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# THE ROLE OF CYTOKINES IN SCHIZOPHRENIA

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Schizophrenia, a multisystem condition with an unclear cause, is linked to immunological dysfunctions, including altered cytokine levels. The possible role that inflammation could play in psychiatric diseases has been the subject of a growing corpus of research in the last 20 years. Individuals with schizophrenia have abnormal cytokine synthesis, abnormal cytokine concentrations, and altered cytokine receptors in their blood and cerebrospinal fluid, suggesting a relationship between inflammation and schizophrenia. Contradictory results have been observed in psychosis, leaving the pathophysiological function of inflammation in psychosis unclear. The population with chronic schizophrenia has been extensively investigated. Still, the group with first-episode psychosis (FEP) provides a unique chance to assess the biological, clinical, and functional consequences of psychotic illnesses. Results regarding cytokine concentration are inconsistent, which is a consequence of different research methodologies. However, it was found that there was a relationship between inflammation markers and disease symptoms. The development of biomarkers as quickly as possible following the onset of a disease might open the way for early disease prevention, which improves the prognosis. Intervention at an early stage stops the progression of the disease and enhances treatment outcomes. The drug-free FEP population is receiving a growing amount of attention from researchers who are conducting studies on a large scale. *Acta Medica Medianae 2023;62(2): 52-60.*

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## Introduction

Approximately 1 in 300 people worldwide have schizophrenia, a persistent and frequently debilitating mental condition that typically develops in late adolescence or early adulthood. It is characterized by positive (delusions, hallucinations and disorganization), negative (such as apathy, avolition or alogia), affective and cognitive symptoms (1, 2) and it is linked with higher mortality rates, severe cognitive impairment, and poor quality of life (3). Over the last two decades, there has been a greater emphasis on early intervention treatments for first-episode psychosis (FEP) (4). A first episode of psychosis (FEP), an acute time during which a person loses some sense of reality, is typically brought on by risk factors for schizophrenia. This may include sporadic hallucinations, delusions, and behavioral, cognitive, and functional disturbances. After receiving treatment, most people experience an initial remission of symptoms. However, symptoms remain and recur for one in three people, which raises the possibility of developing a more persistent condition (5). The clinical progression following a FEP was protracted and unpredictable, resulting in major quality of life losses for patients and their families as well as huge societal expenses. This clinical development accounts for 10% of the global burden of mental diseases in Europe (6).

Inflammation is regarded as a contributory or mediating component in the start of schizophrenia, even though genetic susceptibility and environmental stresses in the earliest years of life are crucial for the course of schizophrenia (7, 8). Neuroinflammation can damage white matter and dysconnectivity, leading to schizophrenia symptoms (9). It is well-established that a

dysregulated immunological response is associated with psychosis. Systemic inflammation can exert a major effect on the brain, as demonstrated by a growing body of studies linking inflammation and immunology to the development of schizophrenia symptoms, resulting in emotional, cognitive, and behavioral abnormalities. A potential link between inflammation and both FEP and schizophrenia has been proposed for decades (10, 11).

In this regard, the peripheral immune system-to-brain communication pathways have been widely investigated in several neuroinflammatory diseases in which inflammatory cytokines are believed to play a significant role (12, 13). It has been hypothesized that the immune responses of the periphery are reflective of the neuroimmune status of the brain. As a result, the concentrations of systemic cytokines are becoming increasingly significant for showing how inflammation may bestow particular symptom patterns in FEP (14).

Cytokines are small proteins that profoundly impact nearly every aspect of biology, from embryonic development and disease etiology to particular and immunological responses that are not specific, cognitive function, and the course of degenerative aging. They play an important role in coordinating inflammation and its response. From the perspective of the pathways they trigger, cytokines are mainly classified as pro-inflammatory and anti-inflammatory (15, 16). Given the powerful impact of cytokines, it is becoming evident that abnormalities in cytokine production, release, and signaling can play a role in the development of many different human illnesses.

The majority of research on schizophrenia and associated disorders is conducted on small patient populations. They refer to patients with a drug-naive first psychotic episode (FEDN), whose condition was monitored before administering antipsychotics to therapy. The following research cohort consists of patients with a first psychotic episode (FEAP) taking antipsychotics. The third category comprises those with subsequent psychotic episodes (relapse), followed by schizophrenia patients in stable remission. Less frequently studied patient groups include those with early-onset psychosis and those at clinically high-risk or ultra-high-risk for psychotic illness.

