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Original Article

The Role of Inflammatory Markers in Schizophrenia: A Multicenter Cross-Sectional Study

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ABSTRACT

Background: Immune dysregulation and low-grade systemic inflammation may contribute to the clinical heterogeneity of schizophrenia, but evidence from Pakistan remains limited. Objective: To examine the associations between selected inflammatory markers, symptom severity, and illness duration among adults with schizophrenia. Methods: This multicentre cross-sectional study included 150 adults receiving psychiatric care in Lahore, Pakistan. Symptom severity was assessed using the Positive and Negative Syndrome Scale. Serum CRP, IL-6, TNF-α, IL-1β, and IL-10 concentrations were measured using enzyme-linked immunosorbent assays. Between-group differences, correlations, and adjusted associations were evaluated. Results: The moderate- and high-severity groups included 78 and 72 participants, respectively. Compared with moderate severity, high severity was associated with higher CRP by 3.40 mg/L (95% CI: 2.46–4.34), IL-6 by 4.90 pg/mL (95% CI: 3.80–6.00), TNF-α by 4.20 pg/mL (95% CI: 2.98–5.42), and IL-1β by 2.20 pg/mL (95% CI: 1.48–2.92), while IL-10 was lower by 1.70 pg/mL (95% CI: 0.87–2.53 lower); all $p<0.001$. IL-6 showed the largest observed correlation with PANSS total score ($r=0.52$), followed by TNF-α ($r=0.46$) and CRP ($r=0.41$); all $p<0.001$. Conclusion: Greater schizophrenia symptom severity was associated with a more pronounced pro-inflammatory profile and lower IL-10 concentration. Longitudinal controlled studies are required to establish temporal direction and clinical utility. Keywords: Schizophrenia; inflammation; C-reactive protein; interleukin-6; cytokines; PANSS; biomarkers; Pakistan.

INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by disturbances in perception, thought, behaviour, emotional expression, and social functioning. Its clinical presentation commonly includes positive symptoms such as hallucinations and delusions, negative symptoms such as reduced motivation and social withdrawal, and cognitive impairments that may affect education, employment, interpersonal relationships, and independent living. Although antipsychotic medications remain central to treatment, a substantial proportion of patients experience persistent symptoms, recurrent episodes, functional impairment, or an incomplete therapeutic response. These observations indicate that schizophrenia is a biologically heterogeneous disorder that cannot be explained by alterations in neurotransmitter systems alone (1).

Growing evidence suggests that immune dysregulation and chronic low-grade inflammation may contribute to the clinical and biological heterogeneity of schizophrenia. Meta-analyses have

demonstrated alterations in circulating cytokines among patients experiencing first-episode psychosis, acute relapse, and chronic schizophrenia, although the magnitude and direction of these abnormalities vary according to illness stage, symptom activity, and treatment exposure (2–4). C-reactive protein (CRP), an acute-phase protein produced primarily in response to inflammatory signalling, has also been reported at higher concentrations in some populations with schizophrenia and has been associated with greater symptom burden and adverse clinical outcomes. However, CRP is not specific to psychiatric illness and may be influenced by smoking, obesity, metabolic abnormalities, infection, physical inactivity, sleep disturbance, and medication exposure (5). Proposed mechanisms linking peripheral inflammation with schizophrenia include microglial activation, oxidative stress, altered neurotransmitter metabolism, impaired neuroplasticity, and disruption of signalling between the immune system and the central nervous system (6–8).

Inflammatory alterations do not appear to be uniform across all patients with schizophrenia. Integrative and updated reviews suggest that some patients may exhibit a more prominent inflammatory phenotype, whereas others demonstrate limited or no measurable immune activation (9–12). Cytokine concentrations may also be affected by antipsychotic treatment, particularly during the early stages of psychosis, and changes in inflammatory profiles may vary according to treatment response, metabolic status, and chronicity of illness (13–16). More recent evidence has further emphasized the potential association of immune dysfunction with treatment resistance, symptom severity, and clinical outcomes, while cautioning that individual inflammatory markers have not been established as diagnostic or prognostic tests for schizophrenia (17–20). Assessment of multiple pro-inflammatory and regulatory markers may therefore provide a more informative representation of immune activity than reliance on a single biomarker.

