currently presenting with an exacerbation.

Exclusion Criteria

- Age <45 years.
- Patients with stable COPD.

Methodology

After taking clearance from the ethical committee, patients admitted to Victoria Hospital during the study period with a diagnosis of COPD in acute exacerbation¹ were enrolled based on the inclusion and exclusion criteria. Medical records were verified, and information regarding case history, all investigations, treatment, course in the hospital, and outcomes were compiled. The NLR, PLR, and LMR were calculated from complete blood counts (CBC), which were done on the day of admission, and the parameters were correlated with the severity of AECOPD as described by Burge and Wedzicha.¹⁴

The inflammatory markers were compared to identify the most sensitive marker for predicting severity and adverse outcomes in patients with AECOPD.

Statistical Analysis

The data that was collected were entered into an MS Excel sheet and analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0. Mean, standard deviation, and percentage were used for analysis of descriptive data where applicable. Categorical data were represented as frequencies and proportions. Parametric and nonparametric tests were used for comparison of data as appropriate.

RESULTS

The results section of this study presents the analysis of the collected data from 130 patients who were admitted to Victoria Hospital, Bengaluru, with a diagnosis of acute exacerbation of COPD. The data were thoroughly examined to establish the correlation between the inflammatory markers N/L ratio, P/L ratio, and L/M ratio, and the severity of AECOPD. Additionally, these markers were compared against each other to identify the most sensitive one in predicting AECOPD severity. The results were derived through statistical analysis and are represented in various formats, including tables and graphs, for better comprehensibility. These findings help in understanding the role of inflammatory markers in managing and predicting outcomes in patients with AECOPD, thus providing valuable insights for healthcare professionals involved in the management of COPD.

Table 1 presents the categorization of the severity of AECOPD among the study's 130 participants.

More than half of the participants, specifically 58.5%, were categorized under the two most severe categories: very severe and life-threatening. This underscores the serious nature of AECOPD within the study's patient population.

Table 2 presents the distribution of AECOPD severity among the 130 study participants, stratified by age and sex.



Age-group Analysis

Overall, the mean age for the study population was 67 ± 10 years, indicating a similar age distribution across all severity categories.

The p-value of 0.695 suggests that the difference in mean ages across the severity levels was not statistically significant. This implies that age may not be a significant determinant of AECOPD severity in this study population.

Sex Analysis

There were 43 female patients (33.1% of the total), distributed across all severity categories, with the largest numbers in the mild and very severe categories.

Among the 87 male patients (66.9% of the total), most were in the very severe category. The *p*-value was 0.561, suggesting that there was no statistically significant difference in the distribution of severity between males and females.

In summary, the majority of patients across all age-groups were in the very severe category, with no significant differences in distribution within age groups or between sexes. However, the most severe category, life-threatening, had a slightly higher proportion of older patients (75–94 years) and males.

Table 1: Distribution of AECOPD severity among study participants

	Category	n	%
Severity	Mild	14	10.80%
	Moderate	27	20.80%
	Severe	13	10.00%
	Very severe	42	32.30%
	Life threatening	34	26.20%
	Total	130	100.00%

Table 3 delineates the mean values and associated standard deviations (±SD) of various laboratory parameters across distinct severity strata of AECOPD.

Upon statistical analysis (p-value < 0.05), noteworthy findings include:

Platelet/Lymphocyte Ratio

The PLR ratio was seen to be markedly increased in the group with life-threatening exacerbation when compared with the other groups. The *p*-value of 0.036 is statistically significant, implying that it is a reliable inflammatory marker in predicting the severity of acute exacerbation. It denotes that as the PLR increases, the severity of the disease also increases, thus raising the chances of mortality.

Neutrophil/Lymphocyte Ratio

The NLR ratio was seen to be increased in the cohort with life-threatening exacerbation when compared with the other severity groups. The p-value of 0.032 is statistically significant, indicating that an increase in this parameter denotes increased disease severity and highlights its importance as a reliable inflammatory marker that can be used in predicting the severity of acute exacerbation.

Lymphocyte/Monocyte Ratio

The LMR ratio was also seen to be considerably increased in the group with life-threatening exacerbation when compared to the other groups. The *p*-value of 0.033 proves that it is statistically significant, implying that it is a reliable inflammatory marker in predicting the severity of acute exacerbation. Thus, any increase in the LMR should be considered significant.

Table 4 delineates the average duration of hospital stay, ICU stay, and the duration of usage of noninvasive ventilation and invasive mechanical ventilation across different severity strata of AECOPD. All parameters show statistically significant differences across severity groups (*p*-value < 0.05).

