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Evaluation of mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and red cell distribution width in patients with diagnosis of major depressive disorder

Major depresif bozukluk tanılı hastalarda ortalama trombosit hacmi, nötrofil lenfosit oranı, platelet lenfosit oranı, kırmızı küre dağılım genişliğinin belirlenmesi

Nermin GÜNDÜZ[1], Özge TİMUR[2], Erkal ERZİNCAN[3], Celaleddin TURGUT[4], Hatice TURAN[1], Zeynep Yıldız AKBEY[5]

ABSTRACT

The aim of this study was to evaluate the changes in hematologic inflammatory markers such as neutrophil /lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR), red cell distribution width (RDW) and mean platelet volume (MPV) in patients with diagnosis of Major Depressive Disorder (MDD). Seventy-five patients between the ages of 18 and 75 who were not currently undergoing any psychiatric treatment and diagnosed having the first episode of MDD according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria in the outpatient clinic of the Department of Psychiatry of the Erzurum Regional Training and Research Hospital between June 2016 and September 2016 were included in the study. The control group was selected from relatives of the hospital employees. Fifty-seven volunteers with similar sociodemographic characteristics and body mass indices selected from relatives of the hospital staff who had not any psychiatric and other clinical conditions were included as a control group. Sociodemographic form, Structured Clinical Interview for DSM IV Axis I Disorders (SCID I), Hamilton Depression Rating Scale (HDRS) and Clinical Global Impression Scale (CGI-S) were applied to the patients. Sociodemographic form and SCID I were applied to the control group. There was not any significant difference between groups in terms of hematologic parameters like hemoglobin, hematocrit, leukocyte count, platelet count, lymphocyte count and neutrophil count. Although there was no significant difference between groups in terms of NLR, PLR and RDW, there existed significant difference between groups in terms of MPV. In the patient group HDRS and CGI-S were not significantly correlated with NLR, PLR, RDW and MPV. As a conclusion; we found increased MPV in MDD group compared with the control group. Further studies are needed to reveal the relationship between depression and inflammatory markers.

Keywords: *Major depressive disorder, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, red cell distribution width*

ÖZ

Bu çalışmanın amacı, Major Depresif Bozukluk (MDB) tanılı hastalarda Nötrofil lenfosit oranı (NLO), platelet lenfosit oranı (PLO), kırmızı küre dağılım genişliği (RDW) ortalama trombosit hacmi (MPV) gibi hematolojik inflamatuvar göstergeçlerin değerlendirilmesiydi. Çalışmaya Haziran 2016 ile Eylül 2016 tarihleri arasında Erzurum Bölge Eğitim ve Araştırma Hastanesi Psikiyatri Polikliniğine başvuran ve DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) ile ilk atak MDB tanısı alan, herhangi bir ilaç kullanımı olmayan, 18-75 yaş arası 75 hasta dahil edildi. Hastane çalışanlarının yakınlarından, hasta grubuna beden kitle göstergesi ve sosyodemografik özellikler açısından benzer, psikiyatrik ya da diğer tıbbi hastalık öyküsü olmayan 57 sağlıklı gönüllü kontrol grubu olarak belirlendi. Hasta grubuna DSM-IV Eksen I bozuklukları için Yapılandırılmış Klinik Görüşme Ölçeği (SCID-I), sosyodemografik veri formu, Hamilton Depresyon Değerlendirme Ölçeği (HDDÖ) ve Klinik Global İzlem Ölçeği (CGİ-S) uygulandı. Kontrol grubuna ise DSM-IV Eksen I bozuklukları için Yapılandırılmış Klinik Görüşme Ölçeği (SCID-I), sosyodemografik veri formu uygulandı. İki grup arasında hemoglobin, hematokrit, lökosit, nötrofil, lenfosit ve trombosit sayıları arasında anlamlı bir farklılık belirlenmedi. Gruplar arasında NLO, PLO ve RDW arasında anlamlı bir farklılık belirlenemezken, MPV açısından anlamlı bir farlılık saptandı. Ayrıca hasta grubunda HDDÖ ve CGI-S ile NLO, PLO, RDW ve MPV karşılaştırıldığında anlamlı ilişki saptanmadı. Sonuç olarak, çalışmamızda, MDB tanılı hastalarda MPV sağlıklı kontrol grubuna göre artmış olarak belirlendi. Depresyon ve inflamatuvar göstergeçler arasındaki ilişkinin ortaya konması için yapılacak yeni çalışmalara ihtiyaç vardır.

