**Received:** 25 Aug 2024 | **Accepted:** 05 Dec 2024 **Genel Tıp Derg. Volume** 34/**Issue** 6 (December), 846-852
DOI: 10.54005/geneltip.1538269

**ORIGINAL ARTICLE**

# Do Peripheral Blood Inflammation Indices Differ Among Schizophrenia Patients with Clozapine Treatment? A Cross-sectional Investigation

# Klozapin Tedavisi Gören Şizofreni Hastalarında Periferik Kan İnflamasyon İndeksleri Farklılaşır mı? Kesitsel bir Çalışma.

[1]İhsan AKSOY, [2]Hüseyin UÇAR

[1]Psychiatry, Ataturk Sanatorium Training and Research Hospital, Ankara, Türkiye
[2]Psychiatry, Ataturk Sanatorium Training and Research Hospital, Ankara, Türkiye

**Correspondence**

Ihsan Aksoy
Department of Psychiatry, Ataturk Sanatorium Training and Research Hospital, Ankara, Türkiye.

**E-Mail:** drihsanaksoy@gmail.com

**How to cite ?**

Aksoy İ, Uçar H. Do Peripheral Blood Inflammation Indices Differ Among Schizophrenia Patients with Clozapine Treatment? A Cross-sectional Investigation. Genel Tıp Derg. 2024;34(6):849-852

**ABSTRACT**

**Background/Aims:** There remains a need to investigate alternative pathophysiological processes in schizophrenia such as neuroinflammatory processes. We aimed to compare blood count levels, with a particular focus on peripheral blood inflammatory cell levels, among three distinct groups of participants: schizophrenia patients taking clozapine, schizophrenia patients taking antipsychotics other than clozapine, and healthy controls. We also evaluated the relationship between these findings and clinical characteristics.
**Methods:** The SC group included 47, the SA group included 61 patients and the HC group included 65 healthy controls. The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) were calculated by dividing the respective cell counts from white blood cell count (WBC). The relationship between these measures and clinical characteristics are done with the Positive and Negative Syndrome Scale (PANSS).
**Results:** WBC counts were significantly higher in the SC group than in the SA and HC groups. The log transformed NLR (LnNLR) was significantly higher in the SC group than the HC group and SA group, but there were no difference between the the SA and HC groups. LnNLR was significantly correlated with PANSS positive, general and total scores, but not significantly correlated with PANNS negative score. LnNLR was significantly different between groups after adjusting for age and gender using ANCOVA.
**Conclusions:** The current study sheds light on the potential immunological alterations associated with schizophrenia and its treatment with clozapine. The elevated NLR in individuals receiving clozapine treatment underscores the need for further research to elucidate the underlying mechanisms and clinical implications of this observation.

**Keywords:** Schizophrenia, Clozapine, Inflammation, Neutrophil-lymphocyte ratio

**ÖZ**

**Amaç:** Şizofrenide nöroinflamatuar süreçler gibi alternatif patofizyolojik süreçlerin araştırılması önemlidir. Ayrıca antipsikotik ilaçların inflamatuar etkilerine dair yayınlar mevcuttur. Bu çalışmada, klozapin kullanan (SC) ve kullanmayan (SA) şizofreni hastalarını ve sağlıklı kişileri (HC), periferik kan inflamatuar indeksleri açısından karşılaştırmayı ve klinik özellikler ile ilişkilerini araştırmayı amaçladık.
**Gereç ve Yöntem:** SC grubunda 47, SA grubunda 61 hasta ve HC grubunda 65 sağlıklı kontrol yer aldı. Nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve monosit-lenfosit oranı (MLR), son 6 aydaki tam kan sayımlarından retrospektif olarak taranarak hesaplandı. Bu ölçümler ile klinik özellikler arasındaki ilişki Pozitif ve Negatif Sendrom Ölçeği (PVNSÖ) ile araştırıldı.
**Bulgular:** Beyaz küre (BK) sayıları SC grubunda, SA ve HC gruplarına göre anlamlı derecede yüksekti. Log dönüştürülmüş NLR (LnNLR), SC grubunda HC grubu ve SA grubuna göre anlamlı derecede yüksekti ancak SA ve HC grupları arasında fark yoktu. LnNLR, PANSS pozitif, genel ve toplam puanlarıyla anlamlı düzeyde korelasyon gösterirken PVNSÖ negatif puanıyla ilişkili bulunmadı. ANCOVA kullanılarak yaş ve cinsiyet etkisi arındırıldıktan sonra LnNLR halen SC grubunda anlamlı olarak yüksek tespit edildi.
**Sonuç:** Bu çalışmanın sonuçları şizofreni etyolojisinde immünolojik süreçlerin rolüne ve klozapinin periferik kan inflamatuar indeksleri üzerine etkisine ışık tutmaktadır. Retrospektif ve kesitsel dizaynı nedeniyle nedensellik bağı kurulamamıştır, ancak prospektif çalışmalara olan ihtiyacı göstermektedir.

