

Clinical and Sociodemographic Correlates of Serum Unconjugated Bilirubin in Patients with Severe Psychiatric Disorders

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ABSTRACT

Background: Serum unconjugated bilirubin (UCB) is studied as a peripheral oxidative-stress marker in severe psychiatric illness, but levels are also shaped by sociodemographic and clinical factors age, sex, marital status, tobacco use, family history, illness duration that must be characterised first. The present study aimed to characterise clinical and sociodemographic correlates of serum UCB in schizophrenia and bipolar affective disorder (BPAD) versus controls, and determine whether diagnostic UCB differences persist independently of these correlates. **Methods:** This cross-sectional study at the Institute of Mental Health and Hospital, Agra, enrolled 180 subjects (60 each: schizophrenia, BPAD, controls) via consecutive purposive sampling, with diagnoses per ICD-10 and controls screened using GHQ-12. Fasting UCB (total minus conjugated bilirubin) and sociodemographic/clinical data were recorded via structured proforma. Group differences were tested with one-way ANOVA, Tukey's post-hoc test, and ANCOVA adjusting for age, sex, tobacco use, family history, illness duration; $p < 0.05$ was significant. **Results:** Groups were matched for age/sex but differed in marital status, family history, tobacco use, and illness duration. Mean UCB was 0.61 ± 0.32 mg/dL in controls, 0.83 ± 0.36 in BPAD, and 0.93 ± 0.36 in schizophrenia, with elevated UCB in 11.66%, 41.66%, and 61.66%, respectively. ANOVA showed a significant group effect ($F = 17.45$, $p < 0.001$) with a schizophrenia > BPAD > controls gradient, significant after ANCOVA adjustment (adjusted $F = 15.82$, $p < 0.001$). **Conclusion:** Serum UCB in schizophrenia and BPAD reflects sociodemographic and clinical correlates, yet its diagnostic gradient persists independently, supporting candidacy as an oxidative-stress biomarker. Tobacco use, family history, and illness duration should be documented and adjusted for when UCB is used as a psychiatric marker.

Keywords: Bipolar affective disorder; clinical correlates; oxidative stress; schizophrenia; sociodemographic correlates; unconjugated bilirubin

INTRODUCTION

Unconjugated bilirubin, which was traditionally seen only as a metabolic waste product of haem metabolism, is now considered an endogenous antioxidant with physiological activity that can neutralise free radicals and reduce lipid peroxidation.¹ A number of scientific studies have established that unconjugated bilirubin is associated with oxidative stress mechanisms involved in

the development of serious psychiatric diseases and can be used as a peripheral biomarker for schizophrenia and bipolar affective disorder (BPAD).²

Nonetheless, serum bilirubin does not occur in isolation; it is affected by many different sociodemographic and clinical variables, such as age, gender, marital status, smoking, psychiatric illness in the family, length of illness, and clinical type.³ It is crucial to understand

these covariates in order to properly interpret unconjugated bilirubin as a biomarker of disease since otherwise all that may happen is to mistakenly attribute variation due to covariation to illness biology.

Age and gender have been identified to influence basal levels of bilirubin, whereby levels of the compound tend to be higher in men and increase slightly with age.⁴ Nicotine use is relevant because it causes an imbalance in the redox state, affects the functioning of the liver and has been found to affect the metabolism of bilirubin, and is highly prevalent among those suffering from schizophrenia.⁵ A family history of psychiatric illnesses is an indication of high heritability for schizophrenia and BPAD, as well as a possible indicator of biological predisposition to oxidative imbalance.⁶ The other possible correlate can be the chronicity of the illness: the greater duration of illness means higher cumulative exposure to psychosocial stress, relapse, and dysregulation, all of which have potential effects on the body's antioxidative compensation.⁷ Regarding BPAD, the changes in the levels of oxidative markers during the different mood states make another correlate for further research.⁸

Although marital status is not a biological factor that directly determines the amount of bilirubin, it acts as an indirect indicator of psychological and occupational function, and the distribution of this variable among the different diagnostic categories can help reveal the burden of illness associated with each disorder.⁹ There is evidence of symptom associations too; there is a correlation between the levels of bilirubin and positive symptoms in schizophrenia.¹⁰

Even with this growing body of evidence, there is a lack of any systematic investigation of the relationship between sociodemographic and clinical variables and serum unconjugated bilirubin levels in schizophrenia, BPAD, and healthy controls on a comparative basis, especially from an Indian population in which the associations may be influenced by environmental and genetic factors specific to the study population.

