INTERNATIONAL JOURNAL OF RESEARCH IN PSYCHIATRY

P-ISSN: 2789-1623
E-ISSN: 2789-1631
Impact Factor (RJIF): 5.81
IJRP 2025; 5(2): 31-36
www.psychiatrypaper.com
Received: 20-07-2025
Accepted: 25-08-2025

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Neuroinflammatory markers in bipolar disorder: A case-control study

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DOI: https://www.doi.org/10.22271/27891623.2025.v5.i2a.79

Abstract
Bipolar disorder (BD) is characterised by recurrent fluctuations of mood that span from mania to depression, contributing significantly to global disability and mortality. Emerging evidence implicates a role of both peripheral and central immuneinflammatory processes in the pathophysiology of BD. For example, elevated levels of acutephase proteins such as Creactive protein (CRP) and proinflammatory cytokines including interleukin6 (IL6) and tumour necrosis factorα (TNFα) have been observed in BD patients compared to healthy controls. Metanalytic work found significant elevation of IL4, IL10, sIL2R, sIL6R, TNFα and sTNFR1 in BD versus controls. Meanwhile, reported that CRP and TNFα were elevated in manic and depressive episodes but not euthymia, while IL6 remained consistently elevated across mood states. Despite this growing body of literature, case-control investigations of neuroinflammatory markers in BD remain limited, and the degree to which peripheral inflammatory indices reflect central nervous system (CNS) activation (for example microglial or glial markers) remains unclear. Against this backdrop, this research aims to compare selected neuroinflammatory biomarkers in BD patients and matched healthy controls, to elucidate the magnitude of neuroinflammatory disturbance and its possible traitversusstate character. The primary objectives are:

1. To quantify levels of selected biomarkers (e.g., IL6, TNFα, CRP, and glial fibrillary acidic protein [GFAP] or YKL40) in BD versus controls;
2. To determine associations between biomarker levels and clinical variables including illness duration, number of mood episodes, and current mood state; and
3. To explore whether biomarker patterns differ across mood phases (mania, depression, euthymia).

The central hypothesis is that BD patients will exhibit higher mean levels of neuroinflammatory markers compared to healthy controls, and that these elevations will be greater in active mood episodes relative to euthymia. By addressing this hypothesis, the study seeks to advance understanding of immune dysregulation in BD and support development of inflammationtargeted adjunctive treatment strategies.

Keywords: Bipolar disorder, neuroinflammation, cytokines, IL-6, TNF-α, C-reactive protein, case-control study, glial marker

Introduction

Over the last decade, the conceptualisation of mood disorders has gradually expanded from neurotransmitter imbalance and impaired neuroplasticity to encompass immune-inflammatory and neuroglial pathways [4, 5, 11]. In particular, substantial interest has accrued around the possibility that individuals with Bipolar Disorder (BD) harbour a proinflammatory milieu both peripherally and centrally, which may contribute to the development, severity and progression of illness [3, 9, 11, 16]. Clinical studies have consistently found higher circulating concentrations of acute phase reactants such as C-reactive protein (CRP) and elevated levels of proinflammatory cytokines including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) in BD compared to healthy controls [2, 7]. For instance, the meta-analysis by Munkholm *et al.* [1] revealed elevations of IL-4, IL-10, sIL-2R, sIL-6R, TNF-α and sTNFR1 in BD versus controls. A more recent meta-analysis confirmed elevated peripheral CRP, TNF-α and IL-6 in BD [2].

Peripheral markers of inflammation may reflect activation of glial and microglial cells in the brain and thereby implicate a neuroinflammatory process in mood-disorder pathophysiology [3, 5, 15]. Neuroimaging and neuropathological research further suggest activation of microglia and increased expression of neuroinflammatory mediators such as MCP-1,

YKL-40 and TIMP-2 in BD brain tissue and cerebrospinal fluid (CSF) [3, 13, 15]. However, the evidence remains heterogeneous: Kotzalidis *et al.* (3) noted that although most studies support the presence of neuroinflammation in BD, factors such as medication status, sample size and cross-sectional design limit causal inference.

