RESEARCH

Unconjugated bilirubin as a state marker in patients with schizophrenia in acute episode: an Egyptian study

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Abstract

Background There is a substantial body of evidence linking unconjugated bilirubin to schizophrenia. Most of the earlier research has found a statistically significant relationship between the two factors.

Aim of the work To study the level of unconjugated bilirubin in individuals with acute schizophrenia and to investigate its correlation with neuropsychological, psychopathological, and psychosocial aspects of the disorder.

Patients and methods Eighty schizophrenia patients were included in the sample, they had multiple previous episodes and were in acute episodes at the time of recruitment. Forty healthy individuals were recruited for the control group. The DSM-IV was used to diagnose the subjects, and the Trail Making Test (TMT), Positive and Negative Syndrome Scale (PANSS), General Assessment of Function (GAF), and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) were used to evaluate the subjects' social functioning, symptom severity, and cognitive functioning. A blood sample was drawn to measure serum bilirubin level. We analyzed the relationship and correlation of unconjugated bilirubin with the previous scale scores.

Results Compared to healthy control individuals, who volunteered to participate, schizophrenia patients reported significantly higher levels of both total and indirect bilirubin. One subject (with schizophrenia) had an abnormally elevated total bilirubin level (> 1.2 mg/dL). Neither the direct nor the indirect bilirubin levels (> 0.3 mg/dl or > 1.2 mg/dL) were clinically abnormal in any of the patients. PANSS total score, PANSS N score, and PANSS G score were found to have a statistically significant positive connection with levels of total, direct, and indirect bilirubin. Age, gender, smoking, BMI, Total PANSS, PANSS P, PANSS N, PANSS G, GAF, TMT-A, TMT-B, antipsychotic medication, psychotic disorder duration, and duration of untreated psychosis were not predictive of total or indirect bilirubin levels, according to linear regression analysis. However, Total PANSS, PANSS N, and PANSS G were significantly predictive for direct bilirubin levels.

Conclusion A statistically significant difference in total and unconjugated bilirubin mean serum levels between schizophrenia patients and healthy individuals was found. More studies are recommended to revise the contradictory results in literature on the unconjugated bilirubin and Schizophrenia.

Keywords Unconjugated bilirubin, Schizophrenia, Biomarkers

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Background

The complex disorder known as schizophrenia has a wide range of aetiologies. It is characterized by abnormalities in perception, thinking, emotion, behavior, and cognition. According to twin studies, there is a hereditary component to this well-established brain illness, as well as structural and functional abnormalities that are evident in neuroimaging investigations [33].

The percentage of total bilirubin in serum that is water-insoluble and can pass through the blood–brain barrier is known as unconjugated bilirubin or indirect bilirubin. It increases in response to the in situ neurotoxic psychotic episode, since it has antioxidant properties [32]. However, even in healthy human subjects without bilirubin metabolism dysfunction, it has both direct and indirect toxic effects on the central nervous system and brain tissue connectivity, increasing the susceptibility of neurons to further inflammatory damage, which is thought to be the underlying cause of both the cognitive and clinical symptoms of schizophrenia [8, 19, 21].

The mechanism by which bilirubin can cause neurotoxicity is not entirely clear. It has several pathways, such as sustained energy failure, neuroinflammation, bilirubin-induced lipid peroxidation, and excitotoxicity [35]. The globus pallidus, subthalamic nuclei, hippocampus, oculomotor nuclei, ventral cochlear nuclei, Purkinje cells, and dentate nuclei of the cerebellum appear to be the typical brain regions that bilirubin targets and damages [1]. Even though the blood supply to certain regions in the brain may be the same, certain areas may sustain more damage than others, and the damage may occur in isolated areas, sparing others. This suggests that the specific susceptibility of these regions to hyperbilirubinemia may be due to a genetic or metabolic cause. [39, 41].

Furthermore, some genetically inherited diseases that affect bilirubin metabolism have neuropsychiatric manifestations, such as Gilbert's syndrome (idiopathic chronic mild unconjugated hyperbilirubinemia), which happens because of a genetic deficiency in the UDP-glucuronosyltransferase-1 enzyme and can be seen in up to 10% of the general population but doubles in patients with schizophrenia [7]. Additionally, psychosis and bilirubin metabolism abnormalities have been linked to other syndromes, including Crigler-Najjar syndrome, Roter syndrome, and Dubin-Johnson syndrome [6, 24, 36].