This study aimed at characterizing the clinical and sociodemographic determinants of unconjugated bilirubin in serum from patients with schizophrenia and BPAD relative to healthy subjects so as to understand what patient factors need to be considered when evaluating unconjugated bilirubin as a potential biomarker for severe mental disorders.

METHODOLOGY

Study Setting and Design

This institution-based, cross-sectional study was conducted at the Institute of Mental Health and Hospital (IMHH), Agra, which is a government-owned tertiary care psychiatric institute, where subjects were selected from both outpatients and inpatients. Normal healthy

control subjects were selected from the same place as patients so that they could be comparable demographically with each other. All subjects were tested once and were enrolled during a period of two years.

Sample Size

The sample size calculation was done using the equation $n = [(Za/2 + Zb)^2 \times 2 \times \sigma^2] / d^2$, where the level of unconjugated bilirubin from the study of Gama Marques & Arantes-Goncalves (schizophrenia 0.39 ± 0.16 mg/dL; bipolar disorder 0.29 ± 0.13 mg/dL; mean difference 0.10 mg/dL) is used, and where $Za/2 = 1.96$ (95% confidence) and $Zb = 0.842$ (80% power). It resulted in a minimum sample of 34 subjects per arm; adjusting for losses, a sample size of 60 subjects per arm was recruited, amounting to 180 subjects in total - 60 subjects with schizophrenia, 60 with BPAD

Selection Criteria

Inclusion criteria included being diagnosed with ICD-10 category of either schizophrenia or BPAD, having an age between 18-65 years, being fluent in either Hindi or English, and consenting through writing to participate in the study. Those who had any other ICD-10 psychiatric diagnosis, major physical ailment (like diabetes mellitus, hypertension, severe obesity or malnutrition), pregnant females, those with substance abuse disorder except that of nicotine/tobacco, and those who did not consent in the study were excluded from the study. The healthy control subjects should satisfy the age and language criterion and should score less than 2 on GHQ-12 test.

Correlate Variables and Instruments

Information regarding the demographic and clinical parameters were collected using a systematic proforma that included age, gender, marital status, family history of mental disorders, smoking habit, disease duration, and clinical form (mania or depression for BPAD). General Health Questionnaire-12 (GHQ-12) was employed as a screening instrument for the detection of any hidden psychiatric disorder among healthy individuals, with a cut-off point of 2. Unconjugated bilirubin was not measured directly, but was calculated for each subject using the formula "total bilirubin minus conjugated bilirubin" from a fasting venous blood sample.

Procedure

The process of recruitment could only commence upon obtaining ethical clearance from the Institutional Ethics Committee of IMHH, Agra. Drug naive in-patients belonging to the family ward and drug non-compliant out-patients who had not attended for more than three months were evaluated based on the inclusion criteria; those that met the selection criteria were then recruited

after obtaining informed consent from the eligible participants, and in case the competency of the patients was in doubt, their consent was sought from a family member of the patient. The healthy subjects for the prospective control group were selected through screening using the GHQ-12; only those who scored less than 2 were selected. Venous fasting blood samples of all the participants were obtained after overnight fasting through aseptic techniques and infection control measures, and total and conjugated bilirubin were determined.

Statistical Analysis

The data were recorded in Microsoft Excel and analyzed using the IBM SPSS Statistics version 27 software

RESULTS

In all, 180 subjects were analyzed through three equally divided groups of 60: schizophrenic patients, BPAD patients, and healthy control subjects. Each participant enrolled in the study followed the entire experimental protocol without any loss of data.