Table 2: Distribution of AECOPD severity among study participants by age and sex

			Severity												
			Mild	Мо	derate	Severe		Very severe		Life threatening		Total			
		n	%	n	%	n	%	n	%	n	%	n	%	p-value	
Age	45-54	1	7.14%	5	18.52%	1	7.69%	6	14.29%	2	5.88%	15	11.54%	0.635	
	55-64	3	21.43%	4	14.81%	5	38.46%	12	28.57%	8	23.53%	32	24.62%		
	65-74	5	35.71%	6	22.22%	5	38.46%	16	38.10%	11	32.35%	43	33.08%		
	75-84	5	35.71%	10	37.04%	2	15.38%	7	16.67%	10	29.41%	34	26.15%		
	85-94		0.00%	2	7.41%	0	0.00%	1	2.38%	3	8.82%	6	4.62%		
Sex	F	7	50.00%	10	37.00%	3	23.10%	12	28.60%	11	32.40%	43	33.10%	0.561	
	М	7	50.00%	17	63.00%	10	76.90%	30	71.40%	23	67.60%	87	66.90%		

Table 3: Laboratory characteristics of patients according to AECOPD severity

	Severity													
	M	lild	Mod	erate	Severe Very severe				Life thre	eatening	Total			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value	
НВ	12.69	1.71	13.23	1.98	13.89	2.91	13.37	2.33	12.97	3	13.22	2.45	0.145	
TC	9033	2371	12027	5006	8531	3239	11416	5479	11107	5214	10917	4939	0.362	
PLT	6059.8	22663.0	2225.0	9434.7	2.5	1.0	2.9	1.0	6002.2	18608.5	2685.7	12865.8	0.256	
PLR	178.6	93.6	240.9	325.8	210.2	114.3	323.5	334.8	415.2	386.4	303.4	322.7	0.0362	
NLR	8.4	4.7	10.3	8.4	9.8	5.4	9.7	8.3	17.0	12.2	11.6	9.4	0.032	
LMR	1.5	1.0	1.8	2.2	2.4	1.4	2.4	2.1	3.7	3.2	2.5	2.4	0.033	

Table 4: Duration of hospital and intensive care unit (ICU) stay and ventilatory support according to AECOPD severity

	Severity												
	Mi	ild	Mode	erate	Severe		Very severe		Life threatening		Total		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
ICU stay	0.79	1.31	0.89	1.69	1.69	1.84	1.50	1.95	4.79	1.75	2.18	2.37	0.001
Hospital stay	6.79	1.31	6.44	1.83	7.69	1.80	6.88	2.22	10.03	3.55	7.68	2.83	0.001
No. of days on NIV	2.14	2.18	1.93	2.66	3.38	2.96	2.74	2.77	7.59	3.94	3.84	3.78	0.001
No. of days on IMV	0.00	0.00	0.11	0.58	0.00	0.00	0.07	0.46	0.71	1.31	0.23	0.81	0.001

Table 5: Mortality rates in relation to AECOPD severity

Severity													
	Mild		Moderate		Severe Very severe		y severe	Life threatening		Total			
Mortality	n	%	n	%	n	%	n	%	n	%	n	%	p-value
Alive	14	100.00%	26	96.30%	13	100.00%	41	97.60%	27	79.40%	121	93.10%	0.009
Dead	0	0.00%	0	3.70%	1	7.69%	1	2.40%	7	20.60%	9	6.90%	

Table 6: Correlation between AECOPD severity and blood cell ratios

Correlations											
		PLR	NLR	LMR							
Severity	Pearson correlation	0.241**	0.248**	0.288**							
	Sig. (2-tailed)	0.006	0.005	0.001							

^{**}Indicates that the correlation is statistically significant at *1% level (p < 0.01)

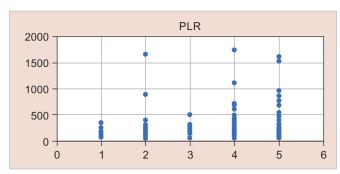


Fig. 1: Correlation between AECOPD severity and PLR

These findings in the table suggest that patients with more severe AECOPD require longer hospital stays, longer durations in the ICU, and extended periods of ventilator support, leading to a worse prognosis.

Table 5 demonstrates the mortality rates associated with different severity strata of AECOPD. There is a statistically significant difference in mortality rates across the severity groups (p-value < 0.05). Mortality rates were found to be zero in the mild and moderate AECOPD groups. In the severe AECOPD group, a mortality rate of 7.69% was observed. The very severe AECOPD group displayed a mortality rate of 2.40%. The highest mortality rate was identified in the life-threatening AECOPD group at 20.60%. Overall, the mortality rate across all severity groups was 6.90%. These results suggest that mortality increases with the severity of AECOPD, with the life-threatening group demonstrating the highest mortality rate. It is essential to identify patients at risk and provide timely and appropriate management to reduce mortality associated with severe AECOPD.

