

Inflammation in Chronic Psychiatric Patients: Neutrophil/Lymphocyte Ratios, Platelet/Lymphocyte Ratios, and Mean Platelet Volume

Kronik Psikiyatrik Hastalarda Enflamasyon: Nötrofil/Lenfosit Oranları, Trombosit/Lenfosit Oranları ve Ortalama Trombosit Hacmi

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Özet

Amaç: Bu çalışmanın amacı ruhsal hastalık tanısı olan ve yatarak tedavi gören hastaların nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), kırmızı kan hücre dağılımı (RDW) ve lökosit hücre düzeylerini sağlıklı kontroller ve bir birleri ile karşılaştırarak incelemektir.

Gereç ve Yöntemler: Çalışmamıza 600 kişi dâhil edildi. Hasta grubu olarak 500 kişi, sağlıklı kontrol grubu olarak 100 kişi alındı. Hastaların DSM-5 kriterlerine göre tanıları sırası ile; 174 (%34.8) şizofreni, 105 (%21) yaygın anksiyete bozukluğu, 72 (%14.4) bipolar affektif bozukluk, 70 (%14) majör depresif bozukluk, 36 (%7.2) uyum bozukluğu, 21 (%4.2) şizoaffektif bozukluk ve 18 (%3.6) diğer psikiyatrik hastalıklar idi. Tüm katılımcıların demografik veri formu ve laboratuvar parametreleri için hemogram testleri alınmıştır.

Bulgular: Çalışmamıza katılanlardan; 315 (%52.5) kişi kadın, 285 (%47.5) kişi erkekti. Yaşları 18-65 arasında değişmekle birlikte, ortalaması 39.6±15.22 idi. Laboratuvar parametrelerinin dağılımı incelendiğinde; hemoglobin, platelet, monosit, kan platelet dağılım genişliği (PCT), RDW-standart sapma üzerinden yüzdeli hesabı (RDW-CV) değerleri gruplar arasında istatistiksel olarak anlamlı farklılık tespit edilmedi (Sırası ile p değerleri; 0.082, 0.214, 0.526, 0.082, 0.771 idi). Hastaların lenfosit, eozinofil, bazofil, ortalama platelet hacmi (MPV), alyuvarlar hücre boyutunun standart sapma olarak hesabı (RDW-SD) değerleri sağlıklı kontroller ile karşılaştırıldığında yüksek olarak hesaplandı (sırası ile p değerleri; 0.002, 0.003, <0.001, <0.001, 0.003 idi). NLO ve PLO hasta grubunda sağlıklı kontrollere göre düşüktü (sırası ile p değeri her iki ölçüm için de <0.001).

Sonuç: Çalışmamızda kronik ruhsal hastalığı olan bireylerin bazı enflamasyon parametrelerinin sağlıklı kontrollerden farklı olduğu saptanmıştır. Ancak enflamasyon parametrelerinin ruhsal hastalıklar ile olan ilişkisini daha iyi ortaya koyabilmek için prospektif nitelikte daha ileri araştırmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Bipolar Bozukluk, İnflamasyon, Nötrofil/Lenfosit oranları, Platelet/Lenfosit oranları, Şizofreni

Abstract

Objective: The aim of this study was to examine the Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratios (PLR), and Mean Platelet Volume (MPV), red blood cell distribution width (RDW) and leukocyte cell levels of inpatients with mental illness by comparing them with each other and healthy controls.

Materials and Methods: A total of 600 people were included in our study, 500 of whom were taken as the patient and 100 as the control group. The diagnosis of patients according to DSM-5-Criteria were 34.8% Schizophrenia, 21% had Generalized-Anxiety-Disorder, 14.4% had Bipolar-Affective-Disorder, 14% had Major-Depressive-Disorder, 7.2% had Adjustment-Disorder, 4.2% had Schizoaffective-Disorder, 3.6% had other psychiatric illnesses.

