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ORIGINAL ARTICLE

# Differences in the indicators of inflammation between patients with bipolar and unipolar depression

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## Summary

**Introduction/Aim:** Patients with bipolar disorder, unrecognized and with a delayed onset of manic or hypomanic episodes are often mistakenly diagnosed with unipolar depression (UD) due to shared symptomatology. The two disorders, however, have related but not identical etiopathogenesis. Immune system alterations might play a crucial role in both the onset and manifestation of these conditions. This study aimed to compare immune markers between patients with bipolar depression (BD) and unipolar depression (UD) and explore their associations with acute episode characteristics and disease progression.

**Material and Methods:** This retrospective study included patients with BD (n=60) and UD (n=242) who were hospitalized within a two-year period and whose sociodemographic information, acute episode and course of illness characteristics, and indicators of inflammation were available.

**Results:** Patients with BD exhibited elevated mean platelet volume (MPV) compared to those with UD. MPV levels correlated with clinical characteristics in both groups; higher MPV was observed in UD patients with an earlier age of onset and a longer duration of illness. In BD patients, elevated MPV was associated with the severity of psychopathology, particularly in individuals with a history of suicide attempts and a prolonged duration of untreated disorder.

**Conclusion:** This study indicates the presence of chronic low-grade inflammation in specific subpopulations of patients with affective disorders. Immune changes are distinct in regard to the polarity of the disorder and could be a potential indicator of the severity of psychopathology and illness chronicity.

**Keywords:** bipolar affective disorder, inflammation, unipolar depression

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## INTRODUCTION

Bipolar disorder (BD) and major depressive disorder (MDD) are among the most common and severe mood disorders. Due to their overlapping symptomatology and often unrecognized or delayed manifestations of manic or hypomanic episodes, patients with bipolar disorder are frequently misdiagnosed with MDD (1). Consequently, inadequate recognition and treatment of bipolar disorder, along with the absence of mood stabilizing therapy, increases the risk of antidepressant-induced mania and the frequency of affective episodes, facilitating disorder progression and impaired functioning. Despite having a spectrum of shared symptoms, bipolar disorder and MDD are related but do not have an identical etiopathogenesis (2–4). Numerous studies describe the association of alterations in immune mediator levels and immune status in general with the etiopathogenesis of mood disorders, regardless of their polarity. Changes in immune signaling molecules are linked not only to depression within MDD and bipolar disorder diagnosis but also to depressive symptoms in patients with primarily somatic illnesses, sub-threshold depressive symptoms, or different types of affective temperaments in the population of mentally healthy individuals (5–9). The data show that altered levels of C-reactive protein (CRP), as well as the number of immune-active cells such as lymphocytes (Ly), neutrophils (Ne), or platelets (PLT), are present in patients with mood disorders. Additionally, some of these indicators of inflammation, including platelet count or mean platelet volume (MPV), may serve as potential markers of specific affective states, such as depression or mania (10). As potential mediators in the clinical presentation of mood disorders, these parameters are also suggestive of the severity of the disorder itself (11). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), MPV, and CRP are direct and easily accessible biomarkers of alterations in neuroimmune functioning that could facilitate the differential diagnosis of these two disorders and enable a more precise treatment (11–14). This finding also suggested that they could play a significant role in the etiology of mood disorders, especially symptoms of depression, or even be an additional aid in discriminating between patients with unipolar (UD) and bipolar depressive episodes (BD). It is additionally important to assess whether patients with specific clinical characteristics belong to the group of those with higher inflammation parameters, as this may indicate disease progression and the occurrence of comorbidities (15–17). However, to date, the values of the selected indicators of inflammation have not been systematically investigated in regard to the aforementioned differences.

The aim of this study was to assess differences in indicators of inflammation (NLR, PLR, MLR, MPV, CRP) between patients with acute episodes of bipolar depression and those with acute depressive episodes within major depressive disorder. Our secondary aim was to examine the associations of indicators of inflammation with the clinical characteristics of acute episodes and the disease course.

## MATERIALS AND METHODS

### Study Design

This study represents a clinical, retrospective, noncommercial assessment of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), mean platelet volume (MPV), and C-reactive protein (CRP) in the blood/serum of patients with BD and UD. The study was approved by the Ethics Committee of the University Clinical Centre of Serbia (No. 622/1).

### Participants

The study included 302 participants of both sexes aged 18 to 79 years. Participants were divided into two groups: the study group of patients with bipolar depression (BD = 60) and the study group of patients with unipolar depression (UD = 242). The sample size necessary for the study with the power of $1 - \beta = 0.80$ at $\alpha = 0.05$ was calculated based on the study by Chang et al. (18) and the values of C-reactive protein levels. The minimum number of participants required to detect differences among groups was determined to be 27 participants per group.

