ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2024;34(1):19-28
DOI:10.5152/pcp.2024.23760

Association Between Mood Disorder Severity, Treatment Response and Systemic Inflammatory Markers: Exploring the Role of NLR, PLR, MLR, and SII

Melike Kucukkarapinar, Damla Erbil, İlker Keles, Filiz Karadag

Department of Psychiatry, Gazi University, Faculty of Medicine, Ankara, Turkey

ABSTRACT

Background: In this study, the relationship between treatment response, clinical features of episodes such as psychosis, suicidal behavior, and agitation, duration of hospitalization, and systemic inflammation markers Systemic Inflammatory Index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) in bipolar affective disorder manic episode (BAD-M), bipolar affective disorder—depressive episode (BAD-D), and major depressive disorder (MDD) were investigated.

Methods: The NLR, MLR, PLR, and log SII were measured using parameters from a complete blood count. Admission and discharge Young Mania Rating Scale and Hamilton Depression Rating Scale scores were evaluated. This is a retrospective study conducted with a total of 451 inpatients, 122 (27.10%) of whom were diagnosed with BAD-M, 60 (13.20%) with BAD-D, and 269 (56.60%) with MDD.

Results: The patients with manic episodes have higher levels of NLR ($P = .019$), MLR ($P = .002$), and log SII ($P = .007$). In the bipolar depression and mania groups, the patients with and without treatment responses did not differ in terms of inflammation markers; the log PLR value was found to be higher in the unipolar depression group in the patients who did not reach remission ($P = .048$).

Conclusion: This study reveals associations between inflammation markers and different types of mood episodes. Higher NLR, MLR, and log SII levels in bipolar mania and lower NLR levels in agitated unipolar depression provide clues about changes in inflammation across different episodes. Studies with larger samples are needed to evaluate the relationship between inflammatory markers, the severity of mania and depression, and the response to treatment.

ARTICLE HISTORY

Received: August 26, 2023
Revision Requested: September 17, 2023
Last Revision Received: November 21, 2023
Accepted: December 05, 2023
Publication Date: March 15, 2024

INTRODUCTION

Mood disorders are conditions that reduce one's quality of life, cause disability, and eventually become chronic. Mood disorders can occur for a variety of reasons. Recent research has revealed the role of the immune system in the etiology of mood disorders.[1]

Acute-phase reactants and cytokines have different values in bipolar disorder and unipolar depression, according to studies.[2] Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are tests that can be easily measured using a complete blood count, can be used as markers of inflammatory processes in diseases such as autoimmune diseases, and have been shown to be prognostic indicators.[3,4] The combination of NLR and PLR revealed the systemic inflammatory index (SII). It is used as a marker of mortality and prognosis in tumors and coronary artery disease.[5] Although the relationship between SII and psychiatric disorders is not well understood, it has been discovered that high SII levels in male diabetic patients are associated with unipolar depression.[6] There have been studies that show higher NLR, PLR, and MLR values in schizophrenia patients compared to healthy controls. In studies comparing manic episodes to healthy control groups, the increase in NRL, MLR, and PLR levels was found to be statistically significant.[7] According to a meta-analysis, the NLR/PLR ratio may be useful in detecting activation.[8] High NLR and PLR values have been linked to the number of episodes and hospitalizations in bipolar disorder, according to research.[9]

Immune system markers may be linked to different treatment responses in bipolar disorder. During acute manic episodes, for example, high baseline levels of transforming growth factor beta 1 predicted a better response to quetiapine and lithium combination therapy.[10] However, it is unclear

Corresponding author: Melike Kucukkarapinar or Filiz Karadag, e-mail: melikekkpinar@gazi.edu.tr or filizkaradag@gazi.edu.tr

Cite this article as: Kucukkarapinar M, Erbil D, Keles İ, Karadag F. Association between mood disorder severity, treatment response and systemic inflammatory markers: Exploring the role of NLR, PLR, MLR, and SII. *Psychiatry Clin Psychopharmacol*. 2024;34(1):19-28.

how other factors, such as comorbidities and obesity, affect immune system markers. Pro-inflammatory markers such as interleukin 1 (IL-1) and CRP have been linked to the severity of bipolar disorder and psychotic symptoms.[11] When compared to healthy controls, those with unipolar depression who did not receive antidepressant treatment had a significantly higher NLR rate. The significant difference vanished after 3 months of treatment.[12] A high NLR value was found to be positively related to the severity of depression.[13] Although the relationship between disease severity and acute inflammatory markers has been investigated, to our knowledge, no study in the literature has examined the relationship with treatment response. In addition, it has been observed that the studies conducted in this area have been cross-sectional.

The purpose of this study is to examine the relationship between treatment response, changes in initial and discharge scale scores, clinical features of episodes such as psychosis, suicidal behavior, and agitation, hospitalization duration, and systemic inflammatory markers such as SII, NLR, PLR, and MLR in bipolar affective disorder—manic episode (BAD-M), bipolar affective disorder—depressive episode (BAD-D), and major depressive disorder (MDD).

MATERIAL AND METHODS

This is a retrospective study of 451 inpatients aged 18-65 years who were diagnosed with BAD-M 122 (27.10%), BAD-D 60 (13.20 %), and MDD 269 (56.60%) using DSM-V criteria and treated at the Gazi University Faculty of Medicine, Psychiatry Department between January 2010 and December 2021. Patients' sociodemographic data, clinical features, hospitalization length, episode type, dose of treatment used, presence of comorbid physical and psychiatric diseases, smoking status, Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) scale scores during hospitalization and discharge, and complete blood count parameters during hospitalization were all evaluated.

All parameters were determined using blood samples collected routinely during the morning service on the first 3 days of hospitalization, between 7:00 AM and 9:00 AM following a 12-hour fast. In our clinic, each sample is analyzed in tubes coated with ethylenediaminetetraacetic acid within 1 hour of collection. Cell counts are determined simultaneously using a bright-lined Neubauer Cell Counting Chamber® (Marienfeld, Germany) and a Sysmex UF-1000i BF (Sysmex, Japan) according to the manufacturers' recommendations.

