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A retrospective comparative study: Novel diagnostical markers of inflammation and cardiovascular risk of bipolar disorder and manic episode

Elif Ozcan Tozoglu

University of Health Sciences, Erzurum Faculty of Medicine, Department of Psychiatry, Erzurum, Türkiye

**Corresponding author: elif.ozcantozoglu@sbu.edu.tr (Elif Ozcan Tozoglu)*

MAIN POINTS

- Inflammatory (PIV, IBI) and atherogenic (AIP) indices were significantly elevated in manic and remission phases of bipolar disorder (BD), compared to healthy controls.
- PIV and IBI emerged as strong predictors of manic episodes and showed positive correlation with episode severity.
- AIP was significantly higher in the remission group, suggesting an underlying atherogenic tendency possibly linked to treatment and lifestyle.
- Easily accessible markers (PIV, IBI, AIP) may serve as novel, cost-effective biomarkers for BD monitoring and manic episode prediction.
- The study included drug-naive patients, enhancing the reliability of biomarker-disease associations.

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ABSTRACT

Aim: The pan-immune inflammation value (PIV), inflammation burden index (IBI), atherogenic index of plasma (AIP), neutrophil/ high-density lipoprotein (HDL) ratio (NHR), lymphocyte/HDL ratio (LHR), monocyte/HDL ratio (MHR), and platelet/HDL ratio (PHR) have recently been investigated as novel inflammatory and cardiovascular markers. Our study aimed to compare these indices with the manic episode and remission period of bipolar disorder (BD) patients with controls and to investigate the relationship between these indices and the clinical characteristics of the patients and whether these indices can be biomarkers for the disease and manic episode.

Materials and Methods: In this retrospective observational study, we collected data from 66 patients in remission, 67 patients with manic episodes, and 70 controls. Differences in PIV, IBI, AIP, NHR, MHR, LHR, and PHR were investigated. We performed logistic regression analysis to identify predictors of manic episodes, and the diagnostic potential of these parameters was evaluated using ROC curves.

Results: Significant differences were found between the three groups in NHR (p<0.001), MHR (p=0.001), LHR (p=0.013), AIP (p<0.001), PIV (p<0.001) and IBI (p<0.001). IBI (p<0.001) and PIV (p:0.001) were found to be positive predictors of manic episodes. ROC analysis showed that IBI (p<0.001) and PIV (p<0.001) can be used to define a manic episode; IBI (p<0.001), PIV (p<0.001) and AIP (p:0.001) can be used to define BD.

Conclusion: Given the inflammatory and atherogenic processes involved in the etiopathogenesis, the novel biomarkers PIV, IBI, and AIP may be promising therapeutic targets for BD. In addition, these biomarkers can be used as easily accessible, inexpensive clinical tools to predict illness and severity of manic episodes.

Keywords: Pan-immune-inflammation value, Inflammatory burden index, Atherogenic index of plasma, Bipolar disorder, Biomarker

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INTRODUCTION

Bipolar Disorder (BD) is a recurrent and chronic illness characterized by mania, hypomania, depression, and mixed-type episodes leading to decreased quality of life, limitation, and mood fluctuations [1]. The worldwide prevalence of BD is reported to be between 2% and 5% [1]. In addition to the hypotheses that genetic factors, disruption in calcium signaling mechanisms, mitochondrial dysfunction, neuroplasticity, and neurotrophic factor disorders, oxidative stress, and neurotransmitter systems play a role in the etiology of BD, inflammatory reactions have recently been thought to play a role in pathogenesis. Therefore, it is suggested that it may be possible to consider BD as a multisystemic inflammatory disease [2]. The relationship between BD and inflammation has recently been the subject of many studies, and the number of publications on the effects of inflammation on disease progression and treatment efficacy is increasing. Studies have shown that the incidence of diseases such as immune-related hyperthy-

roidism, rheumatoid arthritis, and polymyalgia rheumatica is higher in patients with BD compared to the healthy population [3]. In addition, cardiovascular risks and activation of atherogenetic mechanisms are increased in patients with severe mental disorders due to both the lifestyle brought on by the disease and the long-term use of antipsychotics and mood stabilizers. The inflammation observed in BD may be a secondary physiological response that occurs during the course of the disease rather than the primary cause of the disease. However, since the markers used to prove and monitor these conditions are expensive and laborious, indices that can be obtained by routine examinations have recently been used to predict the prognosis of diseases with high inflammatory and cardiogenic risk and cancers.

Studies on inflammation have focused on neutrophil, lymphocyte, platelet, platelet, platelet count, and C-reactive protein (CRP) levels, whereas studies on cardiovascular risk have focused on lipid profiles. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios serve as convenient markers for assessing inflammation in BD because of their derivation from routine blood count tests. Research has identified notable disparities in these ratios when comparing patients with BD to healthy individuals [4]. C-reactive protein (CRP), a key acute-phase reactant, is produced in response to inflammatory triggers and is predominantly controlled by proinflammatory cytokines. Factors such as anemia, protein levels, red blood cell morphology, age, or sex do not affect CRP levels [5]. CRP is considered a reliable biomarker of inflammation and is frequently used to measure low-grade inflammation in both physical and mental health conditions. Research indicates that CRP levels are consistently higher in individuals with bipolar disorder (BD) than in healthy controls, regardless of episodic state, but they tend to rise significantly during manic episodes [6].