**Anahtar kelimeler:** Şizofreni, Klozapin, İnflamasyon, Nötrofil-lenfosit oranı

## Introduction

Schizophrenia is a pervasive mental disorder affecting approximately 1% of the global population. It manifests through a spectrum of symptoms, including positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., social withdrawal, apathy), and cognitive impairments. Existing antipsychotic medications that modulate dopamine and serotonin pathways have been effective in managing psychotic symptoms and reducing relapse risk for some individuals with schizophrenia (1). However, there remains a need to investigate alternative treatment approaches that target other neurobiological mechanisms, such as those involving glutamate receptors or neuroinflammatory processes.

Schizophrenia's causes involve a mix of genetic and environmental factors. There is no single theory explaining its neuropathology, but multiple hypotheses have been proposed (2). Many studies have found that

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

people with schizophrenia have imbalances in their immune systems compared to healthy people (3). The role of the immune system in the pathogenesis of schizophrenia and related psychotic disorders may have important therapeutic implications. Both the innate and adaptive immune responses may be involved in the pathogenesis of schizophrenia. The innate response involves neutrophils and macrophages, while the adaptive response includes T and B lymphocytes. Inflammation may increase the permeability of the blood-brain barrier, facilitating the entry of immune components into the brain, which, along with genetic studies, suggests an immune-mediated cause of schizophrenia (4, 5). Meta-analyses have shown that schizophrenia is associated with changes in the levels and production of cytokines, proteins that regulate the immune system (6), and patients with schizophrenia show signs of low-grade peripheral inflammation (7).

The neutrophil-lymphocyte ratio (NLR) is a simple, inexpensive, and emerging marker of systemic inflammation that can be used as an indicator in various diseases (8). NLR has been studied concerning schizophrenia in several studies. These studies have found that NLR levels are higher in patients with schizophrenia than in healthy controls (9). One meta-analysis found that an inflammatory activation occurs in psychosis and inflammatory ratios, especially NLR and monocyte-lymphocyte ratio (MLR), but not platelet-lymphocyte ratio (PLR) (10). The association between NLR and schizophrenia suggests that inflammation may play a role in the development or progression of the disorder.

Antipsychotic drugs have been shown to affect the NLR in schizophrenia patients, but the results are conflicting, with some studies reporting an increase and others reporting a decrease (11). Particularly clozapine, has known immunomodulatory effects, including the ability to suppress granulopoiesis and lead to neutropenia or agranulocytosis, though the exact mechanism remains unclear (12). Clozapine can also induce various transient hematologic dysfunctions, including neutropenia, eosinophilia, leukocytosis, and minor changes in the numbers of lymphocytes, monocytes, and basophilic granulocytes (13).

Although the profound effect of clozapine on inflammatory cells, we have found no study assessing differences in peripheral inflammatory markers among schizophrenia patients according to their treatment status with clozapine. Based on this information and the hypothesis that schizophrenia patients whose treatment included clozapine could differ in terms of peripheral blood inflammatory cell levels, we aimed to compare blood count levels among three distinct groups of participants: schizophrenia patients who receive clozapine alone and in combination with other antipsychotics, schizophrenia patients taking antipsychotics other than clozapine, and healthy controls. We also evaluated the relationship between these findings and clinical characteristics.

