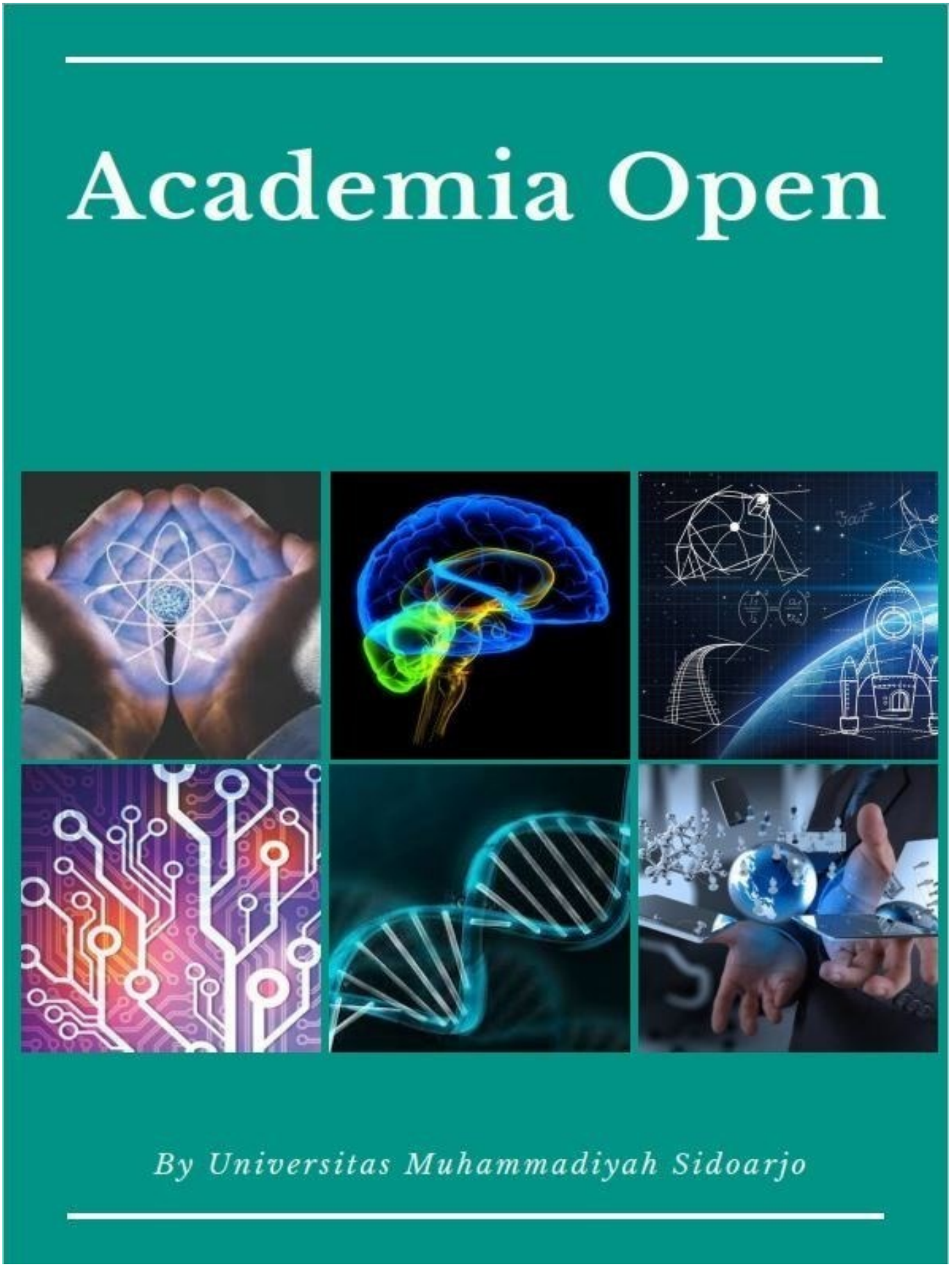
Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12867



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Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12867

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DOI: 10.21070/acopen.10.2025.12867

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Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12867

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Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12867

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Academia Open
Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12867