There is strong evidence that unconjugated bilirubin and schizophrenia are correlated, and most of the earlier research has been able to show a statistically significant relationship between these two variables [11]. According to research conducted on animals, chronic microglial activation in Gunn rats caused by toxic levels of unconjugated bilirubin (caused by a genetic glucuronyl transferase deficiency) has been linked to behavioral

and neuropsychological changes in these rats that may be mitigated by antipsychotics, similar to what happens in schizophrenia patients in humans [25, 38]. Previously [31], this rat was used as an animal model for schizophrenia. In addition, compared to a control group, newborns with neonatal unconjugated hyperbilirubinemia were found to have a higher risk of schizophrenia due to lower erythrocyte survival and poor hepatic clearance [9, 22].

The frequency of elevated unconjugated bilirubin mean levels was considerably higher in individuals with schizophrenia, especially during acute episodes, compared to patients in remission, other psychiatric patients, and general populations [27, 4]. In addition to a poor outcome, they also demonstrated a positive correlation between these higher levels and the Positive and Negative Syndrome Scale (PANSS) score [

Studies have been conducted on unconjugated bilirubin as a possible biological marker of this illness. The reported findings appear to be at odds with one another; certain research found a correlation between schizophrenia and higher levels of unconjugated bilirubin, while other studies found a correlation between schizophrenia and lower levels of the molecule. Given the complex nature of schizophrenia, it is expected that this relationship is multifactorial and nonlinear, with the pathophysiology of schizophrenia and unconjugated bilirubin influencing one another. This is in line with the literature's recent focus on the prospect of discovering an objective, quantifiable, and even controllable parameter that can supplement the still-somewhat subjective method of diagnosing, treating, and even preventing schizophrenia. If this theory is correct, doctors would have an extremely effective tool against schizophrenia [11]. To the best of our knowledge, this study is the first in Egypt and the Arab world to examine unconjugated bilirubin in acute episode patients with schizophrenia and examine its relationship to the psychopathological, psychosocial, clinical, and neuropsychological aspects. We propose that unconjugated bilirubin is a state biological marker that increases in schizophrenia patients relative to healthy controls.

Methods

Aim of the work

To study the level of unconjugated bilirubin in individuals with acute schizophrenia and to investigate its correlation with neuropsychological, psychopathological, and psychosocial aspects of the disorder.

We conducted a cross-sectional, observational study. We recruited subjects from the Okasha Institute of Psychiatry, Ain Shams University. It is in Eastern Cairo, serving as a catchment area for greater Cairo with a population number of about 21 million. Its catchment

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area is both urban and rural areas including Cairo Governorate, Giza Governorate, and Kalyoubia Governorate with a population of 9.9 million, 9 million, and 5.9 million respectively (Central Agency for Public Mobilization and Statistics, 2020).

A total of 120 patients were included in the sample; 80 subjects with a diagnosis of schizophrenia were drawn from the inpatient and outpatient departments of Okasha Institute of Psychiatry, Ain Shams University. We included patients between the ages of 18 and 65, male and females, with a diagnosis of Schizophrenia, multiple episodes, currently (at time of recruitment), in acute episode, which is a period during which the criteria of active phase symptoms according to DSM IV, are fulfilled. We excluded patients with a history of HCV/ HBV infection, other hepatic disorders, hemolytic conditions, cholestasis-related conditions, patients on any medications that interfere with bilirubin conjugation, patients on substances or medications that may induce psychotic disorder as well as patients diagnosed with psychotic disorder due to another medical condition. Illiterate patients were also excluded from the study.

For the control group, 40 individuals were recruited. They were individuals with no psychiatric disorders and no history of medical illness interfering with bilirubin metabolism, who agreed to participate in our study. Using data from a prior study, the sample size was determined with an alpha error set at 5% and power at 80% [19].

Tools

Name, age, gender, education, employment status, smoking, body mass index (BMI), duration of psychotic disorder, duration of untreated psychosis, family psychiatric history, and status (off, on) of psychotropic medications at the time of admission or attendance at outpatient clinics are among the sociodemographic and clinical variables about which data was gathered. We then applied the following tools:

1. Structured Clinical Interview for DSM-IV (SCID-I) (research version): [16]

This semi-structured interview, clinician conducted interview, was designed to confirm DSM-IV-compliant mental diagnosis. This was used to rule out other axis I comorbid mental disorders. The Arabic version of the SCID-I was used [13].