MAIN POINTS

- Patients experiencing manic episodes show elevated NLR, MLR, and log SII, suggesting varying inflammation levels across mood episodes.
- No significant inflammation marker differences are found between responders and non-responders in the bipolar depression and mania groups.
- In MDD, non-remission cases exhibit a higher log PLR, hinting at a potential link between inflammation and treatment outcomes.
- The study underscores the need for larger-scale research to deepen understanding of inflammation's role in mood episodes and treatment responses.

Using Parameters from a Complete Blood Count

At the time of hospitalization, the following inflammatory markers were measured: Neutrophil-lymphocyte ratio NLR, monocyte lymphocyte ratio MLR, and systemic Immune-Inflammation Index SII = Platelet (p; 10^9/L) × Neutrophil (n; 10^9/L)/Lymphocyte (L; 10^9/L).

Comorbid psychiatric diagnosis, acute infection, active or chronic autoimmune diseases, use of anti-inflammatory or immunosuppressive drugs, acute coronary syndrome, chronic kidney failure, chronic liver insufficiency, or a history of cerebrovascular disease, and significant abnormalities in laboratory test results (anemia, leukocytosis, leukopenia, or thrombocytosis) were exclusion criteria.

Scales Used to Follow Up the Episodes

Young Mania Rating Scale: The YMRS scores were retrospectively employed to ascertain the severity of manic episodes. The YMRS scores were categorized into 4 levels of severity: severe (YMRS score > 24), moderate (YMRS score: 14-24), mild (YMRS score: 8-14), and clinically normal (YMRS score 0-8).

The retrospective analysis involved the utilization of patient records containing the YMRS scores. These scores were initially derived from structured assessments conducted by trained professionals during the patients' initial evaluations. The YMRS assessments were based on patient responses, with each item's rating contributing to the total score. All patients with a manic episode had a YMRS score of 14 or more.

Hamilton Depression Rating Scale: The HDRS was employed retrospectively to assess the severity of depressive symptoms. The total Hamilton score was categorized as follows: 8-16 for mild depression, 17-23 for moderate depression, and ≥24 for major depression.[14] For this retrospective analysis, patient records containing the HDRS scores were utilized. These scores were originally assessed through structured interviews conducted by trained psychiatrists, where each item's rating depended on the patient's response. The disease level of patients hospitalized due to manic episodes was moderate or above. To compare the groups, patients who were hospitalized due to depressive episodes with mild levels were excluded. HDRS <17 includes mild depression and the absence of depression. Patients in the moderate and severe depression groups were included in the study.

The study was approved by Ethics Committee of Gazi University (Approval number: 03, Date: February 8, 2022). Due to the retrospective design of the study, informed consent was not taken.

Statistical Analysis

The Statistical Package for the Social Sciences Statistics software, version 16.0 (SPSS Inc.; Chicago, IL, USA), was used for statistical analyses. The normality test of Kolmogorov–Smirnov was used to determine whether the variables were normally distributed. To calculate group differences in demographic and clinical data, an independent sample *t*-test or a Fisher–Freeman–Halton test was used. To analyze non-normal distributed variables, a Mann–Whitney *U*-test, or Kruskal–Wallis' test, was used. Dunn's test was performed as a post hoc analysis. To compare longitudinal changes in patients' YMRS and HDRS scores, a paired sample *t*-test was used. Analysis was performed with log values of PLR and SII that did not fit the normal distribution. We planned to determine whether there was a correlation between serum levels of SII, PLR, NLR, and MLR (with differences between groups) and clinical variables such as YMRS, HDRS scores, changes in scores, length of stay, number of episodes, and duration of illness using Pearson correlation analysis. Responders were defined as subjects who improved by more than or equal to 50% on HDRS and YMRS ratings at discharge compared to baseline; "non-responders" improved less.[15] The relationship between treatment response, common episode features such as suicide attempts, agitation, and psychosis, treatment options, and serum SII, PLR, NLR, and MLR levels was also assessed. The relationship of inflammation markers with the severity of mania and depression and treatment response was analyzed using the linear regression backward method. Inflammation markers (NLR, MLR, log-transformed PLR, and SII, plus all confounding variables were included as independent variables) in the regression models (age, gender, duration of illness, number of attacks, agitation, psychotic symptoms, chronic inflammation-induced disease). The last hospitalization period was also included in the regression equation when constructing models that predicted treatment responses. Furthermore, the statistical significance level was set to 0.05 (2-sided).

RESULTS

A total of 3319 inpatient records were scanned. For patients with multiple hospitalizations, the most recent record information was included in the study. In addition, those with missing YMRS and HDRS and those with missing initial blood parameters were excluded. Thus, 515 inpatients diagnosed with MDD (316, 61.4%), BAD-D (76, 14.8%), and BAD-M (123, 23.9%) were assessed for the study. Those with a HDRS score of 17 were excluded, and the following patients were distributed by diagnosis and gender: 269 (56.60%, 161 females and 108 males) were diagnosed with MDD; 60 (13.20%, 31 females and 29 males) with BAD-D; and 122 (27.10%, 61 females and 61 males) with BAD-M.

In terms of sociodemographic characteristics of the groups, such as median age ($P = .003$), marital status ($P = .002$), and median disease duration ($P < .001$), number of episodes ($P < .001$), accompanying psychotic symptoms ($P < .001$), agitation ($P < .001$) and suicidal attempt history ($P < .001$), there was a significant difference between the study groups. It was revealed that the rate of married patients was higher in the unipolar depression group than in the other 2 groups. Furthermore, patients with accompanying psychotic symptoms and agitation were more common in the mania group, while suicide attempts were more common in the unipolar group than in the other 2 groups.

The median age of BAD-M was found to be lower than the MDD group in post hoc comparisons ($P = .002$). The number of episodes was lower in the MDD group than in the patients hospitalized with BAD-M ($P < .001$), and BAD-D ($P < .001$). Total disease duration was shorter in the unipolar group than in the mania ($P < .001$) and bipolar depression groups ($P < .001$).

In terms of sex, smoking, and the presence of chronic disease, no significant differences were found between the groups. The sociodemographic and clinical characteristics of the groups are presented in Table 1 and Table 2.

A paired-sample *t*-test was performed to evaluate the change in baseline and discharge scores on YMRS for the bipolar mania group ($P < .001$), the change in baseline and discharge scores on HDRS for the bipolar depression group ($P < .001$), and the change in HDRS baseline and discharge scores ($P < .001$) for major depressive disorder. The difference between baseline and discharge scores was significant in all 3 groups.