Neuro-inflammation and Serum Cytokine Levels in Schizophrenia Patients

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Abstract

General Background: Schizophrenia (SCZ) is a chronic and multifactorial neuropsychiatric disorder characterized by disturbances in cognition, emotion, and behavior, affecting approximately one percent of the global population. Specific Background: Recent studies have increasingly implicated neuroinflammation and immune system dysregulation, particularly involving cytokines, in the pathophysiology of SCZ. However, the specific roles and interactions of inflammatory mediators such as interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) remain unclear. Knowledge Gap: Limited empirical data exist on how these cytokines correlate with clinical characteristics and demographic factors in SCZ, especially regarding gender differences and their potential as biomarkers. Aims: This study aimed to assess serum levels of IL-8, IL-10, and TNF-α in SCZ patients compared to healthy controls using ELISA and to analyze their interrelationships. Results: Findings revealed significantly higher serum concentrations of IL-8, IL-10, and TNF-α in SCZ patients ($p<0.0001$), with IL-8 levels notably elevated in female patients. Novelty: This research highlights IL-8 as a gender-sensitive biomarker of neuroinflammation in SCZ, contributing to the understanding of immune involvement in its pathogenesis. Implications: The results suggest that cytokine profiling may aid in identifying inflammatory subtypes of SCZ and support the development of targeted immunomodulatory therapies.

Highlight :

- The study confirms elevated IL-8, IL-10, and TNF-α levels in SCZ patients compared to controls.
- Results suggest that SCZ involves neuro-inflammatory processes linked to immune system activation.
- Cytokines may serve as useful biomarkers for developing targeted therapeutic strategies in SCZ.

Keywords : Schizophrenia (SCZ), Neuroinflammation, IL-8, IL-10, Tumor Necrosis Factor-alpha (TNF-α)

Published date: 2025-11-03

Academia Open
Vol. 10 No. 2 (2025): December
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Introduction

Schizophrenia Disorder (SPD) is a type of progressive mental disorder that affects about one percent of the human population; at the same time, investigators show that more than half of the beds in mental hospitals are occupied by people suffering from this disease. This situation shows the severity of this disease compared to other mental disorders(1).The study of SPD is clinically vital. But due to the lack of extensive research and challenging treatment methods, the disease is less known, and even its misdiagnosis is considered a significant functional disorder. Identifying the phenotype of the SCZ spectrum can help researchers better understand the genetics, pathogenesis, and treatment of psychotic diseases related to it(2). SCZ is known to be a multifactorial disease. In addition to developmental and postnatal risk factors, it is associated with several genetic loci that confer risk (3). More than a century ago, the association between SCZ and the immune system was only a possible hypothesis. The traditional view of the brain says that a brain is an immune-privileged place protected behind the Blood-Brain Barrier (BBB). Still, studies over the past two decades have shown that complex interactions between the immune system, systemic inflammation, and the brain can be effective in mood, cognition, and behavior changes (4). But by conducting extensive epidemiological studies, researchers confirmed that infection and systemic inflammation are effective in a person's SCZ (5, 6). The meta-analysis of many studies confirms a relationship between SCZ and cytokine dysfunction and increased production of pro-inflammatory cytokines (7-9).

During an acute psychotic relapse in schizophrenic people (7), the serum concentration of pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin 1β, and interferon γ, increases, and the concentration of anti-inflammatory interleukin 10 in the serum decrease. After antipsychotic treatment and improvement of symptoms, the concentration of these cytokines usually reaches normal levels (7). Low-grade neuroinflammation is one of the main mechanisms of many psychiatric and cognitive disorders. One of the pro-inflammatory cytokines produced by macrophages and microglia is IL-8, which is more active in the chemical absorption of neutrophils in the bloodstream.

IL-8 in the brain is due to the release from microglia in response to pro-inflammatory stimuli. The evidence of studies on the relationship between IL-8 and depression are contradictory. However, IL-8 can be related to the prognosis of SCZ and treatment response and can affect many symptoms of SCZ. Considering that the exact role of immune changes has not yet been entirely determined, the results of genomic, blood, and brain studies show that several immune dysfunctions, including abnormal levels of circulating cytokines, are involved in SCZ (10).

IL-10 is usually produced by activated macrophages, regulatory T cells, Th2 lymphocytes, and Th3 cells involved in mucosal immunity and protection. These cells can express Th1-related cytokines such as IFN-γ and IL-2 and Inhibit TNF. And as a result, they will reduce the immune and inflammatory response (7). The complexity of the SCZ process and the lack of complete understanding of the various factors that cause it and their mutual effects can significantly pressure global health and well-being. The aim of this study was to investigate the relationship between inflammatory cytokines such as interleukin-8 (IL-8), interleukin-10 (IL-6), and Tumor necrosis factor-alpha (TNF-α) with SCZ. In this study, we have hypothesized that different serum levels of these cytokines might be visible in patients with SCZ and healthy control group.

