Received: 22 Feb 2025 | **Accepted:** 02 Jun 2025 **Genel Tıp Derg. Volume** 35/**Issue** 4 (August), 640-648

DOI: 10.54005/geneltip.1645072

ORIGINAL ARTICLE

The Role of Antipsychotic Treatments in Neutrophil/Lymphocyte, Platelet/Lymphocyte, Monocyte/Lymphocyte, Monocyte/HDL Ratios and Systemic Immune Inflammatory Index Values for Patients with Schizophrenia

Şizofreni Hastalarında Antipsikotik Tedavilerin Nötrofil/Lenfosit, Trombosit/Lenfosit, Monosit/Lenfosit, Monosit/HDL Oranları ve Sistemik İmmün İnflamatuvar İndeks Değerleri Üzerindeki Rolü

[1]Memduha AYDIN, [2]Hacer SÖYLEMEZ

[1]Assoc. Prof., Department of Psychiatry, Faculty of Medicine, Selcuk University, Konya, Türkiye
memduhaaydin@gmail.com
[2]Research Assistant, Department of Psychiatry, Faculty of Medicine, Selcuk University, Konya, Türkiye
soylemezhacer@gmail.com

Correspondence

Memduha AYDIN,
Selcuk University, Faculty of Medicine, Department of Psychiatry, Konya, Türkiye

E-Mail: memduhaaydin@gmail.com

How to cite ?

Aydın M., Söylemez H., The Role of Antipsychotic Treatments in Neutrophil/Lymphocyte, Platelet/Lymphocyte, Monocyte/Lymphocyte, Monocyte/HDL Ratios and Systemic Immune Inflammatory Index Values for Patients with Schizophrenia, Genel Tıp Derg. 2025;35(4):640-648

ABSTRACT

Aim: Abnormal systemic inflammatory responses play a significant role in the pathogenesis of schizophrenia. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), monocyte-HDL ratio (MHR), and systemic immune inflammation index (SII) have recently been used as markers of inflammation. Our study aims to examine the relationship between NLR, PLR, MLR, MHR, and SII values of patients diagnosed with schizophrenia and antipsychotic treatments.
Methods: One hundred ninety-four individuals diagnosed with schizophrenia who were followed up in the Psychotic Disorders Polyclinic of the Selcuk University Faculty of Medicine, Department of Psychiatry, were included in the study. Neutrophil, lymphocyte, platelet, and monocyte counts, and HDL values were obtained retrospectively from blood tests. NLR, PLR, MLR, MHR, and SII were calculated.
Results: The mean age of patients was 44.38±12.67 years. In total, 85 (43.8 %) patients were female. PLR and SII were statistically significantly greater in females than in the male group ($p<0.001$, $p<0.018$). Among the patient groups, MHR levels were significantly higher in the male group than in the female group ($p<0.003$). No significant difference was found between different antipsychotic treatments used in schizophrenia patients in terms of inflammatory markers ($p > 0.05$). However, a negative correlation was found between paliperidone long-acting injectable treatment duration and NLR and SII (PP-LAI and NLR, r: -0.26, p=0.026; PP-LAI and SII, r=-0.26, p=0.03).
Conclusions: Our findings demonstrate a negative correlation between the duration of paliperidone long-acting injectable treatment and NLR and SII. This suggests that a longer duration of paliperidone long-acting treatment may contribute to a reduction in inflammation. Also, differences were found between genders in PLR, MHR, and SII as a result. It is thought that understanding the gender-based differences and the role of antipsychotic treatments on inflammatory markers may provide a better understanding of schizophrenia pathogenesis and help to find better treatment options.
Keywords: Antipsychotic, inflammatory response, monocyte/HDL ratio, monocyte/lymphocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, systemic immune inflammatory index, schizophrenia