Inflammation Markers and Their Relationship with Clinical Variables

When the relationship between inflammation markers and episode type was investigated, it was discovered that NLR ($P = .007$, with 1.91 (0.66-13.23) for bipolar mania group, 1.65 (0.69-5.43) for bipolar depression and 1.76 (0.45-18.22) for major depression group), MLR ($P = .001$, with 0.25 (0.03-1.60) for bipolar mania group, 0.21 (0.08-0.40) for bipolar depression and 0.22 (0.03-5.88) for major depression group), log SII ($P = .003$, 5.68 (4.65-6.49) for bipolar mania, 5.57 (5.10-6.25) for bipolar depression and 5.61 (4.81-6.90) for major depression) values differed significantly between groups (Figure 1 and Supplementary Table 1). Post hoc comparisons revealed that patients hospitalized with a bipolar manic episode had higher NLR

Table 1. Sociodemographic and Clinical Characteristics of Study Groups

Diagnosis	BAD-M (n=122)	BAD-D (n=60)	MDD (n=269)	*P*	Post Hoc Comparisons	
					Groups	*P*
Gender n (%)						
Female	61 (50.00)	31(51.70)	161 (56.90)			
Male	61 (50.00)	29 (48.30)	108 (40.10)	.142		
Education Status n (%)						
Below high school	41 (33.60)	19 (31.70)	125 (46.50)			
High school and college	81 (66.40)	41 (68.30)	144 (53.50)	**.015**	Not significant	
Marital status n (%)						
Single	57 (46.70)	30 (50.00)	85 (31.60)			
Married	65 (53.30)	30 (50.00)	184 (68.40)	**.002**	BAD-M < MDD BAD-D < MDD	**.005** **.010**
Living places n (%)						
Rural	5 (4.10)	3(5.00)	19 (7.10)			
Urban	117 (95.90)	57(95.00)	250 (92.90)	.589		
Smoking Status n (%)						
No	28 (68.30)	11 (64.70)	54 (62.10)			
Yes	13 (31.70)	6 (35.30)	33 (37.90)	.863		
Chronic medical illness n (%)						
No	107 (87.0)	53 (86.9)	231 (86.5)			
Yes	16 (13.0)	8 (13.1)	36 (13.5)	.854		
Clinical features n (%)						
Without psychotic feature	49 (40.20)	45 (75.00)	217(80.70)			
With psychotic feature	73 (59.80)	15 (25.00)	51 (19.30)	**<.001**	BAD-M > BAD-D BAD-M > MDD	**<.001** **<.001**
Without agitation	67 (54.90)	57 (95.00)	260 (96.70)			
With agitation	55 (45.10)	3 (5.00)	9 (3.30)	**<.001**	BAD-M > BAD-D BAD-M > MDD	**<.001** **<.001**
Without past suicide attempts	116 (95.10)	54(90.00)	212 (78.80)			
With past suicide attempts	6 (4.90)	6 (10.00)	57 (20.80)	**<.001**	MDD > BAD-M	**<.001**

Fisher-Freeman-Halton test with Bonferroni adjusted post hoc tests. BAD-M, bipolar affective disorder—mania; BAD-D, bipolar affective disorder—depression; MDD, major depressive disorder.

(*P*=.017) and log SII (*P*=.006) than unipolar depression, while higher MLR values were for both bipolar depression and unipolar depression, respectively, (*P*=.014, *P*=.001). However, there was no difference in inflammation markers between the bipolar depression and unipolar depression groups in post hoc comparisons.

Table 2. Comparative Analysis of Demographic and Clinical Characteristics Among The Groups

Diagnosis	BAD-M (n=122) Median (Minimum-Maximum)	BAD-D (n=60) Median (Minimum-Maximum)	MDD (n=269) Median (Minimum-Maximum)	*P*	Post hoc Comparisons	
					Groups	*P*
Age (years)	36 (17-67)	41(18-68)	44 (18-81)	.003	BM < UD	**.002**
Illness duration (month)	96 (1-564)	126 (1-360)	48 (1-600)	<.001	BM > UD BD > UD	**< .001** **< .001**
Number of episodes	4 (1-20)	5 (1-20)	2 (1-15)	<.001	BM > UD BD > UD	**< .001** **< .001**
Length of hospitalization (days)	25 (4-62)	28 (9-70)	29 (5-88)	.022	BM < UD	.018

Kruskal-Wallis test and the Dunn test as post hoc comparisons. BAD-M, bipolar affective disorder—mania; BAD-D, bipolar affective disorder—depression; MDD, major depressive disorder. BD=Bipolar depression; BM=Bipolar mania; UD=Unipolar Depression.

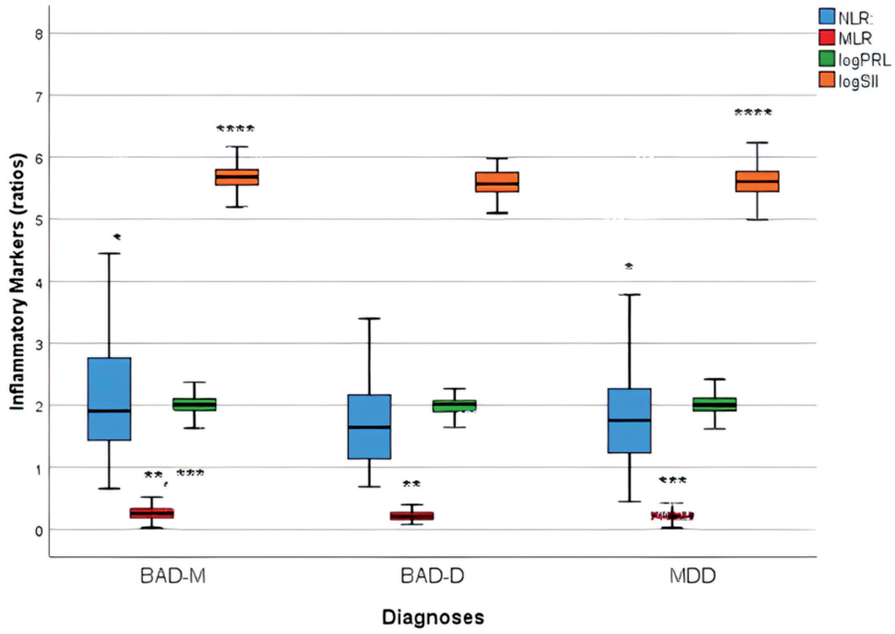

Figure 1. Inflammation markers and their relationship with Patient Groups. Box-and-whisker plots represent median of NLR, MLR, log PRL and log SII ratios. See also Supplementary Table 1 for detailed values.