Evidence concerning inflammatory profiles in schizophrenia remains limited in Pakistan. A Lahore-based investigation reported an association between tumour necrosis factor-alpha-related genetic variation and schizophrenia, supporting the relevance of immune pathways in the local population (21). Other Pakistani studies have examined illness perceptions, patterns of research and treatment, and clinical and genetic factors associated with treatment response (22–24). However, multicentre studies directly examining the relationships of circulating CRP, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-10 (IL-10) with validated measures of symptom severity and illness duration remain scarce. Local investigation is important because genetic background, environmental exposure, infection patterns, lifestyle factors, healthcare access, and medication use may differ from those reported in other populations. This multicentre cross-sectional study therefore aimed to examine the associations between selected systemic inflammatory markers, symptom severity assessed using the Positive and Negative Syndrome Scale, and duration of illness among adults with schizophrenia receiving psychiatric care in Lahore, Pakistan.

MATERIALS AND METHODS

This multicentre cross-sectional study was conducted in selected psychiatric departments and mental health facilities in Lahore, Pakistan, to evaluate the relationships between circulating inflammatory markers and the clinical characteristics of schizophrenia. Recruitment from more than one psychiatric facility was intended to include patients with varied demographic backgrounds, treatment histories, symptom profiles, and durations of illness and to reduce reliance on the patient population of a single institution. The study was reported in accordance with the principles of the Strengthening the Reporting of Observational Studies in Epidemiology statement for cross-sectional research (25).

Adults aged 18–65 years with a confirmed diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria were considered eligible. Participants were recruited consecutively from outpatient psychiatric clinics and inpatient psychiatric units at the participating facilities. Patients were included when they were able to complete the clinical assessment

and provide reliable demographic and clinical information. Ongoing antipsychotic treatment was not an exclusion criterion because the study was designed to reflect patients receiving routine psychiatric care. The type, dose, and duration of antipsychotic medication were recorded as part of the clinical assessment.

Patients were excluded if they had evidence of an acute infection, autoimmune disease, severe concurrent medical illness, recent surgery, substance intoxication, or another clinical condition likely to substantially influence systemic inflammatory-marker concentrations. Pregnant women and patients unable to participate reliably in the psychiatric assessment were also excluded. These criteria were applied to reduce the influence of major nonpsychiatric causes of systemic inflammation. A consecutive sampling approach was used to reduce discretionary participant selection, and all eligible patients presenting during the recruitment period were approached for participation. The final analytical sample comprised 150 participants who completed both clinical assessment and blood-sample collection. The intended sample size was informed by previous studies reporting differences in inflammatory-marker concentrations and associations between inflammatory activity and schizophrenia symptom severity.

Demographic and clinical data were collected using a structured form. Recorded variables included age, sex, educational status, socioeconomic background, smoking status, duration of schizophrenia, number of previous psychiatric admissions, and current treatment history. Information was obtained through participant interviews, review of available medical records, and consultation with the treating psychiatric team when clarification was required. Duration of illness was determined from the documented or reported time since diagnosis, while previous psychiatric admission was recorded as a categorical clinical-history variable. Medication-related information included the type, duration, and dose of current antipsychotic treatment where available.

Schizophrenia symptom severity was assessed using the Positive and Negative Syndrome Scale. Assessments were conducted by trained psychiatric professionals familiar with the administration and scoring of the instrument. The scale evaluates positive symptoms, negative symptoms, and general psychopathology, with higher total scores indicating greater overall symptom severity. The PANSS total score was treated as the principal continuous clinical measure in the association analyses. For descriptive comparisons of inflammatory-marker concentrations, participants were also classified into moderate- and high-symptom-severity groups according to their PANSS total scores. Illness duration was examined as an additional clinical variable representing chronicity.

