








Assessment of the Inflammatory Markers in Patients with First-episode Psychosis: A Comparative Study

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ABSTRACT

Objective: Recently, the importance of inflammatory processes in the etiology of psychotic disorders has been increasingly emphasized. The manner in which the inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), are affected during psychotic disorders is unknown. This study aimed to compare the NLR, MLR, and PLR levels between patients with first-episode psychosis (FEP), patients with chronic psychotic disorder (CPD) and healthy controls (HC).

Methods: This study included 36 patients with FEP, 57 patients with CPD, and 93 HC. The Kruskal-Wallis test was used for intergroup comparisons of inflammatory markers. Linear regression analysis was used to examine the extent to which the NLR levels were affected by age.

Results: The NLR levels of patients diagnosed with CPD were higher than those diagnosed with FEP and HC. There was no difference between the NLR levels of patients with FEP and HC. Even after removing the age effect between the groups, there was a significant difference between the groups in terms of the NLR levels. However, there was no intergroup difference in the MLR and PLR levels.

Conclusion: Higher NLR levels in patients with CPD than in patients with FEP and HC indicated that the inflammatory process was increased in psychotic disorders during the prognosis of the chronic disease. To further understand the underlying causes of psychotic disorder, additional longitudinal studies are required to identify the manner, in which inflammatory processes are impacted by the disorder.

INTRODUCTION

The etiology of psychotic disorders is multifactorial, and these disorders are associated with general impairments in functionality and quality of life. Although the pertinent research in the literature has greatly expanded our knowledge of this disease, the precise mechanisms that contribute to the etiology of the disease remain unknown. Recent studies have suggested the importance of immunological and inflammatory mechanisms in the pathophysiology of the disease. The genes involved in the regulation of the immune system were suggested to be associated with psychosis.^[1] Relevant studies have reported that pro-

inflammatory cytokines,^[2-4] autoantibodies,^[5] and oxidative stress products^[6,7] were increased in patients with schizophrenia. Exposure to various infectious agents during the development of fetus, childhood, and adolescence is known to increase the risk of developing psychosis.^[8-10] In addition, improvements in psychopathology, as reported following the involvement of certain nonsteroidal anti-inflammatory drugs for treatment, emphasized the importance of inflammatory processes in psychosis.^[11]

It has been suggested that the number of neutrophils increases and the number of lymphocytes decreases in response to inflammatory conditions, such as stress;^[12] therefore, the neutrophil-lymphocyte ratio (NLR) was

found to be increased in patients with psychosis. Moreover, C-reactive protein - an important inflammatory marker - has been reported to be strongly correlated with NLR.^[13] Accordingly, the NLR has been considered an easily accessible, inexpensive, and practical parameter for detecting inflammation. To date, various studies have reported that the increased NLR levels are associated with poor prognosis in various systemic diseases, including cardiovascular diseases,^[14] malignancies,^[15-17] and pancreatitis.^[18] Moreover, the NLR levels were found to be increased in psychiatric disorders, such as schizophrenia and bipolar disorder.^[19-22] The NLR levels are increased in patients with schizophrenia during the episodes than in remission; however, the levels remain higher in patients with schizophrenia than in healthy controls (HC), even during the remission.^[20] Furthermore, most relevant studies suggested that the NLR levels cannot indicate the severity of the disease.^[22,23] Although higher NLR levels have been found in patients with first-episode psychosis (FEP) compared to HC in a limited number of studies,^[23-25] there are also studies that do not support this finding.^[26]

Monocyte-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) were defined as inflammatory markers in some systemic diseases.^[27,28] Studies on the association between these markers and psychiatric disorders are limited.^[20,25,29]

The manner in which these inflammatory markers change during the course of psychotic disorders is debatable. To the best of our knowledge, there is no study in the relevant literature investigating the difference in the NLR, MLR, and PLR levels between patients with FEP and those with chronic psychotic disorder (CPD). Understanding the manner in which inflammatory markers change during the illness process is important to get a better insight into the factors underlying the illness as well as to pave the way for its continuation. Accordingly, this study aimed to compare the values of accepted inflammatory markers, including NLR, MLR, and PLR, between patients with FEP, patients with CPD, and HC.

