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ORIGINAL ARTICLE

Comparative Study of Inflammatory Markers in Schizophrenia, First-Episode Psychosis, and Bipolar Disorder

Duygudurumla İlişkili ve Duygudurumla İlişkili Olmayan Psikozlarda Nötrofil-Lenfosit Oranının (NLR) Karşılaştırılması

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ABSTRACT

Objective: Inflammatory markers, particularly an elevated NLR level, are recognized indicators of systemic inflammation and have been proposed as practical tools for understanding psychosis. The primary objective of this study is to investigate blood parameters, including neutrophil, lymphocyte, and monocyte counts, as well as their derived ratios (NLR, MLR, PLR), in both affective and non-affective psychosis. This research aims to shed light on the potential role of these biomarkers in elucidating the pathophysiological underpinnings of psychosis, offering insights that could inform diagnostic and therapeutic approaches.

Materials and Methods: This retrospective case-control study focused on patients diagnosed with schizophrenia (SCH), first-episode psychosis (FEP), and bipolar disorder (BD). Digital medical records spanning from 2016 to 2021 were retrospectively analyzed. A total of 437 patients were included in the study, categorized into three groups: schizophrenia (n = 199), first-episode psychosis (n = 127), and bipolar disorder (n = 111), alongside a healthy control (HC) group (n = 200) composed of individuals without prior psychiatric disorders.

Results: In this study, we observed significant increases in neutrophil and lymphocyte counts in schizophrenia (SCH) and bipolar disorder (BP) patients. Conversely, monocyte counts were significantly decreased in SCH patients compared to the control group. Notably, the neutrophil-to-lymphocyte ratio (NLR) was significantly elevated in first-episode psychosis (FEP) patients compared to controls. Furthermore, no statistically significant differences were found in the monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR) across the study groups ($p > 0.05$ for each comparison).

Conclusion: Our study highlights elevated neutrophil-to-lymphocyte ratio (NLR) in first-episode psychosis (FEP) patients, suggesting NLR's potential in distinguishing acute from chronic phases of psychotic disorders. However, we found no significant NLR differences between bipolar disorder (BP) patients and controls, contrary to some previous studies. Further prospective research is needed to understand the role of inflammatory markers in psychiatric disorders fully.

Keywords: Psychosis, Bipolar, NLR, MLR, PLR

ÖZ

Amaç: İltihaplı belirteçler, özellikle yükselmiş NLR seviyesi, sistemik iltihabın bilinen göstergeleridir ve psikozu anlamak için pratik araçlar olarak önerilmiştir. Bu çalışmanın birincil amacı, hem duygusal hem de duygusal olmayan psikozda nötrofil, lenfosit ve monosit sayıları ve bunların türetilmiş oranları (NLR, MLR, PLR) dahil olmak üzere kan parametrelerini araştırmaktır. Bu araştırma, psikozun patofizyolojik temellerini aydınlatmada bu biyobelirteçlerin potansiyel rolüne ışık tutmayı ve tanı ve tedavi yaklaşımlarını bilgilendirebilecek içgörüler sunmayı amaçlamaktadır.
Materyaller ve Yöntemler: Bu retrospektif vaka kontrol çalışması, şizofreni (SCH), ilk epizod psikoz (FEP) ve bipolar bozukluk (BD) tanısı konmuş hastalara odaklanmıştır. 2016'dan 2021'e kadar olan dijital tıbbi kayıtlar retrospektif olarak analiz edildi. Çalışmaya toplam 437 hasta dahil edildi ve üç gruba ayrıldı: şizofreni (n = 199), ilk atak psikoz (n = 127) ve bipolar bozukluk (n = 111) ve daha önce psikiyatrik bozukluğu olmayan bireylerden oluşan sağlıklı bir kontrol (HC) grubu (n = 200).
Sonuçlar: Bu çalışmada, şizofreni (SCH) ve bipolar bozukluk (BP) hastalarında nötrofil ve lenfosit sayılarında önemli artışlar gözlemledik. Tersine, monosit sayıları SCH hastalarında kontrol grubuna kıyasla önemli ölçüde azaldı. Özellikle, nötrofil-lenfosit oranı (NLR), ilk atak psikoz (FEP) hastalarında kontrollere kıyasla önemli ölçüde yüksekti. Ayrıca, çalışma grupları arasında monosit-lenfosit oranı (MLR) ve trombosit-lenfosit oranı (PLR) açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (her karşılaştırma için $p > 0,05$).
Sonuç: Çalışmamız, ilk epizod psikoz (FEP) hastalarında yüksek nötrofil-lenfosit oranına (NLR) dikkat çekerek, NLR'nin psikotik bozuklukların akut ve kronik evrelerini ayırt etme potansiyeli olduğunu göstermektedir. Ancak, bazı önceki çalışmaların aksine, bipolar bozukluk (BP) hastaları ve kontroller arasında anlamlı bir NLR farkı bulamadık. Psikiyatrik bozukluklarda inflamasyon belirteçlerinin rolünü tam olarak anlamak için daha fazla prospektif araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Psikoz, Bipolar, NLR, MLR, PLR

