Neuropsychiatr Invest. 2024;62(1):15-21

Original Article
10.5152/NeuropsychiatricInvest.2024.23031

The Investigation of Inflammation in Drug-Naive First-Episode Mania by Measuring Ferritin, Peripheral Inflammatory Markers, and Their Ratios

Ümit Haluk Yeşilkaya[1,2], **Ertuğrul Bişgin**[1]

[1]*Department of Psychiatry, Bakırköy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, İstanbul, Turkey*

[2]*Regenerative and Restorative Medicine Research Center (REMER), Institute for Health Sciences and Technologies (SABITA), İstanbul Medipol University, İstanbul, Turkey*

ABSTRACT

Objective: Bipolar disorder (BD) is a complex psychiatric disorder with a multifactorial etiology involving both genetic and environmental factors. Increased inflammatory parameters have been shown in previous studies in bipolar disorder. However, it is not known whether ferritin and other inflammatory markers, primarily involved in autoimmune reactions and inflammation, change at the onset of the first episode. We aimed to investigate whether inflammation levels are elevated in the first episode of mania by measuring peripheral inflammatory markers with their ratios and ferritin.

Methods: Fifty-six drug-naive individuals experiencing their first episode of mania (FEM) were clinically diagnosed in accordance with DSM-5 criteria. A control cohort (HC) comprising 57 individuals matched with the patients was included in the study. During the evaluation, symptoms were assessed using BPRS (Brief Psychiatric Rating Scale) and YMRS (Young Mania Rating Scale). Blood specimens were obtained from all participants to analyze levels of white blood cells (WBC), neutrophils, monocytes, albumin, ferritin, C-reactive protein (CRP), lymphocytes, and platelets and determine specific protein ratio.

Results: Monocyte, Neutrophil-lymphocyte ratio (NLR), Monocyte-lymphocyte ratio (MLR), and neutrophil–albumin ratio (NAR), values were statistically higher in the patient group than in the control group. A statistically significant positive correlation was found between ferritin values, BPRS, and YMRS scores.It was determined that NLR and NAR ratios predict the severity of the disease.

Conclusion: These findings suggest that while inflammation may not be a definitive predictor for BD, it correlates with the disease's severity.

Keywords: Bipolar disorder, ferritin, first episode mania, inflammation

Corresponding author:
Ümit Haluk Yeşilkaya

E-mail:
halukyesilkaya@gmail.com

Received: December 29, 2023
Revision Requested: January 15, 2024
Last Revision Received: January 24, 2024
Accepted: February 5, 2024
Publication Date: March 7, 2024

Cite this article as: Yeşilkaya UH, Bişgin E. The investigation of inflammation in drug-naive first-episode mania by measuring ferritin, peripheral inflammatory markers, and their ratios. *Neuropsychiatr Invest.* 2024;62(1):15-21.

INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent mood episodes, significantly impacting various domains of functioning and posing an elevated risk of mortality. Its clinical course involves alternating periods of depression, mania, or hypomania, each manifesting distinct alterations in mood and behavior. During depressive episodes, individuals experience diminished motivation and anhedonia, while intensified feelings of sadness prevail. Conversely, manic episodes are typified by elevated mood, increased energy, and often irritable or exuberant behavior.[1] Advancements in our understanding of BD's neurobiology consistently highlight the involvement of immune-inflammatory mechanisms in both the central nervous system (CNS) and the periphery. Accumulating evidence from diverse investigations suggests a role for these mechanisms in the etiopathogenesis and comorbidities of BD.[2] Meta-analyses incorporating schizophrenia and depression cohorts have unveiled alterations in cytokine networks, further substantiating the relationship between inflammation and BD.[3] Moreover, BD is increasingly recognized as a systemic inflammatory disorder.[4]

Identified markers linked to reduced cellular resilience and apoptosis have garnered attention in BD research. Cells undergoing apoptosis have been observed to trigger an immune response. Microglia, serving as CNS macrophages, play pivotal roles in brain development, neuroplasticity, and inflammatory processes. Heightened microglial activation, along with its augmentation of inflammation through cytokine release, has been demonstrated in the brains of individuals with BD. Dysregulations in adrenocorticotropic hormone (ACTH) and cortisol responses in BD may lead to an imbalance in pro-inflammatory cytokine production.[5]

