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Inflammatory and Neurodegenerative Biomarkers in Bipolar I Disorder: A Cross-Sectional Study

İlker Taşdemir[1], **Sibel Çakır**[2]

[1]*Department of Psychiatry, Medipol University Faculty of Medicine, İstanbul, Türkiye*
[2]*Bahçeşehir University Faculty of Medicine, İstanbul, Türkiye*

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- *Bipolar disorder involves not only mood instability but also immune dysregulation, glial dysfunction, and neuroprogressive changes.*
- *Biomarkers such as IL-6, TNF-α, IL-1RA, S100B, and NSE have been investigated in this context.*
- *Findings remain inconsistent, and simultaneous evaluation across mood states is limited.*

WHAT THIS STUDY ADDS ON THIS TOPIC?

- *This study shows that IL-6 is consistently elevated in bipolar I disorder, independent of mood state.*
- *IL-6 levels correlate with clinical severity, supporting its role as a potential trait-like biomarker.*
- *Decreases in TNF-α, IL-1RA, S100B, and NSE suggest chronic neurobiological alterations related to illness progression or treatment.*

Corresponding author:
İlker Taşdemir

E-mail:
tasdemirilker@yahoo.com

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ABSTRACT

Objective: Bipolar disorder (BD) is increasingly recognized as a systemic illness involving chronic inflammation, glial dysfunction, and neuronal dysregulation in addition to mood instability. Recent studies have suggested that biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 receptor antagonist (IL-1RA), S100B, and neuron-specific enolase (NSE) may reflect underlying pathophysiological processes in BD. However, findings remain inconsistent, particularly across mood states. This study aimed to investigate serum levels of IL-6, TNF-α, IL-1RA, S100B, and NSE in patients with bipolar I disorder (BD-I) across euthymic, manic, and depressive phases, and to compare them with healthy controls. Additionally, correlations between biomarker levels and clinical symptom severity were examined.

Methods: Serum levels were measured in 77 patients with BD-I (50 euthymic, 20 manic, and 7 depressed) and 50 healthy controls. Correlations were assessed between these levels and the Young Mania Rating Scale (YMRS), the Montgomery–Åsberg Depression Rating Scale, the Clinical Global Impressions-Severity Scale (CGI-S), and the Positive and Negative Syndrome Scale (PANSS)–positive symptoms subscale, as well as other clinical variables.

Results: Indicating a trait-like inflammatory profile, IL-6 levels were considerably higher in the BD group and had a positive correlation with YMRS, PANSS, and CGI scores. Conversely, levels of IL-1RA, TNF-α, S100B, and NSE were markedly decreased in patients. NSE levels exhibited an inverse connection with clinical severity, potentially signifying neuroprogressive alterations.

Conclusion: The findings support the role of IL-6 as a state-independent inflammatory marker in BD, while reductions in NSE may reflect chronic neurobiological dysregulation. These findings may have implications for biomarker-guided monitoring or treatment stratification in BD. Further research is warranted to determine whether these biomarkers can serve as reliable indicators of disease progression, treatment response, and mood state in clinical settings.

Keywords: Bipolar disorder, IL-6, inflammation, neurodegeneration, NSE, trait biomarker

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INTRODUCTION

Bipolar disorder (BD) is a relatively common and severe psychiatric illness, with an estimated lifetime prevalence of approximately 1%, and ranks among the top 10 causes of disability worldwide.[1] While historically understood as a disorder of neurotransmitter dysregulation, recent evidence suggests that BD is also characterized by chronic low-grade inflammation, glial dysfunction, and alterations in neuronal energy metabolism.[2,3] These processes contribute to the neuroprogressive nature of BD, marked by cognitive decline, increased episode frequency, and treatment resistance over time.[2]

Inflammation plays a pivotal role in BD pathophysiology. Pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 receptor antagonist (IL-1RA), are implicated in modulating immune responses and neuronal signaling.[3] Among inflammatory markers, IL-6 has received particular attention due to its central role in mediating pro-inflammatory responses. A recent meta-analysis emphasized that IL-6 levels are not only elevated during acute mood episodes but also remain persistently high during euthymic states, indicating its potential as a trait biomarker for BD.[4] In contrast, TNF-α has been found to increase during manic and depressive episodes but not during euthymia.[5] Similarly, IL-1RA appears to rise selectively during manic phases, with no consistent changes observed in other mood states.[5] These inflammatory markers may reflect systemic immune dysregulation that exacerbates mood instability and neuronal stress.