Introduction

Schizophrenia is a chronic debilitating mental illness characterized by positive, negative, and cognitive symptoms. Although a growing number of evidence has been documented to understand better the pathophysiology of schizophrenia, current hypotheses are primarily dependent upon the neurotransmission of serotonin, dopamine, and glutamate. The pathophysiological mechanism has not yet been established. Dysregulation in the immune system seems to be an alternative hypothesis in schizophrenia. According to data, proinflammatory cytokines are

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increased in both acute and chronic phases of schizophrenia(1,2).Inflammation is considered to play an important role in schizophrenia, and inflammatory biomarkers, in particular, could contribute to improving the effectiveness of diagnosis and treatment in clinical practice(3).

The neutrophil-to-lymphocyte ratio (NLR) is known to be a systemic inflammation marker correlated with increased levels of proinflammatory cytokines. NLR is also considered a measurable and easily accessible biomarker of the balance between the innate and adaptive immune systems. Elevated NLR levels indicate systemic inflammation and are proposed as a valuable tool for guiding treatment strategies(4). Examining NLR values in psychosis, particularly during first-episode psychosis, provides insights into how the immune system responds at different stages of illness. Research consistently demonstrates higher NLR levels in patients with schizophrenia compared to healthy controls(5). Similarly, first-episode psychosis exhibits elevated NLR levels compared to controls, highlighting its potential diagnostic and prognostic significance in psychiatric disorders(6).

In addition to that, studies have explored correlations between schizophrenia and the platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR(7). Recent findings indicates that elevated NLR and MLR levels in patients with schizophrenia compared to healthy controls. On the other hand regarding first-episode psychosis have varied across studies(8,9). The assessment of NLR, PLR, and MLR is straightforward, quick, and cost-effective, involving minimal patient discomfort with peripheral blood sampling)10). Establishing a clear correlation between these biomarkers and psychiatric disorders holds promise for improving diagnostic accuracy and tailoring treatment approaches in schizophrenia. While NLR, PLR, and MLR are established as prognostic biomarkers in various medical conditions such as malignancies (11,12) cardiovascular diseases(13,14) systemic diseases and even their possible complication(15) their validation and consistency in psychiatric disorders remain active areas of research and debate.

In this study, we aimed to contribute additional data to enhance understanding, given the existing limitations and inconsistencies in the literature. We evaluated NLR, MLR, and PLR in psychosis by categorizing patients into three groups: first-episode psychosis (FEP), schizophrenia (SCH), and bipolar disorder with psychotic features (BP). The main aim of comparing these three groups is to demonstrate how inflammatory biomarkers change in different patient groups exhibiting psychotic features. In this study, besides determining the differences in inflammatory biomarkers among the groups, it will also be explored whether NLR, MLR, and PLR variables can be used to diagnose and manage psychotic disorders in daily practice.

Methods and Materials

Participants and Study Design

This retrospective case-control study analyzed digital medical records from 2016 to 2020 of 437 hospitalized patients diagnosed with schizophrenia (SCH), first-episode psychosis (FEP), and bipolar disorder (BP). Patients were diagnosed using a semi-structured clinical interview (SCID) based on DSM-V-TR criteria, focusing on those exhibiting psychotic features. Exclusion criteria were applied using the hospital's digital infrastructure, and patients' histories were evaluated in detail. Participants with chronic infections, those using immunosuppressive drugs, and those diagnosed with chronic metabolic, rheumatologic, or inflammatory diseases were excluded from the study. The study included 637 participants, comprising 437 patients and 200 healthy controls. When selecting the healthy control group, records were evaluated in detail from the digital system, and only individuals who sought clinical consultation for job applications were chosen. These participants were selected as the control group based on the criteria that they had no psychiatric history in their medical records and that there were no issues with their inclusion according to the exclusion criteria (n:200). The first-episode psychosis group consisted of patients without previous psychiatric history, admitted and treated following their initial psychotic episode. Ethics approval was obtained from the Gulhane Training and Research Hospital ethics committee(decision number 2020/499, dated October 17, 2020).

