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RESEARCH ARTICLE

Serum IL-6 as a Potential Biomarker of Metabolic Status in Schizophrenia Patients and Its Correlation with Psychotic Symptoms

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Abstract

Objectives: This study aimed to investigate the serum IL-6 level in schizophrenia patients, considering disease chronicity and metabolic status, and to examine its correlation with psychotic symptom scores. The present study also evaluated the diagnostic value of serum IL-6 as a peripheral biomarker for assessing the metabolic health of schizophrenia patients. **Methods:** Serum IL-6 levels were measured using enzyme-linked immunosorbent assay (ELISA) in 92 schizophrenia patients [44 First Episode Drug Naive (FEDN), 48 chronic schizophrenia (CSZ) patients] and 32 healthy controls. Patients were also stratified into high-risk and no-risk cohorts based on their metabolic status. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). **Findings:** Serum IL-6 levels were significantly higher in schizophrenia patients compared to healthy controls ($p<0.001$), with no difference between FEDN and CSZ patients ($p=0.475$). Elevated IL-6 levels were observed in patients in high-risk group compared to those in no-risk group ($p<0.001$). There was a positive correlation between serum IL-6 levels and BMI ($r=0.557$, $p<0.001$), G score ($r=0.244$, $p=0.01$), and total PANSS score ($r=0.228$, $p=0.02$). Similar associations were found in CSZ patients. The ROC curve analysis showed that serum IL-6 has strong diagnostic potential for distinguishing schizophrenia patients in the high-risk group from those in the no-risk group (AUC=0.875, 95% CI: 0.781-0.969, $p<0.001$), suggesting its value as a biomarker. **Novelty:** This study highlights the stable role of serum IL-6 in schizophrenia patients regardless of disease chronicity. The findings suggest that serum IL-6 levels were significantly associated with disease severity as measured by PANSS and metabolic health of schizophrenia patients, providing new insights into its prognostic and diag-

nostic utility. Early identification and targeted management of high-risk groups can improve patient outcomes and quality of life.

Keywords: Schizophrenia; IL-6; FEDN; Chronic; PANSS; Metabolic status; Biomarker

1 Introduction

Schizophrenia is a complex and chronic mental disorder characterized by disturbances in thought, perception, and behavior [1]. While the etiopathology of schizophrenia remains unclear, both genetic and environmental factors are believed to be associated with the development of the disease. Recent research has increasingly focused on inflammation in the central nervous system and peripheral circulation, highlighting the role of Interleukin-6 (IL-6) in the pathophysiology of schizophrenia [2,3]. Elevated IL-6 levels have been implicated in the inflammatory response associated with neuropsychiatric disorders, including schizophrenia [4,5]. Existing research studies suggest a significant association of proinflammatory cytokines with the psychopathology of schizophrenia [6,7]. Although many studies have described IL-6 levels in schizophrenia patients, comprehensive data from this region, particularly comparing First-Episode Drug Naïve (FEDN) and chronic schizophrenia (CSZ) patients, is lacking.

Assessment of psychotic symptoms in positive and negative syndrome scale is a valuable tool for monitoring disease severity and response to antipsychotic treatment [8]. Findings from earlier studies concerning the association of IL-6 with psychotic symptoms in schizophrenia patients are inconsistent [9–11]. While some research studies explore the relationship between serum IL-6 levels and psychotic symptoms in schizophrenia, gaps remain, particularly regarding how this association varies with disease chronicity.