Neurodegenerative processes in BD are evidenced by alterations in glial and neuronal markers. S100B is a calcium-binding protein predominantly expressed in astrocytes and oligodendrocytes and is widely considered a marker of glial activity and integrity. Following glial cell damage, S100B can leak into the extracellular space and cross the blood–brain barrier, leading to increased serum levels.[6] Elevated S100B levels have therefore been proposed as a peripheral indicator of central nervous system injury.[7] Although inter-study variability exists, a 2020 meta-analysis reported that S100B levels are generally higher in individuals with BD compared to healthy controls.[8]

A glycolytic isoenzyme present in neurons and neuroendocrine cells, neuron-specific enolase (NSE) is believed to be involved in neurodegeneration, neuroinflammation, and neuroprotection.[9] A meta-analysis conducted in 2020 found no significant difference in NSE levels between patients with BD and healthy individuals, although several individual studies included in the analysis reported decreased NSE levels in the patient group.[8] Investigating peripheral abnormalities in S100B and NSE may provide insight into glial and neuronal dysfunction in BD, particularly in relation to illness progression and treatment effects.

Despite the growing interest in inflammatory and neurodegenerative mechanisms in BD, results across studies remain inconsistent, and there is a paucity of research that simultaneously evaluates both inflammatory and neurobiological markers across different mood states. Furthermore, few studies have explored how these biomarkers relate to clinical symptom severity.

The interplay between inflammation and neurodegeneration in BD is complex, with cytokines potentially exacerbating glial and neuronal damage, while glial dysfunction may amplify inflammatory responses.[2,3] Studying IL-6, TNF-α, IL-1RA, S100B, and NSE together offers a unique opportunity to capture both immune and neurobiological dimensions of BD pathophysiology. This integrative approach addresses a critical gap in the literature, as most studies focus on either inflammatory or neurodegenerative markers in isolation, with limited exploration of their combined roles across mood states (euthymic, manic, depressive) or their associations with clinical symptom severity.

This study aimed to evaluate serum levels of IL-6, TNF-α, IL-1RA, S100B, and NSE in patients with bipolar I disorder (BD-I) across euthymic, manic, and depressive phases, compared to healthy controls. By examining these biomarkers simultaneously, it was sought to elucidate their individual and collective contributions to BD pathophysiology, assess their stability across mood states, and explore their correlations with clinical symptom severity, as measured by the Young Mania Rating Scale (YMRS), Montgomery–Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions-Severity Scale (CGI-S), and Positive and Negative Syndrome Scale (PANSS) positive symptoms subscale. It was hypothesized that IL-6 would be elevated across all mood states, reflecting a trait-like inflammatory profile, while TNF-α, IL-1RA, S100B, and NSE would show mood- or treatment-dependent variations, with significant associations to clinical severity.

MATERIAL AND METHODS

Participants

The present study included 77 patients diagnosed with BD-I based on (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) DSM-IV-TR criteria, as well as 50 healthy controls. The patient group was aged between 18 and 65 years, had no psychiatric comorbidities or neurodegenerative diseases, were not using immunomodulatory medications, and had known clinical characteristics and treatment responses. All patients had been followed prospectively for at least 2 years in accordance with a lifetime follow-up chart.

Exclusion criteria included medical conditions affecting immune responses (e.g., autoimmune disorders, infections), use of immunosuppressive agents (e.g., corticosteroids, NSAIDs [Nonsteroidal Anti-Inflammatory Drug]), pregnancy, breastfeeding, intellectual disability, dementia, epilepsy, traumatic brain injury, organic mental disorders, or substance abuse/dependence. The control group consisted of 50 age- and sex-matched healthy volunteers with no current or past psychiatric diagnoses, confirmed via Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) (SCID).

The patients included in the study were recruited from the Mood Disorders Unit, psychiatry general outpatient clinic, and psychiatry service of the Department of Psychiatry, İstanbul University, İstanbul Faculty of Medicine, between June 2013 and May 2014.

Psychiatric Assessment and Clinical Scales

After the participants were informed about the study, those who agreed to participate were given an informed consent form before starting the study. After the psychiatric interview, YMRS, Montgomery–Asberg Depression Rating Scale, PANSS positive, and Clinical Global Impression Scale (CGI) were administered. Patients' clinical variables and Lifetime Follow-up Schedules for treatment response were evaluated. A detailed history of internal, neurologic, and immunologic diseases was taken from the patients and healthy

controls, and those with diseases that may affect the immune system were excluded. The healthy control group underwent SCID (DSM-IV) to evaluate psychiatric diseases, and those with psychiatric diagnoses were excluded.

