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Original Research Article

Association of Serum Interleukin-6 and C Reactive Protein with Disease Severity in Patients with Schizophrenia: A Comparative Cross-Sectional Study

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Abstract

Background: Increasing evidence suggests that immune dysregulation and chronic low grade inflammation contribute to the pathophysiology of schizophrenia. Interleukin-6 (IL-6) and C-reactive protein (CRP) are key inflammatory biomarkers that may reflect disease activity and clinical severity.

Aim: To compare serum IL-6 and CRP levels between patients with schizophrenia and healthy controls and to evaluate their association with disease severity.

Methods: This hospital based comparative cross-sectional study included 50 patients with schizophrenia and 50 age and gender matched healthy controls. Schizophrenia severity was assessed using the Positive and Negative Syndrome Scale (PANSS). Serum IL-6 concentrations were measured using enzyme linked immunosorbent assay (ELISA), while CRP levels were estimated by an immunoturbidimetric method. Statistical analysis was performed using Jamovi.

Results: Patients with schizophrenia demonstrated significantly higher serum IL-6 and CRP levels than healthy controls (both $p<0.001$). Both biomarkers increased progressively with disease severity. Serum IL-6 showed a significant positive correlation with CRP ($r=0.577$, $p<0.001$), indicating coordinated inflammatory activation in schizophrenia.

Conclusion: Elevated serum IL-6 and CRP levels and their association with increasing disease severity support the role of systemic inflammation in schizophrenia. These biomarkers may serve as useful indicators of inflammatory activity and disease severity, although longitudinal studies are required to establish their prognostic and clinical utility.

Keywords: Schizophrenia, Interleukin-6, C-reactive protein, Inflammation, Cytokines, PANSS.
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Introduction

Schizophrenia is a chronic and severe psychiatric disorder characterized by positive symptoms (hallucinations and delusions), negative symptoms (reduced motivation, affective flattening, and social withdrawal), and cognitive impairment, all of which contribute substantially to long term disability and impaired quality of life.[1–6] Affecting nearly 24 million people worldwide, schizophrenia remains a major public health challenge because of its high morbidity, premature mortality, and socioeconomic burden.[7,8]

Although the exact pathophysiology of schizophrenia remains incompletely understood, increasing evidence indicates that immune dysregulation and chronic low grade inflammation play important roles in disease onset and progression.[9] Epidemiological studies have demonstrated associations between maternal infection, prenatal inflammatory exposure, and an increased risk of schizophrenia in offspring, suggesting that inflammatory processes may contribute to abnormal neurodevelopment.[10,11]

Among inflammatory mediators, interleukin-6 (IL-6) has received considerable attention because of its dual pro inflammatory and anti-inflammatory functions. Beyond regulating peripheral immune responses, IL-6 influences central nervous system processes by promoting microglial activation, altering blood brain barrier permeability, and modulating neurotransmitter systems, including dopaminergic and glutamatergic pathways implicated in schizophrenia.[12–17] Persistent elevation of IL-6 may therefore contribute to neuroinflammation, synaptic dysfunction, and cognitive impairment.

C-reactive protein (CRP), an acute phase protein synthesized by the liver primarily in response to IL-6 signaling, serves as an established marker of systemic inflammation. Elevated CRP levels have been consistently reported in schizophrenia and may reflect persistent immune activation associated with disease severity. Simultaneous assessment of IL-6 and CRP provides complementary information regarding inflammatory activity and may improve understanding of the relationship between systemic inflammation and clinical manifestations of schizophrenia.

Despite growing evidence supporting the inflammatory hypothesis, data from the Indian population remain limited, particularly regarding the relationship between IL-6, CRP, and symptom severity. This study therefore compared serum IL-6 and CRP levels between patients with schizophrenia and healthy controls and evaluated their association with disease severity measured using the Positive and Negative Syndrome Scale (PANSS).

