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Correlation of Neutrophil- to-Lymphocyte Ratio with Functional Ability in COPD Patients

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Abstract

***Introduction:** Chronic Obstructive Pulmonary Disease (COPD) remains a leading cause of illness and death worldwide, especially in low- and middle-income countries like India. It is marked by chronic respiratory symptoms and progressive airflow obstruction. In recent years, systemic inflammation has gained recognition as a central factor in COPD progression. Among inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential indicator of disease severity and prognosis. This study aimed to evaluate the relationship between NLR and clinical, radiological, and functional parameters in patients with stable COPD.*

***Methods:** A cross-sectional study was conducted at LLRM Medical College and SVBP Hospital, Meerut, during 2023 – 2024. Sixty-one stable COPD patients aged 35 years or older were enrolled based on post-bronchodilator $FEV_1/FVC < 70\%$ and absence of exacerbation in the prior two months. All patients underwent clinical assessment, spirometry, six-minute walk test (6MWT), chest imaging, and laboratory tests including complete blood count and CRP. NLR was calculated and correlated with clinical indices, GOLD stage, and BODE index.*

***Results:** The mean age was 64.2 years, and 72% were male. The average NLR was 4.36. Most patients were in GOLD 3 category. NLR showed a negative correlation with FEV_1, FEV_1/FVC, 6MWT distance, and SpO, and a positive correlation with CRP and BODE index. NLR levels increased consistently with GOLD stage ($p < 0.001$).*

***Conclusion:** NLR appears to be a simple, cost-effective marker that correlates well with COPD severity and functional decline. It may aid in risk stratification and clinical decision-making.*

***Key words:** Chronic obstructive pulmonary disease, neutrophil-to-lymphocyte ratio.*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable condition marked by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities, often caused by exposure to harmful particles or gases. It is a major global health issue and one of the leading causes of death worldwide. According to the WHO[1], approximately 65 million people suffer from moderate to severe COPD, with most deaths occurring in low- and middle-income countries, particularly in India and China, which together account for 66% of global COPD mortality[2].

India bears a significant COPD burden, with 55.3 million cases reported in 2016[3]. COPD prevalence increases with age and varies by region – ranging from 4.36% in Bangalore to 10% in Delhi. Key risk factors include smoking, biomass fuel use, air pollution, occupational hazards, aging, socio-economic status, and past tuberculosis. COPD also imposes a heavy economic and health-related quality of life burden and is the leading cause of disability among chronic respiratory diseases.

Systemic inflammation plays a central role in COPD pathogenesis and progression. Elevated levels of inflammatory markers such as c-reactive protein (CRP), interleukins, TNF-α, and leukocytes (neutrophilia and leukopenia) are frequently observed. Higher Neutrophil-to-Lymphocyte-Ratio (NLR) levels correlate with disease severity, reduced exercise tolerance, increased dyspnoea, and greater risk of hospitalisation and mortality.

Material and Methods

This cross-sectional study was conducted between 2023 and 2024 in the Department of Medicine at LLRM Medical College and SVBP Hospital, Meerut, Uttar Pradesh. It included patients aged 35 years and above diagnosed with Chronic Obstructive Pulmonary Disease (COPD) who were attending the Medicine and Chest outpatient departments.

All participants were evaluated through a detailed clinical history, including the duration of disease and personal habits such as smoking and alcohol use. A structured proforma was used to document history, physical findings, and investigation results. Each subject underwent a complete

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clinical examination and laboratory workup to ensure eligibility based on inclusion and exclusion criteria.

The inclusion criteria encompassed patients with COPD, defined by a forced expiratory volume in one second (FEV1) ratio forced vital capacity (FVC) less than 70% of the predicted value, and who had no exacerbation in the preceding two months. Individuals with conditions that could interfere with study outcomes – such as infections, recent myocardial infarction, heart failure, malignancies, end-stage renal or liver disease, rheumatoid arthritis, or orthopedic limitations – were excluded.

All enrolled patients underwent a series of diagnostic tests, including routine hematological and biochemical panels, chest X-ray (PA view), ECG, spirometry, and six-minute walk distance (6MWD) test. Additional parameters assessed included body mass index (BMI), BODE index, C-reactive protein (CRP) levels, and total leukocyte count (TLC), with a focus on the neutrophil-to-lymphocyte ratio.