Anahtar kelimeler: *Major depresif bozukluk, ortalama trombosit hacmi, nötrofil lenfosit oranı, platelet lenfosit oranı, kırmızı küre dağılım genişliği*

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Departments of [1]Psychiatry, [2]Internal Medicine, Erzurum Regional Training and Research Hospital, Erzurum, Turkey
[3]Erenkoy Mental Health and Psychiatry Training and Research Hospital, İstanbul, Turkey
[4]Kahramanmaraş Göksun State Hospital, Psychiatry Department, Kahramanmaraş, Turkey
[5]Adapazarı Hendek State Hospital Psychiatry Department, Sakarya, Turkey
Yazışma adresi: Nermin Gündüz, Departments of Psychiatry, Erzurum Regional Training and Research Hospital, Erzurum, Turkey
e-mail: ngunduz2798@hotmail.com

INTRODUCTION

Depressive disorders are among the major and serious public health problems. Indeed, the risk of a suicide attempt is approximately 15% and the prevalence of suicidal thought is about 60% during severe depressive episodes[1]. Many factors have been identified in the etiology of major depressive disorder (MDD)[2]. MDD is associated with changes in the central nervous system, immunoreactivity, and vascular reactivity, which are important in the development of the systemic inflammatory response[3]. Although the relationship between MDD and cytokines like C Reactive Protein (CRP), Interleukin-6 (IL-6), Interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) has been revealed[4,5], the role of inflammotory markers in etiology of MDD has not yet been clarified yet. Nowadays new, readily accessible, repeatable biological inflammatory markers have begun to be addressed in patients with MDD recently[6].

Stress and depression can cause some alterations in white blood cell counts like increased number of leukocytes and neutrophils and decreased number of lymphocytes[7]. Leukocyte count and subtypes are among the determinants of chronic inflammation. Neutrophils and leukocytes play important roles in inflammatory processes. Assessment of neutrophil / lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), which can be calculated through a simple blood count is shown as a new biomarker in determining systemic inflammatory response[8,9]. Clinicians have recently focused on these biomarkers as systemic inflammatory response in psychiatry too. Studies have shown that NLR is higher in patients diagnosed with schizophrenia and Alzheimer's disease compared with healthy controls[10,11]. Also in a recent study conducted by Demircan et al, NLR was found to be higher in major depressive disorder[12].

Red cell distribution width (RDW) is the size of red blood cells. In addition to being used in the differential diagnosis of anemia, studies have also shown that it can be used to demonstrate mortality from acute heart failure, pulmonary embolism, acute myocardial infarction (AMI), peripheral arterial disease, and acute renal failure in the general population[13-15]. Also RDW has recently become a new research field in psychiatry[12].

Mean platelet volume (MPV) indicates platelet volume and platelet volume is a potential indicator of platelet activity. Increased MPV is associated with increased thrombotic activity, such as platelet aggregation, thromboxane synthesis, and release of adhesion molecules. Many studies have shown that increased MPV is a risk factor for cardiovascular disease[16]. Also in some studies increased platelet activity in MDD has been demonstrated[17]. A number of mechanisms have been proposed that can cause platelet abnormalities in MDD: such as, increased plasma 5-HT concentration and epinephrine-induced platelet function, increased platelet function with increased platelet calcium, upregulation of 5-HT2A receptors or alpha-adrenergic receptors, downregulation at 5-HT transporter receptor, alterations in the second messenger signal transduction or altered platelet monoamine and catacolamine concentrations[18].

