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Platelet to Lymphocyte Ratio as a Novel Prognostic Marker in Male Patients with Chronic Obstructive Pulmonary Disease

Sezgi Sahin Duyar[1]*, Yalcin Solak[2], Dilek Tekis[3], Jale Karakaya[4], Ferit Kuscu[5] and Asuman Erarslan[6]

[1]*Karaman State Hospital, Department of Pulmonology, Turkey*

[2]*Karaman State Hospital, Department of Internal Medicine, Division of Nephrology, Turkey*

[3]*Karaman State Hospital, Department of Internal Medicine, Division of Gastroenterology, Turkey*

[4]*Hacettepe University, Faculty of Medicine, Department of Biostatistics, Turkey*

[5]*Beypazarı State Hospital, Department of Infectious Diseases, Turkey*

[6]*Karaman State Hospital, Department of Clinical Biochemistry, Turkey*

***Corresponding author:** *Sezgi Sahin Duyar, Karaman State Hospital, Department of Pulmonology, Alacaatlı Mahallesi 3373/2 Sokak Gezgin 1 Sitesi Yaşamkent, Ankara, Turkey, Tel: 05052975327, E-mail: drsezgisahin@gmail.com*

Abstract

Background and aim: Neutrophil to lymphocyte ratio(NLR) and platalet to lymphocyte ratio (PLR) are recently defined novel inflammatory markers which are readily available. Their prognostic signifigance has been shown for a number of inflammatory diseases. A recent study evaluated the role of NLR in patients with chronic obstructive pulmonary disease(COPD). Thus, we aimed to investigate the relations between NLR, PLR and severity of COPD in male patients who had stable disease.

Patients and methods: The clinical and dermographical charecteristics of 39 patients were reviewed retrospectively. Complete blood cell counts and differential values were recorded from electronic database of the hospital. NLR and PLR were calculated from absolute neutrophil and lymphocyte counts from CBC, respectively.

Results: PLR was higher in high risk group of patients with severe airflow limitation (p = 0.011).

Conclusion: The results of this study showed that PLR could be a candidate as a prognostic marker in showing the severity of stable COPD.

Introduction

The pathogenesis of chronic obstructive pulmonary disease (COPD) is traditionally based on airflow limitation. During the last few decades, local and systemic inflammation which are associated with comorbidities, exacerbations and morbidity and mortality of COPD have also been described as significant components in pathogenesis.

Neutrophil to lymphocyte ratio (NLR) and platalet to lymphocyte ratio (PLR) are novel inflammatory markers which have been investigated for a variety of chronic diseases such as cardiovascular disease, metobolic syndrome, Alzheimer's disease, diabetes mellitus, and cancers such as Hodgkin lymphoma, colorectal, cervical and lung carcinomas [1-10]. On the other hand, there are limited data regarding the role of NLR in COPD. To our knowledge, PLR has not been investigated in context of COPD yet.

The main goal of this study was to investigate the relationship between NLR, PLR and the severity of stable COPD in terms of the stage of the disease, modified Medical Research Council (mMRC) dyspnea scale, airflow limitation (described as FEV1) and rate of exacerbations [11].

Patients and Methods

We retrospectively reviewed the clinical data of the patients who visited one of the pulmonology outpatient clinics in Karaman State Hospital between January 2012 and April 2013, using ICD codes J44.9. We recorded gender, age, history of smoking, cardiovascular (hypertension, atherosclerotic heart disease and valvular diseases) and other comorbidities, FEV1 % during the stable stage of COPD, the number of exacerbations causing ER admission and/or hospitalization or increase in symptoms causing prescription of additional medications during the last year, severity of dyspnea (according to mMRC scale), stage of the disease (according to GOLD guideline revised in 2014) and the results of complete blood count (including number of white blood cells, neutrophils, lymphocytes, plateletes) during stable stage and exacerbations [11]. Data extraction was carried out using computer based patient records of our hospital, and for the missing data we interviewed face to face with patients during their admission to our clinic or emergency room. Out of 220 patients, sufficient data were available for only 40 patients. Three patients were excluded due to long term steroid treatment for rheumatologic diseases and 27 patients were excluded because we could not reach an appropriate pulmonary function test result meeting GOLD criteria. CBC records of 40 patients that was obtained at least two weaks after

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Table 1: The relationship between mean value of N/L, P/L ratio, CRP and clinical characteristics in stable COPD.