### Interleukin 1 (IL – 1β)

In response to lipopolysaccharide (LPS), various cytokines, and complement fragments, the cytokine IL-1ß, a member of the IL-1 family, is largely secreted by monocytes, macrophages, microglia, and lymphocytes. IL-1ß also plays a role in the complement system. It is regarded as one of the most significant pro-inflammatory cytokines (17). Multiple studies indicate that IL-1ß plays a significant role in the etiology and pathophysiology of schizophrenia. Patients with schizophrenia have an elevated release of IL-1β by peripheral monocytes prior to therapy, which is thereafter normalized by antipsychotics (18). Most patients with FEDN (19), adult and pediatric FEAP (20), and patients with chronic illness who were stable, undergoing an acute relapse, or recovering from one (11, 21, 22) had elevated levels of IL-1ß. On the other hand, many studies indicated an increase in IL-1ß levels, the 2008 meta-analysis found no significant changes in IL-1ß levels in vivo and in vitro serum concentrations (23). Serum concentrations of IL-1ß are significantly elevated in patients with acute phases of schizophrenia, independent of age or illness duration (24). Schizophrenia has been linked to a malfunction of dopaminergic and glutamatergic circuits in the brain, and it is known that IL-1 can increase the dopaminergic differentiation of rat mesencephalic progenitor cells (25). It is unclear whether IL-1ß activation causes schizophrenia or results from dopaminergic or glutamatergic dysfunction. Those who have been ill for more than six years and who have a chronic illness have not been found to have a significantly elevated level (26). Of note, a recent study discovered lower IL-1ß levels in FEDN patients with an illness duration of fewer than two years (22). IL-1ß peripheral levels are related to the severity of positive and negative symptoms and the overall psychopathological presentation (16).

### Interleukin 2 (IL-2)

IL-2 is produced by T-helper type 1 and cytotoxic T (Tc) cells in response to CD28 activation. Its anti-inflammatory impact is secondary to its initial pro-inflammatory effect. In addition, IL-2 stimulates the production of IL-6, interferon (IFN), and additional inflammatory mediators (17). Several studies reported that higher levels of IL-2 were associated with fewer negative symptoms and enhanced cognitive performance. If true, IL-2 could play a crucial role in the pathophysiology of schizophrenia (10, 27). IL-2R, a signaling receptor expressed on T cells, has been found to be overexpressed in schizophrenia patients (28). It is described that soluble IL-2R levels are elevated in both treatment-naive and treatment-free patients with schizophrenia and also in patients with acute and chronic disease (29, 30). A positive connection between symptom severity and IL-2R levels supports its function in schizophrenia. IL-2R levels may represent a biomarker for individuals with treatment-resistant psychosis, and a positive correlation with symptom severity and IL-2R levels indicates its role in schizophrenia (31). Several studies have found inconsistent results with those mentioned above. According to them, IL-2 levels do not change in schizophrenia individuals. Patients with FEDN, FEAP, and chronic patients experiencing an acute relapse, recovering from it,

or being stable participated in these studies (11, 19, 21).

**Interleukin 3 (IL-3)**

Chronic schizophrenia individuals have been shown to have aberrant IL-3 levels (32, 33). Fu et al. observed that the IL-3 levels in FEDN patients were significantly lower than those of healthy control subjects and chronically treated schizophrenic patients (34). Similar to what was found in earlier studies, the IL-3 levels and IL-3-like activity (IL-3-LA) were significantly higher in chronically medicated patients with schizophrenia than in control subjects (32, 33). These higher levels of IL-3 may be related to illness progression and antipsychotic treatment. There was a substantial correlation between the Positive and Negative Syndrome Scale (PANSS) general psychopathology subscales and IL-3 in medicated patients with schizophrenia. In contrast, no connection between IL-3 and any clinical psychopathology was identified in FEDN individuals. Decreased IL-3 levels in FEDN patients may be associated with neuronal death and aberrant early brain development, which may contribute to the onset of schizophrenia.

**Interleukin 4 (IL-4)**

Even though Goldsmith et al. found decreased levels of IL-4 in FEDN patients (11), other meta-analyses, including two based on much larger samples, demonstrated that its levels were unaffected compared to healthy controls (19, 35, 36). In addition, lower IL-4 peripheral levels were found in chronic patients experiencing an acute relapse. This meta-analysis of IL-4 blood levels in this population of patients (11) was the only one conducted. No changes in IL-4 levels were detected in the population with stable schizophrenia (11) or individuals with clinical high risk (37). There was a positive correlation between IL-4 peripheral concentration, the intensity of negative symptoms, and the occurrence of depressive symptoms (16). In addition, pediatric FEAP patients (38) and adult chronic patients taking clozapine were observed to have increased levels (39).

