Original Article

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Quick Response Code:

Website: www.eurasianjpulmonol.com

DOI: 10.4103/ejop.ejop_106_20

Importance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in chronic obstructive pulmonary disease exacerbations

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Abstract:

BACKGROUND: The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are markers of inflammation. Many cells and mediators have been found to be involved in the progression of chronic obstructive pulmonary disease (COPD). We aimed to evaluate the association of the NLR and PLR with treatment options, length of hospital stay, and mortality of patients with COPD exacerbation in this study.

MATERIALS AND METHODS: We retrospectively collected the data of COPD patients who were hospitalized with the diagnosis of COPD exacerbation. Demographic data, NLR, PLR, number of exacerbations in the last year, length of hospital stay, and deceased patients were evaluated. Correlations between NLR and PLR with length of hospital stay and treatment options were analyzed. NLR and PLR values were compared between deceased and survived patients.

RESULTS: One hundred and nineteen patients were included in the study. The mean age of patients was 68.74 ± 9.2 years, and the mean length of hospital stay was 19.5 ± 13.5 days. The median NLR and PLR values were 3.7 (minimum–maximum: 1–10.8) and 109 (minimum–maximum: 7.4–890), respectively. NLR values were found to be higher in patients who required systemic steroid or invasive mechanical ventilation (IMV) ($P = 0.001$, $P = 0.017$). The cutoff value of NLR was 2.65 with 73.8% sensitivity and 54.9% specificity (area under the curve [AUC]: 0.675, $P = 0.001$) for systemic steroid requirement, and the cutoff value of NLR for IMV requirement was 4.19 with 77.8% sensitivity and 70.4% specificity (AUC: 0.741, $P = 0.017$). However, PLR values were not related with systemic steroid or IMV.

CONCLUSION: NLR seems to be a superior prognostic inflammatory marker than PLR in COPD exacerbation for predicting treatment options.

Keywords:

Chronic obstructive pulmonary disease, lymphocyte, neutrophil, platelet

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Received: 29-09-2020
Revised: 28-12-2020
Accepted: 04-01-2021
Published: 12-08-2021

How to cite this article: Babaoglu E, Ulasli SS, Keles E, Korkmaz ET, Koksal D, Emri S. Importance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in chronic obstructive pulmonary disease exacerbations. Eurasian J Pulmonol 2021;23:110-5.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation associated with an abnormal inflammatory response of lungs to noxious particles or gasses.[1,2] Exacerbation is defined as an acute worsening of respiratory symptoms that result in additional therapy.[3] It is the most important factor in mortality and morbidity.[4] Exacerbations also impact health status, rates of hospitalization, readmission, and disease progression.[5] The mortality rate in COPD patients is 15%–54%, and it is higher in acute exacerbations.[6,7]

Several types of inflammatory cells and mediators have been found to be involved in the progression of COPD. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive, widely available markers of inflammation.[8-11] NLR is a beneficial marker for the early detection of potential acute exacerbation in COPD.[12] It is associated with the severity of airflow limitation and an independent predictor of mortality.[13,14] Furthermore, NLR was associated with Modified medical research Council (mMRC), 6-min walking test, BODE index, and length of hospital stay in COPD patients.[8,15-17]

PLR is another easily available marker for evaluating the inflammation during stable period and the disease severity during acute exacerbations in COPD patients.[12]

Recent studies have investigated the usefulness of NLR and PLR for predicting the mortality in COPD. However, there are limited data about the relationship between NLR, PLR, and requirement of systemic steroid, invasive mechanical ventilation (IMV), and non-IMV in COPD exacerbation.

We aimed to evaluate the association of the NLR and PLR with the required treatment options, length of hospital stay, and mortality of patients with COPD exacerbations.

Materials and Methods

The study was designed as retrospective cross-sectional. All data were collected retrospectively from the hospital database. Between March 2010 and January 2017, hospitalized patients with the diagnosis of COPD exacerbation were enrolled to the study. To collect the data of patients, ICD code "J44" was used. The study protocol was approved by the ethics committee (ethics committee number: GO 16/636-21) and was in accordance with the Declaration of Helsinki.