The minimum sample size was calculated based on a 2012 study in the *Journal of Thoracic Disease*, using a COPD prevalence of 4.1%, with a 5% absolute precision and 95% confidence interval. Applying the standard statistical formula, the required sample size was estimated to be 61 participants.

Results

The present study primarily included individuals in the older age groups, with the majority (42.62%) between 60 and 69 years. Around 31.15% were below 60 years, while 22.95% belonged to the 70-79-year age range. Only 3.28% of the participants were over 80. The average age was 64.23 years, suggesting that COPD remains a condition largely affecting the elderly.

There was a clear male predominance, with 72.13% of the study population being male, and only 27.87% female. This gender imbalance may reflect known risk factor patterns such as higher smoking prevalence and occupational exposures among men.

Blood profile analysis showed a mean polymorphonuclear cell percentage of 69.45%, while lymphocytes averaged 18.17%. The neutrophil-to-lymphocyte ratio (NLR), had a mean value of 4.36 ± 1.82, indicating underlying chronic inflammation.

Pulmonary function testing revealed a mean pre-bronchodilator FEV_1 of 42.91%, and a mean FEV_1/FVC ratio of 56.02%, consistent with obstructive ventilatory patterns. GOLD staging of airflow limitation categorised the majority (57.38%) under GOLD 3, indicative of severe obstruction. Moderate (GOLD 2) and very severe (GOLD 4) cases accounted for 29.51% and 13.11% respectively.

Table I: Distribution of study participants as per GOLD classification for diagnosing COPD.

FEV1	Group	Frequency	Per cent
	Gold 2 (50 to 79%)	18	29.51%
	Gold 3 (30 to 49%)	35	57.38%
	Gold 4 (<30%)	8	13.11%
	Total	61	100%

Table II: Table describing the subjects in study population in terms of spirometry parameters.

Spirometric parameters	Parameter	Value
FEV1 (Pre) (%)	Mean (SD)	42.91 ± 10.27
	Median (IQR)	44.15 (37.0 - 51.0)
	Min - Max	17.0 - 61.0
FEV1	GOLD 2 (50 to 79%)	18 (29.51%)
	GOLD 3 (30 to 49%)	35 (57.38%)
	GOLD 4 (<30%)	8 (13.11%)
FEV1 (Post-BDR)	Mean (SD)	47.01 (10.43)
	Median (IQR)	48.15 (42.05 - 54.77)
	Min - Max	25.0 - 62.0
FEV1/FVC	Mean (SD)	56.02 (10.7)
	Median (IQR)	57.71 (52.07 - 64.09)
	Min - Max	31.55 - 70.27

This table shows:

- The mean pre-bronchodilator FEV was 42.91 ± 10.27%.
- The majority of patients were classified under GOLD 3 (57.38%, n = 35). 29.51% (n = 18) subjects were classified as GOLD 2, and the remaining 13.11% (n = 8) as GOLD 4.
- Post-bronchodilator FEV showed an improvement, with a mean of 47.01 ± 10.43%.
- The mean FEV/FVC ratio was 56.02 ± 10.7%.

Functional capacity, as evaluated by the six-minute walk test (6MWT), showed an average walking distance of 223.26 meters. The composite BODE index, which integrates body mass, airflow obstruction, dyspnoea, and exercise capacity, had a mean value of 4.48, suggesting moderate disease severity.

Table III: Table describing the subjects in study population in terms of respiratory parameters.

Other respiratory parameters	Parameter		Value
	6 Minute Walk Test (meters)	Mean (SD)	223.26 (40.31)
		Median (IQR)	223.75 (202.15 - 248.05)
		Min - Max	117.0 - 333.0

	BODE	Mean (SD)	4.48 (1.95)
		Median (IQR)	4.0 (3.0 - 6.0)
		Min - Max	2.0 - 9.0
	Chest X-ray	Normal	18 (29.51%)
		Hyperinflated Lung fields with Flattening of diaphragm	43 (70.49%)

This table shows:

- The mean distance covered in the 6-minute walk test by our subjects was 223.26 ± 40.31 meters, reflecting the functional exercise capacity of the study population.
- The BODE index had a mean value of 4.48 ± 1.95.
- Chest X-ray findings revealed that 70.49% (n = 43) of the subjects had hyperinflated lung fields with flattening of the diaphragm, while 29.51% (n = 18) had normal radiographic findings.