**Methods**

**Participants**

Schizophrenia patients (n:108) who met the following inclusion criteria were consecutively included in the study: They were between the ages of 18 and 65, they were being followed at an outpatient clinic of a community mental health center, they had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and they had been receiving treatment with clozapine or other antipsychotics for at least 6 months. Patients were excluded from the study if they had experienced an exacerbation of psychotic symptoms within the last 6 months, needed hospitalization, or had a well-established affective component or substance use disorder history. These exclusions were made to ensure that the blood count levels were not influenced by recent acute changes in symptom severity.

The healthy control group consisted of people (n:65) between the ages of 18 and 65 who applied to the health board for reasons other than illness, such as obtaining a gun license or a pre-employment health clearance. Persons with a history of medical or psychiatric illness and complaints were excluded from the study. Also, no disease was detected in these individuals during their medical examination and psychiatric evaluation according to the DSM-5 at the same hospital.

We reviewed the medical records of all participants to screen out those with chronic diseases, such as chronic obstructive pulmonary disease, heart disease, blood disorders, neurological conditions, and immune system disorders. These diseases and their medications could have affected the participants' inflammation markers or white blood cell (WBC) count. Therefore, all participants with a history of chronic disease

irrespective of their WBC counts were excluded. We also excluded participants with WBC counts outside the normal range (4-10 x 103/µL).

**Data collection**

This study used a descriptive, cross-sectional, and retrospective design. A clinician recorded sociodemographic information, including age and gender, for each participant. The severity of schizophrenia was assessed by a senior psychiatrist using the Positive and Negative Syndrome Scale (PANSS), which was developed by Kay, Fiszbein, and Opfer (14). The PANSS is composed of 3 subscales: Positive Scale, Negative Scale, and General Psychopathology Scale. Each subscale is rated with 1 to 7 points ranging from absent to extreme. The validity and reliability of the Turkish version of the PANSS were established by Kostakoglu et al. (15).

The values of WBC, neutrophils (NE), lymphocytes (LY), platelets (PL), and monocytes (MO) were retrospectively collected from digital medical records of participants who had a complete blood count (CBC) available within the last 6 months from the same hospital and biochemistry laboratory. The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) were calculated by dividing the respective cell counts.

**Statistical analysis**

Data analysis was conducted using SPSS (version 24.0) to describe the demographic and other selected characteristics of the participants. The Kolmogorov–Smirnov test was used to assess the compatibility of data from the groups with normal distribution. The chi-square test was used to compare grouped data, and the Kruskal–Wallis or the one-way analysis of variance (ANOVA) was used to compare three groups. Analysis of covariance (ANCOVA) was used to control for age and gender when looking at group differences. A two-tailed p-value less than 0.05 was considered statistically significant. Significance was set at p=0.05/3 (0.017) for the post-hoc Bonferroni corrected comparisons.

**Results**

The participants in this study included 47 (27.2%) people with schizophrenia who were treated with only clozapine and/or clozapine with other antipsychotics (SC), 61 (35.3%) people with schizophrenia who were treated with antipsychotics other than clozapine (SA), and 65 (37.5%) healthy controls (HC).

The SC group had a higher percentage of males (74.5%) than the SA group (54.1%) or the HC group (64.6%), but the gender difference was not statistically significant (p=0.09). The average age of the participants in the SC group was 42.44 years, in the SA group was 47.39 years, and in the HC group was 36.81 years. The age difference was statistically significant across all groups (p=0.01). Demographic characteristics and the PANNS) values of the participants are given in Table 1.

