Turkish Journal of Psychiatry 2023;34(1):11–15
https://doi.org/10.5080/u26248

Evaluation of Simple Markers of Inflammation and Systemic Immune Inflammation Index in Schizophrenia, Bipolar Disorder Patients and Healthy Controls

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ABSTRACT

Objective: Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), mean platelet volume (MPV), and systemic immune inflammation index (SII) are recently used as indicators of inflammation. NLR, PLR, MLR, and MPV have been evaluated in many studies in patients with schizophrenia and bipolar disorder. However, there are no studies investigating SII. This study aims to evaluate NLR, PLR, MLR, MPV, and SII values and complete blood count elements in patients hospitalized with diagnoses of the schizophrenia with psychotic episode and bipolar disorder with manic episode by comparing them with the control group.

Methods: A total of 149 patients who were hospitalized with diagnoses of the schizophrenia with psychotic episode and bipolar disorder with manic episode and who met the inclusion criteria were included in our study where the control group was composed of 66 healthy individuals. White blood cell (WBC), neutrophil, lymphocyte, platelet, and monocyte counts were obtained retrospectively from complete blood counts at the time of admission, based on which NLR, PLR, MLR, and SII were calculated.

Results: In this study, higher NLR, PLR, and SII values and lower MPV and lymphocyte counts were observed in schizophrenia patients compared to the control group. NLR, PLR, and SII values and neutrophil counts were higher in patients with bipolar disorder compared to the control group. Lower MPV values were found in patients with schizophrenia compared to patients with bipolar disorder.

Conclusion: Simple inflammatory and SII values in our study indicate the presence of low-grade systemic inflammation in schizophrenia and bipolar disorder.

Keywords: Bipolar disorder, schizophrenia, inflammation, biomarkers, laboratory

INTRODUCTION

Inflammation is the defence mechanism of the human immune system against infections, tissue damage, and stress (Xiao 2017). Low-grade systemic inflammation has been stated in many psychiatric disorders such as psychotic disorders, mood disorders, and personality disorders, and it has been described as a non-severe inflammatory response (Osimo et al. 2018).

It has been asserted that neuroinflammation has a place in the aetiology of psychiatric disorders (Najjar et al. 2013). The presence of low-grade systemic inflammation in bipolar disorder and schizophrenia is supported by studies showing an increase in proinflammatory cytokines. It has been shown that while TNF-α, IL-6, and IL-8 are increased in manic and depressive periods of bipolar disorder, IL-2, IL-4, and IL-6 are increased in manic periods (Brietzke et al. 2011). It has been found that TNF-α, IFN-γ, IL-12, and sIL-2R are consistently increased in chronic schizophrenia independent of disease activity, and IL-1β, IL-6, and TGF beta are positively correlated with disease activity (Miller et al. 2011).

Blood biomarkers are the most widely used to study inflammatory processes in psychiatry. However, many of them are costly or difficult to use for purposes of routine examination. Hence, the need for less costly and simpler methods. Accordingly, developed as a simple method to evaluate the level of systemic inflammation in patients with impaired general medical condition, while neutrophil-lymphocyte ratio (NLR) was initially used for this purpose, recently it is used to evaluate systemic inflammation in

Received: 29.12.2020, **Accepted:** 28.06.2021, **Available Online Date:** 06.10.2021

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psychiatric patients (Mazza et al. 2018). In addition to NLR, studies have been conducted, also, to evaluate platelet-lymphocyte ratio (TLR), monocyte-lymphocyte ratio (MLR), and mean platelet volume (MPV) as a marker of subclinical inflammation in various psychiatric patients. In studies comparing manic episodes of bipolar disorder with healthy controls, higher NLR (Kalelioglu et al. 2015, Mayda et al. 2016, Mert and Terzi 2016, Ozdin et al. 2017) higher TLR (Kalelioglu et al. 2015, Mert and Terzi 2016, Ozdin et al. 2017) and higher MLR (Ozdin et al. 2017) were shown in manic episode patients. In studies investigating the bipolar euthymic period, on the other hand, the results are inconsistent. While Aykut et al. did not find a statistically significant difference between euthymic bipolar disorder and control groups regarding NLR and TLR, Ivkovic et al. observed increased NLR in the euthymic group compared to healthy controls (Ivkovic et al. 2016, Aykut et al. 2018). Kalelioglu et al. showed that increased TLR and NLR values continued in both euthymic and manic periods. However, there was no difference between the two phases (Kalelioglu et al. 2015). NLR was found to be higher in patients with schizophrenia compared to healthy controls (Ozdin et al. 2017, Semiz et al. 2014). While two of the three studies investigating first-stage psychotic patients showed significantly higher NLR than the controls (Moody and Miller 2017, Varsak et al. 2017), no difference was found in NLR in one of them (Garcia-Rizo et al. 2019). Studies in which PLR and MPV were compared with healthy controls were shown to be higher in patients with schizophrenia (Ozdin and Boke 2019, Aydin et al. 2018, Ransing et al. 2018).

