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Medicine

ASSOCIATION OF NEUTROPHIL-TO-LYMPHOCYTE RATIO WITH DISEASE SEVERITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT **Background:** Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR), derived from a routine complete blood count, may provide an inexpensive marker of disease burden. **Objectives:** To assess the association of peripheral-blood NLR categories with COPD severity, modified Medical Research Council (mMRC) dyspnoea grade and exercise intolerance. **Methods:** This single-centre observational study included 130 adults with clinically stable COPD attending the medicine outpatient department or admitted to the medicine ward of a tertiary-care centre between March 2024 and September 2025. COPD severity was classified using spirometry and GOLD categories. Dyspnoea was graded using the modified Medical Research Council (mMRC) scale. NLR was calculated by dividing the neutrophil count by the lymphocyte count. Pearson's chi-square test was used when expected-frequency assumptions were satisfied; sparse multi-category tables were evaluated using the Fisher–Freeman–Halton exact test with Monte Carlo simulation. A two-sided $p<0.05$ was considered statistically significant. **Results:** Of 130 participants, 69.2% were male; 42.3% were aged 41-60 years and 38.5% were aged 61-80 years. Moderate and severe COPD accounted for 34.6% and 30.8%, respectively. Mean NLR was 3.9±1.8. Higher NLR categories were associated with increasing COPD severity (Monte Carlo exact $p<0.001$) and worse mMRC grade (Monte Carlo exact $p<0.001$). NLR was also associated with exercise intolerance ($\chi^2=9.10$, $p=0.028$). Among patients with NLR >6, 84.0% had severe or very severe COPD. COPD severity increased significantly with age (Monte Carlo exact $p<0.001$), whereas its association with sex was not statistically significant ($\chi^2=6.64$, $p=0.084$). **Conclusion:** Higher NLR categories were associated with greater COPD severity, worse dyspnoea and exercise intolerance in this cohort of patients with stable COPD. NLR is readily available, but these cross-sectional findings do not establish predictive or prognostic utility.

KEYWORDS : chronic obstructive pulmonary disease; neutrophil-to-lymphocyte ratio; systemic inflammation; GOLD; dyspnoea; spirometry

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable respiratory disorder characterized by persistent respiratory symptoms and airflow limitation resulting from airway and/or alveolar abnormalities. Contemporary COPD assessment combines spirometric confirmation with symptom burden, exacerbation history and comorbidity because the degree of airflow obstruction alone does not fully represent the clinical impact of disease.[1] The ATS/ERS standards similarly emphasize an integrated approach to diagnosis, staging and management.[2]

COPD is a major cause of chronic morbidity, disability, healthcare utilization and mortality worldwide. Its burden is expected to remain substantial because of continued tobacco exposure, household and ambient air pollution, occupational inhalational hazards, population ageing and the long latency between exposure and clinically apparent disease.[3] Cigarette smoking is the best-established risk factor, but COPD is heterogeneous: patients with similar spirometric impairment may differ considerably in symptoms, exercise capacity, nutritional status, exacerbation frequency and systemic manifestations.

Inflammation in COPD is not restricted to the airways. Systemic effects include skeletal-muscle dysfunction, weight loss, cardiovascular and metabolic comorbidity, impaired exercise tolerance and altered circulating inflammatory mediators.[4] A systematic review and meta-analysis demonstrated that circulating inflammatory markers are higher in COPD than in control populations, supporting the presence of a systemic inflammatory component.[5] Persistent inflammation may contribute to progression, comorbidity and adverse clinical outcomes.[6] Metabolic derangement and weight loss have also been linked with increased inflammatory mediators in a subgroup of COPD patients.[7]

Several circulating biomarkers have therefore been explored for phenotyping and risk assessment. C-reactive protein (CRP) is higher in COPD than in control smokers and nonsmokers and has been related to disease burden.[8] In large population studies, combinations of inflammatory biomarkers have identified individuals at increased risk of exacerbation.[9] However, many biomarkers require additional assays, may be unavailable in smaller centres and can add cost to routine assessment.

