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CLINICAL STUDY

Evaluation of systemic immune inflammation index and neutrophil-to-lymphocyte ratio in schizophrenia, bipolar disorder and depression

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ABSTRACT
OBJECTIVES: Numerous studies consistently report on the frequent presence of low-grade systemic inflammation in individuals with schizophrenia, bipolar disorder (BD), and depression. Neutrophil-to-lymphocyte ratio (NLR) and a recently established marker, systemic immune inflammation index (SII), are markers used to assess systemic inflammation and immune response. In this study, NLR and SII index values were examined and compared across patients diagnosed with major psychiatric disorders and healthy controls.
METHODS: The study included, totaling 129 patients, encompassed individuals who were diagnosed with schizophrenia in remission or BD in the euthymic period, and those undergoing treatment for major depressive disorder (MDD). The control group consisted of 62 healthy individuals. White blood cell (WBC), neutrophil, lymphocyte, platelet, and monocyte counts obtained retrospectively from complete blood profiles served as the basis for calculating NLR and SII values.
RESULTS: In this study, higher WBC, neutrophil counts, NLR, and SII values were observed in schizophrenia and BD patients compared to the control group. In patients with MDD, no significant difference was found in terms of inflammatory blood cell markers compared to healthy controls. Higher NLR and Sİİ values were found in patients with schizophrenia and BD compared to patients with MDD.
CONCLUSION: The results of the study indicate that the significant difference in NLR and SII values persists after treatment in patients with schizophrenia and BD, and that the abnormal inflammatory response continues during the treatment process *(Tab. 2, Ref. 41)*. Text in PDF www.elis.sk
KEY WORDS: schizophrenia, bipolar disorder, depression, neutrophil-to-lymphocyte ratio, systemic immune inflammation index.

Introduction

Schizophrenia, bipolar disorder (BD) and major depressive disorder (MDD) are common psychiatric illnesses. In recent years, mounting evidence has fueled the interest in the role of the immune system and increased inflammation in the pathogenesis of these disorders (1). It has been reported that peripheral immune stimulation in various neuropsychiatric disorders affects brain functions and triggers local synthesis of proinflammatory cytokines in brain structures (2). Research studies have demonstrated that psychiatric disorders such as depression, schizophrenia, and bipolar disorder are commonly associated with low-grade systemic inflammation. These studies have shown increased levels of proinflammatory cytokines such as IL-1 and IL-6, acute phase proteins like c-reactive protein (CRP), oxidative stress products, and chemokines in individuals with these psychiatric conditions (3, 4). Additionally, the role of low-grade systemic inflammation has been reported in various psychiatric disorders (5).

Neutrophils and lymphocytes are blood cells that play a crucial role in controlling the inflammatory process in the body. Systemic inflammation is associated with changes in the quantity and composition of circulating blood cells (6). Neutrophils are cells involved in natural immunity and acute inflammation, with functions such as cytokine release, phagocytosis, and apoptosis. Lymphocytes are another type of defense cells representing the regulatory and protective part of the immune system (7). It has been stated that the neutrophil-to-lymphocyte ratio (NLR) calculated from neutrophil and lymphocyte counts, serves as an indicator of systemic inflammation and stress in critical illnesses (8). Furthermore, high NLR values have been found to be associated with elevated levels of cytokines and CRP (9). NLR is increasingly used in psychiatric disorders as an indicator of systemic inflammation (10). Similar to neutrophils, thrombocytes also produce and release various cytokines that can influence the inflammatory response.

Although there are numerous biomarkers used for evaluating inflammation, many are known for their high cost and challenging routine measurement (11). Therefore, in psychiatric disorders as well as in many other diseases, more accessible and cost-effective

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biomarkers obtained from complete blood count have been widely used (12). Among these, NLR is one of the most commonly used parameters to assess immunoinflammatory activity and indicate systemic inflammation. In recent years, the systemic immune inflammation index (SII), obtained by a simple calculation involving neutrophil, lymphocyte, and platelet values, has been proposed as a new biomarker for evaluating systemic inflammation and immune response (13). The SII is calculated as (platelet count x neutrophil count) / lymphocyte count (14). It has been proposed that SII is superior to other inflammatory markers like NLR in reflecting immune status and immune response (15). SII is a relatively new biomarker, and there is an increasing number of studies evaluating its significance in psychiatric disorders.

