Mean platelet volume and neutrophil to lymphocyte ratio decrease in patients with depression and antidepressant treatment

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Abstract

Objective: Not only white blood cells but also platelets are being considered in inflammatory reactions from now on. Mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR) have been shown to change in inflammatory diseases like myocardial infarction, stroke, and implicated in psychiatric disorders nowadays. Our first aim is to investigate the relation of MPV and NLR with depression and secondly to assess if they change with the treatment of depression.

Methods: Forty-nine patients diagnosed with major depressive disorder (MDD) and hospitalized in a university hospital psychiatry inpatient unit retrospectively included in the study. Control group consisted of 48 hospital workers with no known disease. Complete blood count, Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression-Severity Scale (CGI-S) scores at admission and at discharge were noted and compared for the patient group.

Discussion: MPV of depressed patients was higher than controls. When we look at admission and discharge scores of clinical scales, decrement is statistically significant for both HAM-D and CGI-S. There was decline both in MPV and NLR which were both statistically significant.

Conclusion: Decreasing MPV and NLR values with the treatment of depression confirm the involvement of inflammatory processes in the pathophysiology of depression.

Keywords: Mean platelet volume, neutrophil to lymphocyte ratio, depression, treatment, inflammation.

Introduction

Depression and inflammation prime and kindle each other. In this vicious circle, depression elevates inflammatory responses and inflammation raises depression in turn. Inflammation has been raised and blamed in a number of disorders like cardiac failure, renal dysfunction, diabetes mellitus, acute/chronic liver disease, cancer, chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea, acute infections, rheumatoid arthritis, multiple sclerosis, chronic pain, and psoriasis; each of these also features an elevated risk for depression. Not only the white blood cells (neutrophils, lymphocytes, and monocytes) but also platelets have been shown to be in change in inflammatory processes.

The following mechanisms have been suspected of the platelet abnormalities observed in major depression: increased plasma concentrations of 5-hydroxytryptamine (5-HT) and epinephrine in platelets, altered intraplatelet concentrations of monoamines and catecholamines, increased intraplatelet calcium mobilization, up-regulation of 5-HT2A receptors or α adrenoreceptors, down-regulation of 3-HT transporter number, alteration in second messenger signal transduction. Mean platelet volume (MPV) is a machine-calculated measure of the average size of platelets detected in blood. MPV is usually included in blood tests routinely as a part of the complete blood count (CBC) by many laboratories today and its value is more and more reported among the standard parameters of CBC. A normal range of platelet volume is 6–11 fL, equivalent to spheres of 2.65 to 2.9 mm in diameter. It has been demonstrated that platelet size, measured as MPV, correlates with their reactivity. MPV is positively related to indices of platelet function including expression of glycoproteins Ib and IIb/IIIa receptors. There is an uprising interest on MPV as an independent risk factor for thrombotic disorders, including myocardial infarction (MI) and its prognosis, coronary atherosclerosis, and stroke.

Higher values of MPV found in patients with MI and unstable angina as compared with those with stable angina or noncardiac chest pain, and elevated MPV has been accepted as an independent risk factor for MI and stroke. A raised MPV is associated with poor clinical outcome among survivors of MI. Also, a positive relationship between MPV and the severity of acute ischemic cerebrovascular events has been established. Since data have cumulated pointing that depression is associated with platelet activation, it has become obvious that the selective serotonin reuptake inhibitor (SSRI) effect of blocking serotonin reuptake occurs not only in nerve cells but also in platelets, which inhibits their activity.

Neutrophils act as chiefs in inflammatory processes. The neutrophil to lymphocyte ratio (NLR), which may be calculated from the whole blood cell count is a cheap, reproducible test and has been investigated as a novel biomarker for systemic inflammatory response. NLR has been issued as a remarkable inflammatory marker, and high NLR levels are associated with increased mortality in breast cancer, colorectal cancer, gastric cancer.

Therefore we chose MPV and NLR as inflammatory biomarkers and our first aim is to investigate the relation of MPV and NLR with depression and secondly to assess if they change with the treatment of depression.

