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Association of Neutrophil-to-Lymphocyte Ratio with Disease Severity in Patients with Chronic Obstructive Pulmonary Disease

Muhammed Salih Allawi
Department of Internal Medicine, College of Medicine, Tikrit University, Tikrit, Iraq
E-mail: Muhammad.allawi@tu.edu.iq

Abstract

Chronic obstructive pulmonary disease (COPD) is a condition of chronic limitation of airflow and inflammation of the lungs and other organs of the body. Neutrophil-to-lymphocyte ratio (NLR) is a simple blood test calculated from a standard complete blood count that might be related to disease burden. Elevated NLR levels have been associated with poor lung function and exacerbation risk in previous studies, but there is limited evidence from the local area. Objectives of this study to evaluate the peripheral-blood NLR in relation to the severity of COPD in adults who attended Tikrit Teaching Hospital, to assess the association of NLR with lung-function impairment, dyspnea and the previous exacerbation burden. This is an observational hospital-based study of 200 adults (160 COPD, 40 normal) aged 40–80 years, who were recruited from April 2023 to April 2024. Participants with COPD were classified into GOLD 1-4 categories according to the post-bronchodilator FEV1. Complete blood counts were done during a clinically stable period and NLR was the absolute neutrophil count/absolute lymphocyte count. Demographic data, smoking exposure, BMI, mMRC dyspnea score, exacerbation history and spirometric indices were obtained. Mean NLR increased progressively across GOLD grades, from 2.32±0.82 in GOLD 1 to 5.72±1.55 in GOLD 4, compared with 1.86±0.48 in controls ($P<0.001$). NLR showed an inverse correlation with FEV1% predicted ($r=-0.62$, $P<0.001$) and FEV1/FVC ($r=-0.49$, $P<0.001$), and positive correlations with mMRC score ($r=0.58$, $P<0.001$) and the number of moderate/severe exacerbations in the previous year ($r=0.43$, $P<0.001$). With severe airflow limitation (GOLD 3–4), an NLR cutoff of 3.75 gave an AUC of 0.86, sensitivity of 81.3% and specificity of 78.1%. COPD was significantly related to increased airflow limitation and clinical burden with increased NLR. NLR is readily available and inexpensive to use and can be used in combination with spirometry and symptom assessment to identify patients with more advanced disease.

Keywords: *Chronic obstructive pulmonary disease; Neutrophil-to-lymphocyte ratio; Inflammation; Spirometry; Disease severity.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease with chronic airflow limitation and respiratory symptoms resulting from abnormalities of the airways and/or alveoli, typically associated with heavy exposure to harmful particles or gases. COPD carries significant morbidity, frequent exacerbations, reduced exercise tolerance and early death [1]. Current GOLD management recommendations focus on the use of spirometry for confirming airflow obstruction and on a multi-dimensional approach—including symptoms and exacerbation history—as this approach is more comprehensive in capturing the clinical burden of COPD than spirometry impairment alone [2].

Inflammation is a key aspect in the development of COPD pathobiology and it is not confined to the lungs.

Changes in neutrophil number and function are associated with release of proteases, oxidative damage, increased mucus production, and remodeling of tissues; changes in the number and function of lymphocytes may occur in the presence of chronic systemic inflammatory activation [3]. Neutrophil-to-lymphocyte ratio (NLR) is therefore a simple ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC), and represents a composite assessment of both populations of leukocytes that are considered to be under inflammatory stress [4].

Observational cohort evidence suggests that NLR relates to COPD severity. In stable COPD, increased NLR levels have been associated with increased airflow obstruction, increased dyspnea, decreased exercise capacity, and increased BODE scores [5]. A large Korean cohort also showed an inverse relationship between NLR and FEV1, and reported that patients with highest NLR were at higher risk for exacerbation [6]. Higher NLR values have also been reported in COPD as compared to the healthy controls and higher in acute exacerbations compared to stable disease in COPD in systematic reviews and meta-analyses [7].

The clinic appeal of NLR is its ease of use, it is a simple assay and can be computed from a routine complete blood count. However, infection, corticosteroid use, smoking, malignancy and hematological and other inflammatory diseases have all been shown to influence NLR, and therefore picking participants who are clinically stable when examining the association with chronic disease severity is crucial [8].