It is acknowledged that ferritin plays a role in various conditions beyond its involvement in inflammatory, neurodegenerative, and malignant diseases.[6] Elevated ferritin levels, associated with prior acute or chronic inflammatory conditions regardless of infection source, have been demonstrated to play a significant role in the pathogenesis of various inflammatory and autoimmune diseases.[7] In a study focusing on patients with BD, it was reported that ferritin levels exhibited a significant decrease during manic periods compared to both depressive patients and the control group.[8]

Recent investigations have underscored the utility of straightforward and cost-effective assessments such as Complete Blood Count (CBC), Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Albumin Ratio (NAR), and CRP-to-Albumin Ratio (CAR) in comparing inflammatory markers.[9] Recent studies have shown significantly elevated PLR and MLR levels in BD compared to control groups, with manic patients displaying notably higher NLR and MLR values compared to those experiencing mixed episodes. Furthermore, elevated Red Cell Distribution Width (RDW) values were observed in patients undergoing mixed episodes in comparison to control groups. In addition, in a specific study, heightened levels of CRP were identified in patients with a manic episode compared to patients with a depressive episode and the control group.[10] Correlations were noted between higher CRP levels in BD patients and weaker cognitive functions, implying that alterations in inflammatory markers might correlate with the severity of the disease's impact on an individual's functional capacity.[11,12] Additionally, postmortem examinations have reported signs of inflammation, suggesting an escalation of inflammatory markers with disease progression.[13,14]

In this study, we hypothesized that ferritin, inflammation markers, and their ratios are elevated even in the first episode of mania, and we aimed to investigate whether inflammation levels are elevated in the first episode of mania by measuring peripheral inflammatory markers with their ratios and ferritin.

MATERIAL AND METHODS

Participants and Study Setting

The study enrolled 62 drug-naïve FEM individuals. These participants were recruited from psychiatry emergency or outpatient units and diagnosed in accordance with SCID-5 criteria between April 2023 and October 2023. A follow-up assessment was conducted after 1 month to validate the diagnosis. Six participants were excluded from the FEM group due to the absence of a bipolar disorder diagnosis. Additionally, the control group (healthy control; HC) comprised 57 individuals matched for age and gender with the patient cohort. HC subjects were selected from individuals visiting the polyclinic for administrative purposes or from hospital staff undergoing routine occupational health and safety examinations. All participants, aged between 18 and 50, had a BMI ranging from 18 to 25. Since obesity causes inflammation and oxidative stress, the BMI was indicated to be between 18 and 25 kg/m^2. Additionally, they did not exhibit any known mental disabilities that could hinder their participation in the study. None of the participants had diagnoses of chronic systemic diseases or neuropsychiatric disorders (specific to the HC group) or a history of neurodegenerative conditions. Moreover, patients who were using any medication at the time of hospital admission were excluded. Those meeting DSM-5 criteria for substance or alcohol use disorders were also excluded, confirmed via urine tests conducted on all participants. In addition, the acute inflammation history was investigated through the national health system (e-nabiz) for each participant, and those who had an acute inflammatory history within 1 month were excluded. Sample size determination utilized G Power version 3.1.9 considering an effect size of 0.25, α-error of 0.05, and power of 0.85.

Ethical Approval

Before commencement, all participants were briefed about study procedures, and written consent was obtained only from those willing to partake. Ethical clearance for the study was acquired from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital İstanbul (Approval No: 2023/148, Date: April 03, 2023).

Data Collection Tools

Sociodemographic and Clinical Data Forms: Two distinct data forms were designed by the researchers, encompassing queries on sociodemographic traits (e.g., age, gender, education level, marital status, income) and clinical particulars such as illness duration, height, and weight. Both patient and control groups completed these forms.

Young Mania Rating Scale (YMRS): It is an 11-item scale administered by the interviewer to measure changes in the severity of mania. Seven of the items are measured on a 5-point Likert scale, while 4 are assessed using a 9-point Likert scale. Scores range from 0 to 44, with scores of 12 and above indicating hypomania and/or mania. The reliability and validity study of its Turkish version was conducted by Karadağ et al in 2001 (Cronbach's alpha value is 0.79).

Brief Psychiatric Rating Scale (BPRS): Developed by Overall et al, this scale comprises 18 semi-structured items used to measure the severity and changes in psychotic symptoms in schizophrenia and other psychotic disorders. Each item is scored from 0 to 6, and the total score is the sum of all items. Scores between 15 and 30 indicate a minor syndrome, while scores of 30 or higher represent a major syndrome (Cronbach's alpha value is 0.67).