Approximately 5 mL of peripheral venous blood was collected from each participant under aseptic conditions into appropriate collection tubes. Samples were transported in accordance with laboratory safety procedures and processed within the recommended interval. Serum concentrations of CRP, IL-6, TNF-α, IL-1β, and IL-10 were measured. These biomarkers were selected to represent acute-phase, pro-inflammatory, and regulatory immune activity previously implicated in schizophrenia. Cytokine concentrations were determined using commercially available enzyme-linked immunosorbent assay kits in accordance with the manufacturers' instructions. Laboratory personnel were blinded to participants' PANSS scores and other clinical characteristics during sample analysis to reduce measurement bias.

Several procedures were used to improve data quality and reduce bias. Consecutive recruitment was applied across participating facilities, demographic and clinical information was collected using a standardized form, and symptom severity was assessed through a consistent PANSS-based procedure. Laboratory measurements were performed according to the assay manufacturers' protocols, and samples were handled using standardized safety and processing procedures. Clinical and laboratory records were reviewed for completeness, internal consistency, and data-entry errors before statistical analysis. Potential confounding was addressed through the eligibility criteria and by recording relevant demographic, behavioural, clinical, and medication-related variables. Age, sex, smoking status, and available medication characteristics were considered in the adjusted analyses.

Continuous variables were summarized as mean and standard deviation when their distributions were approximately normal and as median and interquartile range when distributions were skewed. Categorical variables were reported as frequencies and percentages. Data distributions were evaluated before inferential testing. Comparisons between two independent groups were performed using the independent-samples t-test for approximately normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Comparisons involving more than two groups were conducted using one-way analysis of variance or the Kruskal–Wallis test, as appropriate.

Associations between inflammatory-marker concentrations, PANSS total scores, and illness duration were examined using correlation analysis. Pearson correlation coefficients were used for approximately normally distributed continuous variables, whereas Spearman rank-correlation coefficients were used when parametric assumptions were not satisfied. Multivariable regression analysis was undertaken to determine whether inflammatory markers remained associated with PANSS total scores after accounting for age, sex, smoking status, and recorded medication characteristics. Statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Data were analysed using IBM SPSS Statistics version 26.0. All included participants completed the clinical assessment and blood-sampling procedures, and analyses were performed using the complete available observations for the variables included in each analysis.

The study protocol received approval from the relevant institutional ethics committees of the participating facilities and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Participants were informed about the study objectives, procedures, potential risks, confidentiality protections, voluntary nature of participation, and right to withdraw without affecting their clinical care. Written informed consent was obtained before enrolment and initiation of study procedures.

RESULTS

All 150 participants completed the clinical assessment and blood-sampling procedures. Their mean age was 34.6 ± 9.2 years, and the mean duration of schizophrenia was 8.1 ± 5.4 years. The sample included 102 men (68.0%) and 48 women (32.0%). Thirty-eight participants (25.3%) were described as having first-episode schizophrenia, whereas 112 (74.7%) had an illness duration exceeding five years. All participants were receiving antipsychotic medication at the time of assessment, 71 (47.3%) had a history of smoking, and 86 (57.3%) had previously been admitted for psychiatric care (Table 1).

Table 1. Demographic and Clinical Characteristics of the Participants (n=150)

Characteristic	Value
Age, years, mean ± SD	34.6 ± 9.2
Age range, years	18–65
Male sex, n (%)	102 (68.0)
Female sex, n (%)	48 (32.0)
Illness duration, years, mean ± SD	8.1 ± 5.4
First-episode schizophrenia, n (%)	38 (25.3)
Illness duration >5 years, n (%)	112 (74.7)
Current antipsychotic use, n (%)	150 (100.0)
History of smoking, n (%)	71 (47.3)
Previous psychiatric admission, n (%)	86 (57.3)

SD: standard deviation.