Sociodemographic Correlates: Age, Sex, and Marital Status: There was an age balance among the groups, as the mean age of the schizophrenia group was 32.25 ± 5.13 , while the mean age of BPAD was 31.98 ± 7.25 , and the mean age of healthy subjects was 31.55 ± 6.62 . There was a slight dominance of females among the three groups, with the control group having the highest percentage of females (61.66%), followed by BPAD (53.33%). The marital status, which can be seen as an indirect measure of psychosocial function, was very different among the groups, with the majority of BPAD (58.33%) and healthy subjects (68.33%) being married, but the majority of schizophrenia patients (68.33%) being unmarried. [Table 1, Figure 1]

Table 1: Sociodemographic Correlates of the Study Population

Variable	BPAD (n=60)	Schizophrenia (n=60)	Healthy Controls (n=60)
Age, Mean $\pm$ SD (years)	31.98 ± 7.25	32.25 ± 5.13	31.55 ± 6.62
Male, n (%)	28 (46.66)	26 (43.33)	23 (38.33)
Female, n (%)	32 (53.33)	34 (56.66)	37 (61.66)
Married, n (%)	35 (58.33)	19 (31.66)	41 (68.33)
Unmarried, n (%)	25 (41.66)	41 (68.33)	19 (31.66)

Groups were broadly comparable for age and sex; marital status differed significantly, reflecting the greater social withdrawal characteristic of schizophrenia.

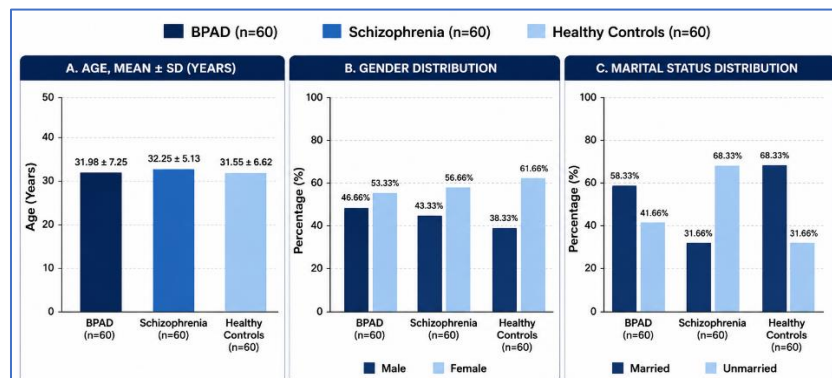


Figure 1. Sociodemographic Correlates of the Study Population

Clinical Correlates: Illness Duration, Subtype, Family History, and Tobacco Use: Illness was persistent in both the patient populations, with a mean illness duration of 10.75 ± 6.50 years in BPAD and 10.41 ± 4.92 years in schizophrenia, indicating that the studied population is suitable for long-term biochemical changes observation. In BPAD, 53.33% of the patients (n=32) were enrolled in mania, while 46.67% of the patients (n=28) were in the depressive state at the time of enrollment. Presence of the family history of any psychiatric disorder, showing the genetic basis of both disorders, was present in 55% of the schizophrenia population (n=33), 40% of the BPAD (n=24) and 8.3% of the control group (n=5) patients. Smoking history, a clinically significant parameter since smoking affects the redox state and the liver functioning, was present in 53.33% of the schizophrenia patients (n=32), 41.6% of the controls (n=25) and 23.33% of the BPAD patients (n=14). [Table 2, Figure 2]

Table 2: Clinical Correlates - Illness Duration, Subtype, Family History, and Tobacco Use

Group	Correlate	Value
BPAD	Duration of illness, Mean $\pm$ SD (yrs)	10.75 $\pm$ 6.50
	Manic subtype, n (%)	32 (53.33)
	Depressive subtype, n (%)	28 (46.67)
	Family history positive, n (%)	24 (40.00)
	Tobacco use, n (%)	14 (23.33)
Schizophrenia	Duration of illness, Mean $\pm$ SD (yrs)	10.41 $\pm$ 4.92
	Family history positive, n (%)	33 (55.00)
	Tobacco use, n (%)	32 (53.33)
Healthy Controls	Family history positive, n (%)	5 (8.33)
	Tobacco use, n (%)	25 (41.60)

Family history and tobacco use were both markedly more prevalent in schizophrenia, consistent with the established heritability of the disorder and its well-documented association with smoking.

