RESEARCH

Assessment of serum interleukin 6 in a sample of Egyptian patients with schizophrenia

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Abstract

Background Inflammation has been demonstrated to play a pathophysiological function in schizophrenia. Raised interleukin-6 (IL-6) levels have been the most consistently linked to schizophrenia. It was hypothesized that IL-6 contributed to the development of both adverse and beneficial symptoms.

The aim of the study was to estimate the level of serum IL-6 in patients with schizophrenia and its relation to positive in addition to negative symptoms.

Patient and methods This case–control descriptive cross-sectional study was conducted on 40 patients, divided into two groups: 20 individuals in Group A (patients group) were treatment-naive for their first episode of schizophrenia, and 20 volunteers in Group B (control group) were matched for gender and age to the patient group. Both groups were evaluated for their serum interleukin-6 levels using the ELISA method. Patients and controls were recruited from the Okasha Institute of Psychiatry, Faculty of Medicine, and Ain Shams University Hospitals.

Results Cases with schizophrenia who were experiencing their first episode and had not yet begun any form of therapy had a considerably higher mean serum IL-6 level compared to the healthy control group.

Conclusion The level of serum interleukin 6 in first-episode treatment-naïve individuals with schizophrenia is higher than that of healthy controls, revealing a probable underlying immunological pathology. However, serum interleukin-6 levels were not significantly correlated with positive, negative, or general psychopathology symptoms.

Keywords Serum IL-6, Schizophrenia, Positive and negative symptoms

Introduction

The General Health Questionnaire administered to over 25,000 individuals in Egypt estimated a prevalence of 24.9% for psychiatric comorbidity, and these mainly included mood (depressive), anxiety, and substance use disorders. Schizophrenia is a severe mental disorder with median lifetime prevalence of 3 per 1000 persons in the world that usually has an onset in early adulthood and then frequently takes a chronic or episodic course. It is a chronic disorder with poor outcomes and is considered one of the major psychotic illnesses in Egypt. According to the Egyptian National Institute of Mental Health, schizophrenia is relatively common, affecting 1.1% of the population [1, 2].

Persistent problems with one's thoughts, perceptions, processes, language, beliefs, and social interactions begin in early adulthood or late adolescence and are characteristic of schizophrenia [3]. Dysfunction in

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the immune system has been linked to the development of schizophrenia. The psychopathology of schizophrenia may involve a number of pathways that affect neurodevelopment, synaptic plasticity, and neurotransmission, and these pathways may be subject to modulation by the inflammatory immune response via cytokines [4].

Interleukin-6 (IL-6) is an important pleiotropic cytokine involved in immune-neurological interactions. Overexpression of interleukin-6 is often bad and plays a part in the development of diseases affecting the central nervous system (CNS) [5], even though IL-6 can help the CNS grow and heal itself. In fact, giving healthy individuals an injection of interleukin-6 causes them to feel down, anxious, and perform poorly mentally. The anti-inflammatory effects of modern antipsychotics are well documented. Finally, elevated serum interleukin-6 has been found in both first-episode psychosis and acute psychotic recurrence, according to meta-analyses of cross-sectional research. However, methodological discrepancies may account for the contradictory findings [6], provided that there have been so few longitudinal investigations of inflammatory markers and psychosis.

Objectives
To examine the relationship between cytokine concentrations and schizophrenia by comparing the serum concentrations of interleukin-6 in first-episode treatment-naive persons to those in healthy individuals and to examine the relationship between IL-6 serum levels and positive and negative symptoms for those with schizophrenia.

Patient and methods
This case–control descriptive cross-sectional study was conducted on 40 patients, divided into two groups: 20 individuals in Group A (patients' group) were treatment-naive for their first episode of schizophrenia, and 20 volunteers in Group B (control group) were matched for gender and age to the patient group. Both groups were evaluated for their serum interleukin-6 levels using the ELISA method. Patients and controls were recruited from the Okasha Institute of Psychiatry, Faculty of Medicine, and Ain Shams University Hospitals with the blessing of the research and ethical committee of Ain Shams University as well as the scientific committee of the neuropsychiatric department. The intensity of disease in the case group was assessed using the Positive and Negative Syndrome Scale (PANSS).

A written informed consent was obtained from all participants after explaining the objectives of the study.