The systemic immune inflammation index (SII) is a comprehensive value based on peripheral lymphocyte, neutrophil, and platelet counts as a new index of inflammation. It is calculated as SII = platelet count × neutrophil/lymphocyte count (Zhang et al. 2019). SII has been used as a marker of subclinical inflammation and prognosis in various studies (Zhang et al. 2019, Ruta et al. 2020, Sayan et al. 2020, Ustundag et al. 2018). However, to the best extent of our research, no studies evaluating SII in patients with a psychiatric diagnosis were found. This study aims to determine and compare NLR, PLR, MLR, MPV, and SII values in patients hospitalized and treated for schizophrenia psychotic exacerbation and bipolar disorder manic episode as well as in healthy controls.

METHODS

This study was conducted in Kars Harakani State Hospital, and the patients in the patient group were selected from patients who were hospitalized in the psychiatry service between January 2015 and December 2020.

The study's inclusion criteria were determined as being hospitalized for bipolar disorder manic episode or schizophrenia psychotic exacerbation and being older than 18 years of age for both groups. The exclusion criteria of the study were determined as being on any anti-inflammatory treatment (non-steroidal anti-inflammatory drug, corticosteroid, immunosuppressive drug) or having a systemic disease (Chronic obstructive pulmonary disease, cardiovascular diseases, hematological diseases, etc.) that may cause blood abnormalities for the patient group. For the cases included in the control group, having 18+ years of age and not having been diagnosed with a psychiatric disease were determined as inclusion criteria in the study. The exclusion criteria applied for the patient group were also applied for the control group. Primarily, the aim and method of the study were explained to the participants and their relatives. Verbal and written consent was obtained from patients who were able to give consent and from the relatives of those who were not.

The study was initially started by taking 189 patients, and 15 patients in the schizophrenia group (10 with systemic diseases and 5 using anti-inflammatory drugs) were excluded from the study since they met the exclusion criteria. 25 patients (17 with systemic disease and 8 using anti-inflammatory drugs) in the bipolar disorder group were excluded from the study for the same reason. The study was continued with 61 patients with bipolar disorder manic episodes and 88 schizophrenia psychotic exacerbation patients. Cases in both patient groups had multiple attacks. A control group was formed with 66 healthy individuals matched by age and gender.

Blood samples were taken from the patients in the patient group at the time of admission to the psychiatry service and examined. From these results, white blood cell (WBC), neutrophil, lymphocyte, platelet, MPV, and monocyte count values were obtained, which we used in the calculation of NLR, TLR, MLR, and SII. Sociodemographic data of those included in the study were also obtained retrospectively from patient files.

The study was approved by the Kafkas University Clinical Research Ethics Committee and was found to be in accordance with the Declaration of Helsinki.

To evaluate the data SPSS version 24.0 software was used. The compatibility of the data from the groups with the normal distribution was evaluated using the Kolmogorov-Smirnov test. As the data were not distributed normally, non-parametric analysis methods were used. The chi-square test was used to compare grouped data, the Kruskal-Wallis test was used to compare numerical data in three groups, and Dunnett's t3 was used for multiple comparisons. Statistical significance level was accepted as $p<0.05$.

RESULTS

149 patients (84 males and 65 females) aged between 18 and 68 years were included in the study. The control group consisted of 32 women and 34 men (n=66), schizophrenia group consisted of 32 women and 56 men (n=88), and the bipolar disorder manic episode group consisted of 33 women and 28 men (n=61). The mean age of the groups was 38.31±11.38 years for the schizophrenia group, 37.80±11.31 years for the bipolar disorder manic episode group, and 37.68±11.62 years for the control group. There was no statistically significant difference between the groups in terms of mean age and gender (p=0.93 and p=0.06, respectively) (Table 1).

