Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(2):207-214
DOI: 10.4274/BMJ.galenos.2024.2024.3-4

Research

Aggregate Index of Systemic Inflammation and Systemic Inflammatory Response Index: Could be Potential Biomarkers to Monitor Bipolar Disorder Patients? An Observational Study

Sistemik Enflamasyonun Toplam İndeksi ve Sistemik Enflamatuvar Yanıt İndeksi; Bipolar Bozukluk Hastalarını İzlemek için Potansiyel Biyobelirteçler Olabilir mi? Gözlemsel Bir Çalışma

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ABSTRACT

Objective: Bipolar disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of mania and depression. Studies have reported the involvement of inflammatory processes in the pathophysiology of BD. This study aims to demonstrate that certain inflammatory markers are elevated in BD patients and to highlight their potential for use in diagnosis, prognosis, and treatment monitoring.

Methods: This study included 57 BD patients and 121 healthy controls (HC). All participants underwent a complete blood count. Subsequently, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) values were calculated. The ethics committee approval for the study was obtained from Maltepe University Faculty of Medicine on January 19, 2022, number 2022/900/02.

Results: The NLR, mean platelet volume (MPV), red cell distribution width (RDW), AISI, and SIRI values were higher in BD patients compared to HC. No significant differences were found in MLR, PLR, and SII levels between the BD and HC groups.

Conclusion: Higher NLR, MPV, RDW, AISI, and SIRI values in BD patients than HC suggest increased inflammatory processes in BD. NLR, MPV, RDW, SIRI, and AISI are believed to be involved in the pathophysiology of BD and hold potential as biomarkers for monitoring disease prognosis and treatment efficacy. To further understand the underlying mechanism of BD, additional longitudinal studies are needed to determine how BD impacts inflammatory processes.

Keywords: Bipolar disorder, neutrophil to lymphocyte ratio, mean platelet volume, systemic inflammatory response index, aggregate index of systemic inflammation, erythrocyte indices, inflammation

ÖZ

Amaç: Bipolar bozukluk (BB), tekrarlayan mani ve depresyon atakları ile karakterize ciddi bir psikiyatrik bozukluktur. Çalışmalar, BB'nin patofizyolojisinde enflamatuvar süreçlerin rol oynadığını bildirmektedir. Bu çalışma, BB hastalarında belirli enflamatuar markerların yükseldiğini göstermeyi ve bu markerların tanı, prognoz ve tedavi izleminde kullanılma potansiyelini vurgulamayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmaya, 57 BB hastası ve 121 sağlık kontrol (SK) dahil edilmiştir. Çalışmaya katılan katılımcılardan tam kan örneği alındı. Ardından, nötrofil-lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), trombosit-lenfosit oranı (TLR), sistemik inflamasyon indeksi (SII), sistemik

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Cite as: Büyüksandalyacı Tunç E, Arat Çelik HE, Kök Kendirlioğlu B, Çörekli Kaymakçı E, Çiftçi HB, Demir Ş. Et al. Aggregate index of systemic inflammation and systemic inflammatory response index: could be potential biomarkers to monitor bipolar disorder patients? an observational study. Med J Bakirkoy. 2025;21(2):207-214

Received: 16.03.2024
Accepted: 27.12.2024
Publication Date: 04.06.2025

ÖZ

enflamatuar yanıt indeksi (SIRI) ve sistemik enflamasyonun toplam indeksi (AISI) değerleri hesaplandı. Çalışmanın etik kurul onayı Maltepe Üniversitesi Tıp Fakültesinden 19.01.2022 tarih, 2022 /900/ 02 no ile alınmıştır.

Bulgular: BB hastalarının NLR, ortalama trombosit hacmi (MPV), eritrosit dağılım genişliği (RDW), SIYI ve SIRI değerleri SK'e göre daha yüksekti. BB grubu ile SK arasında MLR, TLR ve SII seviyeleri arasında anlamlı bir fark yoktu.