Metabolic dysregulation, a significant feature and risk factor for developing metabolic syndrome, is often associated with schizophrenia patients undergoing antipsychotic treatment. This in turn significantly impacts the life expectancy of these groups of patients living with schizophrenia [12,13]. IL-6, a pleiotropic cytokine, modulates obesity by regulating BMI and thereby contributing to metabolic syndrome in schizophrenia patients [14,15]. In overweight and obese patients, adipocytes present in adipose tissue mostly produce IL-6, which is then released to the peripheral circulation [16]. The intersection of these metabolic mechanisms and neuroinflammation is thus believed to play an intrinsic role in psychiatric disorders like schizophrenia, especially those with high BMI and altered metabolic profile [17,18]. Therefore, investigating metabolic dysregulation in schizophrenia patients is crucial when studying peripheral markers of inflammation. Existing literature indicates a possible connection between IL-6-modulated neuroinflammation and psychotic symptoms in schizophrenia patients, though results are inconsistent [11,19]. Most studies focus on the association of inflammatory cytokines, including IL-6, with metabolic syndrome in schizophrenia patients [20–22]. However, there exists a research gap concerning the association of serum IL-6 with metabolic imbalances before developing metabolic syndrome in schizophrenia patients.

Considering these facts and findings, the present study aimed to examine the serum IL-6 levels in FEDN and CSZ patients and its correlation with psychotic symptom scores. This is a novel approach in the context of examining the potential of peripheral IL-6 levels in monitoring the severity of psychotic symptoms as measured by the Positive and Negative Symptom Scale (PANSS).

Finally, the study explores the association of serum IL-6 in schizophrenia patients presenting with metabolic dysregulation. In the same context, we also examined the diagnostic potential of peripheral IL-6 level as a biomarker to differentiate high-risk schizophrenia patients with metabolic dysregulation from those with normal metabolic

status, aiding in the early identification of high-risk patients prone to developing metabolic syndrome.

2 Methodology

This is a case-control study with cross-sectional sampling carried out at the Department of Biotechnology, Gauhati University, Guwahati, Assam, and the Department of Psychiatry, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, Assam. The study was conducted after the approval of the Institutional Ethical Committees of both the institutes.

2.1 Participants Enrolment

Ninety-two patients diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition, DSM-5), consisting of sixty males and thirty-two females were enrolled in the study after obtaining informed consent from their legal guardians. Demographic and clinical parameters were recorded in a semi-structured proforma. The present study included thirty-two age and sex-matched healthy individuals as the control group. Based on chronicity, patients were categorized into two cohorts, i.e., (i) First Episode Drug-Naive and (ii) Chronic Schizophrenia.

First Episode Drug-Naive (FEDN; n=44): Acute cases with no prior antipsychotic medication and a total score of 50 or more on the positive and negative syndrome scale (PANSS).

Chronic Schizophrenia (CSZ; n=48): Chronic cases on steady doses of antipsychotic medication for more than 12 months with a total illness duration of 18 months or more.

Inclusion criteria for FEDN schizophrenia patients were (i) no prior antipsychotic prescription before enrolment and (ii) total PANSS score $\geq$ 50.

Inclusion criteria for chronic schizophrenia patients (CSZ) were (i) duration of illness $\geq$18 months and (ii) under antipsychotic medications for $\geq$ 6 months before enrolment.

Inclusion criteria for healthy individuals were (i) age group of 18-60 years, (ii) no medical history of any psychiatric illness, autoimmune diseases, inflammatory conditions, and/or any other chronic serious health conditions (iii) no medical history of any psychiatric illness in first degree relatives.

Exclusion criteria for schizophrenia patients (both FEDN and CSZ) were (i) those with any comorbid autoimmune, inflammatory, or chronic health conditions, (ii) those with a history of drug abuse and alcohol dependence, (iii) patients taking any immunomodulators and anti-inflammatory drugs and (iv) pregnant and lactating women. Similar exclusion criteria were also applied to healthy individuals enrolled as the control group in the study.

Further, the schizophrenia cases were stratified into two cohorts based on their metabolic profile, i.e., (i) **High-risk group** (higher chances of developing metabolic syndrome) with BMI $\geq$25kg/m^2 and altered lipid profile, and (ii) **No-risk group** (no risk for developing metabolic syndrome) with normal range of BMI level and lipid profile.

2.2 Clinical Assessment and Scoring

Positive and Negative Syndrome Scale (PANSS) (American Psychiatric Association, 1987) was administered by a registered psychiatrist to assign psychopathology scores. This scale includes 7 items related to Positive symptoms (P score), 7 items related to Negative symptoms (N score), and 16 items related to Cognitive or General psychopathology symptoms (G score).