Materials and methods

Patient selection

This is a single center, retrospective case-control study. Patients admitted to the Psychiatry Inpatient Unit of Bezmialem Vakif University diagnosed with major depressive disorder determined with the Structural Clinical Interview Device (SCID-1) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) between 2014–2016 was screened retrospectively. Psychiatry Inpatient...
Unit database is based on the ICD-10 criteria, DSM-IV codes were given as reference. Diagnoses used are from the discharge records through which only F32 codes were selected according to ICD-10. This study was conducted according to the revised version of the Helsinki Declaration. The local ethics committee has approved the study. Demographic and clinical characteristics such as gender, age, duration of disease, co-morbid conditions, and other medical illness obtained from medical records of the patients were reviewed. Patients were eligible if they were (i) adults older than 18 years of age and (ii) diagnosed with major depressive disorder determined with the SCID-I according to DSM-IV. The exclusion criteria included (i) patients whose complete medical history could not be obtained, (ii) patients who had any other comorbidity psychiatric disorder according to DSM-IV, and (iii) patients with a history of cardiac failure, renal dysfunction, diabetes mellitus, acute/chronic liver disease, cancer, any autoimmune disorder (e.g. rheumatoid arthritis, multiple sclerosis), chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea, psoriasis, or acute infections. All the patients underwent an electrocardiogram (ECG) examination, blood pressure measurement, and routine biochemistry tests (including glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), serum iron, total iron-binding capacity, cholesterol, and triglyceride) during their hospital stay. Of inpatients with complete history, 49 consecutive patients were included in the study.

Controls
The control group was prospectively formed from 48 healthy hospital workers with no known medical disease according to both self-declaration and medical records. They were age and sex matched with the study group. They had no history of any psychiatric disorder. They were evaluated with the SCID-I according to DSM-IV by an experienced psychiatrist. All volunteers were free of any Axis-I psychiatric disorder and free of cardiac failure, renal dysfunction, diabetes mellitus, acute/chronic liver disease, cancer, any autoimmune disorder (e.g. rheumatoid arthritis, multiple sclerosis), COPD, asthma, obstructive sleep apnea, psoriasis or acute infections. Blood sample was taken from controls to analyse basic hemogram only.

Smokers are included both in the patient and control groups and patients could still smoke during inpatient stay.

Scales used
Structured Clinical Interview Device-I (SCID-I)
Structured Clinical Interview for DSM-IV (SCID-I) (21), Turkish version (22) translated by Corapcoglu et al. in 1999 was conducted by a trained interviewer.

Hamilton Depression Rating Scale (HAM-D)
HAM-D is a standard scale based on psychiatrists’ assessments and was developed in the late 1950s to measure depressive symptoms. The scale was initially designed to obtain a total score based on 17 of its 21 items. The validity and reliability study of the Turkish version of the scale was done by Akdemir et al. in 2001. The test-retest reliability coefficient of the HAM-D was based on a 5-day interval was .85, with a Cronbach alpha coefficient of .75 and a split-half reliability coefficient of .76. Interrater reliability coefficients based on the independent ratings of four assessors were between .87 and .98; therefore it was shown to be a valid and reliable tool in the assessment of clinical depression.

Clinical Global Impression-Severity Scale (CGI-S)
CGI rating scales are commonly used to measure symptom severity, treatment response, and efficacy of treatment in patients with psychiatric disorders CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of the assessment. The scores are: 1 = not ill; 2 = borderline ill; 3 = slightly ill; 4 = moderately ill; 5 = markedly ill; 6 = very much ill; 7 = severely ill.

The first entry and before discharge HAM-D, Clinic Global Impression Scale, CBC examinations for each patient from the inpatient care unit were used for analysis.

Biochemical and haematological analyses
Usually, the first blood tests are done next day after admission to our units and the last one is done in the morning before hospital discharge. Blood samples were drawn for all patients between 8 and 9 a.m. after 12 hours of overnight fasting. Immediately after collecting blood samples, CBC was determined using Sysmex XS-1000iTM Automated Hematology Analyzer (Sysmex, USA). The following platelet parameters were measured: PLT (expressed in 10^9/mm^3), MPV (expressed in FL) and neutrophil count (expressed in /ul), lymphocyte count (expressed in /ul), NLR and erythrocyte sedimentation rate (ESR) (expressed in mm/h).

Statistical analysis
Statistical analysis was performed using the Statistical Package for the Social Science version 21.0 (IBM SPSS Statistics; Armonk, NY, USA). Simple descriptive statistics (mean ± standard deviation) were generated for continuous variables. Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Student’s t-test was used for continuous variables with normal distribution, and Mann-Whitney U test was used for continuous variables without normal distribution. Chi-square test was used for categorical variables.

Paired t-test was used for repeated data in the patient group. Differences were considered significant at p< 0.05 for all the tests. The receiver operator characteristics (ROC) curve was plotted to verify the accuracy of MPV and NLR.

Results
The sociodemographic and clinical characteristics of participants are presented in Table 1.

Thirty-six female and 13 male patients were included in the patient group, the mean age was 40.86 (ranged between 18-76). More than half of participants educated less than high school level 65.3% were married, 32.7% was smoking. Eighty-five point four percent of patients were in their first hospital stay, 18.8% of them had at least one suicide attempt during their life time. The mean duration of hospitalization was 27.6 days ranging from 10 to 54 days.

