Evaluation of substance induced and substance free first-episode psychosis in terms of inflammatory whole blood count parameters

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SUMMARY

Objective: Substance use is known to trigger psychotic episodes in individuals predisposed to psychosis. Recently, the importance of inflammatory processes in psychotic disorders has been increasingly emphasized. This study aimed to examine the manner in which inflammatory whole blood count (WBC) parameters change in substance-induced first-episode psychosis (siFEP) and substance-free first-episode psychosis (sfFEP).

Method: The present study included 32 patients with siFEP, 48 patients with sfFEP, and 80 healthy controls. For the comparison of inflammatory WBC parameters between the three groups, age and sex were considered as covariates when MANCOVA was applied; further, LSD post hoc test was performed. The relationship between clinical variables and inflammatory WBC parameters was analyzed using Pearson's correlation analysis.

Results: Monocyte levels were higher in patients with siFEP than in those with sfFEP and healthy controls, and platelet-to-lymphocyte ratio values were lower in patients with siFEP than in healthy controls. Furthermore, a moderately significant relationship between duration of illness and monocyte levels was found in the siFEP group.

Discussion: The fact that inflammatory WBC parameters differ among the siFEP, sfFEP, and healthy control groups suggests that inflammatory processes contribute to psychotic disorder. However, the data from the present study are still insufficient to support the use of these parameters in clinical practice.

Key Words: First-episode psychosis, substance-induced first-episode psychosis, substance-free first-episode psychosis, inflammatory whole blood count parameters

INTRODUCTION

Psychotic disorder is a condition that has cognitive and behavioral components and causes significant impairment in functionality and quality of life. As interventions in the early stages of the disorder are believed to have a positive impact on the prognosis, follow-up of patients from the first psychotic episode is of great importance (1,2). Substance use has been reported to precipitate psychotic symptoms in individuals predisposed to psychosis. 7-25% of individuals who have had a psychotic episode for the first time are diagnosed with substance-induced psychotic disorder (3), especially having a family history of alcohol and substance use disorder is a risk for developing this condition (4). Notably, a previous study reported that substance-induced psychosis is associated with a high risk of transforming into schizophrenia (4). In addition, a family history of psychotic disorder is believed to be an important risk factor in the transformation of the disease into schizophrenia (4). Substance-induced first-episode psychosis (siFEP) and substance-free first-episode psychosis (sfFEP) may differ in terms of some clinical features. It is known that forensic events and history of trauma are more common, insight is better, and anxiety and hostility are more pronounced in siFEP than in sfFEP (5). Furthermore, the fact that patients with siFEP have shorter treatment processes and that they are not preferentially enrolled in treatment programs represents an obstacle for them to receive appropriate

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treatment (6). In cases of siFEP and sfFEP, in addition to clinical features, the presence of practical clinical markers, which can provide information about the differential diagnosis and prognosis of the disease, may help such patients to receive treatment at the right time with appropriate dose.

With recent studies in the relevant literature, the importance of inflammatory processes in the neurobiology of psychosis has been increasingly emphasized (7-9). Moreover, the number of studies using inflammatory whole blood count (WBC) parameters has steadily increased because of the readily available, inexpensive, and practical use of these markers. To date, these parameters have been reported to be affected in many systemic diseases, such as malignancies and cardiovascular diseases (10,11). In addition, inflammatory WBC parameters, such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII), vary in many psychiatric disorders (e.g., bipolar, depressive, attention-deficit hyperactivity, and substance and alcohol use disorders) (12-16). Although these parameters are not considered to be disease-specific, they are important for elucidating the underlying inflammatory processes and for monitoring the disease progression.

Most of the studies showed that patients with psychotic symptoms (schizophrenia or bipolar disorder) have increased NLR, PLR, MLR values and decreased lymphocyte levels (12, 17-19). In addition, these inflammatory markers change according to the stage of the illness (e.g., remission or relapse) (17). On the other hand, studies on patients with first-episode psychosis revealed conflicting results (20-23). To date the only study evaluating inflammatory WBC parameters on patients with substance-induced and substance-free first-episode psychosis showed that patients sfFEP have increased leukocyte, neutrophil, monocyte levels and NLR, MLR values compared to healthy controls while patients with siFEP showed differences only on leukocyte, monocyte levels and MLR values (24).