2.3 Sample Collection and Storage

Five milliliters of whole blood samples were collected from the enrolled cases and healthy participants from the forearm veins in clot activator vials. The serum was separated by centrifuging at 1000g for 10 mins. The serum was stored at -80°C until further analysis.

2.4 ELISA-based Quantification of Serum IL-6

Serum IL-6 level was determined using a commercially available Diaclone Human ELISA kit (Catalogue No. 950.030.096). The detection sensitivity of IL-6 was 2 pg/ml with intra-assay and inter-assay coefficients of variation of 3.6% and 7.7%, respectively.

2.5 Statistical Analysis

Statistical analysis was performed using GraphPad prism statistical software (Version 8.0.2) and JASP statistical program (Version 0.17.2.1). Shapiro-Wilk test was performed to evaluate the normality of test variables. Accordingly, normally distributed variables were presented as mean $\pm$ SD, and variables that did not follow normal distribution were presented as

median (1st quartile-3rd quartile). The chi-square test, t-test, and Mann-Whitney U test were used to compare the differences in demographic and clinical variables between the groups. The correlation between IL-6 and study variables in schizophrenia cases was assessed by the Pearson correlation coefficient. The diagnostic value of serum IL-6 levels as a potential inflammatory biomarker between High-risk and No-risk groups (as a binary classifier) was assessed by a receiver operating characteristics (ROC) curve. Statistical significance was considered at p-value < 0.05 for all the tests.

3 Results & Discussion

3.1 Demographic and Clinical Characteristics

A total of 124 participants were enrolled for the study including 92 schizophrenia cases and 32 HC participants. Out of a total of 92 cases, 44 cases were FEDN and 48 cases were CSZ. Further, the schizophrenia cases were stratified based on their metabolic profile. Accordingly, 73 cases with normal metabolic status were categorized as a No-risk group (BMI = 18.5-24.9 kg/m^2 with normal lipid profile), while 19 cases with metabolic dysregulation were categorized as a High-risk group (BMI $\geq$ 25kg/m^2 with altered lipid profile). Demographic and clinical characteristics of study participants are presented in Table 1 and Table 2.

Table 1. Demographic and clinical characteristics of study participants in case-control manner

Characteristics	Case-control cohort		
	Schizophrenia (N=92)	Control (N=32)	Statistics
Gender (Male/Female)	54/38	18/14	X^2=0.058 p=0.809
Age (years)	27 (20-32)	28 (35-22)	U=1295 p=0.313
Disease onset age (years)	23 (19-28)	NA	NA
BMI (kg/m^2)	21.96 (24.06-20.03)	21.75 (±2.07)	U=1613 p=0.422
Triglyceride (mg/dL)	170 (138-184.25)	NA	NA
Cholesterol (mg/dL)	201.5 (146.75-217)	NA	NA
HDL (mg/dL)	40 (38.75-43.25)	NA	NA
LDL (mg/dL)	120.25 (89.52-127.08)	NA	NA
P score	19.50 (16-23)	NA	NA
N score	21.64 (±5.78)	NA	NA
G score	33.65 (±6.74)	NA	NA
Total PANSS score	74.98 (±12.40)	NA	NA
IL-6 (pg/mL)	9.31 (6.13-15.35)	4.13 (3.59-6.36)	U=2420.5 p<0.001**

Notes: All values except gender, are presented as mean ± SD for normally distributed variables and as median (1st quartile-3rd quartile) for non-normally distributed variables. **statistically significant p value.

