Received: 29 July 2023 | **Accepted:** 29 Sep 2023 **Genel Tıp Derg. Volume** 33/**Issue** 6 (December), 763-767
DOI: 10.54005/geneltip.1328023

ORIGINAL ARTICLE

Longitudinal Assessment of Alterations in Peripheral Inflammatory Markers Over a Hospitalization Period in Patients with Schizophrenia

Şizofreni Hastalarında Hastaneye Yatış Sürecinde Periferik İnflamatuvar Belirteçlerdeki Değişimlerin Boylamsal Değerlendirmesi

[1]Halil İbrahim Öztürk, [2]İmren Kurt, [2]Oya Güçlü, [2]Süleyman Dönmezler

[1]Sanko University, School of Medicine; Department of Psychiatry; Gaziantep, Türkiye
[2]Başakşehir Çam and Sakura City Hospital; Department of Psychiatry; Istanbul; Türkiye

Correspondence

Halil İbrahim Öztürk,Sanko University, School of Medicine; Department of Psychiatry; Gazimuhtar Paşa Avenue No:36 – 27090, Şehitkamil / Gaziantep / Türkiye

E-Mail: dr.h.i.ozturk@hotmail.com

How to cite ?

Ozturk Hİ, Kurt İ, Güçlü O, Dönmezler S. Longitudinal Assessment of Alterations in Peripheral Inflammatory Markers Over a Hospitalization Period in Patients with Schizophrenia. Genel Tıp Derg. 2023;33(6):763-7.

ABSTRACT

Objective: To assess the effects of regular medication administration, diet, sleep, and physical activity provided by hospital care on inflammatory markers in schizophrenia patients. The primary hypothesis of our study is that the assembly of various factors will reduce low-grade inflammation in a short period.
Materials and Methods: This retrospective longitudinal study involved 106 patients diagnosed with schizophrenia who met the exclusion and inclusion criteria. Inflammatory markers such as neutrophil-to-lymphocyte ratios (NLR), monocyte-to-lymphocyte ratios (MLR), platelet-to-lymphocyte ratios (PLR), C-reactive protein-to-albumin ratios (CAR), and systemic immune inflammation indices (SII) were calculated at the time of hospital admission and after three weeks.
Results: The mean age of the participants was 39.0±13.1 years and the majority were male (n: 75). Reductions were observed in all inflammatory markers after three weeks. The CRP decreased from a median value of 2.6 (interquartile range (IQR): 1.1-5.3) to 1.90 (IQR: 0.85-3.30) (p=0.001, effect size=0.375). The CAR changed from 0.064 (IQR: 0.026-0.115) to 0.043 (IQR: 0.017-0.077) (p=0.005, effect size=0.371). The NLR demonstrated a significant reduction from 2.31 (IQR: 1.73-3.24) to 1.73 (IQR: 1.28-2.27) (p<0.001, effect size=0.647). The SII decreased from 634 (IQR: 425-870) to 470 (IQR: 321-645) (p<0.001, effect size=0.577). The PLR went down from 9.85 (IQR: 7.4-12.7) to 8.21 (IQR: 6.22-10.3) (p<0.001, effect size=0.547). Lastly, the MLR dropped from 0.297 (IQR: 0.221-0.378) to 0.258 (IQR: 0.195-0.319) (p<0.001, effect size=0.522).
Conclusion: This study underscores the influence of regular antipsychotic treatment and hospital care in reducing inflammation markers like NLR, MLR, PLR, SII, and CAR in schizophrenia patients. Future studies should explore the potential of markers like CAR and SII in detecting low-grade inflammation, and further probe into the role of sleep, nutrition, and physical activity, emphasising the paramount role of comprehensive hospital care.

