ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 17, Issue, 11, pp.35207-35213, November, 2025
DOI: https://doi.org/10.24941/ijcr.49746.11.2025

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

THE CLINICAL OBSERVATION OF INFLAMMATION THEORY FOR SCHIZOPHRENIA: A 12 WEEK INTERVENTIONAL STUDY

[1,*]Sumeesha Jaswal, [2]Ajeet Sidana, [3]Shivangi Mehta, [4]Seema Gupta and [5]Gurjit Kaur

[1]Department of Psychiatry, ESIC Medical College and Hospital, Faridabad, HaryanaIndia
[2,3]Department of Psychiatry, Government Medical College and Hospital, Chandigarh, India
[4]Department of Biochemistry, Government Medical College and Hospital, Chandigarh, India
[5]Department of Physiology, Government Medical College and Hospital, Chandigarh, India

ARTICLE INFO

Article History:
Received 19th August, 2025
Received in revised form
24th September, 2025
Accepted 27th October, 2025
Published online 29th November, 2025

Keywords:

Schizophrenia, Clozapine, Immunoglobulins, Interleukins, Risperidone.

***Corresponding author:**
Sumeesha Jaswal

ABSTRACT

Background: Recent research highlights the neuroinflammatory basis of Schizophrenia with an intrigue into biomarkers for schizophrenia. The involvement of immunological dysfunction in schizophrenic patients with a blunted type 1 (i.e., IL-2, gamma interferon, IL-12 and TNF-β) and an increased type 2 cytokine pattern (i.e., IL-4, IL-5, IL-6, IL-10 and IL-13) has been seen. **Aim:** To assess the baseline immunological parameters in drug naïve patients of schizophrenia, compare the levels of interleukins-2,6 and 8 in patients on clozapine and risperidone at baseline, 6 weeks and 12 weeks and study their correlation with clinical response. **Material and methods**: It was a prospective, randomized, and comparative study. Patients with ICD 11 diagnosis of Schizophrenia were randomized to receive either clozapine or risperidone after baseline assessment of socio- demographic and clinical parameters, baseline blood investigations, immunoglobulins and estimation of interleukin (IL-2, 6 and 8) levels. Levels of interleukins were reassessed at 6 weeks and 12 weeks along with application of PANSS and Glasgow antipsychotic side effect check list. **Results**: 54 of 65 patients completed the study; 30 patients in clozapine group and 24 in risperidone group. A significant rise was seen in IL-2 levels over 12 weeks. There was decrease in IL-6 levels which correlated with the decrease in positive symptoms at week 12. IL-8 had a negative correlation with the general psychopathology score at week 6 which continued till week 12. Risperidone did not have a significant alteration in the interleukin levels over the 12 weeks. **Conclusion**: It can be concluded that the elevated cytokine levels (IL-6) at baseline in both clozapine and risperidone groups validate the inflammatory basis of schizophrenia and may be used as the state marker for schizophrenia.

Citation: Sumeesha Jaswal, Ajeet Sidana, Shivangi Mehta, Seema Gupta and Gurjit Kaur. 2025. "The clinical observation of inflammation theory for schizophrenia: a 12 week interventional study.". *International Journal of Current Research, 17, (11), 35207-35213.*

INTRODUCTION

Schizophrenia has been associated with chronic inflammation in the central nervous system.[1] Aberrant immune mechanisms involving both the peripheral and central nervous systems have been implicated in the etiology of schizophrenia and in the pathophysiology of psychotic symptoms that characterize the disorder. These mechanisms exert their effects through alterations in monoamine metabolism, neuroendocrine function, and synaptic plasticity.[2,3] A substantial body of evidence has documented immunological dysfunction in patients with schizophrenia.[4,5,6] Several studies have reported a diminished Type 1 cytokine response (e.g., IL-2, gamma interferon, IL-12, TNF-β) and an enhanced Type 2 cytokine profile (e.g., IL-4, IL-5, IL-6, IL-10, IL-13) in untreated individuals with schizophrenia.[7,8] Antipsychotic medications have also been shown to influence immunological parameters, including interleukin and immunoglobulin levels. Clozapine, regarded as the most effective antipsychotic for schizophrenia, exhibits immunomodulatory properties and has been reported to alter humoral immunity by modulating levels of immunoglobulin-producing cytokines such as IL-2 and IL-6.[9]

Similarly, risperidone, another widely utilized antipsychotic agent, may exert direct effects on inflammatory status, significantly altering interleukin and immunoglobulin concentrations in patients with schizophrenia.[10,11,12] Despite growing evidence globally, Indian literature on the immune profile of schizophrenia remains limited. Therefore, the present study was designed to assess inflammatory parameters in drug-naïve patients with schizophrenia or those who had been off treatment for at least two weeks. The study further aimed to compare the effects of clozapine and risperidone on interleukin levels (IL-2, IL-6, IL-8) and to investigate their correlation with clinical response.