The Pan-immune inflammation value (PIV) and inflammatory burden index (IBI), which are based on these, are newly defined biomarkers that can potentially reflect the body's immune response and systemic inflammation status. PIV, initially introduced by Fuca et al., is calculated by dividing the combined product of neutrophil, platelet, and monocyte counts by the lymphocyte count [7]. This metric has been linked to disease prognosis in various inflammation-related conditions, including colorectal cancer, antineutrophil cytoplasmic antibody-associated vasculitis, and ST-segment elevation myocardial infarction [7-9].

The Inflammatory Burden Index (IBI) is an emerging marker used to evaluate systemic inflammation and immune function. The value is calculated by multiplying C-reactive protein (CRP) by the neutrophil-to-lymphocyte ratio (NLR). Initially introduced by Xie et al, IBI serves as a tool for measuring the inflammatory burden in various cancers and predicting patient prognosis [10]. A study involving patients with Alzheimer's disease, a condition in which inflammation is believed to play a role in its development, found that IBI levels were significantly higher in patients than in healthy controls [11].

Recent evidence highlights the crucial role of inflammation in the development of atherosclerosis. Research on chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis has demonstrated the contribution of systemic inflammation to the progression of atherosclerosis. These conditions are also linked to an increased risk of cardiovascular disease and early-onset atherosclerosis [12]. Among the modifiable risk factors for atherosclerotic cardiovascular disease, the lipid profile is particularly significant [13]. Lipid profile assessments typically include total cholesterol (TC), high-density-lipoprotein (HDL), low-density-lipoprotein (LDL), and triglycerides (TG).

HDL plays a vital role in the lipid profile by preventing the buildup of free cholesterol and triglycerides (TG) in blood vessels. It shields endothelial cells from the harmful effects of LDL and inhibits LDL oxidation. Additionally, HDL offers numerous protective benefits, such as anti-inflammatory, antioxidant, antithrombotic, anti-infective, and immunomodulatory effects [14]. Studies suggest that HDL interacts with immune cells like neutrophils, lymphocytes, monocytes, and platelets, limiting neutrophil activation, adhesion, migration, and monocyte-driven processes [15].

Considering the roles of neutrophils, monocytes, lymphocytes, platelets, and HDL in inflammatory processes, several ratios, such as the neutrophil/HDL ratio (NHR), lymphocyte/HDL ratio (LHR), monocyte/HDL ratio (MHR), and platelet/HDL ratio (PHR), have recently been introduced as novel markers of inflammation. These ratios have been proposed as potential indicators of systemic inflammation and oxidative stress under various inflammatory conditions [16, 17]. Studies have identified a strong association between these ratios and the onset and prognosis of cardiovascular diseases, Parkinson's disease, and certain physical health conditions [16, 17].

Although studies investigating these ratios in psychiatric conditions are scarce, a retrospective analysis of individuals with severe mental illnesses demonstrated significant differences in NHR, LHR, MHR, and PHR values in those with bipolar disorder (BD) compared to healthy subjects. Considering the intricate relationships among neutrophils, lymphocytes, monocytes, platelets, and HDL, a composite marker incorporating NHR, LHR, MHR, and PHR may offer a more comprehensive assessment of inflammation levels than individual metrics. However, in cardiovascular conditions, TG levels have been predominantly accepted as an independent risk factor in various studies [18]. For this reason, the atherogenic index of plasma (AIP), which is thought to be a more objective indicator of atherosclerosis, was introduced. AIP was calculated as the logarithm of the ratio of plasma triglyceride (TG) level to high-density lipoprotein (HDL) level with base 10 [log (TG/HDL) ratio]. AIP reflects the balance between protective and atherogenic lipoproteins [19]. Recently,

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AIP has been reported to be a good marker for the early detection of subclinical cardiovascular disease in diseases characterized by chronic inflammation, such as Behçet's disease and ankylosing spondylitis [20, 21]. There are also a few studies on BD [22, 23].

Although there are many biomarkers indicating inflammation, since these biomarkers require additional financial resources, we believe that it is more valuable to detect biomarkers that can be obtained during routine examinations.

When we look at the literature, studies on BD have many limitations, especially regarding the use of drugs, and only the acute phases of the disease have been addressed.

It is thought that there is still a need to define specific and sensitive markers that can show that the inflammatory process in BD changes during the disease, during remission, and during manic episodes, especially biomarkers that are easily measurable, cost-effective, and reproducible, reflect the dynamism and clinical progression of the disease, and are easy to interpret by clinicians.

In our study, we aimed to examine whether the hemogram and biochemical parameters of patients with BD in the remission and manic episode periods and healthy controls, who were included in the study with strict exclusion criteria especially related to drug use and even naive manic episode patients were included to observe the effects of drug use, whether a difference that could be a biomarker could be detected from these parameters, and to evaluate the relationship between clinical variables and these parameters.

MATERIALS AND METHODS

Procedure

Our study focused on the retrospective comparison of the clinical, hemogram, and biochemical parameters of three groups: patients in remission and manic episodes who applied to the Erzurum City Hospital Psychiatry Outpatient Clinic between December 2023 and December 2024, who were diagnosed with BD Type 1 according to DSM-5 diagnostic criteria, and controls who applied to the psychiatry outpatient clinic for reporting purposes (starting work, single physician's report reporting status). Outpatient clinic and clinic records will be used to obtain the data of patients and controls included in the study.