Inclusion criteria: Group A
The participants were all diagnosed with schizophrenia according to the criteria outlined in the Diagnostic

and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV). Patients with the first episode of schizophrenia only, both males and females, were included. Age: 18–65; Egyptians only. Group B: both genders were included, age 18–65, including Egyptians only.

Exclusion criteria: Group A
Comorbid medical conditions affecting eating behavior, diet, or body mass index (BMI), psychiatric disorders, substance use disorders, thyroid disease, autoimmune disorders, recent electroconvulsive therapy (ECT) treatment, active infections, allergies, BMI > 30, smoking, head trauma history, and those who received any psychotropic medications before. Group B: individuals with Axis I psychiatric disorder, BMI > 30, smoking, serious medical conditions, seizure disorders, active infections, significant head trauma, allergies, and immunomodulatory medicines.

Sample size
This study is based on a study carried out by Challah F. and Seifu et al. [7]. Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: 95% two-sided confidence level, with a power of 80%, and an α error of 5%. The final maximum sample size taken from the Epi-Info output was 17 in each group. Thus, the sample size was increased to 20 subjects in each group to assume any dropout cases during follow-up

$$(n = [DEFF \times Np(1-p)]/[(d^2/Z^2_{1-\alpha/2} \times (N-1) + p \times (1-p)]).$$

Procedure of the study
The investigator interviewed both the case and control groups, taking a short history from them, then applied the following: the SCID1 (structured clinical interview for DSM-IV) questionnaire, serum IL6 levels using the "Enzyme-Linked Immunosorbent Technique Assay Kit," and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) for the case group only.

A short, predesigned sheet includes age, gender, education, residency, occupation, past and current general medical history, past and current psychiatric history, and family psychiatric history.

The structured clinical interview for DSM-IV axis-I disorders (SCID-I) [8]: the Arabic version [9]
For the purpose of conducting psychopathology evaluations, clinicians can employ the Structured Clinical Interview for DSM-IV Axis-I Disorder (SCID-I), a semistructured interview that can be done with both mental patients and community members who are not patients.

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In accordance with the DSM-IV, the SCID-I was designed to cover a wide range of mental diagnoses. Its designers aimed for reduced administration time by making it more efficient and user-friendly than competing tools. The purpose of this test was to identify any current or previous co-morbidities of these conditions [8]. According to El Missiry A et al. [9], the Arabic version was translated. The average time to apply it was 30 min. In Serum IL6 levels using the Enzyme-linked immunosorbent technique for the assay, we added 50 l of blank standard (500 pg/ml), a test sample, and then sample diluents to the relevant wells on the strips. Next, we added 50 l of ready-to-use green biotin antibody. After being washed with wash buffer, 100 μL of a ready-to-use horseradish peroxidase streptavidin (HRP-streptavidin) (peroxidase-labeled streptavidin) solution were added. The samples were left to sit at room temperature for 90 min. They underwent washing with wash buffer once more, incubating at room temperature for 30 min, followed by adding 50 μL of TMB (tetramethylbenzidine) one-step substrate reagent to each well, and left to react for 20 min. Finally, 25 μL of stop solution sulfuric acid (H_2SO_4) were added to each well, and the absorbance was measured at 450 nm against 630 nm.

The Positive and Negative Syndrome Scale for Schizophrenia (PANSS) is for the case group only

The gold standard for evaluating the severity of symptoms in people with schizophrenia is a semi-structured clinical scale. Thirty elements spanning positive symptoms, negative symptoms, and general psychopathology make up the [10] clinician's toolbox for making significant clinical judgments on individual cases. The patient's interview and reports from family members or primary care hospital staff were used to grade these 30 symptoms on a scale from one to seven. The patient could not have a total PANSS score lower than 30, as one was used as the lowest score instead of zero.

Statistical analysis

IBM's SPSS version 20.0 was used to examine the data that was input into the computer. IBM Corp., Armonk, New York. Quantitative and percentage descriptions were employed for qualitative information. To ensure a normally distributed sample, the Kolmogorov–Smirnov test was performed. Quantitative information was summarized with the use of mean, median, and standard deviation, in addition to interquartile range (IQR) plots. The outcomes obtained were deemed significant at the 5% level. The chi-square test was used to compare groups based on categorical variables, while the Student *t*-test was utilized to compare groups based on quantitative information that followed a normal distribution.