Materails and Methods

2.1. The Ethical code, Demographic data, and clinical characteristics of SCZ patients

All research on human individuals, samples, or data has been performed by ethical rules for medicine involving human subjects, materials, and data. We obtained Ethical approval (Ethical code: ??) from the relevant ethics committee of the Arak University review board to confirm that this study meets national human research guidelines. Some socio-demographic and clinical characteristics affect the quality of life of schizophrenic patients and should be considered in inpatient evaluation and planning appropriate and effective strategies for their psychosocial rehabilitation. Socio-demographic factors evaluated were gender, age, education, marital status, and occupational/professional status. Clinical factors include medication, the duration of the disorder, the number of hospitalization, and the presence of a subtype of paranoia diagnosis (11). Thirty people agreed to participate in this research, taking into account the diagnostic criteria of the psychiatrist to be recognized as having a schizophrenic disorder. Those who decided to enter this study and met the requirements were identified as SCZ patients. The control group included 15 healthy people.

2.2. Human IL-8, IL-10, and TNFα ELISA assays

A unique serum separating tube (SST) was used to prepare human serum. Moreover, the samples were kept for 120 minutes at a temperature of 18 to 25 oC to form a clot. Then the samples were centrifuged at 1000 x g for 16 minutes. Serum samples were slowly removed from the upper surface of the centrifuge tube with a micropipette. They were divided into parts and kept in a freezer at -18 to -20 oC until ELISA Assays. The Human Pre-Coated ELISA kits (Elabscience, Cat No: E-EL-H6008, Cat No: ab185986, and Cat No: EK0525) are solid-phase immunoassays specifically designed to quantify Human IL-8, IL-10, and TNF, respectively. The procedures were carried out according to the manufacturer's protocols (12).

2.3. Statistical analysis

The statistical analyses were conducted using the GraphPad prism Version 9.0 software. The Kolmogorov-Smirnov test, which assesses the compatibility of quantitative data with a normal distribution, was employed to determine whether a sample likely originates from such a distribution. Additionally, we utilized the Unpaired t-test and the Mann-Whitney U test to compare quantitative values between the SCZ patients and the control group, considering both parametric and non-parametric data. Furthermore, the Spearman and Pearson tests were employed to analyze the relationships between quantitative variables, with significance levels set at a P value less than 0.05.

Results and Discussion

3.1. Inflammatory response assays

The concentration of the IL-8 in the SCZ patients was analyzed and compared to the control group. The result showed a significantly higher concentration of IL-8 in the SCZ patients compared to the control group ($p<0.0001$****) (Figure1A). According to the result of the unpaired t-test, there was a significant difference in the IL-10 level between healthy individuals and SCZ patients, in which the IL-10 concentration was significantly higher than the control group (**** $p<0.0001$) (Figure 1B). To compare the difference in the serum TNF-α level between control

individuals and SCZ patients, the Mann-Whitney U test was used due to non-parametric data. As shown in Figure 1C, the result demonstrated a significantly higher level of TNF-α in the SCZ patients compared to the control healthy group ($p<0.0001$).

3.2. Correlation of Age, Gender, IL-8, IL-10, and TNF-α amongst SCZ Patients

A correlation matrix was used to evaluate the relationship between Age, Gender, IL-8, TNF-α, and IL-10 factors amongst SCZ patients and to show how strong and in what direction these factors. are related. As shown in the Heatmap Figure 2, every cell includes a correlation coefficient where, correlation coefficient 1 is considered a strong association between variables, 0, is a neutral connection, and -1: is not a strong connection. The correlations |r| more than or equal to 0.7 are "strong." A correlation coefficient between 0.25 and 0.5 is regarded a “weak” correlation between two variables. The correlations less than 0.3 are "weak.

3.3. The regression analysis between Age, Gender, IL-8, TNF-α, and IL-10 factors amongst SCZ patients

The regression analysis was also performed, and the results did not show any significant association between Age, Gender, IL-8, TNF-α, and IL-10 factors amongst SCZ patients in this study, except the association of the IL-8 with Gender, where the concentration of the IL-8 was significantly increased in women compared to males according to regression analysis (R squared 0.1882, $p=0.0166$), and also to non-parametric Mann-Whitney test (*$p=0.0128$). Figure 3 shows the regression analysis (Figure 3A) and Mann-Whitney test (Figure 3 B) results of the significant association of the IL-8 with Gender in the SCZ patients.

