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Neutrophil Lymphocyte Ratio in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a disabling condition that is characterized by ir reversible airflow limitation and inflammation. Exacerbated COPD is a common cause of hospitalization and death. Aims: to determine the significance of neutrophil-lymphocyte ratio (NLR) in exacerbated COPD patients. This is a cross sectional study that included outpatients with stable and ER, inpatients exacerbated COPD. The study included 60 patients with exacerbated COPD, 60 patients with stable COPD and 60 age- and gender matched apparently healthy subjects. Blood samples were collected from each participant, and NRL was calculated for complete blood count. Total leukocyte and neutrophil count but not lymphocyte count were significantly higher in COPD patients than controls. Exacerbated patients displayed higher NLR (4.47±1.9) than either stable patients (3.19± 1.71) or controls (1.81±0.65) with highly significant differences between the three groups. In the context of discrimination between exacerbated patients and controls, the area under the curve of receiver operating characteristics curve was 0.942, 95%CI= 0.905-0.979, p<0.001. The sensitivity and specificity of the test at cut off values of NLR= 2.41 were 0.88 and 0.82 respectively, indicating a very good diagnostic value. The NLR demonstrated a a negative significant correlation with forced expiratory volume during the first second (r= -0.269, p= 0.038). Exacerbated COPD patients had higher NLR compared with stable patients and healthy controls. The NLR has a very good diagnostic value of NLR especially in the context of discrimination between exacerbated patients and healthy controls.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive, and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1]. COPD prevalence using this criterion varying from 6% in Hannover, Germany, to 19% in Cape Town, South Africa. In these studies, a

substantial prevalence (3% to 11%) of COPD among never-smokers was also found [3]. Risk factors of COPD are; 1) cigarette smoking is the most commonly encountered risk factor for COPD. Smoking during pregnancy poses a risk for the fetus, by affecting lung growth and development in utero, 2) a significant familial risk of airflow limitation has been observed in smoking siblings of patients with severe COPD, suggesting that genetic, together with environmental factors, could influence this susceptibility, 3) Occupational exposures are a recognized risk factor for COPD [5], [7], [9]. The diagnosis of COPD should be suspected in individuals with respiratory symptoms, such as cough, expectoration of sputum, shortness of breath upon exertion or lower respiratory tract infections occurring more frequently or lasting longer than expected (>2 weeks). The suspicion should increase if the individuals also report risk factors for COPD, such as exposure to cigarette smoke, environmental or occupational pollutants and/or the presence of a family history of obstructive lung diseases [16]. Although there are no reliable radiographic signs that correlate with the severity of airflow limitation, a chest X-ray is essential to identify alternative diagnoses, such as cardiac failure, other complications of smoking such as lung cancer, and the presence of bullae. A blood count is useful to exclude anaemia or polycythaemia, and in younger patients with predominantly basal emphysema, α1-antiproteinase should be assayed. Measurement of lung volumes provides an assessment of hyperinflation. This is generally performed by using the helium dilution technique; in patients with severe COPD, and with large bullae in particular, body plethysmography is preferred because the use of helium may underestimate lung volumes [21]. COPD exacerbations are episodes of symptom worsening that are usually associated with increased airway inflammation and systemic inflammatory effects [22].

Most COPD exacerbations are triggered by respiratory viral infections, especially rhinovirus, which is the cause of the common cold and thus more common in winter. Respiratory viruses can be identified in the airway by polymerase chain reaction (PCR) in up to 60% of exacerbations [23]. The total leukocyte count, its subtypes and neutrophil-to-lymphocyte ratio (NLR) is an important cheap, readily available and sensitive indicator of the inflammatory status [28]. A high NLR is considered the most reliable predictor than all the leukocyte parameters as it represents a combination of two major components of chronic inflammatory conditions (neutrophils and lymphocytes) [29]. The immune response to various physiological challenges is characterized by increased neutrophil and decrease lymphocyte counts [30]. Increased neutrophil count is a marker of ongoing destructive nonspecific inflammatory process, while a decreased lymphocyte count indicates relatively inadequate immune regulation as well as a quiescent immune pathway [31]. An index has recently been generated to reflect both neutrophil elevation, which demonstrates the acute state of inflammation, and lymphopenia, which occurs following physiological stress. This index, i.e. the neutrophil/lymphocyte ratio, has been suggested as a favorable indicator of the inflammatory status [32]. The present study aimed to determine the significance of neutrophil lymphocyte ratio in COPD patient with exacerbation as early marker and also as prognostic marker in post hospitalization patients.