Table 6 denotes the correlation between the blood cell ratios and AECOPD severity, stating that all the ratios have a statistically significant correlation with AECOPD severity.

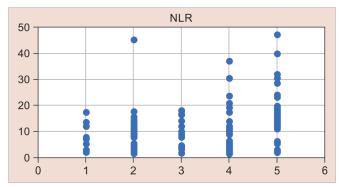


Fig. 2: Correlation between AECOPD severity and NLR

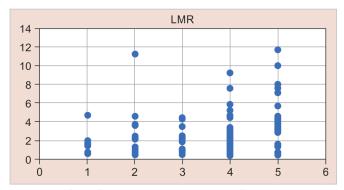


Fig. 3: Correlation between AECOPD severity and LMR

In relation to Figures 1 to 3, AECOPD severity can be correlated positively with the P/L ratio (r = 0.241; p = 0.006). This indicates that as the severity of AECOPD increases, the PLR ratio also tends to increase. Similarly, AECOPD severity is correlated positively with the NLR ratio (r = 0.248; p = 0.005). This suggests that an increase in AECOPD severity is associated with an increase in the NLR ratio. AECOPD severity shows the strongest positive correlation with the LMR ratio (r = 0.288; p = 0.001). This implies that a higher severity of AECOPD is significantly associated with a higher LMR ratio.

Figure 4 denotes the receiver-operating characteristic (ROC) curve representing the sensitivity (Sn) and specificity (Sp) of all the blood cell ratios, indicating that the PLR is the most sensitive and the NLR is the most specific among the three ratios.



Table 7: Area under the curve of blood cell ratios for predicting AECOPD severity

Area under the curve											
				Asymptotic 95%	confidence interval						
Test result variable(s)	Area	Std. error	p-value	Lower bound	Upper bound	Sensitivity	Specificity	PPV	NPV		
PLR	0.639	0.048	0.007	0.544	0.734	52.63	77.95	0.9	53.8		
NLR	0.562	0.05	0.227	0.463	0.661	25.12	98.51	95	48		
LMR	0.611	0.049	0.031	0.515	0.707	44.74	83.33	79.1	51.7		

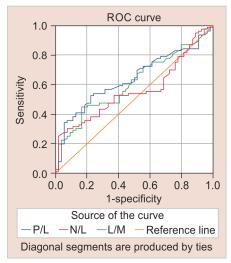


Fig. 4: ROC curve

According to Table 7, the results are as follows.

The platelet-to-lymphocyte ratio (PLR) has an AUC of 0.639 (p = 0.007,95% CI: 0.544–0.734), with a sensitivity (Sn) of 52.63%, specificity (Sp) of 77.95%, positive predictive value (PPV) of 76.9%, and negative predictive value (NPV) of 53.8%. This suggests that the PLR ratio has a moderate predictive ability for AECOPD severity.

The neutrophil-to-lymphocyte ratio (NLR) has an AUC of 0.562 (p = 0.227, 95% Cl: 0.463–0.661), with a low sensitivity (Sn) of 25.12% but a high specificity (Sp) of 98.51%. Its positive predictive value (PPV) is 95%, and its negative predictive value (NPV) is 48%. The NLR ratio's predictive ability for AECOPD severity is somewhat limited due to its lower AUC and sensitivity.

The lymphocyte-to-monocyte ratio (LMR) has an AUC of 0.611 ($p=0.031,\,95\%$ CI: 0.515–0.707), with a sensitivity (Sn) of 44.74%, specificity (Sp) of 83.33%, positive predictive value (PPV) of 79.1%, and negative predictive value (NPV) of 51.7%. The LMR ratio demonstrates a fair predictive ability for AECOPD severity.

In summary, the blood cell ratios have potential as biomarkers for predicting AECOPD severity, with the PLR ratio showing the highest AUC. This study also concludes that the NLR ratio has the highest specificity among the markers.

It is also evident that increased severity of the disease can increase mortality. Parameters such as increased duration of hospital stay, ICU stay, and prolonged use of ventilator support denote increased severity of the disease and higher chances of mortality. However, considering the moderate AUC values and varying sensitivity and specificity, the clinical utility of these hematological markers should be evaluated further.

Discussion

In this study, the role of inflammatory markers in determining the severity of COPD in hospitalized patients was investigated. The findings revealed significant associations between inflammatory markers and the severity of AECOPD. These results are similar to prior studies that have explored the relationship between COPD severity and inflammatory markers.

This study revealed that there is no statistical significance in severity among age and gender of the patients. As the severity increased, the hospital stay duration, ICU stay duration, duration of IMV, duration of NIV, and mortality were found to increase, and this was found to be statistically significant.