ÖZ

Amaç: Anormal sistemik inflamatuar yanıtlar şizofreni patogenezinde önemli bir rol oynamaktadır. Nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), monosit-lenfosit oranı (MLR), monosit-HDL oranı (MHR) ve sistemik immün inflamasyon indeksi (SII) son zamanlarda inflamasyon belirteçleri olarak kullanılmaktadır. Çalışmamızın amacı şizofreni hastalarında NLR, PLR, MLR, MHR ve SII değerleri ile antipsikotik tedaviler arasındaki ilişkiyi incelemektir.
Gereç ve Yöntemler: Selçuk Üniversitesi Tıp Fakültesi, Psikiyatri Ana Bilim Dalı, Psikotik Bozukluklar Polikliniği'nde takip edilen şizofreni tanılı yüz doksan dört birey çalışmaya dahil edilmiştir. Nötrofil, lenfosit, trombosit ve monosit sayıları, HDL değerleri kan testlerinden retrospektif olarak elde edildi. NLR, PLR, MLR, MHR ve SII hesaplandı.
Bulgular: Hastaların yaş ortalaması 44,38 ± 12,67 yıldı. Toplam 85 (%43,8) hasta kadındı. PLR ve SII kadınlarda erkeklere göre istatistiksel olarak anlamlı derecede yüksekti ($p<0.001$, $p<0.018$). Hasta grupları arasında, MHR düzeyleri erkek grupta kadın gruba göre istatistiksel olarak anlamlı derecede yüksekti ($p<0.003$). Şizofreni hastalarında kullanılan farklı antipsikotik tedaviler arasında inflamatuar belirteçler açısından anlamlı bir farklılık saptanmadı ($p> 0.05$). Ancak, paliperidon uzun etkili enjektabl tedavi süresi ile NLR ve SII arasında negatif bir korelasyon bulundu (PP-LAI ve NLR, r:-0.26, p=0.026; PP-LAI ve SII, r:-0.26, p=0.03).
Sonuçlar: Bulgularımız, paliperidon uzun etkili enjektabl tedavi süresi ile NLR ve SII arasında negatif bir korelasyon olduğunu göstermektedir. Bu sonuç daha uzun süreli paliperidon uzun etkili tedavinin inflamasyonun azalmasına katkıda bulunabileceğini düşündürmektedir. Ayrıca, sonuç olarak PLR, MHR ve SII'de cinsiyetler arasında farklılıklar bulunmuştur. Cinsiyete dayalı farklılıkların ve antipsikotik tedavilerin inflamatuar belirteçler üzerindeki rolünün anlaşılmasının şizofreni patogenezinin daha iyi anlaşılmasını sağlayabileceği ve daha iyi tedavi seçeneklerinin bulunmasına yardımcı olabileceği düşünülmektedir.

Anahtar Kelimeler: Antipsikotik, inflamatuar yanıt, monosit/HDL oranı, monosit/lenfosit oranı, nötrofil/lenfosit oranı, trombosit/lenfosit oranı, sistemik immün inflamatuar indeks, şizofreni

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - intihal.net
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/

INTRODUCTION

Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, disorganized speech and behavior, negative symptoms, emotional blunting, and impaired functioning (1). The worldwide prevalence of schizophrenia is estimated to be approximately 0.5-1% (2,3). The etiology and pathophysiology of schizophrenia remain incompletely understood today. Furthermore, increasing evidence suggests that the development of schizophrenia involves a multifactorial process involving genetic predisposition, neurodevelopmental abnormalities, neurodegenerative changes, and inflammatory mechanisms (4,5).

Neuroimaging studies on schizophrenia provide substantial evidence supporting the neurodevelopmental hypothesis. These studies have identified neuroanatomical changes such as gray matter volume reductions, white matter abnormalities, and ventricular enlargements, highlighting the potential role of neurodevelopmental processes in the pathogenesis of schizophrenia (6). Researches indicate that these neuroanatomical changes may exist even before the onset of clinical symptoms. This highlights the potential role of abnormal brain development in the pathogenesis of schizophrenia (7,8). In the pathogenesis of schizophrenia, inflammatory hypotheses hold an important place alongside neurodevelopmental and neurodegenerative models (9). These hypotheses highlight the role of inflammation in the development of schizophrenia.