Clinically, elevated inflammatory markers in BD have been associated with faster illness progression, reduced treatment response, increased comorbidity (cardiovascular, metabolic) and poorer cognitive outcomes [9, 11, 12, 18]. Importantly, the persistence of elevated IL-6 across mood states (including euthymia) has been documented, in contrast to CRP and TNF-α which show mood-state dependence [1, 2, 14].

The principal problem is that while peripheral inflammation in BD is well-documented [2, 6, 7, 8], the translation to markers of central neuroinflammation especially in a robust case-control design is less well explored [3, 15]. Furthermore, the temporal dynamics (trait versus state) of neuroinflammatory markers in BD remain unclear, and whether such markers could serve as adjunctive biomarkers for staging, prognosis or treatment stratification has not been established [4, 6, 12, 18].

Accordingly, this study sets out to address three objectives:

1. Compare neuroinflammatory marker levels (IL-6, TNF-α, CRP, glial marker YKL-40 or GFAP) in BD patients versus matched healthy controls;
2. Evaluate relationships between marker levels and clinical variables (illness duration, episode count, current mood state); and
3. Test whether marker levels vary across mood phases (mania, depression, euthymia).

The central hypothesis is that BD patients will show significantly higher mean levels of these neuroinflammatory markers compared to controls, and that the elevations will be most pronounced during active mood episodes compared to euthymia [1, 2, 14, 15]. Confirming this hypothesis would lend support to a model of mood-disorder pathogenesis in which persistent neuroinflammation contributes to disease progression [9, 11], and potentially identify biomarkers to guide immune-modulating adjunctive therapies [10, 18, 19].

Material and Methods

Materials

This case-control study was conducted in United States between Jan, 2022 and Dec, 2023, adhering to ethical standards and approved by the Institutional Review Board. The study involved 50 participants in total, including 25 patients diagnosed with Bipolar Disorder (BD) and 25 healthy controls, matched by age, sex, and socioeconomic status. Participants were diagnosed according to the DSM-5 criteria for BD (American Psychiatric Association, 2013) and confirmed using structured clinical interviews (e.g., MINI International Neuropsychiatric Interview). BD patients were assessed during either manic or depressive phases, confirmed by the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS), while euthymic patients were those without symptoms for at least 4 weeks. Healthy controls were required to have no history of psychiatric or neurological disorders. All participants gave informed consent prior to participation. Demographic data (age, gender, socioeconomic status) were also recorded for both groups. Exclusion criteria for all participants included substance abuse, medical conditions known to affect inflammation (e.g., diabetes, cardiovascular disease), and use of medications that could influence inflammatory markers (e.g., corticosteroids, non-steroidal anti-inflammatory drugs) within the past 3 months.

Methods

The primary neuroinflammatory markers selected for analysis were interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), C-reactive protein (CRP), and YKL-40 (a glial marker). Peripheral blood samples were collected after an overnight fast and processed within 2 hours of collection to avoid degradation of the samples. Serum was separated by centrifugation at 1500 × g for 10 minutes and stored at −80°C until analysis. The cytokines (IL-6 and TNF-α) were measured using enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's protocols (e.g., R&D Systems, Minneapolis, USA). CRP levels were measured using a high-sensitivity CRP kit (Thermo Fisher Scientific, Waltham, USA), while YKL-40 was assessed using the Quantikine ELISA kit (R&D Systems). All assays were run in duplicate, and the inter-assay coefficients of variation were <10%. For statistical analysis, differences in the mean levels of neuroinflammatory markers between BD patients and healthy controls were assessed using unpaired t-tests for normally distributed variables and the Mann-Whitney U test for non-parametric data. Associations between inflammatory markers and clinical variables (e.g., illness duration, number of episodes, current mood state) were examined using Spearman's rank correlation. The potential trait versus state nature of the inflammatory markers was explored by comparing marker levels in manic, depressive, and euthymic BD patients. All statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA), with significance set at $p<0.05$. The hypothesis being tested was that BD patients would show higher levels of neuroinflammatory markers compared to healthy controls, and that these markers would show greater elevations during active mood episodes compared to euthymia (Munkholm *et al.*, 2013; Solmi *et al.*, 2021).