	# of patients	NLR		PLR	
		median (IQR)	p-value	median (IQR)	p-value
History of smoking					
quited smoking	23 (58.9)	2.06 (1.44-2.82)	0.669	132.09 (87.44-185.06)	0.392
still smoking	16 (41.1)	2.19 (1.51-3.04)		154.51 (100.30-189.33)	
CV comorbidities					
+	17 (43.6)	2.50 (1.41-3.68)	0.539	157.50 (89.99-187.83)	0.605
-	22 (56.4)	1.90 (1.52-2.84)		131.47 (98.58-209.21)	
GOLD stage					
A+B	14 (35.9)	1.74 (1.42-2.35)	0.091	98.86 (80.00-156.50)	0.011
C+D	25 (63.1)	2.55 (1.64-3.15)		157.55(118.67- 206.16)	
Exacerbetions					
< 2/year	31 (79.5)	2.03 (1.44-2.92)	0.332	131.47 (90.59-178.95)	0.176
≥ 2/year	8 (20.5)	2.55 (1.85-3.78)		184.94 (110.76-213.58)	
Severity of dyspnea					
mMRC < 2	10 (25.6)	1.65(1.30-2.39)	0.497	115.60 (87.44-157.55)	0.100
mMRC ≥ 2	29 (74.4)	2.43 (1.60-3.15)		151.52 (100.49-201.16)	
FEV1					
< 50%	26 (66.7)	2.55 (1.64-3.15)	0.091	157.55 (118.67-206.16)	0.011
≥ 50%	13 (33.3)	1.74 (1.42-2.35)		98.86 (80.00-156.50)	

CRP: C-reactive protein; FEV1: Forced Expiratory Volume in the first second; GOLD: The Global Initiative for Chronic Obstructive Lung Disease; IQR: Inter quartile range; mMRC: The Modified Medical Research Council Dyspnea Scale; NLR: neutrophil- to lymphocyte ratio; PLR: platalet to lymphocyte ratio

the last exacerbation were found retrospectively. There was only one female patient with sufficient data so we excluded it and 39 male patients were analyzed.

Neutrophil and lymphocyte counts were taken from complete blood count and differentials which were studied by Fluorescence Flow Cytometry method. Platelet counts were studied with Direct Current-Sheath-Flow Detection method by Roche Sysmex XT2000İ (Roche Diagnostic GmbH, Mannheim, Germany) analyzers.

Statistical Analysis

The normality for continuous variables was checked by using Kolmogorov-Smirnov test. Mann Whitney U test was performed to compare the distribution of two groups for numerical data. Wilcoxon test was applied for the dependent two group comparisons. Chi-square test was used to examine difference between groups for categorical variables. Descriptive statistics were presented as Median (interquartile range) for quantitative data and frequency (percentages) for qualitative data. A $p < 0.05$ was accepted as statistically significant. Data analysis was performed by IBM SPSS Statistics 21.0 software package.

Results

The dermographic characteristics and median NLR and PLR values of 39 patients were summarized in Table 1. The median age of the study group was 67 and all patients were male. 44% of the patients have cardiovascular comorbidities (hypertension, atherosclerotic heart disease and valvular diseases). Other comorbidities were obstructive sleep apnea (2 patients), lung cancer (1 patients), diabetes mellitus (4 patients) and Alzheimer disease (1 patient). The frequent exacerbations (≥ 2/year) were seen in 20.5% of the patients and 74.4% of the patients were more symptomatic in terms of severity of dyspnea (mmrc ≥ 2). 63.1% of the patients was grouped in GOLD stage C and D.