Venous Blood Collection and Enzyme-Linked Immunosorbent Assay–Based Serum Assays

Venous blood samples (10 mL) were collected from all participants between 8:00 AM and 10:00 AM to minimize circadian variations, using vacutainer tubes with ethylenediaminetetraacetic acid (EDTA) for plasma separation. Samples were centrifuged at 3000 rpm for 10 minutes within 30 minutes of collection, and plasma was stored at –80°C until analysis. Serum levels of IL-6, TNF-α, IL-1RA, S100B, and NSE were measured using enzyme-linked immunosorbent assay kits (IL-6, TNF-α: [Assaypro]; IL-1RA, S100B: [Hangzhou EastBiopharm]; NSE: [DRG Diagnostics]). Assays were performed according to manufacturer protocols. All measurements were conducted in duplicate, and mean values were used for analysis.

Ethics Committee Approval Date and Number

This study was approved by the Ethics Committee of İstanbul University Faculty of Medicine Clinical Research Ethics Committee at its meeting dated March 8, 2013 and numbered 273 and found to be in accordance with ethical values. Written informed consent was obtained from the individuals who participated in this study.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). The normality of numerical variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables are reported as means ± SDs, while non-normally distributed variables are presented as medians (minimum-maximum).

Age differences between the BD-I and control groups were analyzed using Student's *t*-test, and sex distribution was compared using the chi-square test. Within the BD-I group, age differences across episode subgroups (euthymic, manic, depressive) were examined using one-way ANOVA, while non-normally distributed clinical variables (e.g., duration of illness, number of episodes) and biomarker levels were compared using the Kruskal–Wallis test. Comparisons of biomarker levels between the BD-I and control groups were performed using the Mann–Whitney *U* test. These non-parametric tests were specifically chosen to accommodate the small sample size of the depressive group (n = 7), ensuring robust statistical comparisons despite limited statistical power. Pairwise comparisons between episode subgroups and the control group were adjusted for multiple testing using the Bonferroni correction.

Correlations between biomarker levels and clinical scale scores (Young Mania Rating Scale, Montgomery–Åsberg Depression Rating Scale, Clinical Global Impressions-Severity Scale, and PANSS positive subscale) were evaluated using Spearman's rho correlation coefficient. All analyses were conducted using SPSS version 22.0, with a significance threshold of $P < .05$.

RESULTS

Demographic Profiles

The study comprised 77 patients diagnosed with BD-I. Of these patients, 50 (64.9%) were in a euthymic state, 20 (26.0%) were experiencing a manic episode, and 7 (9.1%) were in a depressed episode.

Table 1. Sociodemographic Characteristics of the Bipolar I Disorder and Control Groups

Variable	BD-I (n = 77) Mean (SD)	Control (n = 50) Mean (SD)	*t* (df) / χ^2	*P*
Age	37.8 (11.9)	35.9 (9.1)	–1 (121.7)	.315
	n (%)	**n (%)**	χ^2	***P***
Sex, n (%)			0.121	.727
Female	44 (57.1)	27 (54)		
Male	33 (42.9)	23 (46)		

Mean ± SD reported.
BD-I, bipolar I disorder; df, degrees of freedom; χ^2, chi-square statistic.

There were no statistically significant differences in age or sex between the patient and control groups (Table 1).

The average age of patients in the euthymic group was 40.04 ± 11.54 years, and their average years of educational attainment was 11.40 ± 3.71. Individuals in the manic episode cohort exhibited a mean age of 33.55 ± 10.84 years and an average educational attainment of 9.05 ± 3.27 years. For those in the depressive episode group, the mean age was 34.00 ± 14.75 years, and the mean years of education was 12.71 ± 3.73.

No statistically significant age difference was seen across the groups ($P > .05$). A statistically significant difference in years of education was observed among the groups ($\chi^2(2) = 7.71$; $P = .02$).