Markers that clinically distinguish siFEP from sfFEP can be useful for the appropriate diagnosis, follow-up, and treatment. Therefore, the present study aimed to compare inflammatory WBC parameters of patients with siFEP, patients with sfFEP, and healthy controls. In this study, it was hypothesized that patients with siFEP, patients with sfFEP and healthy controls would differ from each other in terms of inflamatory WBC parameters.

METHODS

This is a retrospective observational study. The records of a total of 1599 patients who were hospitalized at Maltepe University, Faculty of Medicine, Department of Psychiatry between January 2013 and October 2022, were reviewed. After excluding other psychiatric diagnostic groups and readmissions, it was found that 191 patients who had acute psychotic spectrum diagnoses admitted for the treatment. The first psychotic episode was defined as the Diagnostic and Statistical Manual of Mental Disorders-5-based diagnosis of psychotic disorders or bipolar disorder (manic episode with psychotic features) in patients who admitted to a healthcare service following the manifestation of psychotic symptoms started for the first time within the past 1 year. Patients who had recurrent psychotic episodes, or comorbid medical illness were excluded from the study. Patients with insufficient data were not included in the study. As a result, a total of 80 patients (siFEP (n=32) and sfFEP (n=48)) were eligible for inclusion.

80 healthy controls were randomly selected from individuals with no history of psychiatric disorders and substance use who had applied to Maltepe University Faculty of Medicine for health screening or obtaining medical board report between 2020 and 2022.

Patients aged 17–50 years were included in the present study. Blood samples from patients admitted to the psychiatric unit for siFEP or sfFEP were collected within the first 24 hours. Participants with concomitant hypertension, diabetes mellitus, heart disease, inflammatory or autoimmune diseases, cancer, and active infection and those taking immunosuppressive drugs were excluded from the study. For sfFEP group, patients with a history of

substance use were excluded from the study. Moreover, for healthy control group, individuals who were considered to have an acute or lifelong psychiatric disease based on a psychiatric interview were not included. This study was approved by the Maltepe University Faculty of Medicine Clinical Research Ethics Committee (Number: 2022/900/02; Date: 19.01.2022).

Statistical Analysis

IBM SPSS Statistics 23.0 (Chicago IL, USA) was used for all statistical analyses. Categorical variables were compared using the chi-square test. The Kolmogorov–Smirnov test was used to determine whether the continuous data corresponded to the normal distribution, and appropriate transformations were performed for data that did not correspond to the normal distribution. In addition, paired group comparisons were performed using the Student's t-test. Moreover, ANOVA and Bonferroni post hoc test were used for multiple group comparisons. For the comparison of inflammatory WBC markers between the diagnostic groups, age and sex were used as covariates when MANCOVA was applied, and LSD post hoc test was performed. Furthermore, the relationship between clinical variables and inflammatory whole blood parameters was analyzed in both patient groups separately using Pearson's correlation analysis. A p-value of < 0.05 was considered statistically significant. The power analysis is performed by G Power 3.1.

RESULTS

A comparison of the demographic and clinical characteristics between the study groups is presented in Table 1. No significant difference was found between the patients and healthy controls in terms of age, but a significant difference was found between the study groups in terms of sex ($p< 0.001$).

When comparing inflammatory WBC parameters between the study groups using age and sex as covariates, monocyte levels were significantly higher in patients with siFEP than in patients with sfFEP ($p = 0.004$) and healthy controls ($p= 0.022$). In addition, PLR values in patients with siFEP were significantly lower than those in healthy controls ($p = 0.006$). Notably, no significant difference was found between the groups in leukocyte, neutrophil, lymphocyte, platelet, NLR, MLR, and SII values (Table 2).

In the correlation analyses between age at onset of substance use, duration of substance use, age at onset of disease, duration of, and inflammatory WBC parameters, a moderately significant association between disease duration and monocyte levels was found in the siFEP group ($p=0.021$, $r=0.435$). Power analysis conducted by calculating effect size and sample size has resulted in a power of 0.69 for the study.