There was no significant difference between the WBC, neutrophil, platelet, and MLR values of the groups (p>0.05). However, in multiple comparisons, a significant difference between the neutrophil values of the bipolar disorder manic episode and the control group (p=0.03) was observed. A significant difference was also found between the lymphocyte, MPV, NLR, TLR, and SII values of schizophrenia and control groups (p=0.03, p<0.001, p<0.001, p=0.01, and p=0.01, respectively). A significant difference was found between the NLR, TLR, and SII values of bipolar disorder manic episode and control groups (p<0.001, p=0.01, and p=0.01, respectively). A significant difference was found between MPV values of schizophrenia and bipolar disorder manic episode groups (p=0.03) (Table 2).

Table 1. Demographic Characteristics of Participants

	Schizophrenia	Bipolar disorder manic episode	Control	p
Gender				
Female	32	33	32	0.06
Male	56	28	34	
Age (Mean±Sd)	38.31±11.38	37.80±11.31	37.68±11.62	0.93

SD: Standart Derivation

Table 2. Comparison of Blood Count Parameters Between Groups

	Schizophrenia	Bipolar manic episode	Control	KW	P	P1[2]	P2[2]	P3[2]
WBC 10^3/uL	7.16±1.97	7.22±2.25	7.03±1.43	7.14	0.99	0.96	0.92	0.99
Lymphocyte 10^3/uL	2.07±0.83	1.98±0.76	2.37±0.61	2.14	0.01	0.03	0.05	0.85
Neutrophil 10^3/uL	4.35±1.57	4.67±2.01	3.92±1.01	4.31	0.15	0.12	0.03	0.65
Monocyte 10^3/uL	0.51±0.23	0.51±0.20	0.57±0.18	0.53	0.04	0.26	0.20	0.99
Platelet 10^3/uL	246.35±60.52	247.31±58.71	240.70±46.02	244.89	0.88	0.88	0.86	1.00
MPV	8.85±0.89	9.41±1.04	9.87±0.92	9.32	<0.001	<0.001	0.29	0.03
NLR	2.43±1.40	2.67±1.51	1.75±0.68	2.29	<0.001	<0.001	<0.001	0.70
MLR	0.27±0.14	0.28±0.13	0.25±0.94	0.27	0.84	0.79	0.42	0.91
PLR	136.74±63.04	144.59±67.76	107.76±35.85	130.07	0.02	0.01	0.01	0.85
Sİİ	605.30±421.41	687.90±475.04	420.63±187.64	572.05	<0.001	0.01	<0.001	0.62

Mean±Standart Derivation, KW: Kruskal–Wallis; WBC: White blood cell; NLR: Neutrophil-lymphocyte ratio; MPV: Mean Platelet Volume; MLO: Monocyte-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; P1: Schizophrenia-Control; P2: Manic-Control; P3: Schizophrenia-Manic; P[2]: Dual comparison

DISCUSSION

Immunological changes in bipolar disorder play an active role in the neurobiology of the disease. Post-mortem studies showed an increase in various inflammatory cytokines and a decrease in anti-inflammatory cytokines that increase neuroinflammation in brain regions such as the frontal cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex, which play a role in mood and cognitive processes associated with bipolar disorder. (Barbosa et al. 2014, Rao et al. 2010, Dean et al. 2013). In a meta-analysis study, NLR, PLR, and MLR were reported to be helpful in demonstrating an inflammatory activation in mood disorders (Mazza et al. 2018).

In previous studies comparing bipolar disorder manic episode and healthy controls, NLR (Kalelioglu et al. 2015, Mayda et al. 2016, Mert and Terzi 2016, Ozdin et al. 2017) and TLR (Kalelioglu et al. 2015, Mert and Terzi 2016, Ozdin et al. 2017) values were found to be significantly higher in the patient group. In our study, NLR, TLR, and SII values were found to be significantly higher in bipolar disorder patients hospitalized for manic episodes compared to the control group. In previous studies comparing manic episode-control

in bipolar disorder, MLR value, which was considered a systemic inflammatory marker, was evaluated between the two groups, and a significant difference was found (Ozdin et al. 2017, Inanli et al. 2019). However, this study found no significant difference. SII has not been studied in bipolar disorder to date. Thus, the SII value being significantly higher than the control group in the manic period of bipolar disorder is a new finding. NLR, TLR values, which are compatible with other studies, and the new finding, SII, have shown that there may be an increased inflammatory response in the body during the manic phase of bipolar disorder.