METHODS

Study Design and Setting: This prospective, randomized, comparative study was conducted at both outpatient and inpatient facilities of the Department of Psychiatry, a tertiary care teaching hospital in North India. Based on prior literature regarding percentage changes in immune parameters, the sample size was calculated with a 90% confidence level and 15% absolute precision. After accounting for potential loss to follow-up, a final sample size of 60 patients was determined.

Participants: Patients aged 18–45 years with a diagnosis of schizophrenia according to ICD-11 (WHO)[13], who had not received antipsychotic treatment for at least two weeks, and who had the capacity and willingness to provide written informed consent were recruited. In cases where patients lacked capacity, written informed consent was obtained from their nominated representatives. Patients were additionally assessed for eligibility to initiate clozapine therapy, defined as having previously failed at least two antipsychotic trials.
Exclusion criteria included: ongoing immunosuppressant therapy, active infection within the past two weeks, hematological disorders, chronic liver or kidney disease, autoimmune disorders, chronic inflammatory disease, recent antibiotic use (including chloramphenicol, tetracycline, rifampicin, polymyxin B, nitrofurantoin), known immunodeficiency, epilepsy, agranulocytosis or granulocytopenia, paralytic ileus, central nervous system depression, myeloproliferative disorders, substance use disorders (other than tobacco and caffeine), pregnancy, lactation, and prior depot antipsychotic use within the past three months. These exclusion criteria were applied to minimize confounding variables.

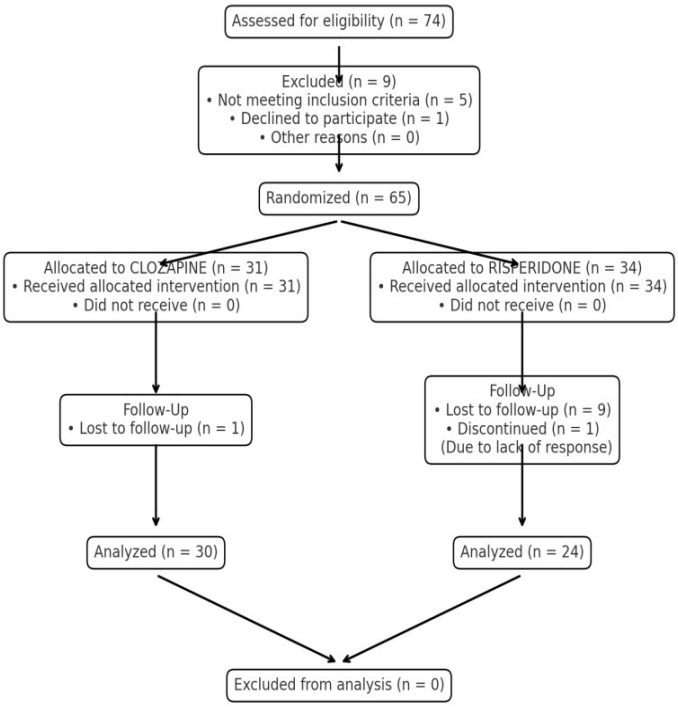
Procedure: Patients meeting inclusion and exclusion criteria were enrolled after obtaining written informed consent. Baseline socio-demographic and clinical data were recorded using a standardized pro forma. The severity of psychopathology was assessed at baseline using the Positive and Negative Syndrome Scale (PANSS). Baseline laboratory assessments included a 4 mL blood sample for complete blood count, fasting blood sugar, liver and renal function tests, and lipid profile. An additional 5 mL sample was collected to measure serum levels of IL-2, IL-6, and IL-8 using the Diaclone Human Interleukin ELISA kit. The normal reference ranges were defined as: IL-2 <7 pg/mL; IL-6 <2 pg/mL; and IL-8 <29 pg/mL. Following baseline assessments, patients were randomized to receive either clozapine or risperidone based on a computer-generated random number table. Dosages were maintained within the therapeutic range as per the Maudsley Prescribing Guidelines (Clozapine: up to 900 mg/day; Risperidone: 2–8 mg/day). Clozapine was initiated at 12.5 mg/day and titrated gradually to the maximum tolerated therapeutic dose over 4–6 weeks. Risperidone was initiated at 2 mg/day and similarly titrated to the maximum tolerated dose over 4–6 weeks. Treatment response was defined as a ≥50% reduction in PANSS scores from baseline.[15] Responders continued on their stabilized doses until the end of the 12-week study period and thereafter for ongoing clinical care. For agitation or aggression, benzodiazepines (sublingual or intramuscular clonazepam, diazepam, or lorazepam) were permitted. Trihexyphenidyl was allowed for the management of extrapyramidal symptoms, and the dosages of these adjunctive medications were documented for both groups.

