Original Research

Neutrophil–Lymphocyte Ratio, Monocyte–Lymphocyte Ratio and Platelet–Lymphocyte Ratio in Manic Episode Patients with Bipolar Disorder

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ABSTRACT

Objective: Inflammation is one of several etiopathological mechanisms contributing to bipolar disorder. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) are relatively cheap hematological parameters recommended to measure the level of inflammation. In this study, the NLR, MLR, and PLR values of the same patients during manic and euthymic periods were compared to a healthy control group.

Methods: This retrospective study was conducted on inpatients with bipolar disorder manic episodes at the Karamanoglu Mehmetbey University Faculty of Medicine psychiatry clinic. Ninety-nine patients with manic episodes of bipolar disorder and age and gender-matched 101 volunteers without prior psychiatric illness were included in the study. Neutrophil, lymphocyte, monocyte, and platelet counts during the disease period were recorded, and NLR, MLR, and PLR values were calculated from these values. Similar hematological parameters of the same patients in the euthymic period after discharge were compared.

Results: Of the patients, 52 (52.6%) were male and 47 (47.4%) were female. The mean age of the patients was 35.3±13.09 years. Patients with manic episodes were shown to have significantly higher neutrophil, platelet, NLR, MLR, and PLR levels than the control group (p<0.001). Monocyte count was significantly lower in manic episode patients compared to controls (p<0.001). Neutrophil and monocyte counts were significantly lower during the euthymic period compared to the control group, while NLR, MLR, and PLR levels were higher (p<0.001).

Conclusions: The fact that NLR, MLR, and PLR are higher in BD patients compared to the healthy control group in both manic and euthymic periods indicates that they can be used as trait biomarkers. For biomarker studies, prospective studies with large samples are needed.

Keywords: Bipolar disorder; inflammation; biomarkers; neutrophil-lymphocyte ratio

INTRODUCTION

Bipolar disorder (BD) is a multifactorial chronic disease marked by mood swings between manic/hypomanic episodes and depressive periods. Bipolar disorder has a 4.4 percent lifetime prevalence, has a negative economic and social effect, and is one of the top causes of disease-related disability globally [1]. If untreated, it can lead to suicide [2]. Despite the current medications, the disease's progress is frequently unrelenting and a group of patients is resistant to treatment [3]. Inadequate therapy may be due to a lack of understanding of the physiopathology of BD. There is no specific laboratory finding or biomarker for diagnosis, and detailed clinical evaluation is the keystone of diagnosis [4]. Biomarkers are essential in understanding the pathophysiology of a disease, identifying new treatment targets, and monitoring

the response to therapy [5]. The discovery of pathophysiological biomarkers in BD may be crucial in developing novel molecular treatments [6]. Inflammation is one of many etiopathological mechanisms of bipolar disorder that have recently been highlighted [7]. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) have all been proposed as inflammatory markers [8]. NLR, MLR, and PLR biomarkers are widely available, cheap, and widely used.

The aim of this study was to investigate how NLR, MLR, and PLR alter during bipolar manic and euthymic episodes.

To achieve this, firstly, NLR, MLR, and PLR values in mania and euthymia in Patients with BD were compared to healthy controls

and secondly, changes in NLR, MLR, and PLR values in BD patients were assessed from the manic to the subsequent euthymic period.

METHODS
This retrospective survey was carried out on bipolar disorder inpatients. (DSM-V) manic episodes at the Karamanoglu Mehmetbey University Faculty of Medicine psychiatry clinic between January 1, 2016, and January 1, 2022. All data were collected from patient files in the hospital's electronic medical record database; patients with full blood counts within the first 24 hours of admission were included. Those who have any local and systemic inflammatory disease, use anti-inflammatory therapy and have acute and chronic illnesses that may cause abnormal inflammatory parameters were left out of the research. Those under the influence of drugs and pregnant women were also withdrawn from participating in the research.

After obtaining the necessary permissions, the data were scanned retrospectively from the hospital archive. A total of 162 BD patients' records were accessed. The study excluded 21 diabetes patients, 15 hypertension patients, 13 people with various rheumatological disorders, 6 pregnant women, and 8 adults over the age of 65.