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Health Sciences University Erzurum Faculty of Medicine Scientific Research Ethics Committee with the decision numbered BAEK 2024/12-215.

Research sample

Criterion sampling, a purposive sampling method, was used in our study [24]. This sampling type is based on samples that meet certain predetermined criteria. The criteria determined by the researcher to explain the situations examined can be used for this type of sampling. In criterion sampling, the individuals planned to be included in the study are determined according to certain criteria. The criteria or criteria used can be created by the researcher, or a previously prepared list of criteria can be used. For our study, the data of all patients with BD type 1 who applied to our outpatient clinic within the specified date intervals were evaluated. Patients who did not meet the inclusion criteria were excluded, and a sample was formed. Healthy controls were selected from those who applied to our outpatient clinic to confirm that they were healthy. When their health records and interviews were examined, it was determined that they had not previously consulted a psychiatrist and had no known chronic or acute physical or mental illness. When the hospital records were examined, it was confirmed that the person did not have any psychopathology as a result of the current mental status examination and psychometric evaluations. The inclusion criteria for participants who were evaluated in the psychiatry outpatient clinic in the desiganted period are summarized in Table 1.

A flow diagram illustrating the recruitment process is summarized in Figure 1.

Data collection tools

Sociodemographic and Clinical Data Form: Medical records of all participants were analyzed. Characteristics such as age, height, weight, BMI, and number of episodes were obtained from hospital records.

Hamilton Depression Scale: This scale is not diagnostic but is used to measure the severity of depression. The test is formed on a three- and five-point Likert scale. Turkish validity and reliability studies were conducted [26].

The Young Mania Rating Scale (YMRS): It is used to determine the severity of a manic episode. The test is constructed on a five-point likert scale. A high score indicates that mania is severe. A Turkish validity and reliability study was conducted [27].

Complete blood count and biochemical analysis

Blood analyses were performed in the biochemistry laboratory using an automated hematological analyzer (Sysmex XN-1000) and a biochemistry analyzer (Atellica, siemens Healthineers).

Normal reference ranges are as follows: neutrophils, 1,8-6,98×10^9 /L: lymphocytes, 1,21-3,77×10^9 /L; monocytes, 0,29-0,95×10^9 /L; platelets, 152-383×10^9 /L; HDL, 35-55 mg/dL; LDL, 100-129 mg/dL; triglycerides, 0-200 mg/dL; total cholesterol, 0-200 mg/dL; and CRP, 0-5 mg/L.

The indexes used in our study were calculated using the following formulas:

NHR = neutrophil/HDL ratio; MHR = monocyte/HDL ratio; LHR = lymphocyte/HDL ratio; PHR = platelet/HDL ratio.

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Table 1. Comparison of sociodemographic data, clinical results, blood parameters and calculated indices of the groups.

	Control N:70 Mean±SD	Remission N:66 Mean±SD	Manic episode N:67 Mean±SD	χ^2 /F value	p value
Age	38.14	39.33	31.61	9.151	p<0.001
Gender				1.522	0.467
Women	26	30	24		
Men	44	36	43		
Marital Status				10.628	0.00
Single	28	42	43		
Married	42	24	24		
Smoking Status				10.782	5.005
No	42	48	30		
Yes	28	18	37		
Alcohol Use Status				9.118	0.010
No	62	66	58		
Yes	8	15	9		
BMI	25.11	28.29	26.60	26.899	p<0.001
Duration of disease(year)	-	13.42±6.32	8.46±10.38	3.328	0.001
Number of Episodes	-	6.03±2.91	4.70±4.57	1.999	0.048
Number of Manic Episodes	-	3±1.54	2.40±1.73	2.094	0.038
Number of Depressive Episodes	-	3.03±1.43	1.89±2.32	3.387	0.001
Neutrophil count x 10^9/ L	3.90±1.42	4.81±1.94	6.29±1.49	37.299	p<0.001
Monocyte count x 10^9/ L	0.59±0.13	0.60±0.19	0.76±0.25	16.192	p<0.001
Lymphocyte count x 10^9/ L	2.28±0.59	2.62±0.83	2.21±0.74	6.247	p<0.001
Platelet count x 10^9/ L	54.92±6.56	95.53±11.75	71.20±4.99	0.208	0.813
CRP (mg/L)	2.66±2.06	3.47±3.00	5.28±4.54	10.893	.000
Triglyceride (mmol/L)	1.26±0.58	1.84±0.81	1.57±0.79	10.375	p<0.001
Total Cholesterol (mmol/L)	4.52±0.94	4.31±0.66	3.88±0.90	9.875	p<0.001
HDL (mmol/L)	1.05±0.26	0.99±0.38	1.07±0.35	0.931	0.396
LDL (mmol/L)	3.23±0.93	3.04±0.55	2.83±1.02	3.634	0.028
NHR	3.93±1.79	5.45±3.19	6.48±2.55	17.107	p<0.001
MHR	0.60±0.21	0.67±031	0.81±0.42	7.883	0.001
LHR	2.33±0.97	2.88±1.14	2.43±1.29	4.473	0.013
PHR	272.64±80.21	291.79±127.54	285.36±116.69	0.541	0.583
AIP	0.041±0.26	0.24±0.27	0.12±0.33	8.219	p<0.001
PIV	289.22±151.43	387.35±342.95	444.41±338.04	28.324	p<0.001
IBI	5.46±7.43	6.81±6.48	17.56±18.73	19.978	p<0.001

BMI: Body mass index, CRP:C-reactive protein, NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR:Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, SD: Standard Deviation, N: number of participants, χ^2: Chi-square, F: one-way ANOVA test value, p<0.05: statistical significance level.