Patients were monitored weekly. Complete blood counts were obtained weekly before any dose escalation of clozapine. Serum interleukin levels (IL-2, IL-6, IL-8) were re-assessed at weeks 6 and 12, along with PANSS scores and administration of the Glasgow Antipsychotic Side Effect Scale. In the clozapine group, patients were withdrawn from the study and managed as per protocol if the total leukocyte count fell below 4000/mm³ or the absolute neutrophil count dropped below 1000/mm³. The study was approved by the Institutional Ethics Committee and registered with the Clinical Trial Registry-India (http://ctri.nic.in/) under registration number CTRI/202/02/023214, dated 10/02/2020 (REF/2019/12/030332). All methods were carried out in accordance with relevant guidelines and regulations.

Statistical Analysis: The normality of the variables was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Most of the variables were found to follow a normal distribution. For variables with a non-normal (skewed) distribution, appropriate non-parametric tests were employed. Comparisons between two independent groups (Clozapine vs. Risperidone) were performed using the Mann–Whitney U test. For within-group comparisons across time points (baseline, week 6, and week 12), the Wilcoxon signed-rank test was applied. Spearman's rank correlation coefficients were computed to explore the relationships between continuous variables. Kendall's tau-b was used to assess associations between ordinal variables. Categorical variables were summarized as frequencies and percentages. Group comparisons of categorical data were performed using the Chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant. Data analysis was performed using [SPSS version 31].

RESULTS

A total of 65 patients were screened and enrolled in the study, as illustrated in Figure 1. (CONSORT Flowchart). Hence, 54 patients who completed the study and were analyzed for the results.



The sociodemographic profile of patients included in the study are given in Table 1. Both the groups were comparable on socio-demographic profile. Sex-related or age-related immunological differences were not present. The total duration of illness ranged from 2 to 25 years in the Clozapine group and from 6 months to 20 years in the Risperidone group. The duration of the current exacerbation of symptoms ranged from 2 to 8 months in the Clozapine group and from 1 to 6 months in the Risperidone group. The total PANSS score was significantly higher in the Clozapine group (Mean ± SD: 60.27 ± 10.94) compared to the Risperidone group (Mean ± SD: 49.83 ± 6.11) across all assessments, with a p-value of 0.0001. Additionally, there were significant differences in the general psychopathology scores (p = 0.009) and positive symptom scores (p = 0.003), as presented in Table 2. Further, GAS score was significantly higher in the clozapine group at week 6 and week 12 than risperidone group as shown in table 2. There was a significant difference in IL-6 level at baseline between Clozapine and Risperidone groups. Interleukin profile showed that at week 6 and 12, there was no significant difference in the IL-2, 6 and 8 levels between the Clozapine and Risperidone groups (Table 3). Over the 12 weeks, within group comparison showed a significant fall in all parameters of PANSS for the Clozapine group (Table 4). A significant rise was seen in IL- 2 level with more individuals having greater than normal values over 12 weeks. IL- 6 had a significant fall at week 6 but not at week 12. IL-8 values did not differ significantly over 12 weeks (Table 5). For both antipsychotics, at baseline a positive correlation was seen between IL-6 and positive symptom subscale of PANSS. Another positive correlation was seen between IL-8 and Positive symptom subscale of PANSS. A highly significant correlation was seen with the Total score and IL- 6. IL-8 had a negative correlation with the general psychopathology score at week 6 and this effect continued till week 12 as shown in table 6.

Table 1. Sociodemographic profile of the patients

		CLOZAPINE (n=30) Experimental group(A)		RISPERIDONE (n=24) Control group (B)		Chi-Square	p-value
Parameter		**N**	**%**	**N**	**%**		
Age	<30 years	11	36.7%	12	50%	0.969	0.325
	>30 years	19	63.3%	12	50%		
Sex	Male	18	60%	15	62.5%	0.035	0.851
	Female	12	40%	9	37.5%		
Marital status	Single	19	63.3%	16	66.7%	0.823	0.663
	Married	10	33.3%	8	33.3%		
	Divorced	1	3.3%	0	0%		
Education	Illiterate	1	3.3%	2	8.3%	7.554	0.273
	Primary	1	3.3%	1	4.2%		
	Middle	6	20%	3	12.5%		
	Matric	10	33.3%	8	33.3%		
	Inter	6	20%	6	25%		
	Graduate	6	20%	1	4.2%		
	Postgraduate	0	0%	3	12.5%		
Occupation	Professional	0	0	0	0	3.250	0.662
	Semi-Professional	3	10.0%	0	0		
	Clerical	4	13.3%	3	12.5%		
	Skilled	7	23.3%	7	29.2%		
	Household	8	26.7%	7	29.2%		
	Unemployed	7	23.3%	5	20.8%		
	Student	1	3.3%	2	8.3%		
Area	Urban	19	63.3%	12	50%	0.969	0.325
	Rural	11	36.7%	12	50%		
Religion	Hindu	20	66.7%	17	70.8%	5.212	0.074
	Muslim	0	0	3	12.5%		
	Sikh	10	33.3%	4	16.7%		
Type of Family	Nuclear	19	63.3%	14	58.3%	0.140	0.708
	Joint	11	36.7%	10	41.7%		
Socio Economic Status	Lower	7	29.2%	7	29.2%	7.628	0.054
	Lower Middle	11	36.7%	9	37.5%		
	Upper Middle	12	40.0%	4	16.7%		
	Upper	0	0	4	16.7%		