The study comprised 99 participants with bipolar illness and manic episodes. Patients' sociodemographic characteristics and clinical features were collected. Whole blood count was performed on the first day of hospitalization. Blood samples were collected on EDTA tubes. Neutrophil, monocyte, thrombocyte, and lymphocyte numbers values, were measured on an automatic whole blood analyzer. The NLR, MLR, and PLR were calculated.

The numbers of neutrophils, monocytes, platelets, and lymphocytes at the first hospitalization were recorded and used to calculate NLR, MLR and PLR values. Neutrophil, monocyte, thrombocyte, and lymphocyte counts, NLR, MLR, and PLR values were retaken while the same patients were in the euthymic period after they were discharged. Euthymic period blood values were taken between two months and twelve months after remission.

The control group consisted of people who donated to the hospital blood bank. Examinations were made to show that those who want to donate blood do not have any chronic diseases, infectious diseases, or drug use. Written consent was obtained

for future studies like this study. Blood values of age- and gender-matched 101 volunteers without prior psychiatric illness were recorded retrospectively.

Exclusion criteria for all participants were;
(i) those with autoimmune disease
(ii) severe systemic diseases like hematological, endocrinological, neurological, renal, hepatic disease, cardiovascular diseases, lung disease, and infectious diseases
(iii) all other acute and chronic diseases
(iv) use of any drug including anti-inflammatory and anticoagulant drugs
(v) alcohol and substance use disorders
(vi) neurodevelopmental disorders
(vii) traumatic injury
(viii) pregnancy
(ix) body mass index (BMI) greater than 30 kg/m^2.

This study was carried out in accordance with the updated version of the Helsinki Declaration.

Karamanoglu Mehmetbey University Faculty of Medicine Clinical Research Ethics Committee approved the study 104096.

Statistical Analysis
The data were analyzed using the IBM SPSS 26 packet data software, with 95% confidence limits (p=0.05). Descriptive statistics of continuous measurements are given as mean, standard deviation, min-max, and median values. The Kolmogorov-Smirnov test and the skewness-kurtosis criterion were used to determine the normality test of continuous measurements. The t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables were used to compare the two groups. The Wilcoxon test was used to compare before and after measures, such as the patients' euthymic and manic episodes.

RESULTS
Table 1 shows demographic statistics. The research included 200 individuals, including 101 healthy controls and 99 bipolar disorder patients. The groups did not differ in terms of age or gender. The mean disease duration in the bipolar disorder group was 12.44 years. 54% of the patients had psychotic symptoms. Six patients suffered from their first manic episode (Table 1).

Neutrophil, platelet count, NLR (Figure 1), MLR (Figure 2), and PLR (Figure 3) values were found to be significantly higher in patients with manic episodes compared to the control group. Monocyte count was significantly lower in manic episode patients compared to controls.

In the euthymic period, neutrophil and monocyte counts were significantly lower, and NLR, MLR, and PLR were higher than in the control group. There was no significant difference in platelet count between the euthymic and control groups. When compared to the manic stage, there was a significant rise in lymphocyte count during the remission period (Table 2).

Main points

• In our study, NLR, MLR and PLR were found to be high in BD manic patients.

• The persistence of NLR, MLR, and PLR elevations in the euthymic period of patients indicates that it may be a trait marker.

• Our findings show that inflammation persists even when patients recover.

Table 1. Sociodemographic data of the groups

		Bipolar-Manic Disorder (n:99)		Control Group (n:101)		p Value
Age, mean ± SD		35.3±13.09		34.8±11.7		0.190
Gender	Female	47	47.4%	41	40.6%	0.327
	Male	52	52.6%	60	59.4%	
Psychotic symptom	Yes	54(55%)				
	No	45(45%)				
First episode	Yes	6(6%)				
	No	93(%93)				
Duration of disease		12.44± 8.3				
Treatment						
Valproate		31(31%)				
Lithium		53(53%)				
Valproate+Lithium		7(7%)				
Other mood stabilizer		3(3%)				
Antipsychotic		83(83%)				