Rationale of the Study: Although elevated IL-6 and CRP concentrations have been reported in schizophrenia, their relationship with clinical severity remains inconsistent across different populations. Evidence from India, particularly central India, is limited, and few studies have simultaneously evaluated IL-6, CRP, and PANSS defined symptom severity in drug naive or medication free patients. This study was undertaken to address this gap and to further evaluate the association between inflammatory biomarkers and disease severity, thereby contributing to the understanding of immune mediated mechanisms in schizophrenia.

Objectives: Primary Objective: To estimate and compare serum IL-6 and CRP levels between patients with schizophrenia and healthy controls.

Secondary Objective: To evaluate the correlation between serum IL-6, CRP, and the severity of schizophrenia.

Materials and Methods

This hospital based comparative cross sectional study was conducted over one year after obtaining approval from the Institutional Ethics Committee. The study evaluated serum IL-6 and CRP levels in patients with schizophrenia and healthy controls.

Study Design: Comparative cross sectional study.

Study Setting: The study was conducted in the Departments of Biochemistry and Psychiatry, M.G.M. Medical College and M.Y. Hospital, Indore, Madhya Pradesh, India.

Study Duration: One year following Institutional Ethics Committee approval.

Study Participants: Fifty patients with schizophrenia and fifty age and gender matched healthy controls were enrolled. Patients were recruited from the Psychiatry Outpatient Department of M.Y. Hospital, Indore. Schizophrenia was diagnosed according to ICD-10 criteria. Only drug naive patients or those who had remained medication free for at least three months before enrolment were included. Healthy controls comprised individuals attending the hospital for routine health check-ups, matched for age and gender.

Inclusion Criteria: Adults aged between 18 and 40 years, ready to provide written informed consent. Diagnosed of schizophrenia according to ICD-10 criteria (cases) and healthy controls.

Exclusion Criteria: Participants with conditions known to influence inflammatory markers were excluded, including: Acute infection or sepsis, Diabetes mellitus, Chronic liver disease, Chronic kidney disease, Cardiovascular disease, Autoimmune disorders, Obesity related inflammatory conditions, Recent surgery, Alcohol or substance dependence, Smoking, Pregnancy or lactation, Current NSAID or corticosteroid therapy

Sample Size: Sample size was calculated using the standard formula for comparison between two groups based on previously published literature.[18] The minimum required sample size was 44 participants per group. To improve statistical power and reliability, 50 participants were included in each group, giving a total sample size of 100.

Potential Sources of Bias: Because this was a hospital based study, selection bias cannot be completely excluded. Potential confounding variables including age, gender, body mass index (BMI), duration of illness, medication history, and family history were recorded and considered during analysis.

Study Variables: The exposure variable was study group (schizophrenia or healthy control). Primary

outcome variables included: Serum IL-6 concentration, Serum CRP concentration and PANSS score. Demographic and clinical variables including age, gender, BMI, duration of illness, medication history, and family history were recorded as potential confounders.

Data Collection and Laboratory Methods: After obtaining written informed consent, demographic and clinical information was collected using a structured proforma. Clinical severity was assessed using the Positive and Negative Syndrome Scale (PANSS).[19]

Following overnight fasting, venous blood samples were collected under aseptic precautions. Serum CRP was measured using an immunoturbidimetric method with the CRP FS reagent (DiaSys Diagnostic Systems GmbH, Germany) on a Beckman Coulter AU5800 fully automated clinical chemistry analyzer, according to the manufacturer's instructions. Serum IL-6 concentrations were determined using the Human IL-6 CK-Research ELISA Kit (CK-bio; Catalogue No. CK-bio-12137) following the manufacturer's protocol.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using Jamovi Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. Data normality was assessed using the Shapiro-Wilk test. Comparisons between schizophrenia patients and healthy controls were performed using the unpaired Student's t-test for continuous variables and the Chi-square test for categorical variables. Correlations between serum IL-6 and CRP levels were evaluated using Pearson's correlation coefficient. A two sided p-value <0.05 was considered statistically significant.