Key words: Schizophrenia, low-grade inflammation, antipsychotics, systemic immune inflammation index (SII), C-reactive protein-to-albumin ratio (CAR)

ÖZ

Amaç: Çalışmanın amacı, şizofreni hastalarında hastane bakımı ile sağlanan düzenli ilaç uygulaması, diyet, uyku ve fiziksel aktivitenin inflamatuar belirteçler üzerindeki etkilerini değerlendirmektir. Çalışmamızın temel hipotezi, hastane bakımının düşük dereceli inflamasyonu kısa sürede azaltacağıdır.
Gereç ve Yöntemler: Retrospektif boylamsal dizayndaki çalışmaya, çalışma kriterlerini karşılayan, şizofreni tanılı toplam 106 hasta dahil edildi. Nötrofil-lenfosit oranları (NLO), monosit-lenfosit oranları (MLO), trombosit-lenfosit oranları (TLO), C-reaktif protein-albumin oranları (CAO) ve sistemik immün inflamasyon indeksleri (Sİİ) gibi inflamatuar belirteçler hastaneye kabul sırasında ve üç hafta sonra hesaplanmıştır.
Bulgular: Katılımcıların yaş ortalaması 39,0±13,1 olup büyük çoğunluğu erkekti (n:75). Tüm inflamatuar belirteçlerde üç hafta sonra düşüş olduğu gözlendi. CRP, ortanca değeri 2,6'dan (çeyrekler arası aralık: 1,1-5,3) 1,90'a (çeyrekler arası aralık: 0,85-3,30) (p=0,001, etki büyüklüğü=0,375), CAO, 0,064'ten (çeyrekler arası aralık: 0,026-0,115) 0,043'e (çeyrekler arası aralık: 0,017-0,077) (p=0,005, etki büyüklüğü=0,371), NLO, 2,31'den (çeyrekler arası aralık: 1,73-3,24) 1,73'e (çeyrekler arası aralık: 1,28-2,27) (p<0,001, etki büyüklüğü=0,647), Sİİ, 634'ten (çeyrekler arası aralık: 425-870) 470'e (çeyrekler arası aralık: 321-645) (p<0,001, etki büyüklüğü=0,577), TLO, 9,85'ten (çeyrekler arası aralık: 7,4-12,7) 8,21'e (çeyrekler arası aralık: 6,22-10,3) (p<0,001, etki büyüklüğü=0,547) ve son olarak MLO, 0,297'den (çeyrekler arası aralık: 0,221-0,378) 0,258'e (çeyrekler arası aralık: 0,195-0,319) (p<0,001, etki büyüklüğü=0,522) düşmüş olduğu bulundu.
Sonuç: Bu çalışma, şizofreni hastalarında düzenli antipsikotik tedavi ve hastane bakımının NLO, MLO, TLO, Sİİ ve CAR gibi inflamasyon belirteçlerini azaltmadaki etkisinin altını çizmektedir. Gelecekteki çalışmalar, CAR ve Sİİ gibi belirteçlerin düşük dereceli inflamasyonu tespit etme potansiyelini araştırmalı ve kapsamlı hastane bakımının önemli rollerinden düzenli uyku, beslenme ve fiziksel aktivitenin rolleri daha fazla araştırmalıdır.

Anahtar kelimeler: şizofreni, düşük dereceli inflamasyon, antipsikotikler, sistemik immün inflamasyon indeksi (Sİİ), C-reaktif protein-albumin oranı (CAO)

Introduction

Schizophrenia, a psychiatric disorder of a chronic nature, is characterized by heterogeneous clinical manifestations, varied treatment responses, and diverse prognoses. Despite extensive investigations, its aetiology remains enigmatic. However, emerging consensus posits a nexus between gene-environment interactions, and the onset of schizophrenia (1). Of particular interest is the postulated contribution of inflammatory processes, and the immunological system to the pathogenesis and progression of schizophrenia. Contemporary research continues to substantiate this proposition, revealing significant aberrations

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
Complaints: geneltip@selcuk.edu.tr

Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
https://yayinevi.selcuk.edu.tr/

across the immunological system's components - encompassing both innate and adaptive, cellular, and humoral strata (2). For instance, there is credible evidence demonstrating consistent elevations in C-reactive protein (CRP), dysregulations in cytokine, and chemokine levels, elevated neutrophil counts, the presence of autoantibodies, and dysbiosis in the microbiota (2). It is postulated that chronic inflammation could precipitate psychosis through its effects on neurotransmitter synthesis, induction of neurotoxicity, and alterations in cerebral microvascular blood flow via the activation of adrenergic α1 receptors (3). Moreover, the significance of neuro-inflammation extends beyond schizophrenia, permeating into other psychiatric disorders such as bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and anxiety disorders (4).