Participants were classified into moderate-symptom-severity and high-symptom-severity groups according to their PANSS total scores. The moderate-severity group included 78 participants, and the high-severity group included 72 participants. Concentrations of CRP, IL-6, TNF-α, and IL-1β were higher in the high-severity group, whereas IL-10 concentrations were lower (Table 2).

The largest between-group difference was observed for IL-6, with a mean concentration of 10.6 ± 4.1 pg/mL in the high-severity group compared with 5.7 ± 2.4 pg/mL in the moderate-severity group. The resulting mean difference was 4.90 pg/mL (95% CI: 3.80–6.00), corresponding to a large standardized effect of 1.47. TNF-α was also higher in the high-severity group by 4.20 pg/mL (95% CI: 2.98–5.42; Hedges' g=1.13), while CRP was higher by 3.40 mg/L (95% CI: 2.46–4.34; Hedges' g=1.18).

Participants with high symptom severity had a mean IL-1β concentration 2.20 pg/mL greater than participants with moderate severity (95% CI: 1.48–2.92; Hedges' g=1.00). In contrast, the mean IL-10 concentration was 1.70 pg/mL lower in the high-severity group (95% CI: −2.53 to −0.87; Hedges' g=−0.65). All five between-group comparisons were statistically significant at p<0.001.

Table 2. Inflammatory-Marker Concentrations According to Symptom Severity

Marker	Moderate Severity (n=78), Mean ± SD	High Severity (n=72), Mean ± SD	Mean Difference, High−Moderate	95% CI	Hedges' g	p-value
CRP, mg/L	4.8 ± 2.1	8.2 ± 3.5	3.40	2.46 to 4.34	1.18	<0.001
IL-6, pg/mL	5.7 ± 2.4	10.6 ± 4.1	4.90	3.80 to 6.00	1.47	<0.001
TNF-α, pg/mL	7.2 ± 2.8	11.4 ± 4.5	4.20	2.98 to 5.42	1.13	<0.001
IL-1β, pg/mL	3.9 ± 1.7	6.1 ± 2.6	2.20	1.48 to 2.92	1.00	<0.001
IL-10, pg/mL	6.8 ± 2.9	5.1 ± 2.2	−1.70	−2.53 to −0.87	−0.65	<0.001

CI: confidence interval; CRP: C-reactive protein; IL: interleukin; SD: standard deviation; TNF-α: tumour necrosis factor-alpha. Between-group estimates and p-values were calculated from the reported sample sizes, means, and standard deviations using Welch's independent-samples t-test. Hedges' g was calculated using the pooled standard deviation with correction for small-sample bias. A positive effect indicates a higher concentration in the high-severity group; a negative effect indicates a lower concentration.

Correlation analysis demonstrated positive associations between PANSS total scores and the reported pro-inflammatory markers. IL-6 had the largest observed correlation with PANSS total score (r=0.52, 95% CI: 0.39–0.63; p<0.001), followed by TNF-α (r=0.46, 95% CI: 0.32–0.58; p<0.001) and CRP (r=0.41, 95% CI: 0.27–0.54; p<0.001). These coefficients indicated moderate positive associations, with higher marker concentrations generally accompanying greater symptom severity (Table 3).

Table 3. Correlations of Inflammatory Markers With PANSS Total Score

Marker	Correlation Coefficient, r	95% CI	p-value
IL-6	0.52	0.39 to 0.63	<0.001
TNF-α	0.46	0.32 to 0.58	<0.001
CRP	0.41	0.27 to 0.54	<0.001

CI: confidence interval; CRP: C-reactive protein; IL-6: interleukin-6; PANSS: Positive and Negative Syndrome Scale; TNF-α: tumour necrosis factor-alpha. Confidence intervals were derived using Fisher's z transformation based on n=150.

Higher concentrations of CRP and the measured pro-inflammatory cytokines were also observed among participants with longer illness duration. In the reported adjusted analysis, IL-6 and CRP remained significantly associated with PANSS total score after accounting for age, sex, smoking status, and recorded medication characteristics. Overall, the findings demonstrated a consistent inflammatory gradient across the symptom-severity groups, characterized by higher pro-inflammatory-marker concentrations and lower IL-10 concentrations among participants with more severe symptoms.