2. Method

This is a cross sectional study which was conducted at Baghdad Teaching Hospital during the period from August 2019 to september 2020. It included outpatients with stable and ER Inpatients exacerbated COPD. The COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease guidelines if the ratio of post-bronchodilator forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) was <0.7. An exacerbation of COPD was defined if there was acute deterioration of the patient's respiratory symptoms beyond normal day-today variations, and there was a need for additional steroids or antibiotics. Stable COPD was defined as the absence of significant changes in symptom along with no further requirements to additional treatment or doses of daily inhaler treatment for 3 months. This study was approved by the Review Board of Arab Council for Medical Specializations.

Inclusion criteria: 1) Adult patients (40 years old or over) with exacerbated COPD. 2) Stable COPD patients with no history of acute exacerbation during the past 3 months.

Exclusion criteria: 1) Severe structural lung disease such as tuberculosis; bronchiectasis, 2) A concurrent active inflammatory disease other than COPD, 3) Bronchial asthma, 4) Having any infectious, chronic inflammatory diseases, or malignancy. Socio-demographic and clinical data including, age, sex, body mass index (BMI), smoking (pack/years), history of toxic gas exposure and duration of COPD were collected through direct interviews or from patients' records. Three milliliter of peripheral blood were collected from each participant. Hematology auto analyzer (Huroba ABX/India) was used to measure blood parameters. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte. Statistical analyses were performed using SPSS version 25.0. Analysis of variance (ANOVA) test was used for the comparison of continuous variables, while Chi square was used for the comparison of binomial variables. Pearson's correlation was used between NLR and other inflammatory markers. Receiver operating characteristic (ROC) curves were constructed for the WBC and NLR 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 of 0.05 or less was considered statistically significant.

3. Results

Exacerbated patients showed lower FEV1 and FEV1/FVC (43.65±12.25% and 58.1±9.1, respectively) than stable patients (54.76±9.97% and 62.54±7.64%, respectively) with highly significant differences. Although controls groups displayed higher frequency of no-comorbid subjects (41.67%) than either exacerbated patients (25%) or stable patients (26.67%), the differences were no significant. There were mainly two types of comorbidities (DM and HTN) which were almost distributed evenly between the three groups with no significant differences (Table 1).

Table 1: Clinical characteristics of the study population

Variables	Exacerbated COPD (n=60)	Stable COPD (n=60)	Controls (n=60)	pvalue
FEV1% Mean ± SD Range	43.65±12.25 23-70	54.76±9.97 30-78	--------	**<0.001**
FEV1/FVC% Mean ± SD Range	58.1±9.1 46-74	62.54±7.64 46-74	-------	**0.005**
Comorbidities No Comorbidity DM HTN DM and HTN	15(25%) 13(21.67%) 16(26.67%) 16(26.67%)	16(26.67%) 16(26.67%) 13(21.67%) 5(8.33%)	25(41.67%) 12(20%) 10(16.67%) 13(21.67%)	0.471

SD: standard deviation

The hematological parameters of the three groups are illustrated in table 2. Total WBC count in exacerbated, stable patients and controls was 9.57±2.07×10^3/ml, 8.53±1.79×10^3/ml and 5.64±1.07×10^3/ml, respectively with highly significant differences between the three groups. The absolute neutrophils count had also similar

pattern with highly significant differences. Absolute lymphocyte count was comparable between stable patients and controls ($2.12\pm0.83\times10^3$/ml versus $2.13\pm0.73\times10^3$/ml). Which was higher than that of exacerbated patients ($1.75\pm0.59\times10^3$/ml) with highly significant difference.

