Effect of Increased Neutrophil-to-Lymphocyte Ratio (NLR) and Decreased Mean Platelet Volume (MPV) Values on Inflammation in Acute Mania

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ABSTRACT

Introduction: The neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) are simple, low-cost, and useful inflammatory markers detected in routine complete blood count (CBC), and their use has recently become widespread. In this study, we aimed to investigate the presence of an inflammatory state in manic patients on the basis of NLR and MPV values.

Methods: This retrospective study was performed on 76 patients with acute mania who were admitted to the Inpatients Psychiatry Clinic of Afyon Kocatepe University Hospital in Turkey. Diagnoses were based on Diagnostic and Statistical Manual of Mental disorder (DSM-IV). The control group consisted of 74 healthy individuals recruited from the community. They were age- and sex-matched with the study group.

Results: NLR values of the manic patient group were 2.2 ± 1.4 and those of the control group were 1.6 ± 0.5 . NLR values were significantly higher ($p=0.004$) and MPV values were significantly lower in the manic patient group than in the control group (10.0 ± 1.2 vs. 10.9 ± 2.3 , $p=0.027$).

Conclusion: Increased NLR and decreased MPV levels may reflect inflammation in manic patients, and inflammation may play a role in the complex pathophysiology of acute mania.

Keywords: Neutrophil-to-lymphocyte ratio, mean platelet volume, acute mania

INTRODUCTION

Inflammation is a biological condition characterized by cytokine cascades, cellular immune responses, and increased levels of acute phase proteins and complement factor; however, it is worth noting that inflammation is accompanied by psychiatric disorders in recent years (1,2). Most studies suggest an association between inflammation and psychopathology in mood disorder (3,4). In bipolar disorder (BD), the precise mechanism underlying inflammation-related events has not been fully clarified to date (5). However, recent studies support this notion by demonstrating the following: (a) The immune response system is activated by macrophages and T lymphocytes, which results in the release of proinflammatory cytokines. These cytokines play a role in attenuating the release of neurotransmitters such as noradrenalin and serotonin in the brain. (b) Activated microglia in the brain may have adverse effects on the neuroprotective system, as implicated in the symptoms of BD, which is mediated by activated proinflammatory cytokines (6,7). In the literature, Breunis et al. reported that activated-T cell and soluble IL-2 receptor (sIL-2R) levels were significantly higher in euthymic, manic, and depressed bipolar patients than in healthy controls and sIL-2R levels were significantly higher in manic patients than in depressed patients (8,9). In addition, they found that IL-2, IL-4, and IL-6 levels in the serum of manic patients were significantly higher than those in the serum of healthy controls. Kim et al. reported that TNF- α and IL-6 levels were significantly higher in manic patients than in healthy controls and that compared with baseline, IL-6 levels showed a significant decrease after 6 weeks of treatment (10). Hope et al. (11) demonstrated a positive association between inflammatory markers and elevated mood in patients with BD. Inflammation has been considered to be a risk indicator for cognitive deficits in bipolar affective disorder (12). These results suggest that inflammation plays an important role in the neurobiology of bipolar affective disorder. The neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) are simple, cost-effective, and useful inflammatory markers detected in routine complete blood count (CBC).

In this study, we aimed to investigate the presence of an inflammatory state in acute manic patients using NLR and MPV values. The ultimate purpose of our study was to understand the biological factors that contribute to the risk of a manic episode in patients with bipolar affective disorder.

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METHODS

Patient Selection

This retrospective study was performed on 76 patients with acute mania who were admitted to the Inpatients Psychiatry Clinic of our university hospital between July 1, 2011 and July 1, 2013. The study was conducted according to the revised version of the Declaration of Helsinki. All the patients were recalled to the hospital and informed about the study protocol. All the patients provided written informed consent. The local ethics committee approved the study. Demographic and clinical characteristics such as gender, age, number of manic episodes, duration of disease, co-morbid condition, and other medical illness obtained from medical records of the patients were reviewed. Patients were eligible if they were (i) between 18–65 years of age and (ii) diagnosed with bipolar affective disorder, determined using the Structured Clinical Interview Device for Diagnostic and Statistical Manual of Mental disorder (DSM-IV) (SCID-I). The exclusion criteria included patients whose complete medical history could not be obtained, patients with any other comorbid psychiatric disorder according to DSM-IV, and patients with a history of cardiac failure, renal dysfunction, diabetes mellitus, acute/chronic liver disease, cancer, chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea, or acute infections. All the patients underwent 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]. Of inpatients with complete history, 76 patients were included regardless of the duration of mood state in acute mania. Ten patients with acute mania were excluded from this study because of their comorbid conditions and incomplete medical records.