The aim of our study is to examine the changes in hematological inflammatory markers in MDD patients through readily available markers such as NLR, PLR, RDW and MPV.

MATERIALS and METHOD

Seventy-five patients between the ages of 18 and 75 who were diagnosed as having the first episode MDD according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)[19] criteria in the Department of Psychiatry of the Erzurum Regional Training and Research Hospital between June 2016 and September 2016 were included in the study. Healthy control subjects of the study with no psychiatric history or other physical or clinical condition were selected from relatives of hospital employees. Fifty-seven subjects with similar sociodemographic characteristics and body mass indices were included as a control group.

Before the study, approval of the ethics committee was obtained from local medical ethics committee of Erzurum Regional Training and Research Hospital on May 2016. Detailed information about the study was given to all patricipants and written informed consent was obtained from each participant.

Participants:

Patients who were admitted to the outpatient clinics of Department of Psychiatry of the Erzurum Regional Training and Research Hospital and diagnosed as having the first episode of Major Depressive Disorder according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)[19] were included in this study. Patients who had not any psychiatric history or currently undergoing any psychiatric treatment and referred to the psychiatry outpatient clinic for the first time were selected for the study. Patients's psychiatric history was evaluated from their self reports and hospital records. Also it was questioned from their relatives. Patients with mental retardation, psychotic disorder, bipolar disorder, autism spectrum disorder, alcohol and substance use disorders and patients with chronic neurological disorders which can cause severe cognitive disability such as epilepsy and cerebrovascular dissease, diabetes mellitus, hypertension, hyperlipidemia, chronic heart disease, organic brain damage were excluded. Pregnant and breast-feeding women were also excluded. In addition, patients with disease status hematopoietic disease, malignancy, acute infection, chronic inflammatory diseases, chronic renal failure, liver failure and user of the drugs (chemotherapeutics, glucocorticoid therapy within the last 3 months) that may affect the number of leukocytes were not included in the study. Patients with smoking and obesity (body mass index, BMI>30) were also excluded. Other medical conditions of the patients were evaluated from hospital medical records and self reports of the patients. Height and weight of the participants were evaluated based on self declarations of participants and body mass ındices of the participants were calculated manually by the clinician. Past medical records were also evaluated for excluding hyperlipidemia.

Subjects with the same exclusion criteria as the patient group and having similar sociodemographic characteristics and body mass indices with patient group were included as a control group.

Data Collection Tools:

Sociodemographic Form:

The "Sociodemographic Form" prepared by the researchers contains the materials used to identify the participants' personal information and some other specified variables. Participants were asked not to use their names but only nicknames. Age, gender, marital status, educational level and working status were determined as sociodemographic data of the participants.

Structured Clinical Interview for DSM IV Axis I Disorders (SCID I):

SCID I is a semi-structured clinical interview scale developed for the introduction of basic Axis I diagnoses[19]. Apart from clinical diagnosis, family history, the age of onset of the disease, and the presence of stressful life events allow the evaluation of variables. In 1983, the National Institute of Mental Health, recognized the need for a clinical diagnostic assessment for DSM-III and SCID-I was developed by Spitzer[20]. The adaptation and reliability studies in Turkish were carried out by Çorapçıoğlu et al.[21]. SCID-I consists of a reusable user's guide and a single-use score card. SCID-I contains full diagnostic criteria for most of the diseases. It consists of six modules and a total of 38 DSM-IV Axis, and 10 Axis I disturbances are being investigated without diagnostic criteria.

