Research Article / Araştırma Makalesi

Comparison of Some Hematological Parameters in Unipolar and Bipolar Depressive Disorder

Unipolar ve Bipolar Depresif Bozuklukta Bazı Hematolojik Parametrelerin Karşılaştırılması

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Abstract

Background: Major depressive disorder and bipolar disorder, which are the most severe types of mood disorders, are among the diseases that cause the most disability worldwide. One of the biggest challenges in providing early and effective treatment in mood disorders is the inability to make an early differential diagnosis between UD and BD. Many studies have suggested that neuroinflammation may play a role in the pathophysiology of mood disorders. The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR), as well as the systemic immune-inflammation index (SII), c-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), are all inexpensive and easily accessible markers that are recommended for measuring the level of inflammation. In this study, NLR, PLR, MLR, SII, CRP, and ESR were analyzed to investigate the potential role of these inflammatory markers in the differential diagnosis of UD and BD.
Materials and Methods: Our study group consisted of 54 patients (UD: 31 individuals, BD: 23 individuals) and 40 healthy controls (HC). NLR, PLO, MLO, SII, CRP, and ESR markers were compared among the UD, BD, and SC groups.
Results: Significant differences were found among the groups in terms of monocyte, NLR, SII, CRP, and ESR levels in this study (respectively: p=0.011, p=0.011, p=0.020, p=0.010, p=0.017). Considering the source of the difference; the NLR, SII, CRP, and ESR were higher in the UD group compared to the HC group (respectively: p=0.009, p=0.015, p=0.012, p=0.012). however, there was no significant difference between the BP and HC groups in terms of these parameters ($p > 0.05$, for all). In terms of monoist level, there was a significant difference between UD and BP groups ($p = 0.024$). Meanwhile, there was a significant difference between the UD and BP groups in terms of monoist level ($p = 0.024$).
Conclusions: In our study, it was determined that there were significant differences among groups in terms of monocyte, NLR, SII, CRP, and ESR values. Therefore, the elevation of these markers may be beneficial in predicting disease and differential diagnosis of UD. Large-scale, prospective studies, including post-treatment values, are required to evaluate it as a disease-specific marker.

Key Words: Major Depressive Disorder, Bipolar Disorder, Hemogram, Inflammation, Biomarker

Öz

Amaç: Duygudurum bozukluklarının en şiddetli türleri olan majör depresif bozukluk ve bipolar bozukluk, dünya çapında en fazla yeti yitimi oluşturan hastalıklar arasında yer almaktadır. Unipolar depresif bozukluk (UD) ve bipolar depresif bozuklukta (BD) etkin tedavi sağlamanın önündeki en büyük zorluklardan biri, UD ile BD arasında erken ayırıcı tanının yapılamamasıdır. Bu nedenle klinik olarak ayırt edilemeyen olgularda ayırıcı tanıda kullanılabilecek basit ve ucuz biyobelirteçlerin bulunması büyük önem taşımaktadır. Birçok çalışma, duygudurum bozukluklarının patofizyolojisinde nöroinflamasyonun rol oynayabileceğini öne sürmüştür. Nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), monosit/lenfosit oranı (MLO), sistemik bağışıklık-enflamasyon indeksi (SII), C reaktif protein (CRP) ve eritrosit sedimantasyon hızı(ESR) inflamasyon düzeyini ölçmek için önerilen nispeten ucuz hematolojik parametrelerdir. Bu çalışmada, NLO, PLO, MLO, SII, CRP, ESR analiz edilerek bu inflamatuar belirteçlerin UD ve BD ayırıcı tanısındaki potansiyel rolü araştırıldı.
Materyal ve Metod: Çalışma grubumuz 54 hasta (UD: 31 kişi, BD: 23 kişi) ve 40 sağlıklı kontrol (SK) kişisinden oluştu. UD, BD ve SK grupları arasındaki NLO, PLO, MLO, SII, CRP ve ESR belirteçleri karşılaştırdı.
Bulgular: Çalışmada analiz edilen belirteçler arasında monosit, NLO, SII, CRP ve ESR düzeyleri açısından gruplar arasında anlamlı fark bulundu (sırasıyla: p=0.011, p=0.011, p=0.020, p=0.010, p=0.017). Farkın kaynağına bakıldığında NLO, SII, CRP ve ESR değerleri UD grubunda SK grubuna göre daha yüksekti (sırasıyla: p=0.009, p=0.015, p=0.012, p=0.012). BP ve SK grubu arasında ise bu parametreler açısından anlamlı farklılık saptanmadı ($p > 0.05$, hepsi için). Monoist düzeyi açısından bakıldığında ise UD ve BP grupları arasında anlamlı bir farklılık olduğu tespit edildi ($p = 0.024$).
Sonuç: Çalışmamızda monosit, NLO, SII, CRP ve ESR değerleri açısından gruplar arasında anlamlı farklılıkların olduğu tespit edilmiştir. Dolayısıyla bu belirteçlerin yüksekliği, UD bozuklukta hastalığı öngörmede ve ayırıcı tanıda yararlı olabilir. Ancak, hastalığa özgü bir belirteç olarak değerlendirebilmek için tedavi sonrası değerlerin de dahil edildiği ileriye dönük, geniş çaplı araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Majör Depresyon, Bipolar Depresyon, Hemogram, Enflamasyon, Biyobelirteç