Table 2. Blood counts and NLR, MLR, and PLR values of the groups

Variables	Bipolar-manic (n:99) Median (min-max)	Bipolar-euthymic (n:99) Median (min-max)	Control (101) Median (min-max)	p(1)	p(2)	p(3)
Neutrophil	5.03(1.89–13.3)	4.25(2.19–7.88)	4.82(2.4–16.6)	p<0.001	0.004	0.688
Lymphocyte	2.25(0.7–5.2)	2.31(1.26–4.31)	2.56(1.2–4.8)	0.224	0.256	p<0.001
Monocyte	0.54(0.3–1.06)	0.45(0.18–0.99)	0.57(0.06–1.06)	p<0.001	p<0.001	0.542
Platelet	259(138–548)	244(100–420)	247(143–450)	0.043	0.32	0.514
NLR	2.23(0.87–7.63)	2.2(0.91–7.57)	1.7(0.8–5.3)	p<0.001	p<0.001	0.686
MLR	0.24(0.11–0.96)	0.25(0.03–0.56)	0.19(0.1–0.6)	p<0.001	p<0.001	0.483
PLR	118.75(36.4–314.7)	118.05(27.6–302.9)	105.6(51.86–265.9)	0.001	0.008	0.606

NLR; Neutrophil-to-lymphocyte ratio, MLR; monocyte-to-lymphocyte ratio, PLR; platelet-to-lymphocyte ratio
Data are expressed as median(min-max).
P1: The bipolar-manic episode and the control group comparison.
P2: Bipolar remission phase and control group comparison.
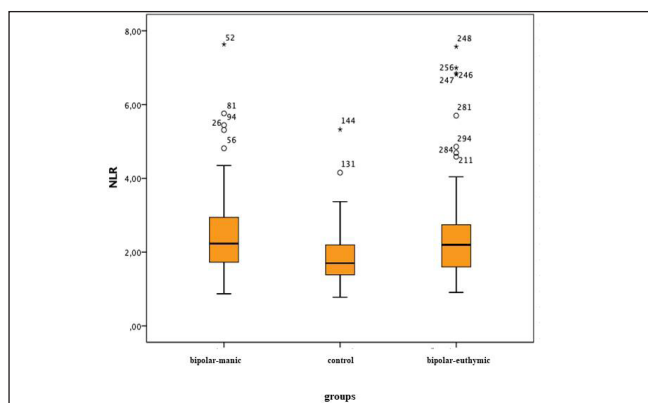P3: Bipolar manic and remission periods are comparison.

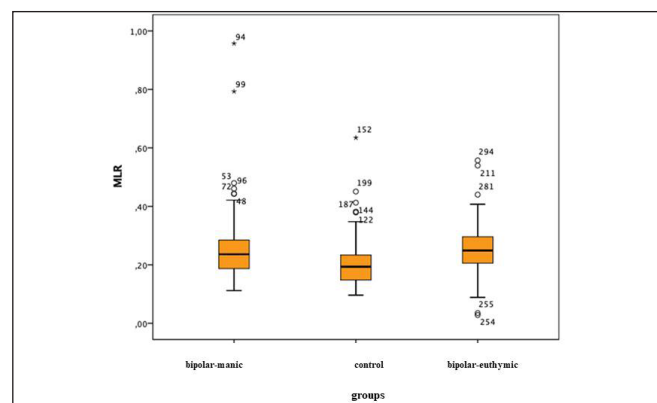**Figure 1.** NLR distribution of groups
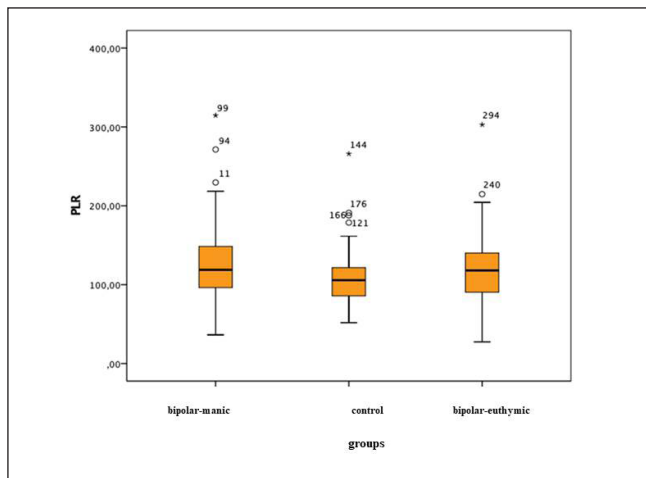