Results

Table 1 shows that the mean age of the patient group was 30 ± 8.19 years and 31.25 ± 7.37 years in the control group. Regarding gender, 50% of the control group were males and 50% were females, while in the case group, 45% were males and 55% were females.

Table 2 shows the distribution of the case group regarding the PANSS scores. The mean PANSS positive subscore was 34.85 ± 8.34, the PANSS negative subscore was 30.35 ± 5.34 standard deviation (SD), the mean PANSS general subscore was 27.8 ± 13.24 SD, and the mean PANSS total score was 93 ± 16.63 SD.

Table 3 shows the comparison among the two study groups regarding serum IL-6 concentration. The mean serum IL-6 of group A was 35.94 ± 7.46 standard deviation (SD) with a range of 20.2–48.5, and the mean serum IL-6 of group B was 27.47 ± 7.18 with a range of 16.1–39.3. A statistically significant alteration among the examined groups regarding serum IL-6 was found, $p < 0.01$.

Receiver operating characteristic curve (ROC) analysis was used to discriminate among cases and control groups regarding serum IL-6. The cutoff of 33.7 can differentiate between cases and controls with an area under the curve (AUC) of 0.794, specificity of 75%, level of sensitivity of 75%, negative predictive values (NPV) of 75%, positive predictive values (PPV) of 75%, and accuracy of 75% (Table 4 and Fig. 1).

Table 5 and Fig. 2 show the association between serum IL-6 and PANSS scores. There was a negative link between serum IL-6 and PANSS scores. However, this correlation is not statistically significant.

Discussion

As regard the demographic data, in this research, the age of the participants fluctuated between 19 and 45 years, with a mean age of 30 ± 8.19 years in the patient's group and 31.25 ± 7.37 years in the control group. There was not a statistically significant variance in age between cases and controls.

Regarding gender among participants, 50% of the control group were males and 50% were females, while in the case group, 45% were males and 55% were females. There was a slightly different ratio between males and females in the case group.

In the same line, Li et al. reported a total of 360 patients with first-episode psychosis, of whom 43.6% were male ($n = 157$) and 56.4% were female ($n = 203$) [11].

Regarding marital status, there was a significant change; 45% of the controls were married and 55% were unmarried. In comparison, only 20% of the patients were married and 80% were unmarried. This may be explained by the affection for social skills and lack of emotional

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Table 1 Description of the schizophrenia and healthy control groups regarding demographic data

Variables	Group A (*n* = 20)		Group B (*n* = 20)		Total	
	No	%	No	%	No	%
Sex						
Female	11	55.0	10	50.0	21	52.5
Male	9	45.0	10	50.0	19	47.5
Education						
Primary	2	10.0	3	15.0	5	12.5
Preparatory	3	15.0	3	15.0	6	15.0
Secondary	8	40.0	2	10.0	10	25
College	7	35.0	12	60.0	19	47.5
Occupation						
Not working	16	80.0	3	15.0	19	47.5
Working	4	20.0	17	85.0	21	52.5
Marital status						
Married	4	20.0	9	45.0	13	32.5
Single	16	80.0	11	55.0	27	67.5
Age (years)						
Range	19–42		20–45		19–45	
Mean ± SD	30.9 ± 8.19		31.25 ± 7.37		31.08 ± 7.69	
Median (IQR)	29.0 (16)		31.5 (12)		30.5 (14)	

Table 2 Distribution of the examined cases in accordance with PANSS scores

	GroupA (*n* = 20)
PANSS positive subscore	
Range	17–47
Mean ± SD	34.85 ± 8.34
PANSS negative subscore	
Range	22–41
Mean ± SD	30.35 ± 5.34
PANSS general subscore	
Range	4–49
Mean ± SD	27.8 ± 13.24
PANSS total score	
Range	67–118
Mean ± SD	93 ± 16.63

Table 3 Comparison among studied cases according to serum IL-6

	Group A (*n* = 20)	Group B (*n* = 20)	Test of Sig	*P*
Serum IL-6 (pg/ml)				
Range	20.2–48.5	16.1–39.3	*t* = 3.658	0.001[*]
Mean ± SD	35.94 ± 7.46	27.47 ± 7.18		

SD standard deviation, *t* Student *t*-test, *p* *p*-value for comparing between studied groups

[*] Statistically significant at *p* ≤ 0.05

reciprocity in schizophrenia, as well as the low rate of employment making them unable to support a family and thus reducing the rate of marriage in the patients' group [12]. As well as the cultural restrictions regarding marriage.