Controls

The control group consisted of 74 healthy individuals who were prospectively recruited from the community. They were age- and sex-matched with the study group. They had no personal history of bipolar affective disorder or other psychiatric disorders. Their psychiatric conditions were evaluated by psychiatrists (BE and MH) and with the Structured Clinical Interview for DSM-IV Axis I. All volunteers were free of Axis-I disorders. Individuals with active infection, chronic inflammatory or autoimmune disorders, and endocrinological, hepatic, renal, pulmonary, and neurological diseases were excluded.

Biochemical and Hematological Analyses

Laboratory data of CBC and biochemical analyses were obtained from past hospital records of the patients when had a manic episode. Blood samples were drawn from the patients within 24 h of their first admission with this episode. After the collection of all venous blood samples in potassium–ethylenediaminetetraacetic acid tubes (dipotassium EDTA tube), the Sysmex-XE 2000i automated blood cell analyzer (Sysmex, Kobe, Japan) was used to analyze CBC within 1 h following venous sampling. NLR was noted as a simple ratio between the absolute neutrophil and absolute lymphocyte counts. MPV was calculated by the following formula: $MPV (fL) = [(plateletcrit (\%)/platelet count (\times 10^9/l))] \times 10^5$.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Science version 18.0 (IBM SPSS Statistics; Armonk, NY, USA). 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. Correlation analysis was performed by the Pearson correlation test.

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 NLR and MPV.

RESULTS

The socio-demographic variables are shown in Table 1. Manic patient and control groups were evaluated according to gender and age, and no significant differences were found between the groups. NLR values of the patient group were 2.2 ± 1.4 , while those of the control group were 1.6 ± 0.5 . NLR values were significantly higher in the manic patient group than in the control group ($p = 0.004$) (Table 2). MPV values in the manic patient group were significantly lower than those in the control group (10.0 ± 1.2 vs. 10.9 ± 2.3 , $p = 0.027$) (Table 2). Laboratory findings of the patients and controls are presented in Table 2. Finally, we found no correlation between NLR and MPV values ($r = -0.14$, $p = 0.867$). The ROC curve for NLR is shown in Figure 1. The area under the ROC was 0.620; the sensitivity and specificity were 0.45% and 0.81%, respectively. The ROC curve for MPV is shown in Figure 2. The area under the ROC curve was 0.604; the sensitivity and specificity were 0.96% and 0.47%, respectively.

DISCUSSION

Bipolar affective disorder is an episodic, long-term, and severe mental illness characterized by mood disturbances (13). Inflammation has been implicated in the pathophysiology of BD (14). In a recent study, NLR has been shown to be elevated in both manic and euthymic patients compared with the control group (15). In the present study, we found higher NLR levels and lower MPV levels in the manic patient group than in the control group. These results could reveal the presence of inflammation in the manic phase of BD. To date, no single parameter can be recommended as the gold standard to indicate inflammation in patients. NLR has attracted considerable interest as a potential marker to determine inflammation (16). In addition, NLR has been found to be higher in case of familial Mediterranean fever (FMF) (17), bacterial and viral infection (18), and peptic ulcer disease (19) than in controls, suggesting that has prognostic significance in cerebrovascular disease (20). Platelets have been suggested to play an important role in inflammatory processes (21). MPV is commonly used as a measure of platelet size, and it has been known to be a marker of platelet activity (22). To the best of our knowledge, MPV values in patients with bipolar affective disorder have not been studied

Table 1. Socio-demographic variables and disease characteristics of participants

	Patient (n=76)	Control (n=74)	p
Mean age (years) (mean±SD)	38.7±13.9	38.1±10.5	0.448
Gender (male/female)	41/35	45/29	0.395
Marital status (married/single)	51/25	46/28	0.527
Education years (mean±SD)	11.1±2.5	10.6±2.0	0.147
Patients			
Mean disease onset (years)	28.08±10.9		
Mean duration of disease (years)	10.1±8.7		
Mean number of manic episodes	3.2±2.01		
Median hospitalization time (days)	2		
Family history of bipolar disorder (-/+)	54/22		
Treatment (n, %) (mood stabilizer and/or antipsychotic)	25 (32.9%)		
No treatment (n, %)	51 (67.1%)		
p: independent t-test			

