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Original Article

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Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Fibromyalgia

Erdem İlgün[1], Ömer Akyürek[2], Ali Osman Kalkan[2], Fethi Demir[1], Mehmet Demirayak[3], Mustafa Bilgi[2].

ABSTRACT

***Objective**: We aimed at contributing to the understanding of the pathophysiology of Fibromyalgia (FM) by measuring neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), which are the systemic inflammatory response (SIR) markers in patients with fibromyalgia. **Method**: The study population consisted of 70 patients newly diagnosed with FM (mean (SD) age: 43.9 (±9.8) years, 80% were female) and 52 healthy volunteers (mean (SD) age: 43.4 (±10.4) years, 76.9% were female). American College of Rheumatology-ACR 1990 criteria regarding the evaluation of widespread pain and tender points were used for the diagnosis of FM. Demographic characteristics, anthropometrics and laboratory findings were used to make comparisons between patient and control groups. **Results**: PLR was 128.0 (±40.2) in the patient group while it was 110.5 (±33.6) in the control group and the difference was found to be significant (p=0.03). NLR was similar in both groups. The tender point count was significantly higher in the patient group (p<0.001) whereas there was a negative correlation between the tender point count and the lymphocyte count (r= -0.200; p=0.020) and a strong positive correlation with PLR (r=0.022; p=0.001). **Conclusion**: Our findings indicate that NLR levels were similar in both groups while the PLR values of the FM patients were found to be significantly higher than those of the control group and there was a positive correlation between PLR and the tender point count.*

***Key words**: Fibromyalgia, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio*

Fibromiyaljide nötrofil/lenfosit oranı ve platelet/lenfosit oranı

ÖZET

***Amaç**: Fibromiyalji (FM) hastalarında sistemik inflamatuar cevap markırı (SIR) olan nötrofil/lenfosit oranı (NLR) ve platelet/lenfosit oranı (PLR) ölçerek hastalığın patofizyolojisinin anlaşılmasına katkıda bulunmayı amaçladık. **Yöntem**: Çalışma populasyonu 70 yeni tanı FM hastası (ortalama (SD) yaş: 43.9±9.8 yıl, 80% bayan) ve 52 sağlıklı gönüllü (ortalama (SD) yaş: 43.4±10.4 yıl, 76.9% bayan). FM tanısında, yaygın ağrı ve hassas nokta değerlendirmesini içeren Amerikan Romatoloji Birliği (American College of Rheumatology-ACR) 1990 kriterleri kullanıldı. Her iki grup demografik karekterler antropometik ve labovatuar bulguları yönünden karşılaştırıldı. **Bulgular**: PLR hasta grupta 128.0±40.2 iken kontrol grubunda 110.5±33.6 ölçüldü ve fark istatiksel olarak anlamlı bulundu (p=0.03). NLR her iki grupta benzer düzeydeydi. Hassas nokta sayısı hasta grubta anlamlı derecede yüksek iken (p<0.001) hassas nokta sayısı ile lenfosit seviyesi arasında negatif korelasyon (r= -0.200; p=0.020) ve PLR ile kuvvetli pozitif korelasyon saptandı (r=0.022; p=0.001). **Sonuç**: Bizim bulgularımıza göre her iki grupta NLR değerleri benzerken FM hastalarında PLR değeri kontrol grubuna göre anlamlı derecede yüksek bulundu ve PLR ile hassas nokta sayısı arasında pozitif korelasyon mevcuttu.*

***Anahtar kelimeler**: Fibromiyalji, nötrofil/lenfosit oranı, platelet/lenfosit oranı*

Mevlana University Faculty of Medicine, Department of Physical Therapy and Rhabilitation[1], Internal Medicine[2] and Orthopedics and Traumatology[3], Konya, Turkey

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***Correspondence**: Ömer Akyürek*
Mevlana University Faculty of Medicine, Department of Internal Medicine, Konya, Turkey

E-mail: dromerakyurek@gmail.com

INTRODUCTION

Fibromyalgia (FM) is a musculoskeletal disease with unknown etiology that is characterized by widespread body pain and tender points, lower pain threshold, sleep disorders, fatigue and affective disorders (1). The incidence of FM may reach up to 5% in the world population while it is a chronic pain syndrome that is more common among women between the ages of 40 and 55 (2). Although the genetic and environmental factors as well as the peripheral and central mechanisms are inculpated in its etiopathogenesis, the pathophysiological mechanism could not be fully understood yet. Genetic predisposition (3), trauma (4), psychopathologic causes (5), viral infections (6) and immunological mechanisms (7-11) are thought to influence its pathogenesis. There are data showing that the symptoms of FM are caused by the interaction between the autonomous central nervous system (SSS) (11-13), hypothalamus-pituitary-adrenal axis (14-16) and the immune system (8).

