Original article

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

Ahmet Öztürk[1], Ebru Şahan[1], Ali Barlas Mirçik[1], Erdem Deveci[1], Onur Yilmaz[1], İsmet Kirpinar[1]

[1] Bezmialem Vakif University, Department of Psychiatry, Istanbul, Turkey.

Received: 7/25/2018 – **Accepted:** 1/17/2019

DOI: 10.1590/0101-60830000000184

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 ofdepression.

Öztürk A et al. / Arch Clin Psychiatry. 2019;46(1):9-13

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[1]. 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 5-HT transporter number, alteration in second messenger signal transduction[2]. 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)[3] and its prognosis[4], coronary atherosclerosis[5] and stroke[6].

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[2].

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[7], colorectal cancer[8], gastric cancer[9].

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-I) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) between 2014-2016 was screened retrospectively. Psychiatry Inpatient

Address for correspondence: Ebru Şahan. Department of Psychiatry, Bezmialem Vakif University. Adnan Menderes Boulevard (Vatan Street) P.K., 34093, Fatih, Istanbul, Turkey.
Telephone: +905054028722. Fax: +902124531869. E-mail: ebrushaan@hotmail.com

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 comorbid 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[10] 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 Interwiev Device-I (SCID-I)

Structured Clinical Interview for DSM-IV (SCID-I)[11], Turkish version[10] translated by Corapcıoğlu *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[12].

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[13].

The first entry and before discharge HAM-D, Clinic Global Impression Scale, CBC examinations for each patient from the inpatient care unit wer 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 $10^3/mm^3$), 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 eduated 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

		Patient (n: 49)		Control (n: 48)		p value
Age		40.86 ± 14.7		36.85 ± 10.1		123
		n	%	n	%	
Sex	Female	36	73.5	36	75	.524
	Male	13	36.5	12	25	
Educational status	Uneducated	2	4.1	0	0	.000
	Primary school	5	10.2	7	14.6	
	Secondary school	27	55.1	8	16.7	
	High school	8	16.3	4	8.3	
	University	7	14.2	29	60.4	
Marital status	Single	11	22.4	17	35.4	.342
	Married	32	65.3	28	58.3	
	Widowed	4	8.2	1	2.1	
	Divorced	2	4.1	2	4.2	
Smoking	No	33	67.3	31	64.6	.555
	Yes	16	32.7	17	35.4	
Number of hospitalizations	1	41	85.4			
	2	4	8.3			
	3	3	4.2			
	6	1	2.1			
Suicide attempt	0	39	81.2			
	1	8	16.7			
	7	2	2.1			

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

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

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

*p < 0.05; **p < 0.01; ***p < 0.001; independent t-test.
MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio.

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

Clinical Scales and Laboratory Parameters	Mean ± SS		P values
	Admission	Discharge	
HAM-D	17.38 ± 6.37	6.88 ± 3.94	**.000*** **
CGI-S	4.75 ± 1.00	2.79 ± 0.87	**.000*** **
Platelet(/ul)	239333 ± 52210	236112 ± 62710	.582
MPV (fl)	9.13 ± 2.13	8.55 ± 1.47	**.031***
Neutrophil (/ul)	4537 ± 1606	4118 ± 1496	.108
Lymphocyte (/ul)	2130 ± 716	2335 ± 628	**.025***
NLR	2.29 ± 1.02	1.86 ± 0.81	**.003****
ESR (mm/h)	12.55 ± 9.9	13.41 ± 12.9	.675

*p < 0.05; **p < 0.01; ***p < 0.001; paired t-test for parametric values; Wilcoxon test for nonparametric values.
HAM-D: Hamilton Depression Rating Scale; CGI-S: Clinical Global Impression-Severity Scale; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio.

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].

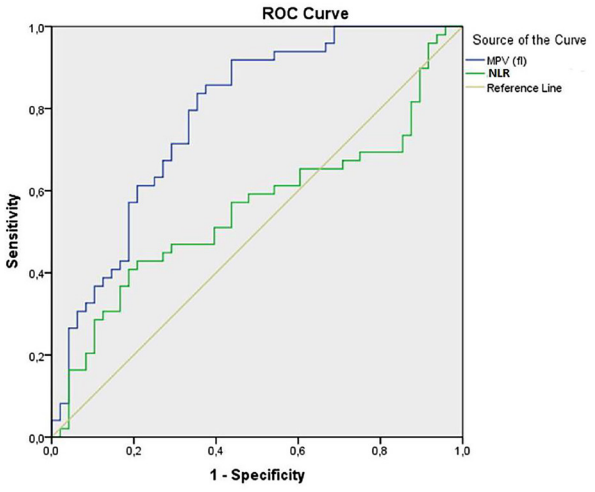

Figure 1. Receiver operator characteristics curve for MPV and NLR. AUC: area under the curve.

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)[14]. 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-2Rs levels in acute and euthymic manic patients were published[15,16]. 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-1b, 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 references[2,4,6-9,14,20-22].

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 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 platelets[23].

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 mania[21]. 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 controls[24].

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 depression[2,20,25]. In the study by Ataoğlu *et al.*, MPV was higher in patients with depression at baseline and decreased 8 weeks of treatment with escitalopram[2]. 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 also[20,25] and correlated with severity of depression, supposed to be an independent predictor of severe depression[20]. 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 MDD[26]. NLR found to be higher in patients with major depression than those who had suicide attempts but the difference was not significant[27].