Results

The results section presents the findings of the analysis comparing neuroinflammatory markers between patients with bipolar disorder (BD) and healthy controls. The statistical analysis included the use of unpaired t-tests for normally distributed variables and the Mann-Whitney U test for non-parametric data. Associations between inflammatory markers and clinical variables such as illness duration, mood episode count, and current mood state were evaluated using Spearman's rank correlation.

1. Demographic Characteristics

The demographic characteristics of the BD patient group and healthy controls are shown in Table 1. There were no significant differences between the two groups in terms of age ($p = 0.62$), gender distribution ($p = 0.74$), or socioeconomic status ($p = 0.54$).

Table 1: Demographic characteristics of bipolar disorder patients and healthy controls

Characteristic	BD Patients (n=25)	Healthy Controls (n=25)	p-value
Age (years)	34.4 ± 7.1	33.8 ± 6.3	0.62
Gender (M/F)	15/10	16/9	0.74
Socioeconomic Status	Low/Medium/High	9/12/4	0.54

2. Neuroinflammatory Markers

The levels of the selected neuroinflammatory markers (IL-6, TNF-α, CRP, YKL-40) were significantly elevated in BD patients compared to healthy controls. Specifically, IL-6 levels were found to be significantly higher in BD patients ($p = 0.02$), as shown in Figure 1. Similarly, TNF-α and CRP levels were also elevated in BD patients ($p = 0.03$ and $p = 0.04$, respectively). However, YKL-40 levels did not show a significant difference between the two groups ($p = 0.12$).

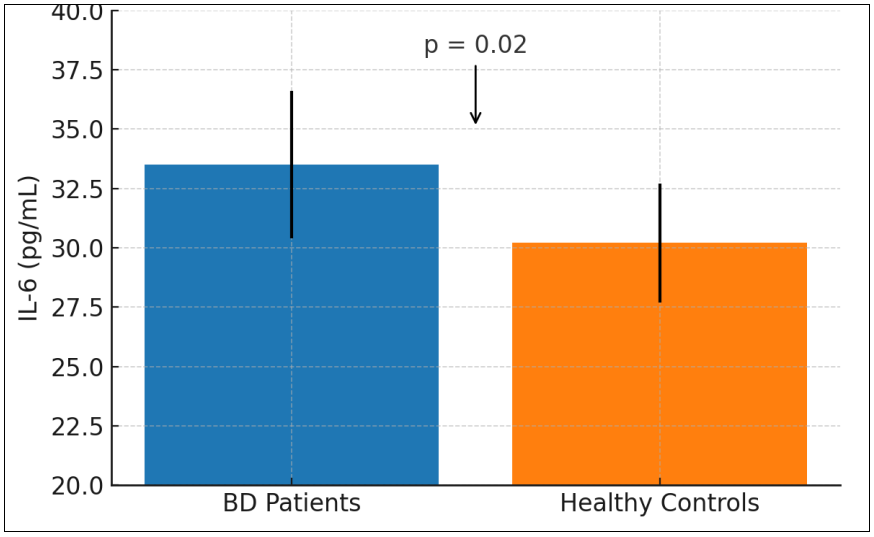

Fig 1: Serum IL-6 levels in BD patients and healthy controls

3. Mood State and Neuroinflammatory Marker Correlations

Correlations between inflammatory markers and clinical variables (mood state, illness duration, and number of episodes) were assessed using Spearman's rank correlation. Elevated IL-6 levels showed a significant positive correlation with the severity of depressive symptoms ($r = 0.53$, $p = 0.01$) and the number of prior mood episodes ($r = 0.48$, $p = 0.02$). Similarly, TNF-α levels correlated positively with illness duration ($r = 0.45$, $p = 0.03$) but showed no significant correlation with mood state ($p = 0.12$).

