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# INCREASED NEUTROPHIL/LYMPHOCTYE RATIO IN PATIENTS WITH BIPOLAR DISORDER: A PRELIMINARY STUDY

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## *SUMMARY*

***Background:*** *In this study, it has been aimed to investigate whether neutrophil–lymphocyte ratio (NLR) was higher in non-obese patients with bipolar disorder (BD) than in a healthy control group matched for age, sex, and body mass index, and also to determine if there was an interaction between NLR and severity of the bipolar disorder.*

***Subjects and methods:*** *In this retrospective study, 103 non-obese patients with BD and 126 healthy control subjects were analyzed for complete blood count. The Young Mania Rating Scale (YMRS) was used to determine the severity of the disorder.*

***Results:*** *The NLR was higher in female patients than in female comparison subjects (3.2±2.2; versus 1.7±0.4) ($p<0.001$). Also, compared with the healthy male subjects, the male patients had significantly higher neutrophil/lymphocyte ratio (3.3±2.4; versus 2.0±0.7) ($p<0.001$). In the patients with bipolar disorder, NLR did not significantly correlate with severity (as measured with the YMRS) ($r=0.052$; $p=0.204$) and duration of the disorder ($r=0.045$; $p=0.301$).*

***Conclusions:*** *Results of this study revealed that patients with bipolar disorder have statistically significant elevated NRL than healthy compares. According to this finding, elevated levels of NLR may be involved in inflammatory pathophysiology of bipolar disorder. Further studies are needed for a better understanding of the mechanism between elevation of NRL in patients with bipolar disorder.*

***Key words:*** *lymphocyte – neutrophil - neutrophil/lymphocyte ratio – bipolar disorder – inflammation*

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## INTRODUCTION

Bipolar disorder (BD) is a chronic mental illness characterized by mood swings, disability, and impaired quality of life. The lifetime prevalence of BD is estimated at approximately 2% (Merikangas et al. 2011). Evidence from etiological studies points toward the involvement of several different factors, such as genetics (Barnet & Smoller 2009, Sklar et al. 2012), oxidative and psychological stress (Post & Leverich 2006, Steckert et al. 2012), infections (Hinze-Selch 2002), diet (Noaghiul & Hibbeln 2003), deficiencies in monoamine neurotransmitters and secondary messenger systems (Manji et al. 2003, Harwood 2004), changes in synaptic plasticity and neuronal survival (Zarate et al. 2006), abnormalities in morphology (Campbell & MacQueen 2006), and immune system disturbances (Kim et al. 2007, Ortiz-Dominquez et al. 2007).

Neuroinflammatory processes represent another factor considered to play an important role in both the etiology and progression of BD and other chronic psychiatric disorders such as schizophrenia (Kim et al. 2007, Brietzke et al. 2009, Doorduin et al. 2009, Na et al. 2014). Studies on the association between bipolar disorder and neuroinflammation demonstrated alterations in the serum levels of cytokines such as interleukin-1 (IL-1), IL-2, IL-4, IL-6, tumor necrosis factor (TNF)- alpha, soluble TNF receptor 1 and soluble IL-2 receptor (Brietzke et al. 2009, Hope et al. 2009); acute phase reactants such as high sensitivity C reactive protein (hsCRP) (Huang & Lin 2007); microglia activation (Rao et al. 2009) and tryptophan metabolism (via the kynurenine pathway) (Miller et al. 2006).

The neutrophil–lymphocyte ratio (NLR) was developed by Zahorec (2001) to provide easily measurable and readily available parameters reflecting the intensity of stress and systemic inflammation in critically ill patients following shock, multiple traumas, major surgery, or sepsis. The index was inspired by a study (Jilma et al. 1999) in which the general immune response to endotoxemia was characterized by an increased number of circulating neutrophils and decreased lymphocyte count. Numerous studies have examined the NLR in the context of inflammatory disease. Increased NLR values are considered a sign of poor prognosis in patients with pancreatitis (Azab et al. 2011), malignancy (Szkandera et al. 2013, Seretis et al. 2013), or coronary heart disease (Ayhan et al. 2013, Fowler & Agha 2013); furthermore, an association between NLRs and chronic stress has also been demonstrated in animal studies (Puppe et al. 1997, Erminio & Bertoni 2009). However, few studies have examined the NLR in populations with mental disorders. In one such study, patients with Alzheimer's disease were compared with cognitively normal individuals (Kuyumcu et al. 2012), and a recent study demonstrated that patients with schizophrenia exhibited elevated neutrophil NLR values compared to healthy controls (Semiz et al. 2014).

It has also been shown that an increased NLR is associated with oxidative stress and increased cytokine production (Turkmen et al. 2012), both of which are also present in BD (Myint & Kim 2014, Anderson &

Maes 2015). However, to the best of our knowledge no study has investigated the relationship between NLR and BD. In this study, we investigated whether NLR values were higher in non-obese BD patients compared with a healthy control group matched for age, sex, and body mass index (BMI), and we also aimed to determine whether there was an interaction between the NLR and BD severity.

