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Original Research Article

Association between mood episode severity and c-reactive protein levels in bipolar disorder: an exploratory cross-sectional study

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ABSTRACT

Background: Bipolar disorder is a chronic, recurrent mood disorder associated with significant disability, functional impairment, and medical comorbidities. Increasing evidence suggests that immune-inflammatory mechanisms contribute to its pathophysiology. C-reactive protein (CRP), a widely used biomarker of systemic inflammation, has been reported to be elevated in bipolar disorder, particularly during manic episodes. However, data from the Indian population examining the association between CRP levels and severity of mood episodes using standardized rating scales remain limited. Therefore, this study was conducted to evaluate the association between severity of manic and depressive episodes and serum CRP levels in patients with bipolar disorder.
Methods: This hospital-based cross-sectional analytical study was conducted at a tertiary care center. Thirty patients diagnosed with bipolar disorder were assessed during either a manic episode (n=15) or a depressive episode (n=15). Severity was evaluated using the young mania rating scale (YMRS) and Hamilton depression rating scale (HAM-D). Serum CRP levels were measured and categorized as normal (≤5 mg/l) or elevated (>5 mg/l). Correlations were analysed using Pearson's correlation coefficient.
Results: Fourteen participants (46.7%) had elevated CRP levels. Mean CRP levels were higher in manic episodes (17.82±16.38 mg/l) than depressive episodes (9.80±8.14 mg/l). A significant positive correlation was found between YMRS scores and CRP levels (r=0.5622, p=0.0292), whereas no significant correlation was observed between HAM-D scores and CRP levels (r=−0.1672, p=0.5515).
Conclusions: Severity of manic symptoms is positively associated with systemic inflammation, supporting inflammation as a state-dependent correlate of mania.

Keywords: Bipolar disorder, C-reactive protein, Depression, Inflammation, Mania

INTRODUCTION

Bipolar disorder is a severe and chronic psychiatric illness characterized by recurrent episodes of mania, hypomania, and depression. It is associated with substantial psychosocial dysfunction, high relapse rates, increased suicide risk, and substantial medical comorbidity. Globally, the lifetime prevalence of bipolar disorder ranges between 0.7-1.0%, while bipolar spectrum conditions affect approximately 1.4% of the population.[1,2]

In India, findings of the National Mental Health Survey (2015-16) estimated the lifetime prevalence of bipolar disorder to be approximately 0.5-0.6%.[3] Despite its comparatively lower prevalence than depressive and anxiety disorders, bipolar disorder contributes disproportionately to years lived with disability due to its early onset and recurrent episodes.

Traditional etiological models of bipolar disorder have primarily focused on neurotransmitter dysregulation. However, recent research has highlighted the critical role of immune-inflammatory mechanisms in its pathogenesis.

Elevated levels of pro-inflammatory cytokines and acute-phase reactants have been consistently reported during acute mood episodes, indicating that inflammation may be involved in both the onset and progression of the disorder.[4]

C-reactive protein (CRP), synthesized by hepatocytes in response to inflammatory cytokines such as interleukin-6 is a sensitive marker of systemic inflammation. Several meta-analyses have demonstrated elevated CRP levels in individuals with bipolar disorder compared to healthy controls, with particularly higher levels observed during manic episodes.[5] However, limited Indian studies have systematically evaluated the relationship of CRP levels with mood episode severity.[6]

This gap highlights the need to better understand whether systemic inflammation correlates with clinical severity in bipolar disorder, which could have implications for disease monitoring and therapeutic strategies. The present study was therefore designed to evaluate serum CRP levels in patients with bipolar disorder during manic and depressive episodes and to examine their association with the severity of these mood states. It was hypothesized that higher severity of mood episodes, particularly mania, would be associated with elevated CRP levels. Additionally, the study aimed to estimate the proportion of patients with normal and elevated CRP levels and to assess the correlation between CRP levels and standardized measures of manic and depressive symptom severity.

METHODS

Study design

This was a hospital-based cross-sectional analytical study conducted over a period of one-year from August 2016 to July 2017. Participants were recruited using consecutive sampling from outpatient and inpatient psychiatric services.

The sample size consisted of 30 participants, based on the availability of eligible patients during the study period, and was considered suitable for this exploratory analysis.