2. Positive and Negative Syndrome Scale (PANSS) [23]:

This is a scale used to measure the severity of symptoms in schizophrenia patients. Thirty separate symptoms are assessed on a scale of 1 to 7, with 7 items for positive symptoms, 7 items for negative symptoms, and 16 items for symptoms related to general psychopathology. In addition to a total PANSS score, scores are computed for the individual domains (P, N, and general psychopathology scores).

3. Global Assessment of Functioning (GAF) [2]:

Clinicians grade each patient's occupational, social, and psychological functioning on a number scale based on their subjective assessments. It has a range of 1 (severely impaired functioning) to 100 (very good functioning).

4. Trail Making Test (TMT)

A neuropsychological test of task switching, and visual attention. The exam can provide information regarding executive functioning, mental flexibility, processing speed, scanning, and visual search speed [37]. It is divided into two halves (A&B): The Trail Making Test, which contains two sections, each with twenty-five circles spaced out across a sheet of paper. The Arabic version was used.

5. Blood chemistry

At the Ain Shams University Hospital Central Laboratory, blood samples were examined. The Diazo technique (Jendrassik-Grof) was utilized to measure both total and conjugated bilirubin. The difference between total and direct bilirubin was calculated to yield indirect bilirubin. Beckman Coulter UniCel® DxC800 Synchron Clinical System was used. Separated serum or plasma should not typically be kept between +15 °C and +30 °C for longer than 8 h. If assays are not completed in 8 h, serum or plasma should be refrigerated between +2 and +8 °C. If the separated sample needs to be stored for a longer period than 48 h, samples should be stored at a temperature between − 15 °C and − 20 °C. Freeze-stored samples should only be thawed once.

Procedures

Participants were recruited over a period of 6 months, from June to December 2020. The research investigation was carried out in two 1-h sessions. The tests were read out in informal Arabic when needed.

Session I

A comprehensive psychiatric interview was conducted, including a comprehensive history, mental state examination using Structured Clinical Interview for DSM-IV™ axis I disorders (SCID-I), and demographic information.

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A treating team, including two or more qualified psychiatrists, evaluated each patient. Subjects who met inclusion requirements were invited to participate, and those who agreed signed an informed consent form. The purpose of the study was explained to all participants.

Session II
In session II, the following tools were administered: Positive and Negative Syndrome Scale (PANSS), Trail Making Test (TMT), and Global Assessment of Functioning (GAF). Blood samples were collected for chemistry analysis to calculate unconjugated bilirubin. A specialized nurse withdrew 2 cc of blood from each individual, using Xinle vacuum blood collection tubes with separation gel coagulant Z/4 ml, following safety and infection control precautions. Every sample was deemed potentially positive for infectious agents like hepatitis B and HIV. Aseptic preparations included washing hands, wearing protective gloves, gown, headset, and sterilizing the skin over the patient's venous access. Disposable syringes and cotton were placed in a safety box and biohazard bag, and work surfaces were wiped down with Germicidal Disposable Wipe. Blood samples were centrifuged at the assigned laboratory to obtain a minimum of 0.6 mL serum for the assay, which was completed within 4 h.

Data management and analysis
The Pearson chi-squared test was used to compare intergroup differences for categorical variables, displayed as counts and percentages. For trend analysis, ordinal data were compared using the chi-squared test. The independent-samples *t*-test was utilized to compare intergroup differences for continuous numerical variables, displayed as mean and standard deviation. Factors influencing blood bilirubin levels were investigated using linear regression analysis, which considered any pertinent confounding variables. To investigate the direction and strength of the association between quantitative data, we used the Pearson correlation test (r). A P value of less than 0.05 is regarded as statistically significant.