COPD patients with bronchiectasis, pneumonia, tuberculosis, pulmonary embolism, malignancy, chronic renal failure, and liver failure were excluded. Furthermore, transferred patients from other hospitals or intensive care units (ICUs) were excluded. Patients were previously diagnosed as COPD by a pulmonologist who detected airflow obstruction on spirometry (postbronchodilator forced expiratory volume in 1 [FEV1]/forced vital capacity <70%) with compatible history. The exacerbation was defined as acute worsening of a patient's respiratory symptoms that resulted in additional therapy. Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness, acute respiratory failure, onset of new clinical signs (cyanosis and peripheral edema), failure of an exacerbation to respond to initial medical management, presence of serious comorbidities (heart failure and newly occurring arrhythmias), or insufficient home support were the indications for hospitalization.[1]

All patients in need of IMV were taken into ICU. Patients' age, gender, mMRC score, smoking behavior, NLR, PLR, time of COPD diagnosis, number of exacerbations in the last year, length of hospital stay, echocardiographic evaluation (presence of cor pulmonale and value of systolic pulmonary arterial pressure), applied treatments, and deceased patients both in ward and ICU were recorded. NLR and PLR were calculated as the ratio of neutrophils to lymphocytes and the ratio of platelets to lymphocytes at the admission to hospital with COPD exacerbation.

Statistical analysis

Statistical analyses were performed using SPSS software version 20 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA). The variables were investigated using visual and analytical methods (Kolmogorov–Smirnov test) to determine the distribution status. Descriptive analyses were presented as mean ± standard deviation, median (minimum–maximum), and percentage values.

Nonnormally distributed variables of groups were compared using Mann–Whitney *U*-test. *t*-test was used to compare normally distributed variables between groups.

The associations between nonnormally distributed variables were investigated with Spearman correlation coefficient. A 5% type I error level was used to infer statistical significance.

The capacity of NLR in predicting the need of systemic steroid and IMV was analyzed using receiver operating characteristic curve analysis. When a significant cutoff value was observed, sensitivity and specificity values were presented. While evaluating the area under the curve (AUC), a 5% type I error level was used to accept a statistically significant predictive value of NLR.

Results

Two hundred and sixteen COPD patients were hospitalized between March 2010 and January 2017 with exacerbations, but 97 of them were excluded due to coexistence with comorbidities such as bronchiectasis, pneumonia, tuberculosis, pulmonary embolism, malignancy, chronic renal failure, and liver failure.

One hundred and nineteen hospitalized patients (female/male: 45/74) were included in the study. Twenty-five patients were taken to ICU because they needed IMV. The demographic, clinical, and laboratory findings of the patients are summarized in Table 1. Mean pulmonary artery pressure values were higher in deceased patients than discharged patients (P = 0.008). There was no statistically significant difference between deceased and discharged patients in terms of age, sex, mMRC score, smoking status at the admission of hospital, cumulative dose of smoking (package per year), NLR, PLR, time of COPD diagnosis, number of exacerbations in the last year, length of hospital stay, and the presence of cor pulmonale.

The mean NLR and PLR values of subgroups according to gender, age, smoking behavior, echocardiographic evaluation, number of exacerbations in the last year, and applied treatments in hospital are summarized in Table 2. NLR values were found higher in patients who required systemic steroid or IMV (P = 0.001, P = 0.017) [Figures 1 and 2]. PLR values were found to be higher in female patients (P = 0.041) [Table 2].

The cutoff value of NLR was 2.65 with 73.8% sensitivity, 54.9% specificity, positive predictive value: 66.4%, and negative predictive value: 58.9% (AUC: 0.675, P = 0.001) for systemic steroid requirement, and for IMV requirement, it was 4.19 with 77.8% sensitivity, 70.4% specificity, positive predictive value: 18.8%, and negative predictive value: 92.5% (AUC: 0.741, P = 0.017) [Figures 3 and 4].