DISCUSSION

In the present study, patients diagnosed with siFEP and sfFEP and healthy controls were compared in terms of inflammatory WBC parameters. Monocyte levels were higher in patients with siFEP than in those with sfFEP and healthy controls, and PLR values were lower in patients with siFEP than

Table 1. Comparison of sociodemographic and clinical characteristics between the study groups

	siFEP (n=32)	sfFEP (n=48)	HC (n=80)	Test statistic F/x^2	p
Age	28.38 (8.20)	29.54 (9.75)	27.83 (6.68)	0.691	0.503
Sex (n, %)				27.058	**<0.001**
Female	2 (6.2)	24 (50)	12 (15)		
Male	30 (93.8)	24 (50)	68 (85)		
Duration of illness (month)	5.63 (4.13)	4.75 (4.66)	-	0.910	0.366
Age of illness onset	27.00 (8.80)	29.13 (9.94)	-	1.059	0.294
Age of first substance use	20.00 (8.35)	-	-		
Duration of substance use (month)	94.96 (74.98)	-	-		
Substance type (n, %)		-	-		
Cannabinoid	11 (34.38)				
Cocaine	3 (9.38)				
Polysubstance*	18 (56.25)				

siFEP: Substance-induced first-episode psychosis; sfFEP: substance-free first-episode psychosis; HC: Healthy control *Number of patients and type of substance used for polysubstance users: Cannabinoids (n=17), stimulants (n=17), opioids (n=3), sedatives (n=1)

Table 2. Comparison of inflammatory whole blood parameters between the study groups

	siFEP (n=32)	sfFEP (n=48)	HC (n=80)	Test statistic F	p
Leukocyte (/mm^3)	7873 (1712)	7044 (17949	7335 (1473)	1.863	0.159
Neutrophil (/mm^3)	4132 (1412)	3838 (1402)	3983 (1095)	0.484	0.618
Lymphocyte (/mm^3)	2757 (625)	2461 (716)	2508 (624)	2.092	0.127
Monocyte (/mm^3)	706 (207)	567 (198)	604 (158)	4.395	0.014 siFEP>sfFEP p=0.004 siFEP>HC p=0.022
Platelet (/mm^3)	224372 (48135)	231498 (46639)	244411 (51483)	2.805	0.064
NLR	1.59 (0.76)	1.69 (0.80)	1.67 (0.59)	0.530	0.590
MLR	0.27 (0.09)	0.24 (0.09)	0.25 (0.07)	0.522	0.595
PLR	84.61 (25.31)	101.47 (36.32)	103.00 (31.99)	3.939	0.021 HC> siFEP p=0.006
SII	357852 (181051)	394494 (216801)	411603 (178721)	1.639	0.198

siFEP: Substance induced first episode psychosis; sfFEP : substance-free first-episode psychosis; HC: Healthy control; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte -to-lymphocyte ratio; PLR: Platelet -to-lymphocyte ratio; SII: systemic immune inflammation index

in healthy controls.

Although studies in the relevant literature have reported increased NLR, PLR, MLR values and decreased lymphocyte levels in schizophrenia and bipolar disorder (12, 17-19), there are conflicting results in studies conducted during the first episode of psychosis (20-23). One large sample sized study found that patients with first episode psychosis have increased NLR, MLR, and PLR values compared to healthy controls (23), while other did not (22). In a previous study that compared patients diagnosed with a substance-induced psychotic disorder to patients diagnosed with a substance-free psychotic disorder in terms of inflammatory WBC parameters (24) - leukocyte, neutrophil, monocyte, and MLR values were found to be higher in patients diagnosed with siFEP and sfFEP than in healthy controls. In contrast, that study reported that compared with healthy controls, NLR values were higher only in patients diagnosed with sfFEP. Consistent with this study, our results showed that monocyte levels increase in patients diagnosed with siFEP compared to healthy controls. However, we did not find any differences in leukocyte, neutrophil levels or MLR values. The absence of differences in some of the inflammatory WBC parameters, between patients with first psychotic episode and healthy controls in our study may indicate that the inflammatory burden, which becomes clear in the later stages of psychosis, does not become evident in the early stages of the illness. Notably, to the best of our knowledge, the finding of monocyte levels being higher in patients diagnosed with siFEP than in those diagnosed with sfFEP reported in our study has not been reported in any studies till date. It is known that monocytes play an important role in the immune system by transforming into macrophages, secreting acute phase reactants, phagocytosing foreign molecules, and presenting these molecules to lymphocytes (25). Moreover, in the study by Orum et al., it was found that monocyte levels and MLR values were significantly higher in cannabis users than in opioid users (26). Cannabis was the substance used by almost all of the individuals who were using polysubstance in this study. Notably, patients with cannabis and polysubstance use in the siFEP group constituted a large proportion of the sample. Accordingly, monocyte levels may have been higher in patients diagnosed with siFEP than in those diagnosed with sfFEP and healthy controls owing to the effect of substance used and the type of substance.