Observations and Results

Table 1: Age wise comparison of participants between cases and controls

Age Group (years)	Groups				Total	
	Schizophrenia		Healthy Controls			
	No.	%	No.	%	No.	%
18-25 years	15	30.0%	16	32.0%	31	31.0%
26-30 years	11	22.0%	9	18.0%	20	20.0%
31-35 years	10	20.0%	14	28.0%	24	24.0%
36-40 years	14	28.0%	11	22.0%	25	25.0%
Total	50	100.0%	50	100.0%	100	100.0%

Pearson Chi Square test = 1.259, p value = 0.739, Not Significant

Table 2: Distribution of Participants according to gender between the Groups

Gender	Groups				Odds Ratio (95% CI)	p value
	Schizophrenia		Healthy Controls			
	No.	%	No.	%		
Male	30	60.0%	28	56.0%	1.18 (0.53-2.61)	0.685
Female	20	40.0%	22	44.0%		
Total	50	100.0%	50	100.0%		

Pearson Chi Square = .164, OR = 1.18 (95% CI: 0.53-2.61), p value =.685, Not Significant

Table 3: Comparison of Body Mass Index (BMI) between the Groups

Body Mass Index Classification (kg/m2)	Groups				Total	
	Schizophrenia		Healthy Controls			
	No.	%	No.	%	No.	%
Normal	19	38.0%	22	44.0%	41	41.0%
Obese	3	6.0%	5	10.0%	8	8.0%
Overweight	15	30.0%	13	26.0%	28	28.0%
Underweight	13	26.0%	10	20.0%	23	23.0%
Total	50	100.0%	50	100.0%	100	100.0%

Pearson Chi Square test = 1.254, p value = 0.740, Not Significant

Table 4: Distribution according to family history between the Groups

Family History	Groups				Odds Ratio (95% CI)	p value
	Schizophrenia		Healthy Controls			
	No.	%	No.	%		
Yes	22	44.0%	12	24.0%	2.49 (1.06 - 5.86)	0.035
No	28	56.0%	38	76.0%		
Total	50	100.0%	50	100.0%		

Pearson Chi Square = 4.456, OR = 2.49 (1.06 - 5.86), p value = .035 Significant

Table 5: Comparison of Serum IL-6 and CRP Levels between Schizophrenia Patients and Healthy Controls

Parameter	Schizophrenia Mean±SD	Healthy Controls Mean±SD	Mean Difference (95% CI)	p value
IL 6 (pg/ml)	15.06 ± 5.07	2.88 ± 1.21	12.18 (10.72 to 13.64)	<0.001
CRP (mg/L)	9.97±3.13	1.78±0.77	8.20 (7.29 to 9.10)	<0.001

Unpaired t test; P<0.05 statistically significant.

Table 6: Comparison of Serum IL-6 and CRP Levels according to Severity of Schizophrenia

Severity	Number Of Cases	IL 6 (pg/ml) [Mean±SD]	95% CI of Mean	CRP Levels (mg/L)[Mean±SD]	95% CI of Mean	p value
Mild	3	6.73±1.33	2.77-10.68	4.23±0.81	2.06-6.40	<0.001
Moderate	16	11.08±2.9	9.37-12.79	7.39±1.81	6.45-8.33	
Severe	31	17.92±3.72	16.69-19.15	11.86±1.94	11.19-12.54	
Total	50	15.06±5.07	-	9.97±3.13	-	Significant

One way ANOVA; P<0.05 statistically significant.

Table 7: Correlation between Serum IL-6 and CRP Levels in Schizophrenia Patients

Pearson Correlation	IL 6 (pg/ml)	CRP (mg/L)	95% CI for r	P value
IL 6 (pg/ml)	1	0.577*	0.36–0.74	<0.001
CRP (mg/L)	0.577*	1	-	<0.001

***Correlation is significant at the 0.01 level.**

Table 8: Comparison Levels of Serum IL-6 and CRP according to Gender among Schizophrenia Patients

Parameter	Female (n=20) Mean ± SD	Male (n=30) Mean ± SD	Mean Difference (95% CI)	p value
IL-6 (pg/ml)	14.71 ± 4.78	15.29 ± 5.32	-0.58 (-3.55 to 2.39)	0.698
CRP (mg/L)	10.04 ± 3.02	9.93 ± 3.25	0.12 (-1.72 to 1.95)	0.898

Unpaired t test; P<0.05 statistically significant.