The inflammation markers and their relationship with clinical variables are presented in Figure 1, Supplementary Table 1 and Supplementary Table 2.

The Relationship Between the Clinical Features of the Episodes and the Markers of Inflammation

When the relationship between the clinical features of the episodes and the markers of inflammation was examined, there was no significant difference in terms of inflammation markers between the groups with and without suicide attempts in patients with bipolar mania, bipolar depression, and unipolar depression. Similarly, for all 3 diagnostic groups, there was no significant difference between psychosis and non-psychotic groups. While there was no significant difference between patients with and without agitation in the bipolar mania and bipolar depression groups, patients with agitation had significantly lower NLR (P=.021; 0.99 (0.94-1.95), 1.76 (0.45-18.22), respectively) and log SII (P=.028; 5.41 (5.34-5.82), 5.62 (4.81-6.90), respectively) values in unipolar depression compared to patients without agitation. However, there were 9 patients with agitation out of the 269 patients in the major depression group (Table 3).

Inflammation Markers and Response in Bipolar Depression, Major Depression, and Mania Groups

There was a weak positive correlation between hospitalization YMRS scores and log SII values in bipolar mania patients (r=1.18; P=.045), but no significant correlation between YMRS score percentage change, disease duration, number of episodes, length of hospital stays, and inflammation markers. While the number of episodes and log SII values were significantly correlated in bipolar depression patients (r=−0.325; P=.011), no correlation was found between hospitalization and discharge HDRS scores, HDRS score change percentage, disease duration, and

Table 3. Relationship Between Agitation, Treatment Response, and Inflammation Markers in Major Depressive Disorder

	Treatment response (n=136) Median (Minimum-Maximum)	Treatment no response (n=133) Median (Minimum-Maximum)	P^*	With Agitation (n=9) Median (Minimum-Maximum)	Without Agitation (n=260) Median (Minimum-Maximum)	P^*
NLR	1.78 (0.45-18.22)	1.69 (0.53-11.38)	.574	0.99 (0.94-1.95)	1.76 (0.45-18.22)	**.021**
MLR	0.21 (0.03-5.88)	0.28 (0.09-0.51)	.534	0.22 (0.12-0.25)	0.21 (0.03-5.88)	.958
Log PLR	1.98 (1.42-3.03)	2.05 (1.70-2.55)	.048	1.88 (1.75-2.34)	2.01 (1.42-3.03)	.136
Log SII	5.62 (4.81-6.90)	5.62 (5.06-6.63)	.411	5.41 (5.34-5.82)	5.62 (4.81-6.90)	**.028**

Other clinical features of the episodes are presented in Supplementary Table 2.
NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic inflammatory index.
*Mann-Whitney *U*-test.

Table 4. Correlation Between Clinical Variables and Markers of Inflammation

Groups								
Bipolar Mania (n = 122)		Age	YMRS Scores Baseline	YMRS Scores at Discharge	%Change YMRS	Illness Duration	No. of Episodes	Duration of Hospitalization
NLR	*r**	0.139	0.170	0.034	0.037	0.029	−0.012	0.011
	P	.128	.061	.710	.683	.506	.796	.806
MLR	*r*	0.151	0.099	0.038	-0.039	0.008	0.036	−0.059
	P	.096	.278	.675	.667	.864	.423	.180
Log PLR	*r*	0.152	0.052	0.104	-0.058	0.045	−0.036	0.061
	P	.094	.571	.252	.521	.305	.430	.164
Log SII	*r*	**0.203***	**0.181***	0.087	-0.025	0.043	0.000	0.008
	P	**.025**	**.045**	.339	.783	.336	.992	.861
Bipolar depression n = 60		**Age**	**HDRS Scores Baseline**	**HDRS Scores at Discharge**	**%Change HDRS**	**Illness Duration**	**No. of Episodes**	**Duration of Hospitalization**
NLR	*r**	−0.159	−0.131	0.075	−.207	0.005	−0.239	−0.034
	P	.225	.324	.569	.101	.972	.063	.797
MLR	*r*	**−0.309***	−0.079	0.018	-0.096	0.007	0.003	−0.127
	P	**.016**	.549	.892	.450	.955	.984	.333
Log PLR	*r*	−0.128	−0.027	−0.022	−0.047	−0.022	−0.228	0.084
	P	.329	.842	.865	.711	.865	.077	.522
Log SII	*r*	−0.123	−0.132	0.071	−0.160	0.029	**−0.325***	0.031
	P	.348	.445	.596	.207	.824	**.011**	.812
Major depression n = 259		**Age**	**HDRS scores baseline**	**HDRS scores at discharge**	**%Change HDRS**	**Illness duration**	**No. of episodes**	**Duration of hospitalization**
NLR	*r**	0.081	0.028	−0.018	0.043	−0.045	−0.034	−0.048
	P	.186	.651	.77	.478	.466	.582	.436
MLR	*r*	0.040	−0.009	−0.041	0.047	−0.007	−0.019	−0.028
	P	.512	.884	.498	.437	.905	.763	.651
Log PLR	*r*	0.063	0.041	0.018	−0.071	0.035	−0.016	−0.022
	P	.307	.502	.772	.241	.573	.798	.726
Log SII	*r*	0.065	0.023	−0.026	0.012	−0.027	−0.043	−0.065
	P	.294	.748	.667	.849	.744	.481	.296

HDRS, Hamilton Depression Rating Scale; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic inflammatory index; YMRS, Young Mania Rating Scale. Items written in bold are statistically significant.
*Pearson correlation coefficient.

inflammation markers. Similarly, there was no significant relationship between inflammatory markers and clinical variables in unipolar depression patients (Table 4).