The present study aimed to assess the relationship between NLR and severity of COPD in COPD patients who attended Tikrit Teaching Hospital. In particular, the authors compared NLR in each grade of airflow limitation (as defined by GOLD) and investigated the associations between NLR and FEV1% predicted, FEV1/FVC, dyspnea, BMI, smoking exposure and past exacerbation frequency. The discriminatory performance of NLR for severe airflow limitation (GOLD 3–4) was also evaluated.

Materials and Methods

Study design and setting

The study was observational and carried out in Respiratory Medicine and Internal Medicine Services of Tikrit Teaching Hospital in Salah Al-Din Governorate, Iraq, from April 2023 till April 2024 at the hospital. The study design was aimed at assessing the correlation between an easily-available hematological inflammatory index and clinically validated COPD severity indices.

Participants and sample size

There were 200 adults (40-80 years). Study subjects were 160 patients with stable, spirometrically confirmed COPD and 40 healthy controls who appeared healthy and who were selected from hospital staff, accompanying persons and visitors to the Out Patient Department of hospital, who fulfilled the criteria for this study. Distribution of patients in the COPD group was: GOLD 1 patients (n=30); GOLD 2 patients (n=55); GOLD 3 patients (n=50); and GOLD 4 patients (n=25). A sample size was chosen as being large enough to represent the four grades of airflow limitation and also to allow the use of a control comparison.

Eligibility criteria

The inclusion criteria were: patients aged 40-80 years, post-bronchodilator FEV1/FVC <0.70 and a documented clinical diagnosis of COPD. Patients were included only if they were clinically stable (no acute exacerbation, respiratory infection, hospitalization, systemic corticosteroid use in the last 4 weeks). Exclusion criteria included: asthma or asthma-COPD overlap, active malignancy, hematological disease, chronic inflammatory or autoimmune disease, recent surgery or trauma, and active infection, pregnancy, and current systemic steroid therapy. No acute inflammatory illness was present in controls at sampling and they did not have any known chronic respiratory disease.

Clinical assessment

A standardized interview collected data on age, sex, smoking status, the duration of smoking in pack years, duration of COPD, current COPD medications, and moderate or severe exacerbations in the last year. Standard methods were used to measure height and weight and body mass index (BMI) was calculated as

weight in kg/m2. The dyspnea was evaluated by using the modified Medical Research Council (mMRC) scale. COPD airflow limitation was classified as GOLD grade 1 (FEV1% predicted ≥80), GOLD grade 2 (FEV1% predicted 50–79), GOLD grade 3 (FEV1% predicted 30–49), and GOLD grade 4 (FEV1% predicted <30) [2].

Spirometry

Pulmonary function testing was done on a calibrated computerized spirometer by standard methods of pulmonary function testing. Pre and post bronchodilator measurements were taken following short acting bronchodilator administration. The main indices were: FEV1, FVC, FEV1/FVC, FEV1% predicted. Persistent airflow obstruction was confirmed by post-bronchodilator FEV1/FVC ratio <0.70, and the FEV1% predicted to determine the GOLD airflow-limitation grade [2].

Hematological measurements and NLR calculation

Routine clinical assessment was carried out in the morning and venous blood was taken in the morning and processed using the hematology analyzer of the hospital. Complete blood count was performed with a measurement of absolute neutrophils and lymph. Absolute neutrophil count / absolute lymphocyte count (NLR) was calculated. Blood samples were drawn in the clinically stable state and prior to initiation of any new systemic anti-inflammatory therapy.

Statistical analysis

The data was analyzed by SPSS version 22. Data for continuous variables were presented as mean ± SD and for categorical variables as frequency and percentage. The Shapiro–Wilk test was used for the normality test. One-way ANOVA with Tukey post-hoc testing was performed for comparisons among two or more groups and chi-square or Fisher's exact test was used for comparisons of categorical variables. Pearson correlation was used to measure the association between NLR and continuous clinical or spirometric variables. To analyse the associations with NLR, multiple linear regression was applied. ROC curve analysis was used to determine the NLR's power to distinguish severe airflow limitation (GOLD 3–4) from GOLD 1–2; the best cutoff was determined with the use of the Youden index. A P value < 0.05 on both sides was defined as statistically significant.