Sonuç: BB hastalarında SK'e kıyasla daha yüksek NLR, MPV, RDW, AISI ve SIRI değerleri, BB'da artmış inflamatuvar süreçleri işaret etmektedir. NLR, MPV, RDW, SIRI ve AISI'nin, BB'un patofizyolojisinde yeri olduğu, ayrıca hastalığın prognozunu ve tedavinin etkinliğini izlemek için potansiyel biyobelirteçler olduğu düşünülmüştür. BB'nin temel nedenlerini daha iyi anlamak ve bozukluğun inflamatuvar süreçleri nasıl etkilediğini belirlemek için ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bipolar bozukluk, nötrofil-lenfosit oranı, eritrosit indeksleri, sistemik inflamatuar yanıt indeksi, sistemik enflamasyonun toplam indeksi, Ortalama trombosit hacmi, İnflamasyon

INTRODUCTION

Bipolar disorder (BD) is a severe mood disorder affecting millions worldwide, characterized by episodes of mania and depression. While genetic, environmental, and neurobiological factors are implicated in its etiology, growing evidence suggests that systemic inflammation and immunological abnormalities are crucial components in the pathogenesis of BD. According to studies, during manic and depressive episodes, patients with BD exhibit higher pro-inflammatory cytokines, acute-phase proteins, and immune activation markers (1). This inflammatory state may contribute to neuroprogression and mood symptoms. Various hypotheses have been proposed for how cytokines enter the central nervous system (CNS). Three potential mechanisms are the binding to cytokine-specific carrier molecules generated by the endothelium, the stimulation of vagal afferent pathways that transmit cytokine signals to various brain nuclei, and access to areas without a blood-brain barrier, such as circumventricular organs. Cytokines enter the CNS through one or more of these pathways, causing neuroinflammation (1,2). Focusing on various inflammatory markers is essential to better understand the inflammatory processes of BD. These markers play a critical role in monitoring the course of the disorder and assessing treatment responses. In particular, markers that reflect the level of systemic inflammation may help to elucidate possible mechanisms in the pathogenesis of BD. In addition, these inflammatory markers may vary depending on the clinical condition of the patients, allowing for the development of individualized treatment strategies. A closer look at some inflammatory markers and their effects on BD is needed (3).

The systemic inflammatory index (SII), the aggregate index of systemic inflammation (AISI), systemic inflammation response index (SIRI), neutrophil/ lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR) values have been investigated for evaluating inflammatory dysregulation in long-term illnesses like cancer, diabetes mellitus and heart disease (4). White blood cell assays can quickly determine these values in a laboratory setting. Neutrophils serve as the initial line of defense of the immune system. However, lymphocytes are also essential for mediating adaptive immune reactions. Platelets affect immune response management, coagulation, and serotonin release in inflammatory conditions. Significantly, serotonin, in turn, elevates cytokine levels. Monocytes are a subset of leukocytes known for their pro-inflammatory effects (5).

According to the complete blood count, mean platelet volume (MPV) denotes the average size of platelets, and an increase in MPV is associated with inflammatory processes. An increase in MPV indicates that large platelets are being circulated, supporting the idea that MPV can indicate active inflammation. It has been identified as a new potential biomarker for diagnosing several diseases. These include neoplastic disease, cardiovascular diseases, inflammatory bowel diseases, cerebrovascular events, and neurodegenerative diseases (6,7). Since inflammation is also seen in BD, MPV might be a possible biomarker (8,9). Red cell distribution width (RDW), a measure of heterogeneity in the size of circulating red blood cells, is a percentage determined from the hemogram using the standard deviation (SD) of red blood cell volume divided by the mean corpuscular volume and expressed as a percentage. Increased RDW levels are linked to poor erythropoiesis or erythrocyte breakdown. Recent research has studied RDW as an inflammatory marker in several clinical disorders, such as rheumatoid arthritis, inflammatory bowel disease, colon cancer, and celiac disease (10). Higher RDW levels have been linked to chronic inflammatory disorders, and this increase might also present in BD (11)

NLR, a simple and affordable indicator of systemic inflammation, is calculated as the NLR ratio in peripheral blood. Higher NLR indicates an enhanced pro-inflammatory state and has been linked to various neuropsychiatric disorders, including BD. Recent studies have shown significantly higher NLR values in BD patients during manic

and depressive episodes, suggesting NLR may help assess mood states (8). PLR highlights the interaction between platelets, involved in coagulation and inflammation, and lymphocytes, which are essential for immune regulation. Higher PLR is a straightforward and effective measure of inflammation severity. High PLR has been observed in BD patients, especially during manic episodes, highlighting the potential role of platelet-mediated inflammation in the disorder (12). The MLR has also gained attention in BD research. Higher MLR has been associated with more severe manic symptoms, suggesting a possible link between monocyte-mediated inflammation and BD severity (3,12).

