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Clinical significance of neutrophil-lymphocyte and platelet-lymphocyte ratios in bipolar patients: An 18-month prospective study

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ABSTRACT

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have recently been investigated as inexpensive and reproducible markers of systemic inflammation in many diseases. However, few studies evaluate clinical and prognostic value of NLR and PLR in psychiatric patients. The objective of this study is to investigate the clinical repercussions of NLR and PLR in patients with bipolar disorder (BD). An 18-month prospective study followed up eighty euthymic BD outpatients. Baseline data included an interviewer-administered questionnaire, behavioral scales and a blood count to calculate NLR and PLR. The occurrence of mood episodes and hospitalizations was assessed monthly for 18 months. Higher NLR and PRL were associated with more anxious symptoms and poorer functioning. BD patients with Night Eating Syndrome (NES) had higher PLR and tended to higher NLR. No association with other sleep parameters was evidenced. Higher NLR and PRL were also associated with more episodes and hospitalizations after 18 months. However, only higher baseline NLR was related to more (hypo)mania episodes. NLR and PLR are important prognostic factor for BD. This study suggested the importance of a simple blood count, an inexpensive and reproducible exam, in evaluating the course of the BD. Further studies must be performed to confirm these results.

Significant outcomes

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- This may be the first study to demonstrate clinical repercussions of increased NLR and PRL after 18-month follow-up, predicting more mood episodes and psychiatric hospitalizations.
- Higher NLR and PRL were associated with more anxiety and poorer functioning in BD. Additionally, BD patients with NES had higher PLR and tended to higher NLR.
- This study suggested the importance of a simple blood count, an inexpensive and reproducible exam, in evaluating the course of the BD

Limitations

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- Sleep parameters were only based on the subjective impression of patients.
- Larger sample could have improved the reliability of reported data.
- Reduced follow-up time probably limited some conclusions.

1. Introduction

Bipolar Disorder (BD) is a chronic mental illness associated with high prevalence, premature mortality and increased suicide risk

Abbreviations and symbols: BD, bipolar disorder; CRP, C-reactive protein; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ESS, Epworth Sleepiness Scale; FAST, Functioning Assessment Short-Test; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; IL, interleukin; ISI, Insomnia Severity Index; MDD, major depressive disorder; NES, Night Eating Syndrome; NEQ, Night Eating Questionnaire; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PSQI, Pittsburgh Sleep Quality Index; SPSS, Statistical Package for Social Sciences; TNF- α, tumor necrosis factor-α; YMRS, Young Mania Rating Scale

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(Clemente et al., 2015; Costa Lda et al., 2015; Hayes et al., 2015). Longer term functional impairment is evidenced, mainly linked to depression (including subsyndromal states) and persistent neurocognitive dysfunction (Gitlin and Miklowitz, 2017).

Inflammatory reactions and immune modulation play an important role in the pathophysiology of BD (Rosenblat and McIntyre, 2017; Sayana et al., 2017). C-reactive protein (CRP) concentrations are increased in BD regardless of mood state but are higher during manic episodes than in depression and euthymia, suggesting an increased inflammatory response in mania (Fernandes et al., 2016). Alterations of serum and cerebrospinal fluid cytokines, tryptophan catabolite, tumor necrosis factor-α (TNF-α) and soluble cytokine receptors were also evidenced in BD, as well as major depressive disorder (MDD) and schizophrenia (Goldsmith et al., 2016; Wang and Miller, 2018). Inflammatory markers probably have structural and functional abnormalities correlates in BD, as thinner cortex in the right middle temporal gyrus and loss of connectivity between the medial prefrontal cortex and amygdala (Tu et al., 2017). Wiener et al. (2017) suggested that interleukin (IL)-6 and IL-10 levels were positively correlated with functional impairment among drug-free subjects with BD. A systematic review revealed an influence of inflammatory mediators (as CRP, IL-1 receptor antagonist, IL-6 and TNF-α) on cognitive impairment in BD (Misiak et al., 2018).