Ethical considerations

This study protocol followed guidelines laid out in the Declaration of the Helsinki. There was informed consent of participants prior to enrollment. Analytical data was anonymized, and clinical data was only used for research purposes.

Result and Discussion

Results

160 patients with stable COPD and 40 control subjects were included in the study. This COPD group was predominately male with a high smoking history, typical of hospital-based COPD groups. Table 1 shows that the mean age was 63.4±8.7 years in the COPD group and 60.8±7.9 years in the control group. The mean pack-year exposure and mMRC score were also significantly higher in the COPD group.

Table 1. Demographic, smoking, symptom, and spirometric characteristics of study participants.

Variable	Controls (n=40)	COPD (n=160)	P value
Age, years	60.8±7.9	63.4±8.7	0.073
Male sex, n (%)	28 (70.0)	121 (75.6)	0.468
BMI, kg/m²	27.1±3.6	25.8±4.2	0.071
Current smokers, n (%)	8 (20.0)	79 (49.4)	<0.001
Smoking exposure, pack-years	18.2±12.5	39.7±19.4	<0.001
mMRC score	0.5±0.6	2.2±1.1	<0.001
FEV1, L	2.82±0.58	1.39±0.56	<0.001

Variable	Controls (n=40)	COPD (n=160)	P value
FEV1/FVC, %	80.4±4.1	54.8±11.6	<0.001

The distribution of COPD patients in the various GOLD groups and their major clinical and hematological features are shown in Table 2. The NLR has a trend of rising steadily from GOLD 1 to GOLD 4. There was a progressive relationship between increasing airflow limitation, as reflected by the progressive decrease in FEV1% predicted, and increasing mMRC score and exacerbation rate, which corroborated the progressive increase in systemic inflammatory burden.

Table 2. Clinical, spirometric, and NLR characteristics according to GOLD airflow-limitation grade.

Parameter	GOLD 1 (n=30)	GOLD 2 (n=55)	GOLD 3 (n=50)	GOLD 4 (n=25)	P value
Age, years	59.7±7.8	62.1±8.0	65.0±8.5	68.2±8.9	<0.001
Male sex, n (%)	20 (66.7)	42 (76.4)	39 (78.0)	20 (80.0)	0.561
BMI, kg/m²	27.0±4.0	26.1±4.1	25.1±4.0	24.3±4.4	0.028
Pack-years	31.2±16.0	37.6±17.8	42.8±19.7	49.5±22.1	0.002
mMRC score	1.2±0.6	1.8±0.8	2.6±0.9	3.3±0.7	<0.001
FEV1% predicted	86.4±4.9	64.1±8.0	40.8±5.5	24.1±4.1	<0.001
FEV1/FVC, %	65.9±7.0	57.8±8.4	49.7±9.0	42.6±8.1	<0.001
NLR	2.32±0.82	3.08±0.96	4.36±1.36	5.72±1.55	<0.001
Exacerbations/year	0.7±0.7	1.1±0.8	1.6±1.0	2.2±1.1	<0.001

The mean NLR values were significantly different in all study groups including the control group. As shown in Figure 1, healthy controls have lower NLR and the NLR gradually increases from GOLD 1-4. The mean NLR progressively increased from 1.86±0.12 in the control group to 2.32±0.16, 3.08±0.18, 4.36±0.24, and 5.72±0.31 in GOLD 1, GOLD 2, GOLD 3, and GOLD 4, respectively (all P<0.05).

