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Evaluation of inflammatory markers in bipolar disorder: A comparative study

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Abstract

Bipolar disorder is characterized by recurrent mood episodes and its pathophysiology remains a mystery. Inflammation is thought to be core feature in pathophysiology of bipolar disorder. The aim of this study is to compare neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR) and mean platelet volume (MPV) as systemic inflammatory markers between different mood episodes in same patients and healthy controls, to evaluate whether these may serve as a possible trait or state biomarker of bipolar disorder. This retrospective study was performed on 127 patients and 98 healthy controls. Among the patients, only 27 presented euthymia, mania, and depression, 89 presented mania and euthymia, 47 presented mania and depression and 45 presented depression and euthymia at different times. This study indicated that NLR and MLR values in mania were higher than in euthymia of same patients ($p=0.014$, $p=0.023$). Additionally, we found that patients in mania had higher levels of MPV, NLR and MLR than controls ($p=0.015$, $p=0.030$, $p=0.045$). Our results support the association of bipolar disorder with systemic inflammation and suggest that NLR and MLR may be potential state biomarkers for in manic episodes.

Keywords: Bipolar disorder, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, monocyte/lymphocyte ratio

Introduction

Bipolar Disorder (BD) is a multifactorial and heterogeneous disease, and its etiology remains unclear; neuroinflammation, neurotransmission, chronobiology, oxidative stress, etc all seem to play a part in BD [1]. A lot of evidence of the role of inflammatory reactions and immune modulation has been found repeatedly in patients with BD and has increasingly been proposed as a central pathophysiological mechanism in bipolar disorder [2]. Recent studies have shown elevated levels of tumor necrosis factor (TNF)- α , soluble TNF receptor type 1, activated lymphocyte cell subsets, increased C-reactive protein (CRP) concentrations, altered absolute neutrophil counts, altered platelet counts, and altered ratios of inflammatory cells as increased inflammatory responses in patients with BD [2-7]. Previous studies have determined variations in pro-inflammatory and anti-inflammatory cytokines

during different mood episodes of BD. This variability in cytokine profiles, with studies showing an increase, decrease, or no changes in immunological and inflammatory markers might suggest immune and inflammatory alterations during different episodes of BD [2,5,7].

Complete blood count measurements are easy, routine, and cheap and can provide useful information about systemic inflammation. The physiological immune response to infection and other stressful events is characterized by an increase in neutrophil count and a decrease in lymphocyte count [9]. Neutrophils are major leukocyte subclass and represent the first line of immune defense. They are exhibiting phagocytic and apoptotic effects through the secretion of various inflammatory mediators such as cytokines which inflammation triggered can induce further inflammation due to cell dysfunction and oxidative stress [10-12].

In contrast, lymphocytes are specific inflammatory cells, with a regulatory or protective function; lymphopenia reflects the strength and intensity of the stressful event, as well as the resistance and adaptability of the immune system [11,13]. Levels of monocytes are elevated in patients with psychiatric disorders, due to an enhanced expression of immune genes and an overproduction of monocytes/

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macrophage-related cytokines which signal transduction between microglia and circulating monocytes is mediated by pro-inflammatory cytokines, such as IL-1 β , IL-6, IL-8, or TNF- α [4,14]. Platelets are specific first-line inflammatory cells that regulate other mediators, like neutrophils and macrophages and their effector functions, and endothelial permeability [12,14,15]. Their activation is mediated by inflammatory factors such as serotonin, dopamine, glutamate, and cytokines which have an important role in the pathophysiology of psychiatric disorders [12,14].

Neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), and mean platelet volume (MPV) have been investigated as a cost-effective and easily obtainable circulating clinical marker of systemic, low-grade inflammation in many diseases (10,16-18). Recent studies have shown that patients with BD have altered NLR, PLR, MLR, and MPV values compared to healthy controls [12,19]. There are also studies suggesting an association between bipolar disorder and indicated inflammatory variables in terms of clinical features, prognosis, and episodes. The NLR has been reported to correlate with a suicide attempt and cognitive functions in BD [20,21]. In some clinical studies, NLR and PLR have been suggested as important prognostic factors for BD. NLR and PLR were found to be related to more episodes and hospitalizations, more anxiety, poorer functioning, and its stages in BD [17,23].

There are some studies investigating levels of inflammatory markers in acute affective episodes compared with euthymia, and there is no sufficient evidence finding state-related differences. While some studies have reported elevated NLR, PLR and MPV in manic episodes and euthymia in patients with BD compared with healthy controls, the others have found no difference in NLR and PLR among euthymic adolescents with BD and healthy controls [17,23-25]. In one study, MPV is decreased in patients with the manic episodes compared to healthy individuals [26]. We think more studies controlling other variables that may be related to inflammation are needed to investigate the relation between low-grade systemic inflammation markers and mood episodes.

The present study focused on comparing plasma values of NLR, PLR, MLR, and MPV as systemic inflammation markers during different affective episodes (depressive, manic, and euthymic), and evaluating whether plasma values of NLR, PLR, MLR, and MPV may serve as a possible trait or state biomarker of bipolar disorder. In contrast to previous studies, this study compares different mood episodes of the same patient with BD and provides the same patient to serve as his or her control. In this way, we aimed to minimize the effect of other covariates such as ethnicity, genetic characteristics, lifestyles, and nutrition patterns that may affect inflammatory response.

Materials and Methods

Study sample

This retrospective study was performed on 127 inpatients and outpatients with BD who were admitted to the Psychiatry Clinic between March 1, 2015, and March 1, 2019. All the data was retrieved from each patient's hospital record stored in our hospital's electronic database of medical records. These records include sociodemographic features such as gender, age, marital status, and clinical features such as date of diagnosis, diagnosis at

the time of hospitalization using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR), medical services provided or drugs prescribed, inpatient or outpatient status, comorbid diseases, and laboratory test results. Inclusion criteria for the BD group were the following: (1) 18 years and older, (2) Met the diagnostic criteria for BD type I according to the DSM-IV-TR criteria. The control group consisted of 98 healthy individuals who were recruited from the local community, a semi-structured sociodemographic data questionnaire was completed, and medical records were carefully reviewed. A questionnaire including the sociodemographic and medical status of controls was prepared by the authors. This included into gender, age, education, Body Mass Index (BMI), and the presence of past and present medical conditions and psychiatric diseases.

Those who accepted to participate in the study were included in the study. They were age and gender-matched with the patient group and had no personal history of any psychiatric disorders and suicide attempts. Exclusion criteria for groups of patient and control were the following: (1) Having an autoimmune disease, acute infection, severe systemic disease, epilepsy, diabetes mellitus, hypertension, antiplatelet-anticoagulant drug use, bone marrow disease/myelodysplastic syndrome, or another kind of cardiovascular disease, as well as endocrinological, hepatic, renal, pulmonary, or neurological diseases; (2) Mental retardation or neurodevelopmental disorders, traumatic brain injuries, or pregnancy; (3) History of dependence or abuse of alcohol and other kinds of substances related disorders; (4) BMI greater than 30 kg/m².

Measures

Seven hundred sixty-seven patients diagnosed with BD who met the inclusion and exclusion criteria constituted the initial sample. Among these 767 patients who presented at least two different affective episodes were selected. All records of these patients were reviewed and clinical and laboratory test results of depressive, manic, or euthymic episodes of the same patients were examined. If the patient did not meet the criteria of inclusion and exclusion in any of the affective episodes, was excluded from the study. The remaining 127 patients' results were recorded as 3 dependent groups: depressive, manic, or euthymic. Socio-demographic and clinical characteristics of the patients were obtained from their most recent hospital records. To obtain the characteristics required for the study, the hospital records of each patient were examined individually by the authors.

