

**Increased neutrophil-lymphocyte ratio in patients with COPD: case-control study**

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**Abstract**

Chronic obstructive pulmonary disease (COPD) is one of the major causes of chronic morbidity and mortality and one of the major public health problems worldwide that affects millions of people all over the world. It is characterized by persistent airflow obstruction associated with enhanced inflammation in the airways and the lungs in response to noxious particles or gases. The main objective of this study is to investigate the neutrophil-lymphocyte ratio in patients with COPD as a case-control study. Between November 01, 2022, and February 28, 2023, patients were admitted to Al Hussain Teaching Hospital in Al Muthanna Governorate, Department of Medicine. The study included 51 patients with an approved diagnosis of COPD (the mean age was 51.5 years, and 51 patients as control with other diseases mean age was 51.3 years). The subjects in all groups were 32 male and 19 female. Complete blood count (CBC) was measured from blood samples taken from patients. In the present study 51 COPD cases and 51 controls. No significant difference was observed between COPD cases and controls regarding age ( $p = 0.092$ ); the average age of COPD cases was 51.5 years. No significant differences were observed between COPD cases and controls regarding gender ( $p = 0.085$ ). At baseline, 21.0%, 40.3%, 25.7%, and 13% were diagnosed as COPD grade 1, 2, 3, and 4, respectively based on the (GOLD) classification. Baseline NLR significantly increased with the severity of COPD grade (1.3 vs. 2.7 vs. 2.2 vs. 2.9),  $p = 0.002$ ). The cutoff for neutrophil-to-lymphocyte ratio, CRP, WBC, and ESR were 3.28, 2.32, 1.22, and 4.21 respectively. It has 85% sensitivity for detection of COPD exacerbation. and 89% specificity (AUC 0.798,  $p = 0.001$ ). In conclusion, Blood NLR is a simple, inexpensive, widely available index that has been intensively evaluated in recent years in several clinical applications and in various diseases, including COPD.

**Keywords:** COPD; Neutrophil-lymphocyte; Complete blood count

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**Introduction**

Chronic obstructive pulmonary disease (COPD) is common worldwide and is a major healthcare concern [1, 2]. COPD is characterized by low-grade chronic systemic inflammation



[3], and several biomarkers such as C-reactive protein (CRP) [4], IL-6 [5], and surfactant protein D (SPD) [6] have been reported to be associated with increased risk of death in COPD patients [7]. Although many biomarkers of systemic inflammation have recently been evaluated to identify some features of COPD [8], excessive costs and technical factors prevent their clinical use [9]. Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by the presence of poorly reversible airflow limitation and airway inflammation [1]. COPD has become the leading cause of morbidity and mortality around the world, where global mortality which estimated at three million deaths annually [2]. COPD is a disease with various pathological changes in airways, lung parenchyma, and pulmonary vasculature [3] yet; COPD is a multifactorial disease with complex pathophysiological mechanisms and different syndromes that can alter the accuracy of the diagnosis and the treatment of the disease [4]. An acute exacerbation is defined as the acute worsening of the patient's baseline of dyspnea, cough and sputum production which is the hallmark of the symptoms of the disease [5] and is associated with an increase in inflammatory markers that results in the reduction of lung function tests [6]. Although pulmonary function tests are the most common traditional criteria used to assess the severity of the clinical phenotypes and the disease progression, lung function tests alone are not usually enough to diagnose the exacerbations of COPD [7]. According to those challenges, such inflammatory markers become reasonable to assess the severity and treatment of the disease. Leucocyte count and its subtypes are well-known markers of inflammation [10]. Since the physiological response of the leucocytes in circulation against stress precipitates an increase in neutrophil count and a decrease in the lymphocyte count, the ratio of these two sub-groups to one another is employed in the intensive care practice [11]. In various recent studies, the neutrophil-to-lymphocyte ratio (NLR) has been evaluated for its probable role in the inflammation periods of chronic diseases [12]. Neutrophil-to-lymphocyte ratio (NLR) is a parameter used to assess the inflammatory status of a subject. It can easily be calculated from a complete blood count, a commonly used blood test. NLR has previously been shown to predict outcomes in a variety of conditions including different types of malignancies, as well as in cardiovascular and rheumatic diseases [13]. Studies have also shown NLR to be useful in predicting outcomes of different types of infections, including community-acquired pneumonia, bacteremia, and endocarditis. NLR has been studied and proved to be useful in differentiating between patients hospitalized with fever due to infection and those with fever due to non-infectious causes [14]. It has been seen that NLR is a sign of poor prognosis in patients who have undergone cardiovascular involvement and an independent determinant of mortality in patients with acute coronary syndrome [15]. In addition, increased NLR in patients with COPD has been identified a marker that could be used to determine inflammation, detect acute exacerbation in early stages, and it has also been confirmed that it could be an independent marker for all-cause mortality [16].

