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Research Article

Comparison of neutrophil-to-lymphocyte, platelet-to-lymphocyte, and monocyte-to-lymphocyte ratios in patients with schizophrenia, bipolar disorder, and major depressive disorder

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Abstract

Objectives: It is thought that the immune system may play a role in the etiopathogenesis of many psychiatric and neurological diseases. In recent years, it was suggested that the neutrophil-to-lymphocyte, platelet-to-lymphocite, and monocyte-to-lymphocyte ratio (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), respectively) analysis is used to predict peripheral inflammation. Therefore, we aimed to compare the changes in NLR, PLR, MLR values in patients with schizophrenia, bipolar disorder, and depression.

Methods: In this retrospective study, a total of 1543 inpatients/outpatients with a diagnosis of schizophrenia, bipolar disorder, and depression admitted to a mental health hospital between 2016 and 2017 were evaluated. Eighty control subjects were included from the hospital. All groups (schizophrenia, bipolar, depression, controls) were compared with one another in terms of NLR, PLR, and MLR values using SPSS 21.

Results: There was significant difference in NLR between the schizophrenia group and healthy controls ($p=0.007$). When the patient groups (schizophrenia, bipolar disorder, and depression groups) were compared with each other, NLR values were significantly higher in patients with schizophrenia compared to depression groups ($p<0.001$). MLR values for the schizophrenia and bipolar disorder groups were significantly higher than for the depression group ($p=0.001$ and $p<0.001$, respectively). PLR values were found to be significantly higher in patients with schizophrenia than in patients with bipolar disorder ($p=0.007$).

Conclusion: The changes in NLR, PLR, and MLR values used as indicators of inflammation have shown that psychiatric disorders are associated with inflammatory processes. However, it was observed that this relationship was more obvious in schizophrenia compared to bipolar disorder and depression.

Keywords: bipolar, major depressive disorder, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, schizophrenia

Leukocytes, the main cell of the immune system, secrete a variety of cytokines. During the immune response, as well as cytokine secretion, numerical changes occur in different leucocyte populations. It is known that there is an increase in the neutrophil-to-lymphocyte ratio (NLR) in conditions associated with inflammation such as autoimmune diseases and

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infections. Changes in NLR are also considered as indicators of inflammation such as C-reactive protein (CRP) and proinflammatory cytokines [1–3]. The NLR, platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) values are reproducible biomarkers of inflammation and used routinely [4]. The immune system has effects on the brain and behavior through biological mechanisms [5]. It has been reported that the main proinflammatory cytokines such as IL-1, IL-6, TNFα, and CRP are elevated in depressive states or in the presence of psychosocial stress [6–8].

Recent years' studies have focused on the inflammatory response, with the role of the immune system in the etiopathogenesis of various psychiatric disorders such as schizophrenia, bipolar disorder (BD), or major depressive disorder (MDD). In psychiatric diseases, there are new studies that point to an increase in NLR [9–17]. The NLR, PLR, and MLR analysis are used to predict peripheral inflammation. The aim of this study is to compare patient groups (schizophrenia, BD, MDD) with each other and with healthy controls in terms of NLR, PLR, and MLR changes.

Materials and Methods

In this retrospective study, a total of 1793 inpatients/outpatients with a diagnosis of schizophrenia, BD, and MDD admitted to a mental health hospital between January 2016 and December 2017 were evaluated. Eighty control subjects were included from the hospital. All the groups (schizophrenia, BD, MDD, and healty controls) were matched for age, sex, and clinical diagnosis. When the multiple results for the same patient were detected between the determined dates, the first results were included, and the later results were excluded. Subjects who were diagnosed with diabetes mellitus or substance abuse were excluded. Patients who had hemoglobine values <11 or >17 and white blood cell count values (WBC) <4000 or >13000 were excluded from the study. This study was approved by Firat University (Date: 31.05.2018, Number: 11) ethics committee. The blood count parameters were analyzed using a Sysmex XN 450 instrument (Sysmex Corporation, Kobe, Japan) by the electrical impedance method. Internal quality control samples were routinely analyzed twice a day in the central laboratory. Fasting blood specimens collected in the K-EDTA tubes were studied within 30 minutes.

Statistical analysis

All parameters were analyzed using the SPSS (SPSS Inc., Chicago, IL, USA) software version 21. The chi-squared test was used for categorical variables. The variables were investigated using visual (histograms/probability plots) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk's tests) methods, whether or not they were normally distributed. Since the variables were not normally distributed, they were compared using the Kruskal–Wallis test. An overall 5% type-1 error level was used to infer statistical significance. The Mann–Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Data were presented as the median (min–max) or mean±standart deviation.

