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Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders

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ABSTRACT

Objective: Neutrophil-lymphocyte, monocyte-lymphocyte and platelet-lymphocyte ratio are inexpensive and reproducible biomarkers of inflammation found to be elevated in mood disorders. This study aimed to compare inflammatory ratios between bipolar disorder and major depressive disorder and between bipolar disorder manic episodes and bipolar disorder depressive episodes.

Method: We included 142 Caucasian patients (major depressive disorder: $n = 36$; bipolar disorder manic episode: $n = 66$; bipolar disorder depressive episode: $n = 40$). We measured white blood cells, neutrophils, lymphocytes, monocytes, platelets, glucose, and total cholesterol. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio, and platelet-lymphocyte ratio were calculated.

Results: Neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio were significantly higher in bipolar disorder manic episodes when compared to bipolar disorder depressive episodes and major depressive disorder episodes after adjustment for age, sex, body mass index, and smoking.

Conclusion: To our knowledge, our study is the first one to compare inflammatory ratios between different bipolar disorder phases and major depressive disorder episodes. In accord with previous studies on other inflammatory mediators, we found higher neutrophil-lymphocyte and monocyte-lymphocyte ratios in bipolar manic episodes, suggesting that inflammatory changes occur especially during acute episodes of mania.

1. Introduction

Bipolar disorder (BD) and major depressive disorder (MDD), like most psychiatric disorders, are multifactorial and heterogeneous diseases. Neurotransmission, neuroinflammation and immune dysfunction, chronobiology, mitochondrial dysfunction, hypothalamic-pituitary-adrenal axis over-activation, oxidative stress, and psychosocial stressors all seem to play a part in mood disorders [1]. Growing evidence supports the role of the immune and inflammatory pathways in the aetiology of mood disorders [2–4]. A pro-inflammatory state with higher concentrations of pro-inflammatory cytokines and lower concentrations of anti-inflammatory cytokines has been observed in BD and MDD [5,6]. Studies also showed pro- and anti-inflammatory cytokines' variations during different phases of BD [6]. Studies of acute experimental activation of the immune system with endotoxin and of chronic activation during interferon-alpha treatment showed that inflammation could induce depression [7]. CRP concentrations were found to be increased in both in MDD [8] and in BD regardless of mood state, but seem to be higher during mania than in depression and euthymia, suggesting an increased inflammatory burden in mania [9]. There is also emerging evidence that BD is strongly associated with immune dysfunction; while in a subset of BD, immune dysfunction is likely playing a key role in the pathophysiology of disease progression [3]. It is known that inflammation may impair cognitive function in patients with mood disorders and affects sleep, mood and mental status [10]. Finally, animal studies suggest that immune and inflammatory responses in the nervous system also cause psychiatric symptoms [11].

Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and monocyte to lymphocyte ratio (MLR) are low-cost and reproducible tests easily calculated from white blood cell essays that can be determined under simple laboratory conditions. NLR was developed by intensivists and used to assess the intensity of stress and systemic inflammation in critically ill patients [12]. NLR is the ratio between neutrophils, the first line of innate immune defense, and lymphocytes that are specific inflammatory mediators in the adaptive immune response [13]. MLR is the ratio between monocyte and lymphocytes and

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could represent a peripheral marker of microglia activation. It has been demonstrated that levels of circulating monocytes are elevated in patients with psychiatric disorders such as BD, MDD, and schizophrenia, due to enhanced expression of immune genes and overproduction of monocytes/macrophage-related cytokines [14]. Microglia plays an important role in synaptic pruning and neuroplasticity [15]. PLR considers together platelets and lymphocytes, and it may predict the inflammatory response [16]. Platelets are a non-specific first line inflammatory marker; they modulate endothelial permeability and recruitment of neutrophils and macrophages. The activation of platelets and their agreeability, mediated by cytokines, serotonin, glutamate, dopamine, and P-selectin, play an important role in psychiatric disorders [17].

Several researchers have proven that these ratios have value as biomarkers of poor prognosis or significant inflammation among patients with chronic medical conditions such as cardiovascular diseases, malignancies, acute pancreatitis, autoimmune diseases, and chronic obstructive pulmonary disease [18–24].