As we all know, forced expiratory volume in 1s (FEV1) is the most widely used marker to assess COPD severity. However, this index is poorly correlated with some symptoms and may not



reflect the inflammatory status. Moreover, this FEV1 is not routinely used during the acute exacerbation [17]. Therefore, other biomarkers are needed to aid with diagnosis and treatment.

The neutrophil–lymphocyte ratio (NLR) is a quick, easy, and inexpensive index, which can be easily obtained from blood routine examination [18]. Recent studies have reported that NLR could be a new inflammatory marker to assess the inflammation in many diseases, including inflammatory bowel diseases [17], pancreatitis [19], coronary syndrome, and even tumor [20]. It is also reported that NLR can be an independent predictor in appendicitis [21].

### Literature review

Persistent respiratory symptoms and airflow limitation characterize chronic obstructive pulmonary disease (COPD) It is a leading cause of both morbidity and mortality worldwide, which leads to a substantial economic and social burden. In 2017, there were approximately 300 million cases of COPD reported globally, with approximately 3.2 million COPD-related deaths, ranking the disease seventh in a global list of causes of disability, and third in the leading global causes of death [5].

Risk factors for COPD include tobacco smoking, environmental factors (such as air pollution and a reduction in air quality due to the burning of biomass fuels), and genetic susceptibility. The burden of COPD is projected to increase in the coming decades due to continued exposure to environmental COPD risk factors and an aging population [23].

Currently available treatments are directed toward improving symptoms, functional capacity, and quality of life while reducing the COPD exacerbation risk. Stable COPD is typically managed using non-pharmacological means, including smoking cessation, increasing physical activity (including pulmonary rehabilitation), other lifestyle changes, and pharmacological therapy [24]. The cornerstones of pharmacological therapy for COPD are long-acting bronchodilators (long-acting muscarinic antagonists and long-acting  $\beta_2$  agonists), which function to relax the smooth muscle of the airways and reduce lung hyperinflation [25]. Together, these can be used individually or in combination with inhaled corticosteroids (ICS) as dual or triple therapy. ICS target the inflammatory aspects of COPD, and the magnitude of their effect can be predicted by measuring blood eosinophil levels. Triple therapy is typically reserved for patients with a high symptom burden and a high risk of exacerbations despite previous combination therapies [26].

### Patients and Methods

#### Study patients

Between November 01, 2022, and February 28, 2023, patients admitted to Al Hussain teaching hospital in Al Muthanna Governorate, Department of Medicine with COPD were prospectively enrolled into this study. The study included 51 COPD patients with mean age was 51.5 years,



and 51 patients as control with other diseases mean age was 51.3 years). The subjects in all groups were males. Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), and C Reactive protein (CRP) were measured from blood samples taken from patients.

### Study designs

All COPD patients Al Hussain teaching hospital in Al Muthanna Governorate, Department of Medicine was the study population.