Table 2: Hematological parameters of the different groups

Variables	Exacerbated COPD (n=60)	Stable COPD (n=60)	Controls (n=60)	pvalue
Total WBC×10^3/ml Mean±SD Range	9.57±2.07[a] 6.6-14.3	8.53±1.79[b] 5.3-12.7	5.64±1.07[c] 4.6-9.6	**<0.001**
Neutrophils×10^3/ml Mean±SD Range	7.06±1.97[a] 2.1-11.0	5.68±1.45[b] 2.8-8.0	3.5±0.77[c] 2.4-7.0	**<0.001**
Lymphocyte×10^3/ml Mean±SD Range	1.75±0.59[a] 0.7-3.1	2.12±0.83[b] 1-3.8	2.13±0.73[b] 1-4.1	**0.005**

SD: standard deviation, different small letters indicate significant differences.

Exacerbated patients displayed higher NLR (4.47±1.9) than either stable patients (3.19± 1.71) or controls (1.81±0.65) with highly significant differences between the three groups (Figure1).

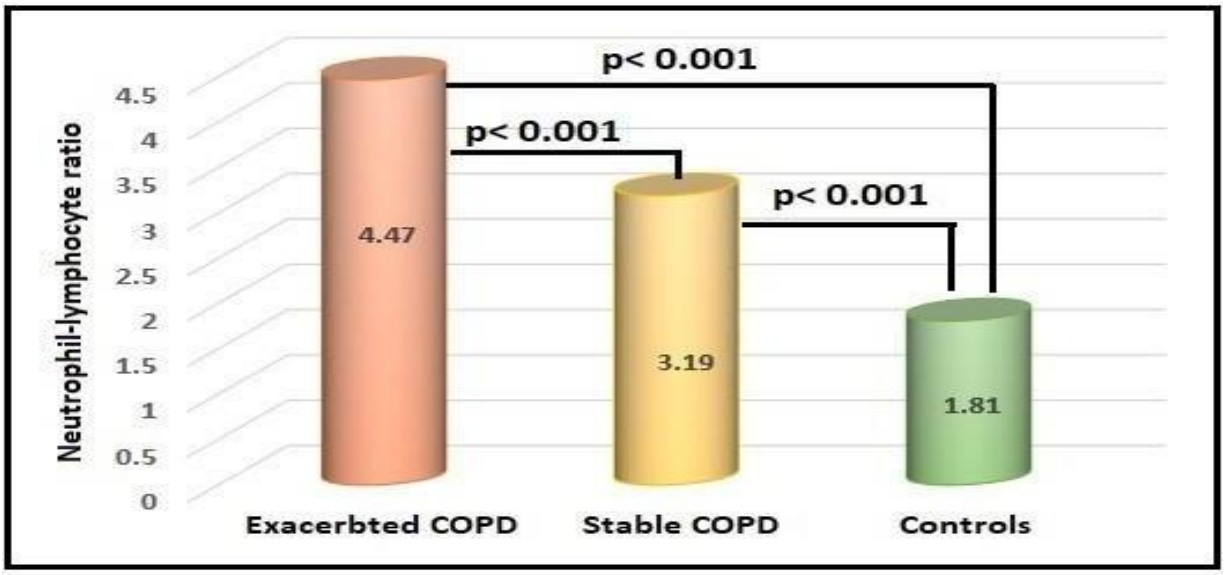

Figure 1: Neutrophil-lymphocyte ratio in different groups.

Receiver operating curve was used to evaluate the diagnostic value of protein NLR in in the detection of cases with exacerbated COPD. In the context of discrimination between exacerbated and stable patients, the area under the curve (AUC) was 0.717, 95%CI= 0.642-0.809, p<0.001. The sensitivity and specificity of the test at cut off values of NLR= 2.83 were 0.78 and 0.55 respectively, indicating a poor diagnostic value (figure 2).