**Table 1.** Characteristics of patients with schizophrenia and healthy comparison subjects.

| | SC (n=47) | SA (n=61) | HC (n=65) | Test Statistics | p |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male n (%) | 35 (74.5) | 33 (54.1) | 42 (64.6) | 4.805 | 0.09[a] |
| Female n (%) | 12 (25.5) | 28 (45.9) | 23 (35.4) | | |
| **Age** (mean ± SD) | 42.44 ± 9.97 | 47.39 ± 11.36 | 36.81 ± 13.62 | 12.393 | **0.01**[b] |
| **PANNS** | | | | | |
| Positive (mean ± SD) | 14.42 ± 4.12 | 9.47 ± 1.59 | - | 8.589 | **0.001**[c] |
| Negative (mean ± SD) | 23.63 ± 4.51 | 16.70 ± 3.65 | - | 8.818 | **0.001**[c] |
| General (mean ± SD) | 44.55 ± 10.27 | 33.18 ± 6.88 | - | 6.878 | **0.001**[c] |
| Total (mean ± SD) | 82.62 ± 16.43 | 59.36 ± 10.64 | - | 8.897 | **0.001**[c] |

[a]Chi-Square Test, [b]One-way ANOVA, [c]Student t-test, PANSS: Positive and negative syndrome scale, SC: Schizophrenia patients on clozapine and/or clozapine with other antipsychotics, SA: Schizophrenia patients on non-clozapine antipsychotics, HC: Healthy controls

WBC counts were significantly higher in the SC group than in the SA and HC groups (p=0.001). However, there was no significant difference in WBC counts between the SA and HC groups. Neutrophil counts were also significantly higher in the SC group than in the SA and HC groups (p=0.001). However, there was no significant difference in neutrophil counts between the SA and HC groups. Lymphocyte, monocyte, and platelet levels were not significantly different across all

groups.

To obtain a normal distribution, the NLR, PLR, and MLR values were log-transformed. The log-transformed NLR (LnNLR), log-transformed PLR (LnPLR), and log-transformed MLR (LnMLR) showed no correlation with age (r = 0.076, p = 0.321; r = 0.080, p = 0.293; r = 0.053, p = 0.485, respectively). Gender was weakly correlated with LnPLR (r = -0.158, p = 0.038) and age (r = -0.239, p = 0.002), with women tending to be older and have higher LnPLR values. Gender was not correlated with LnNLR and LnMLR. Additionally, LnNLR was strongly correlated with LnPLR (r = 0.687, p = 0.001) and LnMLR (r = 0.704, p = 0.001).

The LnNLR was significantly higher in the SC group than the HC group (p = 0.001) and SA group (p = 0.007), but there was no difference between the SA and HC groups (p = 0.262) in post-hoc analysis, as the p-value was set to 0.017 after multiple comparison correction. There were no statistically significant differences between the groups in terms of the LnPLR or the LnMLR (Table 2).

In the correlation of inflammatory indices with clinical characteristics: LnNLR was significantly correlated with PANSS positive score (r = 0.290, p = 0.002), PANSS general score (r = 0.338, p = 0.001), and PANNS total score (r = 0.308, p = 0.001) but not significantly correlated with PANNS negative score (r = 0.168, p = 0.083). There was no correlation between PANSS scores and LnMLR and LnPLR values.