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in peripheral blood are the markers of simple systemic inflammatory response (SIR). They are evaluated through blood parameters. NLR is highly important for the diagnosis of certain pathologies that are characterized by systemic or local inflammatory response such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis (16-18). The proportion of these two cell types helps detecting inflammation (19). Endogenous residual anticancer preinflammatory and pre-coagulative response that occurs in malignancies can be detected by using PLR as a marker. It is suggested that PLR is a more sensitive marker while it is also assumed that is has a prognostic value for breast cancer as well as ovarian and colorectal cancers (20).

As the disease is thought to have a pathological process that is based on increased systemic inflammation, there is an increasing number of studies focusing on this aspect of FM. In practice, the systematic inflammation level can be evaluated easily by using specific blood parameters or formulations. We also aimed at contributing to the better understanding of this disease by evaluating NLR and PLR of FM patients that are acknowledged as SIR markers in the literature and becoming more common in clinical use among.

MATERIAL AND METHODS

The study population consisted of 70 patients newly diagnosed with FM. The healthy volunteers had the same clinical variables as the group of patients who were referred to the Mevlana University's Physical Therapy and Rehabilitation Outpatient Clinic between July 2014 and March 2015. The study was approved by the ethics board and written informed consent was obtained from all study participants.

American College of Rheumatology-ACR 1990 criteria regarding the evaluation of widespread pain and tender points were used for the diagnosis of FM. According to these criteria, 11 of 18 tender points must be positive in four quadrants of the body including the axial region during the physical examination. Tender point was identified as the anatomical site where the patient complained about pain when 4 kg pressure was applied on (enough to turn the thumbnail of the examiner white) (21). Other possible causes of chronic pain were excluded through clinical and laboratory tests, while the causes of inflammation and infection were ruled out. Patients with hypothyroidism, hyperthyroidism, inflammatory rheumatic disease and autoimmune disease were not included in the study. Patients with a history of major depression, cerebrovascular events and malignancy were excluded from the study. Patients were also excluded if they had cardiovascular disease, hypertension, peripheral artery disease, active chronic obstructive lung disease, heart failure, chronic kidney disease, diabetes mellitus, pulmonary or neurological disease, peripheral neuropathy, hepatic disease, alcohol abuse problems or BMIs indicating morbid obesity (BMI≥40kg/m^2). The control group consisted of healthy individuals who did not have chronic kidney disease, cardiovascular disease, vasculitic lesions, diabetes mellitus, hypertension, hepatic parenchymal disease or acute infection.

Weight and height were measured in light clothing and without shoes. BMI was calculated by dividing the weight by the height squared (kg/m^2). Blood pressure of each patient was measured in the seated position, using a standard mercury sphygmomanometer on the right arm. 5-7cc of peripheral venous blood was collected from all patients and control subjects into sterile EDTA (Ethylenediaminetetraacetic acid) tubes. Hematological parameters were analyzed using a hematology analyzer (Abbott CELL DYN 3700, Boston, USA) within 30 minutes after the blood was collected. Leucocyte (103/µL), neu-

***Table 1**. Demographic and clinical characteristics in patient and control groups*

	Fibromyalgia group (n:70)	***Control group (n:52)***	*p value*
Age (years)	***43.9±9.8***	***43.4±10.4***	***0.800***
Gender (female/male)	*56/14*	*40/12*	***0.168***
Height (cm)	***161.4***±3.7	***162.4***±4.8	***0.326***
Body weight (kg)	***74.8***±14.9	***73.6***±7.7	***0.912***
Body mass index (kg/m²)	***28.3***±5.2	***28.2±2.8***	***0.415***
Tender Point Count	***15.0±1.9***	***4.4***±2.4	***<0.001***
White Blood Cell (10³µl)	***7.3***±1.6	***7.5***±1.5	***0.396***
Lymphocyte (10³µl)	***2.3***±0.6	***2.6***±0.7	***0.728***
Hemoglobin (gr/dl)	***12.9±1.4***	***12.9***±0.9	***0.919***
Platelets (mm³)	***280.8***±55.6	***273.3***±61.3	***0.402***
C-reaktif Protein (mg/l)	***3.0***±2.2	***3.1±1.6***	***0.600***
Erythrocyte Sedimentation Rate (mm/h)	*10.7(5.6)*	*10.2(5.6)*	***0.417***
Platelet/Lymphocyte Ratio	*128.0(40.2)*	*110.5(33.6)*	***0.030***
Neutrophil/Lymphocyte Ratio	*1.9(0.6)*	*1.7(0.6)*	***0.734***

trophil (103/µL), lymphocyte (103/µL) and platelet (103/µL) counts were recorded. The results were expressed in 103/µL. NLR and PLR were calculated using the results of these parameters. Hemoglobin values were expressed in g/dL.