Demographic Data and Substance Use

Gender distribution across the study groups revealed that the control group comprised 200 males exclusively. In contrast, the first-episode psychosis (FEP), schizophrenia (SCH), and bipolar disorder (BP) groups showed mixed gender ratios (FEP: 101 males, 26 females; SCH: 169 males, 31 females; BP: 69 males, 41 females). Substance use patterns varied among groups, with FEP showing 80.2% without substance use

and 19.8% with, SCH with 75.4% without and 24.6% with, and BP with 86.5% without and 13.5% with substance use. Educational backgrounds were predominantly high school for FEP (67.7%), SCH (52.0%), and BP (42.3%), followed by university education (FEP: 7.1%, SCH: 5.0%, BP: 9.9%), with smaller proportions having unknown or lower educational attainment levels.

Blood Sample

According to the digital records, blood samples were collected from patients in the early morning (8 a.m.) following their admission to the clinic. Complete blood count (CBC) results were retrospectively obtained, and the NLR, MLR, and PLR were calculated for each patient. These parameters were then compared with those of the healthy control group. Advanced analytical techniques were employed to evaluate the results derived from the CBC data.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS software, version 20.0. The normality of the data distribution was assessed using the Shapiro-Wilk test. The Mann-Whitney U test and the Kruskal-Wallis test were utilized for continuous variables that did not conform to a normal distribution. Categorical variables were analyzed using Chi-square tests. A significance level of $p < 0.05$ was adopted to determine statistical significance.

Table 1. Properties and laboratory parameters of the study population¥, %(n)

Variable	Healthy Controls	FEP	SCH	BP
Age	19.33 ± 1.07 (18.00-21.00)	21.50 ± 2.40 (18.00-27.00)	22.74 ± 2.51 (18.00-27.00)	23.05 ± 2.35 (18.00-27.00)
Platelet Count	254.44 ± 49.97 (69.00-390.00)	254.28 ± 63.53 (132.00-494.00)	243.08 ± 71.20 (139.00-873.00)	262.06 ± 61.98 (131.00-459.00)
Neutrophil Count	1145.76 ± 1611.24 (328.00-6700.00)	1628.12 ± 2200.28 (351.00-8280.00)	1822.47 ± 2257.01 (364.00-8470.00)	2359.32 ± 2420.39 (347.00-7810.00)
Lymphocyte Count	302.34 ± 113.40 (23.00-576.00)	533.39 ± 866.47 (8.70-5050.00)	696.35 ± 1128.86 (13.00-6650.00)	1166.66 ± 1438.40 (26.00-5020.00)
Monocyte Count	73.10 ± 30.31 (6.00-151.00)	70.67 ± 37.15 (5.70-166.00)	62.35 ± 35.33 (5.20-156.00)	62.36 ± 75.57 (4.00-701.00)

Table 2. Comparison of NLR between control, FEP, SCH and BP group %(n)

GROUP	NLR Mean Ratio (Range)	MLR Mean Ratio (Range)	PLR Mean Ratio (Range)
Healthy Controls	5.26 (0.15-10.37)	0.41 (0.01-2.42)	1.47 (0.34-3.60)
FEP	25.62 (0.33-51.91)	0.31 (0.01-0.63)	1.85 (0.05-6.35)
SCH	16.11 (0.19-32.03)	0.37 (0.01-1.36)	1.67 (0.01-8.32)
BP	10.19 (0.14-19.21)	0.36 (0.01-1.63)	1.57 (0.01-7.27)

Results

There were no differences in mean age between patients with schizophrenia (SCH) (22.74) and bipolar disorder (BP) (23.05). The healthy control group (19.33) had the lowest average age, and patients with FEP (21.50) were significantly younger compared to both SCH and BP patients ($p<0.05$ for each comparison). Regarding gender, first-episode psychosis (FEP) and schizophrenia (SCH) patients showed similar gender distributions. However, healthy controls included more males, whereas patients with bipolar disorder (BD) included more females compared to the other groups. Schizophrenia (SCH) patients exhibited lower mean platelet counts (243.08) compared to the other groups. In contrast, platelet counts did not differ significantly between bipolar disorder (BP) (262.06) and first-episode psychosis (FEP) (254.28) patients (see details in Table 1).