### Inclusion criteria

Specific inclusion criteria for the BD and UD patients were as follows: a) age ≥ 18 years; b) patients experiencing an acute exacerbation of the illness, hospitalized at the Clinic of Psychiatry over a two year period, for UD or BD according to the criteria of the 10th International Classification of Diseases (19); and c) completed laboratory work-up, including leukocyte count, neutrophil count, lymphocyte count, platelet count, mean platelet volume, and C-reactive protein, conducted no later than three days following admission.

### Exclusion criteria

The exclusion criteria based on available medical records were as follows: a) comorbidity with acute inflammatory, neurodegenerative, or infectious diseases and other severe decompensated conditions; b) pregnancy or lactation; and c) the presence of another psychiatric comorbidity other than personality disorders.

## Semi-Structured Psychiatric Questionnaire

At the beginning of the study, data relevant to the research were collected from medical records using a semistructured psychiatric questionnaire, including a) general sociodemographic data (gender, age, marital status, education); b) data related to the clinical characteristics of the acute episode (time elapsed until initial remission, current psychotic symptoms, current suicide risk); c) data related to the clinical characteristics of the disease course (age at the onset of initial symptoms, the duration of untreated illness, the duration of illness, a total number and type of previous affective episodes, the number of hospitalizations, the number of previous suicide attempts, the analysis of previous complementary diagnostics – MRI, CT, psychological evaluation); d) personal medical history (history of alcohol and psychoactive substance abuse, the presence of acute or chronic somatic illnesses); e) family medical history; and f) complete blood count and biochemical analysis (absolute leukocyte count, absolute neutrophil count, absolute lymphocyte count, absolute platelet count, mean platelet volume, and C-reactive protein).

Variables such as age at the onset of initial symptoms, a total number of previous episodes, type of previous episode, number of hospitalizations, and number of suicide attempts were obtained from medical records. Regarding the variable "current psychotic symptoms" (binary variable), psychotic features were assessed as present (assigned a value of 1) if the patient was diagnosed with any of the affective disorders with psychotic symptoms (19) upon admission by the attending psychiatrist. The value of 0 was assigned for this variable for other examined diagnoses. Data on current suicide risk, assessed through the current presence of suicidal phenomena (suicidal thoughts, intentions, attempts), were expressed through a single binary variable, "current suicide risk" (without suicidal phenomena - 0, with suicidal phenomena - thoughts or intentions currently and attempt within the period of up to one week before admission) - 1), based on data from the mental status examination and medical history.

Certain clinical characteristics for which there is no consensus (duration of untreated disorder, stage of the disorder) were defined based on current research findings. The duration of untreated disorder was defined as the time elapsed from the onset of initial symptoms to the initiation of appropriate treatment. In the context of UD, "appropriate treatment" involves the use of antidepressants, while mood stabilizers are regarded as adequate pharmacotherapy for bipolar disorder (20). To determine differences in immune indicators related to the progression of the disorder, the patients were categorized into early (up to 5 years after the onset of initial symptoms), middle (from 5 to 10 years after the onset of initial symptoms), and late stages of illness development (over 10 years after the onset of initial symptoms), using the criteria of Pedrini et al. (21).

## Laboratory analyses

The analysis of absolute neutrophil, lymphocyte, monocyte, and platelet counts and MPV was performed on Sysmex XN-1000 and Beckman Coulter LH 750 machines, while the analysis of C-reactive protein levels was carried out on the Abbott Alinity C instrument. The neutrophil-to-lymphocyte ratio was calculated as the quotient of the absolute neutrophil count and the absolute lymphocyte count. The monocyte-to-lymphocyte ratio was calculated as the quotient of the absolute monocyte count and the absolute lymphocyte count. The platelet-to-lymphocyte ratio was calculated as the quotient of the platelet count and the absolute lymphocyte count.

## Statistical data analysis

The database was created in Microsoft Office Excel for Windows 2007, and data analysis was conducted using the Statistical Package for Social Sciences (SPSS) for Windows v. 21.0 (SPSS Inc., Chicago, IL). Descriptive statistical methods, including measures of central tendency and variability, were used to illustrate the sample characteristics.

Bivariate analytical statistical methods included tests examining the association between indicators of inflammation and other variables (independent samples Student's t test for independent samples, $\chi 2$ test with Yates's correction, Fisher's exact probability test, and correlation using Pearson's correlation coefficient). Multivariate statistical methods involved partial correlation and analysis of covariance (ANCOVA) with a post hoc least significant difference (LSD) test. Sex and age were used as covariates in all multivariate analyses. The choice of the covariates was based on previous studies finding an association between inflammatory parameters and these sociodemographic variables (22).