The regression analysis and Pearson Correlation test including, Pearson r, 95% confidence interval, R squared, and p-value was assessed, and the Tabular result (Table 1), showed that these factors are not related and there was not significant correlation of IL-8 vs. TNF-α, IL-8 vs. IL-10, and TNF-α vs. IL-10 amongst SCZ patients. The Figure 4 shows the linear regression of the IL-8 vs. TNF-α (4A), IL-8 vs. IL-10 (4B), and TNF-α vs. IL-10 (4C) amongst SCZ patients.

3.4. Correlation of IL-8, IL-10, and TNF-α amongst control group

The correlation of IL-8, TNF-α, and IL-10 amongst the control group was analyzed as same as SCZ patients. According to Pearson r and Spearman r for parametric and non-parametric data, respectively, 95% confidence interval, R squared (parametric Pearson test), and p-value, there was no significant correlation between IL-8, TNF-α, and IL-10 in the healthy individuals. The tabular result and the Heatmap of the correlation are presented as Table 2, and Figure 5, respectively. There is no significant correlation between three assessed factors in the control group.

Discussion

4.1. The association of the IL-8 with SCZ

Our research showed the elevated level of IL-8 in individuals with SCZ compared to healthy individuals. The significantly higher level of the IL-8 in the present study is line with the study by Andres et al 2015 (10), Zang et al, 2002 (13),and other studies (14-18). Therefore, this result indicated that the neuroinflammation in the SCZ patients is associated with increase in the level of IL-8. Of course, it should be noted that some other studies could not report a significant relationship between the blood levels of IL-8 in people with SCZ and healthy people (19-22). There are several potential reasons for the elevation of IL-10 in SCZ patients including: Inflammatory response dysregulation (23)., Immune activation and SCZ (24), Brain-Immune System Crosstalk (22), Stress and trauma (20), Genetic and Environmental Factors (25), Medication effects (26).

SCZ is increasingly recognized as involving neuro-inflammatory processes. The immune system, including cytokines like IL-8, may be dysregulated in individuals with SCZ, leading to an exaggerated or prolonged inflammatory response(23). Immune dysregulation, neuro-inflammation, and immune activation have been associated with SCZ. Increased levels of IL-8 may indicate ongoing immune system activation and inflammation in the central nervous system, which could contribute to the development or progression of SCZ (24). IL-8 can cross the blood-brain barrier, and it is produced not only in immune cells but also in brain cells (e.g., astrocytes, microglia). Elevated IL-8 in the blood could be indicative of increased production in the brain, reflecting a neuro-inflammatory response in SCZ (22).

Chronic stress and trauma, which are potential risk factors for SCZ, can trigger an inflammatory response and affect cytokine levels. Elevated IL-8 may be a consequence of stress-related immune activation in individuals with SCZ (20). Genetic predispositions and environmental factors can influence the immune response and cytokine levels. Certain genetic variations or environmental factors may lead to an increased production of IL-8 in individuals predisposed to SCZ (25). Medication Effects: Antipsychotic medications commonly used to treat SCZ can influence the immune system and cytokine levels. Some antipsychotics may affect cytokine production, including IL-8, either directly or indirectly (26).

In addition, regarding the significantly higher level of IL-8 in women compared to the men in the SCZ group, some notes can be explained, in which sex-based differences in cytokine levels, including IL-8, can be attributed to various biological, genetic, hormonal, and environmental factors. IL-8 is a proinflammatory cytokine known for its role in promoting inflammation and immune responses. The differences in the IL-8 levels between men and women may be influenced by the following factors such as Hormonal differences(27), Immune response and inflammation (27), Genetic variations (25), Infection and disease patterns(28, 29), Lifestyle and environmental factors (30), Reproductive health (31), and Systemic inflammation (4).

Sex hormones, such as estrogen and testosterone, play a significant role in modulating the immune response. Estrogen, more prevalent in women, cans upregulate the expression of IL-8 and other pro-inflammatory cytokines. Testosterone, more prevalent in men, may have a suppressing effect on IL-8 production (27).Women generally exhibit stronger immune responses and heightened inflammatory reactions compared to men. This heightened immune response may lead to higher levels of pro-inflammatory cytokines, including IL-8 (27). Genetic differences between men and women can influence cytokine production and immune responses. Certain genetic variations may predispose individuals to produce higher levels of IL-8 (25).