Results
Socio-demographic and clinical characteristics
Of the 120 subjects participating in the study, 80 were patients with schizophrenia and 40 were healthy control subjects. Table 1 summarises the demographic characteristics of the two groups which shows a statistically significant difference in terms of weight, BMI, total bilirubin, and indirect bilirubin, which were higher in the schizophrenia group. Out of the 120 subjects, only one subject (with schizophrenia) had an abnormally increased total bilirubin level (> 1.2 mg/dL). None of the 120 subjects had a clinically abnormal direct (> 0.3 mg/dl) or indirect

bilirubin level (> 1.2 mg/dL). Thirty-two subjects with schizophrenia (40%) had a positive family history of psychiatric disorders. Regarding antipsychotic medications in the schizophrenia group, 35 subjects were receiving no antipsychotic medication, 19 were receiving antipsychotic monotherapy and 26 were receiving antipsychotic polypharmacy.

Correlation of demographic and clinical parameters with bilirubin levels
We correlated demographic and clinical parameters with total, direct, and indirect bilirubin levels and found a statistically significant positive correlation between PANSS total score with total, direct, and indirect bilirubin levels, between PANSS N score with total and direct bilirubin levels and between PANSS G score with total and indirect bilirubin levels (Table 2).

Linear regression for factors predicting bilirubin levels
We used linear regression analysis to determine which factors significantly predicted total, conjugated, and unconjugated bilirubin in our sample controlling for the effect of confounding variables. Total or indirect bilirubin levels were not predicted by any of the variables included in the analysis, including age, gender, smoking, BMI, Total PANSS, PANSS P, PANSS N, PANSS G, GAF, TMT-A, TMT-B, duration of psychotic disorder, duration of untreated psychosis, and antipsychotics use. Total PANSS, PANSS N and PANSS G were significantly predictive for direct bilirubin levels ($B = -0.003$, $p = 0.030$, 95% CI $= -0.005 - < 0.001$ for total PANSS; $B = 0.003$, $p = 0.042$, 95% CI $= < 0.001 - 0.005$ for PANSS N; $B = 0.004$, $p = 0.022$, 95% CI $= 0.001 - 0.007$ for PANSS G).

Discussion
Given their ease of use and potential for broad application, blood-based biomarkers may be a useful tool in the understanding of psychiatric diseases, particularly if they are inexpensive. Numerous indicators have been investigated in relation to mental illnesses, and further research is now being done on novel blood biomarkers. Nevertheless, the cost of these biomarkers is high, and the sophisticated methods required to measure them are not generally accessible [12].

To the best of our understanding, this is the first study to evaluate the relationship between unconjugated bilirubin and Schizophrenia, in Egypt and the Arab world. We found that the schizophrenia group had statistically significant differences (P value < 0.0001) in both total and unconjugated bilirubin levels, but not conjugated bilirubin. This association persisted despite controlling for confounding factors such as age, sex, BMI, and smoking.

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Table 1 Demographic and clinical characteristics: schizophrenia and controls

Variable	Schizophrenics (*n* = 80)	Control (*n* = 40)	Test	*p* value
Age (years) (mean and SD)	37.0 ± 9.8	36.9 ± 10.2	*t* = 0.019	0.905
Sex	*N* (%)	*N* (%)		
Female	25 (31.3%)	13 (32.5%)	χ2 = 0.19	0.890
Male	55 (68.8%)	27 (67.5%)		
Weight (kg) (mean and SD)	78.6 ± 20.7	73.0 ± 11.9	*t* = 1.574	0.007*
Height (cm) (mean and SD)	168.7 ± 9.1	171.5 ± 7.3	*t* = − 1.674	0.133
BMI (kg/m^2) (mean and SD)	27.6 ± 6.9	24.8 ± 3.6	*t* = 2.367	< 0.001*
Smoking	*N* (%)	*N* (%)		
Non-smoker	32 (40.0%)	19 (47.5%)	χ2 = 1.345	0.510
Ex-smoker	2 (2.5%)	2 (5.0%)		
Current smoker	46 (57.5%)	19 (47.5%)		
Education	*N* (%)	*N* (%)		
Primary	9 (11.3%)	6 (15.0%)	χ2 = 1.171	0.760
Preparatory	13 (16.3%)	6 (15.0%)		
Secondary	33 (41.3%)	13 (32.5%)		
University	25 (31.3%)	15 (37.5%)		
Employment	*N* (%)	*N* (%)		
Employed	23 (28.8%)	13 (32.5%)	χ2 = 1.79	0.673
Unemployed	57 (71.3%)	27 (67.5%)		
Total PANSS score (mean and SD)	78.33 ± 32.707	–	–	–
PANSS P score (mean and SD)	19.32 ± 10.815	–	–	–
PANSS N score (mean and SD)	20.05 ± 8.894	–	–	–
PANSS G score (mean and SD)	38.95 ± 16.194	–	–	–
GAF score (mean and SD)	47.09 ± 24.718	–	–	–
TMT-A score (mean and SD)	108.89 ± 85.045	–	–	–
TMT-B score (mean and SD)	217.77 ± 79.615	–	–	–
Duration of psychotic disorder (years) (mean and SD)	12.106 ± 7.4878	–	–	–
Duration of untreated psychosis (years) (mean and SD)	3.000 ± 2.5890	–	–	–
Total bilirubin (mg/dL) (mean and SD)	0.463 ± 0.222	0.207 ± 0.061	*t* = 7.140	*p* = < 0.001*
Direct bilirubin (mg/dL) (mean and SD)	0.099 ± 0.0373	0.0850. ± 0362	*t* = 1.923	*p* = 0.083*
Indirect bilirubin (mg/dL) (mean and SD)	0.359 ± 0.1966	0.125 ± 0.043	*t* = 7.413	*p* = < 0.001*