Table 2: Comparison between Clozapine and Risperidone groups in clinical and immunoglobulin profile *at baseline, week 6 and week 12*

	Group		t-value/ Mann-Whitney U (Z)#	p-value
	Clozapine (N=30) **Experimental group(A)**	Risperidone (N=24) **Control group (B)**		
Parameter	Mean ± SD	Mean± SD		
TDI (years)	12.03±6.64	8.77±6.28	1.838	0.072
Current exacerbation duration (months)	4.13±1.61	3.42±1.44	1.699	0.095
BASELINE				
Positive	26.23±9.28	19.67±4.62	3.163	0.003*
Negative	9.03±2.34	9.00±2.40	0.278	0.781
General	25.13±6.39	21.17±3.53	2.723	0.009*
Total PANSS	60.27±10.94	49.83±6.11	4.177	0.0001*
WEEK 6				
Positive	19.17±6.85	15.08±3.81	2.612	0.012*
Negative	8.10±1.94	7.83±1.40	0.214	0.831
General	20.53±3.86	18.29±1.73	2.271	0.023*
Total PANSS	47.80± 7.57	40.79±4.27	4.044	0.0001*
GAS	8.13±4.83	2.63±2.67	4.870	0.0001*
WEEK 12				
Positive	15.43±4.78	12.29±3.04	2.385	0.017*
Negative	7.77±1.52	7.46±0.88	0.649	0.517
General	18.80±3.04	17.46±1.35	1.452	0.147
Total PANSS	42.00±5.69	37.21±3.26	3.670	0.001*
GAS	3.40±3.77	.96±1.73	3.066	.002*

*Significant ** highly significant

DISCUSSION

Through this study, the authors have highlighted the interplay of immune parameters with two commonly used atypical antipsychotics, potentiating the immunological underpinnings in the etiopathogenesis of schizophrenia. The mean age of the sample was 33.63 ± 5.94 years for the Clozapine group and 31.96 ± 6.15 years for the Risperidone group, which is comparable to other studies.[14] [15] Both groups had a higher preponderance of males (60% and 62.5%), as reported in the literature.[17] Although the mean total duration of illness was higher in the Clozapine group, the difference was not statistically significant (12.03 ± 6.64 vs. 8.77 ± 6.28), supporting the common clinical practice of Clozapine use following inadequate response to at least two antipsychotics. The available literature presents varied reports on IL-2 levels in schizophrenia (reduced levels by Ganguli *et al.*[16] and Mahendran *et al.*[17]; elevated levels by Tan *et al.*[18] and Zhang *et al.*[19]). In our study, 96.30% of patients exhibited normal IL-2 levels at baseline. This finding aligns with studies reporting no significant

Table 3. Comparison between Clozapine and Risperidone groups for interleukin profile *atbaseline, week 6 and week 12*

		Group						Chi-Square	p-value
		Clozapine **Experimental group(A)**		Risperidone (B) **Control group (B)**		Total			
		N	%	N	%	N	%		
BASELINE									
IL2 (pg/ml)	Normal(<7)	30	100.00%	22	91.70%	52	96.30%	2.596	0.273
	Increased (>7)	0	0	1	4.20				
IL6 (pg/ml)	Normal (<2)	2	6.7%	12	50.0%	14	25.9%	13.037	0.0001**
	Increased (>2)	28	93.3%	12	50%	40	74.1%		
IL8 (pg/ml)	Normal (<29)	17	56.7%	13	54.2%	30	55.6%	4.118	0.128
	Increased(>29)	13	43.3%	11	45.8%	24	44.4%		
WEEK 6									
IL2 (pg/ml)	Normal(<7)	24	80.0%	18	75.0%	42	77.8%	0.193	0.661
	Increased (>7) (7-2000)	6	20.0%	6	25.0%	12	22.2%		
IL6 (pg/ml)	Normal (<2)	12	40.0%	7	29.2%	19	35.2%	0.995	0.608
	Increased (>2)	18	60%	17	70.8%	35	64.9%		
IL8 (pg/ml)	Normal (<29)	13	43.3%	9	37.5%	22	40.7%	5.670	0.129
	Increased	12	40%	14	58.3%	26	48.2%		
WEEK 12									
IL2 (pg/ml)	Normal(<7)	24	80.0%	23	95.8%	47	87.0%	2.963	0.085
	Increased	6	20.0%	1	4.2%	7	13.0%		
IL6 (pg/ml)	Normal (<2)	7	23.3%	6	25.0%	13	24.1%	0.700	0.705
	Increased	23	76.6%	18	75%	41	76%		
IL8 (pg/ml)	Normal (<29)	20	66.7%	11	45.8%	31	57.4%	2.368	0.306
	Increased	10	43.3%	13	45.2%	23	42.6%		