Eligible participants were screened based on predefined criteria. Patients aged between 18 and 60 years, diagnosed with bipolar disorder as per ICD-10 criteria, and currently experiencing either a manic or depressive episode confirmed by clinical evaluation were included in the study. Individuals with acute infection, inflammatory or autoimmune disorders, chronic systemic or endocrine illnesses affecting inflammatory markers, mixed affective states, substance use disorder (except nicotine) within the past six months, pregnancy or lactation, recent use of anti-inflammatory, immunomodulatory, or corticosteroid medications, as well as those with other axis I psychiatric disorders, intellectual disability, organic mental disorders, or dementia were excluded.

Study variables

The independent variable was mood episode severity, while the dependent variable was serum c-reactive protein (CRP) levels. Potential confounding variables included age, gender, medical comorbidities, and medication status.

Data collection procedure

After confirmation of eligibility using ICD-10 diagnostic criteria for bipolar disorder, sociodemographic and clinical details of participants were recorded using a semi-structured sociodemographic and clinical proforma.

Severity of mood symptoms was assessed using young mania rating scale (YMRS) or Hamilton depression rating scale (HAM-D, 21 items) as appropriate. Venous blood samples were collected from all participants prior to initiation of psychotropic medications. Serum CRP levels were estimated using standardized immunoassay techniques. CRP levels were categorized as normal (≤5 mg/l) or elevated (>5 mg/l).

Statistical analysis

Data were analyzed using GraphPad Instat version 3.1 (GraphPad Software Inc., San Diego, CA, USA). Descriptive statistics were used for sociodemographic and clinical variables. Pearson correlation coefficient was used to evaluate the relationship between serum CRP levels and severity scores (YMRS and HAM-D). A two-tailed p value <0.05 was considered statistically significant and exact p values were reported.

RESULTS

Socio-demographic characteristics

A total of 30 patients with bipolar disorder were included in the study. Among these, majority of patients, i.e., 36.7% belonged to the age group of 26-35 years. The gender distribution was equal with 15 male and 15 female participants. Majority of the participants belonged to rural areas (60%), while 40% belonged to urban areas. Educational status varied among participants with secondary level education being the most common (33.4%). Additionally, 63.3% participants were married, while 30.0% were unmarried and 6.7% were either separated or widowed (Table 1).

Table 1: Sociodemographic profile of patients with bipolar disorder (n=30).

Variables	Categories	Number	Percentage
Age (years)	18-25	6	20.0
	26-35	11	36.7
	36-45	8	26.7
	46-60	5	16.6
Sex	Male	15	50.0
	Female	15	50.0
Residence	Rural	18	60.0
	Urban	12	40.0
Education	Illiterate	4	13.3
	Primary	7	23.3
	Secondary	10	33.4
	Graduate and above	9	30.0
Marital status	Married	19	63.3
	Unmarried	9	30.0
	Separated/Widowed	2	6.7

Distribution and severity of mood episodes

An equal proportion of participants were assessed during manic episodes (n=15, 50%) and depressive episodes (n=15, 50%).

Among patients with mania (n=15), severity assessment using YMRS revealed that highest proportion of patients had moderate mania (46.7%, n=7), followed by mild (33.3%, n=5) and severe (20.0%, n=3).

Similarly, among patients assessed during depressive episodes (n=15), HAM-D score categorization showed that majority of the patients had moderate depression (46.7%, n=7), followed by severe (40.0%, n=6) and mild (13.3%, n=2).

Serum c-reactive protein levels

Among the 30 participants, elevated CRP levels were observed in 14 participants (46.7%), while 16 had normal CRP levels (53.3%). Of the elevated levels, 66.67% of participants were manic patients with mean CRP level of 17.82±16.38 mg/l, whereas 33.3% were depressive episode patients with mean CRP level of 9.80±8.14 mg/l.

A wider variability in CRP levels was observed among manic patients, as indicated by the larger standard deviation.

Correlation between mood episode severity and CRP levels

Correlation analysis was performed to evaluate the relationship between symptom severity and CRP levels, which revealed a statistically significant positive correlation between YMRS scores and serum CRP levels in the patients with mania episodes indicating that a higher manic symptom severity was associated with increased systemic inflammation. Whereas no statistically significant correlation was observed between HAM-D scores and serum CRP levels in depressive episode patients (refer Table 2). This indicates that serum CRP levels were not associated with depressive symptom severity.

Table 2: Correlation between mood episode severity scores and serum CRP levels.

Severity score comparison	Pearson's r	P value
YMRS versus CRP	0.5622	0.0292*
HAM-D versus CRP	-0.1672	0.5515

*Statistically significant.