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have recently been investigated as inexpensive and reproducible markers of systemic inflammation in many diseases. Pretreatment NLR and PLR predicts a worse prognosis for many types of cancer (as hepatocellular carcinoma, biliary tract, esophageal, colorectal, lung, breast, prostate and renal cancer), linked to higher recurrence rates, less recurrence-free survival, and reduced overall survival (Boissier et al., 2017; Najjar et al., 2018; Song et al., 2016; Tang et al., 2017, 2016; Tsai et al., 2016; Wei et al., 2016; Yodying et al., 2016; Zhang et al., 2016; Zhou and Luo, 2017). These markers also have reliable prognostic value in patients with cardiovascular conditions, as peripheral arterial disease, acute coronary syndrome, atrial fibrillation and occlusive vascular diseases (Kucuk et al., 2016; Li et al., 2017; Paquissi, 2016a, 2016b). NLR is associated with increased long-term mortality and morbidity after major cardiac and vascular surgery (Tan et al., 2015). DiGangi (2016) suggested the NLR as an independent predictor of the development and progression of diabetic nephropathy, major adverse cardiac events and subsequent mortality.

Few studies evaluate clinical and prognostic value of NLR and PLR in psychiatric patients. It is suggested that NLR levels are increased in patients with schizophrenia with significant positive relationships with oxidative stress and psychopathological symptoms (Kulaksizoglu and Kulaksizoglu, 2016; Semiz et al., 2014). A preliminary study concluded that the sensitivity of the NLR itself is not robust enough for diagnostic utility in Alzheimer's disease (Rembach et al., 2014). In this study, significant relationships cross sectionally between the NLR and neocortical amyloid burden were found, but this relationship was lost after longitudinal analyses.

Few studies investigated the relationship between BD, NLR and PLR. BD patients frequently had higher NLR and PLR as compared with healthy controls (Cakir et al., 2015; Kalelioglu et al., 2015; Mazza et al., 2018). Ivković et al. (2016) proposed NLR as a positive predictor of suicidal risk in patients with positive family history of suicide attempts. Sağlam Aykut et al. (2018) demonstrated a negative correlation between NLR and attention in cognitive tests. However, no study analyzed the impact of NLR and PLR values on prognosis of BD patients.

The objective of this study is to evaluate the clinical repercussions of NLR and PLR in bipolar patients. To this end, we analyzed the relationship with anxiety, functionating and sleep parameters. Additionally, we investigated the impact of NLR and PLR on future mood episodes and psychiatric hospitalizations in the next 18 months after baseline evaluation.

2. Material and methods

A prospective study was conducted for 18 months. Eighty euthymic BD outpatients were recruited from four institutions in Brazil between July 2016 and December 2017. To be included in the study, participants must be diagnosed with BD, be eighteen years of age or older, and be in euthymia for three months or more. The exclusion criteria were alcohol and / or substance dependence, heavy smoking (more than 20 cigarettes per day), medical conditions associated with changes in inflammatory response, pregnancy, current treatment with corticosteroid, nonsteroidal anti-inflammatory drug, acetylsalicylic acid, or immunosuppressive, fever or leukocytosis, leukopenia, and thrombocytosis at the moment of the biochemical evaluation.

BD diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Three psychiatrists evaluated mood state, attested euthymia and used Hamilton Rating Scale for Depression (HAM-D) and Young Mania Rating Scale (YMRS) to exclude depressive and manic syndromes respectively.

Baseline data included an interviewer-administered questionnaire with sociodemographic information (gender, marital status, age and schooling), brief medical history (type of BD, onset of illness and comorbidities), current medications and behavioral scales (mentioned below). Medications in use were classified into mood stabilizers, antipsychotics, antidepressants, benzodiazepines and others.

All patients collected a blood count. Neutrophil count, lymphocyte count and platelet count were used to calculate NLR and PLR. NLR was obtained by dividing neutrophil count for lymphocyte count; and PLR by dividing platelet count for lymphocyte count.

Patients were monthly evaluated by psychiatrists or psychiatry residents for a period of 18 months. These physicians evaluated the occurrence of mood episodes and classified them into: depressive or (hypo)manic episode (based on DSM-5 criteria). Psychiatric hospitalizations were identified in hospital records.

Hamilton Anxiety Rating Scale (HAM-A) and Functioning Assessment Short-Test (FAST) were administered at baseline and detected anxiety and functioning, respectively. HAM-A is composed by 14 items, each one ranging 0 to 4 points. Anxiety was suggested with HAMA > 17. FAST is divided into six domains: autonomy, occupational functioning, cognitive functioning, capacity of managing the finances, interpersonal relationships and leisure time. Each domain scored 0–3 points. Higher scores in FAST expressed poorer functionality but a cutoff point has not been defined.