### Inclusion criteria

1. Adults male or female (age  $\geq 20$  years).
2. Confirmed diagnosis of Chronic obstructive pulmonary disease (COPD)

### Exclusion criteria

1. Children and adolescents.
2. Smokers.
3. Signs of infection like fever, cough, and sputum.
4. Renal diseases.
5. Liver diseases.
6. Cardiovascular diseases.
7. Other chronic diseases

### Statistical analysis

Statistical analyses were performed using SPSS version 15 01. Independent-samples t-test, paired t-test and Mann–Whitney U tests were used for the comparison of continuous variables. Pearson's correlation was used between NLR and other inflammatory markers. Receiver operating characteristic (ROC) curves were constructed for the WBC, NLR, CRP, and ESR variables, and the areas under the ROC curve values with 95% CIs were calculated and compared with each other. Optimal cut-off values were determined; sensitivity, and specificity were calculated with (95% CI). P value  $\leq 0.05$  was considered statistically significant.

### Result

In present study 51 COPD cases and 51 controls. No significant difference was observed between COPD cases and controls regarding age ( $p=0.092$ ); the average age of COPD cases were 51.5 years. No significant differences were observed between COPD cases and controls regarding gender ( $p=0.085$ ), while the Leucocytes and Lymphocyte with highly significant  $p = 0.002$ ,  $p = 0.002$ . The NLR in COPD group was 2.7, and 1.2 in control cases,  $p = 0.001$  as in Table 1.

**Table 1.**  
 Demographic and laboratory data.

Categories	COPD	Control	<i>P</i>
Number	51	51	
Age	51.5	51.3	0.092
Sex: male female	32 19	30 21	0.085
Leucocytes	9.3	4.3	0.002
Lymphocyte	2.0	2.9	0.002
NLR	2.7	1.2	0.001
Hemoglobin g/dl	15.5	13.1	<0.05
ESR	3.95	2.02	<0.05
CRP	1.8	0.21	0.02

At baseline, 23.0%, 48.9%, 22.3%, and 5.8% were diagnosed as COPD grade 1, 2, 3, and 4, respectively based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [27].

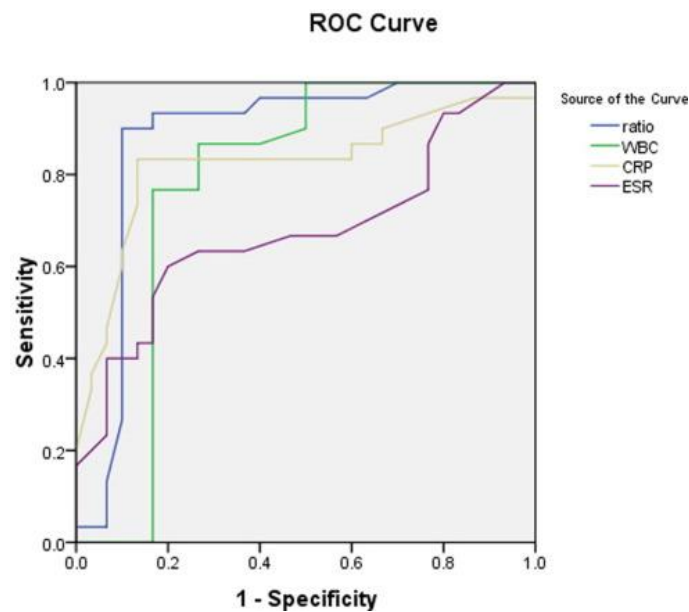
Baseline NLR 21.0%, 40.3%, 25.7%, and 13% were diagnosed as COPD grade 1, 2, 3, and 4, respectively based on the (GOLD) classification. Baseline NLR significantly increased with the severity of COPD grade (1.3 vs. 2.7 vs. 2.2 vs. 2.9),  $p = 0.002$ , table 2.

