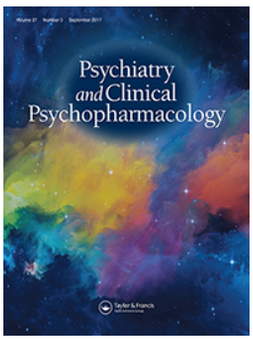

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Neutrophil/lymphocyte and platelet/lymphocyte ratios in all mood states of bipolar disorder

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ABSTRACT

Objectives: This study aims at researching the inflammatory cells and their ratios as inflammation markers in different phases of patients with bipolar disorder (BD).

Methods: In this retrospective study, 79 manic, 61 depressed, 59 euthymic drug-naive patients with BD, and 86 control subjects have been evaluated for their complete blood count.

Results: Neutrophil/lymphocyte ratio (NLR) was found to be significantly higher in manic, euthymic, and depressed patients with BD compared to control group. However, no difference was found between all patient and control groups regarding platelet/lymphocyte ratio (PLR). There was no difference among different phases of patient groups in terms of NLR and PLR.

Conclusions: Our findings suggest that inflammatory process may have a role in all mood episodes of BD and NLR may be a useful trait inflammation marker for BD independent of mood episodes. However, further studies need to be conducted on the effect of inflammatory mechanisms on mood states of BD.

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Bipolar disorder; inflammation; neutrophil/lymphocyte ratio; platelet/lymphocyte ratio

Introduction

Bipolar disorder (BD) is a chronic, severe neuropsychiatric disorder characterized by recurrent mood exacerbations ranging from major depressive episodes to manic episodes with a prevalence of approximately 1% [1,2]. The biological mechanisms of BD still remain unclear, but it can be effectively conceptualized as a multi-systemic inflammatory disease [3]. To date, changes in peripheral inflammatory markers have been reported in BD such as cytokine profiles [4–11], acute phase proteins [12–14], and lymphocyte cell activation [5,15–18].

The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are recently described, simple and inexpensive markers of systemic inflammatory response [19,20]. Higher NLR was shown to be associated with poor prognosis in patients with pancreatitis [21], coronary heart disease [22,23], and malignancy [24,25]. An association between NLR and chronic stress was demonstrated in animal studies [26,27]. Increased levels of NLR were reported to be indicative enhanced cytokine production [28]. NLR was investigated as a systemic inflammation marker in neuropsychiatric disorders such as Alzheimer's disease [29] and schizophrenia [30]. There have also been studies investigated NLR and PLR in BD. In a study, manic and euthymic patients with BD showed an increase in NLR and PLR compared to controls [31]. In another study, patients with BD demonstrated increased NLR compared to controls [32]. In a study by Yildiz et al. [33], NLR has been found to be higher in manic and euthymic patients, while depressive patients did not differ from controls in terms of NLR.

The aim of this study is to investigate the NLR and PLR values in drug-free patients with BD in all three phases; manic, depressive, and euthymic compared to each other and controls.

Methods

In this case–control study, a total of 885 inpatients/outpatients with a diagnosis of BD type 1 (manic and depressive episodes and euthymic state) admitted to our clinic between January 2012 and December 2015 were evaluated. All patients were diagnosed with BD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV TR) and elected as drug-free for at least one month. Patients who were aged ≤18 years, had a treatment with a psychotropic drug, had alcohol and/or substance dependence, other axis 1 disorders, other acute/chronic medical disorders (endocrinological, immunological and autoimmune diseases, diabetes mellitus, hypertension, hepatic or renal failure, heart disease), and obesity (body mass

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Table 1. Characteristics of groups.

	Manic ($n = 79$) Mean ± SD	Depressed ($n = 61$) Mean ± SD	Euthymic ($n = 59$) Mean ± SD	Control ($n = 86$) Mean ± SD	p
Age (years)	36.43 ± 10.10	38.75 ± 8.49	38.63 ± 11.84	36.38 ± 8.84	.300*
Gender					
Female	43 (54.43%)	32 (52.46%)	28 (47.46%)	43 (50.0%)	.862**
Male	36 (45.57%)	29 (47.54%)	31 (52.54%)	43 (50.0%)	
Duration of disease (years)	11.01 ± 9.07	8.18 ± 6.65	8.99 ± 8.09		.355*
Number of hospitalization	4.43 ± 3.22	3.51 ± 2.46	2.85 ± 2.44		.002*

*Kruskal–Wallis test, **χ^2 test; SD, standard deviation.

index ≥ 30 kg/m^2) were excluded from the study. Heavy smoking (more than 15 cigarettes per day), treatment with anti-inflammatory or immuno-suppressive medications and abnormal results of complete blood count were the other exclusion criteria.