Sleep parameters included sleep quality (Pittsburgh Sleep Quality Index – PSQI), daytime sleepiness (Epworth Sleepiness Scale – ESS) and severity of insomnia (Insomnia Severity Index – ISI). Scores of five or more in PSQI indicated a poor sleep quality. Similarly, seven or more points in ISI and ten or more points in ESS revealed insomnia and excessive daytime sleepiness, respectively. Night Eating Syndrome (NES) was screened by Night Eating Questionnaire (NEQ), and the diagnosis was confirmed by clinical criteria (Allison et al., 2010).

The study has been approved by the local Ethics Committee [Register: 44,561,115.5.0000.5051]. All participants aged 18 years or older and provided a written informed consent form.

2.1. Statistical analysis

Analyses were carried out by the Statistical Package for Social Sciences V24.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as mean ± standard error and percent values. Association between NLR/PLR values and anxiety, functioning, sleep parameters, mood episodes and hospitalizations were analyzed.

For normally distributed variables with homogeneity of variance, a two-tailed Student test was performed. For variables that did not meet the homogeneity of variances requirement, non-parametric Mann–Whitney *U* test was used. Categorical variables were analyzed by the Fisher's exact test. Differences were considered statistically

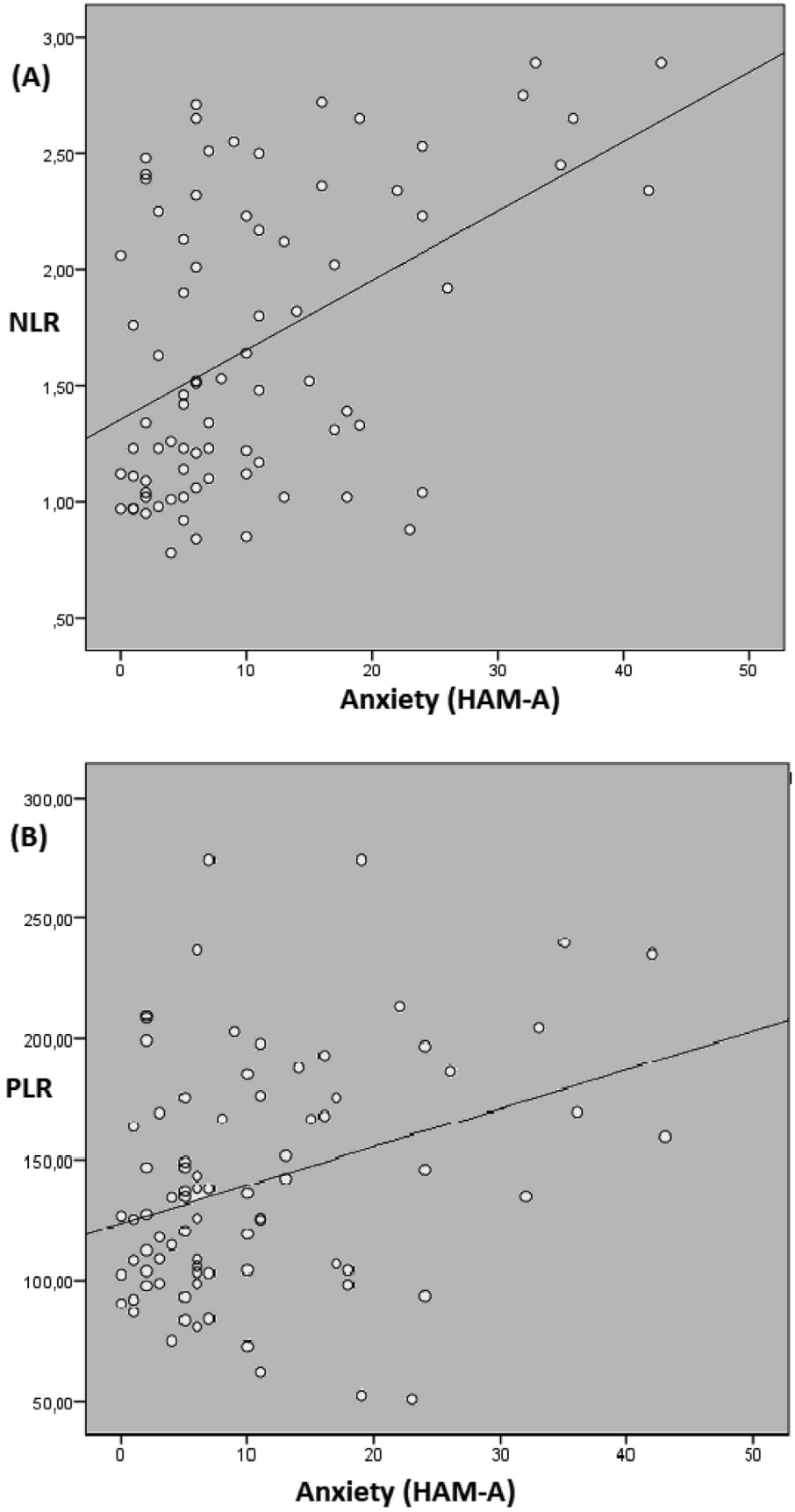

Fig. 1. Association between anxiety and NLR/PLR values.