The most important finding in the current study was the correlation between inflammatory cell ratios, including the P/L ratio, L/M ratio, and N/L ratio, with AECOPD severity. The P/L ratio indicated a moderate positive correlation with AECOPD severity (r = 0.241, p = 0.006). This result is comparable with the study conducted by Li et al., which reported similar findings. Li et al. observed that the PLR ratio was significantly increased in patients of the severe COPD group when compared to those with milder forms of the disease. Li et al. also reported sensitivity and specificity values of 61.9 and 72.3%, respectively, for the PLR ratio in predicting COPD severity. In this study, we observed Sn and Sp values of 52.63% and 77.95%, respectively, for the P/L ratio. These findings suggest that the P/L ratio has a reasonably high specificity in predicting AECOPD severity but a lower sensitivity.

Additionally, a positive correlation was found between the NLR ratio and AECOPD severity (r=0.248; p=0.005) in the study. These findings are supported by the work of Zhang et al., who showed that this N/L ratio was significantly related to COPD severity and exacerbation frequency. Similarly, the L/M ratio showed a significant correlation with AECOPD severity (r=0.288, p=0.001). These results align with the results of the study by Guo et al., where they reported that higher LMR were associated with higher COPD severity and a higher risk of exacerbations. 17

Moreover, the area under the curve (AUC) analysis was used to assess the predictive value of these inflammatory markers for AECOPD severity. The AUC values for the P/L ratio, N/L ratio, and L/M ratio were 0.639, 0.562, and 0.611, respectively. The AUC values indicate a moderate predictive ability for the PLR and LMR, while the NLR showed a lower predictive ability. These findings align with the results obtained by Li et al., who reported AUC values of 0.632 for PLR. The higher AUC of the PLR indicates that the sensitivity of the PLR is highest among all the other inflammatory markers studied.

The use of inflammatory markers as predictors of AECOPD severity holds potential clinical significance. Identifying these patients who are at a higher risk of severe exacerbations early can aid healthcare professionals in making treatment decisions and improving patient outcomes. Incorporating these inflammatory

markers into clinical practice may aid in risk stratification and personalized management strategies for patients with COPD. These hematological indices, being cheaper and readily available, can be used in low-resource settings.

There is said to be significant evidence that multiple factors lead to the development of airway inflammation. This phenomenon appears to be a part of the progressive events that occur in COPD, which is usually characterized by a state of chronic inflammation, both local and systemic, leading to an elevation in the inflammatory markers in the body.¹⁷

Further research is required to explore the underlying mechanisms that cause these inflammatory markers to contribute to AECOPD severity. Investigating the specific pathways and molecular interactions involved can provide a profound understanding of the pathophysiology of AECOPD and potentially identify novel therapeutic targets.

In summary, our study demonstrates a significant association between inflammatory markers and the severity of AECOPD in hospitalized patients. The P/L ratio, L/M ratio, and N/L ratios showed correlations with AECOPD severity and exhibited moderate predictive ability. These findings support the potential use of these inflammatory markers as adjunctive tools in assessing disease severity and guiding treatment decisions in patients with AECOPD. Future research should be directed toward further validating the findings of this study in larger and more diverse cohorts.

Limitations

Firstly, the sample size in this study can be considered small, which might limit the generalizability. Other studies with larger sample sizes may be necessary to validate these results. Additionally, this study concentrated on hospitalized patients with AECOPD, which does not fully represent the entire COPD population. The correlation of these inflammatory markers with other parameters, such as arterial blood gas analysis and baseline spirometry values, has not been studied, which may have been vital in assessing the patient condition.

Conclusion

This study investigated the role of inflammatory markers in determining the severity of COPD exacerbations in hospitalized patients. The results demonstrated significant associations between various inflammatory markers, such as P/L ratio, L/M ratio, and N/L ratio, with the severity of AECOPD. The P/L ratio showed the highest AUC in detecting severe AECOPD, suggesting that it is the most sensitive marker among the three inflammatory markers studied.

These findings suggest that these inflammatory markers have the potential to serve as adjunctive tools in assessing disease severity and guiding treatment decisions in patients with AECOPD. This study contributes to the increasing body of evidence that supports the role of inflammatory markers in determining the severity of COPD exacerbations. Incorporating these markers into clinical practice has the potential to aid in risk stratification, treatment decision-making, and personalized management approaches for patients with AECOPD. This study aims to use these inflammatory markers in low-resource settings, and further investigations into the underlying mechanisms and longitudinal studies are warranted to strengthen our understanding of these markers and their implications in COPD exacerbation management.

Clinical Significance

COPD is said to be a disease with high morbidity and high mortality during exacerbations. This study aims to use the hematological indices, which are easily available in low-resource settings such as in India, to predict the severity of AECOPD and thus aid in providing early intervention, which can lead to a decrease in morbidity and mortality.

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