SII is calculated as SII=platelet count×NLR. SII has been reported to be associated with systemic inflammatory status and short-term adverse outcomes in patients with pancreatic cancer and acute ischemic stroke, and it potentially predicts an adverse prognosis in these patients (13,14). SII is also found to be a risk factor and a predictor for the development of depression in patients with diabetes mellitus (15). In BD, elevated SII has been associated with increased disease severity, suggesting a link between systemic inflammation and symptomatology (16,17). AISI is a relatively new index used to evaluate the relationship between inflammation and various disorders. AISI is calculated as neutrophil x platelet x monocyte/lymphocyte. This index provides a broader view of inflammation, allowing for a more comprehensive evaluation of the body's inflammatory response (4). In two thesis studies, AISI values were higher during the manic period of BD than during the depressive and euthymic periods, although healthy controls (HCs) were not included in these studies (18,19). SIRI is calculated as neutrophils × monocytes/ lymphocytes (20). High levels of SIRI appear to be a marker of chronic inflammation in various medical conditions (20,21). High SIRI levels may indicate worse depressive outcomes in treatment-resistant BD patients with significant depressive symptoms at baseline (20).

Research findings indicate that inflammatory parameters fluctuate in BD, and changes in these parameters may be related to the severity of manic or depressive symptoms. We hypothesized that inflammatory markers such as NLR, SIRI, AISI, and SII levels are elevated in BD patients compared to HC. Furthermore, the relationship between AISI and BD has not yet been sufficiently studied, and we hypothesized that these markers would be higher in the BD group than in HC. This study aims to explore the relationship between BD and the inflammatory markers discussed in the paper, and to contribute to the literature by identifying markers that can be used to monitor and treat BD, where inflammatory processes are active.

METHODS

This is a retrospective observational study. It included 57 patients diagnosed with BD who were hospitalized for treatment at the Maltepe University Faculty of Medicine, Department of Psychiatry, between 2013 and 2022. A total of 121 HCs were selected from individuals without psychiatric disorders who visited Maltepe University Faculty of Medicine, Department of Family Medicine, for routine health checks between 2020 and 2022. The diagnosis of BD was made by an experienced psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders 5 diagnostic criteria. The study was approved by the Clinical Research Ethics Committee of Maltepe University Faculty of Medicine (decision no: 2022 /900/ 02, date: 19.01.2022).

Participants

This study investigated individuals aged 18 to 65 and reviewed their past health data. Within the first 24 hours after admission, blood samples were collected from individuals admitted to the psychiatry inpatient clinic for 36 manic (63.2%) and 21 depressive (36.8%) episodes of BD. Individuals with a history of substance abuse, hypertension, diabetes mellitus, heart disease, autoimmune or inflammatory disorders, cancer, active infections, or individuals using medications that may affect the immune system were excluded from the study. Based on this criterion, 14 individuals were removed from the HC group, and eight were excluded from the BD group. Additionally, in the HC group, individuals suspected of having an acute or lifetime psychiatric disorder or alcohol or substance use disorder were excluded based on routine consultations with their primary care physician.

Statistical Analysis

Descriptive statistics included the mean, SD, median, minimum, maximum, frequency, and ratio values. The Kolmogorov-Smirnov test was used to assess the distribution of the variables. An independent samples t-test and the Mann-Whitney U test were used to analyze quantitative independent data, while the Chi-square test was employed for independent qualitative data. Data analysis was performed using the SPSS 28.0 software. A p-value of 0.05 was considered statistically significant, and the results of all tests were reported as the mean ± SD. According to the power analysis, the difference in group sizes did not affect the significance of our results.

RESULTS

Data from 57 BD patients (35 female, 22 male) and 121 HC (69 female, 52 male) were included in the study. The mean age was 37.5±8.3 years (median: 38.0) in BD patients

and 37.1±11.9 (median: 37.0) in the HC group. There was no significant difference (p>0.05) in age and gender distribution between the HC and BD groups. Neutrophils, monocytes, RDW, and MPV values were significantly higher (p<0.05) in the BD group compared to the HC group. Socio-demographic data and hemogram test results are shown in Table 1.