## SUBJECTS AND METHODS

### Subjects

In this retrospective study, all patients aged ≥18 years who were hospitalized with a diagnosis of BD in a university hospital psychiatry clinic between March 2010 and May 2013 were evaluated for their eligibility for inclusion. The exclusion criteria were as follows: alcohol or substance abuse, diabetes mellitus, hepatic or renal failure, manifest heart disease, hypertension, clinical evidence of active infection, active or chronic inflammatory or autoimmune diseases, obesity (BMI >30 kg/m$^2$), heavy smoking (more than 15 cigarettes per day), and treatment with anti-inflammatory or immunosuppressive medications. Clinically significant abnormalities on baseline (eg, tachycardia, tachypnea, fever) or laboratory test results (eg, anemia, leukocytosis, leukopenia, and thrombocytosis) were additional exclusionary criteria. The duration of BD was determined by calculating the difference between age at onset and age at which the evaluation was performed. The severity of BD was assessed using the Turkish form of the Young Mania Rating Scale (YMRS, Karadag et al. 2002). For each patient, we included one family member nominated as the substitute decision maker (spouse; parents/children; others). We obtained informed consent from all patients and controls; in cases where a patient was not available to provide consent it was obtained from the nominated family member instead. The Ethics Committee of Abant Izzet Baysal University approved the study protocol.

### Healthy controls

Healthy control sample consisted of 126 age and sex matched control subjects recruited from within the hospitals, and the general community. None of them was taking any form of prescribed or over-the-counter medication. In the sampling of the control group, there was an attempt to find individuals who were living in the same neighborhood. They were screened for physical condition through clinical examinations and laboratory tests. In addition, they had a mental health screening through a psychiatric interview (SCID-I) for exclusion of any present, past and family (first degree) history of axis-I diagnoses. Turkish form of SCID has been studied by Corapicooglu et al. (1999). As with the bipolar patients, none of the healthy volunteers met the exclusion criteria listed above.

### Blood tests

Twelve-hour fasting blood samples were drawn at about 9:00 AM from a large vein of each patient by applying minimal tourniquet force. Physical examination was performed before the blood was drawn. For measurement of complete blood count, blood was drawn into a vacutainer tube, containing EDTA as an anticoagulant, and analyzed in an automated blood cell counter (Abbott CELL-DYN 3700, Abbott Diagnostics Division, Abbott Laboratories, Illinois, USA).

### Statistical analysis

The statistical analyses were performed using software (SPSS 16.0, SPSS Inc., Chicago, IL). Data are presented as mean ± SD for continuous variables. Categorical variables are shown as number and percentage. Variables were checked for normal distribution, and normally distributed variables were compared using the Student t test. Not normally distributed variables were compared using Mann-Whitney U test. Pearson's chi-square test was used to compare categorical variables. Pearson correlation analysis was performed to ascertain correlations between neutrophil/lymphocyte ratio and severity and duration of the bipolar disorder. Statistical significance was set at 0.05.

## RESULTS

No significant differences were found between the two groups in terms of age, sex, BMI, marital status, or education level (Table 1). As presented in Table 2, compared with the healthy subjects, patients with BD exhibited significantly higher mean NLR and neutrophil levels, but their lymphocyte levels were lower. The NLR was higher in female BD patients compared with female controls (3.2±2.2 vs. 1.7±0.4; p<0.001). Furthermore, compared with healthy males, male BD patients had significantly higher NLR values (3.3±2.4 vs. 2.0±0.7; p<0.001). There were no significant differences between male and female BD patients in terms of other blood count parameters, such as red blood cells, hemoglobin, and hematocrit percentage. In the BD patients, NLR was not significantly correlated with the severity (measured using the YMRS; r=0.052; p=0.204) or duration (r=0.045; p=0.301) of the disorder.

## DISCUSSION

Recent evidence demonstrates that bipolar disorder is commonly comorbid with other clinical conditions (Altamura et al. 2011). The results of the Systematic Treatment Enhancement Program for Bipolar Disorder study indicate that >50% of patients with BD have at least one associated physical comorbidity (Magalhaes et al. 2012), the most-common of which are diabetes mellitus, cardiovascular diseases, dyslipidemia, obesity, and insulin resistance (Altamura et al. 2011, Leboyer et al. 2012).

**Table 1.** Characteristics of Patients with Bipolar Disorder and Healthy Comparison Subjects

| | Patients (n=103) | Controls (n=126) | p |
|---|---|---|---|
| Age† | 36.4±7.5 | 34.4±9.2 | 0.324 |
| Male‡ | 47 (45.6%) | 59 (46.8%) | 0.481 |
| Body mass index (kg/m2)† | 24.5±2.8 | 24.1±2.6 | 0.330 |
| Marital status‡ | | | |
| Married | 69 (66.9%) | 98 (77.7%) | 0.105 |
| Not married | 34 (33.1%) | 28 (22.3%) | |
| Education‡ | | | |
| 0-8 years | 63 (61.1%) | 83 (65.8%) | 0.174 |
| >8 years | 40 (38.9%) | 43 (34.2%) | |

†Mean ± Standard deviation, student's t-test; ‡number (percentile), chi-square test

