ORIGINAL RESEARCH PAPER

Pulmonary Medicine

USEFULNESS OF NEUTROPHIL TO LYMPHOCYTE RATIO IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A PROSPECTIVE OBSERVATIONAL STUDY

KEY WORDS: Chronic obstructive pulmonary disease, Neutrophil-to-lymphocyte ratio, inflammation.

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ABSTRACT

Background: Neutrophil to lymphocyte ratio (NLR) in peripheral blood is a useful systemic inflammatory response biomarker. However, NLR has not been studied in patients with chronic obstructive pulmonary disease (COPD). This study was aimed to evaluate the usefulness of NLR in patients with COPD.

Materials and Methods: The laboratory results of 206 COPD patients were included into the study, of which 94 patients were in acute exacerbation and 112 patients were at stable period, and there were 80 gender and age-matched healthy controls. Complete blood count (CBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were evaluated. NLR was calculated from CBC.

Results: NLR values of patients with COPD (both acutely exacerbated and stable) were found significantly higher than those of the controls ($p< 0.001$, $p< 0.05$; respectively). For an NLR cutoff of 3.34, sensitivity for detecting exacerbation of COPD was 78.7% and specificity was 73.2% (AUC 0.863, $p< 0.001$).

Conclusion: Our results suggest that NLR may be considered as a reliable and simple indicator in the determination of increased inflammation in patients with COPD. Furthermore, NLR could be useful for the early detection of possible acute exacerbations in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide [1]. Chronic airway inflammation, followed by structural changes and narrowing of the small airways, is a key pathogenic mechanism of COPD [2]. There is a growing interest in pulmonary biomarkers as a mechanism to understand and monitor airway inflammation in patients with COPD [3-5]. Systemic inflammatory response is also a major component of COPD, and is closely related to comorbidities of patients with COPD [6-8]. Recently, the neutrophil to lymphocyte ratio (NLR) in peripheral blood has gatnered attention as a potential systemic inflammatory marker. NLR has been used as an independent prognostic factor in various solid tumors, including lung cancer, colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, and gastric cancer [9-14]. Furthermore, cardiovascular outcomes could be independently predicted by NLR in patients with various cardiovascular diseases (CVDs) [15]. However, studies on the role of NLR in patients with COPD are limited, despite the fact that COPD is a chronic inflammatory disease. The aim of this prospective observational study was to evaluate the potential role of NLR in patients with COPD. We evaluated the potential for NLR to serve as a biomarker of COPD exacerbation, as well as whether NLR could predict the need for respiratory hospitalization.

MATERIAL AND METHODS

Study Population 206 consecutive patients admitted in medicine department of GMC Jammu with the diagnosis of COPD between Januarys 1st2015 to December 31st 2015, were enrolled to this study.

INCLUSION CRITERIA

Age > 18 yrs

COPD diagnosis was confirmed by the results of the pulmonary function test (PFT).

EXCLUSION CRITERIA

- Chronic respiratory disease apart from COPD, a pulmonary-extrapulmonary malignancy Or a systemic disease that could affect leucocyte values and

Patients with insufficient PFT values were excluded from the study. The patients were analysed in two groups of "acute exacerbation" and "stable" as regards their clinical picture. Patients who had not had any significant changes in their symptoms in the last 3 months and the ones who did not need additional inhaler treatment dosages or any other additional treatments were defined as "stable COPD". Patients who had deterioration in the symptoms of the respiratory tract that caused change in medical treatment beyond normal daily variations were classified as "acute exacerbation" [16, 17]. The duration of the disease, history of smoking, clinical data, hemogram, erythrocyte sedimentation rate (ESR), CRP and PFT results were recorded from the digital archive system of the hospital.

The control group included 80 healthy cases that were in the same age group as the patients with COPD. Pulmonary Function Tests (forced vital capacity [FVC] and forced expiratory volume in the first second [FEV1]) were measured using standard spirometry device (Ultima CPX 790705-205; Medgraphics Corporation, St. Paul). FEV1/FVC ratio was calculated. The obtained results were expressed as the percentage of absolute and expected values. Spirometric values were evaluated as regards the standards specified by the European Respiratory Society [18]. Determination of Neutrophil-to-Lymphocyte Ratio all blood samples were put in tubes with potassium EDTA for blood count. Hemoglobin, hematocrit, thrombocyte, and white blood cell and type (neutrophil, lymphocyte, eosinophile and monocyte) were identified with automatic blood count device (Siemens Advia 2120, Diagnostic Solutions, Milan, Italy) by electrical impedance method. NLR was obtained by dividing the neutrophile count in the hemogram blood to the lymphocyte count.

The results were calculated as mean ± standard deviation. P value < 0.05 was considered statistically significant. Student's t-test was used for the comparison of two independent groups.