Statistical Analysis

The statistical analyses were performed using SPSS version 15 software package. The statistical evaluation of the data obtained was performed using "SSPS 15.0 for Windows" software package. The descriptive statistics for the constant variables were expressed as mean, standard deviation, minimum and maximum values while the categorical variables were expressed as numbers and percentages. The compliance of the variables with the normal distribution was evaluated using histogram and probability graphs and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests). To compare the groups of variables, Independent Samples t Test was used for those variables that were normally distributed, while non-parametric Mann-Whitney U test was applied for those variables that were not normally distributed. Pearson correlation coefficient was calculated to determine the relationship between these variables. P<0.05 value was considered to be statistically significant.

RESULTS

The FM patients and control subjects were homogenous in terms of age, gender and anthropometrics status (mean (SD) age: 43.9±9.8 years, 80% were female) and 52 healthy volunteers (mean (SD) age: 43.4±10.4 years, 76.9% were female). The demographical characteristics and laboratory findings of the patient and control groups are summarized in Table 1. The tender point count was significantly higher in the patient group than in the control group (p<0.001). Although PLR was statistically significantly higher in the patient group, there was no difference between the NLR levels (p=0.030, p=0.734 respectively). While there was a negative correlation between the tender point count and lymphocyte count (r= -0.200; p=0.020), the tender point count had a positive correlation with PLR (r=0.022; p=0.001). There was no difference between the groups in terms of platelet count, WBC count, lymphocyte count, CRP and erythrocyte sedimentation rate (Table 1).

DISCUSSION

In this study, we aimed at contributing to the better understanding of the pathophysiology of FM by evaluating the NLR and PLR that are considered as SIR markers. The findings of this study revealed that NLR values were similar in both groups whereas PLR value was significantly

higher among the FM patients than in the control group and there was a positive correlation between PLR and tender point count. The significance of our study is that PLR and NLR was detected for the first time in patients with FM.

FM is a rheumatic disorder with unknown etiology and characterized by widespread body pain and tender points in specific anatomical sites (1,2). In FM, pain is accompanied by several somatic and psychological symptoms including primarily fatigue, morning stiffness, depression and sleep disorder (2). It affects 2-5% of the population and it is more common among women between the ages of 40 and 55 (1). In our study, the mean age of 70 patients with FM that constituted the study group was 43.9±9.8 and 80% of the patients were female, which was consistent with the literature data. The studies conducted show that neuroendocrine, autonomous and immunological mechanisms play a role in FM and genetically predisposed individuals tend to develop the disease under the influence of certain stressors such as environmental, physiological and psychological factors (1-7). There is a strong body of evidence in the literature demonstrating that FM is a neuroendocrine-immune dysfunction (8).

There are noteworthy studies that have been conducted recently and have evaluated SIR markers in peripheral blood such as NLR, PLR that can be easily measured through hemogram test. Neutrophils are related to the hyper-coagulability and viscosity of blood and responsible for the microvascular damage on endothelial surface (22). Lymphocytes play a role in chronic inflammation and low lymphocyte count has an effect on morbidity and mortality (23). On the other hand, platelets plays an active role in plaque destabilization, plaque rupture and clotting cascade (24). The studies conducted show that high NLR and PLR values indicate increased inflammation, and are reported to be associated with impaired renal functions in diabetic patients, increased cardiovascular risk and increased mortality in some malignancies (25,26). NLR and PLR give a sign of advanced stage and extensive ovarian malignancy (27). Azab et al. recently showed that those patients with breast cancer who progressed fast under the estrogenic effects had higher NLR and PLR values (28). In another study, Quirino Lai et al. demonstrated that elevated NLR and PLR values were associated with hepatocellular cancer after liver transplantation in relation with systemic inflammation (29).

The studies show that the NLR is an important marker to determine subclinical inflammation and the risk of developing amyloidosis in patients with FMF [30]. Another study found that patients with familial Mediterranean fever (FMF) had higher NRL values in comparison to the control groups, and the NRL was even higher in patients who had the M694V gene mutation, which is associated with an increased risk of amyloidosis, compared to patients who did not have this gene mutation [31]. In a study where patients with inactive ankylosing spondylitis were included, NLR was found to be similar in the patient and control groups whereas PLR was fond to be statistically higher in the patient group. This finding was interpreted as that PLR could be a subclinical inflammation marker (32). Similarly in our study, PLR was found to be statistically significantly higher in FM group than in the control group. Moreover, there was a strong positive correlation between PLR and tender point count. This finding also indicates not only increased subclinical inflammation in FM patients but also the association between the tender point count and subclinical inflammation findings.

The patients included in the study were a small group of individuals visiting the physical therapy and rehabilitation outpatient clinic, which makes it difficult to extend the present findings to the general population. The study's sample size is adequate to provide sufficient statistical power. However, our findings need to be confirmed and validated in much larger studies using appropriate reclassification statistics to provide value to the existing risk scores.

In conclusion, our findings showed that PLR level was significantly higher in the FM group than in the control group and there was a positive correlation between PLR and tender point count. NLR was found to be similar in both groups. PLR may be a marker for subclinical inflammation in patients with FM. These findings contribute to the argument that a pathological process based on increased systemic inflammation may play a role in the pathophysiology of FM. However, there is a need for further studies.

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