Clinical Characteristics and Symptom Severity Across Biploar Disorder I Episode Subgroups

To evaluate differences in clinical characteristics and symptom severity among BD-I episode subgroups (euthymic, manic, and depressive), variables including age at onset, duration of illness, maintenance treatment duration, number of episodes, hospitalizations, prevalence of psychotic episodes, and scores on clinical scales (PANSS positive, CGI, MADRS, YMRS) were assessed. Table 2 summarizes these comparisons, highlighting significant differences in illness duration, maintenance treatment duration, and symptom severity across episode subgroups.

Medication Use Among Patients

Medication regimens varied by episode status in patients with BD-I. Overall, 75% of BD-I patients (58/77) used antipsychotics, primarily in combination with mood stabilizers, while 90% (69/77) used mood stabilizers, either alone or in combination. In the euthymic group (n = 50), 54% (27/50) used antipsychotics (42% with a mood stabilizer, 12% in other combinations), and 84% (42/50) used mood stabilizers (32% monotherapy, 52% in combinations). In the manic group (n = 20), 80% (16/20) used antipsychotics (45% with a mood stabilizer, 35% in other combinations), and 65% (13/20) used mood stabilizers. In the depressive group (n = 7), 100% (7/7) used antipsychotics (71.4% with a mood stabilizer, 28.6% in other combinations), and 100% (7/7) used mood stabilizers. Additional regimens, mainly in the manic group, included antidepressants or benzodiazepines in combination with antipsychotics (15%, 3/20).

Relationship Between Clinical Characteristics and Cytokine Levels

With the exception of IL-6, the levels of inflammatory markers, S100B, and NSE were markedly reduced in the patient group relative to the control group (Table 3). Conversely, IL-6 levels were markedly elevated in patients compared to healthy controls.

Table 2. Clinical Characteristics and Scale Scores by Episode Groups

Variable	Episodes			χ^2 (df)	*P*
	Euthymic (n = 50) Median (Min-Max)	Manic (n = 20) Median (Min-Max)	Depressive (n = 7) Median (Min-Max)		
Age at onset	20.5 (13-46)	21 (10-45)	18 (15-43)	0.40 (2)	.82
Duration of illness (months)	150 (14-570)	102 (2-300)	60 (9-264)	6.38 (2)	**.04**
Duration of maintenance treatment (months)	96 (2-360)	35 (0-240)	48 (4-200)	8.61 (2)	**.01**
Total number of episodes	6 (1-40)	4 (1-20)	5 (2-10)	3.61 (2)	.17
Episodes per year	0.5 (0.17-2.40)	0.6 (0.2-7.20)	1 (0.33-2.67)	3.98 (2)	.14
Number of hospitalizations	3 (1-8)	3 (1-8)	2 (0-7)	0.82 (2)	.66
Psychotic episodes (%)	48 (0-100)	58 (0-100)	25 (0-100)	4.20 (2)	.12
PANSS positive	7 (0-10)	20.5 (7-33)	15 (7-20)	40.62 (2)	<.001
CGI	3 (2-7)	11 (4-16)	11 (10-14)	53.70 (2)	<.001
MADRS	4 (0-20)	4.5 (0-24)	30 (19-34)	18.95 (2)	<.001
YMRS	0 (0-9)	29.5 (5-38)	4 (0-29)	52.14 (2)	<.001

Data reported as median (minimum–maximum) due to non-normal distribution.
CGI, Clinical Global Impression; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS positive, Positive and Negative Syndrome Scale – Positive subscale; YMRS, Young Mania Rating Scale; χ^2 (df), chi-square (degrees of freedom).
Values in bold indicate statistically significant results ($P < 0.05$).

Table 3. Biomarker Levels in Bipolar I Disorder and Control Groups

Markers	BD-I (n = 77) Median (Min-Max)	Control (n = 50) Median (Min-Max)	*U*	*P*
IL-1RA, ng/L	197.4 (0-614.6)	392.3 (0-614.8)	2.572	.001
S100B, ng/L	414.1 (0-2241.8)	2169.7 (0-4411.4)	3.099	<.001
NSE, ng/mL	4.7 (0-39.9)	20.2 (0-35)	3.127	<.001
IL-6, ng/mL	0.4 (0.3-12.6)	0.3 (0.3-0.8)	1.810	<.001
TNF-α, ng/mL	0.2 (0.2-0.7)	0.5 (0.2-0.6)	3.368	<.001

BD-I, bipolar I disorder; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; NSE, neuron-specific enolase; TNF-α, tumor necrosis factor-alpha; U, Mann–Whitney *U*-test statistic.