Similar to previous studies (Yu et al. 2020, Varsak et al. 2017, Ozdin and Boke, 2019), our findings also indicate an increased inflammatory response in schizophrenia. In our study, NLR, TLR, and SII values were found to be significantly higher in the schizophrenia group compared to the control group, and lymphocyte and MPV values were found to be lower. In previous studies in schizophrenia, higher NLR, TLR values, and lower lymphocyte counts were observed compared to the control group (Semiz et al. 2014, Ozdin and Boke, 2019). In studies comparing MPV value in schizophrenic patients with the control group, MPV value was found to be higher in schizophrenic patients (Aydin et al. 2018, Ransing et al. 2018, Yu et al. 2020). In another study, MPV levels were found to be significantly lower in patients not using any medication compared to patients using atypical antipsychotic drugs (Semiz et al. 2013). It is considered that lower MPV values in schizophrenia patients in our study may be related to the use of antipsychotic drugs. SII has not been previously studied in patients with schizophrenia. Therefore, the SII value which is significantly higher in the schizophrenia attack period group than in the control group is a new finding.

In a study comparing schizophrenia attack episodes and bipolar disorder manic episodes, NLR and TLR values were found to be significantly higher in schizophrenia patients (Ozdin and Boke, 2019). In another study, the TLR value was found to be significantly higher in patients with schizophrenia when comparing patients with bipolar disorder and schizophrenia (Catak et al. 2018). In our study, comparison of patient groups revealed a significant difference only in the MPV value, although it was lower in patients with schizophrenia. In a study conducted by Wysokiński and Szczepocka, platelet parameters were evaluated in patients with schizophrenia, unipolar depression, and bipolar disorder, showing that patients with schizophrenia had significantly higher MPV levels (Wysokiński and Szczepocka, 2016). Moreover, differences in MPV values between gender and age subgroups were also analysed in this study (Wysokiński and Szczepocka, 2016).

Although the results of this study did not include analyses comparing gender and age subgroups, there was no significant difference between our groups in terms of gender and age. Nevertheless, previous studies have reported a decrease in MPV levels in high-grade inflammatory diseases such as active rheumatoid arthritis or FMF attacks, while MPV levels increased in low-grade inflammatory diseases such as cardiovascular disease (Gasparyan et al. 2011, Ulasli et al. 2012). In addition, body mass index was reported to effect MPV levels, and there was a positive correlation between weight loss and a decrease in MPV (Coban et al. 2007). It was thought that MPV could be effected not only by the diagnosis and the level of inflammation but also by age, gender, body mass index, and atypical antipsychotic drugs mentioned earlier.

Considering the relationship between GABAergic, dopaminergic and glutamatergic neurotransmitters in the mechanism of bipolar disorder and schizophrenia, the connection between neurotransmitters and inflammation becomes remarkable (Sigitova et al. 2017, Jagadeesh and Natarajan, 2013). Proinflammatory cytokines can reach the central nervous system and interact with the cytokine network in the brain, effecting brain functions such as neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and cause neuropsychiatric disorders (Capuron and Miller, 2011). Clarifying immune system mechanisms associated with these diseases will be important for the prevention of neuropsychiatric diseases and the development of potential treatments.

This study has some limitations. As it was designed retrospectively, data such as proinflammatory cytokine levels, clinical stages of patients, use of antipsychotics, and mood stabilizers could not be evaluated. Only the results of the blood samples taken during the first application were evaluated, and at the end of the treatment, blood samples were not taken again during discharge, and the results could not be compared. Furthermore, the fact that our study was single-centered and the number of patients was small may restrict the generalizability of the results. More precise results can be achieved with prospective and multicenter studies.

CONCLUSION

This study shows that inflammation markers (NLR, TLR, and SII) are higher in bipolar disorder patients with manic episodes and in patients with schizophrenia psychotic exacerbations compared to control subjects. Additionally, the low lymphocyte level of patients with schizophrenia psychotic exacerbation compared to control subjects supports inflammation in patients with schizophrenia. Low-grade systemic inflammation may occur as a transdiagnostic pathological process in bipolar disorder and schizophrenia. In these disorders, NLR, TLR, and SII may be effective biomarkers to identify patients who may benefit from adjunctive anti-inflammatory pharmacological therapy.

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