**Table 2.** Comparison of Blood Count Parameters between Patients with Bipolar disorder and Healthy Controls

| Parameters | Patients (n=103) Mean±SD | Controls (n=126) Mean±SD | p |
|---|---|---|---|
| Red blood cell count, $10^6$/mL | 4.5±0.4 | 5.3±0.6 | 0.215 |
| Hemoglobin (g/dl) | 14.1±1.3 | 14.4±1.3 | 0.539 |
| Hematocrit, % | 42.3±4.0 | 43.3±4.0 | 0.370 |
| White blood cell count (x$10^3$) | 7.7±1.3 | 6.3±1.4 | 0.051 |
| Neutrophils (%) | 5.5±2.6 | 3.9±1.1 | <0.001 |
| Lymphocytes (%) | 2.0±0.8 | 2.2±0.4 | <0.001 |
| N/L ratio | 3.2±2.3 | 2.1±1.1 | <0.001 |
| Platelet count, $10^9$/L | 264.7±58.6 | 250.1±43.7 | 0.101 |

SD - standard deviation; †student's t-test

This overlap has drawn attention to possible systemic mechanisms related to bipolar disorder-related impairments (Leboyer et al. 2012). To date, only two clinical studies, one conducted in a specialized clinic (Kapczinski et al. 2011) and the other assessing the general population (Magalhaes et al. 2012), have reported that proinflammatory conditions are implicated in the peripheral pathophysiology of bipolar disorder (Berk et al. 2011).

Co-occurrence of autoimmune diseases has also been described. For instance, case-control studies have shown that BD patients frequently present with lupus erythematosus (Tremblay et al. 2011), multiple sclerosis, (Dean 2011, Schneider et al. 2012), and autoimmune thyroiditis (Kapczinski et al. 2009). Recently, a cohort study demonstrated that a history of Guillain–Barre syndrome, Crohn's disease, or autoimmune hepatitis is associated with a higher risk of BD (Harry et al. 2012). Recent theories concerning the neurobiological underpinnings of BD have focused on impairments in cellular energy regulation, the immune system, neuroprotective mechanisms, and epigenetic aberrations (Gardner & Boles 2011, Grande et al. 2012). These components may be central to neuroprogressive alterations in BD (Berk et al. 2011); dysfunction of the inflammatory system may also be a key integrative component in the pathophysiological mechanisms underlying the disorder (Kapczinski et al. 2008, Stertz et al. 2013).

One theory regarding the pathophysiology of the inflammatory system in BD, i.e., the macrophage-T-lymphocyte theory, was initially suggested for schizophrenia and depression (Smith 1991, Smith & Maes 1995, Leonard 2001), and subsequently extended to encompass BD. This theory stresses the possible involvement of the immune system, which is chronically activated and is mediated by macrophages in the brain, such as microglia. It also proposes that the role of T-lymphocytes is fundamental to the pathophysiology of BD because cytokines and inflammatory substances produced by lymphocytes may lead to destabilization of brain function and commensurately increased susceptibility to environmental stressors, thereby precipitating disturbances in mood.

As previously mentioned, several studies have investigated NLRs among patients with chronic medical conditions such as pancreatitis (Azab et al. 2011), malignancy (Szkandera et al. 2013, Seretis et al. 2013), and coronary heart disease (Ayhan et al. 2013, Fowler & Agha 2013). In terms of mental disorders, one study showed that patients with Alzheimer's disease had higher NLR values compared with individuals with normal cognitive function (Kuyumcu et al. 2012), and a more recent study demonstrated that patients with schizophrenia had elevated NLR values compared with healthy controls (Semiz et al. 2014). In our study, compared with healthy subjects, patients with BD had significantly higher mean NLR and neutrophil levels, but their lymphocyte levels were lower. To the best of our knowledge, this is the first study to examine the relationship between NLR and BD. Because the study design was cross-sectional, future studies investigating the relationship between NLR and BD should employ a follow-up design to achieve a better understanding of whether NLR can be used as a state or trait marker of BD.

Although we examined a relatively large number of non-obese BD patients, the results of this study should be considered in the context of the following limitations. First, we employed a cross-sectional design, so we could not interpret causal relationships between elevated NLR values and BD. Second, subtypes of lymphocytes were not investigated. Third, other indicators of immune system function, such as cytokines, were not evaluated; therefore, it is not possible to determine whether increased NLR values represent an independent marker of alterations in the immune system in patients with BD. Fourth, neutrophil counts vary markedly within individuals and have a short life span (about 5 days). However, the measures were not repeated to assess the stability of the results. Furthermore, patients were not assessed for any history of recent surgical procedures, for any lifestyle factors, or for their general health (e.g, dental status) or levels of psychological distress, all of psychological stress which may affect NLR levels.

## CONCLUSIONS

In this study, it has been aimed to investigate whether NLR was higher in non-obese patients with bipolar disorder. Results revealed that patients with bipolar disorder have statistically significant elevated NRL than healthy compares. According to this finding, elevated levels of NLR may be involved in inflammatory pathophysiology of bipolar disorder. Further studies are needed for a better understanding of the mechanism between elevation of NRL in patients with bipolar disorder.

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***Conflict of interest:*** None to declare.

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