Results: It was seen that hemoglobin, platelet, monocyte, blood platelet distribution (PCT), percentage account of RDW (RDW-CV) did not have statistically significant differences between groups (p values were 0.082, 0.214, 0.526, 0.082, 0.771, respectively). The lymphocyte, eosinophil, basophil, MPV, standard deviation of RDW (RDW-SD) were higher compared with healthy controls (p values were 0.002, 0.003, <0.001, <0.001, 0.003, 0.003, respectively). NLR and PLR were low in the patient group compared to healthy controls (p<0.001).

Conclusion: It was found that some of the inflammation parameters of chronic with mental illness were different from those of healthy controls. However, further prospective studies are needed to better reveal the relationship between inflammatory parameters and mental illnesses.

Keywords: Bipolar disorder, Inflammation, Neutrophil/lymphocyte Ratios, Platelet/lymphocyte Ratios, Schizophrenia

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INTRODUCTION

Inflammation occurs as a response to infection, stress, harmful chemicals, and tissue damage (1). Inflammation both protects the body against harmful effects and also damages as in autoimmune and infectious diseases. Similarly, inflammation in Central Nervous System (CNS) has both neuroprotective and neurotoxic effects (2). A number of signals that are activated by the immune system with the effect of internal or external stress factors activate pro-inflammatory or anti-inflammatory cytokines. In this way, inflammation has either harmful or beneficial effects (3). Whether inflammation will be harmful or protective is also linked to the genetic variations and environmental factors (4). It has been reported in recent years that the changes of markers associated with inflammation play roles in psychiatric diseases (4-8). Chronic inflammation was shown to play roles in many psychiatric diseases like Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), and Schizophrenia (3-5).

Markers like Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR) are partially new markers which may be evaluated with simple blood test and which is shown to be highly informative in showing chronic low-grade inflammation. Also, values like leukocytes (eosinophils, monocytes, basophils, neutrophils, and lymphocytes), and red blood cell distribution width (RDW), which can also be measured with simple blood analysis, are the new markers in showing systemic inflammatory response. NLR can easily be measured by dividing the number of neutrophils by the number of lymphocytes, and PLR can easily be calculated by dividing the number of platelets by the number of lymphocytes (6,7).

Studies were conducted in the literature on markers such as NLR and PLR in psychiatric diseases (8-15). However, no studies were detected in the literature review examining NLR, PLR, RDW, Mean Platelet Volume (MPV), and leukocyte together in chronic psychiatric patients. Based on this, we aimed to examine the NLR, PLR, RDW and leukocyte cell levels of patients with any psychiatric disease that required in-hospital treatment according to the DSM-5 Criteria by comparing them each other and with healthy controls.

MATERIALS AND METHODS

Ethical Approval

The study was conducted in line with the Helsinki Declaration and with the approval of the Non-Interventional Local Ethics of Gaziosmanpaşa University School of Medicine.

Clinical Samples

Inclusion and Exclusion Criteria

The study was planned in a retrospective fashion. Patients who were hospitalized for treatment in Tokat Mental Health and Diseases Hospital Psychiatric Ward between 01.01.2018 and 31.12.2019 were included in the study. Patients with psychiatric disease, aged between 18 and 65, requiring in-hospital treatment according to DSM-5 Criteria (Diagnostic and Statistical Manual of Mental Disorder) were included. Patients with poor general condition, chronic disease requiring medical treatment, patients with renal-liver dysfunction, alcohol-substance use disorders, and those with personality disorders were excluded from the study. Patients who met the diagnostic criteria of metabolic syndrome, patients with known malignancies, those with inflammatory diseases like Behcet's Disease, patients with local and/or systemic inflammatory diseases were not included in the study. A total of 100 people who did not have previous or current psychiatric diseases requiring treatment, and those who matched the patient group in terms of demographic data were included in the study as the healthy control group.

The sociodemographic data form that was completed during the psychiatric interviews of all participants was recorded. Then, the full blood count values on the day when the participants were hospitalized in the ward, before their psychiatric treatments started, and when they were fasting were examined.