**Interleukin 5 (IL-5)**

Long-term adult patients who had failed therapy multiple times and FEP children who predominantly took antipsychotics had elevated IL-5 levels (38, 40).

**Interleukin 6 (IL-6)**

Another important cytokine that promotes inflammation is IL-6, produced by macrophages, monocytes, and microglia. Tumor necrosis factor (TNF), interferons, lipopolysaccharide, and viral infections stimulate the secretion of IL-6 (17). C-reactive protein (CRP), which may influence the permeability of the BBB and the proliferation of microglia, is one of the acute-phase proteins whose synthesis is enhanced by IL-6 (17, 37). Reduced glutamate reuptake and disruption of neurogenesis may result from changes in IL-6 levels (41). IL-6 can be regarded as a schizophrenia "state marker." In this context, the blood levels of IL-6 and sIL-6R are higher in schizophrenia patients (19, 42). A substantial number of studies, including meta-analyses, reported elevated levels of IL-6 in several patient categories, including FEDN and FEAP patients (11, 19–21, 38). According to studies, IL-6 levels are elevated in FEP and acute relapse patients, however, normalize following antipsychotic therapy. There is a correlation between treatment-resistant schizophrenia and elevated levels of IL-6 (43), as well as between IL-6 concentration and illness duration (44). The level of IL-6 in the blood is associated with both negative and positive symptoms, as well as general psychopathological manifestations and cognitive deficits (16, 45). Interestingly, Miller at al. (21) also revealed a negative connection between IL-6 CSF levels and the severity of schizophrenia symptoms. There is a correlation between treatment-resistant schizophrenia and elevated levels of IL-6 (43), as well as between IL-6 concentration and illness duration (46). In contrast, some investigations showed no significant differences in IL-6 levels among schizophrenia individuals (47, 48).

**Interleukin 8 (IL-8)**

Serum IL-8 levels are higher in schizophrenia patients and associations with serum IL-2 or IL-8 concentrations at baseline and therapy efficacy have been found (49). Compared to the control group, patients with the diagnosis of paranoid schizophrenia exhibited statistically significant elevations in serum IL-8 levels (50, 51). In FEDN (21, 35) and relapsed chronic patients with schizophrenia (11, 21, 52) but not in FEAP (21, 35), peripheral levels persistently increased (53). In contrast, neither clinically high-risk nor ultra high-risk populations show any changes (38, 39). Western blotting has demonstrated that the expression of IL-8 in the brain tissue of schizophrenia patients is much higher than that of healthy controls. This high IL-8, IL-6, and TNF levels imply that schizophrenia may be an autoimmune neuropsychiatric spectrum disorder which may occur during an autoimmune CNS disease (54). The peripheral concentration of IL-8 correlates positively with the severity of negative symptoms and the overall psychopathological presentation. The prognosis for negative symptoms is lower for patients with increased IL-8 levels. It appears that IL-8 levels go up as the disease progresses (16).

### Interleukin 10 (IL-10)

Despite the fact that one meta-analysis indicated higher levels of IL-10 in FEDN patients (11), two later meta-analyses utilizing larger sample sizes demonstrated that its levels in this group were unaltered relative to healthy controls (35, 36). Intriguingly, relapsed patients with schizophrenia appear to have decreased peripheral IL-10 levels than healthy controls, but these findings are based on two small-scale studies (11, 21). One meta-analysis examined IL-10 peripheral levels in schizophrenia patients, revealing that these levels were unaffected (11). Similarly, peripheral IL-10 levels appear constant relative to healthy controls in people with clinically high and very high risk (37, 55). Peripheral levels of IL-10 have been reported to have positive relationships with the severity of negative symptoms, general psychopathological presentation, attention deficits, and the incidence of aggressive behaviors. On the other hand, researchers have discovered that low levels of IL-10 in the periphery are negatively correlated with cognitive deficits (16). Increased peripheral IL-10 levels were related to loss of microstructural white matter integrity in schizophrenia, supporting the notion that inflammation may play a crucial role in the pathophysiology of microstructural white matter in schizophrenia (34).

### Interleukin 12 (IL-12)

Several studies identified higher levels of IL-12, one of the other T-helper 2 cytokines, in FEP patients, regardless of whether they were drug-naive or not, and in stable chronic patients, undergoing an acute relapse or recovering from one (11, 21, 56). In contrast to the studies that found elevated levels of IL-12, other studies were unable to duplicate these findings. They reported no change in FEAP levels of this cytokine (20, 45) and chronic antipsychotic-treated patients (53, 57). Cognitive deficits appear to be correlated with peripheral IL-12 concentrations (16).