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Introduction

Major depressive disorder and bipolar disorder, which are the most severe types of mood disorders, are among the diseases that cause the most disability worldwide (1,2). Despite treatment, some patients are resistant to treatment and may become chronic (3). Bipolar disorder and unipolar major depressive disorder are the disorders that most often lead to suicide (4,5). The diagnosis of bipolar disorder (BD) requires at least one manic episode. Mania is a state of extreme joy or anger and an elevated mood. There is also an increase in thinking, feelings of grandiosity, and acceleration in speech and movements, but the first episode of bipolar disorder usually begins with depression. For this reason, BD can be confused with UD at the onset of the illness in patients who have not yet had a manic episode. Patients with BD report that the recognition of their disorder is delayed by 8–10 years. This is due to the fact that the depressive states of both disorders are very similar. Differential diagnosis of bipolar depressive disorder (BD) and unipolar depressive disorder (UD) is very important because the treatment and management of both diseases are different. While antidepressants are the first-line treatment option in the treatment of UD, the use of antidepressants in the treatment of BD may adversely affect the long-term prognosis by causing mood instability, manic shifts, and more frequent depressive episodes, and may also lead to the development of treatment resistance. Today, the differential diagnosis of BD and UD is estimated only by history and clinic. Depressive disorders that start at an early age, show atypical features, have psychotic findings, and are resistant to treatment, indicate BD, although it is not certain(6,7). One of the biggest challenges in providing early and effective treatment in mood disorders is the inability to make an early differential diagnosis between UD and BD. Therefore, it is of great importance to find simple and inexpensive biomarkers that can be used for differential diagnosis in cases that cannot be differentiated clinically (8). In addition, if these markers are known, new targeted therapy models can be created in resistant patients.

In order to detect biomarkers, it is necessary to know the conditions that play a role in the pathophysiology of both diseases. Many studies have suggested that neuroinflammation may play a role in the pathophysiology of mood disorders. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) have been suggested as inflammatory markers in peripheral blood(9-13). Systemic Immune-Inflammation Index (SII), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR) are simple and inexpensive biomarkers used to assess inflammation (14-16).

Our aim in this study is to analyze the potential role of these inflammatory markers in the differential diagnosis of UD and BP by analyzing NLR, PLR, MLR, SII, CRP, and ESR values. Our research is important in terms of being an example for the biochemical researches to be done.

Materials and Methods

In this retrospective study, patients aged 18-65 years who were hospitalized with the diagnoses of bipolar affective disorder-depressive episode and major depressive disorder (ICD; severe depression) in the psychiatry clinic of Karamanoglu Mehmetbey University Faculty of Medicine between 1 January 2021 and 1 January 2022 were included. The data were obtained from the electronic medical record files of our hospital. Complete blood count on the first day after hospitalization was included in the study. Those who had any acute and chronic disease, those who took anti-inflammatory treatment, drug intoxication and pregnant women were excluded from the study.

After obtaining ethics committee approval and necessary permissions, electronic medical record files were retrospectively scanned. The study comprised 23 patients (Female %68) with bipolar disorder with depressive episodes and 31 patients (Female %65) with severe depressive disorder. First, the sociodemographic data and clinical characteristics of the patients were recorded. Neutrophils, monocytes, platelets and lymphocytes were recorded at the first hospitalization. NLR, MLR and PLR were calculated based on the available findings.

The control group was composed of people who donated to the blood bank, considering age and gender compatibility. Volunteers who do not have any contagious or chronic diseases and do not use drugs can donate blood after the necessary examinations are made and their written consent is obtained. Acute and chronic diseases, those who use any medication, pregnancy, previous psychiatric disorder was accepted as an exclusion criterion in the control group. This study was conducted according to the revised version of the Declaration of Helsinki.