There are many studies investigating NLR values in schizophrenia, bipolar disorder and major depressive disorder (1, 16–18). However, it is noted that there are fewer studies evaluating the SII as a novel marker in these disorders. The purpose of this study was to investigate and compare the NLR and SII values in subjects with major psychiatric disorders to those in healthy controls. The expected findings might contribute to understanding the mechanism of etiology of common psychiatric disorders.

Methods

The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Amasya University (Date: 13.06.2023, Decision number: 2023/92).

Participants and procedure

After obtaining institutional permission and approval from ethics committee, we retrospectively collected data from the Psychiatry Outpatient Clinic database of a Training and Research Hospital from the period between January 2022 and May 2023. The study included patients diagnosed with BD or schizophrenia in remission, and those aged over 18 years diagnosed with MDD according to DSM-5 diagnostic criteria and who had been on antidepressant treatment for at least three months. Exclusion criteria for both patient and control groups encompassed patients with cardiovascular diseases, endocrinologic diseases, or any conditions that could lead to abnormal blood counts and inflammation. Additionally, individuals using anti-inflammatory drugs, alcohol or psychoactive substances were not included in the study. The control group consisted of healthy individuals aged over 18 years who sought service at the Occupational Medicine outpatient clinic of the same hospital in the same period and had no psychiatric disease. After analyzing the conditions of potential subjects based on all inclusion and exclusion criteria, we included 65 euthymic BD patients, 61 patients with schizophrenia in remission, 65 patients with MDD, and 62 healthy controls. Age, gender, WBC, the lymphocyte, platelet, and monocyte counts of patients and controls were recorded. Additionally, NLR and SII index values for both patients and controls were calculated.

Statistical analysis

The study data were analyzed using IBM SPSS V23. Normal distribution was examined by Kolmogorov–Smirnov test. Categorical variables across groups were compared using the Chi-square test. For normally distributed data involving three or more groups, one-way analysis of variance was employed. For comparing continuous data not following a normal distribution across three or more groups, we utilized the Kruskal–Wallis test followed by multiple comparisons using the Dunn's test. The results of analysis were expressed as mean±standard deviation and as frequency for categorical data. The significance level was set at $p<0.05$.

Results

The study included 191 patients who met all criteria. The data of 61 patients with schizophrenia (30 females, 31 males), 65 patients with BD (32 females, 33 males), 65 patients with MDD (31 females, 31 males), and 62 individuals in the control group (31 females, 31 males) were included in the study. The mean age was 38.41±9.20 years in the schizophrenia group, 39.26±8.63 years in the BD group, 37.37±12.03 years in the MDD group, and 36.05±10.81 years in the control group. There were no statistically significant differences between the patients and control group participants in terms of gender and age ($p=0.896$ and $p=0.192$, respectively) (Tab. 1).

The mean values of hematological parameters are shown in Table 2. No significant differences were found between the groups in terms of lymphocyte, monocyte, and platelet counts ($p>0.05$). However, significant variations across the groups were found in terms of WBC, neutrophil counts, NLR and SII values ($p<0.001$). Subsequent multiple comparisons of variables revealed that WBC and neutrophil counts were significantly higher in patients with schizophrenia and BD compared to the control group ($p<0.001$), as well as in patients with BD compared to patients with MDD ($p<0.05$ and $p<0.001$, respectively). Additionally, the NLR and SII values were significantly higher in patients with schizophrenia and BD compared to the control group ($p<0.001$) and patients with MDD ($p<0.001$ and $p<0.05$, respectively).

Tab. 1. Characteristics of patients and control group participants.

	SCH	BD	MDD	HC	chi-square[1]/KW[2]	p
Age (years)	38.41±9.20	39.26±8.63	37.37±12.03	36.05±10.81	22.199[2]	0.192
Gender (%)					1.087[1]	0.896
Female, n (%)	30 (49.2%)	32 (49.2%)	37 (56.9%)	31 (50.0%)		
Male, n (%)	31 (50.8%)	33 (50.8%)	28 (43.1%)	31 (50.0%)		

SCH – schizophrenia, BD – bipolar disorder, MDD – major depressive disorder, HC – healthy controls. The data are presented as mean± standard deviation and percentages.

Tab. 2. Laboratory findings for the patients and the control group participants.