DISCUSSION

This multicentre cross-sectional study identified a consistent association between inflammatory-marker concentrations and schizophrenia symptom severity among adults receiving psychiatric care in Lahore. Participants in the high-severity PANSS group had higher mean concentrations of CRP, IL-6, TNF-α, and IL-1β and a lower mean concentration of IL-10 than those in the moderate-severity group. The largest standardized difference was observed for IL-6, and IL-6 also had the largest observed correlation with PANSS total score. These findings indicate that greater symptom burden within the study population

was accompanied by a more pronounced pro-inflammatory profile and a comparatively lower concentration of the regulatory cytokine IL-10.

The association between IL-6 and symptom severity is consistent with previous systematic reviews and meta-analyses reporting altered cytokine concentrations in first-episode psychosis, acute relapse, and chronic schizophrenia (2–4). IL-6 is a pleiotropic cytokine involved in acute-phase signalling, immune-cell differentiation, and communication between peripheral immune pathways and the central nervous system. Proposed mechanisms through which increased IL-6 activity may accompany psychiatric symptoms include microglial activation, altered monoamine and glutamate metabolism, oxidative stress, and changes in blood–brain barrier function (6–10). Nevertheless, the present cross-sectional findings cannot determine whether increased IL-6 activity preceded symptom worsening, developed as a consequence of severe illness, or reflected medication, metabolic, behavioural, or environmental influences.

TNF-α and IL-1β were also higher among participants with greater symptom severity. These cytokines participate in innate immune activation and may influence neuronal signalling, synaptic plasticity, and neuroendocrine function. Previous evidence has shown that circulating TNF-α and IL-1β concentrations may vary according to illness phase, medication exposure, and clinical status, and that cytokine abnormalities are not uniformly present in all patients with schizophrenia (3,7,10,12). The large standardized differences observed in the present severity-group analysis support a relationship between inflammatory activity and clinical presentation, but they do not demonstrate that these cytokines are specific to schizophrenia or that they directly produce psychiatric symptoms.

CRP was higher in the high-severity group and showed a moderate positive correlation with PANSS total score. This finding is compatible with meta-analytic evidence demonstrating higher CRP concentrations in some schizophrenia populations and associations between CRP, symptom burden, and adverse clinical characteristics (5,14). CRP is inexpensive and widely available, which makes it potentially useful in observational and stratification research. However, its clinical interpretation is limited by its nonspecific nature. Smoking, obesity, diabetes, metabolic syndrome, acute or chronic infection, reduced physical activity, sleep disturbance, and several medications may independently increase CRP. Consequently, the present results should not be interpreted as establishing CRP as a diagnostic marker or a schizophrenia-specific measure of disease activity.

The lower mean IL-10 concentration among participants with greater symptom severity may reflect an altered balance between pro-inflammatory and regulatory immune activity. IL-10 ordinarily contributes to limiting excessive immune activation, and reduced regulatory signalling in the presence of increased pro-inflammatory cytokines could be consistent with immune imbalance. Previous reviews have similarly suggested that schizophrenia may involve disruption of both pro-inflammatory and anti-inflammatory pathways rather than an isolated abnormality in one cytokine (10–12). Nevertheless, a single IL-10 measurement cannot establish impaired immune regulation, and the observed difference requires confirmation through repeated measurements and more comprehensive immune profiling.

Inflammatory-marker concentrations were also reported to be higher among participants with longer illness duration. Chronic schizophrenia may be accompanied by cumulative exposure to recurrent episodes, psychosocial stress, reduced physical activity, smoking, metabolic complications, and prolonged psychotropic treatment, all of which may influence systemic inflammation. Previous studies have described relationships between cytokine profiles, illness stage, treatment resistance, and long-term clinical characteristics (9,15–20). Illness duration should therefore not be interpreted as an isolated biological exposure. Prospective studies are required to distinguish the effects of ageing, cumulative medication exposure, comorbidity, illness progression, and persistent symptom burden.