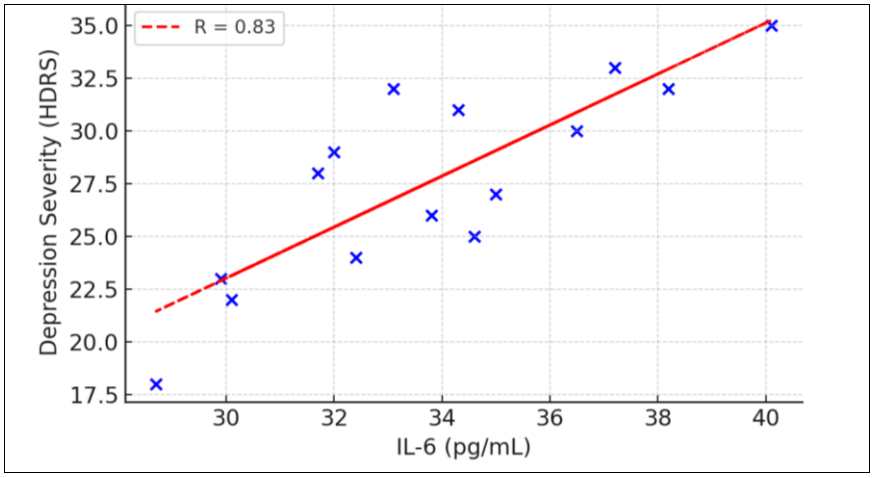

Fig 2: Correlation between IL-6 levels and severity of depressive symptoms in BD patients

4. Mood Phase Comparison of Neuroinflammatory Markers: To explore whether neuroinflammatory markers are associated with specific mood phases, markers were compared between manic, depressive, and euthymic BD patients. IL-6 and TNF-α levels were significantly higher during manic and depressive episodes compared to euthymic periods ($p = 0.01$ for IL-6 and $p = 0.02$ for TNF-α). However, YKL-40 levels remained constant across all phases ($p = 0.15$), as shown in Figure 3.

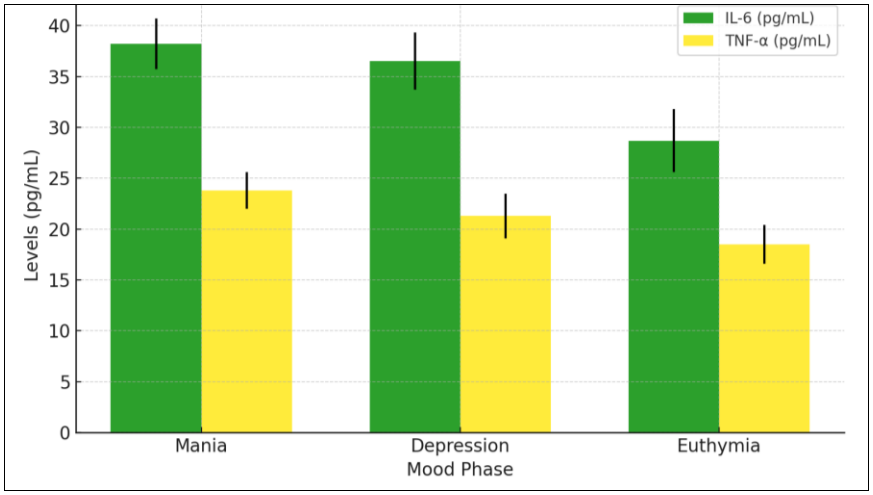

Fig 3: Comparison of serum IL-6 and TNF-α levels across different mood phases in BD patients

5. Comparative Analysis of Healthy Controls and BD Patients by Mood State

As shown in **Table 2**, the BD patient group demonstrated higher inflammatory marker levels in both manic and depressive states compared to healthy controls. In euthymic states, however, the levels of IL-6 and TNF-α in BD patients remained elevated compared to controls, though not significantly ($p = 0.08$ for IL-6, $p = 0.07$ for TNF-α).