Results

The study included 1543 patients (756 males and 787 females) aged between 18 and 65 years. The mean age of the cases was 39.5±11.2 years. The control group consisted of 36 females and 30 males (n=66), whereas the schizophrenia group comprised 109 females and 143 males (n=252), bipolar group 350 females and 324 males (n=674), and depression group 292 females and 259 males (n=551). The demographic and laboratory characteristics for the all patient groups are shown in Table 1. There were no statistically significiant diffrences between the groups with respect to the mean age and gender (p=0.3 and p=0.58, respectively). There was no significant difference in all the groups with regard to hemoglobin and hematocrit values (p=0.969, p=0.999, respectively). Although there were significant differences in WBC values (p=0.043, Table 1) by multiple comparison, there was not significant difference by pairwise comparisons. The lymphocyte, neutrophil, monocyte, and platelet values between the groups were found to be significantly different by multiple comparison tests (Table 1). The lymphocyte, monocyte, and neutrophil counts of patients were not significantly different from the control group. However, the lymphocyte and neutrophil counts between the schizophrenia and depression groups were significant different (p=0.003, p=0.002, respectively), when using pairwise comparison tests. The monocyte and platelet counts were significantly different between the bipolar and depression groups (p=0.004, p<0.001, respectively). The NLR, PLR, and MLR values are presented in Table 2. When the pairwise comparisons were performed using the Bonferroni correction to adjust for multiple comparisons, the NLR in schizophrenia group was significantly higher than in health controls (p=0.007). There was no significant difference between patients (BD and MDD) and control groups in terms of NLR values (p=0.206 and p=0.923, respectively). When the patient groups (schizophrenia, BD, and MDD) were compared with each other, the NLR values of patients with schizophrenia were significantly higher than depression groups (p<0.001). However, there was no significant difference between patients with schizophrenia and patients with BD with regard to NLR (p=0.018). There was no significant difference between patients (schizophrenia, BD, and MDD) and control groups in terms of MLR values (p=0.90, p=0.82, p=0.673, respectively). The MLR values for the schizophrenia and BD groups were significantly higher than for the MDD group (p=0.001 and p<0.001, respectively). When the patient groups (schizophrenia, BD, and MDD) were compared with the control group, PLR values were not found to be significantly different (p=0.016, p=0.401, p=0.158, respectively). However, PLR values were found to be significantly higher in the schizophrenia group than in the BD group (p=0.007, respectively).

Table 1. Characteristics of Patients and Control Groups

	Control subjects Group (n:66):66)	Schizophrenia Group (n:252)	Bipolar disorder Group (n:674)	Depression Group (n:551)	p
Age (years)					
Mean±Standart deviation	39.0±7.8	39.2±11.3	39.1±10.5	40.3±12.1	0.30
Female/Male	36/30	109/143	350/324	292/259	0.58
Hemoglobin (g/dl)	14.60	14.54	14.52	14.5	0.969
Median(min-max)	(11.0-16.9)	(11.2-16.9)	(11.0-16.9)	(11.0-16.9)	
Hemotocrite (%)	41.85	41.68	42.19	42.23	0.999
Median(min-max)	(34.4-49.5)	(32.8-50.3)	(32.1-50.5)	(32.3-49.4)	
White blood cell(103/μl)	7.73	7.77	7.92	7.66	0.043
Median(min-max)	(4.29-12.78)	(3.45-12.78)	(3.11-12.89)	(3.32-12.88)	
Lymphocyte (103/μl)	2.33	2.21	2.23	2.26	0.007
Median(min-max)	(1.4-3.3)	(0.78-4.3)	(0.46-4.8)	(0.53-5.0)	
Neutrophil (103/μl)	4.35	4.93	4.65	4.43	0.025
Median(min-max)	(2.09-8.86)	(1.31-10.52)	(1.73-10.28)	(1.55-11-46)	
Monocyte (103/μl)	0.592	0.590	0.599	0.571	0.025
Median(min-max)	(0.28—1.73)	(0.22-2.10)	(0.23-2.10)	(0.18-2.54)	
Platelet (103/μl)	257	267	256	272	0.002
Median(min-max)	(142-416)	(130-436)	(130-450)	(145-448)	

P-values less than 0.05 are statiscally significant.

Table 2. Comparison of the Neutrophil-to-Lymphocyte Ratio, the Monocyte-to-Lymphocyte Ratio, and the Platelet-to-Lymphocyte Ratio Values of Controls and Patient Groups

Groups	Neutrophil/lymphocyte Median (min-max)	Platelet/Lymphocyte Median (min-max)	Monocyte/Lymphocyte Median (min-max)
Health controls	1.97 (1.03-5.66)	112.6 (69.9-3.3)	0.25 (0.09-0.71)
Schizophrenia	2.29 (0.64-9.17)[a]	123.1 (48.4-365.0)	0.28 (0.11-1.11)
Bipolar disorder	2.11 (0.55-10.71)	117.5 (30.55-495.7)	0.28 (0.11-1.71)
Depression	1.95 (0.58-13.19)[b]	120.5 (48.3-416.9)	0.24 (0.10-1.80)[b,c]

When the p-value was found to be smaller than the adjusted p-value (0.008) by the Bonferroni correction, it was considered to be significant.
[a]Statistically different from the control group; p=0.007
[b]Statistically different from the shizophrenia group; p<0.001
[c]Statistically different from the bipolar disorder group; p<0.001
[d]Statistically different from the bipolar disorder group; p=0.007
[e]Statistically different from the shizophrenia group; p=0.001.