Comparative Analysis of Patient Subgroups Compared to the Control Group

All pairwise comparisons between patient subgroups and the control group had their *P*-values adjusted for multiple testing. Statistically significant changes in S100B levels have been observed across each patient subgroup (euthymic, manic, and depressed) compared to the control group. Nonetheless, no substantial differences were detected across the patient subgroups.

A similar pattern was observed for NSE and IL-6 levels, with all patient subgroups significantly differing from controls but not from each other.

For TNF-α, significant differences were detected only between the euthymic and manic groups versus the control group.

No statistically significant differences were found in IL-1RA levels in any of the pairwise group comparisons (Table 4).

Correlation Between Cytokine Levels and Clinical Scale Scores

A statistically significant, although mild, negative connection was seen between NSE levels and both CGI and YMRS scores.

Interleukin-6 levels showed a positive correlation with all clinical scale scores except MADRS, and these correlations were statistically significant.

The correlation coefficients and significance levels are presented in Table 5.

DISCUSSION

This study aimed to evaluate serum levels of inflammatory (IL-6, TNF-α, IL-1RA) and neurodegenerative (S100B, NSE) biomarkers in patients with BD-I across euthymic (n = 50, 64.9%), manic (n = 20, 26.0%), and depressive (n = 7, 9.1%) mood states, compared to healthy controls (n = 50), and to explore their correlations with clinical symptom severity (YMRS, MADRS, CGI-S, PANSS positive). By examining these biomarkers simultaneously, it was sought to elucidate their contributions to BD-I pathophysiology, assess their stability across mood

Table 4. Biomarker Levels in Episode Subgroups

Biomarkers	Euthymic (n = 50) Median (Min-Max)	Manic (n = 20) Median (Min-Max)	Depressive (n = 7) Median (Min-Max)	Control (n = 50) Median (Min-Max)	χ^2 (df)	*P*
IL1RA, ng/L	202.5 (0-614.6)	194.7 (152.4-548.8)	184.8 (0-443.7)	392.3 (0-614.8)	11.1 (3)	.011
S100B, ng/L	433.4 (0-2241.8)	374.5 (119.9-1982.4)	410.2 (0-838.5)	2169.7 (0-4411.4)	34.7 (3)	<.001
NSE, ng/mL	5.5 (0-36.6)	3.9 (0-39.9)	4.9 (0-24.5)	20.2 (0-35)	38.7 (3)	<.001
IL6, ng/mL	0.4 (0.3-36.6)	0.4 (0.3-0.8)	0.4 (0.4-1.5)	0.3 (0.3-0.8)	49.7 (3)	<.001
TNF-α, ng/mL	0.2 (0.2-0.6)	0.2 (0.2-0.3)	0.2 (0.2-0.7)	0.5 (0.2-0.6)	52.1 (3)	<.001

BD-I, bipolar I disorder; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; NSE, neuron-specific enolase; TNF-α, tumor necrosis factor-alpha; χ^2 (df), chi-square (degrees of freedom).

Table 5. Correlations Between Cytokine Levels and Clinical Scale Scores

	IL-1RA	S100b	NSE	IL-6	TNF-α	PANSSp	CGI	MADRS	YMRS
IL-1RA	1	0.3**	0.3**	0.1	0.3**	0.1	−0.2	−0.1	−0.02
S100b	0.3**	1	0.3**	0.1	0.3**	−0.1	−0.2*	−0.1	−0.1
NSE	0.3**	0.3**	1	0.3**	0.4**	−0.2	−0.2*	−0.003	−0.2*
IL-6	0.1	0.1	0.3**	1	0.5**	0.3*	0.3*	0.1	0.3**
TNF-α	0.3**	0.3**	0.4**	0.5**	1	0.01	−0.1	0.03	−0.02
PANSSp	0.1	−0.1	−0.2	0.3**	0.01	1	0.7**	0.2	0.8**
CGI	−0.2	−0.2	−0.2*	0.3**	−0.1	0.7**	1	0.4**	0.8**
MADRS	−0.1	−0.1	−0.003	0.1	0.03	0.2	0.4**	1	0.2
YMRS	−0.02	−0.1	−0.2*	0.3**	−0.02	0.8**	0.8**	0.2	1

Values are Spearman's rho (ρ) correlation coefficients.
CGI, Clinical Global Impression; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; MADRS, Montgomery–Åsberg Depression Rating Scale; NSE, neuron-specific enolase; PANSSp, Positive and Negative Syndrome Scale – Positive subscale; TNF-α, tumor necrosis factor-alpha; YMRS, Young Mania Rating Scale.
*$P < .05$.
**$P < .01$.

states, and investigate their associations with clinical characteristics, particularly in the context of widespread antipsychotic (75%) and mood stabilizer (90%) use. The findings suggest that BD-I is characterized by a complex interplay of chronic inflammation and neurobiological alterations, with IL-6 emerging as a potential trait marker, while reductions in TNF-α, IL-1RA, S100B, and NSE may reflect neuroprogressive changes or medication effects.