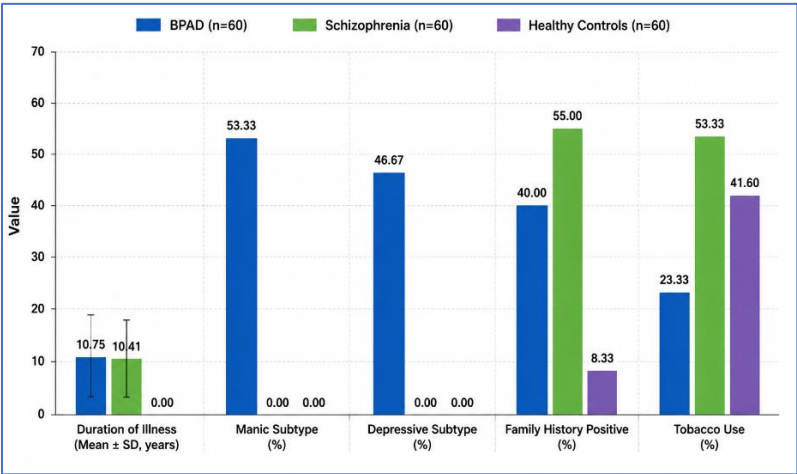


Figure 2: Clinical Correlates - Illness Duration, Subtype, Family History, and Tobacco Use

Serum Bilirubin Profile in Relation to Diagnostic Group: Both total and unconjugated bilirubin were elevated in the two patient groups compared to healthy controls, with mean levels of both variables being highest in patients with schizophrenia. The mean level of unconjugated bilirubin was 0.61 ± 0.32 mg/dL for controls, 0.83 ± 0.36 mg/dL for BPAD, and 0.93 ± 0.36 mg/dL for patients with schizophrenia. The difference in conjugated bilirubin was negligible between groups, suggesting that the between-group differences in bilirubin levels were observed only in unconjugated form of bilirubin. [Table 3]

Table 3: Serum Bilirubin Parameters Across Study Groups

Group	Parameter	Mean $\pm$ SD (mg/dL)	Range (mg/dL)
BPAD	Total bilirubin	1.14 $\pm$ 0.36	1.18
	Unconjugated bilirubin	0.83 $\pm$ 0.36	1.33
	Conjugated bilirubin	0.30 $\pm$ 0.11	0.40

Group	Parameter	Mean $\pm$ SD (mg/dL)	Range (mg/dL)
Schizophrenia	Total bilirubin	1.23 $\pm$ 0.51	3.76
	Unconjugated bilirubin	0.93 $\pm$ 0.36	2.05
	Conjugated bilirubin	0.30 $\pm$ 0.23	1.77
Healthy Controls	Total bilirubin	0.83 $\pm$ 0.34	1.40
	Unconjugated bilirubin	0.61 $\pm$ 0.32	1.39
	Conjugated bilirubin	0.22 $\pm$ 0.10	0.40

Similarly, the results from categorical analysis were consistent with the continuous findings where increased levels of unconjugated bilirubin were found to be evident in 61.66% (n=37) patients of schizophrenia, 41.66% (n=25) of BPAD patients, and just 11.66% (n=7) of healthy individuals. The consistency between the continuous and categorical findings makes it possible to confirm that there is a substantial difference in the level of disruption of bilirubin metabolism in the two mental disorders studied.

Association Between Diagnostic Group and Unconjugated Bilirubin, Independent of Correlates: One-way ANOVA analysis revealed a very significant effect of overall group on serum unconjugated bilirubin levels ($F = 17.45$, $p < 0.001$). Post hoc analysis using Tukey's test revealed that unconjugated bilirubin levels were significantly elevated in both BPAD and schizophrenia groups compared to healthy controls ($p < 0.001$ for both), and levels of unconjugated bilirubin were significantly higher in the schizophrenia group compared to BPAD group ($p = 0.002$). [Table 4]

Table 4: Post-hoc Comparison of Unconjugated Bilirubin Levels

Group Comparison	Mean Difference (mg/dL)	95% CI	p-value
BPAD vs Healthy Controls	0.28	0.11 to 0.44	<0.001*
Schizophrenia vs Healthy Controls	0.37	0.15 to 0.59	<0.001*
BPAD vs Schizophrenia	-0.09	-0.15 to -0.03	0.002*

*Statistically significant, one-way ANOVA with Tukey's post-hoc test, $p < 0.05$.