Radiographic findings supported these clinical patterns, with 70.49% of subjects showing signs of hyperinflation and diaphragm flattening on chest X-rays – hallmarks of emphysematous change.

Importantly, NLR showed significant inverse correlations with several parameters: oxygen saturation (r = -0.9), eosinophil percentage (r = -0.54), FEV both pre- and post-bronchodilator (r = -0.94, -1.0), FEV/FVC (r = -1.0), and 6MWT (r = -0.89). Conversely, it was positively correlated with BODE index (r = 0.89) and CRP levels (r = 0.7), confirming its utility as a surrogate marker for disease severity.

Table IV: Table showing the correlation between neutrophil-to-lymphocyte ratio and various respiratory parameters.

Parameter	Correlation Co-efficient	p value
NLR versus Spo2 (%)	-0.9	**<0.001**
NLR versus Eosinophils (%)	-0.54	**<0.001**
NLR versus FEV1 (Pre) (%)	-0.94	**<0.001**
NLR versus FEV1 (Post BDR)	-1.0	**<0.001**
NLR versus FEV1/FVC	-1.0	**<0.001**
NLR versus 6 Minute Walk Test (meters)	-0.89	**<0.001**
NLR versus BODE	0.89	**<0.001**

This table shows:

- A statistically significant negative correlation was observed between neutrophil-to-lymphocyte ratio and SpO, (%) (r = -0.9, p <0.001), eosinophil percentage (r = -0.54, p <0.001), FEV (Pre-BDR, in %) (r = -0.94, p <0.001), FEV (Post-BDR, in %) (r = -1.0, p <0.001), FEV/FVC (r = -1.0, p <0.001), and the 6-minute walk test (meters) (r = -0.89, p <0.001).
- Neutrophil-to-lymphocyte ratio showed a statistically significant positive correlation with the BODE index (r = 0.89, p <0.001).
- Thus, with increasing Neutrophil-to-lymphocyte ratio, there was a decline in the values of SpO2, FEV1 (Pre-BDR), FEV1 (Post-BDR), FVC (%), FEV1/FVC as well as 6-minute walk test (m), and vice versa. Conversely, higher values of neutrophil-to-lymphocyte ratio were correlated with higher values of BODE index and vice versa.

A progressive increase in mean NLR was observed across GOLD stages: 2.37 in GOLD 2, 4.69 in GOLD 3, and 7.4 in GOLD 4 (p <0.001), suggesting a strong association between systemic inflammation and worsening lung function.

Table V: Table showing the association of FEV1 with neutrophil-to-lymphocyte ratio.

Parameter		FEV1			p value
		GOLD 2 (50 to 79%) (n = 18)	GOLD 3 (30 to 49%) (n = 35)	GOLD 4 (<30%) (n = 8)	
Neutrophil-to-Lymphocyte Ratio	Mean (SD)	2.37(0.51)	4.69(1.15)	7.4(0.38)	**<0.001**[b]
	Median (IQR)	2.3 (2.0 - 2.62)	4.64 (3.74 - 5.61)	7.4 (7.13 - 7.67)	
	Min - Max	1.71 - 3.74	2.8 - 6.73	6.87 - 7.95	

b: One way ANOVA

The mean neutrophil-to-lymphocyte ratio was 2.37 ± 0.51 in GOLD stage 2, 4.69 ± 1.15 in GOLD stage 3, and 7.4 ± 0.38 in GOLD stage 4. There was a statistically significant association between the variables (p <0.001), indicating that increasing neutrophil-to-lymphocyte ratio was associated with worsening respiratory function in COPD.

Discussion

This cross-sectional study focused on patients with chronic obstructive pulmonary disease (COPD), with the majority (42.62%) falling in the 60 - 69 years age group. The mean age of the participants was 64.23 ± 7.28 years, consistent with the observation that COPD predominantly affects older individuals. This finding mirrors previous reports, such as the large-scale study by Liu *et al*[4], where the prevalence of COPD increased from 2.7% in the 18 - 44 age group to 13.2% in those aged 75 and above. Similarly, Gupta *et al*[5]. reported a mean patient age of 64.5 years, aligning closely with the current study's demographic.