Table 9: Comparison of Serum IL-6 and CRP Levels according to Family History among Schizophrenia Patients

Parameter	Yes (n=22) Mean ± SD	No (n=28) Mean ± SD	Mean Difference (95% CI)	p value
IL-6 (pg/ml)	16.79 ± 4.76	13.70 ± 4.97	3.09 (0.30 to 5.89)	0.031
CRP (mg/L)	10.34 ± 2.96	9.68 ± 3.28	0.66 (-1.14 to 2.46)	0.467

Unpaired t test; P<0.05 considered statistically significant.

Results

Half of the subjects were healthy controls and half were schizophrenia sufferers; a total of 100 people participated. Both groups had similar age distributions. People in the 18-25 age group made up the bulk of the sample (30% of cases and 32% of controls). No statistically significant difference was seen in the age distribution between the healthy controls and patients with schizophrenia (p=0.739; Table 1).

Additionally, there was a very consistent distribution of males to females throughout all of the groups. Males constituted 60% of the schizophrenia group and 56% of the control group, while females accounted for 40% and 44%, respectively. The distribution of gender did not show any statistically significant difference (odds ratio = 1.18; 95% CI: 0.53-2.61; p = 0.685) (Table 2). The distribution of body mass index categories, there was minimal variation between the two groups. An underweight 26%, a normal weight 38%, an overweight 30%, and an obese 6% constituted the schizophrenia group. Twenty percent, forty four percent, twenty six percent, and ten percent were the corresponding percentages among the control group. According to Table 3, there was no significant difference between the categories (p=0.740).

In contrast to healthy controls, 44% of people with schizophrenia had a positive family history in comparison to 24% in the control group. There was a statistically significant difference (odds ratio = 2.49; 95% CI: 1.06-5.86; p = 0.035) (Table 4).

When compared to healthy controls, schizophrenia patients had far higher levels of serum inflammatory markers. In schizophrenia group, the mean serum IL-6 level was 15.06 ± 5.07 pg/ml, while in controls it was 2.88 ± 1.21 pg/ml, with a mean difference of 12.18 pg/ml (95% CI: 10.72-13.64). Similarly, the mean serum CRP level was 9.97 ± 3.13 mg/L in schizophrenia patients and 1.78 ± 0.77 mg/L in healthy controls, with a mean difference of 8.20 mg/L (95% CI: 7.29-9.10). The

statistical significance of both differences was strong ($p<0.001$) (Table 5).

There was a linear increase in serum IL-6 levels across disease severity categories when patients were ranked. For mild cases, the average IL-6 level was 6.73 ± 1.33 pg/ml (95% CI: 2.77-10.68), for moderate cases it was 11.08 ± 2.90 pg/ml (95% CI: 9.37-12.79), and for severe cases it was 17.92 ± 3.72 pg/ml (95% CI: 16.69-19.15). A statistically significant correlation ($p<0.001$) was found between IL-6 levels and disease severity (Table 6).

The same was true for serum CRP levels; the levels increased with schizophrenia severity. Severe cases had mean CRP values of 11.86 ± 1.94 mg/L (95% CI: 11.19-12.54), moderate instances 7.39 ± 1.81 mg/L (95% CI: 6.45-8.33), and mild cases 4.23 ± 0.81 mg/L (95% CI: 2.06-6.40). This was highly significant statistically ($p<0.001$).

Among the schizophrenia group, there was a positive correlation between serum IL-6 and CRP levels. A statistically significant moderate positive correlation ($r = 0.577$; 95% CI: 0.36-0.74; $p<0.001$) was found. (Table 7).