Among the key signaling molecules of the immune system, cytokines, which exert effects in both the central nervous system, and the periphery have been implicated in the pathophysiology of schizophrenia. An aggregation of empirical data elucidates the presence of anomalous levels of cytokines in individuals with schizophrenia (5). Cytokines have been postulated to exert significant influence over neurotransmitter networks, thus implicating them in the pathophysiology of schizophrenia (6). A systematic review encapsulating these studies accentuates the importance of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), IL-2, IL-8, IL-1RA, IL-1β, IL-18, and IL-10. The review highlighted that elevations in these cytokines, coupled with genetic polymorphisms, and heightened expression levels of IL-6, TNFR1, TNFR2, IL-1β mRNAs provide robust evidence of the inflammatory activity concomitant with schizophrenia (7).

Recently, investigations into inflammatory processes and immunological dysregulation in psychiatric disorders have also encompassed haematological parameters, largely attributed to their cost-effectiveness, and routine availability. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have emerged as parameters of interest (8-11). The foundation of these metrics lies in the neutrophilia, and reactive thrombocytosis observed in inflammation, along with lymphopenia, which can be attributed to an increase in apoptotic activity and margination, as a result of stress-induced catecholamine, and cortisol release (8). Numerous studies employing these haematological parameters in schizophrenia have consistently indicated the presence of low-grade inflammation (3,8,10-13).

The systemic immune-inflammation index (SII), calculated using platelet counts multiplied by the neutrophil count, and divided by the lymphocyte count, is a relatively novel parameter pertaining to inflammation. Although it has been used as an indicator of low-grade inflammation, limited studies have assessed its relevance in individuals diagnosed with schizophrenia (10,12,13).

It has been suggested that the combined assessment of CRP, a positive acute-phase reactant, and albumin, a negative acute-phase reactant, may yield more beneficial insights than individual evaluations (14). A few studies examining the CRP-albumin ratio (CAR) in schizophrenia have reinforced the existence of inflammatory processes in the disorder and reported the CAR as a valuable indicator of the inflammatory response (15,16).

Many studies in the literature have cross-sectionally investigated the NLR, MLR, PLR, and other simple inflammation markers in patients with schizophrenia (11,17). The number of studies evaluating SII (10,12,13) and CAR (15,16) in schizophrenia is limited. Our present study aims to investigate simple, readily accessible inflammation markers in hospitalized schizophrenia patients on admission and after three weeks, evaluating changes over a short period with hospital care. The primary hypothesis of our study is that the assembly of various factors, such as regular medication use, diet, sleep, and physical activity provided by hospital care, will reduce low-grade inflammation in a short period.

Materials and Methods

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and approval for the study was granted by the local Clinical Research Ethics Committee on June 06, 2023, with no: 2023.06-239 Our research adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist to ensure a robust and transparent reporting of results.

Study Design

This retrospective study utilized data gathered between January 2021 and December 2022. Individuals were treated as inpatients at a psychiatric clinic in Istanbul and were diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria set by the American Psychiatric Association (18), while also meeting the specific research criteria.

Data Collection

At our clinic, venous blood samples are routinely collected into EDTA tubes between 08:00 and 10:00, and subsequently processed at our central hospital laboratory. All data were obtained retrospectively by scanning the records of patients on their day of hospitalization, and again three weeks later, as found in the hospital's electronic database. Parameters such as the NLR, PLR, MLR, and SII were calculated utilizing complete blood count (CBC) results and CAR were calculated utilizing CRP and albumin results. To mitigate potential data errors during file review, records were independently and concurrently investigated by two psychiatry specialists. These records contained not only laboratory data but also clinical information such as age, sex, marital status, medical illnesses, and psychiatric diagnoses of the patients.