The findings contribute evidence from Pakistan, where direct investigation of circulating inflammatory markers in schizophrenia remains limited. Earlier Pakistani research has examined TNF-α-related

genetic variation, illness perceptions, treatment patterns, and clinical or genetic factors associated with treatment response (21–24). The present study extends this literature by examining several inflammatory markers in relation to PANSS-defined symptom severity within a multicentre clinical sample. Locally generated evidence is relevant because genetic background, infection exposure, diet, smoking patterns, socioeconomic conditions, access to care, and medication practices may differ across populations.

The results may support further investigation of inflammatory phenotypes within schizophrenia rather than the use of an individual marker as a universal diagnostic test. Patients with schizophrenia are biologically heterogeneous, and only a subgroup may demonstrate clinically meaningful immune activation (9–12,17–20). Future longitudinal studies should evaluate whether combinations of inflammatory markers predict symptom trajectories, relapse, functional outcomes, or treatment response after controlling for metabolic, behavioural, infectious, and medication-related factors. Although adjunctive anti-inflammatory approaches have been investigated, the current study did not assess an intervention and cannot determine whether participants with higher inflammatory-marker concentrations would benefit from immune-targeted treatment (6,11).

This study has several strengths, including recruitment from multiple psychiatric facilities, simultaneous measurement of pro-inflammatory and regulatory markers, use of PANSS-based symptom assessment, and blinded laboratory analysis. The study also evaluated inflammatory markers as continuous correlates of symptom severity rather than relying solely on categorical comparisons. However, the cross-sectional design prevents determination of temporal sequence or causality. The absence of a healthy comparison group means that the study identifies differences between symptom-severity groups but cannot establish whether marker concentrations were elevated relative to individuals without schizophrenia. Inflammatory markers were measured at one time point and may have been affected by transient biological variation. Residual confounding from body mass index, metabolic disease, infection, diet, physical activity, sleep, antipsychotic dose, polypharmacy, and other medications cannot be excluded. The results may also have been influenced by selection of participating facilities, unmeasured centre-level differences, PANSS categorization, and the lack of repeated biomarker measurements. These limitations should be considered when interpreting the magnitude and clinical applicability of the observed associations.

CONCLUSION

Among adults with schizophrenia receiving psychiatric care in Lahore, greater PANSS-defined symptom severity was associated with higher concentrations of CRP, IL-6, TNF-α, and IL-1β and a lower concentration of IL-10. IL-6 demonstrated the largest between-group difference and the largest observed correlation with PANSS total score. These findings support an association between systemic inflammatory patterns and clinical severity but do not establish causality, disease specificity, or clinical biomarker utility. Longitudinal studies incorporating healthy comparison groups, repeated biomarker measurements, detailed medication exposure, and comprehensive control of metabolic, behavioural, and infectious confounders are needed to clarify the direction and clinical significance of these relationships.

REFERENCES

1. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86–97. doi:10.1016/S0140-6736(15)01121-6.

2. 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):801–808. doi:10.1016/j.biopsych.2007.09.024.

3. 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):663–671. doi:10.1016/j.biopsych.2011.04.013.

4. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry. 2016;21(12):1696–1709. doi:10.1038/mp.2016.3.

5. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry. 2016;21(4):554–564. doi:10.1038/mp.2015.87.

6. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry. 2015;2(3):258–270. doi:10.1016/S2215-0366(14)00122-9.

7. Kirkpatrick B, Miller BJ. Inflammation and schizophrenia. Schizophr Bull. 2013;39(6):1174–1179. doi:10.1093/schbul/sbt141.

8. van Kesteren CFMG, Gremmels H, de Witte LD, Hol EM, van Gool AR, Falkai PG, et al. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry. 2017;7:e1075. doi:10.1038/tp.2017.4.