NLR, SIRI, and AISI values were significantly higher (p<0.05) in the BD group compared to the HC group, while lymphocyte, platelet, MLR, PLR, and SII showed no significant difference (p>0.05) between the two groups (Table 2). The comparison of NLR, SIRI, and AISI levels between the groups is shown in Figure 1.

DISCUSSION

The inflammatory system plays a crucial role in the onset and progression of BD, and numerous studies have been conducted on this topic. In our study, we observed that the BD group had higher neutrophil, monocyte, RDW, MPV levels, as well as NLR, AISI, and SIRI levels compared to the HC group. However, there were no statistically significant changes in lymphocyte and platelet levels, SII, PLR, and MLR. although NLR, PLR, and MLR have been studied extensively in BD patients, RDW, MPV, SII, AISI, and SIRI have rarely been investigated. In particular, the difference in AISI levels between BD and HC has not been studied before.

In a 2020 meta-analysis examining NLR levels in mood disorders, 11 studies were reviewed. NLR levels in BD were consistently higher than in HCs, regardless of whether the episodes were manic, depressive, or euthymic (22). BD patients in their first manic episode had significantly higher NLR levels than chronic patients (23). Additionally, compared to the remission period, BD patients in manic and depressive episodes showed higher NLR levels (3.24). Considering all these findings, the inflammatory response increases during the manic and depressive periods of BD, and NLR is a marker that can be monitored during treatment.

In this study, BD patients had considerably higher RDW values than HCs. RDW is a biomarker that measures the variation in red blood cell size and is commonly used to assess anemia and hematological illnesses. In recent years, increasing evidence has suggested that RDW is linked to

Table 1. Sociodemographic data and hemogram results of bipolar disorder patients and healthy controls

		Healthy control			Bipolar disorder			p-value	
		Median±SD/n-%		Median	Median±SD/n-%		Median		
Age		37.5±8.3		38.0	37.1±11.9		37.0	0.472	m
Gender	Female	69	57.0%		35	61.4%		0.580	X^2
	Male	52	43.0%		22	38.6%			
Neutrophil		4028.7±1216.1		3980.0	5118.0±2448.6		4800.0	**0.006**	m
Lymphocyte		2425.9±684.7		2360.0	2495.5±712.2		2480.0	0.416	m
Monocyte		603.9±199.0		590.0	675.3±207.2		660.0	**0.016**	m
Platelet		246.9±61.8		245.0	246.3±68.1		243.5	0.640	m
RDW		13.3±0.8		13.2	13.9±1.1		13.7	**0.001**	m
MPV		10.2±0.9		10.1	9.8±1.1		9.8	**0.014**	m

m: Mann-Whitney u test, X^2 chi-square test, RDW: Red cell distribution width, MPV: Mean platelet volume

Table 2. Values of inflammatory indices in bipolar disorder patients and healthy controls

	Healthy control		Bipolar disorder		p-value	
	Median.±SD/n-%	Median	Median.±SD/n-%	Median		
NLR	1.76±0.68	1.66	2.27±1.57	1.94	**0.003**	t
MLR	0.26±0.08	0.25	0.29±0.13	0.26	0.202	m
PLR	107.5±33.7	103.8	106.1±39.7	103.0	0.809	t
SII	433.2±196.2	398.9	580.0±501.1	448.6	0.211	m
SIRI	1072.6±566.9	960.5	1582.3±1224.6	1196.4	**0.017**	m
AISI	2744.1±1849.7	2201.0	4096.8±3758.2	2777.8	**0.038**	m

t: Independent samples t-test, m: Man-Whitney u test, X^2 Chi-square test, NLR: Neutrophil/ lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/ Platelet/lymphocyte ratio, SII: Systemic inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of Systemic inflammation