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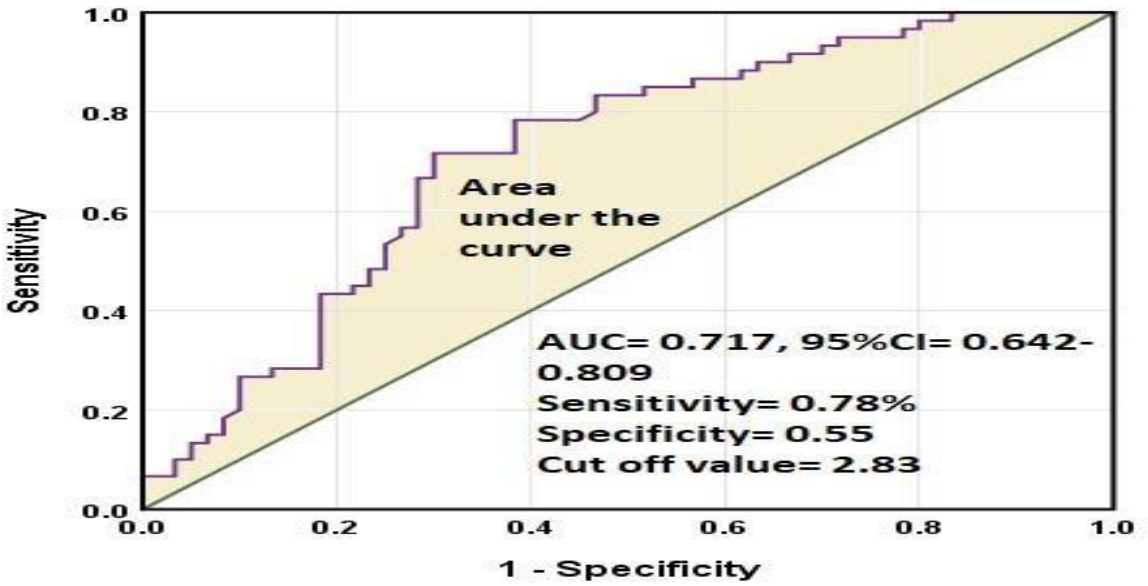

Figure 2: Receiver operating characteristic curve for NLR in the context of discrimination between exacerbated patients from stable patients.

In the context of discrimination between exacerbated patients and controls, the AUC was 0.942, 95%CI= 0.905-0.979, p<0.001. The sensitivity and specificity of the test at cut off values of NLR= 2.41 were 0.88 and 0.82 respectively, indicating a very good diagnostic value (figure 3).

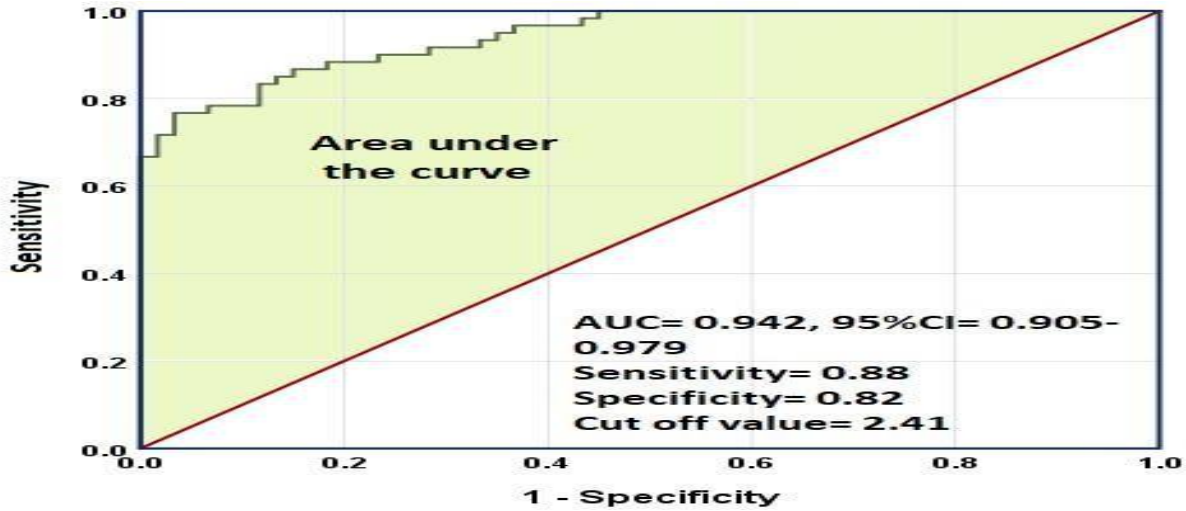

Figure 3: Receiver operating characteristic curve for NLR in the context of discrimination between exacerbated patients from controls.

The regression line between FEV1 as independent variable and NLR is depicted in figure 4. According to this line, a reduction in FEV1 of 20% is associated with a one- unit increase in NLR.