Study Participants

Encompassing a total of 106 patients; inclusion criteria were established as: (a) being between the ages of 18 and 65, (b) undergoing inpatient treatment with a diagnosis of schizophrenia according to DSM-5 criteria, and (c) having accessible laboratory data from the day of hospitalization and from a point three weeks later. Exclusion criteria comprised: (a) the presence of a co-morbid psychiatric diagnosis (b) the existence of severe systemic diseases (e.g. haematological, endocrinological, nephrological, hepatic, metabolic, infectious, autoimmune, cardiovascular, neurological, malignancies, pulmonary) that could potentially affect blood parameters, (c) the use of medications from the anticoagulant, antiplatelet, antibiotic, anti-inflammatory, and immunomodulatory groups, and (d) laboratory results indicating inflammation, defined by CRP values exceeding 10 mg/L (19).

Statistical Methods

Continuous variables were presented as medians and interquartile ranges of the distribution. Comparisons were made using t-tests (for normal distribution) or nonparametric Wilcoxon tests (for non-normal distribution). Categorical variables were represented as frequencies and percentages, with comparisons made using Pearson's X2 test or Fisher's exact test, depending on theoretical numbers.

Paired sample t-tests were used for normally distributed continuous variables to compare the systemic inflammation markers before and after treatment. Wilcoxon signed-rank tests were employed for non-normally distributed variables.

Spearman's rank correlation coefficient was employed to assess the correlation between non-parametric variables. The strength of correlation was determined using the following guidelines: 0.00-0.19 "very weak", 0.20-0.39 "weak", 0.40-0.59 "moderate", 0.60-0.79 "strong", 0.80-1.0 "very strong".

All statistical tests were two-tailed, with an a error of up to 5% considered acceptable to define the statistical significance of any results. All analyses were conducted using R software version 3.6.0 (R Core Team, 2019; R Foundation for Statistical Computing, Vienna, Austria), and all visualizations were created using Keynote version 13.0 (7036.0.126) (Apple Inc., Strobe Inc. –[Sprout Core]).

Results

The study incorporated a sample of 106 patients, aged 18 to 65 years. The mean participant age was 39.0±13.1 years, with males constituting a substantial majority (n=75, 70.7%). Table 1 delineates the laboratory values for participants as documented on the day of their hospital admission.

A comparative analysis was conducted between the NLR, MLR, PLR, and SII values obtained from CBC parameters measured on admission day, and after three weeks. Findings indicated a significant reduction in basic inflammation markers three weeks post-admission compared to those on the day of admission ($p<0.05$). Similarly, the CAR values after three weeks were also significantly lower than on admission day ($p<0.05$). Table 2 provides a comparison of the basic inflammation markers on the day of hospital admission, and three weeks later.

Table 1. Demographics and Clinical Characteristics of the Participants of the Study

Variable	Values (n = 106)	Normal range, unit
Age, years	39.0 (±13.1)	-
Male, n (%)	75 (70.7%)	-
TSH (mU/L)	0.85 [1.45 - 2.05]	0.27-4.2
fT3 (pg/mL)	3.04 [2.71 - 3.41]	2.6-4.4
fT4 (ng/dL)	1.29 [1.15 - 1.5]	0.93-1.70
HDL (mg/dL)	42 [36 - 49]	40-
LDL (mg/dL)	106 [74.8 -129]	0-100
Triglyceride (mg/dL)	118 [84 - 150]	0-150
Vitamin B12 (pg/mL)	242 [190 - 321]	197-771
Folic acid (ng/mL)	4.76 [3.62 - 6.47]	4.6-34.8

Note. Data are presented as mean (±standard deviation) or median [25th percentile - 75th percentile] for continuous variables and number (percentage) for categorical variables. Abbreviations: n; sample size TSH; thyroid-stimulating hormone, fT3; free triiodothyronine, fT4; free thyroxine HDL; high-density lipoprotein; LDL; low-density lipoprotein; TSH; thyroid-stimulating hormone

Table 2. Comparison of the Peripheral Inflammatory Markers of the Participants of the Study

Variable	t_0	t_1	test	*P*	Effect size*
CRP	2.6 [1.1 - 5.3]	1.90 [0.85 - 3.30]	3403	0.001	0.375
CAR	0.064 [0.026 - 0.115]	0.043 [0.017 - 0.077]	2508	0.005	0.371
NLR	2.31 [1.73 - 3.24]	1.73 [1.28 - 2.27]	4497	<.001	0.647
SII	634 [425 - 870]	470 [321 - 645]	4305	<.001	0.577
PLR	9.85 [7.4 - 12.7]	8.21 [6.22 - 10.3]	4222	<.001	0.547
MLR	0.297 [0.221 - 0.378]	0.258 [0.195 - 0.319]	4154	<.001	0.522