Inflammation is a physiological response initiated by the body to protect against both endogenous and exogenous stimuli. While essential for maintaining homeostasis and responding to injury or infection, it is a nonspecific process that is not confined to a particular disease or condition (10). Neutrophil/lymphocyte ratio (NLR) is gaining increasing attention as an easily measured biomarker of inflammation. In addition to NLR, markers such as platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR) are commonly used to evaluate the inflammatory status (11). These markers are frequently used in clinical practice and research to investigate the role of inflammation in many diseases, including psychiatric disorders (12). Recent studies on the pathogenesis of schizophrenia increasingly suggest that abnormal immune responses may play a significant role in its development (13-15). There are also studies showing that the systemic inflammatory response in patients diagnosed with schizophrenia is different from controls (16). NLR, PLR, MLR, monocyte/HDL ratio (MHR), and systemic immune inflammation index (SII) have recently been used as indicators of inflammation in many studies in patients with schizophrenia (17,18). In previous studies, higher SII values were observed in schizophrenia patients compared to the control groups. The systemic immune inflammation index is a marker of inflammation. The platelet x neutrophil/lymphocyte ratio is used to determine it. It was discovered by Hu et al. and has been demonstrated to be a more accurate indicator of the prognosis of cancer than other inflammatory indicators like PLR and NLR (19).

Antipsychotic drugs are widely used in the treatment of schizophrenia. In addition to reducing the symptoms of schizophrenia, studies have shown that antipsychotics also have effects on inflammatory

processes (17,18,20-23). However, the results of existing studies on the effects of antipsychotics on inflammatory processes are contradictory in some points. (23,24). Although the exact method by which antipsychotics reduce inflammation is yet unknown, they are likely to have a direct or indirect impact on a number of immune cells. Moreover, antipsychotics may reduce stress-induced neuroinflammation by reducing the stress that patients endure during psychotic episodes, as stress can trigger neuroinflammation (23). Previous studies have found a bell-shaped change in inflammation markers during treatment. It is suggested that this dual effect may be explained by both the direct anti-inflammatory effects of antipsychotics and their pro-inflammatory effects by causing metabolic changes (23,25).

There are studies on inflammatory processes and markers in schizophrenia in the literature, but the effect of antipsychotics on these processes has not been sufficiently investigated. The results of the limited number of existing studies are contradictory. Our study aims to evaluate the relationship between NLR, PLR, MLR, MHR, and SII values and antipsychotic treatments of patients diagnosed with schizophrenia.

MATERIALS and METHODS

This research was conducted at the Psychotic Disorders Polyclinic of the Selcuk University Faculty of Medicine, Department of Psychiatry, and the cases in the patient group were selected from individuals who presented to the clinic between January 2022 and January 2024. All schizophrenia patients were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria.

A total of 203 schizophrenia patients, whose clinical information and blood tests were obtained by retrospectively scanning the electronic medical record system of the hospital, were included in the study. Six individuals were excluded due to blood hematopoietic diseases, and three were excluded due to inflammatory diseases. The final sample of the study consisted of 194 patients with schizophrenia aged between 18 and 65 years.

The inclusion criteria for patients were: (a) aged between 18 and 65 years of age; and (b) being diagnosed with schizophrenia according to DSM-IV. Exclusion criteria for patients were defined as (a) those with acute and chronic diseases (inflammatory diseases such as infection, advanced cancer, trauma and collagen disease, blood hematopoietic diseases such as leukemia, and also diabetes mellitus, hypertension, epilepsy, head injury), (b) those with additional psychiatric diagnoses, (c) those receiving any treatment which may affect anti-inflammatory status (such as anti-inflammatory, immunosuppressive treatment).

Patients were evaluated after approval was obtained from the Local Ethics Committee of Selcuk University, Faculty of Medicine (Decision No: 2023/482, date: 2023). The study was conducted under the principles of the Declaration of Helsinki.

Statistical Analysis

All data analyses were conducted using the Statistical Package for Social Sciences for Windows, version 22.0 software (SPSS IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess the normality of the distributions for study

variables. Categorical variables were compared using Pearson's chi-square test. For comparisons of normally distributed variables, the Student's t-test was used. Data were presented as mean±standard deviation (SD) and counts of variables. Categorical variables were reported as frequencies and percentages. The relationship between clinical parameters and laboratory findings was analysed by Pearson correlation analysis. Statistical significance was defined as $p<0.05$.