MATERIALS AND METHODS

The present study was designed as a retrospective, descriptive, and observational study. This study included 93 patients with psychotic disorder, including 36 with FEP and 57 with CPD, who were hospitalized at the Department of Psychiatry of the Maltepe University Faculty of Medicine between 2013 and 2022. HC (n=93) were recruited sequentially from individuals who presented to the Department of Family Medicine, Maltepe University Faculty of Medicine for health screening between 2020 and 2022, had no history of any psychiatric disease, and were matched with the patient group by gender. The first psychotic episode was defined as the Diagnostic and Statistical Manual of Mental Disorders-5-based diagnosis of psychotic disorders (schizophrenia, schizoaffective disorder,

and delusional disorder) in patients who presented to a health-care institution following the manifestation of active psychotic symptoms started for the 1st time within the past 1 year. The study was approved by the Clinical Study Ethics Committee of Maltepe University Faculty of Medicine (Number: 2022/900/02 Date: January 19, 2022).

Participants

The included participants were aged 18–65 years. All patient files were retrospectively reviewed. The blood samples of the patients who were admitted to the psychiatry ward for a psychotic episode were collected within the first 24 h of admission. Patients with a history of alcohol or substance use, hypertension, diabetes mellitus, heart disease, autoimmune or inflammatory disease, cancer, active infection, and the use of medications that can probably impair the immune system were excluded from the study. In the healthy control group, individuals who were suspected of having an acute or lifelong psychiatric disorder based on a routine consultation with their general practitioner were excluded from the study.

Statistical Analyses

The IBM Statistical Package for the Social Sciences Statistics 23.0 (Chicago IL, USA) was used for statistical analysis. The Chi-square test was used to compare the categorical variables. The hypothesis of normal distribution was investigated using the Kolmogorov-Smirnov test for the continuous data. Regarding the normally distributed data, ANOVA was used for multigroup comparisons, and the post hoc Tukey's test was performed. The Kruskal-Wallis test was used for the multigroup comparisons that did not satisfy the normal distribution hypothesis, and pairwise group comparisons were performed using pairwise analysis. Linear regression analysis was used to understand the extent to which the NLR values were affected by age. A $p < 0.05$ was considered statistically significant, and the mean \pm standard deviation value was provided for all test results.

RESULTS

An intergroup comparison of demographic and clinical characteristics is shown in Table 1. The mean age of patients with FEP was significantly lower than that of those diagnosed with CPD and HC ($p < 0.001$ and $p = 0.001$, respectively).

The NLR levels were significantly higher in patients with CPD than in patients with FEP and HC ($p = 0.20$ and $p = 0.21$, respectively). There was no significant difference in the NLR levels between patients with FEP and HC ($p = 0.61$). An intergroup comparison of the laboratory results is shown in Table 2. The intergroup difference in terms of the NLR levels remained ($R = 0.213$, $F = 4.341$, $p = 0.015$) significant even after the removal of the age effect between the groups. There was no intergroup difference in the MLR and PLR levels ($p = 0.319$ and $p = 0.787$, respectively).

Table 1. Comparison of demographic and clinical characteristics among study groups

	FEP (n=36)	CPD (n=57)	HC (n=93)	Test statistic F/ χ^2 /t	p-value
Age	28.33 (9.23)	39.51 (14.07)	36.43 (9.80)	11.300 FEP<HC p=0.001 FEP<CPD p<0.001	<0.001
Sex (N, %)					
Female	18 (50.0)	28 (49.1)	46 (49.5)	0.007	0.997
Male	18 (50.0)	29 (50.9)	47 (50.5)		
Duration of illness (month)	5.61 (4.80)	148.21 (109.27)	-	-9.838	<0.001
Schizophrenia	34 (%94.4)	49 (%86.0)	-	1.974	0.373
Schizoaffective disorder	1 (%2.8)	6 (%10.5)			
Delusional disorder	1 (%2.8)	2 (%3.5)			

FEP: First-episode psychosis; CPD: chronic psychotic disorder; HC: Healthy control.