DISCUSSION

The present study examined the association between serum c-reactive protein (CRP) levels and the severity of mood episodes in patients with bipolar disorder. This study was exploratory and hypothesis-generating. Findings of this study demonstrated a significant positive correlation between manic symptom severity and CRP levels, whereas depressive symptom severity did not show a statistically significant association. These results support the growing body of evidence suggesting a role of inflammatory processes in the pathophysiology of bipolar disorder, particularly during manic episodes.

CRP levels in mania versus depression

In this study, the mean CRP level during manic episodes was 17.82±16.38 mg/l, whereas during depressive episodes it was 9.80±8.14 mg/l. This nearly two-fold increase suggests a higher systemic inflammatory burden during mania. The result aligns with prior research by Ortiz-Domínguez et al.[5] which reported mean CRP levels

of 15.8 mg/l in manic patients compared to 8.5 mg/l in depressive episodes, closely mirroring our findings.

Collectively these findings support the hypothesis that mania may be associated with a heightened immune-inflammatory state. This suggests that inflammatory processes may function as state-dependent biological markers, reflecting the acute phase of illness rather than a trait marker of bipolar disorder.

Correlation between symptom severity and CRP levels

The present study demonstrated a statistically significant positive correlation between YMRS scores and CRP levels ($r=0.5622$, $p=0.0292$), indicating that a higher manic severity is associated with increased systemic inflammation. This could suggest that patients experiencing severe manic symptoms are at greater risk of inflammatory comorbidities such as cardiovascular events.

Conversely, depressive severity, as measured by HAM-D scores, did not show any significant correlation with CRP levels ($r=-0.1672$, $p=0.5515$). This finding is consistent with previous literature, Rosenblat and McIntyre which noted that CRP levels during bipolar depression are more variable, with some patients showing mild elevation while others showing levels comparable to euthymic patients, suggesting heterogeneity in inflammatory involvement in depressive states.[8]

Comparison with previous Indian studies

Data from Indian populations remain limited. A hospital-based study conducted in South India reported mean CRP levels of 18.2±14.6 mg/l during mania and 10.2±8.9 mg/l during depression among 40 patients which closely aligns with the present study's results.[6] This consistency between studies reinforces the relevance of systemic inflammation in the clinical presentation of mania among Indian patients and highlights the importance of evaluating inflammatory biomarkers within diverse population settings.

Clinical implications

The significant correlation between manic severity and CRP levels suggests several potential clinical implications. Elevated serum CRP levels may serve as a supplementary biomarker for identifying patients at risk of severe manic episodes. In addition, increased inflammatory burden may help identify individuals at higher risk of cardiometabolic complications, which are known to be prevalent among patients with bipolar disorders. In the present study, nearly two-thirds of patients had substantial symptom burden, which corresponded with high mean CRP levels, further supporting this association.

Furthermore, these findings serve as supportive evidence to the emerging interest in anti-inflammatory therapeutic strategies as adjunctive treatment options in bipolar disorder.

The present study contributes to the limited body of research examining inflammatory biomarkers in bipolar disorder within the north-east Indian population. The use of standardized diagnostic criteria and validated rating scales enhances the reliability of clinical assessment. Additionally, inclusion of both manic and depressive episodes allows for comparative evaluation of inflammatory patterns across different mood states.

Several limitations should be considered while interpreting the findings. The relatively small sample size limits statistical power and generalizability of results. The cross-sectional design restricts the ability to establish causal relationships between inflammatory markers and mood episode severity. Assessment of only a single inflammatory marker may not fully capture the complex immune dysregulation associated with bipolar disorder. Furthermore, the absence of longitudinal follow-up limits understanding of dynamic inflammatory changes across the illness course.

Future research directions

Future studies with larger sample sizes and longitudinal designs are required to further clarify the temporal relationship between inflammatory markers and mood episode progression. Inclusion of multiple inflammatory biomarkers and evaluation of treatment response may provide deeper insights into the role of immune dysregulation in bipolar disorder. Such studies may help establish inflammation-based biomarkers for disease monitoring and therapeutic stratification.

CONCLUSION

The severity of manic symptoms in bipolar disorder is positively associated with systemic inflammation as indicated by serum c-reactive protein levels. No significant association was observed between depressive symptom severity and CRP levels. These findings support inflammation as a state-dependent biomarker of mania. Future longitudinal studies are required to explore the role of inflammatory markers as potential therapeutic targets.

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