RESULTS

Eighty-five of the 194 patients who participated in the study were women, and 109 (56.2%) were male. The mean age of the patients was 44.38±12.67 years, the mean duration of illness was 20.22±10.99 years, and the mean number of hospitalizations was 2.96±2.72 (Table 1). Additionally, no statistically significant differences were found between male and female patients in terms of mean age, duration of illness, and mean number of hospitalizations.

135 (69.6%) of the patients were using oral antipsychotics (only oral antipsychotics and/or with long-acting injectable (LAI) antipsychotics),and75(38.7%)ofthepatients were using clozapine (only clozapine and/or clozapine with other antipsychotics). More than half of the group (57.7%) were using LAI antipsychotic treatment. There was no statistically significant difference between females and males in the rates of LAI use, clozapine use, and oral treatment use. The characteristics of antipsychotic use in patients were explained in Table 2.

Table 1. Demographic and clinical characteristics of all participants.

	Female (n, %) 85 (43.8)	**Male (n, %) 109 (56.2)**	**Total (n, %) 194 (100)**	**p-value**
Age (years) (mean±SD)	46.19±12.09	42.97±12.98	44.38±12.67	0.079
Disease duration (mean±SD)	21.92±11.30	18.89±10.61	20.22±10.99	0.057
Number of hospitalizations (mean±SD)	3.29±2.73	2.69±2.69	2.96±2.72	0.130

SD: Standard deviation

No statistically significant difference was observed between male and female patients in the ratios of typical/atypical antipsychotic, oral/LAI antipsychotic (p=0.154, p=0.349) or clozapine/non-clozapine antipsychotic drug use (p=0.251).

PLR and SII were statistically significantly greater in females than in the male group. Among the patient groups, MHR levels were significantly higher in the male group than in the female group (Table 3). No significant difference was observed between the mean values of inflammatory markers in terms of typical/atypical antipsychotic, oral/LAI antipsychotic, or clozapine/non-clozapine antipsychotic drugs. However, a negative correlation was found between the duration of paliperidone LAI treatment and NLR and SII (PP-LAI and NLR, r: -0.26, p=0.026; PP-LAI and SII, r:-0.26, p=0.03) (Table 4).

Table 2. Characteristics of antipsychotic use

	Female (n, %) 85 (43.8)	**Male (n, %) 109 (56.2)**	**Total (n, %) 194 (100)**	**p-value**
Oral/LAI antipsychotic use				
No Oral Antipsychotic Use/Only LAI Antipsychotic	32 (37.6)	27 (24.8)	59 (30.4)	0.154
Only Oral Antipsychotic Use/No LAI Antipsychotic	32 (37.6)	50 (45.9)	82 (42.3)	
Oral Antipsychotic Use and LAI Antipsychotic	21 (24.7)	32 (29.4)	53 (27.3)	
Clozapine treatment				
No Clozapine Use	56 (65.9)	63 (57.8)	119 (61.3)	0.251
Only Clozapine and/or Clozapine with Other Antipsychotics	29 (34.1)	46 (42.2)	75 (38.7)	
LAI antipsychotic treatment				
No LAI Antipsychotic Treatment	32 (37.6)	50 (45.9)	82 (42.3)	0.349
LAI Antipsychotic Treatment	53 (62.4)	59 (54.1)	112 (57.7)	
Aripiprazole Long-acting			16 (8.2)	
Haloperidol Decanoate			13 (6.7)	
Paliperidone Monthly			41 (21.1)	
Paliperidone 3-Monthly			34 (17.5)	
Risperidone Consta			5 (2.6)	
Zuclopenthixol Decanoate			7 (3.6)	

LAI: Long-acting injectable

Table 3

Table 3. Comparison of laboratory variables between the female and male patient groups.