**Highly Significant

Table 4. Within -group comparison in clinical and immunoglobulin profile over 12 weeks

	Clozapine			Risperidone		
PANSS	Mean ± SD	Wilcoxon Signed Ranks (Z)	p-value	Mean ± SD	Wilcoxon Signed Ranks (Z)	p-value
Positive (baseline)	26.23+9.28			19.67+4.62		
Positive (week 6)	19.17+6.85	4.793	0.0001*	15.08+3.81	4.054	.0001**
Positive (week 12)	15.43+4.78	4.786	0.0001*	12.29+3.04	4.238	.0001**
Negative (baseline)	9.03+2.34			9.00+2.40		
Negative (week 6)	8.10+1.94	3.457	0.001*	7.83+1.40	3.097	.002**
Negative (week 12)	7.77+1.52	2.833	0.005*	7.46+.88	3.322	.001**
General (baseline)	25.13+6.39			21.17+3.53		
General (week 6)	20.53+3.86	4.235	0.0001*	18.29+1.73	3.755	.0001**
General (week 12)	18.80+3.04	4.576	0.0001*	17.46+1.35	3.832	.0001**
Total (baseline)	60.27+10.94			49.83+6.11		
Total (week 6)	47.80+7.57	9.844	0.0001*	40.79+4.27	8.275	.0001**
Total (week 12)	42.00+5.69	11.982	0.0001*	37.21+3.26	12.320	.0001**
GAS						
GAS (week 6)	8.13+4.83			2.63+2.67		
GAS (week 12)	3.40+3.77	4.703	0.0001*	.96+1.73	3.671	.0001**

*Significant **Highly significant

Table 5. Within group comparison in interleukin profile over 12 weeks

	Clozapine		Risperidone	
	Wilcoxon Signed Ranks Test (Z)	p-value	Wilcoxon Signed Ranks Test (Z)	p-value
Difference between Week 6 and baseline for IL-2	2.449	0.014*	1.89	.059
Difference between Week 12 and baseline for IL-2	2.449	0.014*	0	1.000
Difference between Week 6 and baseline for IL-6	2.309	0.021*	1.641	.101
Difference between Week 12 and baseline for IL-6	1.265	0.206	1.886	.059
Difference between Week 6 and baseline for IL-8	0.535	0.593	2.076	.038*
Difference between Week 12 and baseline for IL-8	0.881	0.378	1.396	.163

*Significant

deviations in IL-2 levels[20] [21] but contrasts with studies on first-episode schizophrenia.[22] In the present study, elevated IL-6 levels were observed at baseline in both groups (74.1% of the total study population), consistent with previous reports of raised IL-6 levels in patients with schizophrenia.[23] [24] Miller *et al*., in their meta-analysis, proposed IL-6 as a state marker in schizophrenia due to elevated levels in both patients with schizophrenia and individuals with At-Risk Mental State (ARMS).[20] The present study further supports IL-6 as a potential state marker. Although increased IL-8 expression is generally indicative of chronic inflammatory conditions, it was found to be normal in the majority of patients in both groups, consistent with the meta-analysis by Dawidowski *et al*.[25]

Trends in Interleukins and Immunoglobulins: Our study observed a significant rise in IL-2 levels at week 6, which persisted through 12 weeks in the Clozapine group, consistent with previous findings.[26] This may support the hypothesis of proinflammatory cytokine-mediated adverse effects of Clozapine. Subgroup analysis revealed no significant correlation between IL-2 and symptomatology, though a negative correlation with negative symptoms on PANSS was

Table 6. Correlation between illness severity, immunoglobulin profile and interleukin over 12 weeks in both groups