Moreover, NLR, PLR, and MLR have been investigated in neuropsychiatric disorders. Studies showed elevated NLR, PLR, and MLR values in patients with schizophrenia and Alzheimer's disease compared with healthy controls (HC) [25–27]. Elevated NLR, PLR, and MLR values have been found in patients with BD compared to HC [26,28–32]. Some studies investigated current BD manic phases finding higher NLR, PLR, and MLR in patients in comparison with HC [26,29,31,32]. Inconsistent results were found investigating the euthymic state [29,30,33]. No prior studies investigated bipolar depressive episodes. Patients with MDD have elevated NLR and PLR values in comparison with HC [34–37], these differences seem to be affected by psychopharmacological treatment [35,36]. The NLR value has been positively correlated both with the severity of depression and with age at onset in MDD patients [37–39]. NLR also seems to be a trait marker for the suicidal vulnerability in patients with MDD and BD [30,37]. A recent meta-analysis concluded that subjects with BD and subjects with MDD have higher NLR and PLR as compared with HC; interestingly, bipolar phase appeared relevant [40].

To our knowledge, no prior study has compared NLR, PLR, and MLR between BD and MDD and between BD manic episodes and BD depressive episodes. Thus the objectives of the present study are i) to explore differences in NLR, PLR, and MLR between MDD and BD, ii) to explore differences in NLR, PLR, and MLR during different episodes of BD, iii) to explore differences in NLR, PLR, and MLR between MDD depressive episodes when compared both to BD manic episodes and BD depressive episodes.

2. Methods

2.1. Samples

In this retrospective cohort study, eligible subjects were adults diagnosed as MDD or BD who were consecutively admitted to our inpatient unit presenting manic or depressive episodes from January 2010 to January 2018. Expert psychiatrists using a clinical psychiatric interview evaluated patients. Then, available charts, case notes, and information provided by at least one relative were collected. Finally, the diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. In light of the inpatient setting of the study, we were not able to analyze hypomania cases considering that in our department hypomanic episodes are usually treated in outpatient facilities.

The exclusion criteria were as follows: (a) current diagnosis of any additional psychiatric disorders including alcohol and/or substance dependence; (b) medical conditions associated with gross changes in inflammatory response such as active infection, fever, acute or chronic endocrinological, inflammatory, or autoimmune diseases, hepatic or renal failure, manifest heart disease and cancer; (c) clinical characteristics previously associated with alterations of inflammatory ratios such as pregnancy, body mass index ((BMI) $> 30\,kg/m^2$) and heavy smoking (> 20 cigarettes per day); (d) corticosteroid, nonsteroidal anti-inflammatory drug, acetylsalicylic acid, or immunosuppressive drugs in the past two weeks; (e) non-Caucasians due to racial differences in inflammatory ratios [41,42]. To reduce the risk of possible inclusion of subjects affected by severe inflammation or inflammatory disease, leucocytosis ($> 11 \times 10^3$ cells/mm^3), leukopenia ($< 4 \times 10^3$ cells/mm^3), thrombocytosis ($> 450 \times 10^3$ cells/mm^3), and thrombocytopenia ($< 150 \times 10^3$ cells/mm^3) were additional exclusion criteria.

From the initial sample of 368 patients, 63 patients were excluded because they had additional psychiatric disorders; 38 patients were excluded because they had a medical conditions associated with changes in inflammatory response; two were excluded due to pregnancy, 51 for heavy smoking, and 6 for BMI $> 30\,kg/m^2$; 25 patients were excluded because of recent corticosteroid, nonsteroidal anti-inflammatory drug, acetylsalicylic acid, or immunosuppressive use; and 18 patients were excluded because they were non-Caucasian; finally, 23 patients were excluded due to leucocytosis, leukopenia, thrombocytosis, and/or thrombocytopenia.

After considering all exclusion criteria, 142 adult patients (mean age was 48.4 ± 12.5; 67 male and 75 female) were included in the study; 36 were affected by MDD and 106 were affected by BD, of them, 66 presented with a BD manic episode and 40 presented with a BD depressive episode. We collected BMI and smoking habits for each patient.

We notified our institutional ethics board to apprise them of this low-risk retrospective observational study.