Table 2. Demographic and clinical characteristics of schizophrenia cases by disease chronicity and metabolic profile

Characteristics	Groups based on chronicity			Groups based on metabolic profile		
	FEDN (N=44)	CSZ (N=48)	Statistics	No-risk (N=73)	High-risk (N=19)	Statistics
Gender (Male/Female)	26/18	28/20	X^2=0.005 p=0.941	44/29	10/9	X^2=0.363 p=0.547
Age (years)	22 (18-28)	31.73 (±8.82)	U=1603 p<0.001**	26 (20-30)	37.05 (±8.31)	U=209.5 p<0.001**
Disease onset age (years)	22 (18-28)	24 (20.75-27)	U=1116.5 p=0.637	23 (18-28)	23 (21-26)	U=622 p=0.491
BMI (kg/m^2)	20.82 (±2.18)	24.24 (±4.21)	t=4.825 p<0.001**	21.03 (±2.21)	28.63 (±2.18)	t=-13.386 p<0.001**
Triglyceride (mg/dL)	138 (129.75-142)	184 (176.5-195)	U=2112 p<0.001**	143 (136-182)	184 (174-191.5)	U=304.5 p<0.001**
Cholesterol (mg/dL)	145.52 (±8.59)	218.29 (±11.17)	t=34.802 p<0.001**	154 (144-212)	215 (212-222.5)	U=280 p<0.001**
HDL (mg/dL)	44 (40.75-47)	39 (37-40)	U=170 p<0.001**	41 (38-45)	39.47 (±1.71)	U=884 p<0.065

Continued on next page

Table 2 continued

LDL (mg/dL)	89.23 (±5.36)	127.68 (±5.14)	t=35.122 p<0.001**	94.32 (87.47-125.47)	127.32 (±5.33)	U=294.5 p<0.001**
P score	19 (16-23.25)	19.5(16-22.25)	U=1014.5 p=0.748	18 (16-22)	21 (15.50-23)	U=617 p=0.462
N score	18.41 (±5.60)	24 (21-28)	U=1720.5 p<0.001**	20.94 (±5.89)	24.32 (±4.51)	t=-2.318 p=0.023**
G score	32.29 (±7.22)	34.90 (±6.08)	t=1.874 p<0.064	33.51 (±6.37)	34.21 (±8.18)	t=-0.403 p<0.688
Total PANSS score	70.77 (±11.82)	78.83 (±11.75)	t=3.277 p=0.001**	74.03 (±11.86)	78.63 (±14.04)	t=-1.451 p=0.150
IL-6 (pg/mL)	9.25 (6.48-13.08)	9.31 (6.13-18.54)	U=1148 p=0.475	8.28 (5.69-11.95)	20.85 (±8.51)	U=173 p<0.001**

Notes: All values except gender, are presented as mean ± SD for normally distributed variables and as median (1st quartile-3rd quartile) for non-normally distributed variables. ** denotes statistically significant p value.

Across all the groups of study participants, the number of male participants was more than female participants, with no significant differences in gender distribution (p>0.05).

In the present study, no significant difference in median age was observed between schizophrenia patients and healthy controls (U=1295, p=0.313). However, the mean age of CSZ patients was significantly higher than that of FEDN cases (U=1603, p<0.001). Similarly, the mean age of patients in the high-risk group was significantly higher than those in the No-risk group (U=209.5, p<0.001).

Psychopathology scores of schizophrenia patients were assessed by the Positive and Negative Syndrome Scale (PANSS). Significantly higher negative scores (N score) and total PANSS scores in CSZ patients than those in FEDN patients indicate the presence of more severe psychotic symptoms in CSZ patients than in FEDN patients (U=1720.5, p<0.001 & t=3.277, p<0.001). Similarly high negative scores in high-risk cases showed the presence of severe negative symptoms in patients with metabolic dysregulation than those with normal metabolic status (t=-2.318, p=0.023).

3.2 Serum IL-6 Levels in Schizophrenia Patients

Mann-Whitney U analysis was performed to compare serum IL-6 levels in a case-control manner. We found significantly high levels of serum IL-6 in schizophrenia patients compared to healthy individuals (p<0.001, Figure 1**a**). Further, pairwise comparison analysis revealed no significant difference in IL-6 levels between FEDN and CSZ patients (p=0.475, Figure 1**b**). However, IL-6 levels in FEDN and CSZ patients were significantly higher than those in healthy individuals (p<0.001, Figure 1 **b**).

Comparative analysis showed serum IL-6 levels were significantly elevated in schizophrenia patients with metabolic dysregulation (High-risk group) compared to patients (No-risk group) with normal metabolic profile (p<0.001, Figure 1**c**).