### Interleukin (IL-17)

A study that discovered a higher level of Th17 cell activation in people with recent onset schizophrenia has strengthened the idea that a discrepancy in the IL-17 pathway plays a role in schizophrenia (58). In schizophrenia patients, lower IL-17 levels were observed and a significant decline in Th17 cells (59). There were no changes in peripheral IL-17 levels between patients with FEDN and healthy controls (11, 60). Higher peripheral levels in FEDN were found in the largest sample (36). Studies have shown a negative association between IL-17 and negative symptoms. In contrast, there is a positive correlation between IL-17 and the severity of positive symptoms, the overall psychopathological presentation, and the frequency of aggressive behaviors (16, 45).

### Interleukin 18 (IL-18)

IL-18, a pro-inflammatory cytokine that belongs to the IL-1 family, is secreted by macrophages, dendritic cells, astrocytes, and other epithelial cell types (17) and it is crucial to the Th1 immune response (61). It stimulates the production of gamma interferon IFN-γ in Th1 cells in synergism with IL-12 (62). Goldsmith et al. investigated IL-18 peripheral levels in psychosis, using an entirely FEDN sample and found that level was unchanged compared to healthy controls (11). Tanaka et al. identified increased levels of IL-18 in the serum of schizophrenic patients relative to healthy controls (61). Xiu et al. reported considerably more significant levels of IL-18 in the serum of patients with chronic schizophrenia compared to those with first-episode schizophrenia and healthy controls (63). In addition, significant positive relationships were established between IL-18 and the PANSS score in chronic patients. In FEAP patients, however, there was no significant link between IL-18 and psychopathology. Among chronic patients, there were no differences in IL-18 levels between those medicated with conventional and atypical antipsychotics, independent of treatment dose or duration (63).

### Tumor necrosis factor (TNF-α)

TNF-α is one of the proinflammatory cytokines, and it is produced almost exclusively by macrophages. TNF-α boosts the cytotoxicity of macrophages, as well as the immune system's ability to create oxidative stress. Other cytokines, like IL-1, IL-6, and IFN-γ, are secreted in response to TNF-α. TNF-α is also produced by microglia and may change neuroplasticity and decrease neurogenesis by promoting the death of hippocampus stem cells (17). Multiple studies reported elevated levels of TNF-α, in FEDN patients (19, 21), FEAP patients (11, 64), and chronically ill patients taking antipsychotics, regardless of their acute relapse status (21, 22). It has been found that stable chronic patients receiving atypical antipsychotics had greater levels of TNF-α (65). In contrast, Miller at al. indicated that TNF-α levels in the population with schizophrenia were unaffected (21). FEDN patients with an illness duration of less than two years (22) and chronic patients with a disease duration of more than five years who take antipsychotics have decreased levels of TNF-α (66, 67). A lower TNF-α concentration in chronic patients who use antipsychotics is associated with positive symptoms and higher scores on the PANSS as well as with worse cognitive abilities. At the same time, this correlation was not found in FEDN. Positive

association exists between higher TNF-α levels and negative symptoms (16).

### Interferon gamma (IFN-γ)

Interferon (IFN- γ) is a pro-inflammatory cytokine produced by activated CD4 T helper type 1 (Th1) cells, CD8 cytotoxic T cells, T cells, and natural killer (NK) cells, as well as, to a lesser extent, natural killer T cells (NKT), B cells, and professional antigen-presenting cells (APCs) (17). Several researchers revealed no significant changes in the levels of IFN-γ in FEDN patients (59, 68–70), but others found elevated levels of IFN-γ (21, 71). In contrast, one study discovered lower levels of IFN-γ in FEDN patients (72). Studies revealed higher levels of this cytokine in FEP patients, most of whom had used antipsychotics in the past (11, 20). Several investigations, including several meta-analyses, reported higher levels of IFN-γ in stable or acutely relapsing chronic schizophrenia patients (11, 21, 53). Reduced levels of IFN-γ were identified in individuals with acute psychotic symptoms who had not taken any drugs for at least six months, as well as in patients with chronic illness (73). No alterations of IFN-γ levels were found in clinically high-risk or ultra-high risk populations (37, 55).

### Conclusion

In an attempt to find an inflammatory biomarker for schizophrenia, researchers try to separate different types of deviation from healthy controls in trait markers, which are related to hereditary and neurodevelopmental factors, and state markers related to the disease itself and its symptoms. Meta-studies in this field have come up with contradictory results. This may be due to small sample size, diverse patients` characteristics, heterogeneous population, different sampling methods and the difference between plasma, serum or whole blood cytokine profiles. The population with first-episode psychosis provides a unique opportunity to study the biochemical, clinical, and functional outcomes of psychotic disorders. Antipsychotic medication, comorbidity, and chronicity are all confounding factors that can be avoided with longitudinal study beginning at the onset of illness.