The neutrophil-to-lymphocyte ratio (NLR) is calculated from a routine differential leukocyte count by dividing the neutrophil count by the lymphocyte count. Neutrophilia can reflect innate inflammatory activation, physiological stress or infection, whereas relative lymphopenia may accompany systemic stress and immune dysregulation. By integrating these two cell lines, NLR may provide a pragmatic index of the balance between innate inflammatory activity and adaptive immune status. It is inexpensive, rapidly available and requires no additional blood sample beyond a complete blood count.

Günay et al. reported that NLR was higher in stable COPD than in healthy controls and rose further during acute exacerbations, with relationships to other inflammatory indices.[10] Reviews have subsequently found associations between NLR and lung-function impairment, exacerbation, hospitalization and mortality, while also noting considerable heterogeneity in study populations and proposed thresholds.[11,12,13] Furutate et al. found NLR to be related to disease severity and exacerbation,[14] and Lee et al. reported an inverse relationship with lung function together with incremental value for predicting future exacerbations.[15]

Spirometry remains essential for diagnosis and physiological grading, but it may not capture systemic inflammation, dyspnoea or functional limitation. An inexpensive adjunctive biomarker could therefore be useful, particularly in resource-constrained practice. The present study aimed to assess the association of peripheral-blood NLR categories with COPD severity, mMRC dyspnoea grade and exercise intolerance.

MATERIALS AND METHODS

Study design and setting

An observational study was conducted in the Department of General Medicine (outpatient department and ward) of a Government Medical College and Hospital, Chh. Sambhajinagar from March 2024 to September 2025. A total of 130 eligible participants were included during the study period.

Participants

Adults aged 18 years or older with a confirmed diagnosis of COPD

based on compatible clinical history and spirometric airflow obstruction were included during a clinically stable phase. Stability required absence of a recent respiratory infection or acute exacerbation. Patients with an acute COPD exacerbation, active comorbidity likely to materially alter leukocyte counts, recent surgery or hospitalization, relevant medication exposure, pregnancy, or very recent smoking cessation were excluded.

Clinical and laboratory assessment

Demographic details, smoking history and clinical symptoms were recorded. Spirometry included forced expiratory volume in one second (FEV1) and the FEV1/FVC ratio; disease severity was categorized as mild, moderate, severe or very severe using GOLD classification. Breathlessness was graded using the mMRC scale. Exercise intolerance and hospital visits were recorded. Body mass index was assessed. A complete blood count with differential was obtained, and NLR was calculated as the absolute or proportional neutrophil count divided by the corresponding lymphocyte count. Erythrocyte sedimentation rate and C-reactive protein were also measured.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean±standard deviation. NLR was categorized as <2, 2-4, 4-6 and >6. Pearson's chi-square test was used when expected-frequency assumptions were satisfied. For NLR category versus COPD severity, NLR category versus mMRC grade, and age group versus COPD severity, sparse expected counts were handled using the Fisher–Freeman–Halton exact test with Monte Carlo simulation (1,000,000 random tables; fixed margins). Pearson's chi-square test was retained for NLR category versus exercise intolerance and sex versus COPD severity. A two-sided p-value <0.05 was considered statistically significant.

Ethical considerations

The study was conducted after institutional ethics approval. Patient confidentiality was maintained throughout the study.

RESULTS

The study included 130 participants. Most were aged 41-60 years (42.3%) or 61-80 years (38.5%), and 90 (69.2%) were male. Moderate COPD was the largest severity group (34.6%), followed by severe COPD (30.8%). Nearly half (46.2%) had normal BMI, while 23.1% were underweight, 19.2% overweight and 11.5% obese. Cough was reported by 100 participants (76.9%) and exercise intolerance by 95 (73.1%). The mMRC distribution was concentrated in grades 2 (30.8%) and 3 (26.9%). Hospital utilization was substantial: 50 participants (38.5%) reported 2-3 visits and 40 (30.8%) reported more than three visits.