RESULTS

A total of 206 patients with COPD, of whom 94 (45.63%) were in the exacerbation state and 112 (54.36%) were at the stable period, and 80 healthy controls were evaluated in the study. No statistically significant difference was found among the three groups in terms of age and gender. Neutrophil, lymphocyte and NLR levels were detected statistically significantly high in both COPD groups when compared to the control group. Moreover, NLR was detected statistically significantly high in the COPD exacerbation group when compared to the stable patients with COPD. While no difference was determined between both COPD groups in terms of ESR, CRP levels were found to be statistically higher in the exacerbation group. When only COPD groups were included into the analysis, the duration of the disease was found statistically significantly high in the exacerbation group and FVC

and FEV1 levels were found low. Clinical and laboratory data of the three groups and the duration of the disease, smoking state, and PFT data of the patients are given in Table 1. When all patients with COPD included into the study were incorporated into the correlation analysis, it was observed that there was a good degree of positive correlation between NLR and CRP levels and a poor degree of positive correlation between ESR levels (r= 0.641, p< 0.001; r= 0.276, p= 0.005 respectively) .

Table1. Clinical and laboratory findings of the study groups and the results of the pulmonary function test.

	Copd Exacerbations (n=94)	Copd Stable (n=112)	Control (n=80)
1.age (years)	65.8 ±8.1	65.6±8.7	63.6±8.7
2.gender (male,n{%})	76(75.9)	88(78.6)	64(75)
3.duration Of The Disease(years)	8.65±2.82	6.21±2.73	-
4.laboratory Finding			
A)leucocyte(1000/ul)	7.96±2.33	6.83±1.67	7.05±1.43
B)neutrophil(1000/ul)	6.67±1.84	4.97±1.14	3.88±0.82
C)lymphocyte (1000/Ul)	1.84±0.43	2.34±0.76	2.38±0.58
d)NLR	3.63±4.28	2.12±1.5	1.63±1.41
E)hemoglobin(g/dl)	13.64±2.01	14.65±1.78	14.20±1.84
F)platelet (1000/ul)	244.9±100.7	264.9±81.1	250.2±66.6
g)ESR (mm/Hr)	26.10±22.41	18.05±14.41	7.87±5.4
h)CRP	48.08±43.14	17.42±22.34	3.64±1.10
Pulmonary Function Tests			
a) FVC %	44.94±11.50	56.96±16.25	-
b)FEV1	33.52±10.08	43.05±15.05	-
c)FEV1/FVC	56.31±10.49	56.42±10.77	-

NLR: Neutrophil-to-lymphocyte ratio; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; FVC: Forced vital capacity; FEV1: Forced expiration 1st second volume. The results were given as mean ± standard deviation. * p< 0.001, ** p< 0.005, *** p< 0.01, **** p< 0.05; when compared to the controls a p< 0.001,b p< 0.005; when compared to the patients with stable COPD.

DISCUSSION

It was detected in this study that NLR levels were higher in acute exacerbation or stable patients with COPD when compared with the healthy controls. Additionally, it was seen that there was a positive correlation between NLR levels and CRP and ESR levels, and that NLR had a significant specificity and sensitivity in terms of estimating exacerbation. Parameters, such as serum CRP level, ESR value, leucocyte count, and neutrophil dominance in the leucocyte formula are quite frequently used parameters while following infection in clinical practice. Pathological processes are not specifically localised to the lungs. COPD is a chronic inflammatory disease with high co-morbidity and systemic involvement associated with conditions like metabolic syndrome, osteoporosis, diabetes, and cardiovascular diseases [19]. Levels of various inflammation markers like CRP, fibrinogen and leucocyte count have been detected to rise in COPD patients in the exacerbation period. 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 [20].

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, andmortality rates in COPD [21, 22]. 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. 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. It is known that neutrophils, macrophages and CD8 T-lymphocytes are important inflammatory cells in COPD [23]. It is thought that neutrophils play a role as responsible key cells of lung damage in emphysema [24]. Neutrophil count in circulation rises in systemic inflammation. Elevated neutrophil count is associated with the progression of COPD [25]. Recently, NLR has caught the interest of many researchers as an inflammatory marker. As regards our research, there are 4 studies in the literature which investigate the importance of NLR in patients with COPD. Günay et al. [26] have retrospectively analyzed 178 stable patients with COPD, 91 patients with COPD in the acute exacerbation period and 50 control cases. 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. 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 [27]. 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 [28]. It was detected similarly in our study that NLR levels were higher in patients with COPD at the exacerbation and table 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. Moreover, it was determined that NLR had high specifity 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.

LIMITATIONS

In terms of estimating exacerbation in patients with COPD, it would be more correct to evaluate NLR levels both at the stable and the exacerbation period in the same patient group to detect the significance of NLR since NLR levels could be varying like other inflammation markers while specifying cut-off values.

CONCLUSION

Overall, NLR levels in our study were detected higher in stable patients with COPD and in patients at the exacerbation period when compared to the controls, and they correlated with traditional inflammation indicators. NLR could be a useful and practical inflammation marker to estimate acute exacerbation in patients with COPD and to detect potential inflammation at the stable period.

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