Infections or diseases that trigger IL-8 production might affect men and women differently. The prevalence and types of infections or diseases can vary between the sexes, impacting IL-8 levels accordingly (28, 29). Differences in lifestyle factors, such as diet, physical activity, and stress, can influence cytokine levels. Additionally, environmental exposures and living conditions may contribute to variations in IL-8 levels between men and women (30).Women's reproductive health, including menstrual cycles, pregnancy, and menopause, can impact cytokine levels. Changes in hormone levels during these phases can influence IL-8 production (31). SCZ has been associated with low-grade systemic inflammation. Elevated IL-8 levels may be a reflection of this overall inflammatory state present in the body (4).

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4.2. The association of the TNF-α with SCZ

This study reports the elevated levels of TNF-α in individuals with SCZ compared to healthy individuals. Our research supports many studies in which SCZ is associated with cytokine dysfunction and increased production of pro-inflammatory cytokines (7-9). Our results regard to increased level of the TNF-α in SCZ patients was in accordance with other studies Rao et al 2013 (23) , and Ormel et al 2020(32). TNF-α is a pro-inflammatory cytokine that plays a key role in the body's immune response and inflammatory processes. The reasons for this elevation are not entirely clear, but several factors may contribute to the increased TNF-α level in individuals with SCZ. Growing evidence suggests that SCZ is associated with neuro-inflammatory processes. Immune dysregulation and chronic inflammation in the central nervous system may lead to elevated levels of pro-inflammatory cytokines like TNF-α(4). It's proposed that the immune system, including cytokines like TNF-α, may be activated in individuals with SCZ. This activation can trigger an inflammatory response in the brain, potentially contributing to the development or progression of SCZ (4). Microglia, the resident immune cells in the brain, can become activated and release pro-inflammatory cytokines, including TNF-α, in response to various stimuli. Abnormalities in microglial function and increased TNF-α release may be associated with SCZ (33). Chronic stress and trauma, which are potential risk factors for SCZ, can activate the immune system and lead to increased levels of pro-inflammatory cytokines, including TNF-α (20). Genetic predispositions and environmental factors can influence the immune response and cytokine levels. Certain genetic variations or environmental factors may lead to an increased production of TNF-α in individuals predisposed to SCZ (34). Antipsychotic medications commonly used to treat SCZ can influence the immune system and cytokine levels, including TNF-α. Some antipsychotics may affect cytokine production either directly or indirectly (35). There could be an imbalance between pro-inflammatory cytokines (e.g., TNF-α) and anti-inflammatory mechanisms in individuals with SCZ. This imbalance may result in elevated TNF-α levels (36).

4.3. Association of the IL-10 with SCZ

Our finding regards to increased serum level of the IL-10 was inconsistent with study by Miller et al 2011. They reported lower level of the IL-10 in patients compared to healthy group. It could be noted that all of the SCZ patients in our study were not first recognized cases and most of them were under antipsychotic treatment. So the concentration of the IL-10 could be reached at higher level than before and our declaration is confirmed by Mailler et al 2011 (7)

Regarding the relationship between IL-10 and SCZ, there are also conflicting results. Thus, in some studies, the serum level of IL-10 was increased in patients with SCZ (37, 38). Still, in other studies, this increase in IL-10 in patients with SCZ was not reported significantly compared to the control (39, 40). The specific mechanisms underlying altered interleukin-10 (IL-10) levels in SCZ are not yet fully understood, but research suggests that the immune system and inflammation likely play a significant role. Here are some potential explanations for the observed increase in IL-10 levels in the serum of SCZ patients:

Elevated IL-10 levels could represent a compensatory mechanism by the body to counterbalance excessive inflammation and pro-inflammatory responses often observed in SCZ. IL-10 is an anti-inflammatory cytokine that helps dampen the immune response and reduce inflammation (36).

IL-10 has immunomodulatory effects and can inhibit the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and TNF-α. The increased IL-10 levels may be an attempt by the body to regulate the immune response and prevent further escalation of inflammation (41).