Figure 2. MLR distribution of groups

Figure 3. PLR distribution of groups

DISCUSSION

This study aimed to examine how certain inflammatory markers, such as NLR, MLR, and PLR, change in bipolar disorder patients over time. Thus, the blood parameters of bipolar disorder patients were compared within the disease periods and with healthy controls. NLR, MLR, and PLR values were significantly higher in manic episode BD patients compared to healthy controls. Previous studies also found an increased NLR through manic episode BD patients [8,9]. However, the findings of PLR and MLR are inconsistent. There are some studies showed an increase in all NLR, MLR, and PLR parameters [10], while some others showed an increase in only NLR [11], with MLR [12,13], or with PLR [14]. It's known that NLR has a predictive value in many non-psychiatric disorders treatment responses and prognoses [15,16]. A meta-analysis concluded that NLR predicted acute ischemic stroke, chronic obstructive respiratory disease, acute coronary syndrome mortality, and morbidity [17,18,19]. High NLR has been linked to a bad prognosis in terms of mortality and morbidity in several disorders.. Considering these findings of NLR regarding non-psychiatric conditions, this field of study of psychiatric illnesses is also promising [20]. Indeed, a prospective study in which BD patients were followed for 18 months reported that NLR has predictive significance in people suffering from manic episodes [21]. NLR, MLR, and PLR values were higher in the euthymic period of BD patients, as in the manic episode, compared to the healthy control group. Few studies compare manic and euthymic episodes of the same patients with a healthy control group, and the results are variable. In a study that found NLR, MLR, and PLR were significantly higher in manic episode BD patients compared to healthy controls, only MLR was higher in these patients' euthymic periods. The authors interpreted NLR as PLR as a state marker and MLR as a trait marker [22]. In another study, BD patients were found to have higher NLR and MLR than healthy controls, regardless of the disease periods [23].

This is one of the rare studies that evaluate inflammatory parameters in bipolar disorder patients between mania and remission, and it was discovered that NLR, MLR, and PLR did not alter between manic attack and remission phases. One of the previous studies showed that while NLR increases in mania, MLR and PLR did not change [14]. Another study found that NLR, PLR and MLR, which were elevated during the manic period, decreased during the euthymic period after treatment [18].

Inflammatory parameters (NLR, MLR, PLR) were higher in the BD group in both mania and remission periods than in healthy controls. However, there was no difference in the attack and remission phases of the same patients, indicating that these parameters may be trait markers. Our findings support that inflammation persists even during the remission period in bipolar disorder[24]. Subthreshold symptoms and loss of psychosocial functionality can be seen in the euthymic period of bipolar disorder, and it may be related to the ongoing inflammatory process [25]. This finding suggests that anti-inflammatory drugs could be used as a therapy option. A small-sample randomized controlled trial reports that N-acetyl cysteine (NAC), an anti-inflammatory agent, is effective in treating mania and hypomania [26]. In yet another randomized controlled study, Celecoxib, a Non-Steroidal Anti-Inflammatory Drug (NSAID), was shown to be effective in treating manic attacks [27].

The effect of anti-inflammatory therapy on treating manic episodes is still unclear [28]. To identify novel therapy targets, the inflammatory processes that may play a role in the etiology should be fully understood. Examining inflammatory markers in different periods of the BD may give some clues to understanding these inflammatory processes. In addition, a possible inflammatory marker can guide determining treatment targets, monitoring treatment response and prognosis, and diagnosing when clinical data are insufficient.

Limitations

This research has certain limitations. This was, first and primarily, a retrospective research. Secondly, psychiatric medications and smoking may influence inflammatory parameters, and the purpose of this research was not to rule out this possibility. Third, patients did not participate in the study on depressive episodes. Prospective studies that include depressive episodes in the same patients are required. On the other hand, one of our study's strengths was that we evaluated the same patient group on different episodes.

CONCLUSION

BD markers have been studied as trait markers and state markers. Trait markers remain stable even during relapse and remission in BD and differ from healthy controls. State markers, on the other hand, differ between the disease's attack and remission periods. Our study showed NLR, MLR, and PLR values in manic and euthymic episodes of BD patients were significantly higher than in healthy controls. These findings suggest that inflammation persists even when patients recover, and Inflammation is crucial in the pathophysiology of BD. The fact that NLR, MLR, and PLR are high in both the disease and the euthymic period suggests they can be used as trait biomarkers. There are preliminary studies in BD patients examining different periods of the same patients. More studies are needed to determine whether NLR, MLR, and PLR markers are trait or state markers.

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