Baseline					
			IL-2	IL-6	IL-8
Kendall's tau b	Positive	Correlation Coefficient	-0.159	0.237	0.236
		p-value	0.167	0.040*	0.035*
	Negative	Correlation Coefficient	-0.020	0.004	-0.175
		p-value	0.869	0.976	0.140
	General	Correlation Coefficient	0.030	0.250	-0.203
		p-value	0.797	0.032*	0.073
	Total	Correlation Coefficient	-0.125	0.391	0.066
		p-value	0.275	0.001*	0.552
Week 6					
Kendall's tau b	Positive	Correlation Coefficient	0.145	0.007	-0.019
		p-value	0.211	0.953	0.863
	Negative	Correlation Coefficient	-0.003	-0.082	-0.013
		p-value	0.981	0.508	0.912
	General	Correlation Coefficient	-0.065	-0.012	-0.255
		p-value	0.584	0.918	0.025*
	Total	Correlation Coefficient	0.103	-0.005	-0.069
		p-value	0.375	0.966	0.532
Week 12					
Kendall's tau b	Positive	Correlation Coefficient	0.049	0.204	0.049
		p-value	0.678	0.076	0.664
	Negative	Correlation Coefficient	-0.094	-0.143	-0.019
		p-value	0.472	0.263	0.883
	General	Correlation Coefficient	0.029	-0.058	-0.287
		p-value	0.813	0.624	0.014*
	Total	Correlation Coefficient	0.028	0.101	-0.044
		p-value	0.806	0.372	0.690

*Significant **Highly significant

observed, similar to findings by Asevedo *et al*.[27] The increased IL-6 is generally associated with Clozapine-induced fever; however, the initial decrease in IL-6 in our study may explain the absence of fever among our patients.[28] Furthermore, the reduction in IL-6 levels correlated with the improvement in positive symptoms at week 12, consistent with the literature.[29] Changes in IL-8 levels over 12 weeks were not statistically significant, though a trend towards normalization was observed, similar to Maes *et al*.[30] This contrasts with Capannolo *et al*., who reported a decrease in IL-8 levels following Clozapine treatment.[31]The discrepancy may stem from methodological differences, as IL-8 levels in their study were measured in cultured cells exposed to Clozapine, whereas our study measured in vivo levels. IL-8 levels negatively correlated with the general symptom domain of PANSS at both week 6 and week 12, consistent with Enache *et al*.[32] who suggested IL-8 as a potential immune marker predicting antipsychotic nonresponse. IL-8 maintained a negative correlation with the general psychopathology score at week 6, which persisted through week 12, suggesting its role as a marker of general psychopathology in schizophrenia. In contrast, while IL-2 has previously been reported to negatively correlate with the negative PANSS subscale,[33] this was not observed in our study. The difference may be explained by the higher negative subscale scores in the Asevedo *et al*. study (mean 17.14 ± 5.35) compared to the present sample. The role of IL-6 as a state marker has also been highlighted in previous studies, where it positively correlated with general psychopathology and positive PANSS subscales.[34] Our baseline IL-6 findings similarly correlated with positive, general psychopathology, and total PANSS scores. The present study has several strengths, including randomization, which minimized selection bias, and a prospective design. Laboratory investigations ruled out relevant medical conditions at baseline, and confounding factors such as immunomodulating drugs were excluded, ensuring methodological robustness. The use of standardized tools such as PANSS facilitated comparison with international literature. Repeated assessments at three time points allowed for reliable observation of trends. This study contributes to the limited body of literature from India examining the effects of antipsychotics on immune parameters in schizophrenia. Nevertheless, certain limitations should be acknowledged. The small sample size limits the generalizability of the findings. The short duration of follow-up, limited cytokine panel, and absence of serum Clozapine and Risperidone levels precluded a more comprehensive understanding of immune mechanisms. The absence of a healthy control group also limits interpretation of cytokine levels. Moreover, significant baseline differences in PANSS scores between the Clozapine and Risperidone groups represent a confounding factor in cross-group comparisons.

CONCLUSION

The study findings suggest an inflammatory basis for schizophrenia, as evidenced by elevated baseline IL-6 levels in both Clozapine and Risperidone groups. The elevated IL-6 levels further support its potential role as a state marker for schizophrenia. Although short-term fluctuations in cytokine levels were observed over the 12-week study period, longer-term follow-up is necessary to evaluate the stability and trajectory of these biomarkers. This study not only strengthens the biological basis of schizophrenia but also opens avenues for further exploration of cytokines as potential biomarkers for diagnosis, prognosis, and treatment response.