Establishing biomarkers as promptly as feasible after acquiring a disease can prevent early illness, increasing the prognosis. Early intervention reduces disease development and improves treatment results. Drug naïve FEP population has become an increasing research focus, with large-scale studies being done in both the United States and Europe.

### References


1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Publishing; 2013. [CrossRef]
2. World Health Organization. Schizophrenia. World Health Organization. [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/schizophrenia
3. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1789–858. [CrossRef][PubMed]
4. Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, et al. Remission and recovery from first-episode psychosis in adults: A systematic review and meta-analysis of long-term outcome studies. Schizophr Bull 2017;43(1):73–81. [CrossRef][PubMed]
5. Addington D, Jean Addington MD, Patten S. Relapse rates in an early psychosis treatment service. Acta Psychiatr Scand 2007;115(2):126–31. [CrossRef][PubMed]
6. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, “just the facts” 4. Clinical features and conceptualization. Schizophr Res 2009;110(1–3):1–23. [CrossRef][PubMed]
7. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. Mol Psychiatry 2005;10(1):40–68. [CrossRef][PubMed]

8. Fan X, Goff DC, Henderson DC. Inflammation and schizophrenia. Expert Rev Neurother 2007;7(7):789–96. [CrossRef][PubMed]
9. Dawidowski B, Górniak A, Podwalski P, Lebiecka Z, Misiak B, Samochowiec J. The Role of Cytokines in the Pathogenesis of Schizophrenia. J Clin Med 2021;10(17):10. [CrossRef][PubMed]
10. Ganguli R, Rabin BS, Belle SH. Decreased interleukin-2 production in schizophrenic patients. Biol Psychiatry 1989;26(4):427–30. [CrossRef][PubMed]
11. 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):1696–709. [CrossRef][PubMed]
12. D'Angelo C, Reale M, Costantini E, Di Nicola M, Porfilio I, de Andrés C, et al. Profiling of canonical and non-traditional cytokine levels in interferon-β-treated relapsing-remitting-multiple sclerosis patients. Front Immunol 2018;9(JUN):1240. [CrossRef][PubMed]
13. Reale M, D'Angelo C, Costantini E, Di Nicola M, Yarla NS, Kamal MA, et al. Expression Profiling of Cytokine, Cholinergic Markers, and Amyloid-β Deposition in the APPSWE/PS1dE9 Mouse Model of Alzheimer's Disease Pathology. J Alzheimer's Dis 2018;62(1):467. [CrossRef][PubMed]
14. Goldsmith DR, Rapaport MH. Inflammation and Negative Symptoms of Schizophrenia: Implications for Reward Processing and Motivational Deficits. Front Psychiatry 2020;11. [CrossRef][PubMed]
15. Liu C, Chu D, Kalantar-Zadeh K, George J, Young HA, Liu G. Cytokines: From Clinical Significance to Quantification. Adv Sci 2021;8(15):2004433. [CrossRef][PubMed]
16. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine Alterations in Schizophrenia: An Updated Review. Front Psychiatry 2019;10. [CrossRef][PubMed]
17. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. J Allergy Clin Immunol 2016;138(4):984–1010. [CrossRef][PubMed]
18. Kowalski J, Blada P, Kucia K, Madej A, Herman ZS. Neuroleptics normalize increased release of interleukin-1β and tumor necrosis factor-α from monocytes in schizophrenia. Schizophr Res 2001;50(3):169–75. [CrossRef][PubMed]
19. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr Res 2014;155(1–3):101–8. [CrossRef][PubMed]
20. Lesh TA, Careaga M, Rose DR, McAllister AK, Van de Water J, Carter CS, et al. Cytokine alterations in first-episode schizophrenia and bipolar disorder: Relationships to brain structure and symptoms. J Neuroinflammation 2018;15(1):1–11. [CrossRef][PubMed]
21. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects. Biol Psychiatry 2011;70(7):663. [CrossRef][PubMed]
22. Zhu F, Zhang L, Liu F, Wu R, Guo W, Ou J, et al. Altered serum tumor necrosis factor and interleukin-1β in first-episode drug-naive and chronic schizophrenia. Front Neurosci 2018;12(MAY):296. [CrossRef][PubMed]
23. 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(8):801–8. [CrossRef][PubMed]
24. Katila H, Appelberg B, Hurme M, Rimón R. Plasma levels of interleukin-1 beta and interleukin-6 in schizophrenia, other psychoses, and affective disorders. Schizophr Res 1994;12(1):29–34. [CrossRef][PubMed]
25. Potter ED, Ling ZD, Carvey PM. Cytokine-induced conversion of mesencephalic-derived progenitor cells into dopamine neurons. Cell Tissue Res 1999;296(2):235–46. [CrossRef][PubMed]
26. Balõtšev R, Koido K, Vasar V, Janno S, Kriisa K, Mahlapuu R, et al. Inflammatory, cardio-metabolic and diabetic profiling of chronic schizophrenia. Eur Psychiatry 2017;39:1–10. [CrossRef][PubMed]
27. Mahendran R, Mahendran R, Chan YH. Interleukin-2 levels in chronic schizophrenia patients. Ann Acad Med Singapore 2004;33(3):320–3. [PubMed]
28. Ghazaryan H, Petrek M, Boyajyan A. Chronic schizophrenia is associated with over-expression of the interleukin-2 receptor gamma gene. Psychiatry Res 2014;217(3):158–62. [CrossRef][PubMed]
29. Rapaport MH, Mcallister CG, Pickar D, Nelson DL, Paul SM. Elevated levels of soluble interleukin 2 receptors in schizophrenia. Arch Gen Psychiatry 1989;46(3):291–2. [CrossRef][PubMed]
30. Rapaport MH, McAllister CG, Kim YS, Han JH, Pickar D, Nelson DL, et al. Increased serum soluble interleukin-2 receptors in Caucasian and Korean schizophrenic patients. Biol Psychiatry 1994;35(10):767–71. [CrossRef][PubMed]
31. Bresee C, Rapaport MH. Persistently increased serum soluble interleukin-2 receptors in continuously ill patients with schizophrenia. Int J Neuropsychopharmacol 2009;12(6):861–5. [CrossRef][PubMed]
32. Sirota P, Schild K, Elizur A, Djaldetti M, Fishman P. Increased interleukin-1 and interleukin-3 like activity in schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 1995;19(1):75–83. [CrossRef][PubMed]
33. Xiu MH, Lin CG, Tian L, Tan YL, Chen J, Chen S, et al. Increased IL-3 serum levels in chronic patients with schizophrenia: Associated with psychopathology. Psychiatry Res 2015;229(1–2):225–9. [CrossRef][PubMed]
34. Fu YY, Zhang T, Xiu MH, Tang W, Han M, Yun LT, et al. Altered serum levels of interleukin-3 in first-episode drug-naive and chronic medicated schizophrenia. Schizophr Res 2016;176(2–3):196–200. [CrossRef][PubMed]
35. Çakici N, Sutterland AL, Penninx BWJH, Dalm VA, de Haan L, van Beveren NJM. Altered peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis. Brain Behav Immun 2020;88:547–58. [CrossRef][PubMed]
36. Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD. A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis. Schizophr Bull 2019;45(5):1120. [CrossRef][PubMed]