Table 1. Baseline demographic and clinical characteristics (N=130)

Characteristic	Category	n (%)
Age group (years)	18-40	15 (11.5)
	41-60	55 (42.3)
	61-80	50 (38.5)
	>80	10 (7.7)
Sex	Male	90 (69.2)
	Female	40 (30.8)
COPD severity	Mild	25 (19.2)
	Moderate	45 (34.6)
	Severe	40 (30.8)
	Very severe	20 (15.4)
NLR category	<2	20 (15.4)
	2-4	50 (38.5)
	4-6	35 (26.9)
	>6	25 (19.2)
mMRC grade	0	10 (7.7)
	1	25 (19.2)
	2	40 (30.8)
	3	35 (26.9)
	4	20 (15.4)

The mean NLR was 3.9±1.8. The mean FEV1/FVC ratio was 0.58±0.09. The inflammatory profile included a mean ESR of 28±12 mm/hour and CRP of 6.5±3.2 mg/L.+

Table 2. Laboratory and functional parameters

Parameter	Mean±SD
Haemoglobin (g/dL)	12.8±1.6
Total leukocyte count (cells/mm³)	8,900±2,100
Neutrophils (%)	68.5±8.2
Lymphocytes (%)	22.4±6.5
NLR	3.9±1.8
Platelet count (lakh/mm³)	2.6±0.7
ESR (mm/hour)	28±12
C-reactive protein (mg/L)	6.5±3.2
FEV1/FVC ratio	0.58±0.09

There was a clear shift toward advanced COPD with increasing NLR. Sixty per cent of participants with NLR <2 had mild COPD, whereas 84.0% of those with NLR >6 had severe or very severe COPD. The overall association was statistically significant (Fisher–Freeman–Halton Monte Carlo exact p<0.001).

Table 3. Association between NLR category and COPD severity

NLR	Mild	Moderate	Severe	Very severe	Total
<2	12	6	2	0	20
2-4	10	25	10	5	50
4-6	3	10	15	7	35
>6	0	4	13	8	25
Total	25	45	40	20	130

Fisher–Freeman–Halton Monte Carlo exact p<0.001.

Higher NLR was also associated with worse breathlessness. No participant with NLR >6 had mMRC grade 0 or 1, while 80.0% had grade 3 or 4 dyspnoea (Fisher–Freeman–Halton Monte Carlo exact p<0.001). Exercise intolerance was present in 50.0% of participants with NLR <2, compared with 85.7% in the 4-6 group and 80.0% in the >6 group (χ^2=9.10, 3 df, p=0.028).

Table 4. Associations of NLR with dyspnoea and exercise intolerance

Outcome / NLR	<2	2-4	4-6	>6	Total	p-value
mMRC 0	6	4	0	0	10	<0.001*
mMRC 1	8	12	5	0	25	
mMRC 2	5	18	12	5	40	
mMRC 3	1	10	12	12	35	0.028
mMRC 4	0	6	6	8	20	
Exercise intolerance present	10	35	30	20	95	
Exercise intolerance absent	10	15	5	5	35	

*Fisher–Freeman–Halton Monte Carlo exact test.

COPD severity increased significantly with age (Fisher–Freeman–Halton Monte Carlo exact p<0.001). Two-thirds of participants aged 18-40 years had mild disease, whereas 70.0% of those aged >80 years had very severe COPD. The association between sex and COPD severity did not reach statistical significance after recalculation from the displayed counts (χ^2=6.64, 3 df, p=0.084).