This study provides new evidence that IL-6 may serve as a trait-like biomarker in BD-I, as elevated levels were observed independent of mood phase and were positively correlated with clinical symptom severity. In contrast, significantly reduced levels of TNF-α, IL-1RA, S100B, and NSE were observed, particularly in a sample predominantly composed of euthymic patients (64.9%, n = 50), followed by manic (26.0%, n = 20) and depressive (9.1%, n = 7) patients, likely influenced by widespread use of antipsychotics (75%) and mood stabilizers (90%).

The results revealed significantly elevated IL-6 levels in BD-I patients compared to controls, consistent across euthymic, manic, and depressive subgroups, supporting its role as a state-independent inflammatory marker. IL-6 levels also showed positive correlations with YMRS, PANSS positive, and CGI-S scores (all $P < .01$), suggesting that IL-6 is associated with clinical severity, particularly in manic and mixed states. These results are consistent with recent literature; for instance, a meta-analysis by Solmi et al[4] reported persistently elevated IL-6 levels in individuals with BPD, regardless of mood phase, suggesting that IL-6 may serve as a trait marker for the disorder.[10,11] The positive correlations between IL-6 levels and clinical severity scales (YMRS, CGI-S, PANSS positive; all $P < .01$) in this study are consistent with prior research, which has demonstrated that elevated IL-6 is associated with manic symptom severity and overall disease activity in BD.[3,4,12] For instance, Solmi et al[4] (2021) reported significant correlations between IL-6 and YMRS and CGI-S scores in manic phases ($P < .01$), supporting IL-6's role as a marker of clinical severity. However, the lack of correlation with MADRS in the depressive subgroup (n = 7) aligns with findings from Brietzke et al[12] (2009), who noted weaker associations between IL-6 and depressive symptoms, potentially due to the small sample size or the suppressive effects of antipsychotics (75%) and mood stabilizers (90%) on inflammatory markers. The consistent elevation of IL-6 in this study, even in the euthymic majority (64.9%), underscores its role in chronic low-grade inflammation, which may contribute to the neuroprogressive nature of BD, including cognitive decline and episode recurrence.

In contrast, IL-1RA levels were significantly lower in the patient group compared to controls. While some individual studies have found elevated IL-1RA levels in BPD,[13] a meta-analysis including 3 studies reported no significant difference between patients and healthy individuals.[4] More recently, Solmi et al[4] concluded that IL-1RA elevation appears to be restricted to manic episodes, with no significant alterations in depressive or euthymic states. Since the majority of participants in this study were in the depressive or euthymic phases, this may partially account for the lower IL-1RA levels observed. Furthermore, it has been shown that various antipsychotics exert anti-inflammatory effects by suppressing pro-inflammatory cytokines.[14,15] In the sample, 75% of the patients were receiving antipsychotic treatment, which could further explain the reduced IL-1RA and TNF-α levels.

Although previous studies, including a meta-analysis by Modabbernia et al[13] (2013), reported elevated TNF-α levels in BPD, the findings indicated significantly lower levels.[16] This discrepancy may also be attributed to long-term treatment with mood stabilizers. Himmerich et al[17] demonstrated that lithium, valproic acid, and carbamazepine significantly reduce stimulated cytokine levels, including IL-1β, IL-2, and TNF-α. The majority of the patient sample was undergoing mood stabilizer therapy, which may have contributed to the lower TNF-α levels observed. Additionally, Solmi et al[4] noted that TNF-α levels do not significantly increase during the euthymic period, which aligns with the sample composition.