The Kolmogorov-Smirnov test with Lilliefors correction revealed a non-normal distribution for some variables (NLR, TLR, MLR, CRP). Parametric method results were considered statistically significant if significance was confirmed by the "bootstrapping" procedure on 1000 subsamples, as the population did not exhibit a normal distribution for most inflammatory parameters. The test values were considered statistically significant if $p < 0.05$. The confidence interval value in the "bootstrapping" method was regarded as more informative and superior to the p value in cases with borderline p values. Therefore, the confidence intervals are presented in the text for variables that showed statistical significance in the analyses (23).

# RESULTS

The sociodemographic characteristics of the participants are presented in **Table 1**. Apart from statistically

**Table 1.** Sociodemographic and clinical characteristics of the patients

| Sociodemographic characteristics | BD (n = 60) | UD (n=242) | Test | p value | CI |
|---|---|---|---|---|---|
| Gender (male/female) | 6/54 | 106/136 | - | 0.000 [a] | |
| Age (years) | 48.46 ± 12.36 | 51.67 ± 11.10 | t=-1.948 | 0.071 [b] | -6.90 – 0.36 |
| Marital status (has a partner/does not have a partner, N) | 33/27 | 149/93 | $\chi^2$=0.678 | 0.447 [c] | |
| Education (years) | 12.18 ± 2.46 | 12.59 ± 3.34 | t=-0,873 | 0.383[b] | -1.15 – 0.37 |
| **Clinical characteristics** | | | | | |
| Age at the onset (years) | 30.47 ± 11.09 | 37.52 ± 13.78 | t = -3.676 | 0.000[b] | -10.38 – -3.79* |
| Duration of untreated disorder (months) | 107.67 ± 101.04 | 38.53 ± 70.03 | t = 6.044 | 0.001[b] | 42.06 – 97.13* |
| Duration of illness (years) | 18.01 ± 11.52 | 14.84 ± 12.27 | t = 1.810 | 0.071[b] | 0.01 – 6.69* |
| Total number of previous episodes | 10.57 ± 7.09 | 4.73 ± 3.30 | t = 1.810 | 0.071[b] | 0.01 – 6.69* |
| Number of depressive episodes | 6.51 ± 4.70 | 4.73 ± 3.30 | t = 3.258 | 0.013[b] | 0.47 – 3.33* |
| Number of manic episodes | 2.81 ± 2.37 | – | – | – | – |
| Number of mixed episodes | 1.91 ± 3.03 | – | – | – | – |
| Time elapsed until remission (days) | 37.96 ± 15.06 | 43.16 ± 28.30 | t = -1.374 | 0.042[b] | -9.84 – 0.12 |
| Current psychotic symptoms (yes/no, N) | 21/39 | 44/198 | $\chi^2$=7.086 | 0.008[c] | – |
| Number of hospitalizations | 7.77±7.22 | 4.41±3.95 | t = 4.869 | 0.001[b] | 1.61 – 5.46 |
| Stage of disorder (<5 years, 5-10, ≥10 years, N) | 12/8/40 | 65/48/129 | $\chi^2$=3.571 | 0.168[d] | |
| Heredity (yes/no, N) | 32/28 | 105/137 | $\chi^2$=1.538 | 0.215[c] | |
| Current suicide risk (yes/no, N) | 36/24 | 78/164 | $\chi^2$=13.203 | 0.000[c] | – |
| Previous suicide attempt (yes/no, N) | 30/30 | 100/202 | $\chi^2$=8.713 | 0.003 | – |
| Number of suicide attempts (yes/no, N) | 1 | 0 | t = 2.848 | 0.017 | 0.11– 0.89 |

The values are presented as the means ± standard deviations unless otherwise stated. [a]Fisher's exact probability test, [b]Independent samples t test, [c]chi-square test with Yates' correction; d Pearson's chi-square test, *Statistical significance, relative to confidence intervals. Abbreviations: BD = bipolar depression, UD = unipolar depression, CI = confidence interval

significant differences in gender (10.0% vs. 43.8%, $p < 0.001$), individuals with BD and UD did not differ in terms of age, marital status, or education. When comparing clinical characteristics, BD patients had a significantly longer duration of untreated illness (107,67 ± 101,04 vs. 38.,53 ± 70,03 months, $p = 0.001$), higher number of depressive episodes (6,51 ± 4,70 vs. 4,73 ± 3,30, $p = 0.013$), a shorter time to remission (37,96 vs. 43.16, p = 0.042), and a higher number of prior hospitalizations (7.77 ± 7,22 vs. 4.41 ± 3,95, p = 0.001). In addition, BD patients more frequently exhibited psychotic symptoms at the time of admission (53.8% vs. 22.2%, $p = 0.008$) and suicidal behavior (100% vs. 49.5%, p = 0.003).