Table 1: Demographic, clinical, and laboratory findings of the patients

	All patients (*n*=119)	Discharged patients (*n*=69)	Deceased patients (*n*=50)	*P*
Age (years), mean±SD	68.74±9.2	68.1±10.0	69.4±8.4	0.48
Female, *n* (%)	45 (37.8)	22 (31.8)	23 (46)	
Male, *n* (%)	74 (62.1)	47 (68.1)	27 (54)	
mMRC	3 (1-4)*	3 (1-4)*	3.5 (3-4)*	0.28
Smoking at hospital admission	50	27	23	
Cumulative dose of smoking (ppy)	58.6±34.6	58±32.3	60.6±39.3	0.76
NLR	3.7 (1-10.8)*	2.7 (0.45-27)*	3.6 (0.47-20)*	0.08
PLR	103.5 (20.2-303.1)*	109 (7.4-890)*	119 (32-420)*	0.201
Time of COPD diagnosis (years)	5 (1-40)*	6 (1-40)*	5 (1-30)*	0.35
Number of exacerbations in the last year	1 (0-6)*	1 (0-6)*	1.5 (1-3)*	0.14
Length of hospital stay (days)	19.5±13.5	14.7±12.8	19.5±13.5	0.056
Cor pulmonale	9	5	4	
Mean PAP	45 (25-90)*	37.5 (25-85)*	55 (30-90)*	0.008

*Results are demonstrated as median (minimum–maximum). NLR: Neutrophil-to-lymphocyte ratio, PAP: Pulmonary arterial pressure, PLR: Platelet-to-lymphocyte ratio, mMRC: Modified medical research Council, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

Table 2: Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio values in subgroups

	NLR	*P*	PLR	*P*
Female	3.1 (0.6-21.4)*	0.86	119.4 (7.4-890.9)*	0.041
Male	3 (0.45-27.3)*		103.4 (20-540)*	
Age ≥ 65 years	3.08 (0.45-27.3)*	0.75	114.1 (7.4-890.9)*	0.91
Age<65 years	3.06 (1.19-20)*		107.7 (42.6-286.2)*	
Smoker	3.7 (0.47-16.6)*	0.8	103.4 (7.4-420)*	0.21
Nonsmoker	3.6 (1.04-21.4)*		118.4 (20.2-890.9)*	
Cor pulmonale+	3.09 (1.2-4.5)*	0.82	103.5 (42.6-198.4)*	0.59
Cor pulmonale–	3.05 8 (0.45-27.3)*		113.5 (7.4-890.9)*	
Systemic steroid+	3.7 (0.7-27.3)*	0.001	118.1 (20.23-890.9)*	0.12
Systemic steroid–	2.56 (0.45-17.7)*		103.6 (7.4-452.8)*	
NIMV+	3.66 (0.6-21.4)*	0.17	107.03 (7.4-452.8)*	0.21
NIMV–	2.95 (0.45-27.3)*		116.1 (32.3-890.9)*	
IMV+	5.75 (2.6-27.3)*	0.017	112.3 (56.1-540)*	0.87
IMV–	3.04 (0.45-21.4)*		113.5 (7.4-890.9)*	

*Results are demonstrated as median (minimum–maximum). IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

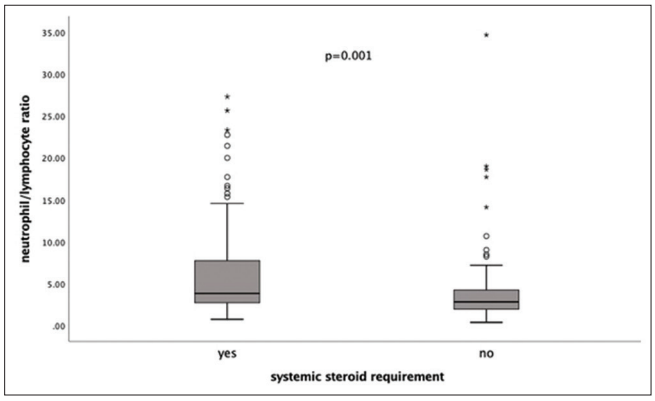

Figure 1: Neutrophil-to-lymphocyte ratio values in systemic steroid required and nonrequired patients