Table 5. Associations of age and sex with COPD severity

Variable	Mild	Moderate	Severe	Very severe	Total	p-value
Age 18-40 year	10	5	0	0	15	
Age 41-60 year	10	25	15	5	55	
Age 61-80 year	5	12	25	8	50	<0.001
Age >80 years	0	3	0	7	10	
Male	15	35	30	10	90	0.084
Female	10	10	10	10	40	

*Fisher–Freeman–Halton Monte Carlo exact test; sex comparison used Pearson's chi-square test.

DISCUSSION

The principal finding of this study was a strong, graded association between NLR and COPD severity. Patients with NLR <2 were concentrated in the mild and moderate groups, whereas 84.0% of those with NLR >6 had severe or very severe COPD. The association remained highly significant when all four NLR and GOLD categories were considered (p<0.001). Higher NLR was also associated with worse mMRC dyspnoea and exercise intolerance. The findings demonstrated significant associations of NLR categories with COPD severity, mMRC dyspnoea grade and exercise intolerance.

The mean NLR was 3.9±1.8 in this cohort. This agrees with Günay et

al., who showed higher NLR in stable COPD than in healthy controls and a further increase during exacerbation.[10] Furutate et al. also found NLR to be related to disease severity and exacerbation.[14] Lee et al. reported an inverse association between NLR and airflow limitation and showed improved prediction of future exacerbations when NLR was added to FEV1.[15] The present study complements these reports by demonstrating a clear stepwise shift across four clinical NLR categories.

Bilir et al. examined the predictive role of NLR in COPD and supported its relationship with clinically important disease characteristics.[16] İn et al. likewise identified NLR as a potentially useful inflammatory index in COPD assessment.[17] Chis and Pop reported correlations between NLR, eosinophils and clinical characteristics, suggesting that cell-count-derived indices may help describe inflammatory and clinical phenotypes.[18] El-Gazzar et al. found prognostic value for both NLR and the platelet-to-lymphocyte ratio.[19] Although the outcomes and thresholds differed, these studies collectively support the direction of the present findings.

The relationship between NLR and disease severity is biologically plausible. COPD is characterized by neutrophil recruitment and activation, oxidative stress, protease activity and tissue injury. More severe or persistently active disease may therefore be accompanied by circulating neutrophilia. At the same time, physiological stress and immune dysregulation may produce relative lymphopenia, increasing the ratio. MacNee described oxidative stress and inflammatory mechanisms as central components of COPD pathogenesis,[20] while the ECLIPSE cohort demonstrated substantial heterogeneity in systemic and clinical expression despite a common diagnostic label.[21] NLR may capture one component of this heterogeneous inflammatory burden.

The mean CRP and ESR values observed in the study population were 6.5±3.2 mg/L and 28±12 mm/hour, respectively. Prior evidence has shown relationships between circulating inflammation and COPD severity or comorbidity. In the Framingham Heart Study, systemic inflammatory markers were associated with COPD-related phenotypes.[22] Thomsen et al. demonstrated that elevated inflammatory biomarkers identified individuals at higher risk of COPD exacerbations,[9] and also examined the relationship between inflammatory biomarkers and comorbidities in COPD.[23] These findings provide a broader context for interpreting NLR as part of an inflammatory profile rather than as an isolated disease-specific marker. The strong relationship between NLR and mMRC grade is clinically important. Most participants with NLR <2 had grade 0-2 dyspnoea, whereas 80.0% of those with NLR >6 had grade 3 or 4 dyspnoea. Dyspnoea reflects airflow limitation, hyperinflation, gas-exchange abnormalities, peripheral-muscle dysfunction, cardiovascular status, anaemia, deconditioning and symptom perception. The association observed here therefore suggests that higher systemic inflammatory activity accompanies greater overall clinical burden, although it does not establish that inflammation directly causes breathlessness.