A reduction of 50% or more in scale scores was classified as a response to treatment. In the bipolar depression and mania groups, the patients with and without treatment responses did not differ in terms of inflammation markers; the log PLR value was found to be higher in the unipolar depression group in the patients who did not reach remission (2.05 (1.70-2.55)) than treatment responders (1.98 (1.42-3.03)), (*P* = .048) (Table 3).

Relationship of Inflammation Markers with Mania and Depression Severity, Treatment Response: Linear Regression Analysis

Backward linear regression was used to examine the relationship between inflammatory markers and other variables mentioned in the Methods section with mania and depression severity and treatment response. Despite the statistical significance of the models, the value of the coefficient of determination in the models generated was not reported because it explained less than 40% of the variance.

DISCUSSION

This is the first study to evaluate the association between inflammatory ratios, quantified by NLR, MLR, PLR, and SII index, and episode type, episode severity, treatment response, and clinical features of episodes in patients with different phases of BD and MDD.

Inflammatory ratios such as PLR, NLR, and MLR are easily obtained, low-cost markers that have been studied in a variety of psychiatric disorders[16] and have been shown

to have higher predictive values than neutrophils, platelets, and monocytes.[8] In contrast, the SII index has been investigated as a prognostic factor in cardiovascular disease, cancer, and interstitial lung disease.[5,17,18] However, research on the relationship between the SII index and affective disorders is scarce.[19] In this study, we noticed that, when compared to the depressive phase, the manic phase is characterized by increased inflammation as measured by the NLR, MLR, and SII indexes.

Currently, research on the relationship between different stages of affective disorders and inflammatory ratios yields slightly disparate results. Since Koureta et al[20] found that NLR values were significantly higher only in bipolar manic episodes and MLR values were significantly higher in both stages of bipolar disorder compared to MDD, Mazza et al[8] found that manic patients had higher NLR and MLR compared to patients with unipolar and bipolar depression, with no significant difference between unipolar and bipolar depression. In clinical practice, distinguishing between bipolar and unipolar depression can be difficult. Although a few studies found significantly higher NLR or MLR values in bipolar depression than in unipolar depression, most studies observed no significant difference, which is consistent with previous findings.[20,21]

In contrast to most previous studies, we reported a higher SII index in the BAD-M group than in the BAD-D group. Among other inflammatory markers, the SII index has received the least attention. A study published in the literature found that the SII index is significantly higher in the BAD-M group than in the MDD and BAD-D groups.[21] Our findings are in line with the existing literature, supporting the evidence that mania is associated with higher levels of inflammation than bipolar depression. In contrast to previous research, our results showed no significant difference between MDD and BAD-M. This could be because MDD had higher inflammation ratios than those in previous studies because we only included patients with at least moderate depression. To summarize, the reasons for these inconsistencies in the relationship between inflammatory ratios and different phases of affective disorders could be explained by a variety of factors influencing inflammation status, such as smoking, body mass index, disease duration, or the presence of depression.

So far, studies examining the relationship between episode severity and inflammatory ratios have only looked at MDD.[22] To the best of our knowledge, this is the first study that examines the relationship between inflammatory ratios and the severity of BD manic and depressive episodes. The lack of a significant difference in NLR, MLR, PLR, and SII values between severe and non-severe depressive episodes of MDD and BD was one of the study's unique findings. Only a few studies, with mixed results, have looked at the relationship between inflammatory ratios in patients with MDD and depression severity.[23-25] Neutrophil -to-lymphocyte ratio and PLR were found to be related to depression severity.[24] On the other hand, Kayhan et al[23] found no difference in NLR values between different levels of depression severity and suggested that PLR might be more related to severity. There has only been 1 study that included only patients with MDD and found that SII at admission was significantly associated with moderate and severe MDD.[25] Because those studies divided their groups into severe and very severe, with higher HAM-D cutoff points, our study's results may have been inconsistent with the existing findings. In terms of bipolar disorder, we found a weak positive correlation between YMRS score at admission and SII index, even though there was no significant difference in inflammatory ratios between severe and non-severe manic episodes. Therefore, there is a lack of studies regarding the correlation between manic episode severity and inflammatory ratios. This weak but novel finding can be used as guidance for future studies.

This is the first study to investigate the relationship between treatment response (with change in HDRS and YMSR scores at admission and discharge) and NLR, MLR, PLR, and SII values. Although no link was found between the inflammatory ratios of severe and non-severe MDD, treatment non-responders had significantly higher PLR values than treatment responders. Our findings were supported in part by the findings of a previous study that looked at NLR and PLR ratios in patients with varying degrees of depression severity. PLRs were also found to be higher in severe depression with psychotic features, indicating that PLR can be used as a predictor of treatment response or prognosis in MDD patients.[23] In terms of using inflammatory markers to predict treatment response, some preliminary studies in MDD reported that baseline IL-6 and tumor necrosis factor alpha (TNF-α) levels may be correlated with symptom changes during the treatment process and may predict treatment response.[26] Until now, research on the relationship between treatment response and inflammation in BD has concentrated on pro-inflammatory markers such as soluble IL-2 receptor, IL-6, and TNF-α. While some studies found a link between sIL-2R and IL-6 markers and treatment response and/or symptom resolution,[27] most studies found no such link.[28,29]

Suicide attempts, psychotic features, or the presence of agitation in general are important predictors of the severity and prognosis of affective episodes. Because suicide attempts and their consequences are more dangerous than other characteristics, most studies have concentrated on the potential predictive value of inflammatory markers for suicide. In suicide attempters, both peripheral and central inflammation has been reported.[30,31] Higher levels of CRP,[32] IL-6,[33] IL-8,[33] white blood cell count,[33,34] and TNF-α[35] were found to be significantly associated with suicidal behavior or idealization in studies with MDD. Several studies have found a link between NLRs and suicidal ideation or risk of self-harm in both MDD and BD patients.[36]

The findings of studies examining the relationship between suicide and inflammatory rates have been mostly incompatible. While some studies show a negative relationship between platelet levels and suicide,[37] others show that MLR increases, and platelet levels decrease in people with anxiety disorders who attempt suicide.[38] Although higher levels of NLR have been reported in those who have attempted suicide compared to those who have not attempted suicide,[39] many studies have found no correlation and/or a negative correlation.[40,41] Some studies have found an increase in NLR in patients with and without suicide attempts, but this is not statistically significant.[42,43] NLR values were found to be higher only in MDD patients who attempted suicide than in the healthy control group, with no difference in NLR values between patients who attempted suicide and those who did not.[44] Another study comparing MDD patients with and without a suicide attempt concluded that there was no difference in NLR and PLR values between the 2 groups.[45] The lack of a control group may explain why we were unable to confirm any relationship between suicide attempts and inflammatory rates.