9. Kroken RA, Sommer IE, Steen VM, Dieset I, Johnsen E. Constructing the immune signature of schizophrenia for clinical use and research: an integrative review. Front Psychiatry. 2019;9:753. doi:10.3389/fpsyt.2018.00753.

10. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in schizophrenia: an updated review. Front Psychiatry. 2019;10:892. doi:10.3389/fpsyt.2019.00892.

11. Reale M, Costantini E, Greig NH. Cytokine imbalance in schizophrenia: a hope or hype for biomarkers and treatment? Front Psychiatry. 2021;12:536257. doi:10.3389/fpsyt.2021.536257.

12. 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):3849. doi:10.3390/jcm10173849.

13. Marcinowicz P, Więdłocha M, Dębowska W, Szczotkowska A, Szulc A. A meta-analysis of the influence of antipsychotics on cytokine levels in first-episode psychosis. J Clin Med. 2021;10(11):2488. doi:10.3390/jcm10112488.

14. Ullah I, Awan HA, Aamir A, Diwan MN, de Filippis R, Awan S, et al. Role and perspectives of inflammation and C-reactive protein in psychosis: an economic and widespread tool for assessing the disease. Int J Mol Sci. 2021;22(23):13032. doi:10.3390/ijms222313032.

15. Shnayder NA, Khasanova AK, Strelnik AI, Al-Zamil M, Otmakhov AP, Neznanov NG, et al. Cytokine imbalance as a biomarker of treatment-resistant schizophrenia. Int J Mol Sci. 2022;23(19):11324. doi:10.3390/ijms231911324.

16. Mednova IA, Boiko AS, Kornetova EG, Parshukova DA, Semke AV, Bokhan NA, et al. Cytokines as potential biomarkers of clinical characteristics of schizophrenia. Life. 2022;12(12):1972. doi:10.3390/life12121972.

17. Gangadin SS, Enthoven AD, van Beveren NJM, Laman JD, Sommer IEC. Immune dysfunction in schizophrenia spectrum disorders. Annu Rev Clin Psychol. 2024;20:229–257. doi:10.1146/annurev-clinpsy-081122-013201.

18. Chaves C, Dursun SM, Tusconi M, Hallak JEC. Neuroinflammation and schizophrenia—is there a link? Front Psychiatry. 2024;15:1356975. doi:10.3389/fpsyt.2024.1356975.

19. Lv H, Zhang Y, Li Y, Wang X, Huang J, Zhang Y, et al. The interrelationships between cytokines and schizophrenia: a systematic review. Int J Mol Sci. 2024;25(15):8477. doi:10.3390/ijms25158477.

20. Speers LJ, Wang J, Kim Y, Miller BJ, Goldsmith DR, Kirkpatrick B, et al. Inflammation in schizophrenia: the role of disordered immunity in its pathophysiology and treatment. Cells. 2025;14(9):650. doi:10.3390/cells14090650.

21. Naz M, Riaz M, Saleem M. Potential role of Neuregulin 1 and TNF-alpha −308 polymorphism in schizophrenia patients visiting hospitals in Lahore, Pakistan. Mol Biol Rep. 2011;38(7):4709–4714. doi:10.1007/s11033-010-0606-0.

22. Hussain S, Imran N, Hotiana UA, Mazhar N, Asif A. Illness perceptions in patients of schizophrenia: a preliminary investigation from Lahore, Pakistan. Pak J Med Sci. 2017;33(4):829–834. doi:10.12669/pjms.334.13128.

23. Nawaz R, Gul S, Amin R, Huma T, Al Mughairbi F. Overview of schizophrenia research and treatment in Pakistan. Heliyon. 2020;6(11):e05545. doi:10.1016/j.heliyon.2020.e05545.

24. Habiba U, Malik A, Raja GK, Memon MR, Nizami ATD, Ishaq R, et al. Differential treatment responses in Pakistani schizophrenia samples: association with clinical and genetic factors. Brain Sci. 2023;13(3):407. doi:10.3390/brainsci13030407.

25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–1457. doi:10.1016/S0140-6736(07)61602-X.