PIV = Neutrophil (10^9/L) × Platelet (10^9/L) × Monocyte (10^9/L)/Lymphocyte (10^9/L).

IBI = CRP × Neutrophil/Lymphocyte.

AIP: $\log_{10}$(TG/HDL).

Statistical analysis

Statistical analyses were performed using the Statistical software Package for Social Sciences version 26 (SPSS Statistics version 26.0) (IBM, Armonk, USA). Descriptive statistics, including means, standard deviations, and frequencies, were calculated. Normality was assessed by examining skewness and kurtosis values, with all variables falling within the acceptable range of -2 to +2. Categorical variables were analyzed using the chi-square test. For comparisons between two independent groups meeting normality assumptions, the independent samples t-test was employed. Comparisons involving more than two independent groups with normally distributed data were conducted using one-way ANOVA. Where ANOVA yielded significant results, post hoc comparisons were performed using the Bonferroni test for equal variances and Tamhane's T2 test for unequal variances. The relationship between quantitative variables was assessed using Pearson's correlation coefficient. Binary logistic regression analysis was used to identify significant predictors of the dependent variable. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic utility of continuous variables and to determine appropriate cut-off values. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

The study included data from 66 patients with BD in remission, 67 patients with a manic episode, and 70 healthy controls. In the manic episode group, 32 patients experi-

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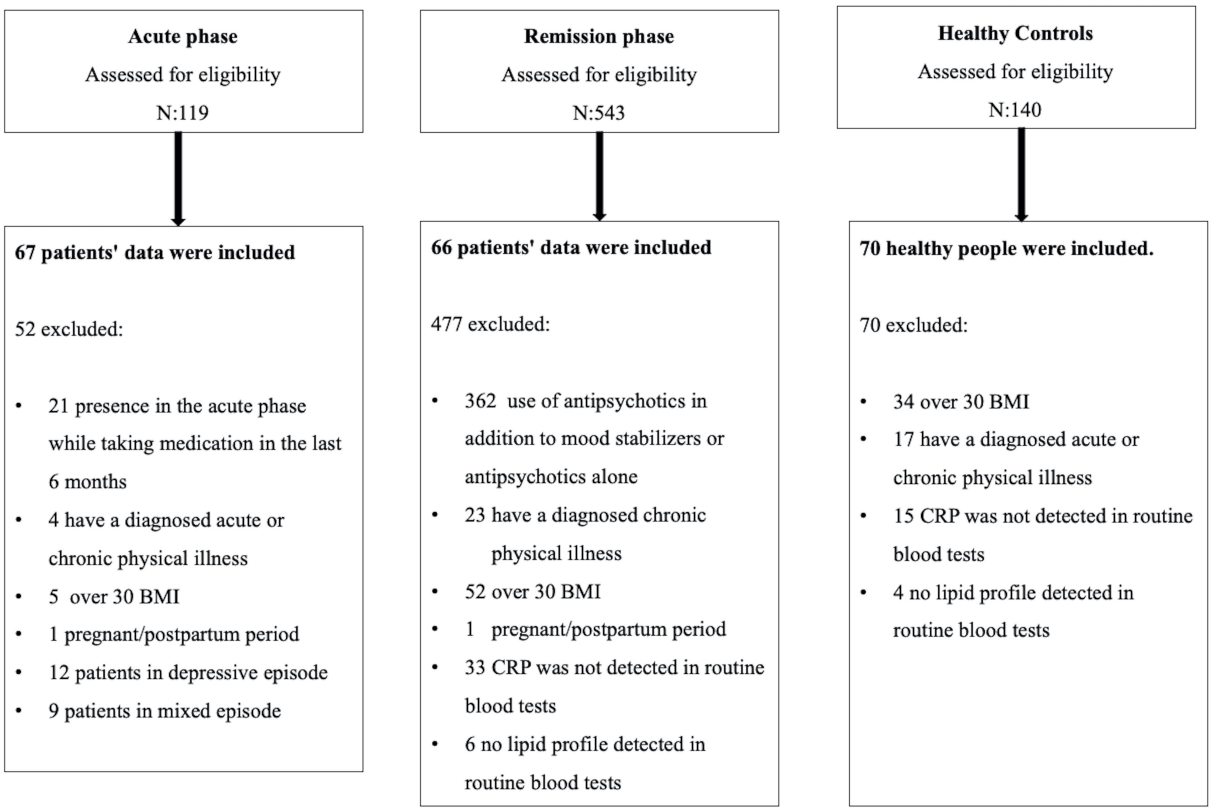

Figure 1. A flow diagram summarizing the recruitment procedures.