Agitation or aggression is a common feature of manic episodes, and it has been shown to be significantly associated with the level of inflammation in both healthy and psychiatric populations.[46] While 1 study found that MLR may be a risk factor for physical violence in bipolar manic episode patients,[47] another found that there is no significant relationship between agitation in the depressive phase of bipolar disorder and NLR, MLR, and PLR values.[48] We identified no relationship between inflammatory rates and the presence of agitation in bipolar disorder. We believe our findings are noteworthy because there has been no study specifically conducted for agitation on this subject. However, a larger sample is needed to evaluate the difference between groups.

The presence of psychotic features in both depressive and manic episodes is thought to indicate a poor prognosis and high severity. While only 1 study found that patients with MDD with psychotic features had significantly higher PLRs than patients with severe depression without psychosis,[23] this current study found that the presence of psychotic features in MDD, bipolar depressive, and bipolar manic episodes had no effect on inflammatory rates. Compared to the previous study, the higher number of MDD and BAD-D patients and the number of patients with psychotic symptoms may explain the difference between the findings. In terms of inflammatory rates, no previous research has examined whether they are linked to the psychotic manifestations of bipolar disorder manic episodes. Soluble TNF-R1 and IL-1 receptor antogonist levels were found to be associated with the psychotic state of total bipolar disorder and schizophrenia patients in a study on the subject. However, when only bipolar disorder patients were included, this relationship was not significant.[11]

Limitations

Our study has several strengths and limitations. The novelty of this study lies in the inclusion of HDRS and YMRS scores to classify patients according to severity and to evaluate the inflammatory predictors of treatment response in patients with BAD and MDD. In addition, we included several notable clinical features that may influence inflammatory status, such as psychotic, agitated, and suicidal features. However, our study has several limitations. First, it was a retrospective study including only inpatients, so we could not evaluate patients with mild symptoms. Second, because of its retrospective nature, we could not follow-up patients to investigate the effect of treatment on inflammatory ratios. Thirdly, we did not include control groups, so we cannot suggest any conclusive association between different phases of disorders and inflammation ratios. Finally, this study has revealed that the R^2 values in our analyses are relatively low, indicating that they prevented making accurate predictions. This is a common challenge in the context of mood disorders, which are influenced by a multitude of complex variables. Nevertheless, it is crucial to emphasize that the field of mental health research still faces gaps in the available data.

In conclusion, this study has shed light on the relationships between inflammation markers and various types of mood disorder episodes. The significant increase in NLR, MRL, and log SII values in cases of bipolar manic episodes suggests a possible link between inflammation and states of heightened mood. Furthermore, the intriguing finding of reduced NLR and log SII in agitated unipolar depression patients adds another layer of complexity to our understanding of agitation's pathophysiology.

Finally, this research adds to the complex web of relationships between inflammation markers, episode types, and symptomatology in the context of mood disorders. The study's limitations, including the model's relative weakness, point to future research directions, requiring robust and expansive datasets to comprehensively explore the complexities of these connections.

Data Availability: The data for this study can be obtained from the corresponding author upon request.

Ethics Committee Approval: The study was approved by Ethics Committee of Gazi University (Approval number: 03, Date: February 8, 2022).

Informed Consent: This was a retrospective study, performed by examining patient records retrospectively. Due to the study's design informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., F.K.; Design – M.K., F.K.; Supervision – F.K.; Resources – D.E., I.K.; Materials – D.E., I.K.; Data Collection and/or Processing – D.E., I.K., M.K.; Analysis and/or Interpretation – M.K., F.K.; Literature Search – D.E., I.K., M.K.; Writing – D.E., I.K., M.K., F.K.; Critical Review – M.K., F.K.