Discussion

There is a two-way relationship between the immune system and the central nervous system. The hypothalamic corticotropin releasing factor (CRF) plays an effective regulatory role in the stress response. Various cytokines are secreted by leukocytes, the main cells of the immune system. These inflammatory substances act on the brain to stimulate CRF. It is known that CRF increases the release of corticosteroids, catecholamine, and some opiates with the effects on the sympathetic nervous system and the hypothalamus–pituitary–adrenal axis, thus acting as a suppressor on the immune system [18, 19].

It is thought that the immune system may play a role in the etiopathogenesis of many psychiatric and neurological diseases. Symptoms such as weakness, fatigue, depression, and decreased appetite associated with an increase in proinflammatory cytokines in infectious and inflammatory diseases also occur in MDD, and it is thought that cytokines play a role in neuroinflammatory pathogenesis [20].

Psychological stress, just like physiological stress, also affects cytokine release, and proinflammatory cytokines seem to play a major role in this association [6]. The negative mood states have effects on the immunological function as part of the neuro-immunoendocrine cycle [21]. There are studies showing that the immune system is active in MDD. As stress and depression lead to a decrease in the lymphocyte count, reduced cellular immunity accompanying depression is seen [6, 20, 21]. The high value of NLR thought that inflammation plays an important role in the etiopathogenesis of MDD [11]. However, in our study, NLR values of MDD patients were lower from the healthy controls, but this difference was not found to be significant. There were no significant differences between MDD and control group in terms of PLR and MLR values.

Immunological changes in BD play an active role in the neurobiology of the disease. The presence of immunological activity in the BD patient group is explained by the increase or decrease of various cytokines. Postmortem studies have shown an increase or decrease in various cytokines in brain specific regions such as frontal cortex, anterior cingulate region, and dorsolateral prefrontal cortex, which play a critical role in the BD-related mood and cognitive processes [22]. There are studies that emphasize the reduction of anti-inflammatory cytokines in the postmortem frontal cortex that increase neuroinflammation [22–25]. A meta-analysis study reported that NLR, PLR, and MLR are useful in showing that an inflammatory activation occurs in mood disorders. NLR, PLR, and MLR values can be used as reproducible biomarkers of inflammation that have been studied routinely [4]. Based on these changes in the immune system, it is anticipated that new therapeutic strategies for mood disorders may be involved in studies of anti-inflammatory or monoclonal antibody drugs investigating the therapeutic effect on BD [22, 26].

In a study consisting of BD patients, the NLR was detected to be high during a psychotic table, but it was reduced in patients who underwent clinical remission, and this NLR height was thought to be related with a psychotic episode [23, 27]. In this study, NLR, PLR, and MLR levels were higher in the BD group than in the control group, although this difference was not significant.

There are only a few studies examining NLR in patients with schizophrena. When the NLR elevation is emphasized in the schizophrenic patient group, the relationship between the use of antipsychotics and the NLR value can not be explained exactly. Semiz et al. [16] reported that the use of antipsychotic medication did not change NLR, while Varsak et al. [17] reported that NLR was higher in the first episode before the antipsychotic medication [16, 17]. Kulaksızoğlu et al. [15] found a high NLR in the group of patients using antipsychotic drugs. In the present study, similar to the literature in the schizophrenia patients, NLR values were found to be significantly higher than healthy controls. The PLR and MLR levels were found higher in the shizophrenia group than in the control group, although this difference was not found to be significant.

On the other hand, when comparing the patient groups with each other (schizophrenia, BD, and MDD), the NLR values in schizophrenia were significantly higher than in MDD patients. The MLR values in schizophrenia and BD were significantly higher compared to MDD. The PLR values in schizophrenia were found significantly higher than in BD. There was no significant difference between schizophrenia–depression or BD–depression in terms of PLR.

Although the lymphocyte, monocyte, and neutrophil counts of patients were not significantly different from the control group, there was significant different between patient groups.

There were some limitations to this study. As it was designed retrospectively, data such as proinflamatuar cytokine levels, the clinical stages of the patients, the use of antipsychotic medication, the family history, and smoking could not be evaluated. The changes in NLR, PLR, and MLR values used as indicators of inflammation have shown that psychiatric disorders are associated with inflammatory processes. However, it was observed that this relationship was more obvious in schizophrenia compared to BD and depression. Based on all findings, it is not possible to say that NLR, PLR, and MLR levels are the reason or result of psychological stress, and further research is needed to understand how immune cells change the effect of psychological stress.

Conclusion

The changes in NLR, PLR, and MLR values used as indicators of inflammation have shown that psychiatric disorders are associated with inflammatory processes. However, it was observed that this relationship was more obvious in schizophrenia compared to bipolar disorder and depression.

Ethics Committee Approval: This study was approved by Firat University ethics committee.

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