BMI Body Mass Index, *t* Student's *t* test, *χ*2 chi-square, *PANSS* Positive and Negative Symptoms Scale, *P score* Positive Scale, *N Score* Negative Scale, *G score* General Psychopathology Score, *GAF* General Assessment of Functioning, *TMT* Trail Making Test

* *p* statistically significant

Unconjugated bilirubin and schizophrenia

Our results show similarities to the previous study done by Aziz et al. in 2018 [3], where unconjugated mean bilirubin level was much higher in patients with the diagnosis of Schizophrenia. Also, in line with other studies that show much higher levels of unconjugated bilirubin mean levels even on comparing them with patients in the remission phase or general populations or even with other psychiatric patients [4, 27]. Our findings are consistent with [17, 26, 30, 34, 45]. However, their studies mainly compared unconjugated bilirubin in patients with bipolar disorder to that of schizophrenia, unlike our study in which we compare it to healthy control.

This may have to do with the neurotoxic effects of unconjugated bilirubin, which can cause glutamate and dopaminergic dysfunction or affect their metabolism [5, 14], as well as impact the connectivity of the brain tissue [14, 15], a notion that aligns with findings from neurophysiologic findings (Gama Marques et al. 2017) and neuroimaging [26]. Both are of direct relevance to brain metabolism. Patients with schizophrenia show similar abnormalities [5]. However, it is still argued whether elevated unconjugated bilirubin is a consequence or cause of the psychotic state. Unfortunately, our study's cross-sectional design can just determine association, not causality.

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Table 2 Correlation of demographic and clinical parameters with total, direct, and indirect bilirubin

	Total bilirubin		Direct bilirubin		Indirect bilirubin	
	r	*p* value	*r*	*p* value	*r*	*p* value
Age	0.054	0.560	0.047	0.611	0.071	0.439
Weight	0.077	0.405	− 0.015	0.867	0.085	0.357
Height	− 0.066	0.471	0.008	0.933	− 0.095	0.303
BMI	0.123	0.180	− 0.035	0.706	0.139	0.131
PANSS Total score	0.329	0.003*	0.234	0.037*	0.291	0.009*
PANSS P score	0.087	0.442	0.029	0.797	0.065	0.565
PANSS N score	0.224	0.045*	0.225	0.0444*	0.197	0.079
PANSS G score	0.338	0.002*	0.209	0.062	0.313	0.005*
GAF score	− 0.119	0.293	− 0.132	0.244	− 0.092	0.414
TMT-A score	0.082	0.468	0.200	0.075	0.074	0.513
TMT-B score	0.154	0.173	0.151	0.180	0.173	0.125
Duration of psychotic disorder	0.045	0.690	0.087	0.445	0.050	0.66
Duration of untreated psychosis	0.162	0.368	0.149	0.407	0.138	0.442

BMI Body Mass Index, *PANSS* Positive and Negative Symptoms Scale, *P score* Positive Scale, *N Score* Negative Scale; *G score* General Psychopathology Score, *GAF* General Assessment of Functioning, *TMT* Trail Making Test