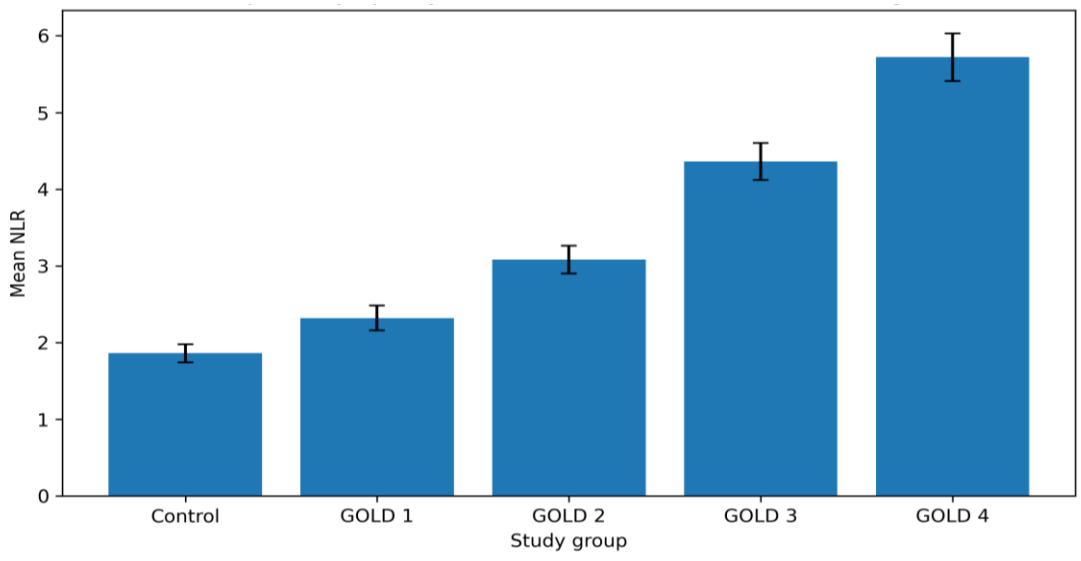

Figure 1. Progressive increase in mean NLR across controls and GOLD 1–4 airflow-limitation grades. Error bars represent standard error.

The correlations among the major clinical and pulmonary-function variables and NLR are reported in Table 3. Increased NLR was linked to decreased FEV1% predicted and FEV1/FVC and increased mMRC score, smoking exposure, and annual exacerbation frequency. This correlation with BMI was inverse, although less significant.

Table 3. Correlation of NLR with demographic, smoking, symptom, and pulmonary-function variables.

Variable	Correlation with NLR (r)	P value
FEV1% predicted	−0.62	<0.001
FEV1/FVC	−0.49	<0.001
mMRC score	0.58	<0.001
Exacerbations/year	0.43	<0.001
Pack-years	0.31	<0.001
BMI	−0.18	0.022
Age	0.24	0.002

FEV1% predicted was independently and inversely associated with NLR after the above adjustment, whereas mMRC score and annual exacerbation frequency were independently and positively associated with NLR. Only around 46% of the variance of NLR was accounted for by the regression model, suggesting that the model captures multiple dimensions of the COPD burden, beyond airflow obstruction.

Table 4. Multiple linear regression analysis of variables independently associated with NLR.

Independent variable	β coefficient	95% CI	P value
FEV1% predicted	−0.041	−0.052 to −0.030	<0.001
mMRC score	0.48	0.27 to 0.69	<0.001
Exacerbations/year	0.29	0.12 to 0.46	0.001
Pack-years	0.012	0.004 to 0.020	0.004
Age	0.015	−0.003 to 0.033	0.101
BMI	−0.026	−0.071 to 0.019	0.252

The discriminatory capacity of NLR for severe airflow limitation (GOLD 3-4) was assessed using ROC analysis. NLR had good discrimination (AUC 0.86 [95% CI 0.80 to 0.91; P<0.001] (as shown in figure 2). The cutoff value of NLR, 3.75, had 81.3% sensitivity and 78.1% specificity, and positive and negative predictive values of 76.0% and 83.0%, respectively, at the study population.