Table 2. Posthoc analysis results of calculated indices.

	p value		
	Control-Remission	Control-Manic Episode	Manic Episode-Remission
NHR	0.003	p<0.001	0.126
MHR	0.326	0.001	0.072
LHR	0.009	0.944	0.98
PHR	0.657	0.843	0.987
AIP	0.045	0.051	0.052
PIV	0.103	p<0.001	p<0.001
IBI	0.593	p<0.001	p<0.001

NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR: Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index.

enced their first manic episode and had not received psychiatric treatment before the study. Of the 66 patients in remission, 35 were on sodium valproate+valproic acid, 23 received lithium carbonate, and 8 received both lithium carbonate and sodium valproate+valproic acid. The drug blood levels of patients using sodium valproate+valproic acid were approximately 60-80 μg/mL, whereas the drug blood levels of patients using lithium carbonate were between 0.6 and 0.8 mEq/L.

The sociodemographic data, blood parameters, calculated indices, and clinical characteristics of the patients are presented in Table 1. The manic episode group had significantly lower age, illness duration, and number of episodes compared to the remission group (p: <0.001, <0.001, 0.001, respectively), as it included patients in their first episode. Significant differences in the calculated indices (NHR, MHR, LHR, AIP, PIV, IBI) were observed among the three groups (p values: <0.001, 0.001, 0.013, <0.001, <0.001, <0.001, respectively). Post hoc analyses for the indices are presented in Table 2. NHR was significantly lower in the control group compared with both the manic episode and remission groups (p: <0.001, 0.003). MHR was significantly higher in the manic episode group compared with the control group (p: 0.001). LHR and AIP were higher in the remission group than in the control group (p: 0.009 and 0.045). PIV and IBI values were significantly higher in the manic episode group compared with both the

Table 3. Comparison of indices calculated from blood parameters of bipolar disorder patients with drug naive first manic episode and recurrent manic episode.

	First manic episode, drug-naïve	Manic Episode	t	p
NHR	7.35±3.03	5.67±1.71	-2.758	0.008
MHR	0.94±0.48	0.70±031	-2.424	0.019
LHR	2.87±1.30	2.02±1.16	-2.808	0.007
PHR	322±137.48	251.87±82.34	-2.504	0.016
AIP	0.21±0.32	0.04±0.32	-2.095	0.040
PIV	590.88±212.73	728.49±455.09	1.607	0.114
IBI	12.03±12.93	22.61±21.76	2.388	0.020

NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR: Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, t: independent samples t-test, p<0.05: statistical significance level.

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Table 4. Correlation of clinical characteristics and laboratory results in patients with Bipolar Disorder.

		Age	BMI	DOD	NOE	NDE	NME	NHR	MHR	LHR	PHR	AIP	PIV	IBI
Age	r	1	0.278**	0.757**	0.545**	0.582**	0.540**	0.013	-0.138	-0.060	0.115	0.146	0.002	0.036
	p		0.001	0.000	0.000	0.000	0.000	0.879	0.114	0.490	0.187	0.093	0.981	0.679
BMI	r		1	.178*	0.015	0.040	0.059	0.478**	0.461**	0.506**	0.538**	0.435**	0.138	0.013
	p			0.040	0.867	0.648	0.498	0.000	0.000	0.000	0.000	0.000	0.113	0.886
DOD	r			1	.804**	0.827**	0.768**	-0.069	-0.188*	-0.208*	-0.052	0.010	0.134	0.181*
	p				0.000	0.000	0.000	0.431	0.030	0.016	0.554	0.905	0.124	0.037
NOE	r				1	0.960**	0.958**	0.009	-0.112	-0.257**	-0.043	-0.047	0.256**	0.275**
	p					0.000	0.000	0.916	0.199	0.003	0.626	0.591	0.003	0.001
NDE	r					1	0.925**	-0.037	-0.159	-0.204*	-0.018	-0.035	0.111	0.203*
	p						0.000	0.674	0.067	0.019	0.833	0.693	0.202	0.019
NME	r						1	0.046	-0.104	-0.217*	0.009	-0.008	0.210*	0.177*
	p							0.597	0.233	0.012	0.919	0.930	0.015	0.042
NHR	r							1	0.809**	0.469**	0.770**	0.529**	0.539**	0.100
	p								0.000	0.000	0.000	0.000	0.000	0.250
MHR	r								1	0.612**	0.610**	0.566**	0.367**	0.126
	p									0.000	0.000	0.000	0.000	0.149
LHR	r									1	0.586**	0.650**	-0.252**	-0.280**
	p										0.000	0.000	0.003	0.001
PHR	r										1	0.637**	0.279**	-0.150
	p											0.000	0.001	0.085
AIP	r											1	-0.063	-0.250**
	p												0.470	0.004
PIV	r												1	0.443**
	p													0.000
IBI	r													1

*BMI: Body mass index, NHR:Neutrophil/HDL ratio, LHR:Lymphocyte/HDL ratio, MHR:Monocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, **. Correlation is significant at the 0.01 level.*. Correlation is significant at the 0.05 level., DOD: Duration of Disease, NOE: Number of Episodes, NDE: Number of Depressive Episodes, NME: Number of Manic Episodes*

Table 5. Predictive Factors for Manic Episode- Logistic Regression Bacward Conditional Model.