**Table 2.** Comparison of peripheral blood count parameters between groups.

| | SC | SA | HC | Statistic | p | SC-SA [1] | SC-HC [1] | SA-HC [1] |
|---|---|---|---|---|---|---|---|---|
| WBC | | | | | | | | |
| (mean±SD) | 8.24 ± 1.35 | 7.54 ± 1.52 | 7.14 ± 1.45 | 7.810* | **0.001** | **0.014** | **0.001** | 0.125 |
| Mean rank | 108.54 | 85.71 | 72.63 | | | | | |
| **Neutrophil** ($10^3$/ µL) | | | | | | | | |
| (mean±SD) | 5.39 ± 1.20 | 4.42 ± 1.35 | 4.01 ± 1.04 | 18518* | **0.001** | **0.001** | **0.001** | 0.054 |
| Mean rank | 119.66 | 82.93 | 67.20 | | | | | |
| **Lymphocyte** ($10^3$/ µL) | | | | | | | | |
| (mean±SD) | 2.26 ± 0.74 | 2.42± 0.92 | 2.43 ± 0.58 | 0.828* | 0.439 | 0.267 | 0.245 | 0.969 |
| Mean rank | 77.82 | 89.21 | 91.56 | | | | | |
| **Platelet** ($10^3$/ µL) | | | | | | | | |
| (mean±SD) | 255.17 ± 59.31 | 271.88 ± 62.72 | 262.75 ± 58.88 | 1.300** | 0.522 | 0.407 | 0.878 | 0.786 |
| Mean rank | 81.22 | 92.21 | 86.28 | | | | | |
| **Monocyte** ($10^3$/ µL) | | | | | | | | |
| (mean±SD) | 0.47 ± 0.14 | 0.48 ± 0.12 | 0.46 ± 0.14 | 2.375** | 0.305 | 0.947 | 0.942 | 0.609 |
| Mean rank | 87.01 | 94.09 | 80.34 | | | | | |
| NLR | | | | | | | | |
| LnNLR | 0.39 ± 0.20 | 0.27 ± 0.24 | 0.21 ± 0.13 | 11.291* | 0.001 | 0.007 | 0.001 | 0.262 |
| Mean rank | 114.24 | 84.26 | 69.87 | | | | | |
| PLR | | | | | | | | |
| LnPLR | 2.06 ± 0.18 | 2.07 ± 0.18 | 2.03 ± 0.13 | 0.878* | 0.417 | 0.838 | 0.340 | 0.213 |
| Mean rank | 87.39 | 91.20 | 82.77 | | | | | |
| MLR | | | | | | | | |
| LnMLR | 0.19 ± 0.02 | 0.19 ± 0.02 | 0.13 ± 0.01 | 1.963* | 0.144 | 0.858 | 0.087 | 0.100 |
| Mean rank | 92.44 | 91.59 | 78.76 | | | | | |

*One-way ANOVA; **Kruskal–Wallis; Bold values are statistically significant findings. (p<0.017), NLR: Neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; MLR: monocyte-lymphocyte ratio. SC: Schizophrenia patients on clozapine and/or clozapine with other antipsychotics, SA: Schizophrenia patients on non-clozapine antipsychotics, HC: Healthy controls

[1]Two-way comparisons of groups

Finally, levels of LnNLR were significantly different between the three groups after adjusting for age and gender using ANCOVA (F=10.529, p=0.001). The difference between the SA and HC groups was not significant (p=0.438), but the difference between the SC and SA groups (p=0.002) and the SC and HC groups (p=0.007) remained significant after post-hoc analysis.

**Discussion**

The present study has yielded intriguing insights into the potential immunological alterations associated with schizophrenia and its treatment with clozapine. Our main finding was elevated LnNLR levels in the SC group more than SA and HC groups. NLR has been proposed as an indicator of systemic inflammation and immune response, with higher values often associated with poorer clinical outcomes in various medical conditions (16). Our finding aligns with previous studies that have reported increased NLR levels in individuals with schizophrenia more than in healthy controls (17, 18). These studies collectively underscore the disruption of the neutrophil-lymphocyte ratio (NLR) in the context of the disorder, highlighting its potential significance as an immune marker. While the exact mechanisms underlying these alterations remain unclear, they may reflect systemic inflammation or immune dysregulation associated with the disorder and its treatment. Also in first-episode psychosis, there was a tendency toward a higher total WBC count, with significantly increased levels of neutrophils and monocytes compared to controls. These findings suggest that schizophrenia is associated with alterations in blood inflammatory markers, including cytokines in treatment naive individuals (19). Interestingly, the lack of significant differences in LnPLR and LnMLR across the groups suggests that platelet and monocyte counts might not be as prominently influenced by the schizophrenia diagnosis or its treatment.