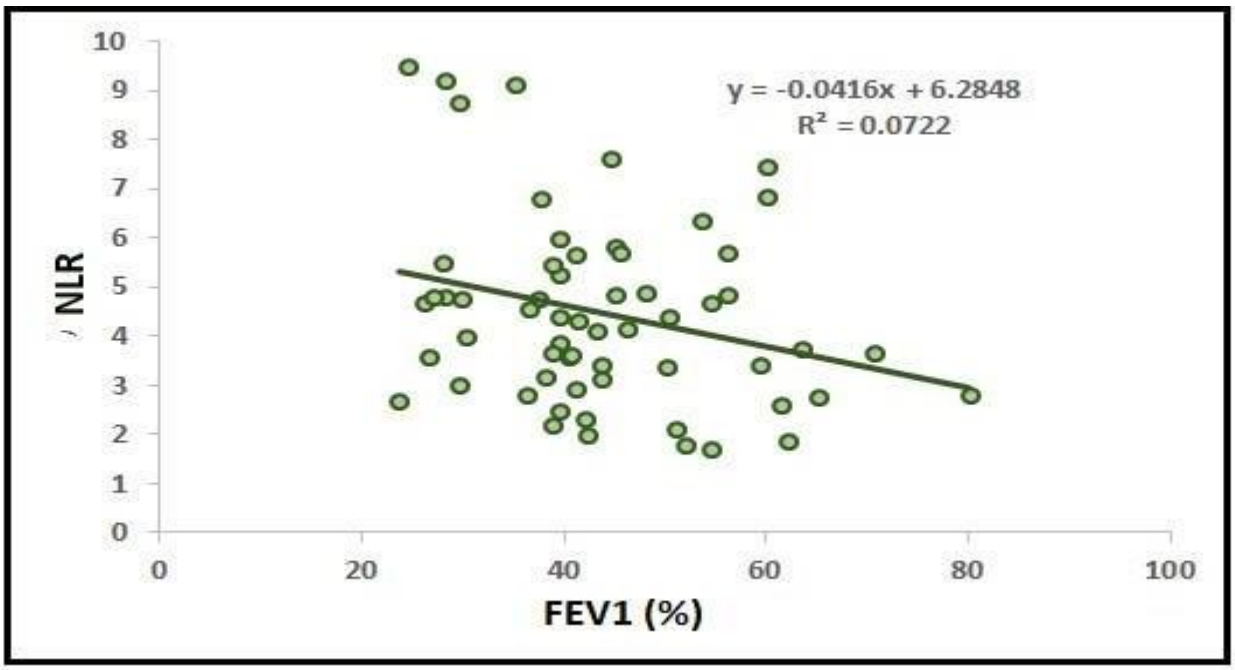

Figure 4: Regression line between FEV1 and NLR in patients with exacerbated COPD.

4. Discussion

The present study aimed to determine the significance of neutrophil lymphocyte ratio in COPD patient with exacerbation as early marker and as prognostic marker in post hospitalization patients. According to the results of the study, total WBC and neutrophil count were significantly higher in CODP patients (whether stable or exacerbated) than controls, while the reverse was true for lymphocyte. In accordance with these results are many previous studies worldwide. In Turkey, [36] respectively investigated the complete blood count for 100 patients with COPD (exacerbated and stable) and compared them with control subjects. Mean WBC, neutrophil and lymphocyte count in exacerbated COPD patients were 10.11±3.11×103/ml, 7.75±3.5×103/ml and 1.4±0.68×103/ml respectively, compared with 7.53±1.75×103/ml, 4.85±1.35×103/ml and 1.9±0.1×103/ml, respectively in stable COPD and 6.71±1.44×103/ml, 3.62±1.1×103/ml and 2.4 ±0.7×103/ml, respectively in controls, with highly significant differences. Almost similar results were obtained by many other studies [37]. The overall relative leukocytosis in COPD patients can mainly be attributed to neutrophilia, because the second main contributor in differential leukocyte count (lymphocyte) is relatively low. Two main factors could be the culprit of this elevation in neutrophils count in COPD in general and in exacerbated patients in particular. Firstly, this pattern supports the role of inflammation as a driver of disease severity and consistent with previous studies that suggested the presence of systemic inflammation in patients with COPD [40]. Secondly, the regular use of corticosteroids can be also implicated in neutrophilia and lymphopenia as indicated by several previous studies [41]. Another interesting finding in the present study is the significantly higher NLR in exacerbated patients compared with stable patients who in turn had significantly higher NLR than controls. These results are in accordance with [40] who investigated the hospital records of 269 COPD patients as well as 50 healthy controls. There was a significant difference in NLR values between healthy controls (1.71±0.65), stable COPD (2.59±1.79) and exacerbated COPD (4.28±4.12). In another study, [43] prospectively measured NLR in 59 patients with COPD exacerbation, 61 patients with stable disease and 28 healthy controls. NLR values were significantly higher in patients with COPD exacerbation when compared to those with stable disease and healthy controls (12.4±10.6, 2.4±0.7 and 1.4±0.5, respectively). Moreover, patients recovering from exacerbations had a significantly lower NLR value, compared with values during the exacerbations (4.5±4.6 versus 11.5±8.8). [36] reported that the NLR