Hamilton Depression Rating Scale (HDRS):

It measures the level of depression and changes in its severity. It facilitates follow-up during treatment. It is not suitable for diagnosis. It is applied by the clinician. It consists of 17 items that question the complaints of depression experienced within the last week. It's more concerned with melancholic and

physical complaints of depression because it was first developed for hospitalized patients. Items related to sleeping difficulty, nighttime awakening, early morning waking, somatic complaints, genital complaints, weakening and insight were scored between 0-2, and other items between 0-4 points.The highest score is 53 points. 0-7 points indicate no depression, 8-15 points mild, 16-28 points moderate , and ≥ 29 points severe depression. It was developed by Williams[22]. Turkish validity and reliability of the scale were also tested by Akdemir et al.[23].

Clinical Global Impression Scale (CGI-S):

It is a three-dimensional measure to ensure that the psychiatrist records the clinical impression of the patient's functioning before and after treatment in all psychiatric disorders[24]. It was developed by Guy et al.[24]. Severity of the disease in the first, improvement in the second, and severity of the side effect of the drug in the third dimension are evaluated. In our study, the first dimension was used.

Blood Tests:

Blood samples drawn from antecubital vein after 12 hours of fasting were stored in EDTA tubes. A BeckmanCoulter LH 750 (ImpedanceMethod) analyzer was used for the measurement of whole blood count. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated manually from hemogram results.

Statistical Analysis:

The data obtained in the study were analyzed using the Statistical Program for Social Sciences (SPSS version 17). Normally-distributed continuous variables were expressed as mean±standard deviation. The significance of the differences between the groups was assessed using Student's t and the median values by the Mann-Whitney U test. A significance level of 0.05 was used and $p<0.05$ was considered to be statistically significant. The relationship between numerical variables with non-normal distribution is investigated by Spearman Correlation Analysis.

RESULTS

Seventy-five MDD and 57 healthy controls were included in the study. There was no statistically significant difference between groups in terms of

Table 1. Sociodemographic characteristics of groups.

	MDD (n=75)	Control (n=57)		p
Age (year)	31.71±10.9 (18.0-72.0)	32.39±11.10 (18.0-64.0)	U=2023.0 Z=-0.527	0.5999
Gender				
Female	56 (74.7%)	37 (64.9%)	x^2=1.480 df=1	0.224
Male	19 (25.3%)	20 (35.1%)		
Marital Status				
Married	31 (41.3%)	28 (49.1%)	x^2=0.795 df=1	0.373
Single	44 (58.7%)	29 (50.9%)		
Working Status				
Yes	27 (36%)	42 (73.7%)	x^2=18.435 df=1	<0,0001*
No	48 (64%)	13 (26.3%)		
Educational Level				
Illiterate	5 (6.7%)	3 (5.3%)		
Literate	3 (4%)	3 (5.3%)		
Primary School Graduate	22 (29.3%)	14 (24.6%)	x^2=1.475 df=5	0.916
Secondary School Graduate	10 (13.3%)	11 (19.3%)		
High School Graduate	25 (33.3%)	17 (29.8%)		
University	10 (13.3%)	9 (15.8%)		

Mann Whitney U test was used for the comparing the age; chi square test was used for comparing the variables like gender, marital status, working status and educational level
** significant at p <0.05 level.*

Table 2. Biochemical data of study groups.

	MDD (n=75)	Control (n=57)		p
Hemoglobin (gr/dl)	14.74±1.64 (10.36-19.20)	14.92±1.65 (11.17-18.29)	t=0.596 df=130	0.599
Hematocrit (%)	44.23±4.48 (34.70-57.10)	44.77±3.75 (36.31-53.06)	t=0.726 df=130	0.379
Leukocyte (10^3/uL)	8.11±2.2 (4.22-15.01)	8.01±2.0 (4.62-14.55)	U=2081.5 Z=-0.257	0.797
Platelet (10^3/uL)	293.87±65.0 (145.7-459.0)	297.24±61.10 (170.8-452.7)	t=0.303df=130	0.785
MPV (fL)	8.12±1.70 (5.38-12.44)	7.26±1.28 (5.04-11.27)	U=1528.0 Z=-2.800	0.005*
Lymphocyte (10^3/uL)	2.51±0.70 (1.25-5.41)	2.45±0.71 (1.32-5.03)	U=2058 Z=-0.478	0.717
Neutrophil (10^3/uL)	4.80±0.20 (1.76-10.77)	4.90±0.25 (1.76-2.26)	U=2058.5 Z=-0.363	0.633
NLR	2.05±0.86 (0.67-4.99)	2.08±0.69 (0.91-3.77)	U=2016.5 Z=-0.556	0.578
PLR	127.31±45.89 (60.56-252.64)	126.96±34.93 (54.78-232.42)	U=2017 Z=-0.554	0.580
RDW	12.38±1,75 (10.54-22.29)	11.97±1.10 (10.11-16.38)	U=1833.0 Z=-1.399	0.162