The immune system in individuals with SCZ may be dysregulated, resulting in an imbalance of pro-inflammatory and anti-inflammatory cytokines, including an increase in IL-10 levels (42). Both genetic predisposition and environmental factors may contribute to altered IL-10 levels in SCZ. Genetic variations in genes related to IL-10 or its signaling pathways could influence its production and regulation. Additionally, environmental factors, such as stress or infections, may trigger an immune response leading to increased IL-10 production (43). Emerging research suggests that gut microbiota can influence the immune system and potentially play a role in SCZ. Alterations in the gut microbiota may lead to changes in IL-10 levels and other cytokines, impacting the immune response and potentially contributing to SCZ pathophysiology (44). IL-10 may play a neuroprotective role in the central nervous system. The increased IL-10 levels in SCZ might be a response to neuro-inflammatory processes occurring in the brain, aiming to mitigate neuronal damage and inflammation within the central nervous system (45).

Conclusion

The significantly higher serum levels of the IL-8, IL10, and TNF-α in the SCZ patients compared to the healthy control group confirmed that SCZ is associated with neuro-inflammatory processes and indicated that ongoing immune system activation and inflammation in the central nervous system could contribute to the development or progression of SCZ. In addition, assessment of these cytokines as helpful biomarkers and their potential implications for SCZ could be beneficial for developing targeted therapeutic approaches and managing SCZ and related symptoms.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Acknowledgments:

Figure captions

Figure 1: Comparing the IL-8 (A), IL-10 (B), TNF-α (C) concentration between SCZ patients and control group

Figure 2: Heatmap correlation of Age, Gender, IL-8, IL-10, and TNF-α amongst SCZ Patients

Figure 3: Significant association of the IL-8 with Gender in the SCZ patients: A) Regression analysis; B) Mann-Whitney test

Figure 4: Linear regression of IL-8 vs. TNF-α (A); IL-8 vs. IL-10 (B); TNF-α vs. IL-10 (C)

Figure 5: Heatmap Correlation of IL-8, TNF-α, and IL-10 amongst the control group

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Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12867

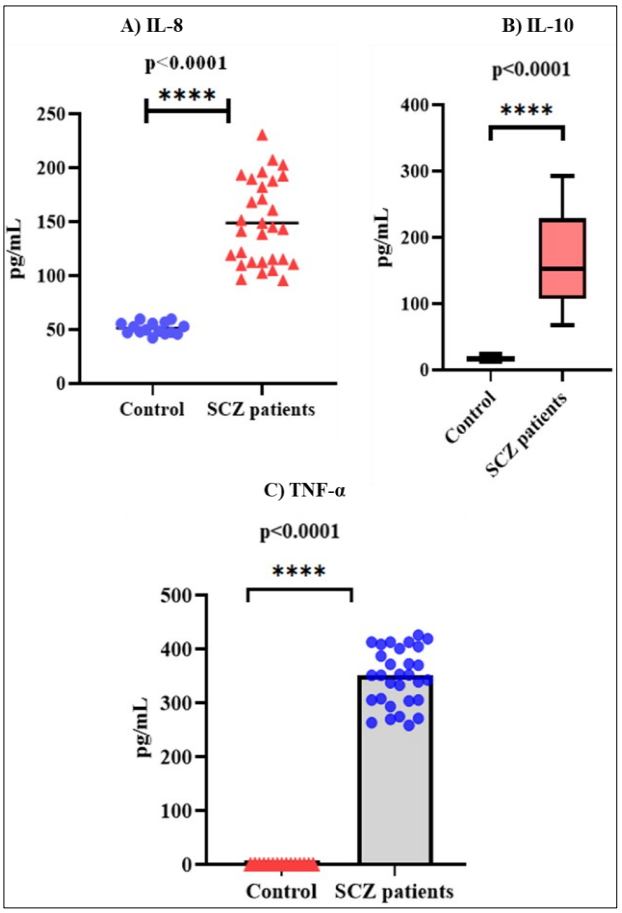

Figure 1: Comparing the IL-8 (A), IL-10 (B), TNF-α (C) concentration between SCZ patients and control group