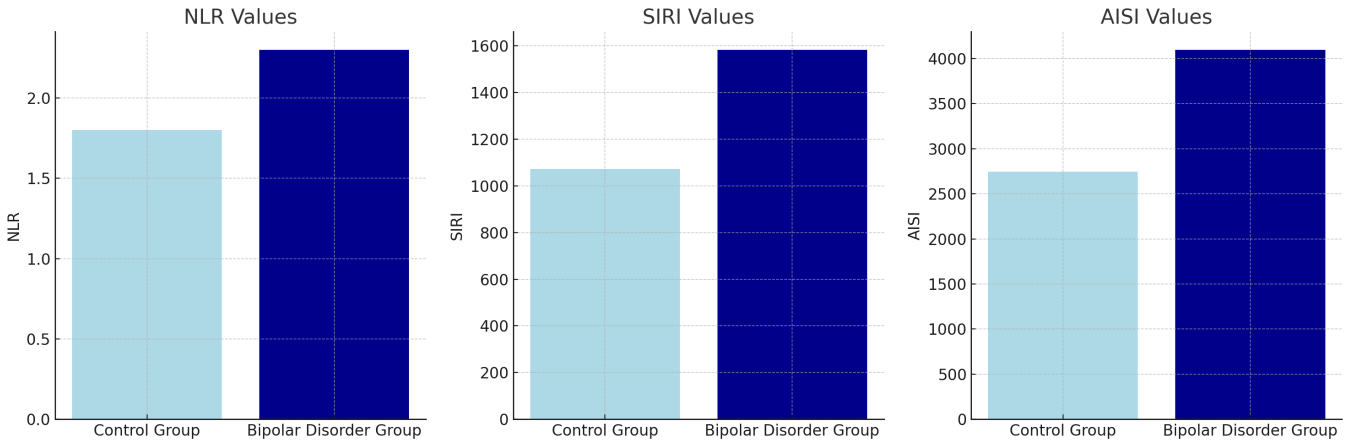

Figure 1. Comparison of NLR, SIRI and AISI levels of groups

NLR: Neutrophil/lymphocyte ratio, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

systemic inflammation. Elevated RDW has been associated with chronic inflammatory diseases such as cardiovascular disease and it is believed that this rise may also occur in neuropsychiatric disorders like BD (11,25). Previous studies have found higher levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha in BD patients. These cytokines influence erythropoiesis and are thought to promote red blood cell size variability. Increased oxidative stress can damage red blood cell membrane integrity, leading to elevated RDW (26) Kirlioglu et al. (27) evaluated inflammatory markers based on complete blood counts in BD mania and mixed episodes, discovering a link between inflammation and hematologic parameters. In contrast to previous research, the investigation of RDW in BD suggests that can be employed as a biomarker of inflammatory processes.

To our knowledge, the relationship between BD and SIRI and AISI has not been adequately examined in the literature. AISI and SIRI are new indices that reflect the inflammatory and immune status. According to a study's finding, high SIRI levels may predict worse depressive outcomes in treatment-resistant BD patients with significant depressive symptoms at baseline (20). Another study found that SIRI correlates with endothelial dysfunction in BD patients during depressive episodes (28). A study comparing SIRI values between BD patients, schizophrenia patients, and HCs found that the SIRI levels were higher in both BD and schizophrenia patients than in HCs. In light of this, SIRI may be a useful inflammatory marker to distinguish these patients (17). AISI, a more recently developed inflammatory marker, has been studied less in general literature, and in psychiatry literature. AISI may also have other clinical applications in systemic pro-inflammatory diseases, such as cancer. White blood cell, neutrophil, monocyte, lymphocyte, and platelet counts alone in predicting four-year survival. Based on this, the presence and severity of inflammation seem to be directly proportional to the higher AISI values (29). As far as we know, the psychiatric studies on AISI are limited to two theses. According to the results of these studies, AISI values of BD patients during manic episodes were found to be higher than those during BD depressive and euthymic periods (18,19). While our study supports the results of these two theses, comparing BD patients to HC revealed a new finding. In light of all these data, it is thought that AISI could be used as an inflammatory marker and that it may be more specific to manic episodes. It would be appropriate to support these findings with more comprehensive studies. Considering the research in the literature, elevated AISI and SIRI are known to indicate prognostic features in inflammatory diseases. Similar results have been found in the limited number of studies conducted in BD so far, and it is thought that BD is an inflammatory disorder, with AISI and SIRI potentially serving as prognostic markers. Undoubtedly, there is a need for more studies with larger patient samples to explore the contributions of AISI and SIRI in monitoring treatment response and prognosis in BD.