37. Park S, Miller BJ. Meta-analysis of cytokine and C-reactive protein levels in high-risk psychosis. Schizophr Res 2020;226:5–12. [CrossRef][PubMed]
38. Falcone T, Carlton E, Lee C, Janigro M, Fazio V, Forcen FE, et al. Does Systemic Inflammation Play a Role in Pediatric Psychosis? Clin Schizophr Relat Psychoses 2015;9(2):65. [CrossRef][PubMed]
39. Eftekharian MM, Omrani MD, Arsang-Jang S, Taheri M, Ghafouri-Fard S. Serum cytokine profile in schizophrenic patients. Hum Antibodies 2019;27(1):23–9. [CrossRef][PubMed]
40. Maxeiner HG, Marion Schneider E, Kurfiss ST, Brettschneider J, Tumani H, Bechter K. Cerebrospinal fluid and serum cytokine profiling to detect immune control of infectious and inflammatory neurological and psychiatric diseases. Cytokine 2014;69(1):62–7. [CrossRef][PubMed]
41. Allswede DM, Buka SL, Yolken RH, Torrey EF, Cannon TD. Elevated maternal cytokine levels at birth and risk for psychosis in adult offspring. Schizophr Res 2016;172(1–3):41–5. [CrossRef][PubMed]
42. Chase KA, Cone JJ, Rosen C, Sharma RP. The value of interleukin 6 as a peripheral diagnostic marker in schizophrenia. BMC Psychiatry 2016;16(1):1–7. [CrossRef][PubMed]
43. Lin A, Kenis G, Bignotti S, Tura GJB, De Jong R, Bosmans E, et al. The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res 1998;32(1):9–15. [CrossRef][PubMed]
44. Ganguli R, Yang Z, Shurin G, Chengappa KNR, Brar JS, Gubbi AV, et al. Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness. Psychiatry Res 1994;51(1):1–10. [CrossRef][PubMed]
45. Li H, Zhang Q, Li N, Wang F, Xiang H, Zhang Z, et al. Plasma levels of Th17-related cytokines and complement C3 correlated with aggressive behavior in patients with schizophrenia. Psychiatry Res 2016;246:700–6. [CrossRef][PubMed]
46. Sasayama D, Hattori K, Wakabayashi C, Teraishi T, Hori H, Ota M, et al. Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. J Psychiatr Res 2013;47(3):401–6. [CrossRef][PubMed]
47. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, et al. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord 2009;11(7):726–34. [CrossRef][PubMed]
48. Wei L, Du Y, Wu W, Fu X, Xia Q. Elevation of plasma neutrophil gelatinase-associated lipocalin (NGAL) levels in schizophrenia patients. J Affect Disord 2018;226:307–12. [CrossRef][PubMed]
49. Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY, Shen YC. Changes in serum interleukin-2, -6, and -8 levels before and during treatment with risperidone and haloperidol: relationship to outcome in schizophrenia. J Clin Psychiatry 2004;65(7):940–7. [CrossRef][PubMed]
50. Zhang XY, Zhou DF, Zhang PY, Wu GY, Cao LY, Shen YC. Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: Association with psychopathology. Schizophr Res 2002;57(2–3):247–58. [CrossRef][PubMed]
51. Kamińska T, Wysocka A, Marmurowska-Michałowska H, Dubas-Ślemp H, Kandefer-Szerszeń M. Investigation of serum cytokine levels and cytokine production in whole blood cultures of paranoid schizophrenic patients. Arch Immunol Ther Exp (Warsz) 2001;49(6):439–45. [PubMed]
52. Wang AK, Miller BJ. Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression. Schizophr Bull 2018;44(1):75–83. [CrossRef][PubMed]
53. Frydecka D, Krzystek-Korpacka M, Lubeiro A, Stramecki F, Stańczykiewicz B, Beszłej JA, et al. Profiling inflammatory signatures of schizophrenia: A cross-sectional and meta-analysis study. Brain Behav Immun 2018;71:28–36. [CrossRef][PubMed]
54. Yum SY, Yum SK, Kim T, Hwang MY. Clinical perspectives on autoimmune processes in schizophrenia. Psychiatr Clin North Am 2009;32(4):795–808. [CrossRef][PubMed]
55. Misiak B, Bartoli F, Carrà G, Stańczykiewicz B, Gładka A, Frydecka D, et al. Immune-inflammatory markers and psychosis risk: A systematic review and meta-analysis. Psychoneuroendocrinology 2021;127. [CrossRef][PubMed]
56. Bedrossian N, Haidar M, Fares J, Kobeissy FH, Fares Y. Inflammation and Elevation of Interleukin-12p40 in Patients with Schizophrenia. Front Mol Neurosci 2016;9(MAR). [CrossRef][PubMed]
57. Boerrigter D, Weickert TW, Lenroot R, O'Donnell M, Galletly C, Liu D, et al. Using blood cytokine measures to define high inflammatory biotype of schizophrenia and schizoaffective disorder. J Neuroinflammation 2017;14(1):1–15. [CrossRef][PubMed]
58. Drexhage RC, Hoogenboezem TA, Cohen D, Versnel MA, Nolen WA, Van Beveren NJM, et al. An activated set point of T-cell and monocyte inflammatory networks in recent-onset schizophrenia patients involves both pro- and anti-inflammatory forces. Int J Neuropsychopharmacol 2011;14(6):746–55. [CrossRef][PubMed]
59. Borovcanin M, Jovanovic I, Radosavljevic G, Djukic Dejanovic S, Bankovic D, Arsenijevic N, et al. Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. J Psychiatr Res 2012;46(11):1421–6. [CrossRef][PubMed]
60. Fang X, Zhang Y, Fan W, Tang W, Zhang C. Interleukin-17 Alteration in First-Episode Psychosis: A Meta-Analysis. Mol Neuropsychiatry 2018;3(3):135. [CrossRef][PubMed]
61. Tanaka KF, Shintani F, Fujii Y, Yagi G, Asai M. Serum interleukin-18 levels are elevated in schizophrenia. Psychiatry Res 2000;96(1):75–80. [CrossRef][PubMed]
62. Alboni S, Cervia D, Sugama S, Conti B. Interleukin 18 in the CNS. J Neuroinflammation 2010;7(1):1–12. [CrossRef][PubMed]
63. Xiu MH, Chen DC, Wang D, Zhang K, Dong AL, Tang W, et al. Elevated interleukin-18 serum levels in chronic schizophrenia: Association with psychopathology. J Psychiatr Res 2012;46(8):1093–8. [CrossRef][PubMed]
64. Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, et al. Serum and gene