Blood Sample Collection

Upon patients' arrival at the emergency service and following an overnight fast, venous blood specimens (5 mL) were drawn during routine examination hours (07:00-09:00 AM) into coagulant tubes with gel. The samples were allowed to clot at room temperature for 2 hours, followed by centrifugation at 3000 rpm and 4°C for 20°C min to yield serum. Subsequently, aliquots of 0.5 mL were separated and stored at –0°C until analysis.

Protein Assays

The serum albumin levels were assessed using a Siemens automated biochemistry analyzer (Germany) and albumin test kits (Roche Diagnostics GmbH, Mannheim, Germany) utilizing bromocresol green colorimetry. Hemogram tests were conducted via Abbott Cell Dyne 3700 (Abbott Diagnostic Systems, Ill, USA). Serum CRP was quantified employing kinetic nephelometry on an immunochemical system (IMMAGE®; Beckman, Marburg, Germany).

Statistical Analysis

Demographic and clinical characteristics of the cases evaluated in the study were examined using descriptive statistical analyses (count, percentage, mean, standard deviation, etc.). The conformity of quantitative variables to a normal distribution was assessed using the Kolmogorov–Smirnov test. In comparing demographic features such as age and duration of education, inflammation values, and ratios between the patient and control groups, the Mann–Whitney *U*-test was employed for non-parametric distributed data, while the Independent Samples *t*-test was used for parametric distributed data. Proportional data such as gender and smoking status between the patient and control groups were compared using the chi-square test. Relationships between age, BPRS, YMRS scores, blood values, and inflammation ratios in the patient group were examined using Spearman Correlation Analysis. Hierarchical Regression Analysis was conducted to assess variables influencing YMRS scores. A significance level of $P < .05$ was set for all analyses. Data normality was checked using kurtosis and skewness values (±1.5). The Statistical Package for Social Sciences version 26.0 software (IBM Corp.; Armonk, NY, USA) was utilized for the analysis.

RESULTS

Demographic and Clinical Data

The average age of the participants in the patient group was calculated as 32.37 ± 11.40 years, while in the control group, it was 32.97 ± 8.83 years. When examining the gender distribution among the volunteers involved in the study, it was determined that among the patient group, 27 (45%) were male and 33 (55%) were female. In the control group, 28 (46.7%) were male and 32 (53.3%) were female. There was no significant difference in age ($P = .89$), gender ratio ($P = .60$), level of smoking ($P = .1$), and education levels ($P = .11$). Detailed clinical data and demographic information are shown in Table 1.

Table 1. Comparison of Sociodemographic and Clinical Data of Patients with FEM and Healthy Control

		FEM		HC			
		n (56)/ mean	%/SD	n (57)/ mean	%/SD	Analysis	*P*
Age (year)		32.37	11.40	32,97	8.83	$t = -0.32$	.748
Education (year)		10.58	4.68	9,38	3.35	$t = 1.60$	.112
Sex	Male	26	47.0	27	47.4	$X^2 = 0.03$	.848.
	Female	30	53.0	30	52.6		
Smoking	Yes	31	55.3	27	47.4	$X^2 = 0.30$	.484
	No	25	45.7	30	52.6		
Marital Status	Single	30	53.0	20	35.0	$X^2 = 2.86$	.239
	Other	3	5.3	5	8.9		
	Married	23	41.7	32	56.1		
Family Life	Family	50	89.2	45	80.0	$X^2 = 1.68$	.431
	Other	4	8.3	3	5.2		
	Single	2	8.3	9	14.8		
BPRS		32.8	6.63				
YMRS		33.68	4.18				

*$P < .05$; **$P < .001$, chi-Square Test, Mann–Whitney *U*-test, and Student *t*-test were used for statistical analyses.
BPRS, Brief Psychiatric Rating Scale; FEM, First Episode Mania; HC, healthy control; YMRS, Young Mania Rating Scale.

Comparison of the Inflammatory Markers Between All Patient Groups and HC

Table 2 and Table 3 show a comparison of the inflammatory markers between the patients with FEM and HC. The statistical analysis revealed that in the patient group, compared to the control group, the Monocyte ($P < .001$), NLR ($P = .032$), MLR ($P < .001$), and NAR ($P = .035$) values were significantly higher. Conversely, in the control group, albumin levels were found to be statistically significantly higher compared to the patient group ($P = .013$).