	Female (n, %) 85 (43.8)	Male (n, %) 109 (56.2)	Total (n, %) 194 (100)	p-value
NLR	2.54±1.23	2.45±1.24	2.49±1.24	0.614
PLR	144.0±53.26	112.74±43.43	126.44±50.31	**<0.001***
MLR	0.25±0.10	0.30±0.20	0.28±0.16	0.063
MHR	0.01±0.00	0.02±0.02	0.01±0.01	**0.003***
SII	696.85±422.99	563.68±357.16	622.03±391.97	0.018*

*The significance of the bold value indicates p < 0.05. MLR: Monocyte/lymphocyte ratio, MHR: Monocyte/HDL ratio, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SII: Systemic immune inflammation index

Table 4

Table 4. Correlation between inflammation markers and duration of use of paliperidone LAI antipsychotic*

	Duration of Use of Paliperidone LAI Antipsychotic	
	r	p-value
NLR	-.257	**0.026****
PLR	-.117	.318
MLR	-.009	.938
MHR	.046	.696
SII	-.251	**.030****

*Duration of use of paliperidone LAI antipsychotic: paliperidone monthly and paliperidone 3 monthly, total duration of paliperidone LAI antipsychotic use. **The significance of the bold value indicates p<0.05. LAI: Long-acting injectable, MHR: Monocyte/HDL ratio, MLR: Monocyte/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SII: Systemic immune inflammation index

DISCUSSION

In this study, 194 schizophrenia patients were examined, and the relationship between inflammatory markers and antipsychotic treatments was evaluated. The results of the study did not reveal significant differences in inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), monocyte-to-HDL ratio (MHR), and systemic immune-inflammatory index (SII) among different antipsychotic treatments. However, a negative correlation was observed between the duration of paliperidone LAI treatment and NLR and SII levels.

Clinical and demographic differences of schizophrenia patients were analysed, and their characteristics related to antipsychotic treatment were evaluated. The results of the study showed that there were no differences between genders in terms of age, duration of illness, and number of hospitalisations, rates of LAI antipsychotic use, clozapine use, and oral treatment use. This may suggest that clinical and treatment parameters did not play a confounding role in some of our findings that differed between genders. In our study, differences were found between genders in PLR, MHR, and SII. PLR and SII values were higher in the female group, and MHR values were found to be higher in the male group. Differences in inflammatory markers

in the two sexes have been discussed in other articles on inflammation-related diseases other than schizophrenia (26). This study suggests that testosterone has an immunosuppressive effect and that men are at risk for worse outcomes in terms of infection. Hampton (27) stated that neutrophils were particularly responsible for this difference and that neutrophils of women were more active and mature due to the effect of sex hormones. In addition to these, Haiti et al. suggested that the lifestyle of men is also effective in sex differences in inflammatory response (28). In particular, it is thought that understanding the gender-based differences of such inflammatory markers may contribute to studies on the treatment of schizophrenia.

Results of this study indicated a negative correlation between the duration of paliperidone LAI treatment and NLR and SII. Prior studies have indicated that antipsychotic medications, particularly those of the second generation, may have anti-inflammatory qualities (13,16,17). Since the most reliable source of information in this context was the use of LAIs, all LAIs were included in our study. Probably due to the higher proportion of patients using paliperidone LAIs, the longer duration of use, and the more regularity of records, only paliperidone yielded statistically significant results in this study. The underlying mechanism through which antipsychotics affect inflammation remains unexplained, but they are likely to affect the immune system both directly and indirectly. Firstly, antipsychotics can directly inhibit the activation of immune cells and production of pro-inflammatory cytokines by immune cells, including microglia activation (17,20). Another explanation for the effect of antipsychotics in reducing inflammation is the effect on stress levels. Based on the knowledge that stress may cause neuroinflammation, it is suggested that antipsychotics may limit stress-induced neuroinflammation by reducing the stress experienced by the patient during psychotic episodes (17). As in our study, LAI antipsychotic drugs, which provide long-term regular use of antipsychotics, may have positively affected the stress factor because they prevented relapses better (29).

On the other hand, the negative correlation between inflammatory markers and the duration of long-term antipsychotic use contradicts the results showing that patients receiving drug treatment have higher inflammatory markers compared to patients not receiving drug treatment (25). This contradiction may be explained by the bell-shaped change mentioned in Zhang et al. The longitudinal change of pro-inflammatory cytokines is likened to a bell curve. It is suggested that the bell curve-shaped change may be closely related to the fact that the direct anti-inflammatory effect of antipsychotics is at the forefront in the beginning, and in the longer term, the metabolic changes caused by the drugs mediate the increase in chronic inflammation production. The bell-shaped change of these inflammation markers may help explain why schizophrenia has a long treatment duration and high relapse rate despite a short-term response (17,23).