Statistical analysis

All data were analyzed using the SPSS 25.0 package program in a computer environment. Parametric statistical tests were used when the data fit the normal distribution, and nonparametric tests were preferred when the data did not fit the normal distribution. The normality assumption was tested with Kolmogorov-Smirnow, Shapiro-Wilk, q-q plots, and skewnes. Continuous data that did not show a normal distribution were tested for conformity to the normal distribution by data transformation. In the comparison of more than two independent groups, one-way ANOVA was used for normally distributed data, and the Kruskal-Wallis Test was used for non-normally distributed data. When a significant difference was detected in the analysis of multiple groups, the post hoc Tukey Test was used for normally distributed groups with homogeneous variances, and the post hoc Dunn Test was used for non-normally distributed groups. Categorical data were compared by the Chi-Square test. For all analysis results, a significance level of $p < 0.05$ was accepted.

Results

A total of 54 patients (UD: 31 individuals, BD: 23 individuals) and 40 healthy controls were included in this study. Gender status did not differ among bipolar, unipolar, and control groups (x2 = 0.479; df = 2; p = 0.787) (Table 1).

The clinic and laboratory parameters of the study groups are demonstrated in Table 2. It was observed that monocyte counts differed between the groups (p = 0.011). When the source of the difference was examined, it was seen that the median value of the bipolar group was higher compared to the unipolar and control groups (p = 0.024; p = 0.020, respectively). NLR differed between the groups (p=0.011). The median value of the unipolar group was higher than the control group (p=0.009). SII differed between the groups (x2 = 7.84; p = 0.020). When the source of the difference was examined, it was seen that the median value of the unipolar group was higher compared to the control group (p=0.015). CRP differed between the groups (p = 0.010). When the source of the difference was examined, it was seen that the median value of the unipolar group was higher compared to the control group (p=0.012). Sedimentation differed between the groups (p = 0.017). When the source of the difference was examined, it was seen that the median value of the unipolar group was higher compared to the control group (p = 0.016).

Table 1. Sociodemographic data of the groups

	BP (n = 23)	UD (n = 31)	Control (n = 40)	P*
Gender (%)				
Female	15 (65.2)	21 (67.7)	24 (60)	0.787
Male	8 (34.8)	10 (32.3)	16 (40)	

** Chi-Square Test*

BD; bipolar depression, HC; healty control, UD; Unipolar depression

Table 2. Comparison of Hematological Parameters of Unipolar Disorder, Bipolar Depressive Disorder and Healthy Control

	BP (n = 23)	UD (n = 31)	Control (n = 40)	P	P1	P2	P3
Age	36.48±9.07	38.52±9.71	34.45±10.34	0.229*	0.733	0.711	0.201
Neutrophil	4,39(4,01-5,36)	5,28(4,21-6,48)	4,50(3,74-5,47)	0.203Ω	>0.05	>0.05	>0.05
Lymphocyte	2.47± 0.76	2.43± 0.64	2.65± 0.65	0.358*	0.966	0.591	0.366
Monocyte	0,61(0,47-0,68)	0,50(0,37-0,55)	0,48(0,40-0,58)	**0.011Ω**	**0.024**	**0.020**	0.999
Platelet	238(219-290)	254(210-327)	244(213,75-289)	0.699Ω	>0.05	>0.05	>0.05
NLR	1,94(1,46-2,88)	2,40(1,80-3,04)	1,77(1,37-2,11)	**0.011Ω**	0.780	0.381	**0.009**
MLR	0,23(0,18-0,33)	0,21(0,15-0,28)	0,18(0,15-0,24)	0.530Ω	>0.05	>0.05	>0.05
PLR	97,53(86,25-122,49)	110,09(82,29-138,29)	96,37(80,73-113,32)	0.108Ω	>0.05	>0.05	>0.05
SII	454,07(395,89-649,07)	567,61(431,56-807,94)	438,52(338,83-555,89)	**0.020Ω**	0.507	0.796	**0.015**
CRP	3(1-7,9)	4,50(1,60-8,30)	1,75(0,80-3,10)	**0.010Ω**	0.999	0.118	**0.012**
ESR	6(4-19)	13(8-21)	6(4-13,5)	**0.017Ω**	0.177	0.999	**0.016**

**Oneway ANOVA(Mean±SD); Ω Kruskal-Wallis Test (Medıan (25-75 IQR)),*

The same subscript letter indicates that the within-group mean or median did not differ from each other at the 0.05 level. BD;bipolar depression, HC; healty control, UD; Unipolar depression, SD; Standard deviation, BD; bipolar depression, HC; healty control, MLR; monocyte-to-lymphocyte ratio, NLR; Neutrophil-to-lymphocyte ratio, PLR; platelet-to-lymphocyte ratio, SII; systemic immune-inflammation index (SII), CRP; c-reactive protein (CRP), ESR; erythrocyte sedimentation rate.