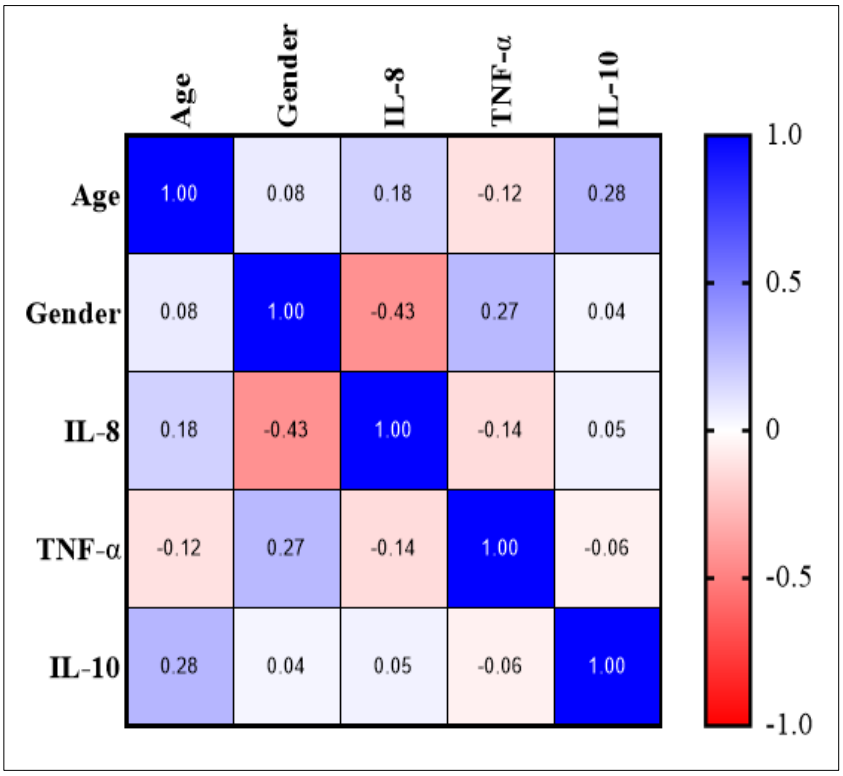

Figure 2: Heatmap correlation of Age, Gender, IL-8, IL-10, and TNF-α amongst SCZ Patients

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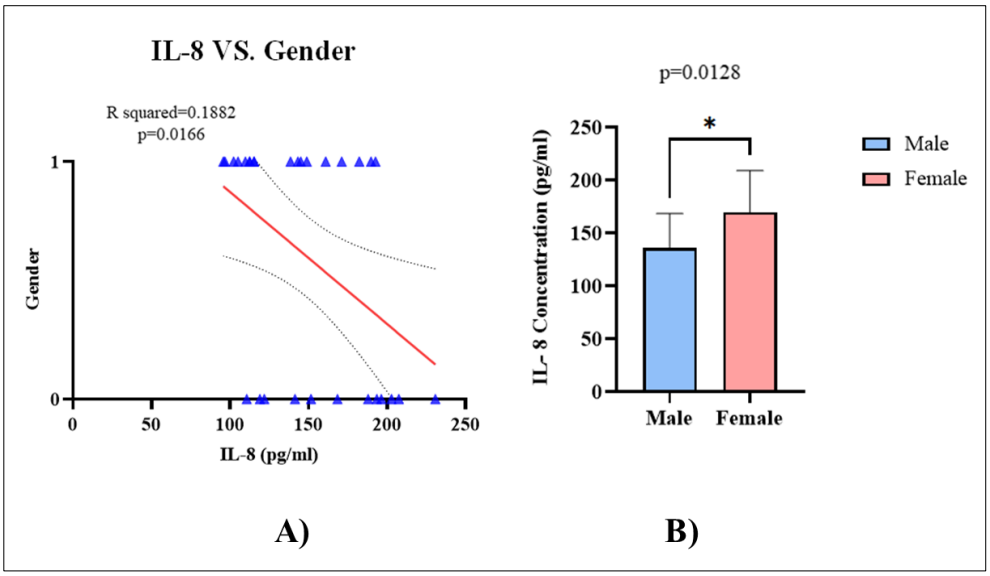

Figure 3: Significant association of the IL-8 with Gender in the SCZ patients.