Correlation of Biochemical Markers, Ratio of Biochemical Markers, BPRS, and YMRS scores

In the patient group, a statistically significant positive correlation was observed between ferritin levels and BPRS scores ($P = .017$), as well as YMRS scores ($P = .008$). Additionally, within the same group, a statistically significant negative correlation was found between age and albumin levels ($P = .006$), as well as between YMRS scores and PLR values ($P = .029$). Detailed clinical data and demographic information are shown in Table 4.

Hierarchical Regression Analysis Associated with Predicting YMRS Scores in the Patient Group

An evaluation of age, the education level, the NLR, MLR, PLR, NAR, and CAR ratios to predict the YMRS scores in patients with FEM with a hierarchical model is shown in Table 4. The conducted hierarchical regression analysis indicated that age and duration of education were not statistically significant variables in explaining YMRS scores. However, upon adding hematological ratios to the model, it was observed that 51% of the variance in YMRS scores was explained. Further examination of the model's sub-variables revealed that NLR ($P = .028$) and NAR ($P = .007$) ratios were statistically significant variables.

DISCUSSION

In this study, peripheral inflammatory parameters with their ratios such as NLR, MLR, PLR, NAR, and CAR, and ferritin were examined

Table 2. Comparison of the Inflammatory Markers Between the Groups

	FEM				HC					
	n	Med.	%25	%75	n	Med.	%25	%75	Z	P
WBC	56	7980,00	6220,00	9940,00	57	7360,00	6160,00	8530,00	−1,806	.071
Neutrophil	56	4525,00	3670,00	6785,00	57	4340,00	3440,00	5180,00	−1,561	.119
Monocyte	56	570,00	460,00	785,00	57	405,00	340,00	490,00	**−4,989**	**<.001**
Platelet	56	259500,00	206000,0	294500,0	57	240000,00	210000,0	293000,0	−0,272	.786
Lymphocyte	56	2140,00	1815,00	2780,00	57	2290,00	1920,00	2680,00	−0,587	.557
CRP	50	1,61	,62	3,79	54	1,62	,66	2,67	−0,444	.657
Ferritin	52	49,47	23,70	117,60	54	59,38	25,15	95,86	−0,408	.683
Albumin	50	43,00	40,00	45,00	52	44,00	43,00	46,00	**−2,489**	**.013**

*$P < .05$ **$P < .001$, Mann–Whitney *U*-test was used for statistical analyses.
WBC, white blood cells.

Table 3. Comparison of Ratio of Biochemical Markers Between the Groups

	FEM				HC					
	n	Med.	%25	%75	*n*	Med.	%25	%75	*Z*	*P*
NLR	56	2.13	1.55	3.18	57	1.77	1.52	2.41	−2,142	**.032**
MLR	56	.26	.19	.32	57	.18	.15	.21	−4.694	**<.001**
PLR	56	115.27	86.85	145.41	57	104.10	90.41	136.46	−0.824	.410
NAR	50	106.37	87.64	157.56	52	94.02	75.38	114.95	−2.108	**.035**
CAR	50	.04	.01	.09	52	.04	.02	.06	−0.112	.911

*$P < .05$; **$P < .001$, Mann Whitney *U*-test was used for statistical analyses.
CAR, CRP–albumin ratio; MLR, monocyte–lymphocyte ratio; NAR, neutrophil–albumin ratio; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio.

in drug-free patients diagnosed with BD for the first time during a manic episode. The investigation aimed to explore whether these values could predict the occurrence of the initial manic attack.

The main findings of our study revealed that monocyte, NLR, MLR, and NAR values were statistically higher in the patient group compared to the control group. Additionally, a positive correlation was found between BPRS and YMRS scores and ferritin levels. It was determined that NLR and NAR ratios predict the severity of the disease.

Table 4. Investigation of the Relationship Between Biochemical Markers, Ratio of Biochemical Markers with BPRS Scores, and YMRS Scores

	Age	*BPRS*	*YMRS*
WBC	−0.09	−0.09	0.17
Neutrophil	0.003	−0.15	0.10
Monocyte	−0.11	0.08	0.23
Platelet	−0.17	−0.14	−0.18
Lymphocyte	−0.13	0.18	0.18
CRP	0.09	−0.01	0.04
Ferritin	0.06	**0.32**	**0.36**
Albumin	**−0.35**	−0.15	−0.11
NLR	0.14	−0.20	−0.05
MLR	0.13	−0.09	0.05
PLR	0.03	−0.21	**−0.28**
NAR	0.10	−0.11	0.16
CAR	0.10	−0.03	0.02

*$P < .05$; **$P < .001$, Spearman (rho) correlation analysis test was performed for statistical analyses.
CAR, CRP–albumin ratio; MLR, monocyte–lymphocyte ratio; NAR, neutrophil–albumin ratio; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; WBC, white blood cells.