Similarly, there are no definitive results regarding the direction of changes in inflammatory WBC parameters in substance use disorder. There are studies that report an increase in NLR and PLR values among opioid users compared with healthy controls (13,27,28). On the other hand, a previous study found no difference in NLR values (29), and some studies reported a decrease in MLR and PLR values (26,29). To the best of our knowledge, this is the first study to report that PLR values are lower in patients with siFEP than in healthy controls. In the study by Onur et al., no difference was found between patients with first-episode psychosis and healthy controls in terms of PLR values (24). Notably, platelets are known to play an important role in inflammation and immune response (30). In addition, they secrete many mediators that are not involved in hemostasis, and some of these media-

tors modulate leukocyte and endothelial responses to a variety of inflammatory stimuli. In contrast, in a meta-analysis by Miller et al., they demonstrated that lymphocyte counts were higher in patients with first-episode psychosis than in healthy controls, and these counts decreased in recurrent episodes (31). In chronic disease, elevated cortisol levels and chronic inflammatory processes cause apoptosis in lymphocytes as well as lymphopenia (32,33). Based on the abovementioned findings, it can be reported that PLR values in patients diagnosed with siFEP are lower than those in healthy individuals owing to the acute course of the disease. However, based on the results of the limited number of studies conducted to date, it is still too early to make a definitive judgment on how PLR levels are affected in siFEP and sfFEP.

In the present study, a moderately significant relationship was found between disease duration and monocyte levels in the siFEP group. Although inflammatory WBC parameters have been reported to be associated with various clinical features, particularly the disease prognosis, in various systemic diseases in the literature (10,11,34), the number of studies on psychotic disorders remains limited. Monocyte levels have been found to affect pulse pressure—an important cardiovascular risk marker—in patients with first-episode psychosis (20). Although there are also studies that found no association between disease duration and NLR levels in patients diagnosed with schizophrenia (18,19), no study has examined the association between monocyte levels and disease progression.

This study has some limitations. First, this was a retrospective study. All participants were retrospectively screened from hospital records. Second, based on the information obtained from the hospital records, the fact that the diagnosis of the first episode psychosis was made by different physicians is an important limitation of the study. Third, the relatively small number of people in the patient groups may have introduced a type 2 error. Fourth, patient groups included different types of psychotic conditions such as patients with psychotic disorders or bipolar disorder (manic episode with psychotic features). This is an important issue to keep in mind when interpreting the findings, as it can lead to diagnostic heterogeneity among patient groups. Fifth, this study included different type of substances which may also cause heterogeneity in inflammatory WBC parameters in siFEP group. In the study by Orum et al., it was shown that the levels of monocytes and MLR values increased while PLR values decreased in patients with cannabinoid use disorder compared to those with opioid use disorder (26). Sixth, smoking, which is thought to be an important factor affecting inflammatory WBC parameters (35), could not be controlled in this study. Finally, other limitation of the study is that lifestyle differences, dietary preferences, body mass index, and previous treatments with psychotropic drugs were not included in the evaluation.

In conclusion, although most studies in the relevant literature report that inflammatory WBC parameters are elevated in patients with psychiatric disorders compared with healthy controls, some studies report the opposite conclusion or find no significant difference. These results may be an indicator that there is not a unidirectional change in these parameters throughout the course of the illness. Based on this perspective, it can be reported that there is insufficient evidence to support the use of inflammatory WBC parameters in clinical practice for the differential diagnosis of siFEP and sfFEP. On the other hand, these parameters are of great importance in demonstrating the underlying inflammatory burden of both siFEP and sfFEP. Understanding the direction of changes in these parameters throughout the follow-up process from the onset of the illness will be helpful in elucidating the etiology of the disease. To understand the clinical importance of these parameters, studies with a longitudinal design, large sample size, and common inclusion criteria are needed.

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