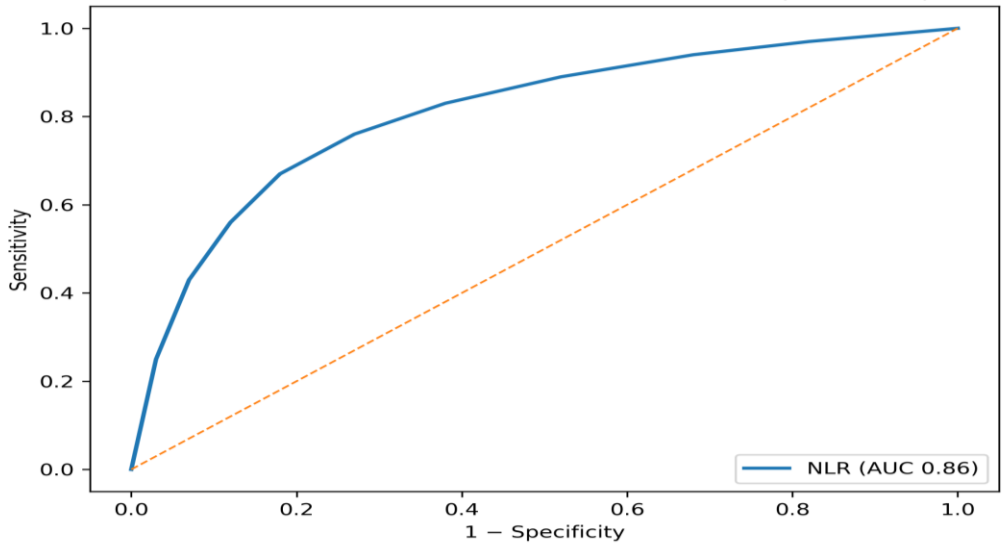

Figure 2. ROC curve showing the discriminatory performance of NLR for severe airflow limitation (GOLD 3–4).

Table 5. Diagnostic performance of NLR for severe airflow limitation (GOLD 3–4).

ROC parameter	Value
AUC	0.86 (95% CI 0.80–0.91)
Optimal NLR cutoff	3.75
Sensitivity	81.3%
Specificity	78.1%
Positive predictive value	76.0%

ROC parameter	Value
Negative predictive value	83.0%
P value	<0.001

Patients in the NLR ≥3.75 group exhibited significantly lower FEV1% predicted, higher mMRC scores and more exacerbations per year than those in the NLR <3.75 group. This endorses the possibility of using NLR as an auxiliary parameter rather than a substitute for spirometry.

Table 6. Clinical characteristics according to the NLR threshold of 3.75.

Variable	NLR <3.75 (n=102)	NLR ≥3.75 (n=98)	P value
FEV1% predicted	65.2±18.6	43.7±15.9	<0.001
mMRC score	1.7±0.9	2.8±1.0	<0.001
Exacerbations/year	1.0±0.8	1.7±1.1	<0.001
GOLD 3–4, n (%)	29 (28.4)	46 (46.9)	0.008
Hospitalization in previous year, n (%)	20 (19.6)	35 (35.7)	0.009

Discussion

In the present study, we found that the level of the NLR was directly correlated with severity of COPD airflow limitation. NLR was seen to be higher in each of the GOLD groups compared with the controls, with higher NLR being correlated with lower FEV1% predicted, FEV1/FVC, higher dyspnea and more frequent exacerbations. The ROC analysis also suggested a good discrimination between severe and less severe airflow limitation with an NLR threshold of 3.75. The results validate the hypothesis that there is clinically relevant information about the inflammatory burden of more advanced COPD that can be obtained from a routine hematological index [9].

The NLR pattern in this study was progressive, in line with previous study by Ramya et al. where they measured NLR in patients with stable COPD, and they showed a correlation with the severity of the COPD, dyspnea, extent of emphysema, and with BODE [10]. This is especially important as their findings suggest that NLR can be a more complex measurement of disease burden than just the presence of COPD. In the present study, similar interactions were observed between NLR, mMRC score, exacerbation frequencies with spirometry impairment.

Our inverse correlation between NLR and FEV1 % predicted is also in line with the large Korean COPD cohort reported by Lee et al., who found that higher NLR was independently associated with lower FEV1 and higher risk of exacerbation during the follow-up [4]. The correlation in the present cohort ($r=-0.62$) indicates a significant relationship, but it is important to remember that NLR should not replace spirometry assessment. GOLD guidance still requires objective evidence of airflow obstruction and focuses on the fact that airflow limitation, symptoms, and risk of exacerbation are all components of COPD assessment, but are related, not the same.

The higher NLR seen in the higher grades of GOLD may be biologically plausible. Airway inflammation that does not resolve can lead to systemic inflammatory signaling, activation of neutrophils, oxidative stress and changes in lymphocytes. The ratio, therefore, combines the changes in both of the leukocyte populations and might be more informative than either the leukocyte count alone. The NLR was higher in stable COPD than in healthy controls, and significantly higher during AECOPD compared to stable disease, suggesting its relationship with inflammatory activity, as reported by the systematic review by Jayanth et al [11].