List of abbreviations

IL: Interleukin
PANSS: Positive and Negative Syndrome Scale
ICD: International Classification of Disease
CNS: Central Nervous System
GAS: Glasgow Antipsychotic Side-effect Scale

Declarations

Ethics approval

The principles enunciated in the Declaration of Helsinki and the Indian Council of Medical Research were complied with and the study was approved by the Institutional Ethics Committee. The study was approved by institutional ethics committee at Government Medical College and Hospital, Chandigarh and registered with Clinical Trial Registry India (http://ctri.nic.in/) under registration number CTRI/202/02/023214, dated 10/02/2020 (REF/2019/12/030332).

Consent to participate: Informed consents (Consent to Participate) was obtained from all participants. In cases where patients lacked

capacity, written informed consent was obtained from their nominated representatives.

Consent for publication: Written Consent from publication was taken from all participants during the study.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' contributions: AS , SM, SG, GK were contributed to the conception and design of work SJ was involved in acquisition, analysis, interpretation of data, drafting the work, AS, SM, SJ revised the work, SJ, SM wrote the main manuscript text, prepared the figures and text All authors reviewed the manuscript

Acknowledgements

Late Dr. BS Chavan for inspiring the work, Dr Priti Arun for her constant guidance and support

REFERENCES

1. Anderson G, Berk M, Dodd S, *et al*. Immuno-inflammatory, oxidative and nitrosative stress and neuroprogressive pathways in the etiology, course, and treatment of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2013;42:1–4.
2. Müller N and Schwarz M. Neuroimmune-endocrine crosstalk in schizophrenia and mood disorders. Expert Rev Neurother 2006;6:1017–1038.
3. Erbağci A, Herken H, Köylüoglu O,*et al*. Serum IL-1beta, sIL-2R, IL-6, IL-8 and TNF-alpha in schizophrenic patients, relation with symptomatology and responsiveness to risperidone treatment. Mediators Inflamm 2001;10:109-115.
4. Miller B, Buckley P, Seabolt W, *et al*. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011;70:663–671.
5. Dahan S, Bragazzi N, Yogev A, *et al*. The relationship between serum cytokine levels and degree of psychosis in patients with schizophrenia. Psychiatry Res 2018;268:467-472.
6. Rao N, Gopinath P, Jayasimha N, *et al*. Serum Immunoglobulins and Schizophrenia. Indian J Psychiatry 1985;27:325-329.
7. Tiwari S, Lal N, Trivedi J, *et al* . Relationship of immunoglobulins with the number & duration of schizophrenic episodes. Indian J Med Res 1989;90:229-32.
8. Roge R, Moller B, Andersen C, *et al*. Immunomodulatory effects of clozapine and their clinical implications: What have we learned so far? Schizophr Res 2012;140:204–213.
9. Lozano R, Marin R, Santacruz M, *et al*. Effect of clozapine on immunoglobulin M plasma levels. Ther Adv Psychopharmacol 2016;6:58–60.
10. Hinze S, Becker E, Stein G, *et al*. Effects of Clozapine on In Vitro Immune Parameters: A Longitudinal Study in Clozapine-Treated Schizophrenic Patients. Neuropsychopharmacology 1998;19:114-122.
11. Ponsford M, Castle D, Tahir T, *et al*. Clozapine is associated with secondary antibody deficiency. Br J Psychiatry 2019;214:83–89.
12. Clark S, Warren N, Kim G, *et al*. Elevated clozapine levels associated with infection: A systematic review. Schizophr Res 2018;192:50-56.
13. Feng Z, Zhang Y, You X, *et al*. Effects of risperidone on blood levels of interleukin-6 in schizophrenia: A meta-analysis. Medicine (Baltimore). 2020;99:19694.
14. Kay SR, Fiszbein A and Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-276.
15. Leucht S, Davis J, Engel R, *et al*. Definitions of response and remission in schizophrenia: recommendations for their use and their presentation. Acta Psychiatr Scand Suppl 2009;438:7-14.
16. Ramchand R, Wei J, Ramchand C, *et al*. Increased serum IgE in schizophrenic patients who responded poorly to neuroleptic treatment. Life Sciences 1994; 54(21): 1579–1584.
17. Ganguli R, Brar J, Chengappa K, Yang Z, *et al*. Autoimmunity in schizophrenia: a review of recent findings. Ann Med 1993;25:489–496.
18. Ganguli R, Brar J and Rabin B. Immune abnormalities in schizophrenia: evidence for the autoimmune hypothesis. Harv Rev Psychiatry 1994;2:70-83.
19. Mahendran R, Mahendran R and Chan Y. Interleukin-2 levels in chronic schizophrenia patients. Ann Acad Med Singap 2004 ;33:320-323.
20. Tan Y, Li Y, Tan S, *et al*. Increased interleukin-2 serum levels were associated with psychopathological symptoms and cognitive deficits in treatment-resistant schizophrenia. Schizophr Res 2015;169:16-21.
21. Zhang X, Zhou D, Zhang P, *et al* . Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. Schizophr Res 2002;57,247–258.
22. Upthegrove R, Manzanares-Teson N and Barnes N. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr Res 2014;155:101–108.
23. Momtazmanesh S, Zare-Shahabadi A and Rezaei N. Cytokine Alterations in Schizophrenia: An Updated Review. Front Psychiatry 2019; 10:892.
24. Xiong P, Zeng Y, Wan J, *et al*. The role of NGF and IL-2 serum level in assisting the diagnosis in first episode schizophrenia. Psychiatry Res 2011;189:72-7.
25. Akiyama K. Serum levels of soluble IL-2 receptor alpha, IL-6 and IL-1 receptor antagonist in schizophrenia before and during neuroleptic administration. Schizophr Res 1999;37:97-106. Available on doi: 10.1016/s0920-9964(98)00140-6. PMID: 10227112. Last Accessed on January 7, 2022.
26. Kalmady S, Shivakumar V, Jose D, *et al*. Plasma cytokines in minimally treated schizophrenia. Schizophr Res 2018;199:292-296.
27. Dawidowski B, Górniak A, Podwalski P ,*et al*. The Role of Cytokines in the Pathogenesis of Schizophrenia. Journal of Clinical Medicine 2021;10;17.
28. Rudolf S, Peters M, Rothermudt M, *et al*. The influence of typical and atypical neuroleptic drugs in the production of interleukin 2 and interferon gamma in vitro. Neuropsychobiology 2002;46:180-185.
29. Asevedo E, Rizzo L, Gadelha A, *et al*. Peripheral interleukin-2 level is associated with negative symptoms and cognitive performance in schizophrenia. Physiol Behav 2014;129:194-198.
30. Hung Y, Wang C, Yen C, *et al*. Role of cytokine changes in clozapine induced fever: A cohort prospective study. Psychiatry And Clinical Neurosciences 2017;71:395-402.
31. Luo Y, He H, Zhang J, *et al*. Changes in serum TNF-α, IL-18, and IL-6 concentrations in patients with chronic schizophrenia at admission and at discharge. Comprehensive Psychiatry 2019;90:82-87.
32. Maes M. Increased serum interleukin-8 and interleukin-10 in schizophrenic patients resistant to treatment with neuroleptics and the stimulatory effects of clozapine on serum leukemia inhibitory factor receptor. Schizophr Res 2002; 54, 281–91. Available on doi:10.1016/s0920-9964(00)00094-3. Last accessed on 7 January, 2022.
33. Capannolo M, Fasciani I, Romeo S, *et al*. The atypical antipsychotic clozapine selectively inhibits interleukin 8 (IL-8)-induced neutrophil chemotaxis. Eur Neuropsychopharmacol 2015;25:413-424.
34. Enache D, Nikkheslat N, Fathalla D, *et al*. Peripheral immune markers and antipsychotic non-response in psychosis. Schizophr Res 2021; 230,1-8.
35. Ponsford M, Steven R, Bramhall K, *et al*. Clinical and laboratory characteristics of clozapine-treated patients with schizophrenia