The median values of NLR and PLR, in stable stage were depicted according to the demographic and clinic characteristics of the patients in Table 1. We could not showany statistically significant relation between NLR values and the clinical parameters including smoking history, cardiovascular comorbidities, rate of exacerbations, airflow limtation and GOLD stage ($p > 0.05$). On the other hand, PLR was nearly 1.6 fold higher in patients with severe airway limitation (FEV1 < 50%)andhigh risk group (GOLD class C and D) than in patients with mild and moderate airway limitation and low risk group (GOLD class A and B), ($p = 0.011$).

Discussion

Many different inflammatory cells and mediators play role in pathogenesis of COPD [12]. Recent studies revealed that markers of systemic inflammation such as CRP, fibrinogen and leukocyte count seem as helpful tools in indentifying COPD patients with poor prognosis in terms of comorbidities, frequent exacerbations and overall mortality [13].

Preliminary evidence has suggested that leukocyte subtypes can be used as a measure of systemic inflammation in some chronic diseases. Neutrophil to lymphocyte ratio and platalet to lymphocyteratio have gained significant attention as readily available, cheap and easy to calculate markers.

Various inflammatory events lead to a physiological increase in circulating leukocytes and platelets and a decline in the release of lymphocytes into the circulation [14]. Inflammatory cytokines such as TNF-α and IL6, which also implicated in the patogenesis of COPD, affect the maturation and secretion of platelets [15]. Margination, redistribution and accelerated apoptosis cause lymphocytopenia, whereas demargination, delayed apoptosis and stimulation of stem cells by growth factors lead to neutrophilia [14].

In 1995, first Goodman et al. [16] described NLR as a potential marker in diagnosis of appendicitis. Subsequent studies proved its prognostic value in cardiovascular diseases and its capacity in predicting cardiovascular comorbidities [4,9,17,18]. Its use as a marker of systemic inflammation was further explored by a study of Zahorec et al. [19]. Another study indicated a significant correlation between the criteria of metabolic syndrome and inflammation on the basis of NLR [2]. In a study of Imtiaz et al. [20], an obvious association between NLR and likelihood of having hypertension and diabetes mellitus was shown. De Jager et al. [14] showed that in patients with community acquired pneumonia, increased NLR was correlated with poor clinical outcome. NLR was also shown as a predictor of survival and response to treatment in many cancers such as non-small cell lung cancer, colorectal carcinoma, hodgkin lymphoma and cervical carcinoma [3,5,8,10,21]. The results of a recent study indicated NLR as a predictor of 30-day mortality in acute pulmonary embolism [22].

Likewise, PLR has emerged as a prognostic marker in cadiovascular disease and some cancers. PLR proved to be a marker of long-term mortality in patients presented with non-ST segment elevation myocardial infarction and in-hospital mortality in acute coronary syndrome [1,23]. Higher levels of PLR was associated with poor prognosis in various cancers such as colorectal carcinoma, pancreatic ductal adenocarcinoma, gastric carcinoma, hepatoceluler carcinoma, ovarian cancer and non-small cell lung cancer [7,24-26].

Increased platelet activation in patients with stable stage and

acute exacerbation of COPD was shown in a study by Maclay et al. [27]. However, the place of these new inflammatory markers in diagnosis and follow-up of the patients with COPD has not been investigated so far. To our knowledge there is only one study which showed a significant increase in NLR in COPD patients compared to healthy controls. This study also showed that there was a further increase in NLR during acute exacerbation [28]. In this study, we investigated the relationship between clinical characteristics and the level of these markers. PLR, was elevated in male patients with severe airway limitation (FEV1 < 50%) and in GOLD stage C and D. Thus, in stable stage, PLR can be a candidate for defining COPD patients with high risk. To our knowledge, this is the first study showing the possible clinical value of PLR in stable COPD.

Limitations of the study

The number of study subjects was lower than we expected due to missing data. The study group included only male patients. The study design is retrospective and thus causative inferences cannot be made based on our results. Despite these limitations the results are promising but must be further investigated in a prospective study.

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