In order to see whether the diagnostic gradient found here could be attributed to the sociodemographic and clinical variables described above, ANCOVA analysis was conducted controlling for age, gender, tobacco use, family history of mental illness, and duration of illness. The effect of group on unconjugated bilirubin was still very strong even after controlling for these variables (F adjusted = 15.82, $p < 0.001$), and post-hoc testing using the Bonferroni correction revealed that both patient groups differed significantly from the control group, while schizophrenia also differed significantly from BPAD. It can thus be concluded that the diagnostic gradient of unconjugated bilirubin does not reflect only the associations with these variables, but is also independent of them. [Table 5]

Table 5: Adjusted (ANCOVA) Post-hoc Comparison of Unconjugated Bilirubin

Group Comparison	Adjusted Mean Difference (mg/dL)	95% CI	p-value
BPAD vs Healthy Controls	0.26	0.14 to 0.38	<0.001*
Schizophrenia vs Healthy Controls	0.35	0.23 to 0.47	<0.001*
BPAD vs Schizophrenia	-0.09	-0.15 to -0.03	0.004*

*Statistically significant after adjustment for age, sex, tobacco use, family history, and illness duration (ANCOVA with Bonferroni correction), $p < 0.05$.

DISCUSSION

In this study, the purpose was to evaluate the sociodemographic and clinical correlates of unconjugated bilirubin in the blood serum of schizophrenic and BPAD patients compared to the healthy control group, as well as the persistence of the diagnostic gradient of unconjugated bilirubin, regardless of these factors. The main result is that there was a marked graded elevation of unconjugated bilirubin – schizophrenia > BPAD > healthy control subjects, even after the adjustment for sociodemographic and clinical correlates.

Sociodemographic Profile: Age and Sex

One clear advantage in methodology used in the current study was the age equivalence of the three groups in terms of their mean age, which is significant since it has been established that baseline bilirubin levels are related not only to age but also to gender, with the bilirubin levels usually higher in men and increase gradually with age.⁴ Thus, this equivalence in age and gender among the different groups improves the internal validity of the between group differences in serum unconjugated bilirubin levels.

Marital Status and Social Functioning

The important difference was in the marital status where although 58.33% of BPAD patients and 68.33% of healthy subjects were married, only 31.66% of schizophrenia patients were married, the rest being mostly unmarried. This could be easily understood since Schizophrenia entails a great deal of social withdrawal, poor interpersonal skills, occupational dysfunction, and stigmatization that may impact marriage. Illness-induced disability, age at onset, premorbid psychological and social adjustment problems, and family factors have previously been cited as factors determining the outcome of marriage in schizophrenia.⁹ The high rate of unmarried persons in the case of schizophrenia patients in the current study is indicative of the wider psychosocial ramifications of the illness.

Confounding Factors Affecting Unconjugated Bilirubin

Several parameters with the ability to interfere with the measurement of serum unconjugated bilirubin were methodically evaluated in the study and included the age, gender, family history of psychiatric disorders, and use of tobacco. Family history of psychiatric disease was observed in 40% of BPAD, 55% of schizophrenia and only 8.3% of controls, corroborating the known heritability of both diseases. Smoking was seen in 23.33% of BPAD, 53.33% of schizophrenia and 41.6% of controls, which was clinically significant because the effect of nicotine on redox status and bilirubin metabolism has been documented.⁵ A well-established global correlation between the occurrence of schizophrenia and tobacco smoking has been described in the literature, hence the significance of this covariate for studies of schizophrenia.⁵ Unconjugated bilirubin can be influenced by various factors such as hepatic status, fasting state, metabolic profile and tobacco smoking.