In the same context, according to the study of Ba et al., it was reported that single people were the most frequent in their study, with 61% unmarried, equated to (31.1%) married, (5.5%) divorced, and (2.5%) widowed [13].

As regards the educational level in our trial, there was a significant alteration, as we noted in the patient's group that there were 2 (10%) with primary education, 3 (15%) with preparatory education, 8 (40%) with secondary education, and 7 (35%) with college, but in the healthy group, there were 3 (15%) with primary education, 3 (15%) with preparatory education, 2 (10%) with secondary education, and 12 (60%) with college. Kaikoushi et al. participated in this research with a total of 406 people (262 men and 144 females). There were roughly 24.9% of respondents who possessed a bachelor's degree, and 39.9% of them had completed their high school education [14].

As regards the occupation, in our study, among cases, 80% were not working and 20% were working; in controls, 15% were not working and 85% were working. In the same vein, Kaikoushi et al. determined that the majority of the people who took part in his research did not have jobs (77.6%), and approximately half of them received financial reimbursement from the state (49.5%). This could be

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Table 4 Roc curve analysis for the use of serum IL-6 to discriminate between cases and controls

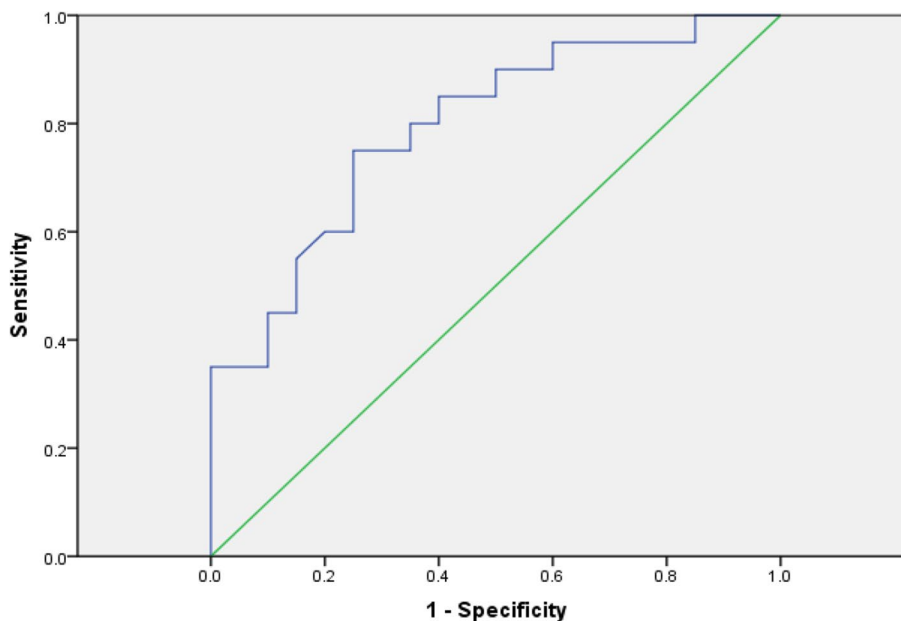|	Cut-off	AUC	Sens%	Spec%	PPV%	NPV%	Acc%
Serum IL-6	33.7	0.794	75.0	75.0	75.0	75.0	75.0

Fig. 1 Receiver operating characteristic curve analysis for the use of serum IL-6 to discriminate between cases and control

Table 5 Correlation among serum IL-6 and PANSS score

	Serum IL-6	
	r	*P*
PANSS positive subscore	-0.389	0.090
PANSS negative subscore	-0.228	0.333
PANSS general subscore	-0.085	0.721
PANSS total score	-0.336	0.148

because of cultural restrictions and the fear of being stigmatized, in addition to the fact that a lesser degree of education could impede work opportunities [14].