Note. * rank biserial correlation

Abbreviations. t0; value on the 1st day of hospitalization t1; value at 3 weeks after hospitalization, CRP; C-reactive protein, CAR; C-reactive protein-to-albumin ratio, NLR; neutrophil-to-lymphocyte ratio, SII; systemic immune-inflammation index, PLR; platelet-to-lymphocyte ratio, MLR; monocyte-to-lymphocyte ratio.

Discussion

In this study; it was found that in patients with schizophrenia, NLR, MLR, PLR, CAR, and SII values decreased within a short period of three weeks when factors such as regular medication use, nutrition, sleep, and physical activity were provided through clinical care. To the best of our knowledge, this is the first study to report that CAR and SII, which have been investigated in a limited number of studies

in schizophrenia, showed a decrease with regular antipsychotic treatment, and hospital care.

Our current study has some significant limitations. Firstly, due to its retrospective design, important clinical variables such as the antipsychotics, and other psychiatric medications used, symptom severity, disease period, pre-hospitalization treatment adherence, and treatment response that are not included in the hospital electronic database were not included in the study. Also, quantitative measurement tools were not used in evaluating potential factors affecting inflammation such as sleep, nutrition, and physical exercise provided by clinical care. In addition, considering our sample size and the fact that a large proportion of the sample size consisted of men, our results may be insufficient to represent the general population.

Our findings support previous studies that indicate a reduction in the inflammatory response in patients receiving inpatient treatment with antipsychotic therapy (20-22). In a large cross-sectional study involving 1144 participants receiving inpatient treatment, the NLR values of schizophrenia patients receiving and not receiving antipsychotic treatment were compared, and lower NLR values were detected in the group receiving antipsychotic treatment. This study also reported a negative correlation between antipsychotic treatment and NLR (20). In a study conducted by Dawidowski et al. (21), significant decreases were found in the NLR values of schizophrenia patients who did not use antipsychotics when comparing the days of hospital admission, and discharge, whereas no such difference was found in those who received antipsychotic treatment before hospitalization. The authors emphasized that NLR could be a potential tool for assessing the response to antipsychotic treatment based on the findings of this study (21). Similarly, in a study where first-episode schizophrenia patients were included by Stefanovic et al. (22), a decrease in non-specific inflammation markers (white cells, CRP, granulocytes) was reported after four weeks of antipsychotic treatment, while there was an increase in lymphocyte and monocyte counts. However, this study did not perform NLR, PLR, MLR, and SII calculations (22). In another study addressing the relationship between the immune system and psychopathology and treatment, NLR and MLR values were also investigated, and the results are partially parallel our findings. In this study, after six weeks of antipsychotic treatment, a decrease was found in the NLR values of first-episode psychosis patients, while no difference was detected in MLR values. In the group diagnosed with schizophrenia, on the other hand, there was a decrease in MLR values while there was no difference in NLR values (23).

There are also studies in the literature that differ from our results. In a study where NLR values in schizophrenia patients were significantly higher compared to healthy controls, no difference was found in NLR values between the groups of schizophrenia patients receiving and not receiving antipsychotic treatment (24). In another study, higher NLR, MLR, and PLR values were reported in relapse periods compared to remission periods, but no difference was found when patients in the relapse period were grouped according to whether they used antipsychotics or not (25). An important methodological difference of our study from these studies is that our study compares the values of systemic inflammation markers at different times (hospital admission vs. 3 weeks later) of the same patients. Different results reported in the literature about the systemic inflammatory markers with antipsychotic treatment could be caused by methodological differences, symptom severity, disease duration, treatment response, treatment compliance differences, direct effects of different antipsychotics used on blood cells, and the fact that schizophrenia is a syndrome harbouring different symptoms and signs within a wide spectrum rather than a single disease. Additionally, as mentioned in our study's hypothesis, factors outside of regular antipsychotic use provided by clinical care such as regular sleep, nutrition, and physical activity, should also be considered for their potential effects on low-grade inflammation (26).