Duration of Illness and Chronicity

Both populations were chronic in illness, with an average of 10.75 years (± 6.50) for BPAD and 10.41 years (± 4.92) for schizophrenia. This is a key correlate since the illness process is chronic, a history of relapses, prolonged exposure to psychological stresses, and prolonged biological disease process may affect the oxidative process. It has been found that antioxidants have compromised functions while oxidative stress parameters remain high in schizophrenia, indicating that chronic schizophrenia is associated with chronic imbalance of oxidative process.⁷ In case of bipolar disorder, the oxidative changes are chronic too, but they vary according to the mood of the patient.⁸

Clinical Diagnosis and Subtype Distribution

The BPAD subtype included 53.33% manic and 46.67% depressive subjects during the time of recruiting the subjects. This is an important biological difference as there is a systematic variance in oxidative stress markers during mania, depression and euthymia stages in patients suffering from bipolar disorder.⁸ Variations in oxidative stress markers have been seen in patients with bipolar disorders, although with large differences between different studies, and manic and depressive states seem to have their own oxidative status.¹² Having both kinds of mood states included in the BPAD group must have added to the biological heterogeneity in the sample, which explains why unconjugated bilirubin in BPAD was somewhere between control and schizophrenia.

Family History and Tobacco Use as Clinical Correlates

The distribution of family history and smoking habits amongst the different groups is clinically significant. The higher level of family psychiatric disorder in schizophrenic individuals can be attributed to the higher heritability of this condition. On the other hand, the higher level of tobacco use in schizophrenic individuals (53.33%) as compared to BPAD patients (23.33%) can be linked mechanistically considering the role of nicotine in modulating oxidative stress, inflammatory signaling, and bilirubin metabolism.⁵ Schizophrenic individuals are known to be much more prone to smoking compared to the general population. It is also seen in the current study where there are more cases of tobacco use among schizophrenics.

Symptom-Level and Diagnostic Correlates in the Wider Literature

Apart from the sociodemographic and clinical factors investigated directly in the study, other studies have found bilirubin levels to be correlated with the severity of symptoms among people with schizophrenia, implying that unconjugated bilirubin is not only correlated with diagnostic categories but also with symptom levels among patients with one condition.¹⁰ Unconjugated hyperbilirubinaemia idiopathic in nature and resembling the Gilbert's syndrome has been found associated with schizophrenia, indicating that there could be common genetics or metabolic substrates involved in the pathophysiology of both bilirubin metabolism and psychosis.¹³

Diagnostic Gradient and Its Persistence after Adjustment

Significant differences in unconjugated bilirubin levels were found using one-way ANOVA. In addition, by employing Tukey's post-hoc test, it was shown that patients with BPAD and schizophrenia had significantly

higher levels of unconjugated bilirubin than healthy controls and patients with schizophrenia had higher unconjugated bilirubin levels than BPAD patients. Such a pattern may indicate that redox biology plays a role in severe mental disorders.² Importantly, such a pattern remained valid after applying the ANCOVA correction for age, sex, smoking, family history of psychiatric illness and duration of illness, when the group effect was still highly significant. It means that the association between unconjugated bilirubin level and psychiatric illness, especially schizophrenia, could not be explained solely by sociodemographic and clinical variables of this study.

Comparison with Previous Studies

The results of this study are broadly consistent with previous published research. In similar fashion, Pradeep et al. found that unconjugated bilirubin levels were usually higher in patients with schizophrenia compared to BPAD.¹⁴ An association of unconjugated bilirubin with acute schizophrenia was also noted in other published studies, which has been further extended to include the whole range of psychosis including schizoaffective disorder and bipolar disorder.¹⁵ Nevertheless, the findings of the published literature are not all consistent in direction: lowered levels of plasma bilirubin have been seen in first-episode psychosis.¹⁶ This variation among studies in the findings can be attributed to differences in disease severity, previous treatments, symptoms, smoking, metabolism, liver involvement, and the difference between total and unconjugated bilirubin, hence making it imperative for correlation level analysis rather than diagnosis alone to make sense of the bilirubin levels. The results of this study must therefore be considered as part of an emerging literature and not the one and only bilirubin pattern for the whole psychiatric population.¹⁷