2.2. Laboratory

Investigators who were blinded to the diagnostic status of patients conducted all biochemical measurements. We measured white blood cell count, neutrophil count, lymphocyte count, monocyte count, platelet count, glucose and total cholesterol. NLR, MLR, and PLR were calculated, and differences between groups were considered our primary outcome.

Blood samples were taken in the morning (between 8 and 10 a.m.) of the first day of hospitalization, after 12 h of fasting, from a forearm vein. Blood was collected in hemogram tubes containing EDTA and processed within 30 min after collection. The assays were performed in the laboratory of the Hospital of Desio, ASST of Monza.

2.3. Data analysis

The statistical analyses were performed using SPSS software (SPSS 20.0, SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize all of the variables. Continuous data were described as mean ± Standard Deviation (SD). Categorical variables were shown as number and percentage. Considering that each of our groups had > 25 participants, the normality of the variables was assumed in the context of the central limit theorem.

Continuous variables were compared using one-way analysis of variance (ANOVA). Chi-square tests were used to analyze discrete data. Analysis of covariance (ANCOVA) was performed in the context of the General Linear Model to assess the differences in NLR, MLR, and PLR between the different groups.

For each inflammatory ratio, we conducted one ANCOVA considering the inflammatory ratio itself as the dependent variable, while the diagnostic groups (MDD, BD manic episode, and BD depressive episode) were included as fixed factors, and age, sex, BMI, and smoking were included as covariates. Post-hoc analysis was conducted to investigate the differences between groups using the Bonferroni correction.

Significance was set at $p \leq 0.017$ for the Bonferroni-corrected

Table 1
Comparison of socio-demographic, clinical and laboratory variables between groups. Categorical variable are presented as n (%), continuous variables are presented as mean (SD).

	MDD (n = 36)	BD (n = 106)	BD manic episodes (n = 66)	BP depressive episodes (n = 40)	Total sample (n = 142)	BD vs MDD	MDD vs BD manic episodes	MDD vs BD depressive episodes	BD manic episodes vs BD depressive episodes
Sex (male)	11 (30.5%)	66 (62.2%)	44 (66%)	12 (30%)	67 (47.1%)	p = 0.021* $\chi2$ = 5.350	p = 0.001* $\chi2$ = 12.226	p = 0.818 $\chi2$ = 0.053	p = 0.001* $\chi2$ = 13.437
Age (years)	51.56 (7.77)	47.29 (13.63)	44.27 (14.07)	52.28 (11.336)	48.37 (12.516)	p = 0.077 F = 3.166	p = 0.005* F = 8.241	p = 0.751 F = 0.102	p = 0.003* F = 9.271
BMI (kg/m^2)	24.68 (3.234)	26.34 (2.858)	26.27 (2.49)	26.46 (3.411)	25.92 (3.034)	p = 0.004* F = 8.474	p = 0.007* F = 7.625	p = 0.023* F = 5.428	p = 0.735 F = 0.115
Smokers	12 (32.43%)	53 (49.1%)	34 (51.51%)	19 (47.36%)	64 (45.08%)	p = 0.154 $\chi2$ = 2.035	p = 0.102 $\chi2$ = 4.566	p = 0.437 $\chi2$ = 1.656	p = 0.368 $\chi2$ = 0.811
White blood cell (10^3 cells/mm^3)	7.103 (1.911)	7.381 (2.078)	7.72 (2.28)	6.815 (1.563)	7.311 (2.034)	p = 0.480 F = 0.501	p = 0.168 F = 1.932	p = 0.473 F = 0.520	p = 0.028* F = 4.945
Neutrophils (10^3 cells/mm^3)	4.012 (1.426)	4.236 (1.571)	4.67 (1.67)	3.524 (1.071)	4.719 (1.534)	p = 0.450 F = 0.574	p = 0.052 F = 3.960	p = 0.094 F = 2.874	p = 0.001* F = 14.930
Lymphocytes (10^3 cells/mm^3)	2.412 (1.043)	2.258 (0.753)	2.159 (0.77)	2.421 (0.703)	2.297 (0.834)	p = 0.339 F = 0.920	p = 0.166 F = 1.949	p = 0.967 F = 0.002	p = 0.083 F = 3.067
Monocytes (10^3 cells/mm^3)	0.602 (0.211)	0.631 (0.215)	0.667 (0.209)	0.572 (0.213)	0.624 (0.213)	p = 0.491 F = 0.477	p = 0.142 F = 2.187	p = 0.531 F = 0.397	p = 0.026* F = 5.073
Platelet (10^3 cells/mm^3)	251.69 (60.37)	240.83 (56.58)	244.62 (59.88)	234.58 (50.77)	243.58 (57.54)	p = 0.329 F = 0.958	p = 0.571 F = 0.323	p = 0.184 F = 1.801	p = 0.378 F = 0.783
Glucose (mg/dL)	91.88 (12.38)	97.15 (20.533)	97.02 (22.316)	97.38 (17.432)	95.86 (18.949)	p = 0.160 F = 1.997	p = 0.217 F = 1.545	p = 0.130 F = 2.351	p = 0.930 F = 0.008
Total cholesterol (mg/dL)	197.5 (48.65)	189.81 (47.39)	181.5 (46.66)	203.10 (46.04)	191.70 (47.64)	p = 0.416 F = 0.666	p = 0.115 F = 2.534	p = 0.613 F = 0.258	p = 0.023* F = 5.327