values in healthy controls, stable and exacerbated COPD patients were 1.7±0.9, 3.1±2.5 and 7.1±5.4, respectively with highly significant differences. In the study of [39], it has been demonstrated that there had been a significant increase in NLR in stable COPD patients compared to healthy controls. Additionally, a further increase in NLR was observed in exacerbated compared to stable period. Higher NLR was reflected by increased neutrophils and decreased lymphocytes. The mechanisms underlying this high NLR is not very clear, but several factors beside the inflammatory response can be involved. Firstly, it is well known that, inflammation in the lungs could lead to neutrophil recruitment and activation [44]. Secondly, a relationship between bacterial colonization and exacerbations is increasingly recognized [45].

Thus, in some patients with COPD, the disturbed flora may continue to activate the innate immune responses, perpetuating lung inflammation and blood neutrophilia. Thirdly, blood lymphopenia is associated with age [46] and poor nutritional status [47], which could also be applicable to a subset of COPD patients. Collectively, NLR could reflect the presence of systemic inflammatory condition. The present study revealed a very good diagnostic value of NLR especially in the context of discrimination between exacerbated patients and healthy controls (sensitivity 88% and specificity 82% with 2.41 cut off value). [48], showed lower sensitivity (80.8%) and specificity (77.7%) in predicting exacerbations. [49] reported much higher cut off value in another prospective study in 13 patients with stable COPD, 72 patients with exacerbated COPD and 15 healthy volunteers. Using a NLR cut-off of 7.3, the sensitivity and specificity for exacerbated COPD were 76.8% and 73.1%, respectively (the area under the curve was 0.793). In a systematic review, including 22 studies with 7,601 COPD patients and 784 healthy controls [50] demonstrated that a cut-off value of 3.34 for NLR would allow the diagnosis of acute exacerbation with a median AUC of 0.86, sensitivity of 80%, and specificity of 86%. There is almost general agreement among different studies about the importance of NLR in the discrimination of exacerbated COPD. However, the cut off value, sensitivity and specificity differ between these studies. This variation is justifiable because patients differ in their demographics, races, disease duration, doses of corticosteroids, smoking habits and many other factors that influence the inflammatory and immune response, and thus the neutrophil and lymphocyte counts. Based on the results of the present study, there was a significant negative correlation between NLR and FEV1 ($r= -0.269$, $p= 0.038$). In accordance with this result is a study by [51] including 141 COPD patients to evaluate the association between the NLR and clinical parameters in stable disease, and to investigate potential changes during exacerbations in 49 patients. The NLR was significantly correlated with the forced expiratory volume in 1 s (FEV1) as well as airflow obstruction and dyspnoea. [48] performed a wider study enrolling 885 patients from the Korean COPD Subtype Study cohort. The study investigated the relationship between the NLR and the severity of airflow limitation. One interesting finding in this study was that as the NLR quartile increased, respiratory functional parameters significantly deteriorated. This inverse correlation between NLR and FEV1 mainly reflects the activity of neutrophils. The activated neutrophils could release the inflammatory cytokines and proteolytic enzymes (such as matrix metalloproteinase, calprotectin, and elastase), which resulted in the emphysema [48] and decreased FEV1 [53] Lymphocytes played an important role in immune system, and lymphopenia was associated with a high risk of infection [54].

5. Conclusion

Exacerbated COPD patients had higher NLR compared with stable patients and healthy controls. The NLR has a very good diagnostic value of NLR especially in the context of discrimination between exacerbated patients and healthy controls.

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