Clinical Implications

The above conclusions thus demonstrate the role of bilirubin as a readily available, inexpensive peripherally detectable parameter linked to severe psychiatric disorders, which is most evident in schizophrenia, and prove that this linkage does not merely result from the confounding effects of age, sex, smoking status, familial history, and disease duration. Nevertheless, bilirubin cannot be viewed as a sole criterion for diagnosis since the levels of this parameter form a part of the overall homeostatic balance between health and disease and are affected by various other factors not considered in this study, including fasting status, hepatic function, metabolic syndrome, and genetic predispositions like Gilbert's syndrome.¹⁸ The main practical application of this parameter is, therefore, most likely going to be in

combination with a panel of other markers of oxidative and inflammatory damage.

Strengths and Limitations

The main strengths of this study include equally sized groups with similar sociodemographic characteristics; recording of a wide array of sociodemographic and clinical correlates; ANCOVA analysis for confounding factors; and analysis of unconjugated bilirubin in both categorical and continuous form. The weaknesses include the cross-sectional design used that does not allow causal inference about the correlates investigated; a sample collected from one center that might reduce its generalizability; inclusion of BPAD patients during both phases of their disorder (manic and depressive); high level of tobacco consumption among schizophrenia patients and controls; and potential confounding by subclinical liver dysfunction, fasting status, and pharmacogenomics of bilirubin metabolism.

CONCLUSION

The serum level of unconjugated bilirubin in patients with schizophrenia and BPAD is defined by a profile of sociodemographic and clinical correlates, such as age, gender, marital status, familial history of mental disorder, smoking, duration of illness, and subtype of illness. Nonetheless, the diagnostic trend of schizophrenia > BPAD > control subjects in terms of unconjugated bilirubin concentration remained the same even after controlling for these important correlates, which means that the correlation between unconjugated bilirubin and illness is not completely accounted for by these variables alone. The level of unconjugated bilirubin was significantly higher in both groups of patients compared to healthy controls, with the highest increase in patients with schizophrenia, who also had a higher prevalence of high unconjugated bilirubin.

These results suggest that bilirubin is a promising biomarker which could represent oxidative stress, dysregulated inflammation, or antioxidant compensation in severe mental disorders, but at the same time it should be recognized that such risk factors as smoking, familial vulnerability, and duration of illness should be systematically studied and controlled in any future research on biomarkers of severe mental disorders. The future research will need to be oriented on prospective multi-center studies mapping the trajectory of the changes of bilirubin levels with regard to the severity and subtype of illness, the use of multibiomarker panels including markers of oxidative stress, inflammation, and metabolism, and the integration of biochemical peripheral correlates with clinical and neuroimaging data.

Declarations

Ethics Approval and Consent to Participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of the Institute of Mental Health and Hospital (IMHH), Agra, Uttar Pradesh, India, prior to commencement of the study. Written informed consent was obtained from all participants before enrolment. For participants whose capacity to provide informed consent was considered impaired, consent was obtained from an appropriate legally authorized family member in accordance with institutional ethical requirements.

Consent for Publication

Not applicable. No individually identifiable personal data or images are presented in this manuscript.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain clinical information from human participants and are subject to institutional and ethical restrictions. De-identified data may be made available from the corresponding author on reasonable request, subject to appropriate ethical and institutional approval.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Dr. Minakshi Badwal: Study conceptualization, literature review, participant recruitment, clinical assessment, data collection, data interpretation, statistical analysis, and manuscript preparation.

Prof. (Dr.) Dinesh Singh Rathore: Study supervision, clinical and methodological guidance, interpretation of findings, and critical revision of the manuscript.

Prof. (Dr.) Anil Kumar Sisodia: Study supervision, methodological guidance, clinical oversight, interpretation of findings, and critical revision of the manuscript. He also served as the corresponding author.

Dr. Nitika Singh: Clinical assessment, participant recruitment, data collection, interpretation of findings, and critical revision of the manuscript.

All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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