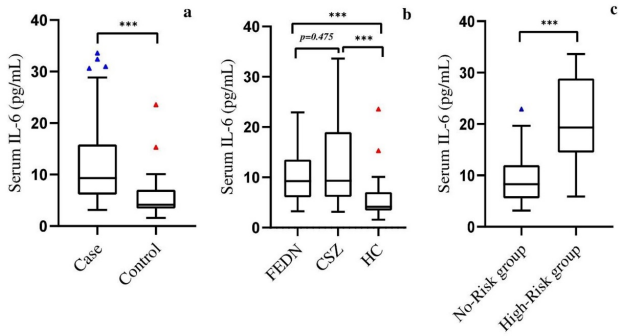

Fig 1. Box and Whisker plot showing serum IL-6 level (a) between schizophrenia cases and healthy individuals (b) among FEDN, CSZ patients, and HC individuals (c) between no-risk and high-risk schizophrenia patients. Note: * indicates a significant difference at p<0.001**

3.3 Correlation between Serum IL-6 Levels and Clinical Parameters

Correlation analysis showed a positive association of serum IL-6 levels with general psychopathology score (r=0.244, p=0.01; Figure 2**a**) and total PANSS score (r=0.228, p=0.02; Figure 2**b**) in schizophrenia cases as measured by Positive and Negative Syndrome Scale (PANSS). Further analysis by disease chronicity indicated that IL-6 levels in chronic schizophrenia patients were positively associated with General psychopathology scores (r=0.308, p=0.03; Figure 2**c**) and total PANSS score (r=0.286, p=0.04; Figure 2 **d**). Additionally, the relationship between serum IL-6 levels and BMI in schizophrenia patients demonstrated a positive correlation (r=0.557, p<0.001; Figure 3).

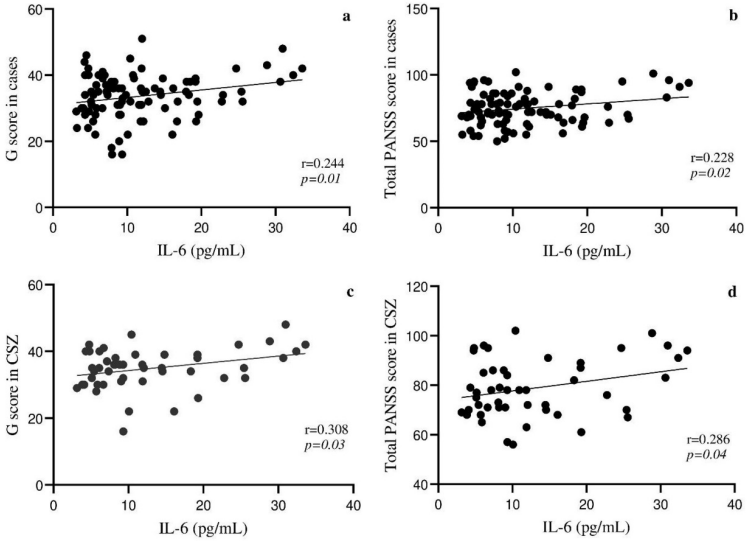

Fig 2. Scatter plot showing the correlation between (a) Serum IL-6 level and G score in cases (b) Serum IL-6 level and total PANSS score in cases (c) Serum IL-6 level and G score in chronic cases, and (d) Serum IL-6 and total PANSS score in chronic cases

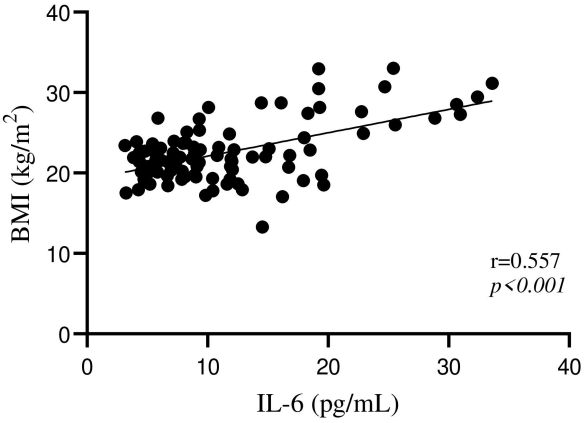

Fig 3. Scatter plotshowing a correlation between serum IL-6 levels and BMI in schizophrenia patients