Laboratory data from basic hemogram tests and biochemical analyses were obtained from previous hospital records of patients with BD. The Sysmex-XN 1000 automated blood cell analyzer (Sysmex, Kobe, Japan) was used to analyze hemograms. Neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios were calculated.

The study was conducted according to the revised version of the Declaration of Helsinki. This article was approved by the Selcuk University, Faculty of Medicine, Ethics Committee on 17/04/2019 (no. 75).

Statistics

Statistical analysis was performed using SPSS version 15.0

(SPSS, Chicago, IL). Simple descriptive statistics (mean $\pm$ standard deviation) were created for continuous variables. For discrete variables, the number and percentage of patients are given. The normal distribution of the data was tested using the Kolmogorov Smirnov normality test. Variables not conforming to normal distribution were analyzed using Mann-Whitney U test, otherwise, an independent t-test was used. A Chi-square test was used to compare categorical data. Firstly, sociodemographic features of all patients and controls were compared. Secondly, the variables of manic, depressive, and euthymic periods of the same patient were accepted as three different dependent groups and the Paired-Samples t-test and Wilcoxon Signed Sequences test

were used to compare these groups. Finally, the manic, depressive, and euthymic variables of the patients were compared with the controls. In statistical analysis, $p < 0.05$ was considered significant.

Results

In this study, 127 patients (71 female and 56 male) and 98 (55 female and 43 male) healthy controls were included. There were no differences between the patients and the controls in terms of age and gender. The mean ages of patients and controls were 36.61 ± 8.8 years and 35.93 ± 8.91 years, respectively. Sociodemographic characteristics about both groups and clinical characteristics of the patients are presented in Table 1.

Table 1. Characteristics of patients with BD and healthy controls

	Bipolar Disorder (n=127) Mean $\pm$ SD, n (%)	Control (n=98) Mean $\pm$ SD, n (%)	P value
Age (years)	36.61 $\pm$ 13.9	35.93 $\pm$ 8.9	0.334
Gender, Male	56 (44.1%)	43 (44.9%)	0.507
Schooling (years)	7.7 $\pm$ 4.3	8.4 $\pm$ 3.5	0.111
Years of disorder	9.17 $\pm$ 4		
Age of first mood episode	24.6 $\pm$ 10		
Seasonality	54 (40%)		
Rapid cycling	11 (8%)		
Remission between episodes	90 (66%)		
Presence of mental illnesses in families	69 (51.1%)		
Presence of bipolar disorder in families	35 (24%)		
Number of manic episodes	4,5 $\pm$ 3,6		
Number of depressive episodes	4 $\pm$ 3.2		
Number of hospitalization	3.5 $\pm$ 3.1		
Number of suicide attempt	51 (38%)		
Smoking	53 (41.7%)	34 (34.6%)	0.345
BMI	26.53 $\pm$ 2.81	25.66 $\pm$ 3.11	0.008

Among the 127 patients, only 27 presented euthymia, mania, and depression at different times. Eighty-nine patients had both mania and euthymia at different times. Forty-seven patients had both mania and depression at different times. Forty-five patients had both euthymia, and depression at different times.

The comparison of different affective episodes in terms of NLR, MLR, PLR, and MPV

The comparison of mania and depression included a total of 47 patients. As a result of the comparisons between the two groups did not differ in terms of NLR, MLR, PLR, and MPV.

The comparison of euthymia and depression included a total of 45 patients. There was no significant difference in terms of NLR, MLR, PLR, and MPV.

The comparison of euthymia and mania included a total of 89 patients. The NLR and MLR values of patients with BD in mania

were significantly greater than in euthymia ($p=0.014$ and $p=0.023$ respectively). Additionally, the mean neutrophil and monocyte counts of patients with BD in mania were significantly higher than in euthymia ($p=0.039$, and $p=0.017$, respectively). The hemogram test results of the patients with BD in different states are indicated in Table 2.