Neutrophil counts were significantly increased in the SCH and BP groups compared to the control group. Additionally, neutrophil counts in the BP group were higher compared to the FEP group. Lymphocyte counts were significantly increased in the BP and SCH groups compared to the control group. Monocyte counts were significantly decreased in SCH groups compared to the control group (see detail in Table 1). The neutrophil-to-lymphocyte ratio (NLR) was significantly increased in FEP groups compared to control groups. The monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR) did not show statistically significant differences among the study groups (see details in Table -2, $p>0.05$ for each comparison).

Discussion

In this study, neutrophil and lymphocyte counts were significantly increased in SCH and BP. On the other hand, monocyte counts were significantly decreased

in SCH groups compared to the control group. The most crucial finding in this study is that NLR significantly increased in FEP groups compared to the control group. Many studies have found evidence that NLR levels increase in schizophrenia patients. A meta-analysis of over 800 schizophrenia patients found a clear link between higher NLR levels and both schizophrenia and first-episode psychosis(5). Further research supports these findings(16). However, when the findings obtained in our study were evaluated, it was shown that there was no significant difference in NLR levels in schizophrenia patients. Although it is not entirely possible to explain the reason for this, it could be due to the average age of 22.74 of the schizophrenia patients included in our study and the relatively shorter duration of the disease. It is well known that chronic stress triggers inflammation. In psychiatric disorders like schizophrenia, which have high-stress levels, inflammation increases with the prolongation of the disease duration or the increase in attack frequency(17). Additionally, the effect of antipsychotics used in treatment may have caused the observed differences among these studies. It has long been known that antipsychotics have immunomodulatory and anti-inflammatory effects(18).

The evaluation of NLR in patients with FEP (16,19) is one of the important findings in our study. In this present study, we have found that our results effectively distinguish between the acute and chronic phases of the disease. We were able to gain insights into how inflammation varies across different psychiatric stages. According to our results, elevated NLR is observed in FEP patients but not in those with chronic schizophrenia, suggesting that NLR may vary between the acute and chronic phases. A recent study supports this finding by highlighting NLR's potential to predict clinical symptom improvement(20). However, another study found that using inflammatory blood cell ratios during remission to predict relapse in schizophrenia over three years had limited effectiveness(21). Future research should address potential confounding factors to improve clinical diagnostic and therapeutic strategies

While many studies have investigated the NLR in schizophrenia and FEP, research on bipolar disorder remains limited (22,23). Contrary to previous findings(7) did not find a significant correlation in NLR between bipolar patients and control groups, contrary to previous findings. Consistent with previous studies, we observed no correlation between PLR and MLR in our patient cohort. However, our results differ from most studies in that they show increased neutrophil and lymphocyte counts in bipolar disorder patients compared to controls(7). This finding suggests that inflammatory markers in bipolar disorder require further investigation to understand their role and clinical significance better.

The inconsistency in findings across publications may be attributed to variations in study design, comorbid pathologies, or other unexplored confounding factors. Although changes in inflammatory biomarker levels in psychiatric disorders have been documented, the underlying mechanisms remain poorly understood. Our study is significant for evaluating diverse patient groups within the psychotic spectrum and demonstrating the lack of significant differences between NLR and other blood parameters. Notably, our study's large sample size enhances its robustness compared to previous research. Nevertheless, the evidence suggests that NLR alone is insufficient for diagnostic or treatment monitoring purposes. Further research is needed to clarify the role of NLR and other inflammatory markers in psychiatric disorders.

Limitation

One of the most critical limitations of this study is its retrospective design. According to prospective studies, the inability to observe the process and how inflammation markers change according to the response to treatment can be defined as a critical deficiency. Another significant limitation is that limited information was obtained about the scales used to evaluate schizophrenia findings and whether the patient had an active infection at that time due to the hospital's digital record system not being well maintained.

Data Availability

All of the data related to the study are recorded in the hospital's digital system. All of the data has been transferred from this system to an excel file for study purposes. There is no ethical issue to access our data.

Role of Funding Source

No funding was received for this study.

Declaration of Interest

There is no conflict of interest between the authors.

Credit authorship contribution statement

Beyazit Garip: Conceptualization, Data curation, Funding acquisition, Methodology, Writing - original

draft, Writing - review & editing.

Öykü İnanç: Conceptualization, Formal analysis, Methodology, Project administration, Writing - original draft, Writing - review & editing.

Şükran Tekin : Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing - original draft.

Begüm Aritan : Data curation, Project administration, Writing - original draft. Writing - review & editing

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