	Variables in the Equation	B	S.E.	p	Exp(B)	95% CI for EXP(B) Lower	Upper
Step 1	LHR	-1.486	14.135	0.916	0.226	0.000	25.318
	PHR	0.019	0.124	0.881	1.019	0.799	1.299
	AIP	-0.605	1.021	0.553	0.546	0.074	4.041
	IBI	0.080	0.028	0.005	1.084	1.025	1.146
	PIV	0.003	0.001	0.012	1.003	1.001	1.005
	Age	-0.045	0.038	0.241	0.956	0.888	1.030
	Duration of disease	-0.097	0.044	0.027	0.907	0.832	0.989
	Constant	0.796	1.155	0.490	2.217	-	-
Step 5	IBI	0.094	0.027	0.000	1.099	1.042	1.159
	PIV	0.002	0.001	0.001	1.002	1.001	1.004
	Duration of disease	-0.137	0.031	0.000	0.872	0.820	0.927
	Constant	-0.709	0.428	0.098	0.492	-	-

LHR:Lymphocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, p<0.05:Statistical significance level.

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Table 6. Bipolar Disorder remission -manic episod ROC analysis results.

Area Under the Curve								
				Asymptotic 95% Confidence Interval				
Predictor	Area	Std. Error	p value	lower bound	upper bound	Cutoff value	Sensivity	Specifiicty
LHR	0.401	0.051	0.048	0.301	0.500	-	-	-
PHR	0.501	0.051	0.982	0.401	0.601	-	-	-
AIP	0.411	0.050	0.077	0.314	0.508	-	-	-
IBI	0.722	0.043	p<0.001	0.637	0.807	6.93	64.2%	66.7%
PIV	0.742	0.045	p<0.001	0.654	0.830	407.89	74.6%	69.7%

LHR:Lymphocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, p<0.05: Statistical significance level.

Table 7. Bipolar disorder patient-control ROC analysis results.

Area Under the Curve								
				Asymptotic 95% Confidence Interval				
Predictor	Area	Std. Error	Asymptotic Sig.	lower bound	upper bound	Cutoff value	Sensivity	Specifiicty
LHR	0.565	0.041	0.130	0.484	0.645	-	-	-
PHR	0.510	0.040	0.819	0.431	0.588	-	-	-
AIP	0.639	0.039	0.001	0.562	0.716	0.85	62.4%	60%
IBI	0.678	0.038	p<0.001	0.603	0.753	4.37	63.9%	65.7%
PIV	0.673	0.037	p<0.001	0.601	0.746	293.55	65.4%	68.6%

LHR:Lymphocyte/HDL ratio, PHR:Platelet/HDL ratio, AIP: Atherogenic Index of Plasma, PIV: Pan-immune inflammation value, IBI: Inflammation Burden Index, p<0.05: Statistical significance level.

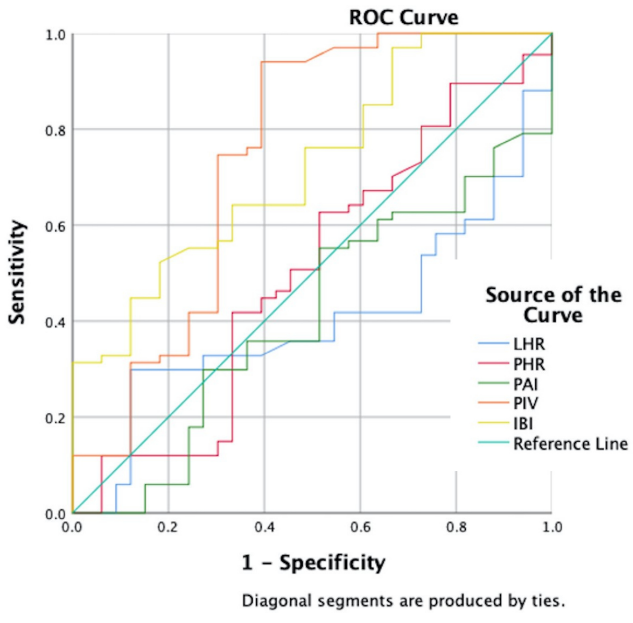

Figure 2. ROC analysis for distinguishing between manic episodes.

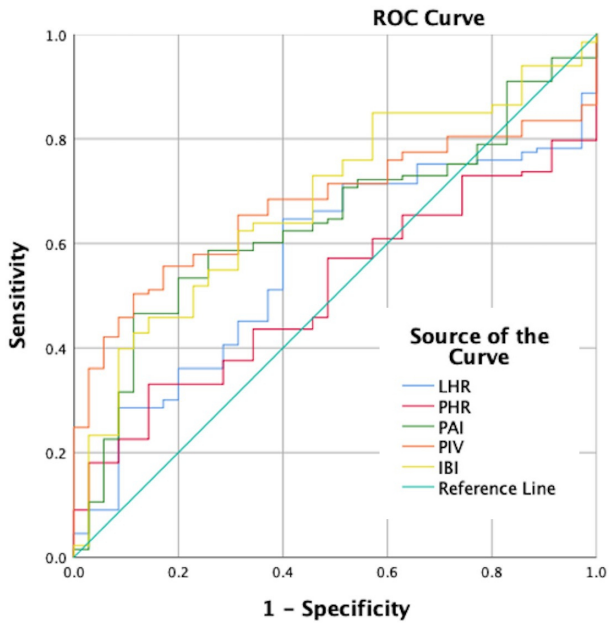

Figure 3. ROC analysis for distinguishing bipolar disorder.

remission and control groups (p<0.001 for both).