referred to a national immunodeficiency clinic reveals a B-cell signature resembling common variable immunodeficiency (CVID). J Clin Pathol 2020;73(9):587-592.
36. Tiwari S. Psychoimmunology and functional psychoses: the Indian scene. Indian J Psychiatry. 1994;36:61-66.
37. Abe S, Suzuki T and Hori T. Hypogammaglobulinemia during antipsychotic therapy. Ther Adv Psychopharmacol 1998;52:115–117.
38. Torrey E, Leweke M, Schwarz M, *et al*. Cytomegalovirus and schizophrenia. CNS Drugs. 2006;20(11):879-885.
39. Flynn S, MacEwan G, Altman S, *et al*. An open comparison of clozapine and risperidone in treatment resistant schizophrenia. Pharmacopsychiatry 1998;31:25-29.
40. Bondolfi G, Dufour H, Patris M, *et al*. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. The Risperidone Study Group. Am J Psychiatry 1998;155:499-504. Available on doi: 10.1176/ajp.155.4.499. PMID: 9545995. Last Accessed on January 7, 2022.
41. Ebert T and Midbari Y. Effect of clozapine and other antipsychotics on the level of platelet-associated autoantibodies in children with schizophrenia: A longitudinal follow-up study. Neuropsychobiology 2015;71;120–124.
42. Solomon G, Allansmith M, McClellan B, *et al*. Immunoglobulins in Psychiatric Patients. Arch Gen Psychiatry 1969;20:272–277.
43. Borovcanin M, Jovanovic I, Radosavljevic G, *et al*. Interleukin-6 in Schizophrenia-Is There a Therapeutic Relevance? Front Psychiatry 2017;8:221.

****