Gender distribution showed a marked male predominance,

with 72.13% of participants being men. This trend aligns with findings from the Global Burden of Disease[6] Study, where male prevalence rates exceeded female rates (17.6% versus 14.7%, as noted by Koul *et al*[7]). On the contrary, studies by Christopher *et al*[8]. and Parasuramalu *et al*[9] found higher female prevalence (56.9% and 51.5%, respectively), likely due to regional differences in risk exposure. In India, men are more likely to smoke and work in pollutant-heavy industries, while women face indoor air pollution due to biomass fuel use – factors that may influence gender distribution across regions.

The mean pre-bronchodilator FEV_1 was 42.91 ± 10.27%, while the post-bronchodilator FEV_1 was 47.01 ± 10.43%. According to GOLD classification, 57.38% of patients were categorised under stage 3 (severe COPD), 29.51% under stage 2 (moderate), and 13.11% under stage 4 (very severe). The FEV/FVC ratio averaged 56.02 ± 10.7%, reinforcing the presence of obstructive airway disease. These values align with the study by Sangroula *et al*[10], which reported similar stage distribution, with most patients in stages 2 - 4.

Exercise capacity was measured using the six-minute walk test (6MWT). The average distance covered was 223.26 ± 40.31 meters, indicating reduced physical endurance, which is typical for patients with advanced disease. In contrast, other[11] studies have reported higher mean distances: 533 meters (Zeng *et al*[12]), 411 meters (Fujitomo *et al*[13]), 360 meters (Kerti *et al*[14]), and 345.76 ± 109.12 meters (Shah *et al*[15]). The differences likely stem from variation in disease severity, baseline fitness, and comorbidities across study populations.

The mean BODE index – an integrated score reflecting BMI, airflow obstruction, dyspnoea, and exercise capacity – was 4.48 ± 1.95. This suggests moderate-to-severe disease. Other studies, such as those by Li *et al*[16] (mean BODE = 3.0 ± 2.1) and Kaur *et al*[17] (mean BODE = 5.66 ± 2.64), have shown varying results based on participant profiles and disease stages.

Radiological findings supported the clinical assessment, with 70.49% showing hyperinflation and flattened diaphragms, consistent with emphysematous changes, while 29.51% had normal chest X-rays, likely representing earlier disease.

An important aspect of this study was the correlation of systemic inflammation, as reflected by neutrophil-to-lymphocyte ratio (NLR), with disease severity. NLR was significantly negatively correlated with FEV_1 both pre- ($r = -0.94$, $p < 0.001$) and post-bronchodilator ($r = -1.0$, $p < 0.001$), 6MWT ($r = -0.89$, $p < 0.001$), and SpO_2, ($r = -0.9$, $p < 0.001$). It also showed a negative correlation with eosinophils ($r = -0.54$, $p < 0.001$), suggesting a neutrophilic inflammatory pattern common in severe COPD.

Conversely, NLR was positively correlated with BODE index ($r = 0.89$, $p < 0.001$) and CRP levels ($r = 0.7$, $p < 0.001$), reaffirming its role as a systemic inflammatory marker. These findings are consistent with studies by Lee *et al*, ($r = 0.458$ for BODE, $p = 0.003$) and Cai *et al*[18], ($r = 0.5319$ for CRP, $p < 0.001$).

Furthermore, NLR increased progressively with GOLD stages: 2.37 ± 0.51 in GOLD stage 2, 4.69 ± 1.15 in GOLD stage 3, and 7.4 ± 0.38 in GOLD stage 4 ($p < 0.001$), indicating a strong link between inflammation and disease progression.

In conclusion, this study highlights the utility of NLR as a simple, accessible biomarker reflecting COPD severity, comparable to more established tools like the BODE index and CRP.

This study has highlighted that there is a significant association between NLR and worsening lung function, reduced exercise capacity, and higher BODE index in COPD patients. Importantly, it has provided evidence regarding the importance of NLR as a biomarker which can be used to assess the severity of disease in COPD.

Neutrophil-to-lymphocyte ratio can be used in low resource settings to:

- Predict exacerbations in COPD patients
- Escalate therapy according to trends in the levels
- Prognosticate COPD patients
- Grade severity of COPD patients.

However, further large-scale studies are required to validate these findings.

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