A) Regression analysis; B) Mann-Whitney test

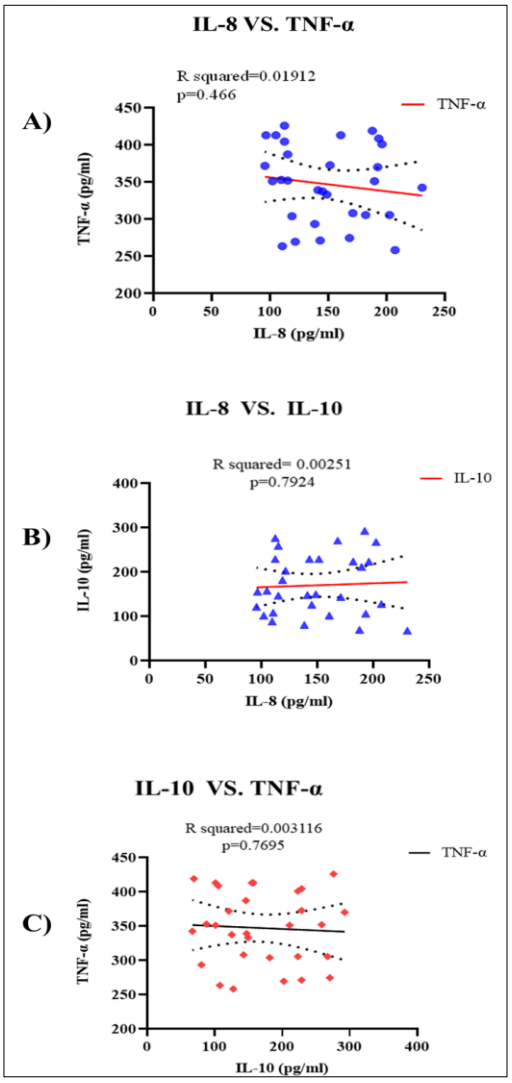

Figure 4: Linear regression of IL-8 vs. TNF-α, IL-8 vs. IL-10 TNF-α vs. IL-10

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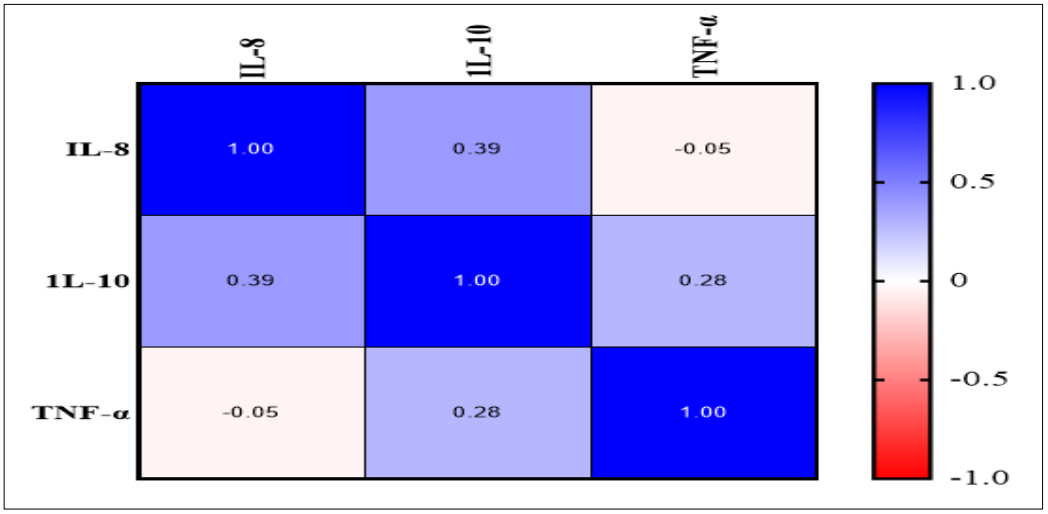

Figure 5: Heatmap Correlation of IL-8, TNF-α, and IL-10 amongst the control group

Table 1: Correlation of IL-8, TNF-α, and IL-10 amongst SCZ patients: Tabular results

Pearson r	**IL-8 vs. TNF-α**	**IL-8 vs. IL-10**	**TNF-α vs. IL-10**
r	-0.1383	0.05014	-0.05582
95% confidence interval	-0.4749 to 0.2336	-0.3158 to 0.4031	-0.4079 to 0.3107
R squared	0.01912	0.002514	0.003116
P value (two-tailed)	0.4662	0.7924	0.7695
Significant? (alpha = 0.05)	No	No	No
Number of XY Pairs	30	30	30

Table 2: Correlation of IL-8, TNF-α, and IL-10 amongst control group

Tabular Result			
Correlation Tabular result	IL-8 vs. 1L-10	IL-8 vs. TNF-α	IL-10 vs. TNF-α
r	Pearson r 0.3929	Spearman r - 0.05378	Spearman r 0.2826
95% confidence interval (CI)	-0.1494 to 0.7535	- 0.5624 to 0.4844	- 0.2840 to 0.7029
R squared	0.1544		
P (two-tailed)	0.1474	0.8520	0.3024
P value summary	ns	ns	ns
Significant? (alpha = 0.05)	No	No	No

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