Platelets, as a non-specific first-line inflammatory signal, along with platelet activation modulated by inflammatory mediators, P-selectin and neurotransmitters, can modify endothelial permeability, allowing neutrophils and macrophages to recruit more efficiently. Since MPV is associated with inflammation and affects both platelet count and function, elevated levels of MPV in BD patients have been proposed as potential indicators of

inflammation. Some studies have demonstrated increased MPV in BD patients (7-9,30,31), while others have shown uncertain or less significant results (11,27). This is most likely due to methodological differences in the research, patient group differentiation, and varying stages of the disease. Therefore, more studies on this subject are needed. PLR can be used to predict the inflammatory response in mood disorders. A meta-analysis found that patients with BD had higher PLR levels than controls (22). However, in the current investigation, no significant difference in platelet count or PLR values was detected between the groups. Other studies have reported altered platelet count and PLR levels in mood disorders, but their findings are inconsistent (26). Studies found NLR to be a more consistent marker of inflammation when compared with PLR. Hence, PLR may not be considered a reliable marker for BD.

Our research showed that monocyte levels in BD patients were considerably higher than those in HC, but there was no significant difference in MLR levels. When examining monocyte and MLR levels, as seen in many psychiatric disorders, BD patients may have higher circulating monocytes due to enhanced immune gene expression and excess production of cytokines linked with monocytes/macrophages. Given that microglial activation could be part of the systemic cytokine activation and the mononuclear phagocyte system, the high MLR during manic episodes in BD might be interpreted as a peripheral marker of brain inflammation (32). However, more understanding of this measure in BD is still needed. In contrast to our findings, studies that examined MLR in BD patients found considerably higher MLR in hypomanic or manic BD groups than in depressive BD groups, even though these patients were not compared to HC (12,22). The observed monocyte levels, despite their significance, did not show a significant difference, which could be due to the relatively small sample size, while MLR levels were not significant in our study. Further research using similar methods is needed to clarify the role of monocytes in BD episodes.

Previous studies have emphasized the significance of SII in predicting the prognosis of various physical illnesses, including tumors (33) and psychiatric disorders (34). Wei et al. (17) found that BD patients exhibited higher SII levels than HC. Furthermore, they discovered that SII values were significantly higher in BD patients experiencing manic episodes than in depressive episodes (35). On the other hand, one study found that while SII levels were elevated in BD patients, there was no significant difference between manic or depressive episodes (16). It has been reported that, in BD, SII levels do not significantly differ from those in HC (36). Additionally, some studies report that SII is higher over the manic episode than the depressive period in BD (17). Since we did not separately compare patients in manic, and depressive episodes in this study, we believe this may explain our results. Prospective studies aimed at distinguishing the episodes should be conducted on this subject.

Study Limitations

Our study would benefit from a larger sample size. Therefore, the results of our research should not be generalized to all BD patients. Another limitation is the study's retrospective nature, which means that patients were not monitored for inflammatory markers during remission. One significant limitation is that we evaluated all episodes as a group, not separately as manic and depressive episodes. Future studies could address this by separating the episodes. Furthermore, while we adjusted for potentially confounding factors such as age and sex, other variables, such as body mass index, medication use, and lifestyle factors, may influence inflammatory markers. Future studies should also consider how treatments and the resolution of manic or depressive episodes impact inflammatory markers in the bloodstream.

Conclusion

Systemic inflammation and immune dysregulation are critical factors in the pathophysiology of BD. NLR, MPV, RDW, AISI, and SIRI are promising biomarkers for BD that can help in understanding the disorder's pathophysiology, diagnosing it, evaluating its prognosis, and monitoring treatment. However, further research is needed to validate their clinical utility, establish standardized cutoff values, and clarify the complex relationships between inflammation and BD. Integrating these biomarkers into clinical practice may offer a more personalized and practical approach to managing this complex psychiatric disorder.

ETHICS

Ethics Committee Approval: This study Maltepe University Clinical Research Ethics Committee (decision no: 2022/900/02, date: 19.01.2022).

Informed Consent: This is a retrospective observational study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: E.B.T., H.E.A.Ç., B.K.K., E.Ç.K., H.B.Ç., Ş.D., S.K., Consept: E.B.T., H.E.A.Ç., B.K.K., Ş.D., Design: E.B.T., H.E.A.Ç., B.K.K., Data Collection or

Processing: E.B.T., E.Ç.K., H.B.Ç., Ş.D., S.K., Analysis or Interpretation: E.B.T., H.E.A.Ç., H.B.Ç., S.K., Literature Search: E.B.T., Writing: E.B.T., H.E.A.Ç., B.K.K., E.Ç.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

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