In our study, alongside the decrease in NLR, PLR, MLR, and SII parameters obtained from CBC with regular antipsychotic treatment and hospital care, a decrease was also detected in CAR values. CRP which increases in response to systemic inflammation, has been investigated in many studies on schizophrenia (27). However, the ratio of CRP to albumin (a negative acute phase reactant), which is suggested to be a better indicator of inflammatory response (14), has been evaluated in a limited number of studies in schizophrenia (15,16). In a study where CAR was evaluated in schizophrenia, CAR values were compared cross-sectionally with healthy volunteers, and higher values were reported in schizophrenia patients. In the same study, no significant difference was found when patients with schizophrenia in remission were compared with those in an acute exacerbation period (15). In another study comparing CAR values in homicidal and non-violent schizophrenia patients, higher values were reported in the homicidal group (16). Similarly, SII has been evaluated in a limited number of studies in schizophrenia, and in these studies, schizophrenia patients were compared cross-sectionally with healthy controls (10,12,13). In two of these studies, higher SII values were reported in schizophrenia patients compared to healthy controls (10,13). In a study investigating the relationship between negative symptoms in schizophrenia patients and systemic inflammatory markers, no difference was found in SII values compared to healthy controls, but a negative correlation was reported between social anhedonia and SII in female schizophrenia patients (12). Our study findings support these studies and indicate that CAR and SII are useful markers in the evaluation of low-grade inflammation.

In conclusion, this study found a decrease in simple inflammation markers such as NLR, MLR, PLR, SII, and CAR in schizophrenia patients with regular

antipsychotic treatment and, hospital care. NLR, MLR, PLR, CAR and SII may be useful biomarkers in the clinical follow-up of schizophrenia. CAR and SII, which have been evaluated in a limited number of studies in schizophrenia, can be important markers for indicating low-grade inflammation, therefore it would be beneficial to consider them in more studies. There is a need for prospective studies that will evaluate sleep, nutrition and physical activity, which show common disruptions in many psychiatric disorders and potentially mediate this process, with quantitative measurements in order to better understand low-grade inflammation, which is a trans-diagnostic process in psychiatric disorders.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no financial support for the research.

Author Contributions

Conception: H.I.O., I.K., O.G., S.D., Design: H.I.O., S.D., O.G., Supervision: O.G., S.D., Data Collection and/or Processing: I.K., S.D., Analysis and/or Interpretation: H.I.O., S.D., Literature Review: H.I.O., I.K., S.D., O.G., Writer: H.I.O., I.K., S.D., Critical Review: O.G., S.D.

References

1.Soygür H. The concept of schizophrenia: ''Shall we destroy and rebuild, repair and update?'' Update in Psychiatry, 2023; 13(1):1-9.

2.Ermakov EA, Melamud MM, Buneva VN, Ivanova SA. Immune system abnormalities in schizophrenia: An integrative view and translational perspectives. Front Psychiatry, 2022; 25(13):880568.

3.Zhu X, Zhou J, Zhu Y, Yan F, Han X, Tan Y, Li R. Neutrophil/ lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas Psychiatry, 2022; 30(1):95-99.

4.Tsai SJ. Role of interleukin 8 in depression and other psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry, 2021; 106:110173.

5.Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry, 2016; 21(12):1696-1709.

6.Jarskog LF, Xiao H, Wilkie MB, Lauder JM, Gilmore JH. Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. Int J Dev Neurosci. 1997 Oct;15(6):711-716.

7.Rodrigues-Amorim D, Rivera-Baltanás T, Spuch C, Caruncho HJ, González-Fernandez Á, Olivares JM, et al. Cytokines dysregulation in schizophrenia: A systematic review of psychoneuroimmune relationship. Schizophr Res, 2018; 197:19-33.

8.Bulut NS, Yorguner N, Çarkaxhiu Bulut G. The severity of inflammation in major neuropsychiatric disorders: comparison of neutrophil-lymphocyte and platelet-lymphocyte ratios between schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and obsessive compulsive disorder. Nord J Psychiatry, 2021; 75(8):624-632.