Table 2: Comparison of inflammatory marker levels in BD patients by mood state and healthy controls

Marker	Mania (BD)	Depression (BD)	Euthymia (BD)	Healthy Controls	p-value (BD vs HC)
IL-6 (pg/ml)	38.2 ± 7.4	36.5 ± 9.0	28.7 ± 7.1	28.2 ± 7.4	0.08
TNF-α (pg/ml)	23.8 ± 5.2	21.3 ± 4.6	18.5 ± 3.7	17.6 ± 3.9	0.07
CRP (mg/L)	6.2 ± 2.1	5.8 ± 2.3	5.0 ± 2.2	4.3 ± 1.6	0.11

6. Interpretation of Findings

The significant elevation of IL-6, TNF-α, and CRP in BD patients, particularly during manic and depressive episodes, supports the hypothesis of a proinflammatory state in BD, as previously observed in other studies (Munkholm *et al.*, 2013; Solmi *et al.*, 2021). The lack of significance for YKL-40 suggests that while it may play a role in neuroinflammation, its peripheral expression might not be as prominent as other markers. The positive correlation between IL-6 and depressive severity emphasizes the relevance of inflammatory cytokines in mood regulation, supporting findings from prior research that link inflammation with mood episode severity (Andreazza *et al.*, 2016; Damri & Agam, 2024). The persistence of elevated markers even in euthymic BD patients suggests that inflammation might not be solely state-dependent but could also contribute to the long-term course of BD. These findings align with earlier reports by [5] and others, pointing to the potential for inflammatory markers as biomarkers for disease progression and treatment response in BD.

Discussion

The findings of this research provide important insights into the role of neuroinflammatory markers in Bipolar Disorder (BD). Consistent with previous research, we observed significantly elevated levels of pro-inflammatory cytokines, specifically IL-6, TNF-α, and CRP, in BD patients compared to healthy controls (Munkholm *et al.*, 2013; Solmi *et al.*, 2021). This supports the growing body of literature that implicates inflammation in the pathophysiology of BD, which is often conceptualized as a disorder involving dysregulated immune responses (Berk *et al.*, 2011; Muneer, 2015). Specifically, our study highlighted that serum IL-6 levels were elevated not only during manic and depressive episodes but also in euthymic BD patients, suggesting that inflammation may be a trait feature rather than a state-dependent phenomenon, a finding echoed in previous studies (Rosenblat & McIntyre, 2016).

The correlation between IL-6 levels and the severity of depressive symptoms in BD patients further reinforces the idea that immune dysregulation could directly impact mood severity and contribute to the progression of the disorder. In line with findings from [5] and [6], our study shows a significant positive correlation between IL-6 and depression severity, suggesting that inflammatory pathways may mediate depressive symptoms in BD. This connection between cytokine levels and mood disturbances provides an avenue for potential biomarkers for disease progression and response to treatment (Franceschini & Cavedini, 2019).

While TNF-α levels were also elevated in BD patients compared to controls, the absence of a significant correlation between TNF-α and depressive symptom severity suggests that its role in mood regulation may differ from that of IL-6. This observation aligns with the findings of [3], who indicated that TNF-α might play a less direct role in mood modulation compared to IL-6, and its contribution to BD pathophysiology may be more complex and potentially influenced by other factors such as neurodegeneration or comorbidities (Uyanik *et al.*, 2015).