BD bipolar disorder; MDD major depressive disorder.
* Significantly different: $p < 0.05$.

Table 2
Descriptive statistics of inflammatory ratios and Bonferroni-corrected ANCOVA results. Continuous variables are presented as mean (SD).

	MDD (n = 36)	BD (n = 106)	BD manic episodes (n = 66)	BP depressive episodes (n = 40)	Total sample (n = 142)	BD vs MDD	MDD vs BD manic episodes	MDD vs BD depressive episodes	BD manic episodes vs BD depressive episodes
Inflammatory ratios									
Neutrophil/lymphocyte ratio	1.838 (0.955)	2.026 (0.903)	2.318 (0.949)	1.544 (0.56)	1.978 (0.917)	p = 0.480 F = 0.503	p = 0.013† F = 5.327	$p = 0.277$ F = 1.202	p = 0.001† F = 12.896
Platelet/lymphocyte ratio	117.34 (45.45)	118.64 (51.73)	127.20 (57.43)	104.51 (37.14)	118.31 (50.06)	$p = 0.989$ F = 0.000	$p = 0.587$ F = 0.298	p = 0.329 F = 0.966	$p = 0.326$ F = 0.974
Monocyte/lymphocyte ratio	0.272 (0.114)	0.304 (0.131)	0.332 (0.119)	0.259 (0.137)	0.296 (0.127)	$p = 0.267$ F = 1.243	p = 0.015† F = 5.971	$p = 0.993$ F = 0.000	p = 0.009† F = 7.076

BD bipolar disorder; MDD major depressive disorder.
† Significantly different: $p \leq 0.017$.

ANCOVA of our primary outcomes and at $p \leq 0.05$ for other comparisons.

3. Results

3.1. Bipolar disorder vs. major depressive disorder

Comparison of socio-demographic and clinical features showed that the BD group had a higher male/female ratio and higher BMI than the MDD group (respectively $p = 0.021$, $\chi2 = 5.4$ and $p = 0.004$, F = 8.5) (Table 1).

No significant statistical differences were found between the BD and MDD groups regarding laboratory findings and inflammatory ratios (Table 2).

3.2. Bipolar disorder manic episodes vs. bipolar disorder depressive episodes

Patients in the BD manic group had higher male/female ratio and younger age than the BD depressive group (respectively $p = 0.001$, $\chi2 = 13.4$ and $p = 0.003$, $\chi2 = 8.8$) (Table 1). The BD manic group had a significantly higher white blood cell ($p = 0.028$, F = 4.9), neutrophil ($p = 0.001$, F = 14.9), and monocyte count ($p = 0.026$, F = 5.1), and a lower value and lower value of total cholesterol ($p = 0.023$, F = 5.3) (Table 1).

NLR (p = 0.001, F = 12.8) and MLR ($p = 0.009$, F = 7.1) were significantly higher in the BD manic group than in the BD depressive group after adjustment for age, sex, BMI, and smoking (Table 2).