In our present study, we found statistically significant differences among the studied groups with regard to serum interleukin 6. The mean serum interleukin-6 of the patient's group was 35.94 ($\pm$ 7.46 SD) with a range of 20.2–48.5, and the mean serum IL-6 of the healthy group was 27.47 ($\pm$ 7.18 SD) with a range of 16.1–39.3. In
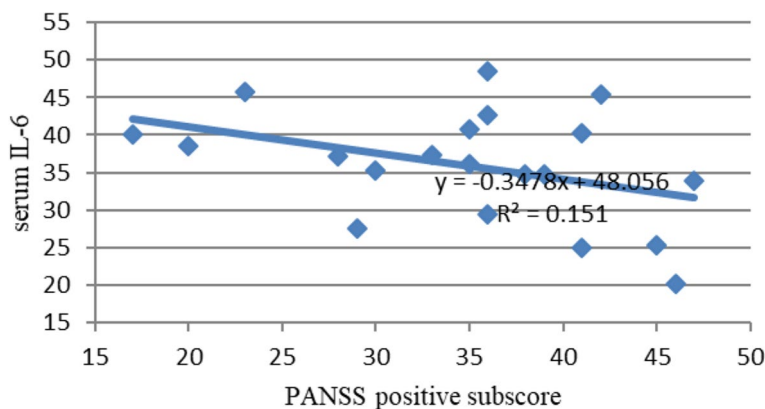

Fig. 2 Correlation among serum IL-6 and PANSS-positive subscores

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the same context, Dunleavy et al. reported based on the findings obtained from the data collected from the ten studies, which gave information on 651 drug-naive schizophrenia cases experiencing their first episode. Twenty-four distinct cytokines were measured peripherally using ELISA, and the results showed that there was a significantly increased concentration of IL-6 among patients (5 trials, 251 individuals, standardized mean difference (SMD) = 1.38, 95% CI 0.54 to 2.22, $Z = 3.21$, $I^2 = 94\%$) when contrasted with subjects serving as controls [15]. However, these findings were not consistent with those of the study conducted by Li et al. Using an enzyme-linked immunosorbent assay, the amounts of IL-1 and IL-6 were found in the plasma and cerebrospinal fluid (CSF) of 14 people with schizophrenia who were taking medication and 9 healthy people who were not on medication. It was revealed that there were almost no measurable amounts of IL-6 in the plasma or cerebrospinal fluid of either patients or controls [16]. These results were conducted by Borovcanin et al., who reported that assessing serum levels of IL-6 did not reveal a statistically significant difference between drug-naïve patients with first-episode psychosis (88) or acute exacerbations of cases with schizophrenia (45) and healthy controls (36) [17].

This discrepancy may be due to the effect of the medications or because our study was cross-sectional and we could not determine the course of immune markers from the time of psychosis onset to the later phases of schizophrenia. Despite the extent of controls performed in our study, heterogeneity remained a concern, such as dietary habits and concomitant use of other medications.

As regard the psychometric data, in our study, the mean PANSS positive subscore of the studied cases was 34.85 (± 8.34 SD), the PANSS negative subscore was 30.35 (± 5.34 SD), the mean PANSS general subscore was 27.8 (± 13.24 SD), and the mean PANSS total score was 93 (± 16.63 SD). Serum IL-6 levels were inversely related to PANSS severity. The blood IL-6 level was not related to any of the PANSS subscores, however, which agreed with what Yang et al. [5] initiated in their experiments.

In the same line, Goldsmith DR et al. found the mean PANSS positive subscore of the studied cases was 15.8 (± 4.8), the PANSS negative subscore was 16.6 (± 6.0), the mean PANSS total score was 60.6 (± 14.5), and the mean PANSS general subscore was 28.2 (± 7.8), with no significant correlation with total, positive, negative, and general PANSS scores [18].

However, according to Dai et al., serum IL-6 levels were considerably higher in the negative and positive groups compared to the controls ($p < 0.001$). Also, the negative group had significantly higher serum levels of IL-6 ($p = 0.004$) than the positive group (patients with mostly positive symptoms), which suggests that the two groups may be two subtypes of schizophrenia with different pathophysiological causes. The neuroimmunological abnormalities in those with negative symptoms are likely to be more severe than those in patients with positive symptoms [19].