Thirty-six female and 12 male hospital workers were included in the control group, the mean age was 36.85. More than half of healthy controls were graduated from university. Fifty-eight point three percent was married. Thirty-five point four percent was smoking. There was no statistically significant difference in terms of age, sex, marital status and smoking between the patient and control groups. Educational level is higher in control group owing to participation of doctors and nurses.

We could not find any association with sociodemographic data (age, sex, marital status and smoking) obtained and severity of depression in the patient group.

Comparisons of laboratory parameters between patients at admission and control group are given in Table 2. MPV value in patients with depression was 9.13 ± 2.1, MPV in controls were 7.19 ± 1.84. Difference in MPV between patients and controls was statistically significant.

However, difference in the NLR between patient and control groups did not reach statistical significance.
Table 1. The sociodemographic and clinical characteristics of study population

<table>
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<th>Patient (n: 49)</th>
<th>Control (n: 48)</th>
<th>p value</th>
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</thead>
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<td><strong>Age</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>40.86 ± 14.7</td>
<td>36.05 ± 10.1</td>
<td>.524</td>
</tr>
<tr>
<td>%</td>
<td>123</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>73.5</td>
<td>75</td>
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</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>26.5</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td><strong>Educational status</strong></td>
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<tr>
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<td>0</td>
<td>.000***</td>
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<tr>
<td>%</td>
<td>4.1</td>
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<td></td>
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<tr>
<td>Primary school</td>
<td>5</td>
<td>7</td>
<td>.031**</td>
</tr>
<tr>
<td>%</td>
<td>10.2</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
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<td>.108</td>
</tr>
<tr>
<td>%</td>
<td>55.1</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>High school</td>
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<td>4</td>
<td>.018**</td>
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<tr>
<td>%</td>
<td>16.3</td>
<td>8.3</td>
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<tr>
<td>University</td>
<td>7</td>
<td>29</td>
<td>.000***</td>
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<tr>
<td>%</td>
<td>14.2</td>
<td>60.4</td>
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<td><strong>Marital status</strong></td>
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<td>Single</td>
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<td>17</td>
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<tr>
<td>%</td>
<td>22.4</td>
<td>35.4</td>
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<tr>
<td>Married</td>
<td>32</td>
<td>28</td>
<td>.031**</td>
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<tr>
<td>%</td>
<td>65.3</td>
<td>58.3</td>
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<td>Widowed</td>
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<td>1</td>
<td>.000***</td>
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<td>%</td>
<td>8.2</td>
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<td>%</td>
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<td>4.2</td>
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<td><strong>Smoking</strong></td>
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<tr>
<td>%</td>
<td>67.3</td>
<td>64.6</td>
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<tr>
<td>Yes</td>
<td>16</td>
<td>17</td>
<td>.000***</td>
</tr>
<tr>
<td>%</td>
<td>32.7</td>
<td>35.4</td>
<td></td>
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<tr>
<td><strong>Number of hospitalizations</strong></td>
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</tr>
<tr>
<td>1</td>
<td>41</td>
<td>85.4</td>
<td></td>
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<tr>
<td>%</td>
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<td>2</td>
<td>4</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>%</td>
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<td></td>
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<tr>
<td>3</td>
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<td>4.2</td>
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</tr>
<tr>
<td>%</td>
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</tr>
<tr>
<td>%</td>
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<td></td>
</tr>
<tr>
<td><strong>Suicide attempt</strong></td>
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<tr>
<td>0</td>
<td>39</td>
<td>81.2</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>8</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
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</tbody>
</table>

For age independent t-test; for other categorical variables chi-square test.

Table 2. Comparisons of the laboratory parameters at admission with control group

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>Patient Admission</th>
<th>Control</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet (/ul)</td>
<td>239333 ± 52210</td>
<td>252611 ± 61048</td>
<td>.496</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>9.13 ± 2.13</td>
<td>7.19 ± 1.84</td>
<td>.000***</td>
</tr>
<tr>
<td>Neutrophil (/ul)</td>
<td>4537 ± 1606</td>
<td>4330 ± 1472</td>
<td>.700</td>
</tr>
<tr>
<td>Lymphocyte (/ul)</td>
<td>2130 ± 716</td>
<td>2186 ± 581</td>
<td>.331</td>
</tr>
<tr>
<td>NLR</td>
<td>2.29 ± 1.02</td>
<td>2.09 ± 0.95</td>
<td>.241</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001; independent t-test.