Although we have found an elevation in the LnNLR in the SC group, the SA group was no different from the HC group. Onder et al. reported increased NLR levels in both chronic schizophrenia and first-episode psychosis (20). Moreover, Sandberg et al., reported that there was a correlation between neutrophil count and NLR with positive symptoms of schizophrenia (11). Additionally, NLR is positively associated with disease severity in drug-free patients (21). The reason for the lack of difference in LnNLR between the SA group and the HC group may be that the patients in the SA group responded better to treatment and were not resistant, and they did not need clozapine treatment before. It is plausible that more treatment-resistant patients under clozapine therapy may exhibit sustained elevated LnNLR levels despite the intervention. In a review, it was concluded that WBC counts could be a feasible biomarker and used to track treatment-resistant schizophrenia patients (22).

Another finding of our study supporting this assumption is that LnNLR was significantly correlated with PANSS scores except for the PANNS negative score. Similarly, Eric et al. have found that higher levels of granulocytosis and lymphopenia in individuals with schizophrenia predicted poorer recovery of positive symptoms after six months of antipsychotic treatment, a relationship that specifically applies to patients with initially significant positive symptoms, while those with primarily negative symptoms have normal leukocyte proportions (23). It is worth noting that, some studies are not in alignment with our findings. In the study by Shen et al., it was found that the correlation between NLR and psychiatric symptoms varied with antipsychotic therapy status, showing a negative correlation between NLR and severe negative symptoms in the drug-therapy subgroup after adjusting for potential confounding factors (24).

Divergent findings are evident in the existing literature regarding the impact of antipsychotic medications on the NLR. For instance, Sandberg et al. suggested that antipsychotic therapy might lead to a reduction in neutrophil count and NLR (11). However, contrasting results emerged from the investigation by Bustan et al., wherein a significant effect of antipsychotic medication on the NLR was not observed (25). No prior research has investigated the NLR specifically among patients undergoing clozapine treatment, despite the robust influence of clozapine on peripheral blood parameters such as agranulocytosis, which is why WBC counts are screened for as a safety measure (12). The present study's outcomes, revealing heightened LnNLR in individuals receiving either clozapine monotherapy or clozapine combined with other antipsychotics, offer an insightful standpoint in this regard. Patients who had suppressed WBC counts such as neutropenia and agranulocytosis were not included in this study. Our finding is interesting in that regard that besides this minority of patients experiencing one of the most dangerous medication side effects of clozapine, the majority of the patients seem to have oppositely elevated neutrophil counts. The findings from the

ANCOVA analysis, which accounted for age and gender, demonstrated that the differences in LnNLR between the groups remained significant. Importantly, the significant differences between the SC and SA groups, as well as between the SC and HC groups, highlight the potential influence of clozapine on immune profiles beyond what can be explained by demographic factors alone. This suggests that clozapine treatment might play a role in shaping immune parameters in individuals with schizophrenia.

**Conclusion**

In conclusion, the current study sheds light on the potential immunological alterations associated with schizophrenia and its treatment with clozapine. The elevated NLR in individuals receiving clozapine treatment underscores the need for further research to elucidate the underlying mechanisms and clinical implications of this observation. Future studies could explore the longitudinal changes in immune parameters with clozapine treatment, investigate potential links between immune alterations and clinical outcomes, and delve into the molecular pathways that might contribute to the observed differences in neutrophil-lymphocyte balance.

**Limitations**

The sample size of each group in our study may have limitations in terms of statistical power and generalizability. Our study adopted a cross-sectional design, which inherently limits our ability to establish causal relationships. Longitudinal studies with multiple time points could offer a clearer picture of the dynamic changes in immune parameters throughout treatment and their association with symptomatology. While our findings suggest an association between clozapine treatment and elevated NLR levels, we did not directly assess the specific mechanisms underlying these effects. And, it should be noted that some patients in the SC group were taking antipsychotics other than clozapine. The potential influence of other factors, such as medication dose, treatment duration, and individual variations in drug response warrants further investigation. Although we controlled for age and gender in our analysis, other potential confounding factors, such as smoking and body mass index, were not fully accounted for and HCs were evaluated only by psychiatric and physical examination, and no scale was used.