However, in the study of Yang H. et al., a significant positive correlation was found between IL-6 levels and the PANSS general psychopathology subscore ($r = 0.485$, $p = 0.006$), which further suggested that inflammatory cytokines may be involved in the etiology of different clinical manifestations [20].

Our receiver operating characteristic curve analysis for the use of serum IL-6 to discriminate between cases and controls using serum IL-6 showed that at 33.7, it can discriminate between cases and controls with an AUC of 0.794, level of sensitivity of 75%, PPV of 75%, NPV of 75%, and accuracy of 75%, and there was a negative correlation between serum IL-6 and the PANSS score with no significant.

In the same context, Huang et al. have shown that an especially useful feature of the receiver operating characteristic is criteria, a cutoff that aims to increase the chances of a true positive (the right diagnosis) while decreasing the chance of an inaccurate diagnosis (the false positive). Using an IL-6 messenger RNA (mRNA) cutoff value of 4.9 (arbitrary units), they found that the true positive rate increased to 53%, while the false positive rate decreased to 17%. Increasing the cutoff value raises the probability of a true positive while reducing the number of false positives. For instance, in our sample, a threshold of 6.0 for interleukin-6 mRNA levels in peripheral blood mononuclear cells (PBMC) would result in a five-fold increase in the likelihood of an accurate diagnosis of schizophrenia. Clinicians would have access to additional information about each patient, allowing them to fine-tune their diagnostic criteria as necessary [21].

Limitations

The cross-sectional nature of the study made it difficult to determine the causality and longitudinal sequence of serum IL6 in patients with schizophrenia. Additionally, our study had a small sample size. The number of patients analyzed was insufficiently large, and it was a single-center study in a limited geographic area. Due to the stigma associated with mental illness, an individual's first episode of psychosis is often not the first attempt to seek medical advice. Moreover, it is clear that the term (the first episode of psychosis) as currently used within clinical and research settings may be misleading regardless of which operational definition is used. Results cannot be generalized due to the small sample size of our investigation, which is comparable to other studies that

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have attempted to investigate variations in blood IL-6 levels among controls and patients with schizophrenia.

Conclusion

There may be an underlying immunological pathology in schizophrenia, as the serum IL-6 levels of 1st-episode treatment-naive cases are higher than those of healthy controls. Serum IL-6 levels were not significantly correlated with negative, positive, or general psychopathology symptoms in treatment-naive patients experiencing their first episode of schizophrenia.

Recommendations

Multicenter studies with larger sample sizes aiming at assessing the serum level of interleukin 6 in patients with schizophrenia and studying its relation with the symptomatology of the patients for better understanding of the possible neuro-inflammatory pathophysiology of schizophrenia and also to elucidate the potential role of interleukin 6 as a biomarker, longitudinal studies to assess the change of symptoms in cases with schizophrenia across the course of their illness and studying their correlation with serum interleukin 6 levels at various intervals, researches to assess the role of anti-inflammatory treatment in amelioration of the various symptoms of schizophrenia are recommended and researches coupling functional brain imaging with symptomatology in patients with schizophrenia for better understanding of the underlying pathophysiology are recommended.

Abbreviations

IL-6	Interleukin-6
ELISA	Enzyme-linked immunosorbent assay
PANSS	Positive and Negative Syndrome Scale
DSM IV	Diagnostic and Statistical Manual of Mental disorders-4th edition
CNS	Central nervous system
BMI	Body mass index
ECT	Electroconvulsive therapy
SCID1	Structured clinical interview for DSM-IV
HRP-streptavidin	Horseradish peroxidase streptavidin
TMB	Tetramethylbenzidine
H2SO4	Sulfuric acid
IQR	Interquartile range
ROC curve	Receiver operating characteristic curve
AUC	Area under the curve
NPV	Negative predictive values
PPV	Positive predictive values
SD	Standard deviation
SMD	Standardized mean difference
CSF	Cerebrospinal fluid
mRNA	Messenger RNA
PBMC	Peripheral blood mononuclear cells

Declarations

Ethics approval and consent to participate
The study was approved by the Ethical Committee of the Faculty of Medicine, Ain Shams University, Egypt (MS 534/ 2022, FWA 000017585). The research was completed in accordance with the Helsinki Declaration. A written informed consent was obtained from all participants after explaining the objectives of the study.

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

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