In numerous studies in the literature, inflammatory processes in BD have been investigated, focusing primarily on cytokine alterations. A comprehensive meta-analysis reviewing 30 studies indicated a significant increase in both anti-inflammatory and pro-inflammatory cytokine levels in BD, highlighting the prominence of the inflammatory hypothesis in BD pathophysiology.[15]

Generally, 2 immune cells, macrophages and monocytes, are key producers of cytokines in the body.[16] Monocytes have traditionally been considered fundamental elements associated with innate immune responses to pathogens, external assaults, infections, and inflammatory processes caused by autoimmune diseases.[17]

Studies examining monocyte and lymphocyte activation in BD have shown an increase in monocyte ratio. A study by Barbosa et al. suggested that monocyte hyperactivity might act as a trigger for mood disorders, emphasizing the necessity to consider the likelihood of peripheral monocyte overactivation in demonstrating CNS mononuclear phagocyte activation in BD patients.[18] Consistent with literature investigating the immune system in BD, our study found statistically higher monocyte values in the patient group compared to the control group.

NLR, PLR, and MLR, as well as other similar ratios, are easily calculable, cost-effective, and reproducible tests. Many researchers have demonstrated their potential value as biomarkers of poor prognosis or major inflammation among patients with chronic medical

Table 5. Demonstration of the Effect of NLR, MLR, PLR, NAR, and CAR ratios on Predicting YMRS Scores by Hierarchical Regression Analysis

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% C.I. for Exp(B)	
		B	SE	Beta	*t*	*P*	Lower	Upper
Step 1	Constant	32,237	3,560		9.05	<.001	24,976	39,498
	Age	–.020	.068	–.061	–.299	.767	–.160	.119
	Education	.193	.166	.237	1.14	.253	–.145	.532
Step 2	Constant	27,663	3,617		7.67	<.001	20,228	35,099
	Age	–.028	.059	-.083	–.475	.638	–.149	.093
	Education	.279	.149	.341	1.86	.072	–.027	.584
	NLR	–3,498	1,501	–.943	–2.3	.028	–6.585	–.412
	MLR	10,757	5,520	.474	1.99	.062	–.588	22,103
	PLR	–.004	.023	–.049	–.184	.856	–.052	.043
	NAR	.077	.026	.715	2.96	.007	.023	.131
	CAR	7,545	7,898	.164	.955	.348	–8.690	23,780

P < .05; *P* < .001
CAR, CRP-albumin ratio; MLR, monocyte-lymphocyte ratio; NAR, neutrophil-albumin ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SE, standard error.

conditions such as cardiovascular diseases, malignancies, and autoimmune diseases. While supporting the hypothesis of an inflammatory activation in mood disorders, particular attention has been drawn to the activation of NLR and PLR.[19]

It is worth noting that inflammation values' ratios have been studied in non-psychiatric fields as well. In a study, it was suggested that Alzheimer's patients have higher NLR compared to healthy controls.[20] Another study exploring the relationship between NLR and post-stroke depression demonstrated that patients developing depressive symptoms 1 month after ischemic stroke had significantly higher NLR levels at admission compared to normal controls and patients who did not experience depression after the stroke.[21] Moreover, other studies have also shown higher NLR, PLR, and MLR values in schizophrenia patients compared to healthy groups.[22,23]

On the other hand, studies comparing BD diagnosed patients with healthy controls have also identified higher NLR values in the patient group.[24,25] Ivkovic et al showed a positive correlation between suicide risk and family history of suicide attempts with NLR values in BD patients.[24] In addition, while in a study comparing inflammatory cell markers during manic episodes in healthy individuals, Mert and Terzi found increased NLR and PLR values,[26] In another study investigating inflammatory cells and ratios in BD, including 61 manic, 55 depressive patients, and 54 healthy controls, both manic and depressive patients showed significantly higher NLR and PLR ratios compared to the control group.[27]