The comparison of patients and healthy controls in terms of NLR, MLR, PLR, and MPV

The MPV, NLR, and PLR values of patients with BD in mania were significantly greater than controls ($p=0.015$, $p=0.030$, and $p=0.045$). Additionally, the mean neutrophil and monocyte counts, and white blood cell (WBC) counts of patients with BD in a mania were significantly higher than healthy controls ($p=0.003$, $p=0.016$, and $p=0.012$, respectively). The mean monocyte counts of patients with BD in depression were significantly greater than healthy controls ($p=0.034$). The hemogram test results of the patients and controls are indicated in Table 3.

Table 2. The comparison of different affective states in terms of NLR, MLR, PLR and MPV

	Depressive (n=65) Mean±SD	Manic (n=109) Mean±SD	Euthymic (n=106) Mean±SD	P¹ (Depressive & Manic)	P² (Depressive & Euthymic)	P³ (Manic & Euthymic)
WBcs (10³/μl)	7.60±2.10	8.20±2.43	7.62±1.65	0.575	0.719	0.081
Hemoglobin (g/dl)	14.37±1.83	14.13±2.66	14.05±3.09	0.354	0.212	0.987
Platelets (10³/μl)	239.67±66.38	258.56±66.98	250.88±71.79	0.212	0.441	0.740
MPV (fl)	10.15±1.06	10.32±1.04	10.2±1.16	0.891	0.301	0.304
Lymphocytes(10³/μl)	2.45±0.75	2.48±0.77	2.39±0.56	0.834	0.853	0.414
Monocytes (10³/μl)	0.61±0.18	0.64±0.22	0.58±0.20	0.626	0.403	0.039
Neutrophils (10³/μl)	4.24±1.38	4.89±2.06	4.30±1.17	0.261	0.431	0.017
NLR	1.88±0.79	2.13±1.14	1.84±0.55	0.978	0.158	0.014
MLR	0.27±0.11	0.28±0.7	0.25±0.08	0.723	0.178	0.023
PLR	107.87±44.48	114.23±45,26	109.47±36.3	0.962	0.864	0.377

Abbreviations: WBC, white blood cell; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio

P¹= The comparison of blood count parameters between depression and mania in same patients with BD (n=45)

P²= The comparison of blood count parameters between depression and euthymia in same patients with BD (n=47)

P³= The comparison of blood count parameters between mania and euthymia in same patients with BD (n=89)

Table 3. The comparison of patients and healthy controls in terms of NLR, MLR, PLR and MPV

	Depressive (n=65) Mean±SD	Manic (n=109) Mean±SD	Euthymic (n=106) Mean±SD	Control (n=98) Mean±SD	P¹ (Depressive & Control)	P² (Manic & Control)	P³ (Euthymic & Control)
WBcs (10³/μl)	7.60±2.10	8.20±2.43	7.62±1.65	7.22±1.69	0.507	0.012	0.107
Hemoglobin (g/dl)	14.37±1.83	14.13±2.66	14.05±3.09	14.17±1.69	0.536	0.218	0.222
Platelets (10³/μl)	239.67±66.38	258.56±66.98	250.88±71.79	258.66±64.98	0.072	0.888	0.377
MPV (fl)	10.15±1.06	10.32±1.04	10.2±1.16	10.01±0.79	0.315	0.015	0.134
Lymphocytes(10³/μl)	2.45±0.75	2.48±0.77	2.39±0.56	2.39±0.56	0.799	0.636	0.980
Monocytes (10³/μl)	0.61±0.18	0.64±0.22	0.58±0.20	0.56±0.20	0.034	0.016	0.341
Neutrophils (10³/μl)	4.24±1.38	4.89±2.06	4.30±1.17	4.01±1.21	0.403	0.003	0.099
NLR	1.88±0.79	2.13±1.14	1.84±0.55	1.70±0.49	0.394	0.030	0.054
MLR	0.27±0.11	0.28±0.7	0.25±0.08	0.24±0.07	0.120	0.045	0.526
PLR	107.87±44.48	114.23±45,26	109.47±36.3	112.27±34.80	0.462	0.814	0.497