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

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

REFERENCES

1. Krishnadas R, Cavanagh J. Depression: An inflammatory illness? *J Neurol Neurosurg Psychiatry*. 2012;83(5):495-502. [CrossRef]
2. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflammation*. 2013;10:43. [CrossRef]
3. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. *Expert Rev Cardiovasc Ther*. 2016;14(5):573-577. [CrossRef]
4. Chandrashekara S, Mukhtar Ahmad M, Renuka P, Anupama KR, Renuka K. Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. *Int J Rheum Dis*. 2017;20(10):1457-1467. [CrossRef]
5. Erdoğan M, Erdöl MA, Öztürk S, Durmaz T. Systemic immune-inflammation index is a novel marker to predict functionally significant coronary artery stenosis. *Biomark Med*. 2020;14(16):1553-1561. [CrossRef]
6. Wang J, Zhou D, Dai Z, Li X. Association between systemic immune-inflammation index and diabetic depression. *Clin Interv Aging*. 2021;16:97-105. [CrossRef]
7. Marazziti D, Torrigiani S, Carbone MG, et al. Neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios in mood disorders. *Curr Med Chem*. 2022;29(36):5758-5781. [CrossRef]
8. Mazza MG, Tringali AGM, Rossetti A, Botti RE, Clerici M. Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. *Gen Hosp Psychiatry*. 2019;58:7-12. [CrossRef]
9. Munkholm K, Jacoby AS, Lenskjold T, Bruunsgaard H, Vinberg M, Kessing LV. Leukocytes in peripheral blood in patients with bipolar disorder - Trait and state alterations and association with levels of cytokines and C-reactive protein. *Psychiatry Res*. 2018;261:383-390. [CrossRef]
10. Li H, Hong W, Zhang C, et al. IL-23 and TGF-β1 levels as potential predictive biomarkers in treatment of bipolar I disorder with acute manic episode. *J Affect Disord*. 2015;174:361-366. [CrossRef]
11. Hope S, Ueland T, Steen NE, et al. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. *Schizophr Res*. 2013;145(1-3):36-42. [CrossRef]
12. Demircan F, Gözel N, Kılınç F, Ulu R, Atmaca M. The impact of red blood cell distribution width and neutrophil/lymphocyte ratio on the diagnosis of major depressive disorder. *Neurol Ther*. 2016;5(1):27-33. [CrossRef]
13. Aydin Sunbul EA, Sunbul M, Yanartas O, et al. Increased neutrophil/lymphocyte ratio in patients with depression is correlated with the severity of depression and cardiovascular risk factors. *Psychiatry Investig*. 2016;13(1):121-126. [CrossRef]
14. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. *J Affect Disord*. 2013;150(2):384-388. [CrossRef]
15. Earley W, Durgam S, Lu K, et al. Clinically relevant response and remission outcomes in cariprazine-treated patients with bipolar I disorder. *J Affect Disord*. 2018;226:239-244. [CrossRef]
16. Bhikram T, Sandor P. Neutrophil-lymphocyte ratios as inflammatory biomarkers in psychiatric patients. *Brain Behav Immun*. 2022;105:237-246. [CrossRef]
17. Ruta VM, Man AM, Alexescu TG, et al. Neutrophil-to-lymphocyte ratio and systemic immune-inflammation index—biomarkers in interstitial lung disease. *Medicina (Kaunas)*. 2020;56(8):1-9. [CrossRef]
18. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. *J Cancer*. 2018;9(18):3295-3302. [CrossRef]
19. Korkmaz ŞA, Kızgın S, Oğuz EF, Neşelioğlu S, Erel Ö. Thiol-disulphide homeostasis, ischemia-modified albumin, complete blood count-derived inflammatory markers and C-reactive protein from acute mania to early remission in bipolar disorder. *J Affect Disord*. 2023;339:426-434. [CrossRef]
20. Koureta A, Asimakopoulos LO, Bozikas VP, Agorastos A. Immune cell ratios are higher in bipolar affective than unipolar depressive disorder and modulated by mood episode: A retrospective, cross-sectional study. *Brain Sci*. 2023;13(3):448. [CrossRef]
21. Dionisie V, Filip GA, Manea MC, et al. Neutrophil-to-lymphocyte ratio, a novel inflammatory marker, as a predictor of bipolar type in depressed patients: A quest for biological markers. *J Clin Med*. 2021;10(9):1924. [CrossRef]
22. Matits L, Munk M, Bizjak DA, et al. Inflammation and severity of depressive symptoms in physically active individuals after COVID-19 - An exploratory immunopsychological study investigating the effect of inflammation on depressive symptom severity. *Brain Behav Immun Health*. 2023;30:100614. [CrossRef]
23. Kayhan F, Gündüz S, Ersoy SA, Kandeger A, Annagür BB. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. *Psychiatry Res*. 2017;247:332-335. [CrossRef]
24. Özyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. *Psychiatry Res*. 2018;268:426-431. [CrossRef]
25. Cui S, Li J, Liu Y, et al. Correlation of systemic immune-inflammation index and moderate/major depression in patients with depressive disorders: A large sample cross-sectional study. *Front Psychiatry*. 2023;14:1159889. [CrossRef]
26. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. 2000;22(4):370-379. [CrossRef]
27. Kim SJ, Lee HJ, Koo HG, et al. Impact of IL-1 receptor antagonist gene polymorphism on schizophrenia and bipolar disorder. *Psychiatr Genet*. 2004;14(3):165-167. [CrossRef]

28. Padmos RC, Hillegers MHJ, Knijff EM, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry*. 2008;65(4):395-407. [CrossRef]
29. Ghelardoni S, Tomita YA, Bell JM, Rapoport SI, Bosetti F. Chronic carbamazepine selectively downregulates cytosolic phospholipase A2 expression and cyclooxygenase activity in rat brain. *Biol Psychiatry*. 2004;56(4):248-254. [CrossRef]
30. Sudol K, Mann JJ. Biomarkers of suicide attempt behavior: towards a biological model of risk. *Curr Psychiatry Rep*. 2017;19(6):31. [CrossRef]
31. Ganança L, Oquendo MA, Tyrka AR, Cisneros-Trujillo S, Mann JJ, Sublette ME. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology*. 2016;63:296-310. [CrossRef]
32. Chen X, Pu J, Liu Y, et al. Increased C-reactive protein concentrations were associated with suicidal behavior in patients with depressive disorders: a meta-analysis. *Psychiatry Res*. 2020;292:113320. [CrossRef]
33. Keaton SA, Madaj ZB, Heilman P, et al. An inflammatory profile linked to increased suicide risk. *J Affect Disord*. 2019;247:57-65. [CrossRef]
34. Russell AE, Mars B, Wen CP, Chang SS Sr, Gunnell D. Evidence for an association between inflammatory markers and suicide: A cohort study based on 359,849 to 462,747 Taiwanese adults. *J Affect Disord*. 2021;281:967-971. [CrossRef]
35. Choi KW, Jang EH, Kim AY, et al. Predictive inflammatory biomarkers for change in suicidal ideation in major depressive disorder and panic disorder: A 12-week follow-up study. *J Psychiatr Res*. 2021;133:73-81. [CrossRef]
36. Flamini W, Torrigiani S, Mucci F, Ivaldi T, Marazziti D, Dell'Osso L. Possible utility of neutrophil/lymphocyte ratio as a predictor of suicidal risk in mood disorders. *Eur Psychiatry*. 2022;65(suppl 1):S837-S838. [CrossRef]
37. Wysokiński A, Szczepocka E. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. *Psychiatry Res*. 2016;237:238-245. [CrossRef]
38. Almis BH, Aksoy I. Mean platelet volume level in patients with generalized anxiety disorder. *Psychiatry Clin Psychopharmacol*. 2018;28(1):43-47. [CrossRef]
39. Taşçı G, Özsoy F. Inflammation in major depressive disorder patients with and without attempted suicide. *Clin Exp Health Sci*. 2023;13(1):205-211. [CrossRef]
40. Ivković M, Pantović-Stefanović M, Dunjić-Kostić B, et al. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: Moderatory effect of family history. *Compr Psychiatry*. 2016;66:87-95. [CrossRef]
41. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;84(A):229-236. [CrossRef]
42. Gundogdu Meydaneri GG, Meydaneri S. Can neutrophil lymphocyte ratio predict the likelihood of suicide in patients with major depression? *Cureus*. 2018;10(4):e2510. [CrossRef]
43. Martínez-Botía P, Velasco A, Rolle V, et al. Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts. *Eur Neuropsychopharmacol*. 2020;40:17-30. [CrossRef]
44. Giynas Ayhan M, Dagistan AA, Sen Tanrikulu C, Yildiz Bozdogan Ş, Eren İ. Increased neutrophil/lymphocyte ratio in suicide attempters. *Anadolu Psikiyatr Derg*. 2019;20(3):305-312. [CrossRef]
45. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. *Psychiatry Res*. 2019;271:131-135. [CrossRef]
46. Coccaro EF, Lee R, Coussons-Read M. Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans. *JAMA Psychiatry*. 2014;71(2):158-165. [CrossRef]
47. Li X, Gao Y, Liu Y, Wang Y, Wu Q. Clinical markers of physical violence in patients with bipolar disorder in manic states. *Risk Manag Healthc Policy*. 2023;16:991-1000. [CrossRef]
48. Lengvenyte A, Strumila R, Belzeaux R, et al. Associations of white blood cell and platelet counts with specific depressive symptom dimensions in patients with bipolar disorder: analysis of data from the FACE-BD cohort. *Brain Behav Immun*. 2023;108:176-187. [CrossRef]