3.4 Receiver Operating Characteristic (ROC) Curve Analysis

A receiver operating characteristic (ROC) curve analysis was performed to examine the diagnostic value of serum IL-6 levels as a potential inflammatory biomarker to differentiate high-risk schizophrenia patients with metabolic dysregulation (High-risk group) from those with normal metabolic profile (No-risk group). The area under the ROC curve (AUC) indicates the potential of using serum IL-6 levels in differentiating schizophrenia patients with metabolic dysregulation from those with normal metabolic profiles. While an AUC value of 0.5 represents no diagnostic or predictive value, a higher AUC value indicates a better ability to distinguish between the groups. In the present study, the AUC of serum IL-6 was 0.875, with a 95% confidence interval of 0.781 to 0.969 (p<0.001, Figure 4). These findings from the ROC analysis demonstrate the potential of serum IL-6 levels to serve as a binary classifier, effectively discriminating between high-risk and no-risk schizophrenia patients.

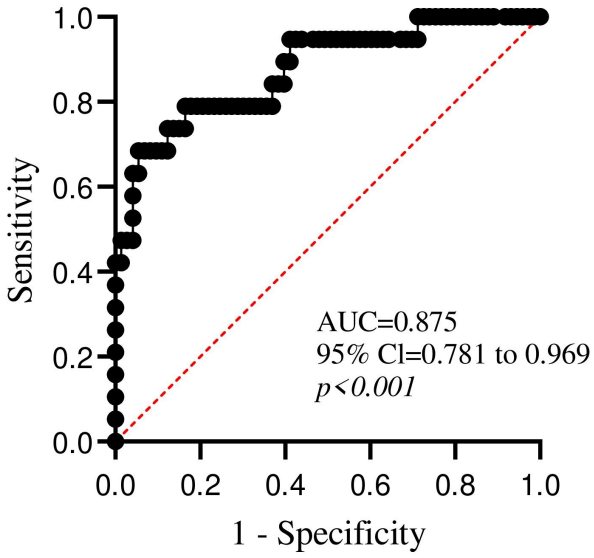

Fig 4. ROC curve demonstrating diagnostic/predictive value of serum IL-6 in differentiating high risk and no risk schizophrenia patients based on metabolic status

The aim of this study was to explore the role of IL-6 in schizophrenia patients along with symptom severity as measured by PANSS score. This study also aimed to evaluate the association of peripheral IL-6 levels in schizophrenia by disease chronicity and metabolic status of the patients. It was found that serum IL-6 levels did not differ significantly between FEDN and CSZ patients [9.25 (6.48-13.08) pg/mL Vs. 9.31 (6.13-18.54) pg/mL, p=0.475; Figure 1**b**]. However, significantly elevated peripheral IL-6 levels [9.31 (6.13-15.35) pg/mL Vs. 4.13 (3.59-6.36) pg/mL, p<0.001] in schizophrenia patients compared to healthy individuals suggest an association of IL-6 in schizophrenia cases irrespective of disease chronicity in our study cohort. Our findings align with previous studies reporting increased peripheral levels of IL-6 in patients with schizophrenia compared to healthy controls [15]. Contradictory results were also reported, showing no significant difference in serum IL-6 concentration between schizophrenia and the control group [15,23]. Elevated IL-6 levels may contribute to oxidative stress, and disruptions in neurotransmitter pathways, all of which exacerbate schizophrenia symptoms [3,24–26]. In the present study, we therefore examine the association of peripheral IL-6 with the severity of psychotic symptoms, as assessed by the Positive and Negative Syndrome Scale. Positive correlations between serum IL-6 levels and General psychopathology score (r=0.244, p=0.01), and total PANSS score (r=0.228, p=0.02) indicate its association with cognitive decline and severity of psychotic symptoms in our cohort. Similarly, correlation studies by disease chronicity showed significantly positive associations of serum IL-6 with General psychopathology score (r=0.308, p=0.03) and total PANSS score (r=0.286, p=0.04). Our findings suggest that with the increase of peripheral IL-6 levels, cognitive and psychotic symptoms of schizophrenia worsen. This is in concordance with other reports suggesting the involvement of inflammatory cytokines in clinical and psychotic manifestations in schizophrenia patients [7,27]. The intrinsic relationship between serum IL-6 levels and psychotic symptoms therefore projects it as a prospective candidate to serve as a prognostic marker for disease severity and treatment response in schizophrenia patients. However, longitudinal follow-up studies are needed to further evaluate the precise role of serum IL-6 in monitoring the symptomatic