expression profile of cytokines in first-episode psychosis. Brain Behav Immun 2013;31:90–5. [CrossRef][PubMed]
65. Al-Hakeim HK, Al-Rammahi DA, Al-Dujaili AH. IL-6, IL-18, sIL-2R, and TNFα proinflammatory markers in depression and schizophrenia patients who are free of overt inflammation. J Affect Disord 2015;182:106–14. [CrossRef][PubMed]
66. Lv MH, Tan YL, Yan SX, Tian L, Chen DC, Tan SP, et al. Decreased serum TNF-alpha levels in chronic schizophrenia patients on long-term antipsychotics: correlation with psychopathology and cognition. Psychopharmacology (Berl) 2015;232(1):165–72. [CrossRef][PubMed]
67. Turhan L, Batmaz S, Kocbiyik S, Soygur AH. The role of tumour necrosis factor alpha and soluble tumour necrosis factor alpha receptors in the symptomatology of schizophrenia. Nord J Psychchiatry 2016;70(5):342–50. [CrossRef][PubMed]
68. Lin Y, Peng Y, He S, Xu J, Shi Y, Su Y, et al. Serum IL-1ra, a novel biomarker predicting olanzapine-induced hypercholesterolemia and hyperleptinemia in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2018;84(Pt A):71–8. [CrossRef][PubMed]
69. De Witte L, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS, et al. Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. Schizophr Res 2014;154(1–3):23–9. [CrossRef][PubMed]
70. Noto C, Ota VK, Santoro ML, Ortiz BB, Rizzo LB, Higuchi CH, et al. Effects of depression on the cytokine profile in drug naïve first-episode psychosis. Schizophr Res 2015;164(1–3):53–8. [CrossRef][PubMed]
71. Ding M, Song X, Zhao J, Gao J, Li X, Yang G, et al. Activation of Th17 cells in drug naïve, first episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2014;51:78–82. [CrossRef][PubMed]
72. Reale M, Patruno A, De Lutiis MA, Pesce M, Felaco M, Di Giannantonio M, et al. Dysregulation of chemo-cytokine production in schizophrenic patients versus healthy controls. BMC Neurosci 2011;12:13. [CrossRef][PubMed]
73. Na KS, Kim YK. Monocytic, Th1 and th2 cytokine alterations in the pathophysiology of schizophrenia. Neuropsychobiology 2007;56(2–3):55–63. [CrossRef][PubMed]