**Table 2.**

Comparison of the baseline NLR stratified by the GOLD COPD grade. From: Clinical utility of blood neutrophil-lymphocyte ratio in COPD patients. Data are shown as median (interquartile range). *P*-values among the four groups; *p* = 0.001.

GOLD COPD grade	COPD %	NLR
1	21.0	1.3
2	40.3	2.7
3	25.7	2.2
4	13	2.9

The cutoff for neutrophil-to-lymphocyte ratio, CRP, WBC and ESR were 3.28, 2.32, 1.22, 4.21 respectively. It has 85% sensitivity for detection of COPD exacerbation. and 89% specificity (AUC 0.798, *P* = 0.001) as in figure 1.



**Figure 1.**

Receiver Operating Curve for neutrophil-to-lymphocyte ratio, CRP, WBC and ESR.



## Discussion

COPD will remain a significant healthcare problem for years to come [28]. Early identification of the disease through primary care screening for the common symptoms in smokers or those exposed to air pollutants or toxins will lead to earlier diagnosis and treatment [29]. Focusing on smoking cessation will have a great impact on the progression of disease.

Advancements in treatment will require translation of a more fundamental understanding of the pathophysiologic pathways involved into disease-modifying interventions. At present, management efforts are directed toward improving patients' symptoms and functional limitations through carefully selected treatment modalities [8].

Consistent with a previous report [30], in this study, we found that NLR was associated with COPD severity and exacerbations. Several studies have reported the appropriate thresholds to predict the natural history of systemic diseases other than COPD. In this study, we revealed the appropriate cut-off value of NLR as 2.7 to predict COPD severity and future exacerbations [31].

The mechanisms underlying these relationships are unknown, but there could be several explanations. Firstly, it is well known that, even after smoking cessation, inflammation in the lungs continue, especially in patients with advanced COPD [32], suggesting that the persistent inflammatory response in the lungs could lead to neutrophil recruitment and activation [33]. When activated, neutrophils release a variety of serine- and metalloproteinases, which contribute to the development and progression of emphysema [34]. It has been shown that sputum neutrophilia is increased in advanced COPD and is associated with severity of airflow limitation [35].

Blood neutrophilia is a hallmark of current smokers [36] and is also a predictor of mortality in COPD patients [37]. Secondly, a relationship between bacterial colonization and exacerbations is increasingly recognized [38]. Thus, in some patients with COPD, the disturbed flora may continue to activate the innate immune responses, perpetuating lung inflammation and blood neutrophilia.

We would like to emphasize that most of the participants in this study were not current smokers. Thirdly, blood lymphopenia is associated with age [39] and poor nutritional status [40], which could also be applicable to a subset of COPD patients. Taken together, NLR along with age and nutritional status could be reflective of the systemic inflammatory condition. Weak correlations between NLR and other biomarkers might be caused by multifactorial determinants of NLR [11].

A set of markers that could be measured in the blood and that could show the presence/severity of an infection and inflammation has been already identified. These can be used as early and sensitive indicators in determining the infective picture. Parameters, such as serum CRP level, ESR value, leucocyte count, and neutrophile dominance in the leucocyte formula are quite frequently used parameters while following infection in clinical practice [41].



Pathological processes are not specifically localized to the lungs. COPD is a chronic inflammatory disease with high comorbidity and systemic involvement associated with conditions like metabolic syndrome, osteoporosis, diabetes, and cardiovascular diseases [42]. Levels of various inflammation markers like CRP, fibrinogen and leucocyte count have been detected to rise in COPD patients in the exacerbation period [3].

Additionally, it is known that acute phase proteins and other inflammatory cytokines increase even in stable patients with COPD and that there is a low-grade chronic inflammation [19]. This chronic inflammatory period seen in patients with COPD has an important role in the pathogenesis of the disease [22]. Furthermore, it has been established that these elevated inflammation markers are associated with the poor prognosis of the disease and with the increase in the comorbidity ratios [12].