Abbreviations: WBC, white blood cell; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio

P¹= The comparison of blood count parameters between in depression of patients with BD and controls

P²= The comparison of blood count parameters between in mania of patients with BD and controls

P³= The comparison of blood count parameters between in euthymia of patients with BD and controls

Discussion

The role of systemic inflammation in the pathophysiology of bipolar disorder has been widely studied and described previously. Alterations in blood count parameters reflect the dynamic balance between functions of the immune system [27]. This study showed that NLR and MLR values, which are markers of systemic inflammation in mania, are higher in patients with the same BD than in euthymia. Additionally, we found that patients with BD in mania had higher levels of WBC, MPV, NLR, and MLR than the controls. Our results support the association of BD with low-grade

inflammation due to the presence of changes in clinical markers of systemic inflammation and suggest that NLR and MLR may be potential state biomarkers for BD in manic episodes.

Several studies are reporting altered levels of inflammation pathways and their mediators in regard to bipolar disorder [5,12]. Even though results are insufficient in the majority of the studies report on increased levels of systemic inflammation markers in patients with BD. NLR, MLR, PLR, and MPV are associated with the presence of inflammation, and it reported that changes in levels

of their related to episodes of BD [12,24,26]. The NLR in manic, depressive, and euthymic states of BD was significantly higher compared to controls in a previous study [24]. Mazza et al. reported in a meta-analysis that especially in patients with mania, NLR had higher values than healthy controls, and further investigations are needed to understand better inflammatory markers of BD [12]. Although there was no difference in depression, NLR was higher in euthymia and mania in patients with BP compared to controls. [28]. Another study reported that NLR was found to be higher in mania and euthymia compared to control group [17]. Mayda et al, in a study evaluating the mania only, observed increased NLR levels in patients with BD [26]. Higher NLR and PLR were also associated with more episodes and only higher NLR was related to more manic episodes in the prospective study [10]. Mert and Terzi reported that NLR, MPV, and PLR values were higher in the patients with BD than healthy controls [25]. Another study found NLR to be a significant positive predictor of suicidal risk in euthymic patients with BD [20]. In another study, we found that patients with BD in manic episodes had higher levels of MPV, NLR, MLR compared to controls, NLR and MLR predicted the manic episode of BD [29]. Mazza et al. indicated that BD manic patients had higher NLR and MLR when compared to patients in MDD episodes [1].

In 2001, Zahorec introduced the NLR as a simple, rapid, and cheap parameter of inflammation, used as a subclinical inflammation [13]. The NLR, being an integrated reflection of two different immune pathways, is more predictive than either parameter alone, and it may be useful to detect the inflammatory response associated with BD [12]. Many studies have shown that NLR increases especially during mania compared to healthy individuals. We found that NLR was higher in the same patients with BD in mania than euthymia, and NLR was higher in the patients with BD than healthy controls. We assert that NLR may be a possible state biomarker of the manic episode of bipolar disorder.

The MLR can be derived from white blood cell count and is a low-cost, effective, and readily available new biomarker. Several studies have evidenced that this ratio can be used as a biomarker of poor prognosis or inflammation among patients with chronic medical conditions such as malignancies, infection-related conditions, mental disorders, and autoimmune diseases [27,30]. Kirlioglu et al. reported that MLR would be considered as a novel state biomarker for affective episodes and greater inflammatory activation may be involved in mania rather than mixed episodes [30]. Ozdin et al. (2017) reported that NLR, PLR, and MLR values were higher in mania, and they noticed that there may be an increased inflammatory response in the body during the mania than controls [19]. Although there are no other studies evaluating the relationship between BD in different mood episodes and MLR in the literature, studies showed increased MLR especially in patients with schizophrenia [18,19]. Chronically activated monocytes/macrophages produce cytokines and inflammatory compounds impacting brain development and predisposing the brain in such a way that genetic and environmental influences can precipitate the symptoms of mood [4]. Padmos et al. indicated that those monocytes have an inflammatory gene expression related to affective episodes of a large proportion of patients with BD [31]. We found that MLR had higher in mania than the euthymia in same patients with BD and MLR was higher than healthy controls

