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# A Review of Neutrophil-Lymphocyte, Monocyte-Lymphocyte, and Platelet-Lymphocyte Ratios Use in Psychiatric Disorders

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## Abstract

The immune and inflammatory system is involved in the etiology of mood disorders. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR) are inexpensive and reproducible biomarkers of inflammation. We reviewed the literature investigating the possible utility of the inflammatory ratios in psychiatric disorders. We searched PubMed, Science Direct, ClinicalTrials.gov and Cochrane Library electronic databases for articles up to July 2018, with no language restrictions combining the following keywords: ("psychosis" OR "psychotic" OR "schizophrenia" OR "FEP" OR "bipolar" OR "mania" OR "manic" OR "depressive" OR "psychiatric") AND ("lymphocyte" OR "platelet" OR "neutrophil" OR "monocyte").

We found higher NLR, PLR, and MLR in bipolar disorder, major depressive disorder and schizophrenia when compared to healthy controls. Association of inflammatory ratios with the severity of disorders and with psychopharmacological treatment was also analyzed with inconsistent results.

It seems that NLR, PLR, and MLR may be useful to detect inflammatory activation that occurs in psychiatric disorders but more researches are needed to better understand the utility and the role of these inflammatory ratios.

**Keywords: Bipolar disorder; Major depressive disorder; Psychosis; FEP; Schizophrenia; Alzheimer; ADHD; Heroin dependence; Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio; Monocyte to lymphocyte ratio; Inflammation**

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## Introduction

Psychiatric disorders are mostly multifactorial and heterogeneous disorders driven by genetic, biochemical, psychological and environmental factors. Evidence from etiological studies showed the involvement of several different biochemical mediators, such as systems of neurotransmitter and neurotrophic factors, neuroinflammation, autoimmunity, cytokines, stress axis activity, chronobiology, mitochondrial dysfunctions and oxidative stress [1].

Increasing evidence suggests that immunological and inflammatory dysfunctions may play an essential role on predisposition, onset, and progression of major psychiatric disorders [2-4].

Genes expressed in tissues that have a central role in the immune system and involved in the regulation of the immunity are associated with increased risk of psychosis and mood disorder [5]. Prenatal viral/bacterial infections and inflammation are an established risk factor for the genesis of psychosis [6,7]. Clinical improvements in patients with a psychiatric disorder are observed after adjunctive treatment with non-steroidal anti-inflammatory drugs (NSAIDs) [8]. 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 [9]. Moreover, several medical conditions related to chronic inflammatory and immunological abnormalities such as diabetes, obesity, autoimmune diseases, malignancies, and multiple sclerosis are considered risk factors for psychiatric disorders [10]. All these findings provide empirical support for the speculated link between the immunological and inflammatory system and psychiatry diseases.

Several studies that explored this association focused on measuring inflammatory mediators such as cytokines, acute phase proteins, chemokines, growth factors, prostaglandins, leukotrienes, nitric oxide and neuropeptides [11-16].

A new, easily calculated from white blood cell essay, and inexpensive option, suitable for routine use to show inflammation, is the measurement of the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) [17,18].

NLR was developed to provide a suitable parameter reflecting the intensity of stress and systemic inflammation in critically ill patients following the shock, multiple trauma, major surgery or sepsis. By now, there is not a shared and approved cut-off value for NLR that discriminate normal from abnormal values. Some studies categorized their patients according to NLR intervals (e.g., tertiles, quartiles, quintiles) while other studies used specific NLR cutoff points [19]. Neutrophils are the first line of immune defense: they exhibit phagocytic and apoptotic action through the secretion of various inflammatory factors, in particular, cytokines [20]. Inflammation triggered by cytokines can induce further inflammation due to cell dysfunction and to oxidative stress. On the other side, lymphocytes are specific inflammatory mediators, with a regulatory or protective function; low lymphocyte counts reflect poor general health and physiologic stress [21]. NLR may be useful to detect the inflammatory response, reflecting the intensity of stress and systemic inflammation, and the following cytokine cascade. Studies have shown significant correlations of NLR with established markers of inflammation like CRP and other pro-inflammatory cytokines, suggesting NLR as a useful marker to detect the inflammatory response, reflecting the intensity of stress and systemic inflammation, and the following cytokines cascade [22,23].

MLR is another low-cost effective and readily available new index. It has been demonstrated that levels of circulating monocytes are elevated in patients with psychiatric disorders such as bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia, due to enhanced expression of immune genes and overproduction of monocytes/macrophage-related cytokines [24]. The macrophage- T lymphocyte theory, initially suggested for schizophrenia and MDD [25] and subsequently extended to BD, turns attention to the chronic immune system's activation in the brain, mediated by macrophages such as microglia. Microglia play an essential role regarding pathologic synaptic pruning and impaired neuroplasticity [26,27].