Values of the indicators of inflammation in the blood and serum of the participants in our study are shown in **Table 2**. Apart from significant differences in mean levels of monocytes (0,55 ± 0,25 vs. 0,46 ± 0.20, $p = 0.002$) and lymphocytes (2.28 ± 0.70 vs. 2.48 ± 2.08, $p = 0.042$), there were no differences in other indicators of inflammation that we assessed. The MLR was higher in patients with bipolar depression than in patients with unipolar depression (0.25 ± 0.12 vs. 0.22 ± 0.14, p = 0.017). Additionally,

**Table 2.** Blood cell count and indicators of inflammation

| The blood cell count | BD (n = 60) | UD (n=242) | Test | p value | CI |
|---|---|---|---|---|---|
| Leukocyte count $10^9$/L | 6.22 ± 1.93 | 8.05 ± 1.38 | t=-1.484 | 0.142 [a] | -6.61– 0.96 |
| Neutrophil count $10^9$/L | 4.19 ± 1.59 | 4.21 ± 1.73 | t=-0.273 | 0.786 [a] | -6.54 – 2.65 |
| Lymphocyte count $10^9$/L | 2.28 ± 0.70 | 2.48 ± 2.08 | t=-2.114 | 0.042 [a] | -1.17 – -0.02* |
| Monocyte count $10^9$/L | 0.55 ± 0.25 | 0.46 ± 0.20 | t=3.029 | 0.002 [a] | 0.10 – 0.46* |
| Platelet count $10^9$/L | 238.34 ± 65.11 | 226.88 ± 65.05 | t=1.148 | 0.252 [a] | -8.18 – 31.10 |
| **Indicators of inflammation** | | | | | |
| NLR | 2.04 ± 1.12 | 2.05 ± 1.51 | F = 0.028 | 0.867[b] | -0.415 – 0.493 |
| MLR | 0.25± 0.12 | 0.22 ± 0.14 | F = 5.750 | 0.017[b] | 0.15 – 0.90* |
| TLR | 113.12 ± 41.96 | 107.37 ± 48.93 | F = 0.396 | 0.530 [b] | -9.55 – 18.75 |
| MPV (fL) | 9.49 ± 1.37 | 8.97 ± 1.20 | F = 6.739 | 0.010 [b] | -0.93 – -0.18* |
| CRP (mg/L) | 4.62 ± 5.93 | 6.62 ± 3.38 | F = 0.523 | 0.471 [b] | -8.82 – 1.54 |

The values are presented as the means ± standard deviations unless otherwise stated. [a]Independent samples t test with the bootstrapping method, [b]Analysis of covariance (ANCOVA) with bootstrapping methods (covariates: sex and age). *statistically significant relative to the confidence interval. Abbreviations: BD = bipolar depression, UD = unipolar depression, CI = confidence interval, NLR = ratio of neutrophils to lymphocytes, MLR = ratio of monocytes to lymphocytes, PLR = ratio of platelets to lymphocytes, MPV = mean platelet volume, CRP = C-reactive protein

**Table 3.** Associations between indicators of inflammation and clinical characteristics of acute episodes and disease course in patients with BD

| Clinical characteristics | NLR | MLR | PLR | MPV(fL) | CRP(mg/L) |
|---|---|---|---|---|---|
| Age at the onset of initial symptoms (years) | r=-0.197, p=0.171 | r=-0.147, p=0.310 | r=-0.111, p=0.443 | r=0.042, p=0.774 | r=-0.096, p=0.641 |
| Duration of untreated disorder (months) | r=0.126, p=0.385 | r=-0.200, p=0.888 | r=0.100, p=0.489 | r=0.277, p=0.047* | r=0.192, p=0.146 |
| Duration of disorder (years) | r=0.217, p=0.130 | r=0.163, p=0.259 | r=0.116, p=0.432 | r=0.047, p=0.747 | r=0.087, p=0.671 |
| Total number of previous episodes | r=0.093, p=0.520 | r=0.042, p=0.770 | r=-0.065, p=0.659 | r=-0.070, p=0.629 | r=-0.091, p=0.658 |
| Number of depressive episodes | r=-0.044, p=0.763 | r=-0.074, p=0.611 | r=-0.115, p=0.426 | r=-0.229, p=0.109 | r=-0.122, p=0.552 |
| Number of manic episodes | r=-0.042, p=0.773 | r=-0.111, p=0.443 | r=0.020, p=0.889 | r=0.010, p=0.945 | r=-0.091, p=0.657 |
| Number of mixed episodes | r=0.187, p=0.500 | r=0.175, p=0.701 | r=-0.002, p=0.998 | r=0.287, p=0.430 | r=0.056, p=0.785 |
| Time elapsed until remission (days) | r=-0.247, p=0.084 | r=-0.239, p=0.094 | r=-0.022, p=0.879 | r=0.029, p=0.842 | r=0.149, p=0.468 |
| Number of hospitalizations | r=0.067, p=0.645 | r=0.078, p=0.592 | r=-0.117, p=0.420 | r=0.022, p=0.878 | r=-0.162, p=0.428 |
| Number of suicide attempts | r=-0.006, p=0.968 | r=0.165, p=0.253 | r=0.007, p=0.959 | r=0.308, p=0.029* | r=-0.108, p=0.598 |