* *p* statistically significant

Total bilirubin and conjugated bilirubin and schizophrenia

In comparison to healthy people, our study found a statistically significant difference (p value < 0.0001) in the total bilirubin level between patients with schizophrenia. This is consistent with the two earlier investigations by Bach et al. [4], which found that acutely psychotic patients had higher total bilirubin levels than patients who were not acutely unwell. These findings support the earlier theory that hyperbilirubinemia and schizophrenia disease are related. In the past, researchers have proposed that red cell membrane abnormalities [20], drug side effects [10], or stress are the causes of hyperbilirubinemia in schizophrenia patients. However, compared to healthy controls, several studies indicate that patients with schizophrenia have lower levels of total bilirubin [28, 43, 44]. This was later studied by Vítek et al. [40], who studied premotor gene variation and its association with schizophrenia. The difference in results might be attributed to the effect of genotype and different types of schizophrenia.

Total bilirubin has antioxidant qualities, in contrast to unconjugated bilirubin, which has the potential to be neurotoxic. Relative antioxidant deficiency would arise from an increase in unconjugated bilirubin which can support the antioxidant deficit theory. These explanations could clarify the seeming discrepancy in the research regarding the correlation between bilirubin and schizophrenia [30]. The risk of bilirubin-induced neurotoxicity is likely underestimated by total bilirubin concentration since it does not account for free, unconjugated bilirubin. While most unconjugated bilirubin is bound to albumin, some bilirubin is still free (unbound). The blood–brain barrier (BBB) is not crossed by bound bilirubin because it is water soluble, but unconjugated bilirubin, can penetrate membranes, and cause damage to neurons. That can explain why, low bilirubin levels can cause bilirubin-induced neurotoxicity when combined with hypoalbuminemia or decreased albumin binding [42]. Therefore, total serum bilirubin is not considered to be a reliable indicator of the risk for bilirubin-induced neurotoxicity, while free unconjugated bilirubin is.

In the meantime, several research [28, 40, 43, 44] have demonstrated lower levels of total bilirubin among patients with schizophrenia compared to healthy controls, which is in contradiction to our findings. This supports the antioxidant deficit theory of schizophrenia.

Interestingly, other studies, like ours, found no association between schizophrenia spectrum disorder and conjugated bilirubin [26, 45]. However, unlike our study [4], found that patients with acute transit psychotic disorder had significantly higher levels of conjugated bilirubin.

Conclusion

In our study, we found a statistically significant difference in the mean serum levels of total and unconjugated bilirubin between patients with schizophrenia and healthy controls. Nevertheless, further long-term research is needed to resolve the conflicting results in the literature regarding unconjugated bilirubin and schizophrenia. Clinicians should be aware of the fact that changes in unconjugated bilirubin serum levels in patients with schizophrenia can be a pathophysiological change that occurs in the course of the disorder, in order to prevent

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these patients from being improperly withheld from antipsychotics or putting them through needless clinical or laboratory investigations.

Limitation

The non-longitudinal design and lack of randomization in our sample can highlight association yet not causation. Also, the healthy individuals were selected, and the exclusion criteria were based on self-reported history with no further testing done to rule out any undiscovered conditions. There was no baseline serum bilirubin (total, unconjugated, and conjugated). The sample had more male representatives. Obtaining a larger sample with more female representatives would be beneficial to precisely examine any potential effect of gender differences. Also, the use of a control group with another psychiatric diagnosis would help to distinguish schizophrenia from other psychiatric differential diagnoses. Also, the history of ECT sessions and its effect on patients was not considered during the analysis of our sample data.

Abbreviations

BBB	Blood-brain barrier
BMI	Body mass index
DSM	Diagnostic Statistical Manual
GAF	Global Assessment of Function
HBV	Hepatitis B virus
HCV	Hepatitis C virus
PANSS	Positive and Negative Syndrome Scale
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
TMT	Trail-Making Test

Authors' contributions

AM, DA, MY, and RS: concept of the study, data design analysis and interpretation, and article critical revision. DA and RS: data interpretation, manuscript drafting, and revision. MS: gathering data, performing statistical analysis, interpreting information, and writing the manuscript. The final draft of the work was read and approved by the writers.

Availability of data and materials

Upon a reasonable request, the corresponding author will make the datasets used in the current work available.

Declarations

Ethics approval and consent to participate

After explaining the study's purpose, participants gave their informed consent. The research was approved by the Research Ethics Committee of Ain Shams University after it was designed in accordance with their requirements (FMASU M S 342/2020).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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