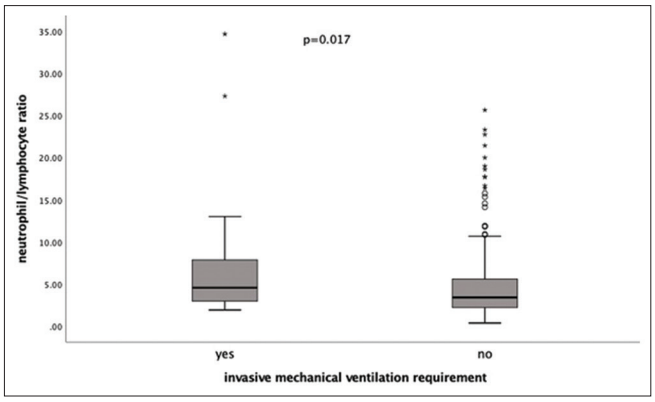

Figure 2: Neutrophil-to-lymphocyte ratio values in invasive mechanical ventilation required and nonrequired patients

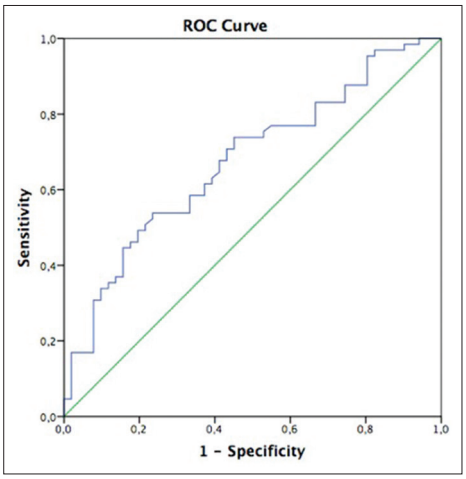

Figure 3: Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio for systemic steroid need. Cutoff value: 2.65, sensitivity = 0.738, specificity = 0.549, positive predictive value: 66.4%, negative predictive value: 58.9%, area under the curve = 0.675, *P* = 0.001

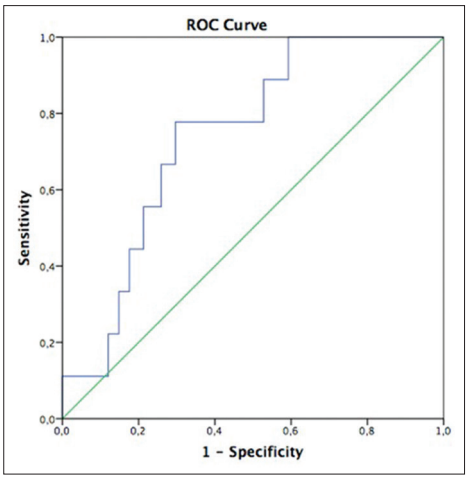

Figure 4: Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio for invasive mechanical ventilation need. Cutoff value = 4.19, sensitivity = 0.778, specificity = 0.704, positive predictive value: 18.8%, negative predictive value: 92.5%, area under the curve = 0.741, *P* = 0.017

There were no statistically significant correlations between NLR and PLR with length of hospital stay, number of exacerbations, pO_2, PCO_2, and SaO_2 values. The correlations are shown in Table 3.

Twenty-five patients (female/male: 20/5) were admitted to ICU. The mean length of ICU stay was 23 days. ICU mortality was 32%.