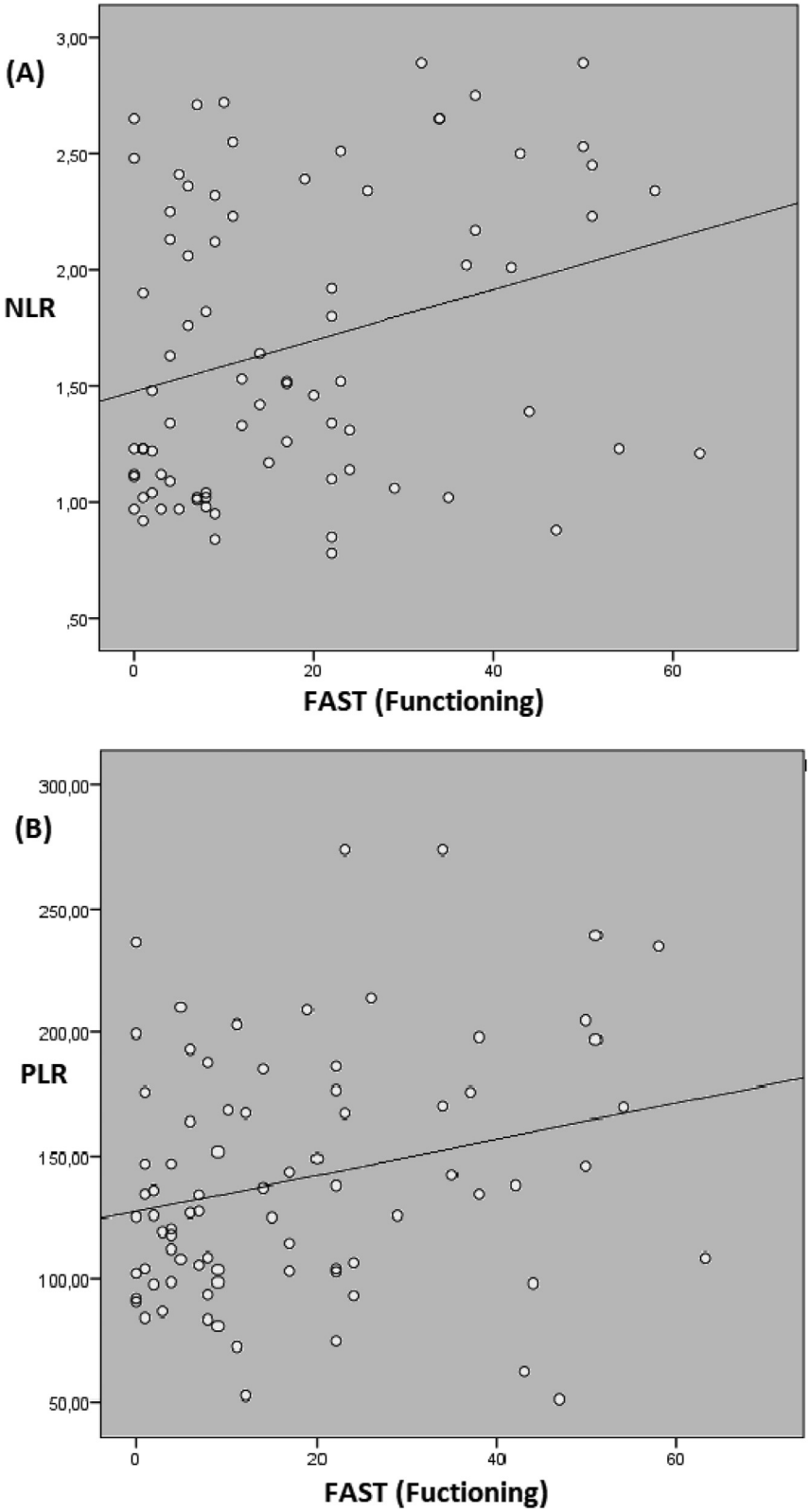

Fig. 2. . Association between functioning and NLR/PLR values.

significant at $p < 0.05$.

3. Results

Most patients were female ($n = 49$; 61.3%), married ($n = 37$; 46.3%), with age ranged from 20 to 68 years (Mean: 42.4 ± 12.7). The majority had BD type 1 (86.3%) and BMC ≥ 25 (78.8%). The mean time of the first crisis was 15(± 11.3) years. Regarding medications, 48 (60%) used lithium, 49 (61.3%) atypical antipsychotics, 37 (46.3%) other mood stabilizers, 17 (21.3%) benzodiazepines and 7 (8.8%) antidepressants.

NLR and PLR ranged from 0.78 to 2.89 (mean: 1.67 ± 0.07) and

Table 1
Relationship between NLR/PLR values and sleep alterations in BD patients.

Sleep parameters*	NLR (mean ± SE)	PLR (mean ± SE)
Insomnia		
Absent	1.62 ± 0.08	136.02 ± 6.64
Present	1.79 ± 0.13	150.82 ± 9.70
p value	0.264	0.215
Sleep quality		
Good	1.56 ± 0.09	135.50 ± 7.31
Poor	1.78 ± 0.10	145.55 ± 8.35
p value	0.124	0.366
Excessive daily sleepiness		
Absent	1.66 ± 0.07	138.27 ± 5.73
Present	1.70 ± 5.73	150.60 ± 16.96
p value	0.858	0.413
Night eating syndrome		
Absent	1.63 ± 0.07	136.66 ± 5.46
Present	2.08 ± 0.26	177.95 ± 24.15
p value	0.070	0.034**

Abbreviations: BD, Bipolar Disorder; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SE, standard error.