There was no difference between male and female patients with schizophrenia in terms of serum IL-6 and CRP levels. The level of IL-6 and CRP did not differ significantly between the two groups of males and females ($p = 0.698$ and $p = 0.898$) (Table 8).

There was a significant difference between the mean serum IL-6 level of schizophrenia patients with a positive family history and those with a negative family history, with the difference of 3.09 pg/ml (95% CI: 0.30–5.89; $p = 0.031$). The difference between the patients with positive and negative family histories was also higher in the patients with positive family history, but there was no significant difference (mean difference: 0.66 mg/L; 95% CI: -1.14 to 2.46; $p = 0.467$) (Table 9).

Discussion

The present study demonstrated that patients with schizophrenia had significantly higher serum IL-6 and CRP concentrations than healthy controls. Furthermore, both biomarkers increased progressively with disease severity and showed a significant positive correlation with each other. These findings support the growing evidence that immune dysregulation and persistent low grade systemic inflammation are closely associated with the pathophysiology and clinical severity of schizophrenia. One of the principal findings of this study was the marked elevation of serum IL-6 in patients with schizophrenia. IL-6 is a pleiotropic cytokine that regulates both innate and adaptive immune responses and serves as a key mediator linking peripheral inflammation with central nervous system dysfunction. Persistent elevation of IL-6 promotes activation of microglia, the resident immune cells of the brain, resulting in sustained neuroinflammation. Activated microglia release additional pro-inflammatory cytokines, reactive oxygen species, and neurotoxic mediators, which may impair synaptic plasticity, neuronal connectivity, and cognitive function. Chronic neuroinflammation has been proposed as an important mechanism underlying the development of both positive and negative symptoms of schizophrenia.

Beyond its immunological effects, IL-6 influences several neurobiological pathways implicated in schizophrenia. Increased IL-6 signalling alters dopaminergic neurotransmission within mesolimbic and mesocortical pathways while also affecting glutamatergic neurotransmission through N-methyl-D-aspartate (NMDA) receptor dysfunction. These alterations may contribute to hallucinations, delusions, cognitive impairment, and negative symptoms. IL-6 has also been associated with disruption of blood-brain barrier integrity, permitting greater entry of circulating inflammatory mediators into the central nervous system and further amplifying neuroinflammatory responses.

The significantly elevated CRP concentrations observed in this study further support the presence of systemic inflammatory activation. CRP is synthesized by hepatocytes primarily in response to IL-6-mediated stimulation through the JAK-STAT signalling pathway. Consequently, elevated CRP reflects downstream activation of the inflammatory cascade initiated by increased IL-6 production. Persistent elevation of CRP may indicate chronic low-grade inflammation rather than an acute inflammatory response, suggesting sustained immune activation in patients with schizophrenia.

The progressive increase in both IL-6 and CRP across increasing disease severity represents one of the most clinically relevant findings of the present study. As symptom severity increased, inflammatory marker concentrations also increased significantly, suggesting that inflammatory activation parallels clinical deterioration. Rather than functioning solely as diagnostic biomarkers, IL-6 and CRP may reflect the magnitude of ongoing neuroimmune dysregulation during disease progression. Chronic inflammatory signalling may progressively impair neuronal communication through increased oxidative stress, mitochondrial dysfunction, abnormal synaptic remodelling, and altered neurotransmitter homeostasis, thereby contributing to worsening psychiatric symptoms.

A significant positive correlation between serum IL-6 and CRP was also observed. This relationship is biologically plausible because IL-6 is the

principal cytokine responsible for hepatic CRP synthesis during the acute-phase response. The moderate positive correlation identified in the present study suggests coordinated activation of inflammatory pathways rather than independent elevations of these biomarkers. Simultaneous assessment of IL-6 and CRP may therefore provide complementary information regarding the inflammatory status of patients with schizophrenia.