Previous studies have shown that NLR rates of first-attack patients were higher than healthy controls (30,31). Since we do not know the NLR values of the patients in the first attack period in our study, we cannot comment on how NLR values change with

or without treatment. Likewise, since we did not have a healthy control group, we cannot make comparisons with healthy individuals. However, according to our records, we were able to study how LAI antipsychotic treatments, which provide reliable information about the treatment use of patients, affect the NLR in the process. Uncertainty about the frequency of change of oral treatments and the duration of treatment led us to exclude the evaluation of inflammatory markers with oral treatments.

Future studies should focus on evaluating disease onset, relapse, and remission periods, as well as treatment duration and dosing, to further clarify the relationship between inflammatory markers and schizophrenia. Additionally, large-scale prospective studies are needed to better understand the long-term effects of antipsychotic treatments on inflammatory markers.

The limitations of this study include its retrospective design, which prevents the establishment of causal relationships between antipsychotic treatments and inflammatory changes. In this retrospective evaluation, we do not know the values of the inflammatory markers before the treatments, so we cannot understand how the drugs affected the inflammatory values. The lack of a healthy control group can be considered another limitation. Moreover, potential confounding factors such as dietary habits, physical activity levels, presence of metabolic syndrome, smoking, and subclinical infections, which could potentially influence inflammatory markers, were not assessed. In addition, the lack of clinical assessment scales can be considered another limitation that prevents the evaluation of whether there is a condition affecting inflammation in terms of disease symptoms. Finally, the study population was limited to a single center, which restricts the generalizability of the findings.

CONCLUSION

In conclusion, this study provides important findings regarding the positive effects of long-term antipsychotic treatment on inflammatory response and differences in inflammatory markers between genders. Our study found that female patients with schizophrenia had higher PLR and SII levels compared to male patients, while MHR levels were higher in male patients, and found no differences in most inflammatory markers between antipsychotic treatments in patients with schizophrenia. However, a negative correlation was observed between the duration of paliperidone LAI use and NLR and SII values, suggesting a potential effect of treatment compliance on systemic inflammation. These findings highlight the importance of considering sex-specific differences in inflammation, the potential role of LAI antipsychotics in modulating the inflammatory state, and the need for further studies to better understand the effects of treatments and gender on inflammatory status.

Conflict of Interest: The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article. The authors declare no conflict of interest, financial or otherwise.

Financial support: The authors declared that this study has received no financial support.

REFERENCES

1.Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr. Res 2009; 110 (1-3):1–23.

2.Moreno-Küstner B, Martín C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analysis. PLoS ONE 2018; 13(4):e0195687.

3.Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. Lancet. 2022; 399(10323):473–486.

4.McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008; 30(1):67-76.

5.Siever LJ, Davis KL. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. Am J Psychiatry 2004; 161(3):398-413.

6.Owen MJ, O'Donovan MC, Thapar A, Craddock N. Neurodevelopmental hypothesis of schizophrenia. Br. J. Psychiatry 2011; 198:173 175.

7.Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2015; 2(3):258–270.

8.González-Peñas J, Alloza C, Brouwer R, Díaz-Caneja CM, Costas J, González-Lois N. Accelerated cortical thinning in schizophrenia is associated with rare and common predisposing variation to schizophrenia and neurodevelopmental disorders. Biol Psychiatry 2024; 96(5):376-389.

9.Kochunov P, Hong LE. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. Schizophr Bull 2014; 40(4):721–728.

10.Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454(7203):428-435.

11.Gökmen F, Akbal A, Reşorlu H, Gökmen E, Güven M, Aras AB, et al. Neutrophil-lymphocyte ratio connected to treatment options and inflammation markers of ankylosing spondylitis. J Clin Lab Anal 2015; 29(4):294-298.