The values are presented as correlation coefficients and p values (covariates: sex and age). Abbreviations: NLR = ratio of neutrophils to lymphocytes, MLR = ratio of monocytes to lymphocytes, PLR = ratio of platelets to lymphocytes, MPV = mean platelet volume, CRP = C-reactive protein. *p < 0.05

MPV was higher in those with bipolar depression (9,49 ± 1,37 vs. 8,97 ± 1,20, $p = 0.010$).

## Indicators of inflammation in patients with bipolar depression

In BD patients with acute suicidality, MPV was higher than in their nonsuicidal counterparts (9,71 ± 1,16 vs. 8,47 ± 0.96, $p < 0.001$). Additionally, within the bipolar depression group, patients with a history of suicide attempts had higher MPV compared to those who had not attempted suicide during their lifetime (9,32 ± 1,23 vs. 8,59 ± 1,20, $p = 0.03$). Moreover, in the same group of patients, MPV was higher in those with a higher number of suicide attempts and in those with a longer duration of untreated illness. All analyses were conducted with the control of sex and age covariates **(Table 3 and Table 4)**.

**Table 4.** Differences in the values of the indicators of inflammation in relation to the clinical characteristics of acute episodes and the disease course in patients with BD

| Clinical characteristic | NLR | MLR | PLR | MPV(fL) | CRP(mg/L) |
|---|---|---|---|---|---|
| Current psychotic symptoms | F=1.195, p=0.322 | F=0.747, p=0.529 | F=0.860, p=0.468 | F=0.273, p=0.884 | F=0.750, p=0.553 |
| Yes | 2.39±1.44 | 0.26±0.10 | 113.58±50.45 | 9.18±0.90 | 3.73±4.07 |
| No | 1.86±0.88 | 0.25±0.13 | 112.90±37.55 | 8.86±1.33 | 4.98±5.59 |
| Stage of disorder | F=0.439, p=0.649 | F=0.683, p=0.515 | F=0.183, p=0.833 | F=0.336, p=0.717 | F=0.310, p=0.737 |
| < 5 years | 2.36±2.24 | 0.27±0.10 | 101.43±59.81 | 8.99±1.13 | 4.94±5.01 |
| 5-10 | 1.72±1.83 | 0.21±0.11 | 109.82±41.48 | 8.33±1.01 | 4.16±3.75 |
| >10 years | 2.25±0.90 | 0.29±0.12 | 119.43±43.74 | 8.66±1.16 | 4.79±6.51 |
| Heredity | F=0.742, p=0.393 | F=0.018, p=0.892 | F=0.036, p=0.851 | F=2.550, p=0.160 | F=0.894, p=0.354 |
| yes | 2.20±1.34 | 0.26±0.12 | 114.35±39.06 | 9.24±1.30 | 5.54±4.53 |
| no | 1.88±0.85 | 0.25±0.11 | 111.92±45.43 | 8.70±1.05 | 3.93±4.54 |
| Current suicidal risk | F=0.060, p=0.800 | F=0.733, p=0.527 | F=0.010, p=0.919 | F=16.950, p=0.000* | F=0.811, p=0.377 |
| yes | 2.00±1.20 | 0.26±0.13 | 112.13±40.09 | 9.71±1.16 | 5.52±5.07 |
| no | 2.11±1.01 | 0.26±0.11 | 114.63±45.55 | 8.47±0.96 | 3.58±4.33 |
| Previous suicidal attempt | F=0.757, p=0.525 | F=0.806, p=0.497 | F=0.888, p=0.454 | F=1.700, p=0.028* | F=0.707, p=0.757 |
| yes | 2.13±1.24 | 0.26±0.12 | 113.85±36.30 | 9.32±1.23 | 5.21±5.20 |
| no | 1.96±1.01 | 0.25±0.12 | 112.48±47.29 | 8.59±1.20 | 3.94±5.78 |

The values are presented as F (ANCOVA) and p values (covariates: sex and age). Abbreviations: NLR = ratio of neutrophils to lymphocytes, MLR = ratio of monocytes to lymphocytes, PLR = ratio of platelets to lymphocytes, MPV = mean platelet volume, CRP = C-reactive protein. *p < 0.05