Student t test was used for comparing hemoglobin, hematocrit, platelet, MPV, lymphocyte, neutrophil, NLR, PLR and RDW. Mann Whitney U Test was used for comparing leukocyte
MPV: Mean Platelet Volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, RDW: Red cell distribution width
** significant at p <0.05 level.*

age (p=0.5999), gender (p=0.224), marital status (p=0.349) and educational level (p=0.916). Only there was a significant difference in terms of working status between groups (p<0.0001). The mean age of MDD group was 31.71±10.9 while it was 32.39±11.10 years in the control group. The MDD group consisted of 56 (74.7%) female and 19 (25.3%) male patients. There were 37 females (64.9%) and 20 males (35.1%) in the control group. There were 31 (41.3%) married, 44 single (58.7%) patients in MDD group, while the control group consisted of 28 (49.1%) married, and 29 (50.9%) single individuals. There was a significant difference in terms of working status between groups (p<0.0001). The sociodemographic characteristics of the patients are presented in Table 1.

There was no significant difference between groups in terms of hematologic parameters like hemoglobin (p=0.599), hematocrit (p=0.379), leukocyte (p=0.797), platelet (p=0.785), lymphocyte (p=0.717) and neutrophil counts(p=0.633). Although there was no significant difference between groups in terms of Neutrophil Lymphocyte Ratio (NLR) (p=0.578), Platelet Lymphocyte Ratio (PLR) (p=0.580) and Red Cell Distribution Width (RDW) (P=0.162), there was significant difference between groups in terms of Mean Platelet Volume (MPV) (p=0.005*). While MPV was calculated as 8.12±1.70 in the MDD, and as 7.26±1.28 in the control group. We found increased MPV in MDD group compared with healthy control group. Biochemical data of the patient and control groups and comparison between the groups are presented in Table 2.

The mean scores for Hamilton Depression Rating Scale was 34.27±6.16 pts, and the Clinical Global Impression Scale was 4.75±1.41 pts in the patient group . The mean scores of the scales are presented in Table 3.

Hamilton depression rating scale and clinical global impression scale were not significantly correlated with NLR, PLR, RDW and MPV. Correlations of NLR, PLR, RDW, MPV with HDRS and CGI-S are presented in Table 4.

Table 3. The mean scores of the scales.

HDRS	34.27±6.16 (23.00-46.00)
CGI-S	4.75±1.41 (3.00-7.00)

Table 4. Correlations of NLR, PLR, RDW, MPV with HDRS and CGI-S.

	NLR	PLR	RDW	MPV
HDRS	rho=-0.155 p=0.184	rho=-0.177 p=0.128	rho=-0.062 p=0.596	rho=0.052 p=0.660
CGI-S	-0.221 p=0.057	-0,196 p=0.092	-0.143 p=0.221	0.044 p=0.706

Spearman Correlation Analysis

DISCUSSION

Although depressive disorders are among the major and serious public health problems, there is still no hematologic marker for diagnosing depression. So, we aimed to evaluate the hematologic inflammatory markers like NLR, RDW, PLR and MPV in patients with MDD.

Although the RDW was higher in the patient group relative to the control group, this difference was not statistically significant. This result may be due to small sample size of the study. In a study conducted by Demircan et al, RDW was found to be higher in the MDD group compared with healthy subjects[12]. Authors suggested that the increased RDW level is the result of release of premature reticulocytes into the circulation during inflammatory and infectious pathologies[12].