The best-known among these markers is CRP. Elevated systemic CRP levels have been found associated with the increase in disease severity, deterioration in health condition, hospitalization, and mortality rates in COPD [10]. In our study, CRP and ESR levels were found higher in both COPD groups when compared with the controls. Moreover, CRP levels were detected higher in patients of COPD at the exacerbation state when compared to the stable ones. It is known that the most frequent cause of exacerbation in patients with COPD is infections [43].

In patients at exacerbation state, CRP values may have been notably elevated depending on infections. However, elevated CRP levels even in stable COPD patients suggest systemic inflammation in these patients. The presence of chronic inflammation in central and peripheral airways along with an increase in various inflammatory cell types and proinflammatory mediators is a fundamental characteristic of COPD. Inflammation causes damage to the lung parenchyma and contribute to the evidencing of airway limitation [44].

It is known that neutrophils, macrophages and CD8 T-lymphocytes are important inflammatory cells in COPD [20]. It is thought that neutrophils play a role as responsible key cells of lung damage in emphysema [11]. Neutrophil count in circulation rises in systemic inflammation. Elevated neutrophil count is associated with the progression of COPD [2].

Recently, NLR has caught the interest of many researchers as an inflammatory marker. NLR has been shown in various studies to be a prognostic marker in several inflammatory diseases, such as cardiovascular diseases, kidney disease and familial Mediterranean fever [45]. As regards our research, there are 4 studies in the literature that investigate the importance of NLR in patients with COPD.

NLR value has been found notably higher in both COPD groups in their study when compared to the controls. Moreover, NLR has been detected statistically significantly higher in patients with COPD in the exacerbation period when compared to the stable ones [7].

In addition, it has been observed in their study that there is a positive correlation between NLR and CRP levels. In a prospective study where 386 mild and severe COPD patients have been





followed-up for 10 years, NLR has been detected as an independent marker for elevated all-cause mortality [46].

It has been expressed in a retrospective study where 140 stable patients with COPD and 50 controls have been included that NLR could be a simple, effective, and practical indicator in the early detection of metabolic syndrome [18]. In another study where 100 patients with COPD first in the acute exacerbation period and then at the stable period and 50 controls were evaluated retrospectively, NLR has been shown to be a marker that could be used to detect elevated inflammation like CRP, leucocyte count and ESR [11].

It was detected similarly in our study that NLR levels were higher in patients with COPD at the exacerbation and stable period when compared to the controls. When all patients with COPD were taken into consideration, a positive correlation was observed between NLR, ESR and CRP [47].

Moreover, it was determined that NLR had high specificity and sensitivity in estimating acute exacerbation. Our results suggest that NLR could be used as an inflammatory biomarker in showing acute exacerbation and chronic inflammation. Other study reported that COPD in elderly population is difficult to diagnose and associated with many co-morbidities [3].

Our study showed that mean NLR of COPD cases was significantly increased with increased age to 50 years and more ( $p = 0.02$ ). Consistently, with other study reported that mean NLR of patients with chronic diseases was increased with the increased age of patients. In other results, data studies revealed that older age patients had more severe COPD than younger age patients and this might be due to the effect of age and duration of COPD. As a result, the NLR ratio was increased with severe COPD which is related to increased age.

## Conclusions

Blood NLR is a simple, inexpensive, widely available index which has been intensively evaluated in recent years in several clinical applications and in various diseases, including COPD. Several NLR cut-off values have been identified in several clinical situations (stable COPD, exacerbations and ICU patients), and with different prediction purposes (COPD itself, exacerbation, infection, and in hospital and general mortality). The routine use of the NLR in clinical practice should be further assessed in large, well-designed, prospective studies.

## Conflict of Interest

No conflict of interest was declared by the authors.

## Financial Disclosure

The authors declared that this study has received no financial support.

## Ethics Statement

Not applicable.



### Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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