**Table 5. Associations between the indicators of inflammation and clinical characteristics of acute episodes and disease course in patients with UD**

| Clinical characteristics | NLR | MLR | PLR | MPV(fL) | CRP(mg/L) |
|---|---|---|---|---|---|
| Age at the onset of initial symptoms (years) | r=-0.020, p=0.766 | r=0.021, p=0.751 | r=0.119, p=0.073 | r=-0.172, p=0.009* | r=-0.100, p=0.354 |
| Duration of untreated disorder (months) | r=-0.015, p=0.834 | r=-0.004, p=0.950 | r=0.008, p=0.909 | r=0.094, p=0.190 | r=0.116, p=0.326 |
| Duration of disorder (years) | r=0.014, p=0.832 | r=-0.032, p=0.627 | r=-0.113, p=0.088 | r=0.155, p=0.019* | r=0.094, p=0.384 |
| The total number of previous episodes | r=-0.063, p=0.400 | r=0.046, p=0.540 | r=-0.011, p=0.883 | r=0.052, p=0.493 | r=0.081, p=0.506 |
| Time elapsed until remission (days) | r=0.024, p=0.713 | r=0.001, p=0.994 | r=-0.068, p=0.302 | r=0.126, p=0.056 | r=0.139, p=0.189 |
| Number of hospitalizations | r=-0.046, p=0.488 | r=-0.006, p=0.931 | r=-0.098, p=0.137 | r=0.057, p=0.395 | r=0.067, p=0.532 |
| Number of suicide attempts | r=0.102, p=0.120 | r=0.111, p=0.093 | r=0.012, p=0.858 | r=-0.060, p=0.361 | r=-0.027, p=0.798 |

The values are presented as correlation coefficients and p values (covariates: sex and age). Abbreviations: NLR = ratio of neutrophils to lymphocytes, MLR = ratio of monocytes to lymphocytes, PLR = ratio of platelets to lymphocytes, MPV = mean platelet volume, CRP = C-reactive protein. *p < 0.05

## Indicators of inflammation in patients with unipolar depression

In UD patients, a statistically significant positive correlation was found for MPV in those with an earlier age of onset (r = 0.172, $p$ = 0.009) and in patients with a longer duration of illness (r = 0.155, $p$ = 0.019). All analyses were conducted with the control of sex and age covariates **(Table 5 and Table 6)**.

## DISCUSSION

The current study, involving a substantial number of patients with bipolar and unipolar depression and including multiple readily available indicators of inflammation in the clinical setting, is among the rare delving into the examination of low-grade inflammation indicators, specifically comparing these two patient groups during the acute phase.

In our research, patients with bipolar depression had higher MLRs and MPVs than did those with unipolar depression. The mean platelet volume also differed in regard to the clinical characteristics of both groups of participants. Namely, for patients with unipolar depression, MPV was higher in those with an earlier age of onset of the disorder and in those with a longer duration of illness. However, in patients with bipolar depression, it was also associated with more severe clinical presentations throughout their lifetime, as well as currently. Patients with a history of suicide attempts or those who were currently at risk for suicide had higher values of this indicator of inflammation. Interestingly, the same parameter was higher in BD patients with a longer duration of untreated disorder.

Changes in the immune system are considered significant factors potentially contributing to the onset and clinical manifestations of mood disorders. Previous studies examining similar indicators of inflammation have highlighted MLR as an indicator of manic episodes in bi-

**Table 6.** Differences in the values of indicators of inflammation in relation to the clinical characteristics of acute episodes and the disease course in patients with UD