Although previous studies have examined NLR and RDW in patients diagnosed with MDD[12], PLR has not been studied previously. To the best our knowledge, our study is the first study evaluating PLR in MDD. We did not find statistically significant difference between groups in terms of PLR. Further large scale studies are needed to clarify the role of PLR as a hematologic inflammatory marker in the pathophysiology of MDD.

Stress and depression can cause some changes in white blood cell counts[7]. Leukocyte counts and its subtypes are some of the determinants of chronic inflammation. Neutrophils and leukocytes play important roles in inflammatory processes[8,9]. In our study there was no statistically significant difference between groups in terms of NLR. Also we did not find correlation between NLR and HDRS and depression severity. In a study conducted by Sunbul et al.[25] authors suggested that HDRS scores were correlated with NLR in depressive patients. In the first study searching the relationship between levels of NLR and MDD it was revealed that NLR was higher in patients diagnosed with MDD and it was suggested as a result of this study that higher NLR levels support the idea of inflammation as a critical factor in the pathophysiology of MDD[6].

There are also studies in the literature that show no significant association between depression severity and inflammatory response. In the study of Miller et al. as the severity of depression increases, changes in immunologic response occur, and the immune response decreases while depression gets worse[26]. Studies have shown that all MDD patients do not release inflammatory cytokines or inflammotory markers and all patients releasing inflammatory cytokines or inflammatory markers do not develop MDD[27]. Although elevated IFN-α levels are thought to be involved in the pathogenesis of MDD, the absence of depression in all IFN-α-treated patients suggests that other mechanisms are also effective[28]. In addition, treatments targeting inflammatory cytokines and inflammatory markers may not always be effective in the treatment of MDD[29]. Considering all these findings, could inflammation-related depression be a subtype? And can evaluation of the inflammatory responses, guide the diagnosis and treatment of depression? Further clinical studies is needed to answer this question.

As a result of our study, MPV was higher in patients diagnosed with MDD compared with the control group. MPV is an important indicator of platelet activity. Many studies in recent years have found a significant association between increased MPV and cardiovascular disease risk[15]. Studies have shown that increased MPV predicts cardiovascular risk factors such as smoking, diabetes, hypertension, obesity[30,31]. Epidemiological studies have revealed high comorbidity between depression and cardiovascular diseases. The risk of developing cardiovascular disease in adults without depression is 2 times higher than in healthy individuals[32].

In our study, there was no significant relationship between depression severity and MPV. It is possible to define high MPV values as an indication of increased cardiovascular risk because the patient group was selected from individuals who had not any known

cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, obesity and smoking, or any disease other than depression, and they did not use drugs. In addition, high MPV values determined by Ataoglu et al. in patients who were diagnosed with depression returned to normal after escitalopram therapy[33]. This finding supports the fact that patients with depression treatment are less likely to have cardiovascular disease. It should be noted that increased MPV levels also contrubite to the association between depression and cardiovascular disease.

There are also some limitations of our study. Small sample size is the main limitation of the study. We did not evaluate the relationship between cardiovascular risk factors like blood triglyceride and total cholesterol level and hematologic markers. Also we did not question the participants' nutrition, lifestyle, physical exercise status. Cross-sectional design of the study is another limitation. Since our study had not a prospective design, we were not able to evaluate the association between the course of depression and the levels of hematologic inflammatory markers. As a result of not determining the subtypes of depression in our study, it is not possible to evaluate the associations between subtypes of depression like atypical subtype or those with melancholic properties and NLR, PLR, RDW, MPV. When all the findings are taken into account, the relationship between inflammatory markers and MDD can not be ruled out, but it should not be forgotten that there may not be an artificial cytokine response in all depressive conditions. Further large-scale prospective studies are needed to reveal the relationship between depression and inflammatory markers.

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