Table 3: Correlations of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio with length of hospital, number of exacerbations, pO_2, PCO_2, and SaO_2

	NLR (*P*, *r*)	PLR (*P*, *r*)
Length of hospital stay	0.36, 0.08	0.66, 0.04
Number of exacerbations in the last year	0.651, 0.04	0.44, 0.075
PO_2	0.58, 0.05	0.87, 0.016
PCO_2	0.78, −0.027	0.25, 0.11
SaO_2	0.66, 0.04	0.41, 0.08

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Discussion

In this study, NLR was found to be a useful marker to guide treatment options such as systemic steroid or IMV in hospitalized COPD patients with exacerbation. NLR seems to be more effective than PLR in predicting treatment options during exacerbation period. This is a novel information because there was no data about treatment options in previous studies. Patients with higher NLR values may need systemic steroid or IMV indicating the severity of exacerbations. Although no correlations were found between NLR and arterial blood gas parameters, patients with NLR values higher than 4.19 during COPD exacerbation were found to need intensive care for IMV in the present study. Therefore, patients with higher NLR values should be followed closely for intensive care need before the impairment of arterial blood gas parameters during COPD exacerbations.

Moreover, the cutoff value of NLR for systemic steroid requirement was 2.65 with 73.8% sensitivity and 54.9%

specificity (AUC: 0.675, $P = 0.001$) in our study. To our knowledge, there was no study evaluating the impact of NLR on systemic steroid requirement during COPD exacerbations in the literature till the present study.

In previous studies, NLR was found as an independent predictor for mortality and a prognostic marker for future exacerbations.[13,14] In accordance with the previous studies, NLR values were also higher in deceased patients than discharged patients in our study. In the study of Taylan *et al*., for an NLR cutoff of 3.29, sensitivity for detecting exacerbation of COPD was 80.8% and specificity was 77.7%.[18] The cutoff value for NLR in predicting mortality was 3.3 in Xiong *et al*. study. They followed up the patients for 24 months in stable stage. Furthermore, NLR was found as a prognostic marker for future exacerbations in patients with COPD.[13]

In the literature, there are some other markers which are associated with the risk of COPD exacerbations such as eosinophils and C-reactive protein. Furthermore, eosinophils are associated with mortality, decline in FEV1, and response to both inhaled and systemic corticosteroids. In our study, we did not evaluate these markers.[19,20]

Hospitalizations for COPD exacerbations have increased significantly over years, but in contrast, length of hospital stay reduced.[21,22] In recent studies, the mean length of hospital stay reduces to 4 days. In our study, the mean length of hospital stay was 19.5 ± 13.5, and there was not any correlation between NLR and length of hospital stay. In some studies, length of hospital stay was correlated to NLR in COPD exacerbation.[15] This difference might be due to the severity of exacerbations and comorbidities of different study populations.

PLR was found a useful tool for evaluating the ongoing inflammation during stable period and the disease severity during exacerbations in COPD patients.[12] In another study, COPD patients had a significantly increased platelet count, along with a reduced MPV when compared to healthy controls.[23] Moreover, El-Gazzar *et al*. reported that NLR and PLR increased in stable COPD patients and further increased during exacerbation which can predict in hospital mortality.[24] Till now, PLR has not been investigated for predicting treatment options. In our study, PLR levels were similar in deceased and discharged patients, and there were no significant correlations between PLR with length of hospital or number of exacerbations.

Furthermore, there are some limitations of our study. As the design of the present study was retrospective, follow-up results were absent in our study. NLR levels were inversely associated with severity of airflow limitation as measured by FEV1% predicted.[13] Unfortunately, we were not able to perform pulmonary function tests to the study population as they had severe exacerbation. Hence, further prospective randomized controlled studies are needed.

Conclusion

NLR was found as a useful marker for predicting treatment options such as systemic steroid or IMV needs in hospitalized COPD patients with exacerbation. Patients with higher NLR values should be monitored closely for intensive care requirement. However, PLR is an inflammatory marker which was found to be unrelevant in predicting treatment options. Therefore, NLR seems to be a superior inflammatory marker than PLR for predicting treatment options and follow-up during exacerbation period.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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