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# ULOGA CITOKINA U SHIZOFRENIJI

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Shizofrenija, multisistemski poremećaj sa nejasnom etiologijom, povezana je i sa imunološkom disfunkcijom, uključujući i izmenjene nivoe citokina. Potencijalna uloga inflamacije u razvoju psihijatrijskih bolesti predmet je sve opsežnijeg istraživanja u poslednje dve decenije. Veza između inflamacije i shizofrenije prethodno je sugerisana zbog već utvrđene abnormalne proizvodnje citokina, njihovih odstupanja u koncentraciji i njihovim receptorima u krvi i cerebrospinalnoj tečnosti kod osoba koje boluju od shizofrenije. Patofiziološki mehanizam inflamacije kod psihoza još uvek je nejasan, te su istraživanja dala kontradiktorne rezultate. Populacija koja boluje od shizofrenije opsežno je istražena. Ipak, grupa bolesnika sa prvom psihotičnom epizodom pruža jedinstvenu šansu u proceni bioloških, kliničkih i funkcionalnih posledica psihoze. Rezultati koji se tiču koncentracije citokina su nedosledni, što je posledica različite metodologije istraživanja. Međutim, ustanovljeno je da postoji veza između markera inflamacije i simptoma bolesti. Razvoj biomarkera na početku ili u ranoj fazi bolesti pruža mogućnost za ranu prevenciju bolesti, što sa sobom nosi bolju prognozu. Intervencije u ranoj fazi usporavaju napredovanje bolesti i poboljšavaju ishod lečenja. Populacija sa prvom psihotičnom epizodom, koja nije tretirana medikamentima, dobija sve veću pažnju u istraživanju. *Acta Medica Medianae 2023;62(2):52-60.*

***Ključne reči:*** *psihoza, inflamacija, shizofrenija, biomarkeri*