Data Collection Tools

Sociodemographic Data Form: It contains the demographic data, such as age, marital status, education level, working status, and economic status. It also includes clinical evaluation questions, such as whether there is previous in-hospital treatment in psychiatric clinic, psychiatric illness requiring treatment in the family, and whether there is alcohol or smoking use.

Laboratory Samples

The blood samples taken from antecubital veins after 12-hour fasting that were stored in tubes with EDTA were examined from all participants. Beckman Coulter LH 750 Analyzer (Impedance Method) was used for full blood count. The distribution of hemoglobin, hematocrit, white sphere, neutrophil, lymphocyte, eosinophil, monocyte, basophil, platelet, red blood cell distribution (RDW), Mean Platelet Volume (MPV), blood platelet percentage (PCT) were recorded. Neutrophil/Lymphocyte Ratio (NLR) and Platelet/Lymphocyte Ratio (PLR) were calculated manually from hemogram results.

Statistical Analysis

The ready-made statistical software SPSS for Windows 20 Package Program (Statistical Package for Social Sciences for Windows 20) was used to evaluate the data obtained from the participants. Descriptive analyses were made to collect data about the general characteristics of the participants. Data for continuous variables are presented as mean \pm standard deviation, or median and quarterly values. Data for categorized variables are given in the form of n (%).

The qualitative variables of the study were demographic data, such as age, marital status, educational status, working status, and economic condition. Cross-table and Chi-Square Tests were used to evaluate whether there were relations between qualitative variables. Quantitative variables were the results of the full blood count. When the mean values of quantitative variables between the groups were compared, the Mann Whitney U-test, or Kruskal Wallis Test when parametric assumptions were not met; and the Difference between Two Mean Values, and One-Way Variance Analysis were used when parametric assumptions were met. Pearson Correlation Analysis was used for the relations between quantitative variables. The p values calculated

in our study were considered statistically significant when they were smaller than 0.05.

RESULTS

A total of 600 people were included in our study, 500 of whom were taken as the patient group, and 100 as the healthy control group. All patients who had psychiatric diagnosis according to DSM-5 Criteria, receiving in-hospital treatment in our clinic within a one-year period were included in the study. The diagnosis of the patients according to DSM-5 Criteria were; 174 patients (34.8%) Schizophrenia, 105 patients (21%) Generalized Anxiety Disorder, 72 patients (14.4%) Bipolar Affective Disorder, 70 patients (14%) Major Depressive Disorder, 36 patients (7.2%) Adjustment Disorder, and 21 patients (4.2%) Schizoaffective Disorder. A total of 18 patients (3.6%) had other psychiatric illnesses, Alzheimer's Disease, behavioral disorder, Obsessive Compulsive Disorder, and conversion disorder. When the general characteristics of the participants were examined, it was seen that 315 (52.5%) were female, and 285 (47.5%) were male, ranging in age between 18 and 65, with an average of 39.6 (Standard deviation=15.22). The demographic characteristics of the participants are given in **Table 1**.

Table 1. Sociodemographic data analysis of the participants

	Patient Group (n=500) N (%)	Healthy Control Group (n=100) N (%)	p
Age (Mean\pmSD)	41.3 \pm 15.53	33.78 \pm 12.17	<0.001
Gender (Male/Female)	260/240 (%52/48)	55/45 (%55/45)	>0.05
Marital status			
Single/Married	145/320(%29/64)	30/70(%30/70)	>0.05
Educational Status			
Primary school grad.	248 (%49.6)	50 (%50)	
High school grad.	124 (%24.8)	25 (%25)	>0.05
University grad.	128 (%25.6)	25 (%25)	
Diagnosis of patients			
Schizophrenia	174 (%34.8)	-	
GAB	105 (%21)	-	
BAB	72 (%14.4)	-	
MDB	70 (%14)	-	
Adjustment Disorder	36 (%7.2)	-	
Schizoaffective Disorder	21 (%4.2)	-	
Other psychiatric diseases	18 (%3.6)	-	

Abbreviations given in the table: GAD: Generalized Anxiety Disorder, BAB: Bipolar Affective Disorder, MDD: Major Depressive Disorder. The healthy control group did not have any psychiatric disease or additional medical disease currently or in their history. Chi-Square Test was used in calculations.