A healthy control group similar to the patient groups in terms of age and gender was included in the study. The same exclusion criteria mentioned above were applied to the control group. Control subjects were ascertained by means of the Structured Clinical Interview for DSM-IV (SCID-I) [34,35]. The subjects who had family history of BD and current and past history of axis 1 disorders were not included in the study.

Written informed consent was obtained from all participants included in the study. The sociodemographic data, duration of illness, number of hospitalization, neutrophil, lymphocyte, and platelet counts of the participants were recorded. Seventy-nine manic, 61 depressed, 59 euthymic drug-naive patients with BD, and 86 control subjects were included in the study. The study was approved by the local ethical committee.

Statistical analysis

Data analysis was conducted using SPSS (version 18.0). The chi-square test was used for categorical variables. Kolmogorov–Smirnov test was used to determine whether the parameters are normally distributed. Kruskal–Wallis test, Mann–Whitney U test, and Student's t test were used for statistical analysis. Statistical significance was accepted as $p < .05$.

Results

The study included 285 participants aged 18–64 years. The mean age of the sample was 37.37 ± 9.83 years. Seventy-nine subjects of all the cases were in the manic group, 61 were in the depressed group, 59 were in the euthymic group, and 86 were in the control group. There was no significant difference among the groups with regard to age and gender ($p = .300$ and $p = .862$, respectively). Demographic and clinical characteristics (duration of illness, number of hospitalization) of the groups are shown in Table 1.

NLR value was 2.23 ± 1.14 in the manic group, 2.07 ± 0.98 in the depressed group, 2.22 ± 1.21 in the euthymic group, and 1.52 ± 0.47 in the control group. When the patient (manic, depressed, and euthymic) and the control groups were compared, NLR values were found to be significantly higher in the patient groups than in the control group ($p = .000$, $p = .000$, and $p = .001$, respectively). There was no significant difference between the patient (manic, depressed, and euthymic) and control groups in terms of PLR values ($p = .184$, $p = .638$, and $p = .257$, respectively). However, there was no significant difference between the patient groups regarding NLR and PLR values. NLR and PLR values, lymphocyte, neutrophil, and platelet counts are summarized in Table 2.

Discussion

In the present study, we investigated the NLR and PLR values in all phases of BD retrospectively. The important findings of this study are: (1) NLR in different phases of BD was significantly higher compared to the control group. (2) No significant difference was observed between the patient and control groups in terms of PLR. (3) There was no difference among the patient groups (manic, depressed, and euthymic) in terms of NLR and PLR.

Table 2. Laboratory findings of subjects.

	Manic ($n = 79$) Mean ± SD	Depressed ($n = 61$) Mean ± SD	Euthymic ($n = 59$) Mean ± SD	Control ($n = 86$) Mean ± SD	p^1	p^2	p^3
NLR[a,b,c,*]	2.23 ± 1.14	2.07 ± 0.98	2.22 ± 1.21	1.52 ± 0.47	.000	.000	.001
PLR[d,e,f,*]	114.64 ± 43.48	108.28 ± 55.91	119.76 ± 61.73	102.59 ± 29.15	.184	.638	.257
Neutrophil** (µl)	4.63 ± 1.41	4.56 ± 1.30	4.45 ± 1.37	3.73 ± 0.88	.000	.000	.003
Lymphocyte* (µl)	2.27 ± 0.54	2.49 ± 0.83	2.34 ± 0.79	2.55 ± 0.65	.003	.444	.025
Platelet* (µl)	245.84 ± 65.96	238.86 ± 77.53	245.20 ± 68.71	250.73 ± 52.90	.324	.192	.269

[a]$p = .579$ manic vs. depressive, [b]$p = .742$ manic vs. euthymic, [c]$p = .801$ depressive vs. euthymic, [d]$p = .189$ manic vs. depressive, [e]$p = .997$ manic vs. euthymic, [f]$p = .281$ depressive vs. euthymic, p^1: manic vs control, p^2: depressive vs control, p^3: euthymic vs. control, *Mann–Whitney U test, **Student's t test, SD, standard deviation, $p < .05$ statistically significant.