* *t* test.
** Statistically significant.

51.01 to 273.93 (140.27 ± 5.51), respectively. No significant relationship between NLR/PLR values and gender (*t*-test, $p = 0.926$ and 0.950, respectively), age (Correlation, $p = 0.911$ and 0.127), marital status (ANOVA, $p = 0.698$ and 0.552), BMI (Correlation, $p = 0.572$ and 0.299), disease duration ($p = 0.142$ and 0.623) was found. Associations between NLR, PLR and use of psychiatric medications were not identified.

Anxiety levels was positively associated with NLR (ANOVA, $R = 4.74$, $p < 0.001$) and PLR (ANOVA, $R = 3.26$, $p = 0.003$) (Fig. 1). A correlation with higher NLR/PLR and poor functioning was also identified (ANOVA, $R = 0.290$ and 0.249, $p = 0.009$ and 0.026, respectively) (Fig. 2). BD patients with NES had higher PLR (*t*-test, $p = 0.034$), and tended to higher NLR (*t*-test, $p = 0.070$). No association with other sleep parameters was evidenced (Table 1).

Higher values of NLR and PRL were associated with more mood episodes in general (*t*-test, $p = 0.001$ and 0.006, respectively) and psychiatric hospitalizations (*t*-test, $p = 0.009$ and 0.029) after 18 months. However, only NLR was related to (hypo)mania (*t*-test, $p = 0.013$) (Table 2).

Table 2
Impact of NLR/PLR values in BD course after 18 months.