**Ethical approval**

It was approved by the institutional ethics committee of an Education and Research Hospital under the Declaration of Helsinki [Protocol No: 27.12.2023-2865].

**Informed consent**

Since participants' data were collected anonymously, with each participant assigned a protocol number, informed consent was not required.

**Conflict of Interest**

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

**Research funding**

None declared.

**Authors' Contributions**

All the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

**References**

1.Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. Lancet. 2022;399(10323):473-86.

2.Zamanpoor M. Schizophrenia in a genomic era: a review from the pathogenesis, genetic and environmental etiology to diagnosis and treatment insights. Psychiatr Genet. 2020;30(1):1-9.

3.Kroken RA, Sommer IE, Steen VM, Dieset I, Johnsen E. Constructing the Immune Signature of Schizophrenia for Clinical Use and Research; An Integrative Review Translating Descriptives Into Diagnostics. Front Psychiatry. 2019;9:753.

4.Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature. 2009;460:753-57.

5.Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu DH, et al. Common variants conferring risk of schizophrenia. Nature. 2009;460:744-47.

6.Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008;63:801-8.

7.Miller B, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011:70;663-71.

8.Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102:5–14.

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

10.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):326-38.

11.Sandberg AA, Steen VM, Torsvik A. Is Elevated Neutrophil Count and Neutrophil-to-Lymphocyte Ratio a Cause or Consequence of Schizophrenia?-A Scoping Review. Front Psychiatry. 2021;16:12.

12.Sperner-Unterweger B, Gaggl S, Fleischhacker WW, Barnas C, Herold M, Geissler D. Effects of clozapine on hematopoiesis and the cytokine system. Biol Psychiatry. 1993;34(8):536-43.

13.Hummer M, Kurz M, Barnas C, Saria A, Fleischhacker WW. Clozapine-induced transient white blood count disorders. J Clin Psychiatry. 1994;55(10):429-32.

14.Kay SR, Fiszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261.

15.Kostakoglu E, Batur S, Tiryaki A, Gogus A. Reliability and Validity of the Turkish version of the Positive and Negative Syndrome Scale. Turk Psikoloji Dergisi. 1999;14:23-32.

16.Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):124.

17.Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, et al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub. 2014;26(3):220-5.

18.Yüksel RN, Ertek IE, Dikmen AU, Göka E. High neutrophil-lymphocyte ratio in schizophrenia independent of infectious and metabolic parameters. Nord J Psychiatry. 2018;72(5):336-40.

19.Jackson AJ, Miller BJ. Meta-analysis of total and differential white blood cell counts in schizophrenia. Acta Psychiatr Scand. 2020;142(1):18-26.

20.Onder A, Surer A, Gizli CO, Bilac O, Kavurma C. Elevated Neutrophil/Lymphocyte Ratio in Adolescents with Early-onset Schizophrenia. Neurochem Journal. 2020;14(4):444-8.

21.Zhu X, Zhou J, Zhu Y, Yan F, Han X, Tan Y, et al. Neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios in schizophrenia. Australas Psychiatry. 2022;30(1):95-9.

22.Jiao S, Cao T, Cai H. Peripheral biomarkers of treatment-resistant schizophrenia: Genetic, inflammation and stress perspectives. Front Pharmacol. 2022;12:13.

23.Zorrilla EP, Cannon TD, Kessler J, Gur RE. Leukocyte differentials predict short-term clinical outcomes following antipsychotic treatment in schizophrenia. Biol Psychiatry. 1998;43(12):887-96.

24.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;30:11..

25.Bustan Y, Drapisz A, Ben DH, Avrahami M, Schwartz-Lifshitz M, Weizman A et al. Elevated neutrophil to lymphocyte ratio in non-affective psychotic adolescent inpatients: Evidence for the early association between inflammation and psychosis. Psychiatry Res. 2018;262:149-53.