When the distributions of the laboratory parameters were examined, it was seen that hemoglobin, platelet, monocyte, blood platelet distribution width (PCT), percentage calculation over standard deviation of red blood cell distribution width (RDW-CV) were not different between groups at statistically significant levels ($p=0.082, 0.214, 0.526, 0.082, 0.771$, respectively). Lymphocyte, eosinophil, basophil, Mean Platelet Volume (MPV), cell size calculated as red blood cell distribution width-standard deviation (RDW-SD) values were high compared with healthy controls ($p=0.002, 0.003, <0.001, <0.001, 0.003, 0.003$, respectively). Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio were low in patient group compared to healthy controls ($p<0.001$ for both measurements). The distribution of quantitative variables calculated with the Mann Whitney U-test of the participants is given in **Tables 2** and **3**.

DISCUSSION

In our study, the NLR, PLR, RDW and leukocyte cell levels of patients with any psychiatric disease requiring in-hospital treatment according to DSM-5 Criteria were examined by comparing these values with each other and with those of healthy controls. In the

evaluation of all patients together, low levels of NLR, PLR, white sphere, erythrocyte, neutrophil, hematocrit and RDW were detected. Lymphocyte, eosinophil, basophil, Mean Platelet Volume (MPV), standard deviation of red blood cell distribution width (RDW-SD) were calculated to be higher in patients.

In our study, NLR were found to be low in the patient group compared to healthy controls. In a study conducted on patients with schizophrenia, NLR was calculated to be higher than the healthy control group. In this study, sixty-four patients with schizophrenia and 61 healthy control individuals were compared. The neutrophil ratios and NLRs of the patients were found to be high than healthy controls. With this result, it was pointed out that inflammation plays very important roles in the pathogenesis of schizophrenia (14). In the literature, in a study that compared schizophrenia and bipolar disorder patients with each other and healthy controls, NLR was high in both groups of diseases compared to the healthy controls. Also, neutrophil values were high in schizophrenia patients and lymphocyte values were low in both diseases (15). In a study conducted on Obsessive Compulsive Disorder (OCD) patients, it was found that patients had high NLR than healthy controls (16). Another study found

Table 2. Distribution of quantitative variables of the participants

	Patient Group (n=500) Mean±SD	Healthy Control Group (n=100) Mean±SD	p
Hemoglobin	13.65±1.79	14.01±1.82	0.082
Hematocrit	40.54±4.70	42.08±4.77	0.004*
White sphere	7.54±2.22	8.38±2.44	0.001*
Platelet	246.46±69.55	256.18±65.54	0.214
Neutrophil	4.26±1.81	5.37±2.29	<0.001*
Lymphocyte	2.5±0.83	2.21±0.8	0.002*
Monocyte	0.56±0.19	0.58±0.37	0.526
Eosinophil	0.18±0.16	0.13±0.1	0.003*
Basophil	0.04±0.02	0.03±0.02	<0.001*
MPV	10.51±1.09	9.32±1.27	<0.001*
RBC	4.71±0.52	4.99±0.51	<0.001*
RDW	12.39±2.18	13.35±2.43	<0.001*
PCT	0.26±0.11	0.24±0.06	0.082
RDW-SD	42.04±3.57	40.91±2.79	0.003*
RDW-CV	13.34±1.46	13.3±1.36	0.771
NLR	1.88±1.09	3.04±2.12	<0.001*
PLR	8.01±3.96	11±4.89	<0.001*

Abbreviations given in the table: MPV: Mean Platelet Volume, RBC: Red Blood Cell, RDW: Distribution range of red blood cells, PCT: Blood platelet distribution width; RDW-SD: Standard deviation value of cell size of red blood cells, RDW-CV: Percentile value of cell size of red blood cells over standard deviation, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, Mean±SD: Mean±Standard Deviation. Mann Whitney U-test was used in the calculations. * $p<0.05$.