Recent evidence from experimental studies has indicated that cytokines in inflammatory processes can be both neurotoxic and neuroprotective. This dual role of inflammation in brain expression areas has led to debates.[28,29] In a study by Aykut et al, the relationship between NLR and PLR ratios and cognitive functions in BD patients was investigated, and neuropsychological tests were administered to patient and control groups. It was found that the NLR value was negatively correlated with cognitive functions in BD.[29] In our study, inflammatory ratios such as NLR, MLR, and NAR were found to be higher in patients, which is in general agreement with the literature, supporting the inflammation hypothesis in BD pathogenesis. Additionally, previous studies have indicated correlations between cognitive functions in BD, disease severity in depression, suicide risk, family history of suicide attempts, and the inflammatory burden, similar to our findings that showed correlations between YMRS scores and inflammation burden. This supports the significant role of inflammation not only in the pathogenesis of the disease but also in its severity.

Albumin plays a crucial role in antioxidant defense under both normal and oxidative stress conditions. It possesses enzymatic and non-enzymatic antioxidant functions, making it an important component in combating oxidative stress.[30] Studies specifically regarding serum albumin in the schizophrenia patient group are present in the literature. Several studies previously reported that oxidative stress plays a role in schizophrenia's pathogenesis. Studies have shown decreased plasma albumin levels in schizophrenia.[31] A study conducted in China reported a negative correlation between serum albumin levels in schizophrenia patients and PANSS depressive scores.[32]

There is increasing evidence suggesting the potential role of oxidative stress in BD pathophysiology.[33] A study conducted in Taiwan, involving 213 patients diagnosed with mood disorders, demonstrated lower serum albumin levels in both manic and major depressive episodes.[34] Our study identified lower albumin levels in the patient group, supporting the inflammatory and oxidative stress hypothesis during manic episodes.

Ferritin acts as an acute-phase reactant and is induced by inflammatory stimuli.[35] Emerging evidence suggests a role for ferritin in modulating immune response and redox biology. Inflammation links iron and redox processes. Therefore, plasma ferritin appears to be closely associated with both cell damage-related circulating iron stores and modulation of inflammatory processes and oxidative stress.[36] Moreover, in a recent study by Munkholm et al, ferritin levels in BD patients were compared with healthy control groups across different mood episodes. The study did not find an increase in ferritin levels during manic episodes. The study suggested that higher ferritin levels in BD depressive patients could indicate the role of iron metabolism in BD pathophysiology.[37] Although we did not find a statistically significant difference in ferritin levels between the patient and control groups in our study, we found a statistically significant positive correlation between ferritin levels and BPRS and YMRS scores. This finding could indicate an association between disease severity and

inflammation in BD. In addition, recent studies have shown that cellular iron levels can affect cognitive function and positive symptoms in schizophrenia patients. We also found a positive correlation between ferritin and BPRS scores. It can also affect psychotic and cognitive symptoms in BD.[38]

The present study presents certain limitations that warrant consideration when interpreting the outcomes. Despite our sample size meeting the criteria established by g power analysis, it is noteworthy that the size of the groups is comparatively smaller. Although we applied SCID to patients and investigated their history, given the complicated and veiled nature of BD, we could not be exactly sure about the first episode of the disease. This is also a limitation of the study. Also, the SCID was not applied to the healthy control group; these participants were selected using self-reports. Moreover, while our research focused on examining levels using cost-effective and replicable markers, there is a necessity to verify these findings by exploring additional inflammatory markers.

The primary outcomes of our investigation revealed statistically elevated levels of monocyte count, NLR, MLR, and NAR in the patient cohort compared to the control cohort. Moreover, while there was no significant distinction in ferritin levels between the patients and the control group, a positive correlation emerged between BPRS and YMRS scores and ferritin concentrations. Notably, NLR and NAR ratios were identified as predictors of disease severity. These findings suggest that while inflammation may not serve as a definitive predictor for BD, it exhibits a correlation with the disease's severity.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Dr. Sadi Konuk Training & Research Hospital, İstanbul (Approval No: 2023/148, Date: April 03, 2023).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – U.H.Y., E.B.; Design – U.H.Y.; Supervision – U.H.Y.; Resource – E.B.; Materials – E.B.; Data Collection and/or Processing – E.B.; Analysis and/or Interpretation – E.B., U.H.Y.; Literature Search – E.B.; Writing – U.H.Y.; Critical Review – U.H.Y., E.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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