S100B levels were also significantly lower in the BPD group compared to controls, with no significant differences across mood states. These findings contrast with previous studies and meta-analyses that have reported elevated S100B levels in BPD.[8,18,19] S100B, primarily released by astrocytes, is involved in glial activation, neuronal damage, and blood–brain barrier integrity. However, S100B is also expressed in adipocytes and other peripheral tissues, complicating its interpretation as a specific marker of glial pathology.[20] Moreover, potential confounding factors such as obesity were not controlled for in the present study, particularly in the control group. This may have influenced the observed results and contributed to inconsistencies with existing literature.

Regarding NSE, the results indicated significantly lower serum levels in the BPD group compared to healthy controls. Although limited research exists on NSE in BPD, a meta-analysis by Bartoli et al[8] found no significant overall difference between patients and controls, but noted that 3 of the 5 included studies reported lower NSE levels in the patient groups. Neuron-specific enolase typically increases in cases of acute neuronal injury, while lower levels may be associated with chronic neurodegenerative processes or reduced neuronal reserve. Streitbürger et al[21] reported reduced NSE levels in both healthy aging individuals and Alzheimer's disease patients with increased brain atrophy. A study including 1132 patients diagnosed with schizophrenia revealed that serum NSE levels were significantly lower compared to a control group. The study indicated a link between NSE levels and symptom severity. The study's authors explained this result by pointing to issues with neural reserve and neurodevelopmental problems.[22] Therefore, the decreased NSE levels observed in the study may reflect long-term neuroprogressive changes or the effects of chronic psychotropic medication.

Limitations

This study possesses some shortcomings worthy of addressing. The majority of patients in the BD cohort were receiving therapy with antipsychotics and mood stabilizers, which are recognized for their impact on cytokine and neurobiological marker levels. As such, the observed reductions in IL-1RA, TNF-α, and NSE may have been confounded by the pharmacological effects of long-term treatment. Second, the cross-sectional design limits the ability to draw conclusions about the temporal dynamics of these biomarkers or their direct relationship to different mood states. Longitudinal studies are needed to determine whether these alterations persist, fluctuate, or normalize with treatment and symptom remission. Third, important confounding variables such as body mass index (BMI), smoking status, metabolic comorbidities, and physical activity levels were not controlled for, particularly in the control group. These factors could significantly impact inflammatory and glial marker levels, thereby influencing between-group comparisons. Lastly, the sample size, although sufficient for primary analyses, may have been underpowered for detecting subtle differences across specific mood states (euthymic, manic, depressive), reducing the generalizability of subgroup findings. The small size of the depressive group (n = 7) limits the statistical power for subgroup comparisons, warranting caution in interpreting these results and highlighting the need for larger studies to confirm these findings.

Implications and Future Directions

The findings of this study have several important implications for future research on the biological underpinnings of BD. The elevated IL-6 levels, regardless of mood phase, support the notion that IL-6 may function as a trait biomarker for chronic inflammation in BPD. Conversely, the reductions in NSE, a marker related to neuronal reserve and energy metabolism, may reflect underlying neuroprogressive processes or metabolic dysfunction associated with long-term illness. These results suggest that immune and neurobiological alterations in BPD are not solely phase-dependent but may also represent stable pathophysiological traits. Future studies should consider longitudinal designs to track biomarker changes across illness phases and treatment trajectories. Moreover, including medication-free or first-episode patients would allow researchers to better isolate the intrinsic effects of the disorder from pharmacological influences. Additional research should also account for potential confounders such as BMI, diet, sleep patterns, and inflammatory comorbidities. Ultimately, combining inflammatory and neurodegenerative markers—such as IL-6 and NSE—may provide a more comprehensive and clinically useful biomarker profile to aid in diagnosis, staging, and individualized treatment planning in BD.

This study provides evidence that IL-6 may serve as a state-independent inflammatory marker in BD-I, given its consistently elevated levels across all mood states and its positive correlation with symptom severity. Conversely, reduced levels of IL-1RA, TNF-α, S100B, and NSE suggest potential neurobiological alterations, which may reflect the effects of long-term illness progression or psychotropic medication. Particularly, the reduction in NSE, a marker associated with neuronal reserve and metabolism, may indicate neuroprogressive changes and support its utility as a trait biomarker. Together, these findings underscore the relevance of both immune and neurodegenerative processes in the pathophysiology of BD and highlight the potential clinical value of integrated biomarker profiling for disease monitoring and treatment stratification.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from İstanbul University Faculty of Medicine Clinical Research Ethics Committee (Approval no: 273; Date: March 8, 2013).

Informed Consent: Written informed consent was obtained from individuals who participated in this study.

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