Last, PLR considers together platelets and lymphocytes, and it may predict the inflammatory response [28]. Platelets are a nonspecific first line inflammatory marker; they modulate endothelial permeability and recruitment of neutrophils and macrophages. Platelets involve a considerable amount of serotonin and glutamate in their dense granules. Notoriously serotonin and glutamate pathways have an important role in the pathophysiology of mood disorders, and some studies suggested that platelets may have an active role in psychiatric disorders [29].

Several studies have evidenced that these inflammatory ratios can be used as biomarkers of poor prognosis or major inflammation among patients with chronic medical conditions such as pediatric infection-related conditions [30,31], cardiovascular diseases [32,33], malignancies [34,35], acute pancreatitis [36,37], autoimmune diseases [38,39], chronic obstructive pulmonary disease [40,41], metabolic syndrome-related conditions [42,43].

The growing interest in inflammation dysfunction in psychiatric disorders and the availability of these easy obtainable inflammatory ratios have resulted in studies investigating NLR, PLR, and MLR in neuropsychiatric disorders. Thus we decided to review the literature to explore the possible utility of the inflammatory ratios in psychiatric disorders.

## Materials and Methods

We searched PubMed, ScienceDirect, ClinicalTrials.gov and Cochrane Library electronic databases for articles up to June 2018, with no language restrictions.

Keywords used to identify specific and relevant studies were ("psychosis" OR "psychotic" OR "schizophrenia" OR "FEP" OR "bipolar" OR "mania" OR "manic" OR "depressive" OR "psychiatric") AND ("lymphocyte" OR "platelet" OR "neutrophil" OR "monocyte") in the title, abstract or keywords. We also screened reference lists from selected articles to identify additional studies. We included observational studies (cross-sectional, retrospective or prospective) investigating the role of NLR, MLR, and PLR in subjects with a diagnosis of any psychiatric disease. No restriction of the study area, age, and publication language were used.

References were managed using Citavi 5 Swiss Academic Software.

## Results

### Mood disorders

Elevated NLR, PLR, and MLR have been found in patients with BD compared to healthy controls [44-49]. Some studies investigated only BD manic episode finding higher NLR [45,47-49], higher PLR [45,48,49], and higher MLR [49] in patients in comparison with healthy controls. Inconsistent results were found investigating euthymic state. Aykut et al., found no statistically significant difference in NLR and PLR between euthymic BD and control group, while Ivkovic et al., observed increased NLR in BD euthymic compared to healthy controls [46,50]. Kalelioglu et al. demonstrated that elevated PLR and NLR values persisted in both the euthymic and manic periods but observed no differences between the two phases [45]. Only one study compared NLR and MLR between schizophrenia patients and BD finding inflammatory ratios higher in schizophrenia then BD [49]. Furthermore, NLR but not PLR value has been negatively correlated with cognitive function in patients with BD [50]. In patients with BD, NLR did not significantly correlate with severity [44]. NLR has been considered a significant positive predictor of suicidal risk in patients with BD and with a positive family history of suicide attempts [46].

Patients with MDD have been found carrying elevated NLR values in comparison with healthy controls [51-54]. Patients without antidepressant therapy showed increased NLR values in comparison with healthy controls [52,53]. Interestingly, Demircan et al. also showed that the difference dissolved after 3 months of SSRI treatment [53]. Moreover, PLR has been found elevated in patients with MDD compared with healthy controls [51,54]. In addition, NLR value has been positively correlated with the severity of depression in patients with MDD [55,56] and seems to be a trait marker for suicidal vulnerability in patients with MDD [54] even if Meydaneri et al., found no significant difference between NLR and PLR in patients who may attempt suicide [57]. NLR also seems to be positively correlated with age at onset in patients with MDD [58]. Comparing elderly MDD patients with healthy controls it was found lower NLR in elderly depressed patients; however, stratifying the patients higher NLR was observed in patients with first-episode depression compared with recurrent depression. The authors explained this

finding with the non-specific effect of treatment with antidepressants or antipsychotics on lowering NLR [56]. A recent meta-analysis concluded that subjects with BD and subjects with MDD have higher NLR and PLR as compared with healthy controls; interestingly it was also observed an influence of bipolar phase on the overall estimate [59].