A similar pattern was observed for exercise intolerance: its prevalence increased from 50.0% in the NLR <2 category to 85.7% in the 4-6 category and 80.0% in the >6 category. Systemic inflammation may contribute to skeletal-muscle dysfunction, impaired nutritional state and reduced exercise capacity, consistent with previously described systemic effects of COPD.[4,7] However, exercise intolerance was recorded as a binary clinical variable rather than measured objectively using the six-minute walk test or cardiopulmonary exercise testing. This limits the precision of the functional interpretation.

COPD severity increased markedly with age. Two-thirds of participants aged 18-40 years had mild disease, whereas 70.0% of those aged >80 years had very severe disease. This pattern is consistent with cumulative exposure, progressive loss of lung function, comorbidity and reduced physiological reserve with advancing age. Male participants constituted 69.2% of the cohort, but the recalculated association between sex and severity was not statistically significant (p=0.084). The male predominance should therefore be reported as a sample characteristic rather than evidence of an independent sex effect.

Cough was present in 76.9% of participants, and a substantial proportion had repeated hospital visits. Infection and airway microbial interactions can contribute to cough, sputum production and exacerbation in COPD.[25] Anthonisen et al. established the clinical relevance of cardinal symptom changes during exacerbations and demonstrated benefit from antibiotics in appropriately selected exacerbations.[26] The current study focused on clinically stable COPD; therefore, its symptom and inflammatory findings should not be extrapolated directly to acute exacerbation management.

The findings are also consistent with systematic reviews that regard NLR as promising but not yet standardized.[11,12,13] Published studies vary in whether they include stable disease, acute exacerbation, infection, corticosteroid exposure or major comorbidity. They also use different NLR thresholds and outcomes. Consequently, the present categories of <2, 2-4, 4-6 and >6 should be understood as analytical groupings rather than universally validated decision cut-offs. Receiver-operating-characteristic analysis and external validation would be required before proposing a clinical threshold.

NLR has practical advantages: it is inexpensive, rapidly available and derived from a routine blood count. It may be particularly useful where advanced biomarkers are unavailable. Nevertheless, it is nonspecific and can be altered by infection, malignancy, cardiovascular disease, metabolic disorders, medication exposure and physiological stress. Other inflammatory biomarkers, including neutrophil gelatinase-associated lipocalin, have also been investigated in COPD,[27] illustrating that no single circulating measure captures the full complexity of the disease. NLR should therefore complement—not replace—spirometry, symptom assessment, exacerbation history and multidimensional indices.

Taken together, the present findings show that higher NLR categories were associated with greater clinical disease burden in this cohort. Its strongest immediate role may be as an adjunct that prompts closer assessment of patients with unexpectedly high values. Prospective multicentre studies should evaluate repeated NLR measurements, continuous dose-response relationships, validated cut-offs and incremental predictive performance over established clinical models.

Strengths and Limitations

The study evaluated NLR alongside COPD severity, mMRC dyspnoea, exercise intolerance and inflammatory markers in a defined stable-COPD cohort. Its principal limitations are the single-centre observational design, modest sample size, absence of a healthy control group, use of prespecified NLR categories without receiver-operating-characteristic validation, and lack of multivariable adjustment for potential confounding. Some contingency-table cells had small expected counts, and the reported associations should therefore be interpreted as exploratory. The cross-sectional analysis cannot establish causality or confirm prognostic utility.

CONCLUSION

NLR increased across COPD severity categories and was significantly associated with worse mMRC dyspnoea and exercise intolerance. These findings show that NLR is an inexpensive, routinely available measure associated with clinical severity in stable COPD. Larger multicentre prospective studies with validated thresholds, multivariable analysis and longitudinal outcomes are needed before NLR can be incorporated into routine risk-stratification algorithms.

DECLARATIONS

Ethics approval: The study was conducted after approval by the institutional ethics committee.
Consent to participate: Informed consent was obtained from study participants.
Funding: No external funding was reported.
Conflict of interest: The authors declare no conflict of interest.
Data availability: Data are available from the corresponding author on reasonable request, subject to institutional and ethical requirements.

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