	SCH	BD	MDD	HC	KW[1]/F [2]	p	Post hoc test
WBC (10^3/uL)	8.23±1.93	8.70±2.05	7.65±1.82	6.76±1.63	34.362[1]	<0.001	HC-SCH** HC-BD** MDD-BD*
Lym (10^3/uL)	2.37±0.72	2.40±0.63	2.43±0.73	2.24±0.53	0.806[2]	0.522	
Neu (10^3/uL)	5.11±1.45	5.42±1.47	4.42±1.30	3.76±1.07	48.107[1]	<0.001	HC-SCH** HC-BD** MDD-BD**
Mon (10^3/uL)	0.60±0.21	0.59±0.19	0.60±0.18	0.52±0.17	9.401[1]	0.052	
Plt (10^3/uL)	270.74±67.70	265.66±52.87	263.51±61.63	243.98±46.23	6.250[1]	0.181	
NLR	2.30±0.78	2.36±0.73	1.93±0.74	1.72±0.49	34.025[1]	<0.001	HC-SCH** HC-BD** MDD-BD** MDD-SCH*
SII	601.96±193.24	624.30±229.15	494.13±13±184.15	410.28±101.11	44.346[1]	<0.001	HC-SCH** HC-BD** MDD-BD* MDD-SCH*

SCH – schizophrenia, BD – bipolar disorder, MDD – major depressive disorder, HC – healthy controls, WBC – white blood cells, Lym – lymphocytes, Neu – neutrophils, Mon – monocytes, Plt – platelets, NLR – neutrophil/lymphocyte ratio, SII – systemic immune inflammation index, KW – Kruskal–Wallis, F – one-way analysis of variance F value. All data are presented as mean± standard deviation. * p<0.05, **p<0.01

Discussion

The pathophysiology of the psychiatric disorders is known to be multifactorial. Recent studies have provided compelling evidence suggesting a substantial role of inflammation in the pathogenesis of psychiatric disorders.

This study explores NLR, one of inflammation markers used in psychiatric disorders, and SII, a recently established index, in association with common psychiatric disorders and compares their values with those of healthy controls. The findings of this study reveal that patients with schizophrenia and BD exhibited significantly higher values of WBC, neutrophil counts, NLR, and SII compared to healthy controls. However, the patients with MDD showed no significant differences in inflammatory blood cell counts and inflammation markers compared to healthy controls.

Evidence supporting the roles of inflammation and immune system abnormalities in the predisposition, onset, and maintenance of schizophrenia is increasingly robust (19). Studies consistently report abnormalities in inflammation markers, immune cell counts, and antibody titers in blood and cerebrospinal fluid of patients with schizophrenia (20). In line with findings reported in previous studies, this study reaffirms an increased inflammatory response in patients with schizophrenia (21–23). In their study, Zhu et al reported that NLR values among patients on antipsychotic treatment for at least two years due to schizophrenia were significantly higher compared to healthy controls. Their findings reveal a persistent and significant difference in NLR values after two years of continuous antipsychotic treatment, indicating the enduring nature of abnormal inflammatory response during the treatment process (24). The effect of using antipsychotic drugs on inflammatory markers remains a topic of debate in the literature, with some researchers suggesting an effect, while others argue for no significant impact (25, 26).

Bipolar disorder is another psychiatric illness increasingly recognized for its evidence-based association with neuroinflammation (27). Our study reveals that during the euthymic period, individuals with BD had significantly higher WBC and neutrophil counts, as well as higher NLR values compared to the control group. Numerous studies into chronic subclinical inflammation markers in BD have reported that inflammation markers such as neutrophil counts and NLR are higher in patients with BD compared to healthy controls (16, 17, 28, 29). However, the results of studies conducted on bipolar patients in the euthymic period are conflicting. While some studies report increased NLR values in in this phase, other studies present different results (17). The study conducted by Kalelioglu et al reports higher NLR values in patients with BD patients during the euthymic period compared to healthy controls (28). However, in a similar investigation conducted by Aykut et al, involving comparable groups, no significant difference was observed in terms of NLR values (30). Further, a study comparing both manic and depressive periods of BD found higher NLR values during the manic period compared to the depressive period (31). Similarly, another study found higher NLR values in the bipolar mania group compared to the bipolar depressive group (32).

Our study was conducted with schizophrenia patients in remission who were under regular antipsychotic treatment for at least 2 years, as well as euthymic BD patients receiving treatment. Elevated levels of WBC, neutrophil counts, and NLR were observed in both groups. These findings suggest that abnormal inflammatory response persists in schizophrenia and BD patients during treatment.