Subgroup analysis demonstrated no significant differences in IL-6 or CRP concentrations between male and female patients, suggesting that the inflammatory abnormalities observed were largely independent of sex within this cohort. In contrast, patients with a positive family history exhibited significantly higher IL-6 concentrations than those without a family history. Although the underlying mechanisms remain uncertain, this finding may indicate that genetic susceptibility contributes not only to disease risk but also to heightened immune activation. Several susceptibility genes associated with schizophrenia have been linked to immune regulation and cytokine signalling, supporting a potential interaction between genetic predisposition and inflammatory pathways.

Our findings are consistent with previous studies reporting elevated IL-6 and CRP concentrations in schizophrenia and with meta-analyses demonstrating persistent inflammatory activation in affected individuals.[20–28] However, the present study extends these observations by demonstrating a clear relationship between inflammatory biomarkers and disease severity in an Indian population. Rather than serving solely as markers of systemic inflammation, IL-6 and CRP may represent components of a broader neuroimmune network involving cytokine signalling, microglial activation, neurotransmitter dysregulation, oxidative stress, and blood-brain barrier dysfunction.

These interconnected mechanisms provide a biologically plausible explanation for the association between inflammatory activation and increasing symptom severity observed in the present study.

The clinical implications of these findings are noteworthy. If confirmed by larger prospective studies, IL-6 and CRP may have utility as accessible biomarkers for monitoring inflammatory activity and disease progression in schizophrenia. Identification of patients with pronounced inflammatory activation may also facilitate future research into individualized therapeutic strategies incorporating immunomodulatory or anti-inflammatory approaches alongside conventional antipsychotic treatment. Nevertheless, longitudinal and interventional studies are required before these biomarkers can be incorporated into routine clinical practice.

Summary: This comparative cross sectional study evaluated serum IL-6 and CRP levels in 50 patients with schizophrenia and 50 healthy controls. Patients with schizophrenia demonstrated significantly higher serum concentrations of both inflammatory biomarkers than healthy controls. Serum IL-6 and CRP levels increased progressively with disease severity and showed a significant positive correlation, supporting an association between inflammatory activation and clinical severity. These findings reinforce the role of immune dysregulation in schizophrenia and suggest that IL-6 and CRP may serve as useful biomarkers of disease activity.

Conclusion

The present study demonstrated significantly elevated serum IL-6 and CRP concentrations in patients with schizophrenia compared with healthy controls. Both biomarkers increased significantly with disease severity, and serum IL-6 showed a positive correlation with CRP, indicating coordinated inflammatory activation.

These findings support the growing evidence that immune dysregulation and chronic low grade inflammation contribute to the pathophysiology of schizophrenia. Although IL-6 and CRP cannot currently be considered diagnostic biomarkers, they may provide valuable information regarding disease activity and clinical severity. Larger multicentric longitudinal studies are required to determine their prognostic significance and potential role in guiding personalized therapeutic strategies.

Strengths of the Study: Age and gender matched comparative study design minimized demographic confounding. Simultaneous evaluation of serum IL-6, CRP, and PANSS scores provided integrated biochemical and clinical assessment. Standardized laboratory methods and validated clinical assessment tools improved measurement reliability. Inclusion of drug naive or medication free patients reduced the potential influence of antipsychotic therapy on inflammatory biomarkers. The study contributes important data regarding inflammatory biomarkers in schizophrenia from an underrepresented Indian population.

Limitations: The cross sectional design precludes causal inference. The single center study and relatively small sample size may limit generalizability. Only IL-6 and CRP were evaluated; additional inflammatory cytokines and oxidative stress markers were not assessed. Residual confounding from dietary habits, psychosocial stress, and other environmental factors cannot be excluded. Longitudinal changes

in inflammatory biomarkers following treatment were not investigated.

Recommendations: Future multicentric longitudinal studies with larger sample sizes should evaluate a broader panel of inflammatory biomarkers and their relationship with clinical outcomes. Serial biomarker assessment before and after treatment may help clarify the temporal relationship between inflammation and disease progression. Further investigation of immunomodulatory therapies may also improve understanding of the role of inflammation in schizophrenia and support the development of personalized treatment strategies.

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