Table 3. Laboratory markers according to diagnoses

	Schizophrenia (N=174)	Generalized Anxiety Disorder (N=105)	Bipolar Disorder (N=72)	Major Depressive Disorder (n=70)	Other psychiatric diseases	p
Hemoglobin	13.69±1,64	13,74±1,74	13,29±1,94	13,95±1,7	13,63±2,06	0.444
Hematocrit	40.38±4.47	40.79±4.8	40.11±4.81	41.26±4.52	40.44±5.29	0.772
Platelet	251.64±73.11	238.91±67.2	236.53±69	254.41±68	246.96±67	0.538
RDW	12.15±2.29	12.61±2.41	12.83±2.04	12.28±2	12.3±1.9	0.334
RDW-SD	42.44±3.72	41.31±3.24	42.29±3.48	41.59±3.34	42.07±3.76	0.262
RDW-CV	13.32±1.21	13.15±1.28	13.814±2.01	13.13±1.01	13.32±1.72	0.098
MPV	10.47±1.32	10.6±1.04	10.63±0.87	10.54±0.86	10.32±0.94	0.547
RBC	4.66±0.53	4.75±0.53	4.75±0.44	4.78±0.5	4.69±0.56	0.578
Eosinophil	0.17±0.2	0.19±0.14	0.2±0.15	0.19±0.15	0.16±0.11	0.784
Basophil	0.04±0.2	0.04±0.02	0.04±0.02	0.04±0.02	0.04±0.02	0.518
Monocyte	0.59±0.19	0.52±0.16	0.57±0.23	0.54±0.18	0.55±0.07	0.130
PCT	0.26±0.07	0.26±0.07	0.26±0.07	0.26±0.07	0.26±0.07	0.733
NLR	1.8±0.71	1.85±0.96	2.06±1.13	1.67±0.76	2.08±1.83	0.223
PLR	7.95±3.44	7.75±3.89	8.11±3.61	7.61±3.16	8.59±5.7	0.741
White sphere	6.05-9.28 [7.53]	5.82-8.47 [6.85]	5.48-8.49 [7.27]	5.56-9.34 [6.42]	6.27-8.18 [7.29]	0.328*
Neutrophil	3.32-5.32 [3.89]	2.9-4.9 [3.62]	2.64-5.38 [3.85]	2.64-4.91 [3.4]	3.08-5.21 [3.82]	0.328*
Lymphocyte	2.03-3.02 [2.46]	1.94-2.78[2.38]	1.69-2.8 [2.36]	1.92-2.87 [2.39]	1.96-3.06 [2.47]	0.520*

Abbreviations given in the table: MPV: Mean Platelet Volume, RBC: Red Blood Cell, RDW: Distribution range of red blood cells, PCT: Blood platelet distribution width; RDW-SD: Standard deviation value of cell size of red blood cells, RDW-CV: Percentile value of cell size of red blood cells over standard deviation, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, Mean±SD: Mean±Standard Deviation. *Mann Whitney U-test, Significance of Difference between Two Averages Test was used in the calculations.

that NLR was much higher if OCD was accompanied by widespread anxiety disorder (17). Contrary to all these studies, a study conducted on patients with major depressive disorder over the age of sixty in the literature, it was reported that the NLR was low in the first late-term depressive disorder attack; however, the same low levels did not continue in recurrent attacks (18). In another similar study, thirty-six adolescents with bipolar disorder were examined for inflammatory parameters. No differences were detected between healthy controls and patients in terms of NLR (19). Similarly, in our study, NLRs were calculated to be low in all patients when compared with healthy controls. Although no statistically significant differences were detected when individual diseases were examined, the highest rates were found in patients with bipolar disorder, followed by common anxiety disorder, schizophrenia, and major depressive disorder, respectively.