### Schizophrenia and related psychosis

The relationship between schizophrenia and related psychosis and NLR also received growing attention. NLR was found to be higher in patients affected by schizophrenia when compared to healthy controls [49,60-63]. Three studies investigated first episodes psychotic (FEP) patients, two of them showed significant higher NLR in patients than in controls [64,65] while one did not find differences in NLR in newly diagnosed naïve patients with non-affective psychosis compared to matched controls [66]. Elevated NLR was also found in psychotic adolescent inpatients aged between 10 to 19 compared to non-psychotic adolescent inpatient [22]. NLR seems not to be correlated with severity of disease [62,63,65] even if in a group of psychotic adolescent it was found a significant decrease in NLR at clinical remission compared with the acute psychotic state [22]. Previous studies that analyses the possible effect of psychotropic medications did not find a significant difference in NLR between patients who received and those who didn't receive psychotropic treatment [62,64]. Total sleep time and sleep efficiency were negatively associated with NLR and PLR patients with schizophrenia [67].

Two studies examined MLR finding higher ratios in schizophrenia patients compared to the controls [49,64] and one study analyzed PLR finding increased ratios in schizophrenia patients than in healthy controls [49].

### Other disorders

Older adults with Alzheimer's disease have higher NLR than healthy control [68], even if this result seems to be more properly related to the age. NLR, PLR, and MLR were found to be significantly higher in ADHD patients than in healthy controls [69]. Finally, the mean NLR and PLR levels of patients with heroin dependence were significantly higher than the control subjects, and positive correlations were found between NLR, PLR, and duration of the disorder. Patients who injected heroin intravenously exhibited significantly increased NLR and PLR compared to control subjects [70].

## Conclusions

Association between immunological and inflammatory dysfunctions and pathophysiology of psychiatric disorders has been suggested [4,71] and NLR, PLR, and MLR represent an easy way to explore inflammation also in psychiatric disorders.

Previous studies on BD and MDD demonstrated abnormal serum levels of some cytokines, chemokines and acute-phase proteins revealing a pro-inflammatory state with higher concentrations of pro-inflammatory cytokines and lower concentrations of anti-inflammatory cytokines [71]. Studies also showed pro- and anti-inflammatory cytokine variations during different phases of BD suggesting that there is a distinctive cytokine pattern for each specific phases of the disease [71]. Several studies that explored inflammatory response in psychosis found increased levels of peripheral proinflammatory cytokines, mainly IL-1 β, IL-6, IL-12,IL-17, IL-23 and TNF- α and elevated CRP levels [3,10,72]. Moreover previous meta-analyses in schizophrenia have found that blood levels of some components of the cytokine network may vary according to psychopharmacology treatment; some cytokines (IL-1β, IL-6, IL-2, and TGF-β) could be considered state markers, decreasing after antipsychotic treatment, others (IL-12, IL-17 IFN-γ, TNF-α, and sIL-2R) may be trait markers [10,72].

Compared with other biomarkers the inflammatory ratio benefit from the low price (especially compared to cytokines), the routinary use also in the general clinical settings (especially compared to CRP and blood sedimentation rates which are not routinely requested but only when there is the suspect of inflammation or infection disease) and the high reproducibility between laboratory considering that the ratios are derived from a white blood cell essay. Inflammatory ratios integrate information on both the innate and adaptive compartments of the immunity and represent a reliable and easily available measure of the inflammatory burden to better understand pathology.

Further researches are needed to better explore inflammatory ratios. First, it would be useful to investigate the comparison between acute phases and remission period to understand if the inflammatory ratios alterations could be considered a trait mark or a state mark of a specific psychiatric disorder. Second, we need to study the effect of psychopharmacological treatment on inflammatory ratios. Inconsistent results were found between pre-and post-medication differences in inflammatory ratios [52,53,62,64]. More studies on drug naïve patients and pre-and post-treatment studies are needed to better understand this aspect. Third, it will be useful to observe the association of other indicators of immune system function, such as cytokines and C-reactive Protein with inflammatory ratios to determine whether increased NLR, PLR and MLR could represent an independent marker of alterations in the immune system in patients with a psychiatric disorder. Fourth, inconsistent results were found regarding the severity of the disorder, suicidality, cognitive impairment and euthymic state in BD; future studies should clarify these issues. Fifth, even if all the reviewed studies excluded from the sample patients with medical conditions associated with changes in inflammatory response and subjects under anti-inflammatory drug other variables such as age, gender, BMI and heavy smoking can affect the inflammatory ratios. Further studies with highly selected patients are needed to exclude the effect of these confounding variable on the inflammatory ratios. Finally, in general, more studies are needed considering the small sample size of the present studies.

In conclusion, it seems that inflammatory ratios are inexpensive, suitable for routine, and reproducible markers of the systemic inflammatory response that can be useful to detect inflammatory activation in psychiatric disorders even if some area remains unclear and needs future investigation especially to better investigate association of inflammatory ratios with the severity of disorders and with psychopharmacological treatment.

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