Table 2. Comparison of laboratory results among study groups

	FEP (n=36)	CPD (n=57)	HC (n=93)	Test statistic F/ χ^2 /t	p-value
Leukocyte	7067.11 (1884.82)	7758.82 (2487.25)	7299.14 (1761.37)	2.050	0.359
Neutrophil	3928.11 (1540.33)	4584.46 (1841.10)	4026.02 (1195.58)	4.500	0.105
Lymphocyte	2390.64 (653.97)	2390.44 (846.63)	2440.43 (654.97)	0.402	0.818
Monocyte	570.06 (215.89)	606.25 (204.92)	606.77 (200.34)	1.992	0.369
Platelet	235302.78 (48406.76)	236912.28 (52741.81)	247892.47 (58090.91)	2.202	0.332
NLR	1.78 (0.87)	2.06 (0.92)	1.72 (0.58)	7.249	0.027
					FEP<CPD p=0.021 HC<CPD p=0.020
MLR	0.25 (0.10)	0.26 (0.08)	0.26 (0.07)	2.286	0.319
PLR	105.66 (37.89)	110.84 (43.95)	107.33 (33.63)	0.479	0.787

FEP: First-episode psychosis; CPD: Chronic psychotic disorder; HC: Healthy control; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

DISCUSSION

According to the current study, NLR levels of patients with CPD were higher than those of patients with FEP and HC, but there was no significant difference in the NLR levels between patients with FEP and HC. To the best of our knowledge, no study in the relevant literature has compared patients with FEP and those with CPD in terms of NLR levels. In a conducted meta-analysis, it has been demonstrated that lymphocyte levels are elevated in patients with FEP compared to HC and that lymphocyte counts decrease with the recurrent episodes.^[30] It is suggested that the elevation of cortisol levels during the chronic disease process contributes to this situation.^[31] Furthermore, conditions causing chronic inflammation are believed to lead to lymphopenia through apoptosis in lymphocytes,^[32] potentially resulting in an increase in NLR

levels. Although it is suggested that neurodevelopmental abnormalities play a major role in psychotic disorders, various factors, such as the early age of onset and increased number of episodes, may adversely affect the prognosis.^[33] This may pave the way for a strong manifestation of the inflammatory burden that is not clearly seen during the first episode of the illness. On the other hand, it is known that the course of psychotic disorder is not the same for every individual, with approximately one-third of patients experiencing episodes and deriving less benefit from medication, whereas one-third tend to have a more favorable course.^[34] Considering that individuals diagnosed with CPD are hospitalized due to the recurrent psychotic exacerbations, it can be thought that their illness progresses are more unfavorable compared to patients with FEP. This can be another factor explaining higher levels of inflammatory markers.

Furthermore, consistent with the results of the previous studies,^[20-22,29] the NLR levels of patients with CPD were higher than those of HCs in the present study. In a recent study conducted by Zhu et al., with a large sample size, it was observed that individuals with schizophrenia exhibited elevated NLR and MLR levels in comparison to the HC.^[29] This finding suggests that inflammatory mechanisms actively contribute to psychotic disorders. To the best of our knowledge, there is no research in the literature that indicates the opposite.

The lack of significant difference in NLR levels between patients with FEP and HC in our study is consistent with the findings of a study conducted by Garcia-Rizo et al. in 2019, which included 75 first-episode non-affective psychosis patients and 80 HC.^[26] In contrast, some studies suggested that the NLR levels are higher in patients with FEP than in HCs.^[23-25] The fact that the inflammatory processes are not visible during the early stages of the disease may have contributed to the current study's finding that the inflammatory markers did not differ from HC at these stages.

In the present study, there was no difference between the patient groups and HC in terms of the MLR and PLR levels. This finding contradicts the study by Özdin and Böke, where they found elevated MLR and PLR levels in individuals with schizophrenia during both relapse and remission periods compared to HC.^[20] In a recent study, individuals with schizophrenia were found to have higher MLR levels compared to HC, whereas PLR levels did not show significant differences between the groups.^[29] In a study on patients experiencing their first psychotic episode, MLR and PLR levels were found to be higher compared to HCs.^[25] To establish MLR and PLR levels as indicators of inflammation in psychotic disorders, it is essential to conduct studies with large sample sizes.

An important limitation of the current study's retrospective design is that it was impossible to investigate the link between the severity of the disease and the NLR levels of patients with psychotic disorders. To date, to the best of our knowledge, no relevant studies have reported a correlation between the disease severity and the NLR levels.^[21-23] The inclusion of individuals diagnosed with schizoaffective disorder and delusional disorder in the study, might have contributed to the heterogeneity of the group. According to a recent study, patients with schizophrenia had considerably higher NLR and MLR levels than those with schizoaffective disorder.^[35] In addition, the relatively small number of patients with FEP is a factor that complicates the interpretation of the patient group. The extent to which a peripheral indicator reflects central influence or the manner in which it can affect the prognosis of psychotic disorders remains controversial. In conclusion, there may be a bidirectional relationship between the central and peripheral systems given that peripheral immune changes can modulate brain functions.^[36]

In our study, the elevated NLR levels in patients with CPD compared to those of patients with FEP and HC highlight a significant finding that emphasizes the increase in inflam-

matory processes in psychotic disorders as the duration of the illness extends. Further longitudinal studies with larger sample sizes will be beneficial for examining how inflammatory processes are affected in the early stages and chronic course of psychotic disorders. Hence, it could enhance our understanding of the illness and aid in preventing factors contributing to the chronicity of the illness.