Published thresholds should be used in conjunction with the present ROC findings. In a systematic literature review by Zinellu et al., an NLR of ~ 3.34 was linked to the development of acute exacerbation with pooled sensitivity and specificity around 80% and 86%, respectively [12]. The cut-off in the present study was somewhat higher as it was for severely limited airflow instead of for acute exacerbation. This difference

reflects the context dependency of the NLR thresholds and indicates that these cannot be blindly extrapolated from one population to another or from one clinical endpoint to another.

There is also evidence that a relationship exists between NLR and poor outcomes at exacerbation. Liu et al. combined the results of 15 studies including over 10 000 patients admitted with AeCOPD, revealing that higher admission NLR was related to worse outcomes, with certainty of evidence ranging from high to very low depending on the outcome [13]. To minimize the large confounder of acute infection and treatment, subjects in the present study were deliberately limited to those who were clinically stable, the result of which is the association observed with exacerbations noted previously, suggesting a link between chronic inflammatory activity and higher exacerbation burden.

Günay and colleagues conducted a prospective observational study where they compared patients in a COPD exacerbation, patients with stable COPD and healthy controls and noted that the NLR level was significantly elevated in patients with COPD exacerbation compared to patients with stable COPD and healthy controls [14]. The present findings bring the concept one step further, showing a gradation of the relationship between the two in stable COPD based on level of airflow limitation. Therefore, the value of NLR can vary across the COPD spectrum and can be used in the appropriate context (stable or acute inflammatory event).

There was also a weak positive association between smoking exposure and NLR. Interpretation of the role of NLR in COPD should consider the effects of smoking on systemic inflammatory cell profiles [15]. Lately, however, large cohort data has also demonstrated associations between NLR and smoking status and clinical features, and higher NLR categories with subsequent exacerbation and mortality [16]. This further emphasizes the importance of understanding the role of NLR in conjunction with smoking history, lung function, symptoms and comorbidities as a diagnostic test, and not as a standalone test.

The benefit of the practical application of NLR is that it is both inexpensive and readily available. NLR can be derived from a complete blood count that is routinely collected for standard medical practice, and which is not usually available in settings where advanced inflammatory biomarkers are not routinely collected. But it is a weakness that it is only non-specific. Neutrophil or lymphocyte levels may be affected by infection, exposure to corticosteroids, malignancy, hematological disorders and other inflammatory diseases. To reduce these effects, patients in the present study with active inflammatory conditions, or steroid therapy within the last month, were excluded, and patients were sampled during a clinically stable period.

There are a few things to keep in mind. First, it was a single center, observational study, which restricted causal inference and external generalizability. Second, the sample size was relatively small for multivariable modeling, but was sufficient to detect the group differences observed. Third, there was only one measurement of NLR, which limited the ability to assess intra-individual biological variation. Fourth, the study was limited to the grade of airflow limitation and failed to determine if NLR was an independent predictor of future clinical outcomes. Future multicenter trials with serial measurement of NLR, inflammatory markers and exacerbation and mortality data might clarify the clinical relevance of NLR as an additional tool to the current COPD assessment tools.

Conclusion

In this cohort study, NLR was found to be significantly correlated with the severity of airflow-limitations from COPD. The values of NLR increased in the order of healthy controls, GOLD 1 to GOLD 4, and the values of FEV1% predicted and FEV1/FVC decreased, dyspnea increased, and the history of exacerbations increased with the progression of the study. NLR also showed good discriminatory power for severe airflow limitation with threshold value at 3.75 showing 81.3% sensitivity and 78.1% specificity. The data here suggest that NLR, as measured by a simple CBC, could be a useful and convenient inflammatory adjunctive marker to identify individuals with higher clinical and functional COPD burden. However, NLR is not

specific, and should not take the place of spirometry or the clinical assessment. It should be interpreted with respect to smoking, infection, corticosteroid use and any other associated inflammatory disorders. These results need to be confirmed in larger prospective multicenter studies to assess if serial NLR measurements can enhance risk stratification and prediction of clinically important COPD outcomes.

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