course and treatment outcomes in schizophrenia. The present findings contribute to the growing body of evidence linking IL-6 imbalance with metabolic dysregulation in schizophrenia. Elevated serum IL-6 especially in high-risk patients with metabolic dysregulation compared to those with normal metabolic status [20.85±8.51 pg/mL Vs. 8.28 (5.69-11.95) pg/mL; p<0.001], underscore the interaction between inflammation and metabolic health in schizophrenia [28]. A positive correlation between serum IL-6 levels and BMI in schizophrenia patients further supports this assumption (r=0.557, p<0.001). Metabolic dysregulation, leading to metabolic syndrome, is often associated with chronic schizophrenia patients under antipsychotic treatments [29]. Metabolic syndrome is a leading cause of reduced life expectancy in schizophrenia patients [20]. This study also evaluated the diagnostic and predictive potential of IL-6 as an inflammatory biomarker for effectively differentiating patients with metabolic dysregulation (High-risk group) from those with normal metabolic profile (No-risk group). With an AUC value of 0.875 at a 95% confidence interval of 0.781 to 0.969 (p<0.001), serum IL-6 could serve as a robust biomarker (as a binary classifier) for high-risk schizophrenia patients with altered metabolic status.

4 Conclusion

Metabolic deregulations may lead to metabolic syndrome which is predominantly associated with chronic schizophrenia patients, identifying them as high-risk groups. Previous research has shown alterations in peripheral IL-6 levels in patients with schizophrenia. However, there are limited findings on its association with disease chronicity. Contrary to earlier studies, the present study did not find a significant difference in serum IL-6 levels between First Episode Drug Naïve (FEDN) and chronic schizophrenia (CSZ) patients [9.25 (6.48-13.08) pg/mL Vs. 9.13 (6.13-18.54) pg/mL; U=1148 & p=0.474)]. However, elevated levels of IL-6 in schizophrenia patients compared to healthy individuals indicate its stable role regardless of disease chronicity [9.31 (6.13-15.35) pg/mL Vs. 4.13 (3.59-6.36) pg/mL; U=2420.5 & p<0.001]. A positive correlation between serum IL-6 levels and psychotic symptom scores highlights its prognostic potential in monitoring disease severity, particularly cognitive decline (as indicated by G score on PANSS) and treatment response. However, a longitudinal follow-up study would be beneficial to validate the precise role of serum IL-6 as a prognostic marker.

Elevated serum IL-6 levels in high-risk schizophrenia patients compared to the patients with normal metabolic status [20.85 ± 8.51 pg/mL Vs. 8.28 (5.69-11.95); U=173, P<0.001], along with a positive correlation between serum IL-6 and BMI (r=0.557, p<0.001), underscore the association of serum IL-6 with the metabolic health of schizophrenia patients. Notably, our study findings suggested serum IL-6 as a robust biomarker for differentiating high-risk patients from those with normal metabolic status (AUC=0.875 at 95% CI of 0.781 to 0.969, p<0.001). By recognizing High-risk groups for schizophrenia early on, targeted strategies can be implemented to manage the associated risks of metabolic syndrome in patients with schizophrenia. This proactive approach can significantly improve patient outcomes and quality of life.

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