Comparisons for admission and discharge scores of clinical scales and parameters are shown in Table 3. Decrement is statistically significant for both HAM-D and CGI-S; meaning that patients had improved. There was a decline both in MPV and NLR which were statistically significant (p < 0.05). Lymphocyte count but not the neutrophil count increased significantly (p < 0.05), platelet count and ESR did not change radically.

Table 3. Clinical scales and laboratory parameters at admission and at discharge

<table>
<thead>
<tr>
<th>Clinical Scales and Laboratory Parameters</th>
<th>Admission</th>
<th>Discharge</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td>17.39 ± 6.37</td>
<td>6.88 ± 3.94</td>
<td>.000***</td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.75 ± 1.00</td>
<td>2.79 ± 0.87</td>
<td>.000***</td>
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<tr>
<td>Platelet (/ul)</td>
<td>239333 ± 52210</td>
<td>238112 ± 62710</td>
<td>.562</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>9.13 ± 2.13</td>
<td>8.55 ± 1.47</td>
<td>.031*</td>
</tr>
<tr>
<td>Neutrophil (/ul)</td>
<td>4537 ± 1606</td>
<td>4118 ± 1496</td>
<td>.108</td>
</tr>
<tr>
<td>Lymphocyte (/ul)</td>
<td>2130 ± 716</td>
<td>2335 ± 629</td>
<td>.025*</td>
</tr>
<tr>
<td>NLR</td>
<td>2.29 ± 1.02</td>
<td>1.86 ± 0.81</td>
<td>.003**</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>12.55 ± 9.9</td>
<td>13.41 ± 12.9</td>
<td>.675</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001; paired t-test for parametric values; Wilcoxon test for nonparametric values.

The ROC curves for MPV and NLR is shown in Figure 1. For MPV, the area under the curve was 0.782; the sensitivity and specificity were 0.83% and 0.35% respectively. For NLR, the area under the curve was 0.553; the sensitivity and specificity were 0.42% and 0.22%, respectively. Confidence interval for MPV was [0.690-0.874] and for NLR it was [0.436-0.674].

![Figure 1. Receiver operator characteristics curve for MPV and NLR. AUC: area under the curve.](image)

Discussion

There is some evidence that many psychiatric disorders are accompanied by activation of inflammatory and cell-mediated immune pathways, for example, mania, schizophrenia, post-traumatic stress disorder (PTSD)\(^1\). In the 1990s, the first papers showing inflammation by increased levels of proinflammatory cytokines, such as IL-6 and acute phase proteins and immune...
activation by increased levels of sIL-2Rαs levels in acute and
euthymic manic patients were published15-18. From the perspective of
depression, three meta-analyses have highlighted proinflammatory
cytokine differences between patients with major depressive disorder
and controls, including interleukin-6 (IL-6), tumor necrosis factor-
alpha (TNF-α), IL-1β, the soluble IL-2 receptor, the IL-1 receptor
antagonist (IL-1ra), and C-reactive protein 3 (CRP)17-19.

Multiple biomarkers may give us more accurate findings for
inflammation in depression and the most linked ones are
interleukins (mostly IL-6) and TNF-α. However these tests are
expensive, there are limited laboratories working on these
biomarkers and the standardization is low between them. In
contrast, CBC is cost effective and have already been ordered
for many patients during routine laboratory work-up before
psychiatric diagnoses and to exclude some organic disorders
during the psychiatric disease course. MPV and NLR can be
obtained from CBC and used as systemic inflammatory markers
with increasing references2,6,9,14,20-22.

There are some studies using either MPV or NLR as biomarkers
of inflammation in psychiatric disorders. In our study, we did
not include the patients with other mental disorders or having any
comorbidity with depression. In the literature, Wysokinski
d and Szczepocka studied comparisons of platelet parameters in
schizophrenia, unipolar depression, and bipolar depression. They
have found that patients with schizophrenia had the lowest mean
number of platelets, while patients with unipolar depression had
highest mean value. Patients with schizophrenia had the highest
mean volume of platelets (MPV) and highest percentage of large
platelets, while patients with bipolar depression had the lowest MPV
and lowest percentage of large platelets23.

In the study by Mayda et al., both MPV and NLR are used as
inflammation biomarkers in acute mania. NLR increased
similarly as in depression but MPV decreased and these findings
may reflect inflammation and role of inflammation in the complex
pathophysiology of acute mania24. As a different psychiatric
disorder group neutrophils were found to be decreased in obsessive
compulsive disorder (OCD) in a study comparing CBC parameters
between patients with OCD and healthy controls24.