In our results, PLR was calculated as low in patients, similar to NLR. It was found in study in the literature that PLR was higher in patients with severe depression

with psychotic features than in other depression types. The same difference was not obtained in NLR (20). In a study conducted on bipolar disorder patients, NLR and PLRs were found to rise during manic period. In depressive period; however, no such elevation was found (21). NLR and PLRs were found to be higher in schizophrenia patients in both attack and remission periods (22). In a study conducted with adolescents, no differences were detected in PLR in patients with depressive disorder compared to healthy controls (23). In our results, PLRs of the entire patient group was lower compared to healthy controls. When all patient groups were compared, it was found that the lowest depressive disorder was in the patient group, followed by common anxiety disorder and schizophrenia. The highest rates were detected in patients with bipolar disorder.

Few studies were conducted in the literature on Mean Platelet Volume (MPV), which is an inexpensive and easily measurable indicator of chronic inflammation, Red Blood Cell (RBC), Red Cell Distribution Width (RDW), and blood platelet distribution width

(PCT). The results found in the literature review were contradictory (24-27). In a study that examined laboratory parameters including MPV and RDW values of patients with attention deficit and hyperactivity disorders, no differences were detected between healthy controls and any blood parameters (24). In a study conducted on bipolar disorder patients, both MPV and PCT were found to be higher than in healthy controls. Also, neutrophil, lymphocyte, NLR, and PLR values were higher than in healthy controls (25). In another study, 30 patients with panic disorders were examined. As a result, MPV and RDW values of patients were found to be higher than in healthy controls (26). MPV values were low and RDW-CV and RDW-SD values were not different from healthy controls in another study conducted on panic disorder patients (27). In our study, it was found that RDW and RBC values of the patients were low compared to healthy controls of a similar nature to this study. MPV and RDW-SD were higher than healthy controls.

Monocyte and monocyte/lymphocyte ratios in psychiatric diseases were examined in fewer studies (21, 22). It was shown that monocyte and monocyte/lymphocyte ratios were elevated in patients with schizophrenia and bipolar disorder (21). In another similar study, it was seen that monocyte/lymphocyte ratios were higher in both remission and attack periods in patients with schizophrenia (22). In a study conducted on patients with depressive disorder, it was found that monocyte, monocyte/lymphocyte ratios were higher (28). In our study; however, the lymphocyte, eosinophil, and basophil levels of the patients were higher, and no differences were detected in monocyte, hemoglobin, and platelet values between the groups. Neutrophil, white sphere, and hematocrit values were found to be low. It was shown that chronic psychiatry patients could have anemia compared to the general population (29). Hematocrit, Red Blood Cell (RBC), and Red Blood Cell Distribution Width (RDW) values were low, which was a result we had expected.

Our results must be evaluated with some limitations in mind; first of all which are the retrospective design of the study. The other limitation is the relatively inadequate number of sampling. The fact that the drugs (e.g. valproic acid, lithium, carbamazepine, antidepressant) used by the patients were ignored was an important limitation. Failure to record the duration of illness creates limitations. Also, the lack of the examination of some parameters, such as C-Reactive Protein and inflammatory cytokines can be considered among the limitations of the study. These limit the generalization and interpretation of our results. Further study are needed with larger sampling groups in order for our findings to gain importance.

Conclusion; we examined some of the inflammation parameters of patients who had any psychiatric disease requiring in-hospital treatment by comparing these with each other and with healthy controls. Although white sphere, erythrocyte, neutrophil, hematocrit, and Red Blood Cell (RDW) levels of patients were low; lymphocyte, eosinophil, basophil, Mean Platelet Volume (MPV), standard deviation of cell size of Red Blood Cells (RDW-SD) were high. NLR and PLR were low in the patient group. Further prospective studies are needed to reveal the relation of inflammation parameters with psychiatric diseases better.

Conflict of Interest: No conflict of interest was declared by the authors.

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Ethics Committee Approval: The study was conducted in line with the Helsinki Declaration and with the approval of the Non-Interventional Local Ethics Committee of Gaziosmanpasa University School of Medicine (Date: 11.06.2020; Number: 83116987-269).

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