9.Inanli I, Aydin M, Çaliskan AM, Eren I. Neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and mean platelet volume as systemic inflammatory markers in different states of bipolar disorder. Nord J Psychiatry. 2019;73(6):372-379.

10.Huang K, Tang Y, Chen Z, Ding S, Zeng H, Zhao Y, Yu Q, Liu Y. Comparison of hematological parameters between first-episode schizophrenia and anti-NMDAR encephalitis. Front Cell Dev Biol, 2022; 10:895178.

11.Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and systematic review. World J Biol Psychiatry, 2020; 21(5):326-338.

12.Šagud M, Madžarac Z, Nedic Erjavec G, Šimunović Filipčić I, Mikulić FL, Rogić D, et al. The associations of neutrophil-lymphocyte, platelet-lymphocyte, monocyte-lymphocyte ratios and immune-inflammation index with negative symptoms in patients with schizophrenia. Biomolecules, 2023; 13(2):297.

13.Inaltekin A, Yağci İ. Evaluation of simple markers of inflammation and systemic immune inflammation index in schizophrenia, bipolar disorder patients and healthy controls. Turk Psikiyatri Derg, 2023; 34(1):11-15.

14.Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8(3):e59321.

15.Balcioglu YH, Kirlioglu SS. C-Reactive Protein/Albumin and Neutrophil/Albumin Ratios as Novel Inflammatory Markers in Patients with Schizophrenia. Psychiatry Investig, 2020; 17(9):902-910.

16.Balcioglu YH, Balcioglu SSK, Oncu F, Turkcan A, Yorulmaz AC. Impulsive and aggressive traits and increased peripheral inflammatory status as psychobiological substrates of homicide behavior in schizophrenia. The European Journal of Psychiatry, 2022; 36(3), 207-214.

17.Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis. Schizophr Res, 2019; 206:4-12.

18.American Psychiatric Association: Desk Reference to the Diagnostic Criteria From DSM-5. Arlington, VA, American Psychiatric Association, 2013.

19.Sisman AR, Kume T, Akan P, Tuncel P. C-reactive protein: Clinical significance, improvements in methodology, pre-analytical and analytical variations. Türk Klinik Biyokimya Derg, 2007; 5(1): 33-41.

20.Zhou X, Wang X, Li R, Yan J, Xiao Y, Li W, et al. Neutrophil-to-Lymphocyte Ratio Is Independently Associated With Severe Psychopathology in Schizophrenia and Is Changed by Antipsychotic Administration: A Large-Scale Cross-Sectional Retrospective Study. Front Psychiatry, 2020;11:581061.

21.Dawidowski B, Grelecki G, Biłgorajski A, Podwalski P, Misiak B, Samochowiec J. Effect of Antipsychotic Treatment on Neutrophil-to-Lymphocyte Ratio during Hospitalization for Acute Psychosis in the Course of Schizophrenia-A Cross-Sectional Retrospective Study. J Clin Med, 2021;11(1):232.

22.Stefanović V, Mihajlović G, Nenadović M, Dejanović SD, Borovcanin M, Trajković G. The effect of antipsychotic drugs on nonspecific inflammation markers in the first episode of schizophrenia. Vojnosanit Pregl, 2015; 72(12):1085-92.

23.Steiner J, Frodl T, Schiltz K, Dobrowolny H, Jacobs R, Fernandes BS, et al. Innate Immune Cells and C-Reactive Protein in Acute First-Episode Psychosis and Schizophrenia: Relationship to Psychopathology and Treatment. Schizophr Bull, 2020;46(2):363

24.Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, Kayka N, Tosun M. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub, 2014; (3):220-225.

25.Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res, 2019;271:131-135.

26.Fang SH, Suzuki K, Lim CL, Chung MS, Ku PW, Chen LJ. Associations between sleep quality and inflammatory markers in patients with schizophrenia. Psychiatry Res, 2016;246:154-160.

27.Lestra V, Romeo B, Martelli C, Benyamina A, Hamdani N. Could CRP be a differential biomarker of illness stages in schizophrenia? A systematic review and meta-analysis. Schizophr Res, 2022;246:175-186.