| Clinical characteristic | NLR | MLR | PLR | MPV(fL) | CRP(mg/L) |
|---|---|---|---|---|---|
| Current psychotics symptoms | F=0.614, p=0.434 | F=0.782, p=0.378 | F=0.876, p=0.350 | F=0.252, p=0.616 | F=1.023, p=0.315 |
| yes | 1.88±1.42 | 0.21±0.13 | 100.93±51.37 | 9.39±1.42 | 12.80±36.13 |
| no | 2.09±1.53 | 0.23±0.15 | 108.83±48.39 | 9.51±1.36 | 6.70±16.33 |
| Stage of disorder | F=0.827, p=0.439 | F=0.325, p=0.723 | F=1.626, p=0.199 | F=0.837, p=0.434 | F=0.632, p=0.534 |
| < 5 years | 2.17±1.51 | 0.25±0.13 | 109.76±44.34 | 9.30±1.67 | 10.06±30.38 |
| 5-10 | 2.28±2.27 | 0.22±0.23 | 117.92±60.71 | 9.43±1.26 | 2.57±2.49 |
| >10 years | 1.93±1.19 | 0.21±0.10 | 102.77±46.96 | 9.60±1.28 | 8.53±19.39 |
| Heredity | F=1.818, p=0.179 | F=2.176, p=0.142 | F=0.013, p=0.908 | F=0.026, p=0.871 | F=0.025, p=0.874 |
| yes | 2.19±1.83 | 0.23±0.17 | 108.48±53.51 | 9.52±1.31 | 7.99±3.15 |
| no | 1.95±1.20 | 0.22±0.11 | 106.50±45.25 | 9.47±1.42 | 7.29±2.98 |
| Current suicidal risk | F=0.250, p=0.617 | F=0.061, p=0.805 | F=0.095, p=0.758 | F=0.027, p=0.870 | F=0.988, p=0.321 |
| yes | 2.11±1.87 | 0.22±0.18 | 106.91±51.60 | 9.49±1.24 | 4.09±5.08 |
| no | 2.02±1.31 | 0.22±0.11 | 107.93±46.37 | 9.50±1.45 | 8.78±24.14 |
| Previous suicide attempt | F=0.225, p=0.636 | F=0.041, p=0.839 | F=0.947, p=0.332 | F=0.742, p=0.390 | F=0.062, p=0.804 |
| yes | 2.13±2.01 | 0.22±0.19 | 103.34±56.28 | 9.37±1.17 | 6.84±14.72 |
| no | 2.02±1.26 | 0.22±0.11 | 109.07±45.58 | 9.54±1.46 | 7.94±83.08 |

Values are presented as F (analysis of covariance, ANCOVA) and p values (covariates: sex and age). Abbreviations: NLR = ratio of neutrophils to lymphocytes, MLR = ratio of monocytes to lymphocytes, PLR = ratio of platelets to lymphocytes, MPV = mean platelet volume, CRP = C-reactive protein.

polar disorder patients (12,13,24,25). While few studies comparing the MLR in patients with bipolar and unipolar depression have shown no differences in the values of this indicator of inflammation, our results show that patients with BD have a higher MLR than those with UD. The discrepancies in the findings may be attributed to the fact that our study included a significantly larger number of participants compared to the study by Mazza et al. (12). Additionally, the same study used different confounding variables compared to our study (12). However, the same study only revealed a difference in the number of lymphocytes in individuals with BD and UD, whereas our study documented differences in both the absolute lymphocyte count and the absolute monocyte count. This discrepancy potentially indicates immune reactivity in both cell groups in our patient population, especially in those with BD. It is important to note that the studies by other authors included younger patients, potentially with less advanced immune changes or fewer functional changes within the cardiovascular system (26, 27).

Research indicates that platelet size, measured as the mean platelet volume, is indeed an indicator of platelet immune reactivity (28). Previous studies comparing MPV in individuals with unipolar and bipolar depression found no difference in the values of this marker (10). However, the majority of studies analyzing individual diagnostic entities have reported increased MPV in individuals with unipolar and bipolar depression (28–30). In our study, patients with bipolar depression had higher MPV than patients with unipolar depression, suggesting increased immune activity in patients with BD. Documented immune activity may represent a risk factor, particularly for cardiovascular diseases, which are more prevalent or more pronounced in individuals with bipolar disorder than in those with major depressive disorder (31). The differences between our findings and those of previous research may stem from different participant selection, including individuals older than 65 years, or from the use of different statistical data processing methods.

Moreover, our study identified low-grade inflammation, with MPV as an indicator, in individual patient groups. Previous studies revealed an association between NLR and suicide risk in individuals with bipolar disorder (32). However, our study did not yield similar results. It is essential to acknowledge that previous studies with positive results were prospective, measured symptomatology during acute episodes using psychometric instruments, and found an association between NLR and suicide risk only in patients with a positive family history of suicide (32), which our study did not assess. Interestingly, our study found an association between other inflammatory parameters and suicide risk in patients with BD. MPV was higher in patients with a history of suicide attempts and those who were acutely suicidal, but it was also associated with a higher number of previous suicide attempts. Moreover, similar NLR values in individuals with unipolar and bipolar depression in our sample could be explained by their association with the type of acute affective symptomatology. Previous research has identified NLR as an indicator of manic states; thus, comparable levels of NLR in individuals with BD and UD in our sample could be expected (13,27). Our study did not find an association between the presence of psychotic symptoms and inflammatory parameters, somewhat in line with previous research. Similarly, Kayhan et al. (33) did not find an association between NLR and psychotic symptoms in individuals with unipolar depression. However, the same authors found an association between psychotic symptoms and PLR in individuals with major depressive disorder, regardless of its severity. The difference in our results may be due to the retrospective nature of our study, which made precise quantification of psychotic symptoms and grading patients in terms of disease severity unattainable.