Variables*	NLR (mean ± SE)	PLR (mean ± SE)
Mood episodes (in general)		
Absent	1.47 ± 0.09	125.86 ± 4.97
Present	1.91 ± 0.09	157.89 ± 9.96
p value	0.001**	0.006**
(Hypo)Mania		
Absent	1.56 ± 0.08	134.42 ± 5.17
Present	1.96 ± 0.13	155.71 ± 14.44
p value	0.013**	0.177
Depression		
Absent	1.63 ± 0.80	135.68 ± 6.11
Present	1.82 ± 0.14	158.67 ± 12.06
p value	0.274	0.096
Psychiatric hospitalizations		
Absent	1.58 ± 0.60	134.51 ± 5.11
Present	2.05 ± 0.16	165.25 ± 18.50
p value	0.009**	0.029**

Abbreviations: BD, Bipolar Disorder; NLR, neutrophil-to-lymphocyte ratio; PLR:, platelet-to-lymphocyte ratio; SE, standard error.
* *t* test.
** Statistically significant.

4. Discussion

This study showed that BD patients with higher NLR and PRL values manifested more anxious symptoms and poorer functioning. Higher NLR and PRL were associated with more episodes and hospitalizations after 18 months. This may be the first study to demonstrate clinical repercussions of increased NLR and PRL after 18-month follow-up.

NLR and PRL are probably important predictors of mood episodes and hospitalizations in BD. It suggested that inflammation can be associated with a poor course of the disease. There is no enough evidence that other inflammatory markers are related to future mood episodes (Balukova et al., 2016).

A slight-moderate positive correlation between NLR, PRL and anxiety levels was found. Previous studies reinforce this association. Xu et al. (2016) suggested higher NLR was an important factor influencing preoperative anxiety and depression in gastric cancer patients. Al-Hussain et al. (2017) identified a link NLR and stress scores in multiple sclerosis patients. People with bipolar disorder are at increased risk of anxiety disorders compared with controls (Pavlova et al., 2015). The co-occurrence of anxiety conditions in BD is associated with poor treatment responses, depressive episodes, substance abuse, and disability (Vazquez et al., 2014). Heightened concentrations of inflammatory signals, including cytokines and C-reactive protein, have been described in anxiety disorders (Michopoulos et al., 2017).

Higher NLR and PRL were associated with poorer functioning. An important impairment in quality of life in BD patients have been observed (Abraham et al., 2014; Martin-Subero et al., 2014; Xiang et al., 2014). However, there was no a consensual definition of quality of life in BD (Morton et al., 2017). Poorer cognitive performance, mainly in attention, verbal memory, working memory and executive functioning, can predict a reduced quality of life (Cotrena et al., 2016; Mackala et al., 2014). Previous studies indicate a relationship between inflammation mediators and functioning. Martinez-cengotitabengoa et al. (2016) demonstrated that alterations in oxidative stress in first mood episode in BD predicted poorer functioning. Sanchez-Autet et al. (2018) indicated that CRP levels predicted and correlated with cognitive performance in BD women. Mora et al. (2017) suggested that brain-derived neurotrophic factor (BDNF) could predict cognitive dysfunction.

A relationship between sleep abnormalities, NLR and PRL was not found. Sleep disturbances are common in BD even during remission (De Crescenzo et al., 2017; Geoffroy et al., 2015; Ng et al., 2015). High-risk individuals already reported irregularity of sleep/wake times, poor sleep and circadian rhythm disruption (Melo et al., 2016). A preliminary study suggested that improving sleep quality may modulate the state of inflammation in patients with schizophrenia (Fang et al., 2016). Another report indicated an association between longer sleep duration and inflammatory mediators, as increased C-reactive protein (CRP) and IL-6 (Prather et al., 2015). However, more studies are needed to investigate the link between sleep and inflammation in BD.

Limitations of this study should be known. Sleep parameters were only based on the subjective impression of patients. The use of actigraphy and polysomnography could have improved the reliability of reported data. Small sample and reduced follow-up time were other limitation. Nevertheless, this study brought significant statistical correlations and showed original and clinically relevant data.

In conclusion, NLR and PLR are relevant prognostic factor for BD, associated with more anxiety and poor functioning and predicting mood episodes and hospitalizations. In this way, a simple blood count can help in evaluating the course of the BD. Further studies must be performed to confirm these results.

Declaration of conflicting interests

The authors declare no conflict of interest with respect to the research, authorship, or publication of this article. The authors are responsible for the content and writing of the paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.10.077.

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