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 depression, a later 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 supported[28]. 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 prognosis[29]. 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 age[30].

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 treatment[3].

In mice studies; larger, more frequent or more prolonged inflammatory responses have negative mental and physical health consequences[1]. The stronger associations in clinical samples compared with community samples provide evidence of dose-response relationships[18].

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 escitalopram[22]. 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 levels[16]. 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 bein 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 psychotropic 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.

Funding details

This work is not supported by any drug or other companies. No grants or fees were taken from any institution or firm.

Disclosure statement

We have no conflicts of interest to disclose.

References

1. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatry. 2015;172(11):1075 91.
2. Ataoglu A, Canan F. Mean platelet volume in patients with major depression: effect of escitalopram treatment. J Clin Psychopharmacol. 2009;29(4):368-71.
3. Cameron HA, Phillips R, Ibbotson RM, Carson PH. Platelet size in myocardial infarction. Br Med J (Clin Res Ed). 1983;287(6390):449-51.
4. Kiliçli-Camur N, Demirtunç R, Konuralp C, Eskiser A, Başaran Y. Could mean platelet volume be a predictive marker for acute myocardial infarction? Med Sci Monit. 2005;11(8):CR387-92.
5. Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. Lancet. 1991;338(8780):1409-11.
6. Greisenegger S, Endler G, Hsieh K, Tentschert S, Mannhalter C, Lalouschek W. Is elevated mean platelet volume associated with a worse outcome in patients with acute ischemic cerebrovascular events? Stroke. 2004;35(7):1688-91.
7. Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short--and long-term mortality in breast cancer patients. Ann Surg Oncol. 2012;19(1):217-24.
8. Walsh S, Cook E, Goulder F, Justin T, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91(3):181-4.
9. Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, et al. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol. 2011;18(12):3362-9.
10. Çorapçıoğlu A, Aydemir Ö, Yıldız M, Esen A, Köroğlu EJAHyb. DSM--IV Eksen I Bozuklukları (SCID-I) için yapılandırılmış klinik görüşme, klinik versiyon. Ankara: Hekimler yayın birliği; 1999.
11. First MB, Spitzer R, Gibbon M, Williams JB. Structured clinical interview for DSM-IV clinical version (SCID-I/CV). Washington, DC: American Psychiatric Press; 1997.
12. Akdemir A, Türkçapar MH, Orsel SD, Demirergi N, Dag I, Ozbay MH. Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. Compr Psychiatry. 2001;42(2):161-5.
13. Busner J, Targum SD. The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. Psychiatry (Edgmont). 2007;4(7):28-37.
14. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013;11:200.
15. Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: Effects of neuroleptics and mood stabilizers. J Psychiatr Res. 1995;29(2):141-52.
16. Maes M, Delange J, Ranjan R, Meltzer HY, Desnyder R, Cooremans W, et al. Acute phase proteins in schizophrenia, mania and major depression: modulation by psychotropic drugs. Psychiatry Res. 1997;66(1):1-11.
17. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A Meta-Analysis of Cytokines in Major Depression. Biol Psychiatry. 2010;67(5):446-57.
18. Howren MB, Lamkin DM, Suls J. Associations of Depression With C--Reactive Protein, IL-1, and IL-6: A Meta-Analysis. Psychosom Med. 2009;71(2):171-86.
19. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta--regression. J Affect Disord. 2012;139(3):230-9. .
20. Aydin Sunbul E, Sunbul M, Yanartas O, Cengiz F, Bozbay M, Sari I, 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):121-6.
21. Mayda H, Ahsen A, Bağcioğlu E, Öztürk A, Bahçeci B, Soyuçok E, et al. Effect of Increased Neutrophil-to-Lymphocyte Ratio (NLR) and Decreased Mean Platelet Volume (MPV) Values on Inflammation in Acute Mania. Noro Psikiyatr Ars. 2016;53(4):317-20.
22. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An Inflammatory Biomarker as a Differential Predictor of Outcome of Depression Treatment With Escitalopram and Nortriptyline. Am J Psychiatry. 2014;171(12):1278-86.
23. Wysokiński A, Szczepocka E. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. Psychiatry Res. 2016;237:238-45
24. Atmaca M, Kilic F, Koseoglu F, Ustundag B. Neutrophils are decreased in obsessive-compulsive disorder: preliminary investigation. Psychiatry Investig. 2011;8(4):362-5.
25. 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.
26. Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord J Psychiatry. 2017;71(8):574-80.
27. Gundogdu Meydaneri G, Meydaneri S. Can Neutrophil Lymphocyte Ratio Predict the Likelihood of Suicide in Patients with Major Depression? Cureus. 2018;10(4):e2510.
28. Euteneuer F, Dannehl K, Del Rey A, Engler H, Schedlowski M, Rief W. Peripheral immune alterations in major depression: the role of subtypes and pathogenetic characteristics. Front Psychiatry. 2017;8:250.
29. Adhikari A, Dikshit R, Karia S, Sonavane S, Shah N, De Sousa A. Neutrophil-lymphocyte Ratio and C-reactive Protein Level in Patients with Major Depressive Disorder Before and After Pharmacotherapy. East Asian Arch Psychiatry. 2018;28(2):53-8.
30. 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(Pt A):229-36.