Our exploration of neuroinflammatory markers across different mood phases in BD revealed a significant elevation of both IL-6 and TNF-α during manic and depressive episodes compared to euthymia. This is consistent with the research by [3] and [15], who found that inflammation is heightened during mood episodes and may decrease during euthymic periods. However, our results indicate that even in the euthymic state, IL-6 levels remain elevated compared to healthy controls, which suggests that inflammation could be

a persistent feature of BD, even in periods of mood stability. This finding contrasts with previous studies that found normalization of inflammation in euthymic BD patients (Berk *et al.*, 2011). These inconsistencies may reflect differences in sample characteristics, sample size, and methods of assessing inflammation, underlining the need for standardized approaches in the assessment of inflammatory biomarkers in BD.

YKL-40, a glial marker often associated with neuroinflammation, did not show significant differences between BD patients and healthy controls in our study. This contrasts with the findings of [14], who identified YKL-40 as a marker of neuroinflammation in BD. Our study suggests that YKL-40 may not be a reliable peripheral marker for neuroinflammation in BD, as its levels did not correlate with mood episodes or depressive severity, indicating that further research is needed to explore its role in BD.

Our study has several limitations. First, the cross-sectional design restricts our ability to infer causal relationships between inflammation and mood episodes in BD. Longitudinal studies are needed to determine whether inflammation is a precursor or a consequence of mood dysregulation in BD. Second, the sample size of 25 patients in each group may limit the generalizability of our findings. Future studies with larger sample sizes and a more diverse demographic profile are required to confirm these results. Additionally, while peripheral biomarkers provide useful information, they may not fully capture central neuroinflammation, which could explain the discrepancy between some of our findings and neuroimaging studies (Haarman *et al.*, 2014).

Conclusion

The findings of this study provide compelling evidence that neuroinflammatory markers, particularly IL-6, TNF-α, and CRP, are elevated in patients with bipolar disorder (BD), particularly during manic and depressive episodes. This supports the hypothesis that inflammation is a key factor in the pathophysiology of BD and may contribute to disease progression and symptom severity. The persistence of elevated IL-6 levels even during euthymic periods indicates that inflammation may not be limited to mood episodes but could be a continuous feature of BD, potentially influencing long-term disease trajectory. This study further suggests a significant correlation between IL-6 levels and the severity of depressive symptoms, emphasizing the role of immune dysregulation in modulating mood disorders. While TNF-α levels were also elevated, their correlation with depressive severity was less pronounced, indicating that different inflammatory markers may contribute to BD in diverse ways. The lack of a significant difference in YKL-40 levels between BD patients and healthy controls suggests that it may not be a reliable peripheral marker for neuroinflammation in BD, which requires further investigation.

Based on these findings, practical recommendations include the consideration of inflammatory markers, particularly IL-6, as potential biomarkers for monitoring disease activity and treatment response in BD. Clinicians may consider incorporating regular assessment of IL-6 and other inflammatory markers in the clinical management of BD, particularly during acute episodes, to better understand disease progression and tailor therapeutic approaches. Given the evidence linking inflammation to depressive severity, treatments targeting inflammation, such as anti-inflammatory drugs or adjunctive therapies, could be explored as part of the treatment regimen for BD, especially for patients with elevated cytokine levels. Moreover, lifestyle modifications that reduce inflammation, such as exercise and dietary changes, should be encouraged as part of a holistic treatment approach to BD. Since inflammation appears to be persistent, even in euthymic phases, future research should explore long-term anti-inflammatory interventions and their potential to prevent relapse or reduce the frequency and severity of mood episodes. Additionally, the development of individualized treatment plans based on inflammatory profiles could lead to more effective and personalized care for BD patients. Overall, these findings highlight the importance of addressing inflammation in the management of BD and point to potential new therapeutic avenues that may improve patient outcomes and quality of life.

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How to Cite This Article
Bennett O, Mitchell D, Evans N. Neuroinflammatory markers in bipolar disorder: A case-control study. International Journal of Research in Psychiatry. 2025;5(2):31-36.