MPV and NLR values of patients were higher than healthy
controls before the inpatient treatment of depression and they
decreased with the treatment of depression supporting the
involvement of inflammatory processes in the pathophysiology of
depression. Our findings are in parallel with the results of other
studies using MPV and NLR as markers for searching the relationship
between inflammation and depression25-27. In the study by Ataoğlu
et al., MPV was higher in patients with depression at baseline and
decreased 8 weeks of treatment with escitalopram. Red blood cell
distribution width (RDW) and NLR was high in depression and
decreased with treatment of depression in the study of Demircan
et al.25. NLR was higher in depressed patients in other studies
also28-30 and correlated with severity of depression, supposed to be
an independent predictor of severe depression26. NLR may be a trait
marker for suicidal vulnerability via a relationship between NLR and
a recent suicide attempt in depressed inpatients. Future prospective
studies are needed to determine the exact roles of NLR, and other
inflammatory markers on suicidality in MDD26. NLR found to be
higher in patients with major depression than those who had suicide
attempts but the difference was not significant27.

In MD, a later age of onset has not only been associated with
inflammation, but also with atherosclerosis. While an earlier age
of onset was associated with a family history of vascular disease.
NLR was related to a later onset of depression. Thus, in line with
the vascular depression hypothesis as one distinct etiopathological
mechanism, a later onset of depression is associated with pathological
pathways relevant for cardiovascular disease has been supported28.
Although NLR was still higher in depressed patients than healthy
controls, in our analysis we could not show a significant difference.

In relation to the gender, we could not find difference between males
and females with respect to NLR. It is hypothesized that females had
a greater inflammatory response than males. In a study NLR was
compared between sexes at baseline or at 12 weeks after treatment.
Only females showed a significant increase in NLR after treatment,
in keeping with increased neutrophil and decreased lymphocyte
percentages. This finding is in contrast to a theory that decreased NLR
occurs with response to treatment. An increased NLR may indicate
that females show an inflammatory pattern in depression and may
serve as a marker of depression with poorer prognosis29. In a recent
metaanalysis subjects with major depressive disorder (MDD) had
higher NLR as compared with healthy controls. Meta-regression
analyses showed that the effect was not influenced by difference in
male proportions and mean age30.

From the perspective of sensitivity and specificity, in the ROC
curve we found the area under the curve for MPV to be larger than
it is for NLR (Figure 1). This finding may support MPV as being
more sensitive and specific than NLR but this must be replicated
in other studies.

High MPV increases cardiovascular disease risk, therefore some
may consider that depression treatment may lessen the morbidity
and mortality also. Platelets are known to have serotonin receptors,
volume changes in platelets may have been caused by different levels
or effects of serotonin associated with depression pathophysiology
and treatment1.

In mice studies; larger, more frequent or more prolonged
inflammatory responses have negative mental and physical health
consequences1. The stronger associations in clinical samples
compared with community samples provide evidence of dose-
response relationships30.

In our study, if we had analyzed MPV and NLR according to
depression severity subgroups, it would be likely to see a higher
level of inflammation than community because our sample is
highly clinical with more severe depression within reason treated
as inpatients.

Perhaps we can guess treatment response to antidepressant
medications from MPV and NLR characteristics and personalize
treatments in a similar way with the study by Uher et al. in which
higher CRP levels were associated with a better response to
nortriptyline than to escitalopram22. Baseline CRP levels were also
detected to moderate the antidepressant effects of a treatment
that directly aims immune pathogenic mechanisms, which was beneficial
only for individuals with high CRP levels29. Taken together, the
evidence to date is agreeable with systematic inflammation working
as a moderator of antidepressant response.

The strengths of our study, it combines more than one
inflammation marker those could be derived from a CBC and high
in depression. Limitations of our study are: this is a retrospective
study so depression treatments were not standardized in contrast,
personalized according to needs of patients in psychiatry ward. The
study sample was relatively small to draw definite conclusions also
antidepressant medications were been actively used for depression
when patients were in the outpatient setting. Moreover, most
of the study population (75% of patients) was female; thus, our
findings may not be generalized to each sex. Body mass index and
blood pressure were not compared with the severity of depression.
Larger, detailed prospective trials with patients who are free of any
psychootropic medication are needed to establish the association
between depression treatment and MPV, NLR.

Conclusion

Inflammation is a complex process involving several cells and
molecules which may play a role in the pathophysiology of
depression. MPV and NLR could be useful together with other
clinical analyzes and evaluations in studies about MDD.

In future, perhaps we might be able to use MPV and NLR in
patients with depression for diagnosis, treatment selection, prediction
of treatment response and long-term follow-up of depression so further studies need to be done in this field.

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We have no conflicts of interest to disclose.

**References**