Ethics Committee Approval

This study approved by the Maltepe University Faculty of Medicine Clinical Research Ethics Committee (Date: 19.01.2022, Decision No: 2022/900/02).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: H.E.A.Ç., A.E.B.T., B.K.K., B.Ç., E.Ç., Ş.D., S.K.; Design: H.E.A.Ç., A.E.B.T., B.K.K.; Supervision: H.E.A.Ç., A.E.B.T., B.K.K., B.Ç., E.Ç., Ş.D., S.K.; Fundings: H.E.A.Ç., A.E.B.T., B.K.K.; Materials: H.E.A.Ç., A.E.B.T., B.K.K., B.Ç., E.Ç., Ş.D., S.K.; Data: H.E.A.Ç., A.E.B.T., B.K.K., E.Ç.; Analysis: H.E.A.Ç., A.E.B.T., B.K.K.; Literature search: H.E.A.Ç., A.E.B.T., B.K.K.; Writing: H.E.A.Ç., A.E.B.T., B.K.K., B.Ç., E.Ç., Ş.D., S.K.; Critical revision: H.E.A.Ç., A.E.B.T., B.K.K., B.Ç., E.Ç., Ş.D., S.K.

Conflict of Interest

None declared.

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İlk Epizod Psikoz Hastalarında İnflamasyon Belirteçlerinin Deęerlendirilmesi: Karşılaştırmalı Çalışma

Amaç: Son yıllarda inflamatuvar süreçlerin psikotik bozuklukların etiyolojisindeki önemine yapılan vurgu giderek artmaktadır. İnflamatuvar belirteçlerden olan nötrofil lenfosit oranı (NLR), monosit lenfosit oranı (MLR) ve platelet lenfosit oranının (PLR) psikotik bozuklukta hastalık süresince ne yönde etkilendięi net olarak bilinmemektedir. Bu çalışmanın amacı, ilk atak psikoz hastalarının, kronik psikotik hastaların ve sağlıklı kontrollerin NLR, MLR ve PLR düzeylerinin karşılaştırılmasıdır.

Gereç ve Yöntem: Çalışmaya ilk kez psikotik atak geçiren 36 birey, kronik psikotik bozukluğu olan 57 birey ve 93 sağlıklı kontrol dahil edildi. Gruplar arasında inflamatuvar belirteçlerin karşılaştırmasında Kruskal-Wallis Testi kullanıldı, ikili grup karşılaştırmaları Pairwise Analizi ile yapıldı. NLR değerlerinin yaştan etkilenme düzeyini belirlemek amacıyla lineer regresyon analizi uygulandı.

Bulgular: Kronik psikotik bozukluk tanılı bireylerin NLR düzeylerinin ilk atak psikoz tanılı bireylerden ve sağlıklı kontrollerden yüksek olduğu saptandı. İlk atak psikoz tanılı bireylerin NLR düzeyleri sağlıklı kontrollerden farklılık göstermedi. Gruplar arasında yaşın etkisi ortadan kaldırıldığında NLR düzeyleri açısından gruplar arasındaki anlamlı farklılık korundu. MLR ve PLR düzeyleri gruplar arasında farklılık göstermedi.

Sonuç: Kronik psikotik bozukluk tanılı bireylerde ilk atak psikoz tanılı bireylere ve sağlıklı kontrollere göre NLR düzeylerinin yüksek saptanması, psikotik bozuklukta inflamatuvar sürecin kronik süreçte arttığını göstermektedir. Uzunlamasına yapılacak çalışmalarla psikotik bozuklukta inflamatuvar süreçlerin nasıl etkilendiğinin incelenmesi, hastalığa katkı sağlayan faktörleri anlamak açısından faydalı olacaktır.

Anahtar Sözcükler: İlk atak psikoz; inflamasyon; nötrofil lenfosit oranı; monosit lenfosit oranı; platelet lenfosit oranı; psikoz.