12.Zahorec R. Neutrophil-to-lymphocyte ratio. A long history of sixteen years since the publication of our article in the Bratislava Medical Journal. Bratisl Lek Listy 2017; 118(6):321-323.

13.Watkins CC, Andrews SR. Clinical studies of neuroinflammatory mechanisms in schizophrenia. Schizophr Res 2016; 176(1):14-22.

14.Rawani NS, Chan AW, Todd KG, Baker GB, Dursun SM. The role of neuroglia in the development and progression of schizophrenia. Biomolecules 2024; 15(1):10.

15.Nayak U, Manikkath J, Arora D, Mudgal J. Impact of neuroinflammation on brain glutamate and dopamine signalling in schizophrenia: an update. Metab Brain Dis 2025; 40(2):119.

16.Inaltekin A ve Yağcı I. Evaluation of simple markers of inflammation and systemic ımmune inflammation index in schizophrenia, bipolar disorder patients and healthy controls. Turkish Journal of Psychiatry 2023; 34(1):11-15.

17.Zhang Y, Tao S, Coid J, Wei W, Wang Q, Yue W. The role of total white blood cell count in antipsychotic treatment for patients with schizophrenia. Curr Neuropharmacol 2024; 22(1):159-167.

18.Koçak MB, Atkaya NÖ, Oruç MA. Evaluation of inflammatory markers obtained from complete blood count in different stages of schizophrenia. Current medical research and opinion 2024; 40(8):1413–1419.

19.Hu B, Yang X-R, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014; 20(23):6212–6222.

20.Aksoy İ, Uçar H. Do peripheral blood ınflammation indices differ among schizophrenia patients with clozapine treatment? A cross-sectional investigation. Genel Tıp Derg 2024; 34(6):846-852.

21.Messina A, Bella F, Maccarone G, Rodolico A, Signorelli MS. Neutrophil-Lymphocyte Ratio values in schizophrenia: A Comparison between oral and long-acting antipsychotic therapies. Brain Sci 2024; 14(6):602.

22.Myles N, Myles H, Xia S, Large M, Bird R, Galletly C, et al. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. Aust N Z J Psychiatry 2019; 53(5):403-412.

23.Zheng Y, Zhou X, Chen K, Fu Z, Zhang P, Zhu Q. Neutrophil/lymphocyte ratio is increased in the acute phase of schizophrenia and regardless of the use and types of antipsychotic drugs. BMC Psychiatry 2024; 24(1):876.

24.Swain CA, Robbs EJ, Verma L, Brandt H, Seppaenen AL, Cavnar PJ. Characterization of the atypical antipsychotic drug aripiprazole cytotoxicity in the neutrophil model cell line HL-60. PLoS One 2025; 20(2):e0318878.

25.Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in Schizophrenia: An updated review. Front. Psychiatry 2019; 10:892.

26.Zubair SM, Chaudhry MW, Zubairi ABS, Shahzad T, Zahid A, Khan IA, et al. The effect of ivermectin on non-severe and severe COVID-19 disease and the gender-based difference of its effectiveness. Monaldi Arch Chest Dis 2022; 92(4):2062.

27.Hampton T. Insight on Sex-Based Immunity Differences, With COVID-19 Implications. JAMA 2020; 324(13):1274.

28.Haitao T, Vermunt JV, Abeykoon J, Ghamrawi R, Gunaratne M, Jayachandran M, et al. COVID-19 and Sex Differences: Mechanisms and Biomarkers. Mayo Clin Proc 2020; 95(10):2189-2203.

29.Clark I, Wallman P, Gee S, Taylor D. Clinical outcomes with paliperidone palmitate 3-monthly injection as monotherapy: observational 3-year follow-up of patients with schizophrenia. Eur Psychiatry 2024; 67(1):e15.

30.Varsak N, Aydın M, Eren İ. The evaluation of neutrophil-lymphocyte ratio in patients with first episode psychosis. Fam Pract Palliat Care 2016; 1(3):65-69.

31.Garip B, Oğur B, Tekin Ş, İnanç Ö. Comparative study of inflammatory markers in schizophrenia, first episode psychosis, and bipolar disorder. Genel Tıp Derg 2024; 34(5):624-628.