Supplementary Table 1. Inflammation Markers and their Relationship with Patient Groups

Diagnosis	Bipolar mania (n = 122)	Bipolar depression (n = 60)	Major depression (n = 269)	*P*	Multiple comparison	
	Median (Min- Max)	Median (Min- Max)	Median (Min- Max)	*P*	z	*P*
NLR	1.91 (0.66-13.23)	1.65 (0.69-5.43)	1.76 (0.45-18.22)	**.007**	2.608[a] 2.772[b]	.027[a] **.017**[b]
MLR	0.25 (0.03-1.60)	0.21 (0.08-0.40)	0.22 (0.03-5.88)	**.001**	2.822[a] 3.482[b]	**.014**[a] **.001**[b]
Log PLR	2.01 (1.06- 2.57)	2.01 (1.61-2.40)	2.00 (1.42-3.03)	.637		
Log SII	5.68 (4.65-6.49)	5.57 (5.10-6.25)	5.61 (4.81-6.90)	**.003**	2.696[a] 3.089[b]	.021[a] **.006**[b]

*: Kruskall Wallis Test; multiple comparisons with post hoc tests (Dunn's test: [a] = Comparison with bipolar mania group and bipolar depression group, [b] = Comparison with bipolar mania group and unipolar depression group)

Supplementary Table 2. Relationship between clinical features of episodes and markers of inflammation*

	Bipolar Mania (n=122)			Bipolar Depression (n=60)			Major Depression (n=269)		
	With Suicide Attempt (n=6) Median (Min-Max)	Without Suicide Attempt (n=116) Median (Min-Max)	*P*	With Suicide Attempt (n=6) Median (Min-Max)	Without Suicide Attempt (n=54) Median (Min-Max)	*P*	With Suicide Attempt (n=57) Median (Min-Max)	Without Suicide Attempt (n=212) Median (Min-Max)	*P*
NLR	1.71 (0.91-5.16)	1.92 (0.66-13.23)	.518	2.46 (0.90-3.31)	1.61 (0.69-5.43)	.088	1.55 (0.47-10.08)	1.78 (0.45-18.22)	.187
MLR	0.33 (0.14-1.60)	0.25 (0.03-1.05)	.418	0.29 (0.14-0.33)	0.21 (0.08-0.40)	.103	0.21 (0.09-0.62)	0.22 (0.03-5.88)	.537
log PLR	2.03 (1.89-2.09)	2.01 (1.06 -2.57)	.963	2.03 (1.81-2.12)	2.01 (1.61-2.40)	.859	1.96 (1.66-2.35)	2.01 (1.42-3.03)	.319
log SII	5.58 (5.40-5.83)	13.1 ± 0.62	.313			.278	5.56 (4.99-6.13)	5.62 (4.81-6.90)	.151
	With Psychosis (n=73)	Without Psychosis (n=49)		With Psychosis (n=15)	Without Psychosis (n=45)		With Psychosis (n=57)	Without Psychosis (n=212)	
NLR	2.00 (0.66-13.23)	1.18 (0.95-8.12)	.683	1.33 (0.76-5.43)	1.69 (0.69-3.40)	.323	1.85 (0.47-5.74)	1.69 (0.45-18.22)	.591
MLR	0.24 (0.12 -1.05)	0.27 (0.03- 1.60)	.473	0.20 (0.13-0.33)	0.23 (0.08-0.40)	.535	0.23 (0.12-0.51)	0.21 (0.03-5.88)	.389
Log PLR	2.03 (1.46 -2.57)	2.00 (1.06 -2.40)	.914	2.03 (1.70-2.18)	2.01 (1.61-2.40)	.482	2.03 (1.75-2.32)	1.99 (1.42-3.03)	.175
Log SII	5.68 (5.06-6.49)	5.69 (4.65 -6.34)	.466	5.50 (5.10-6.25)	5.59 (5.17-5.98)	.580	5.63 (4.99-6.23)	5.60 (4.81-6.90)	.496
	Severe mania (n=84)	Non-severe mania (n=38)		Severe depression n=42	Non-severe depression n=18		Severe depression n=185	Non-severe depression) n=84	
NLR	1.72 (0.71-5.97)	2.04 (0.66-13.23)	.159	1.66 (0.69-5.43)	1.60 (0.81-3.31)	.558	1.74 (0.45-18.22)	1.76 (0.57-10.08)	.665
MLR	0.23 (0.04-0.89)	0.26 (0.03-1.60)	.427	0.21 (0.10-0.40)	0.23 (0.08-0.34)	.981	0.21 (0.03-5.88)	0.22 (0.09-0.62)	.558
Log PLR	1.95 (1.46-2.23)	2.04 (1.06-2.57)	.476	2.03 (1.61-2.40)	1.95 (1.70-2.27)	.159	2.01 (1.42-3.03)	1.99 (1.66-2.42)	.290
Log SII	5.64 (5.09-6.16)	5.72 (4.65-6.49)	.069	5.59 (5.10-6.25)	5.55 (5.17-5.98)	.327	5.62 (4.81-6.90)	5.58 (4.95-6.23)	.327

*Mann-Whitney U Test