MDD stands as another common psychiatric disorder wherein the immune response significantly contributes to its etiology, with research findings indicating the presence of an inflammatory response (33). In studies comparing patients diagnosed with MDD to healthy controls, it has been reported that MDD patients not receiving antidepressant medication exhibit higher NLR values compared to healthy controls (18, 31, 34). Additionally,

a significant decrease in NLR values has been observed in MDD patients after receiving the antidepressant treatment (18). In the study conducted by Cai et al, patients experiencing depression and abstaining from any psychotropic medications for at least 1 month yielded higher NLR, WBC, and neutrophil counts compared to the control group (35). These findings led to the hypothesis suggesting an inflammatory reaction in MDD. However, in our study, we did not find any significant differences in NLR values between patients with MDD and healthy controls. This lack of significant differences in our study may be attributed to the inclusion of patients who had been undergoing antidepressant medication for at least 3 months. In this study, we also observed that in patients with BD during the euthymic period, the WBC and neutrophil counts, as well as NLR were significantly higher compared to patients with MDD.

In our investigation into systemic inflammatory index (SII) in psychiatric disorders, we identified significantly higher SII values in patients with schizophrenia and BD than in the control group. However, upon comparing the SII values between the schizophrenia and BD patient groups, no significant difference was observed. Similarly, Inaltekin and Yagci reported in their study that both schizophrenia and bipolar patients had significantly higher SII values compared to the control group. Their study also revealed that there was no significant difference in SII values between the schizophrenia and BD groups (36). The number of studies focusing on the significance of SII in psychiatric disorders is increasing. These studies emphasize the significance of SII values in psychiatric diseases, illustrating variations across different psychiatric disorders. In a study conducted by Zhu et al, it was reported that both NLR and SII values remained constant over time in schizophrenia patients who were under regular antipsychotic treatment for at least two years (24). Šagud et al found no significant difference in SII values between schizophrenia patients with negative symptoms and healthy controls (36). Conversely, the study of Wei et al revealed higher values SII values in both schizophrenia and BD patients compared to the control group. Moreover, the SII values were higher in schizophrenia patients than in those with BD. Notably, the SII values of the bipolar manic group were higher compared to the bipolar depressive group (37). Dadoli et al found that patients with bipolar manic and depressive episodes had higher SII values compared to healthy controls (38). Dionisie et al reported that SII values were significantly higher in patients with bipolar manic episode compared to patients with bipolar depression as well as in patients with bipolar depression compared to patients with unipolar depression (32). In our study, it was found that both schizophrenia and BD patients exhibited higher SII values compared to patients with MDD.

Studies on depression have shown that SII is an important biomarker. There are several studies in the literature that have investigated SII values in patients with depression (39, 40). Zhu et al conducted a study comparing NLR and SII values across different subtypes of depression. In their study, they found that there was no significant difference between subtypes of depression in terms of NLR values, as well as that SII values were significantly higher in patients with psychotic features and severe depressive disorder without psychotic symptoms compared to healthy controls (39). Cui et al reported that depression patients with high SII scores had a moderate-to-severe level of depression (13). In the study of Wei et al, it was observed that first-episode MDD patients had lower SII values compared to healthy controls. However, in patients with recurrent depression, there was no significant difference in SII values compared to the control group. Additionally, in the BD group, SII values were found to be higher than those in both the MDD group and healthy controls (37). In our study, the SII values in depression patients receiving treatment did not differ significantly from those in healthy controls. However, these values were found to be significantly lower than those observed in patients with BD and schizophrenia. This finding suggests that the treatment received by the patients may have had an impact on inflammation.

This study has several limitations that warrant consideration. Firstly, our focus was on evaluating inflammatory markers in psychiatric disorders. However, it is crucial to acknowledge that psychiatric illnesses are multifactorial, with various factors contributing to their development. Another limitation stems from the retrospective design of our study, which implies that other influencing factors such as smoking status and obesity were not evaluated. Despite these constraints, our study represents a significant step forward in exploring the relationship between psychiatric disorders and inflammation.

Conclusions

The etiology and pathophysiology of psychiatric disorders remain incompletely understood, posing challenges in their management and treatment. In recent years, there has been a growing interest in the role of inflammation in psychiatric disorders. Therefore, the discovery of new potential markers and proliferation of studies exploring each identified marker are of great importance for advancing our understanding, diagnosis and treatment of psychiatric conditions. Additionally, recognizing the significance of inflammation as a contributing factor to the development and course of psychiatric disorders holds substantial value. However, conducting more comprehensive and prospective studies will enhance our understanding of the role the inflammation plays in the pathogenesis and treatment of these disorders. Such studies will help us determine whether inflammation can be a potential target in the treatment of psychiatric disorders, thereby contributing to the development of more effective treatment approaches.

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