An observation stemming from our work relates specifically to platelet reactivity, measured by MPV, which was increased in patients with bipolar depression with a longer duration of untreated disorder. Such data further underline the significance of timely treatment and align with previous research on the immunomodulatory effects of psychopharmacological agents (34). Elevated MPV values have also been documented in individuals with UD compared to healthy participants (30). Although our study did not include a healthy control group, increased MPV values were found in individuals with UD with an earlier onset and longer duration of illness. Prior research specifically indicates increased chronic low-grade inflammation in individuals with affective disorders, which may be associated with the severity and chronicity of the illness (28). Although our study did not directly investigate the association between stressful life events and inflammatory parameters, some studies have suggested that altered immune status, particularly increased inflammation, may result from the cumulative effects of stressors, contributing synergistically to a proinflammatory status and the chronic course of the disorders (35).

This study needs to be viewed in light of its strengths as well as potential limitations that may affect the results and their further interpretation. The most significant disadvantage of this study is its retrospective nature, which prevented a comprehensive assessment of acute psychopathology through psychometric instruments and thus the evaluation of the intensity of acute depressive symptoms in relation to indicators of inflammatory status. Another important limitation is that the association between applied pharmacological treatment and indicators of inflammation was not analyzed, which could impact the interpretation of the results. Nevertheless, bearing in mind that this study has overcome the limitations of previous studies that included a smaller number of participants and lack of control for covariates (10, 28, 32), we believe it provides additional, novel information regarding the

role of inflammation indicators in patients with affective disorders of both polarities. It is important to emphasize that one of the greatest qualities of the current study is its naturalistic, clinical sample, which has yielded additional insights. In practical and clinical terms, the results from such a sample could indicate the possibility that certain subsets of our patients are exposed to increased inflammation and require special attention concerning the prevention of somatic comorbidities (17) that further complicate the disease course and hinder treatment.

## CONCLUSION

Our study highlights the presence of chronic low-grade inflammation in specific subcategories of patients with affective disorders of both polarities. Immune changes differ according to the polarity of the disorder and may serve as indicators of the severity of psychopathology and the absence of timely treatment in patients with bipolar depression. However, in patients with unipolar depression, these immune dysregulations could be mediated by the chronicity of the disease and the potential accumulation of environmental stressors. The results of our study highlight the importance of monitoring particular populations of patients who may be at risk of developing somatic comorbidities due to increased inflammation.

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# RAZLIKE U INDIKATORIMA INFLAMACIJE OBOLELIH OD BIPOLARNE I UNIPOLARNE DEPRESIJE

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**Sažetak**

**Uvod/Cilj:** Usled preklapajuće simptomatologije, a često i neprepoznate ili odložene pojave manične ili hipomanične epizode u bipolarnom poremećaju, pacijenti sa ovim oboljenjem često se nepravilno dijagnostikuju kao oboleli od unipolarne depresije. Ova dva poremećaja imaju srodnu, ali ne i istu etiopatogenezu. Izmene u imunskom sistemu potencijalno značajno doprinose nastanku i kliničkoj ekspresiji poremećaja raspoloženja. Studija ispituje razlike u indikatorima inflamacije kod pacijenata sa bipolarnom (BD) i unipolarnom depresijom (UD) i njihovu povezanost sa kliničkim karakteristikama akutne epizode i toka bolesti oba poremećaja.

**Materijali i metode:** Istraživanje predstavlja retrospektivnu studiju u koju su uključeni pacijenti oboleli od BD (n=60) i UD (n=242), koji su hospitalno lečeni u dvogodišnjem periodu i za koje su evidentirane socio-demografske informacije i karakteristike akutne epizode i toka bolesti i ispitivani indikatori inflamacije.

**Rezultati:** Oboleli od BD imaju viši srednji volumen trombocita u odnosu na obolele od UD. Isti indikator inflamacije je izmenjen i u odnosu na kliničke karakteristike obe grupe ispitanika. Tako je kod pacijenata sa UD njegova vrednost bila viša ukoliko je bolest ranije počela i duže trajala. Kod obolelih od BD, srednji volumen trombocita je povezan sa težinom psihopatologije tokom života, pa su pacijenti sa istorijom pokušaja suicida i oni koji su duže čekali na započinjanje terapije pri prvoj epizodi tokom života takodje imali više vrednosti ovog indikatora inflamacije.

**Zaključak:** Naše istraživanje ukazuje na postojanje hronične inflamacije niskog stepena kod specifičnih subpopulacija obolelih od afektivnih poremećaja. Prisutne imunske izmene razlikuju se u odnosu na polaritet oboljenja i mogu biti potencijalni indikator težine psihopatologije i hroniciteta bolesti.

**Ključne reči**: bipolarni afektivni poremećaj, inflamacija, unipolarna depresija

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