The calculated indices were also compared between patients with first manic episodes who were not taking medication and those with recurrent manic episodes. Significant differences were found in NHR (p: 0.008), MHR (p: 0.019), LHR (p: 0.007), and AIP (p: 0.040), all higher in patients with first manic episode. IBI (p: 0.020) was higher in patients with recurrent episodes, whereas PIV (p: 0.114) showed no signifi-

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cant difference between the two groups (Table 3).

A correlation analysis was performed to examine the relationship between clinical characteristics and calculated blood indices. IBI was positively correlated with illness duration, number of manic episodes, number of depressive episodes, and total number of episodes. PIV was positively correlated with the number of manic episodes and total episodes. AIP showed a positive correlation with BMI, and LHR was positively correlated with BMI, illness duration, and the number of manic and depressive episodes (Table 4).

Additionally, a correlation analysis was conducted between the Young Mania Rating Scale (YMRS) score and calculated blood indices in the manic episode group. Positive correlations were found between the YMRS score and NHR (r: 0.294, p: 0.016), MHR (r: 0.334, p: 0.006), PIV (r: 0.375, p: 0.002), and IBI (r: 0.380, p: 0.002).

Binary logistic regression (Backward Conditional Model) was used to identify the predictors of episodes of manic episodes. The presence of a manic episode was the dependent variable, and age, illness duration, LHR, PHR, AIP, IBI, and PIV were independent variables (Table 5). Due to multi-collinearity, the number of episodes and other related variables was excluded. IBI ($p<0.001$) and PIV (p: 0.001) were identified as positive predictors of manic episodes, whereas illness duration was a negative predictor. A one-unit increase in IBI or PIV doubled the risk of a manic episode (OR: 1.099 and 1.002, respectively), whereas a one-year increase in illness duration reduced the likelihood of a manic episode by 0.8 times (OR: 0.872) (Table 6). The risk of manic episodes decreased as the illness duration increased.

ROC analysis was conducted to evaluate the potential of LHR, PHR, AIP, IBI, and PIV values in distinguishing manic episodes in BD and to establish cutoff values. IBI and PIV were found to be useful for diagnosing manic episodes in BD, with cut-off values of 6.93 for IBI and 407.84 for PIV (Figure 2, Table 6). Additionally, ROC analysis for BD differentiation revealed that AIP, IBI, and PIV values above 0.85, 4.37, and 293.55, respectively, were effective in identifying bipolar disorder (Figure 3, Table 7).

DISCUSSION

This study examined the relationship between NHR, MHR, LHR, PHR, AIP, PIV, and IBI, which are evaluated together with blood cell count and biochemical parameters as inflammatory, immunonutritive, and cardiovascular markers, and BD periods and severity of manic episodes. In this study, the primary endpoints were NHR, MHR, LHR, AIP, PIV, and IBI. Blood parameters included neutrophils, monocytes, lymphocytes, platelets, HDL, TC, LDL, and TG, which were used along with these calculated indices. Clinical features included disease duration, number of episodes, BMI, and YMRS score. Correlation analyses were conducted to examine the relationships between clinical features and the calculated indices, while binary logistic regression was utilized to determine the predictors of manic episodes. Receiver operating characteristic (ROC) analyses were conducted to evaluate the potential of LHR, PHR, AIP, IBI, and PIV in distinguishing manic episodes.

As expected, PIV and IBI were highest during the episodes, and these two values were found to be associated with manic episodes. Although there are many studies in terms of BD inflammation, to the best of our knowledge, there is no study evaluating BD periods and severity in terms of PIV and IBI. In a recent meta-analysis study, CRP levels were higher in patients in the manic period than in healthy controls and patients in depressive and euthymic states [6]. While there are studies showing increased neutrophil and lymphocyte counts in patients with BD compared with controls [28], there are also studies in which no significant difference was found [7]. Again, in a study including 78 patients with manic and 88 remission period BD and 101 controls, the monocyte/lymphocyte ratio was found to be high in the manic episode, while no significant results were found in terms of platelet/lymphocyte and neutrophil/lymphocyte ratio [29]. Although it is difficult to compare these findings with our study results, they are consistent with studies showing inflammation in BD and especially in manic episodes. In the same study, the lipid profile was also examined, and triglyceride, LDL, and total cholesterol levels were found to be higher in the remission group, whereas HDL levels did not show a significant difference [29]. Inflammation during manic episodes may be a reflection of physiological stress and metabolic changes. Insomnia, excessive activity, high energy levels, and increased cortisol and sympathetic nervous system activation during manic episodes may be factors that trigger this inflammation.