in the patients with BD. Although further studies are needed in this area, we believe that MLR may be a possible state new biomarker of the manic episode of BD.

MPV is used as an inflammation biomarker in clinical studies, and there are contradictory and inconclusive results in the various mental disorders [32-34]. A new study reported that platelet parameters including MPV differed between subjects with schizophrenia, unipolar depression, and bipolar disorder (both in the manic and depressive episode) [34]. Mert et al. found that the MPV values of patients with BD in mania were higher than those of the controls [25]. Another study reported that increased NLR and decreased MPV may reflect inflammation in mania, and they explained that decreased MPV levels are observed in high-grade inflammatory diseases, such as active rheumatoid arthritis, etc. [26]. In this study, no difference was found in the comparison of any affective states as measured by MPV in the same patients. Also, the MPV of patients with BD in mania was higher than controls. When we evaluate the results of previous studies, there is not enough data related to whether MPV is a state biomarker and further studies should be done.

PLR, another systemic inflammation marker, may predict the inflammatory response in mood disorders [12]. Few studies are examining PLR levels in patients with BD, and the results are inconsistent [12,17]. A meta-analysis reported higher PLR values in patients with BD when compared to controls [12]. However, in this study, no difference was found in the comparison of any affective episodes as measured by PLR in the same patients with BD. Further research is needed to evaluate the relationship between PLR and bipolar disorder.

The present study has some important limitations. First, the reduced sample size especially the number of patients in the depressive episode may have limited the statistical power necessary to show significant differences between the groups. Second, this is a retrospective study, so no causal relationship can be drawn between NLR, PLR, MLR and MPV, and BD. Furthermore, mixed states may not have been adequately evaluated. Third, the fact that psychotropic drugs such as lithium have not been evaluated, which have been reported to affect pro-inflammatory parameters and counts of WBC, makes it difficult to define a clear result. Fourth, parameters associated with mood episodes' severity could not be evaluated because there were no severity rating scales available in patients' hospital records. Fifth, a correlation between NLR, PLR, MLR, MPV and the severity of the illness, as indicated by the number of hospitalizations, duration of the disorder, sleep-related features, and the number of episodes could not be evaluated because we used the latest clinical futures of the patients in hospital records. Sixth, although values of the same patients in different mood episodes to control other confounding factors were used in this study, a lack of assessment of uncontrollable factors such as BMI that may change during different affective states are possible limitations. It is also a limitation that only descriptive analysis is used. However, the present study has the important advantage of evaluating the same patients in their different mood episodes.

Conclusion

This study that, NLR and MLR as biomarkers of inflammation were found to be higher mania than the euthymia in the same

patients with BD. Additionally, patients in mania had higher levels of MPV, NLR and MLR than controls. This result provides evidence that systemic inflammation plays an important role in the pathophysiology of BD, and NLR and MLR may be used as potential state biomarkers of mania in clinical practice since they can be obtained from both simple and inexpensive blood tests. Further studies in a prospective methodology and with a larger number of patients, using clinical scales to measure the severity and improvement of the disorder are required to assess the response of these biomarkers to treatment. Also, these studies may help the development of new treatment options such as anti-inflammatory agents.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

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Ethical approval

This article was approved by the Selcuk University, Faculty of Medicine Ethics Committee on 17/04/2019 (Approval number: 75).

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