Table 2. Laboratory data of patients and controls

	Patient	Control	p
WBC	7.80±2.36	7.33±1.48	0.140
Neutrophil ($\times 10^3/\text{mm}^3$)	4.52±2.02	3.69±1.02	0.002
Lymphocyte ($\times 10^3/\text{mm}^3$)	2.45±2.05	2.29±0.62	0.548
Monocyte ($\times 10^3/\text{mm}^3$)	0.63±0.20	0.49±0.21	<0.001
Platelet ($\times 10^3/\text{mm}^3$)	249.33±72.66	232.35±54.36	0.108
Hemoglobin	12.4±1.70	12.7±1.45	0.278
RDW	13.60±1.03	13.08±2.56	0.105
NLR	2.2 ± 1.4	1.6 ± 0.5	*0.004
MPV	10.0 ± 1.2	10.9 ± 2.3	*0.027

WBC: white blood cell count; RDW: red cell distribution width; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; *p<0.05, p: independent t-test

previously in the literature. However, higher MPV has been found in patients with depression than in individuals without depression (23). Ataoglu and Canan (24) reported that MPV values are increased in patients with depression and are normalized after 8 weeks of antidepressant treatment. In the aforementioned studies, these increased MPV values are attributed to the mechanism underlying the relationship between major depression and cardiovascular disease. However, a number of previous studies have reported that decreased MPV levels are observed in high-grade inflammatory diseases such as active rheumatoid arthritis or attacks of FMF, while increased MPV levels are observed in low-grade inflammatory diseases such as cardio-cardiovascular disease (25,26). On the other hand, markers of inflammatory reaction are found to be higher in patients with a manic episode than in those with a depressive episode (27). Taken together, it can be concluded that increased NLR and decreased MPV levels may reflect the presence of inflammation in manic patients.

Many studies performed on bipolar patients during a manic episode have suggested activated inflammation with increased acute-phase protein levels (CRP) (28) and proinflammatory cytokine levels (IL-4, IL-6 and IL 8, and TNF- α) (5,9,10) and decreased interferon gamma levels (29). In the present study, we indicated that the inflammatory state has been associated with BD patients with a manic episode; however, the underlying mechanism has not been addressed. Macrophages/monocytes and T lymphocytes may have implications on inflammation in BD patients (30). We did not evaluate the association between the severity of a manic episode and NLR or MPV. Cunha et al. (28) reported that an increase in high-sensitive CRP levels did not show any significant relationship with symptomatic severity. Thus, further studies may be needed to clarify this issue. It will be important to establish whether NLR and MPV are associated with depressed and euthymic states in BD in future studies.

The present study has also some important limitations. First, the relatively small sample size should be considered while interpreting our findings. Second, this was a retrospective study. Third, we did not measure CRP, which is a major component of inflammatory reaction (because this study is designed as retrospective). The last limitation is the medications (atypical antipsychotics and/or mood-stabilizing agents) used by some patients, which may make it difficult to identify a clear outcome, because it has been reported that these medications may affect the proinflammatory parameters (31). To overcome this limitation, the study should ideally be designed with patients who are free of any psychotropic medication.

In the present study, increased NLR and decreased MPV levels in bipolar patients were observed during a manic episode. These findings suggest that inflammation is part of the complex pathophysiology of acute mania.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Afyon Kocatepe University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

- Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yücel M, Gama CS, Dodd S, Dean B, Magalhaes PVS, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev* 2011; 35:804-817. [CrossRef]
- Dean B. Understanding the role of inflammatory-related pathways in the pathophysiology and treatment of psychiatric disorders: evidence from human peripheral studies and CNS studies. *Int J Neuropsychopharmacol* 2011; 14:997-1012. [CrossRef]
- Stertz L, Magalhaes PV, Kapczinski F. Is bipolar disorder an inflammatory condition? The relevance of microglial activation. *Curr Opin Psychiatry* 2013; 26:19-26. [CrossRef]
- Dantzer R, O'Connor JC, Lawson MA, Kelley KW. Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology* 2011; 36:426-436. [CrossRef]
- Brietzke E, Stabellini R, Grassis-Oliveira R, Lafer B. Cytokines in bipolar disorder: recent finding, deleterious effects but promise for future therapeutics. *CNS Spectr* 2011; 16:157-168. [CrossRef]
- Munkholm K, Bräuner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. *J Psychiatry Res* 2013; 47:1119-1133. [CrossRef]
- Munkholm K, Vinberg M, Vedel Kessing L. Cytokines in bipolar disorder: a systematic review and meta-analysis. *J Affect Disord* 2013; 144:16-27. [CrossRef]
- Breunis MN, Kupka RW, Nolen WA, Suppes T, Denicoff KD, Leverich GS, Post RM, Drexhage HA. High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder. *Biol Psychiatry* 2003; 53:157-165. [CrossRef]
- Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, Chies JA, Kapczinski F. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord* 2009; 116:214-217. [CrossRef]
- Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord* 2007; 104:91-95. [CrossRef]
- Hope S, Dieset I, Agartz I, Steen NE, Ueland T, Melle I, Aukrust P, Andreassen OA. Affective symptoms are associated with markers of inflammation and activation in bipolar disorders but not schizophrenia. *J Psychiatr Res* 2011; 45:1608-1616. [CrossRef]
- Dickerson F, Stalling C, Origoni A, Vaughan C, Khushalani S, Yolken R. Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. *J Affect Disord* 2013; 150:456-459. [CrossRef]
- Akiskal HS. "Mood Disorder: Clinical Features" in Sadock BJ, Sadock VA (ed). *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. Lippincott Williams & Wilkins: Philadelphia. 2005.
- Goldstein BI, Kemp DE, Socynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry* 2009; 70:1078-1090. [CrossRef]
- Kalelioglu T, Akkus M, Karamustafalioglu N, Genc A, Genc ES, Cansiz A, Emul M. Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. *Psychiatry Res* 2015; 228:925-927. [CrossRef]
- Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, Demirtas L, Turk S, Tonbul HZ. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil to-lymphocyte ratio in end-stage renal disease patients. *Hemodial Int* 2013; 17:391-396. [CrossRef]
- Ahsen A, Ulu MS, Yuksel S, Demir K, Uysal M, Erdogan M, Acarturk G. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. *Inflammation* 2013; 36:1357-1362. [CrossRef]
- Holub M, Beran O, Kasprkova N, Chalupa P. Neutrophil to lymphocyte count ratio as a biomarker of bacterial infections. *Cent Eur J Med* 2012; 7:258-261.
- Jafarzadeh A, Akbarpoor V, Nabizadeh M, Nemat M, Rezayati MT. Total leukocyte counts and neutrophil-lymphocyte count ratios among helicobacter pylori-infected patients with peptic ulcers: independent of bacterial Cag A status. *Southeast Asian J Trop Med Public Health* 2013; 44:82-88.
- Tokgoz S, Kayrak M, Akpinar Z, Seyithanoglu A, Guney F, Yuruten B. Neutrophil lymphocyte ratio as a predictor of stroke. *J Stroke Cerebrovasc Dis* 2013; 22:1169-1174. [CrossRef]
- Yavuzcan A, Caglar M, Ustun Y, Dilbaz S, Ozdemir I, Yildiz E, Özkara A, Kurnu S. Evaluation of mean platelets volume, neutrophil/lymphocyte ratio, and Platelet/lymphocyte ratio in advanced stage endometriosis with endometrioma. *J Turk Ger Gynecol Assoc* 2013; 14:210-215. [CrossRef]
- Gunay E, Ulasli SS, Kacar E, Halici B, Unlu E, Tunay K, Ozkececi G, Koken T, Unlu M. Can platelet indices predict obstruction level of pulmonary vascular bed in patients with acute pulmonary embolism? *Clin Respir J* 2014; 8:33-40. [CrossRef]
- Canan F, Dikici S, Kutlucan A, Celbek G, Coskun H, Gungor A, Aydin Y, Kocaman G. Association of mean platelet volume with DSM-IV major depression in large community population: the MELEN study. *J Psychiatr Res* 2012; 46:298-302. [CrossRef]
- Ataoglu A, Canan F. Mean platelet volume in patients with major depression: effect of escitalopram treatment. *J Clin Psychopharmacol* 2009; 29:368-371. [CrossRef]
- Gasparyan AY, Ayzvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des* 2011; 17:47-58. [CrossRef]
- Ulasli SS, Ozyurek BA, Yilmaz EB, Ulubay G. Mean platelet volume as an inflammatory marker in acute exacerbation of chronic obstructive pulmonary disease. *Pol Arch Med Wewn* 2012; 122:284-290.
- Huang TL, Lin FC. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31:370-372. [CrossRef]
- Cunha AB, Andreazza AC, Gomez FA, Frey BN, Da Silveira LE, Goncalves CA, Kapczinski F. Investigation of serum high-sensitivity C-reactive protein levels across all mood states in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 2008; 258:300-304. [CrossRef]
- Su KP, Leu SJ, Yang YY, Shen WW, Chou YM, Tsa SY. Reduced production of interferon-gamma but not interleukin-10 in bipolar mania and subsequent remission. *J Affect Disord* 2002; 71:205-209. [CrossRef]
- Liu HC, Yang YY, Chou YM, Chen KP, Shen WW, Leu SJ. Immunologic variables in acute mania of bipolar disorder. *J Neuroimmunol* 2004; 150:116-122. [CrossRef]
- Barbosa IG, Huguet RB, Mendonca VA, Sousa LP, Neves FS, Bauer ME, Teixeira AL. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 2011; 261:139-143. [CrossRef]