3.3. Major depressive disorder vs. bipolar manic episodes and bipolar depressive episodes

The MDD group presented significantly lower BMI compared to the BD manic and the BD depressive groups (respectively $p = 0.007$, F = 7.6 and $p = 0.023$, F = 5.4). The MDD group was also significantly older and had a lower male/female ratio than the BD manic group (respectively $p = 0.005$, F = 8.2 and $p = 0.001$, $\chi2 = 12.2$) (Table 1).

NLR and MLR were significantly lower in the MDD group when compared to the BD manic group after adjustment for age, sex, BMI, and smoking (respectively $p = 0.013$, F = 5.3 and $p = 0.015$, F = 6.0) (Table 2).

4. Discussion

This is the first study to compare NLR, MLR, and PLR in patients with BD versus MDD episodes, and in patients with BD manic versus BD depressive episodes. The main results of the present study were the statistical differences in NLR and MLR between the BD manic phase when compared to both the BD depressive phase and MDD. These findings were not affected by socio-demographic and clinical variables found to be different between groups (age, sex, BMI, and smoking).

Previous studies suggested a partially distinctive pattern of inflammatory response during different phases of BD, focusing on cytokines and other inflammatory markers. When compared to HC, BD manic episodes were characterized by elevated values of Interleukin (IL)-2, IL-4, IL-6, IL-8, IL-12, IL-33, interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF-α); euthymic and remission phases were characterized by elevated IL-1b, IL-13, and IL-33; and BD depressive episodes were characterized by elevated levels of IL-6 and reduced levels of IL-2 [6,43,44]. When comparing manic and depressive BD phases with each other, manic BD patients showed an increase in TNF-α and IL-4, IL-18 along with reduced IL-1β and IL-2 levels, while depressed BD patients revealed elevated levels of IL-6, and TNF-α and decreased IL-2 levels [6]. Serum C reactive protein (CRP) levels were found elevated in manic BD patients when compared to euthymic, depressed BD patients and HC [45]. Our result support a distinctive pattern of inflammation during the different phases of BD suggesting that

inflammatory changes occur especially during acute episodes of mania. Further research is necessary to better understand the fluctuation of inflammatory ratios, their correlation with cytokines and their role in the pathophysiology of BD.

We also found that BD manic patients had higher NLR and MLR when compared to patients in MDD episodes. This result is consistent with previous studies in which BD manic patients had higher levels of some pro-inflammatory cytokines such as soluble IL-6 receptor, CRP, soluble TNF-receptor1, and monocyte chemoattractant protein-1 (MCP-1) compared with patients with MDD, again suggesting more severe inflammatory dysregulation in BD mania [46,47].

Elevated NLR in BD manic episodes suggests an imbalance in favor of innate immunity, as neutrophils are, part of the first line of innate immune defense, and lymphocytes, are cells primarily involved in the adaptive immune response. Elevated MLR in BD manic episodes could represent a peripheral marker of brain inflammation, since activation of the microglia may be part of a systemic activation of the mononuclear phagocyte system [14]. Inflammatory ratios are less affected by exercise, catecholamine release, and other confounding conditions than single leukocyte parameters or other commonly used markers of inflammation [48]. Inflammatory ratios are not limited by costs and assay availability compared to other markers of inflammation such as cytokines. Moreover, studies have shown significant correlations of inflammatory ratios with established markers of inflammation like CRP, oxidative stress and some pro-inflammatory cytokines [49–51].

This paper should be considered in the context of the following limitations. First, we did not evaluate the possible correlation between symptoms severity and ratios. Second, other indicators of immune system function, such as cytokines and CRP, were not evaluated; therefore, it is not possible to determine whether increased NLR and PLR represent an independent marker of alterations in the immune system in patients with BD mania. Third, we did not account for psychopharmacological treatment, which may affect inflammatory ratios. More studies on drug naïve patients and pre-and post-treatment studies are needed to better understand the impact of psychopharmacological treatment on inflammatory ratios. Fourth, the retrospective design of the study and the inpatient setting did not allow us to use a structured psychiatric interview. Fifth, we were not able to control the results for covariates that could influence inflammatory status such us menstrual cycle, eating habits, and physical activity. Finally, we did not include patients with mood disorders who were euthymic, and we did not compare patients in episodes of mood disorder to healthy controls.

Declarations of interest

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