In our study, AIP was significantly higher in the remission period. This was an expected finding due to the atherogenetic effect of long-term medications, eating patterns, and sedentary lifestyles of the patients [30]. In a study conducted by Kalelioğlu et al. with 68 patients with manic attack, it was shown that while pre-treatment AIP values were similar to healthy controls, post-treatment AIP values increased significantly compared with pre-treatment values. This was interpreted as that even short-term treatments may increase cardiogenic risk, that the manic period may have a positive effect on atherogenic risk or at least that it would not have any effect [23]. Although only patients in the remission period who were using mood stabilizers and not antipsychotics were included in our study, AIP values were significantly higher than those of the control group. AIP was significantly higher in patients with a naive first manic episode. This finding suggests that people who are predisposed to this disease are also structurally more vulnerable to atherogenicity regardless of the drug. In a review of 142 studies evaluating metabolism and cardiovascular diseases in BD, mortality rates from cardiovascular disease and pulmonary embolism doubled compared with the general population. Reduced exercise and poor diet, frequent depressive episodes, comorbidity with substance abuse, and poor

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quality general medical care may contribute to the additional risk of these medical problems in people with bipolar disorder. Contrary to popular belief, long-term treatment with lithium, antipsychotics, and tricyclic antidepressants may reduce overall mortality [31]. These findings suggest that there are mixed results regarding cardiovascular risk in patients with BD and that conflicting results may have been found because this may be related to many factors such as ethnic origin, drugs used, anti-inflammatory effects of drugs, genetic predispositions, sedentary lifestyle, and predisposition to drugs and smoking.

Although LHR was significantly higher in the remission period, MHR was significantly higher in the attack period, and NHR was significantly lower in the control group, the ratio of these leukocytes to HDL did not have a predictive effect on disease or attack period. NHR was weakly correlated, and MHR was strongly correlated with the severity of the attack, determined by YMRS only during the attack period. Again, PIV and IBI showed a strong relationship and positive correlation with attack severity. Although no study has compared PIV and IBI one-to-one, the relationship between CRP and YMRS was examined in a study conducted by Kara et al. with 35 patients in the manic period, but no relationship was found [32]. In a study conducted with 116 patients with BD using high-sensitive CRP, which was thought to be more specific for inflammation, a positive correlation was found between YMRS scores and number of attacks and high-sensitive CRP levels [33]. In the present study, IBI was higher in patients with recurrent attacks. IBI increased as the disease duration and the number of episodes increased, whereas PIV increased as the number of episodes, especially manic episodes, increased.

In our study, PIV and IBI were associated with both a manic episode and illness. AIP was also shown to be associated with illness. Patients who were not taking medication during the episode were included; however, patients in remission were taking mood stabilizers. Studies are showing the antiinflammatory effects of mood stabilizers [34]. However, PIV, IBI, and AIP were associated with both inflammation and atherogenicity were high in patients in remission. These findings suggest that the disease is inherently an inflammatory process, although the mechanism of this inflammation has not been fully elucidated.

Our study has some strengths and limitations. The fact that our study sample included patients with a first episode manic episode who had never taken any medication, that those in manic episode were not taking medication for the last 6 months, and that patients in remission were only taking mood stabilizers strengthens our study in terms of reducing the limitation of medication use. In addition, the fact that patients with a BMI >30 were not included in the study due to its effect on both inflammation and atherogenicity, and other strict inclusion criteria, strengthens our study. Confounding factors that may have an impact on inflammatory states, such as sleep, exercise, nutrition, alcohol consumption, smoking status, and lifestyle, were not included in the analysis. Since the manic episode group included patients with their first episode, the age of this group was lower than that of the other two groups. Although the effect of age was controlled in the logistic regression analysis, another limitation is that the ages of the groups were not similar. Although we tried to minimize the effect of drugs on inflammation, the fact that patients in the remission period were taking mood stabilizers, and these drugs have known anti-inflammatory effects, is also a limitation of our study. The fact that inflammation indicators are still high, although patients in the remission period are using drugs known to have anti-inflammatory effects, suggests that there may also be the effect of factors such as alcohol, smoking, and lifestyle changes, which we cannot exclude as a confounding effect in this group of patients. The retrospective and cross-sectional design of the study is an important limitation. This approach prevents the establishment of strong causal relationships between blood parameters, biomarkers, and disease-related outcomes. In addition, differences in the timing of blood collection and whether blood was drawn under appropriate conditions (such as fasting and postprandial) may have caused variations in some parameters (such as lipids). Although strict inclusion and exclusion criteria were applied in this study, since the data were obtained from hospital records, treatments and disease diagnoses not included in hospital records may have been missed. The administration of YMRS to participants by different psychiatrists is both a limitation and an advantage. This may have prevented possible bias. Evaluation of inflammatory and atherogenic parameters in the same patients before the first episode, during the episodes, and during the remission period; analyzing these parameters by detailing the confounding factors will provide more accurate data and can be planned for future longitudinal studies.

Given the inflammatory and atherogenic processes involved in the etiopathogenesis, the novel biomarkers PIV, IBI, and AIP may be promising therapeutic targets for BD. In addition, these biomarkers can be used as easily accessible, inexpensive clinical tools to predict disease, manic episodes, and the severity of manic episodes. Given the limitations of our study, further validation is needed to confirm the clinical validity of our results. Therefore, prospective follow-up of these groups is important to assess progress in the patient and control groups. Longitudinal and well-designed studies involving larger patient groups should be conducted to ensure the results of the study are generalizable. It should be noted that in this study, which aims to reflect a real-world sample of the population, our results may not be representative of the entire population.

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Peer-review: Externally peer-reviewed.

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