NLR has been reported in recent years as a peripheral inflammation marker in several neuropsychiatric disorders [29–32,36]. NLR was reported to be significantly higher in Alzheimer's disease and schizophrenia when compared to controls [29,30]. Studies in which inflammatory mechanisms play a role in the aetiology of BD are becoming increasingly important. According to our knowledge, three studies have investigated the association between NLR or PLR and BD to date [31–33]. However, the results of these studies vary according to different episodes of BD. Cakir et al. [32] showed in a retrospective study that patients with BD had higher NLR compared to healthy controls. However, it is not clear in which phase the patients are in this study [32]. In the other study, it was reported that manic and euthymic male patients had higher NLR and PLR compared to controls [31]. The results of the current study in terms of NLR are consistent with the study of Kalelioglu et al., however, the differences in PLR between the study reported by Kalelioglu et al. and the current study may be due to methodological variations including composition of the study samples (male vs. female), study sizes, medications, heterogeneous body mass index, and smoking status of participants. In addition, it has also been reported that NLR is thought to be a more reliable inflammatory marker [37]. In a study with a similar method by Yıldız et al., PLR was found not to be different in all patient groups compared to the control group in consistent with our results. It has also been reported that NLR was higher only in patients with the euthymic and manic phase and there was no difference between the depressive group and control group in terms of NLR [33]. Including only drug-free patients for at least 1 month in the current study may lead to different results in the patients with depressive phase in terms of NLR. The results of all these studies should be interpreted in view of the anti-inflammatory effect of drugs used in the treatment of BD [38].

Various studies have investigated other inflammatory markers at different states of BD. It was shown that serum soluble IL-2 receptor, interferon-γ, and serum tumour necrosis factor (TNF)-α receptor 1 levels were increased in manic patients compared to euthymic patients and healthy controls [4,10,11]. Additionally, IL-6, TNF-α, and soluble IL-2 receptor were reported to be significantly increased in manic episodes compared to healthy controls [5,7]. On the other hand, Liu et al. [18] found no relationship between manic patients and healthy controls regarding serum IL-2 levels. In a study by Cunha et al. [12], it was reported that serum high-sensitive C-reactive protein (hsCRP) was increased in manic patients compared to euthymic and healthy controls. A meta-analysis showed that elevated levels of serum TNF-α receptor 1, TNF-α, and serum soluble IL-2 receptor were associated with manic episodes; TNF-α levels were also elevated among depressed patients, suggesting that TNF-α may be a potential marker of the disease [8]. In addition, Pandey et al. [39] suggested that the mRNA levels of membrane-bound receptors for proinflammatory cytokines could be a potential biomarker of BD. In these studies mentioned above, results are inconsistent and it was demonstrated that cytokine levels might vary in different states of BD.

Several studies have also demonstrated enhanced activities of inflammatory cells in BD. Drexhage et al. [17] reported an increased number of regulatory T cells in BD compared to controls. Changes in the number of circulating activated T cells and monocytes were also exhibited in BD patients when compared to healthy controls [5,15,16]. However, Karpiński et al. [40] found no significant difference in the number of natural killer cells between BD patients and healthy controls. NLR is recently considered to be a marker of systemic inflammatory response such as the other inflammatory and proinflammatory markers mentioned above. Our finding that NLR is higher in all phases of BD compared to controls may suggest that there is an inflammatory process in all phases of BD.

The current study had some limitations. Firstly, the sample size of the sub-groups was relatively small. Secondly, other inflammatory markers (such as CRP and cytokines) and subtypes of lymphocytes were not evaluated simultaneously because of the retrospective nature of the study. The lack of patients with unipolar depression in the study sample in order to compare with bipolar depression was another limitation.

In conclusion, we found that NLR is higher not only in manic and euthymic patients but also in depressed patients with BD. NLR may be a trait inflammatory marker of BD independent of different episodes. Longitudinal and larger studies are needed to determine the activation of inflammatory systems in different phases of BD.

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No potential conflict of interest was reported by the authors.

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