P1: BPD vs. UPD comparison

P2: BPD vs. Control comparison

P3 UPD vs. Control comparison

Discussion

Significant differences were found in the levels of monocyte, NLR, SII, CRP, and ESR among the markers analyzed in the study. Looking at the source of the difference, the median values of NLR, SII, CRP, and ESR were higher in the UD group than in the HC group. There was no difference between the groups in terms of MLR and PLR. Looking at the literature, there are few studies comparing NLR, MLR, PLR, SII, CRP, and ESR parameters of BD and UD patients. The findings of these studies are inconsistent. In a study, it was reported that when BD patients were compared with UD patients, there was no significant difference in terms of MLR and PLR, but higher NLR in the BD group (17). According to this study, it was suggested that high NLR might be a predictor of bipolar depression and could be used as a marker to differentiate bipolar depression from unipolar depression. In some studies, no significant difference was found between BD and UD patient groups in terms of NLR, PLR and MLR (9,18). In a study, no difference was found between CRP levels UD, BD and HC (19). In another study, higher CRP was found in the BD group than in the UD group (20). In our study, although a higher CRP was found in the UD group than in the HC group, no difference was found between BD and HC. Peripheral biomarker studies in which both BD and UD groups are included and compared with each other are scarce in the literature. Therefore, we analyzed separately the UD and BD studies, which included NLR, MLR, PLR, SII, CRP, and ESR biomarkers.

Numerous studies were found in the literature comparing the NLR, MLR, and PLR values of the UD and HC groups. In a meta-analysis involving 18 studies, it was reported that the UD patient group had higher NLR, PLR, and MLR than the HC group (21). In our study, when the UD and HC groups were compared, there was no difference in terms of MLR and PLR. The UD group had higher NLR. In another meta-analysis, which included studies involving the UD and HC groups with large participation, results similar to our study emerged. High NLR was found in UD patients, but no significant difference was found in terms of MLR and PLR (22). In most of the studies on UD and HC in the literature, high CRP was found in the UD group (23). In one study, high ESR was found to be associated with UD in patients with psoriasis (24).

There are very few studies comparing NLR, MLR, PLR, CRP, and ESR between bipolar depression (BD) and HC group in the literature. The results of the studies are inconsistent. In a study, it was reported that BD patients had higher NLR and MLR compared to the HC group, and there was no significant difference in terms of PLR (25). In another study, no difference was found between BD and HC in terms of NLR, PLR and MLR (26). In a study including all periods of bipolar disorder, higher NLR was found in manic, euthymic and bipolar depressive (BD) patients compared to HC, but no difference was found between the periods. In terms of PLR, similarity was found between the BD and HC groups (27). In a meta-analysis, it was reported that CRP levels increased in all phases of bipolar disorder, but this increase was higher in the manic phase (28). In our study, no difference was found between the BD and HC groups in terms of NLR, MLR, PLR, CRP, and ESR.

The presence of different findings in the literature may be explained by the small number of patients, different duration of the disease, and different severity of the disease. Large-scale, prospective studies that take these situations into account may yield more consistent findings.

BD and UD have been associated with inflammatory changes, but the underlying mechanisms are still poorly understood. Inflammation is likely to play a role in the etiology by affecting neurotransmitters, synaptic plasticity, brain structures, oxidative stress, the immune response, and neurotransmission. More study is needed to evaluate it as a disease-specific marker.

This study has some limitations. The first was that it was only studied retrospectively. Second, the post-treatment remission periods of the same patients were not included in the study. Prospective studies including the remission period of the same patients may give more accurate results. In addition, ignoring smoking, which can affect inflammatory parameters, is another limitation.

Conclusion

In our study, it was determined that there were significant differences among groups in terms of monocyte, NLR, SII, CRP, and ESR values. These easily and inexpensively obtained markers may be useful in predicting the disease differential diagnosis of UD . In addition, it can make an important contribution to monitoring the response to treatment, creating new treatment models in treatment-resistant cases, and determining the prognosis.

Ethical Approval: *Karamanoglu Mehmetbey University Faculty of Medicine Clinical Research Ethics Committee approved the study (date: 27/03/2023, no: 124746).*

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