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Letter to the editor

Neutrophil-lymphocyte, monocyte-lymphocyte and platelet-lymphocyte ratio in schizoaffective disorder compared to schizophrenia

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Epidemiological, genetic, and biomolecular studies suggest that the immune system may play an important role in the predisposition, onset, and progression of schizophrenia spectrum disorders [1]. Neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) are innovative, low-cost, stable, reproducible, and suitable routine markers of the systemic immune response [2]. NLR, MLR, and PLR have been investigated in mood disorders and schizophrenia, with higher inflammatory ratios seen in such patients when compared with healthy controls [3,4].

However, no prior study has compared NLR, MLR, and PLR between those with schizophrenia and those with schizoaffective disorder. Thus, our primary aim was to explore the potential differences of NLR, MLR, and PLR between patients with these two conditions.

In this cross-sectional study, we included adults diagnosed, using DSM-IV-TR criteria, with schizophrenia or schizoaffective disorder who were consecutively admitted to our inpatient unit for an acute exacerbation of the disease from January 2010 to January 2018. Patients were excluded if they met one of the following criteria: (a) current diagnosis of additional psychiatric disorders; (b) medical conditions associated with significant changes in inflammatory response; (c) pregnancy, body mass index (BMI) > 30 kg/m2 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-White racial/ethnic status (due to racial differences in inflammatory ratios). We measured white blood cell count, neutrophil count, lymphocyte count, monocyte count, platelet count, and from these values, we calculated NLR, MLR, and PLR. Independent samples *t*-test were used to compare continuous variables, and Chi-square tests were used to analyze categorical data. Analysis of covariance, adjusting for potential confounding factors (age, sex, BMI, smoking, and drug therapy), was utilized to assess the differences in NLR, MLR, and PLR between the two groups. The study protocol was approved by our Ethical Committee Board.

One hundred eighteen patients were enrolled (n = 86 with schizophrenia; n = 32 with schizoaffective disorder. [15 with schizoaffective depressive subtype and 17 with bipolar subtype]). The schizophrenia group had higher male/female ratio ($\chi 2 = 7.091$, $p = 0.008$), neutrophil count ($F = 11.532$, $p = 0.001$), and monocyte count ($F = 4.837$; $p = 0.030$), and lower lymphocyte count ($F = 5.666$; $p = 0.019$). NLR ($F = 11.100$; $p = 0.001$) and MLR ($F = 4.668$; $p = 0.033$) were significantly higher in the schizophrenia group after adjustment for age, sex, BMI, smoking, and drug therapy (Table 1).

While clinical, genetic, and neuroimaging studies have reported specific alterations for schizoaffective disorder, no valid biomarkers or laboratory measures have yet emerged to distinguish between schizoaffective disorder and schizophrenia [5].

In the present study, we found that NLR and MLR may differ between schizophrenia patients and schizoaffective patients. Elevated NLR in schizophrenia suggests an imbalance in favor of innate immunity, as neutrophils are part of the first line of innate immune defense, while lymphocytes are cells primarily involved in the adaptive immune response [6]. This result is concordant with recent literature showing that alterations in innate immunity may play a significant role in the pathophysiology of schizophrenia and related psychosis-based conditions [7]. Likewise, elevated MLR in schizophrenia could represent a peripheral marker of microglia activation. Monocytes have disease-related functions activated by microglia through signal transduction mediated by pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8 or TNF-α [8]. These cytokines are increased in the blood of psychotic patients suggesting that this activation might underlie a pathological role between microglia and monocytes in psychotic disorders [9]. Thus, based on these preliminary results we could speculate that in schizophrenia, unlike schizoaffective disorder, there is an innate immune response as a cause or consequence of microglia activation, and NLR and MLR may represent markers to differentiate between the two diagnostic groups.

Comparing the results of this study with those found in our previous work [10], we found higher levels of NLR and MLR in schizophrenia exacerbations (respectively 2.61 ± 1.40 and 0.37 ± 0.17), followed by bipolar disorder manic episodes (respectively 2.318 ± 0.949 and 0.332 ± 0.119), schizoaffective disorder exacerbations (respectively 1.65 ± 0.87 and 0.26 ± 0.09) and bipolar disorder depressive episodes (respectively 1.544 ± 0.56 and 0.259 ± 0.137). Our findings are only partially consistent with the notion that schizoaffective disorder is biologically intermediate between schizophrenia and bipolar disorder.

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

	Schizophrenia (n = 86)	Schizoaffective (n = 32)	Total sample (n = 118)	*p*-value
Sex				
Male	65 (76%)	16 (50%)	81 (69%)	$\chi2 = 7.091$; p = 0.008*
Female	21 (24%)	16 (50%)	37 (31%)	
Smokers				
Yes	49 (57%)	17 (53%)	66 (56%)	$\chi2 = 0.062$; $p = 0.484$
No	37 (43%)	15 (47%)	52 (44%)	
Drug therapy				
Typical antipsychotic	20 (23%)	5 (16%)	25 (21%)	$\chi2 = 1.941$; $p = 0.452$
Atypical antipsychotic	53 (62%)	19 (59%)	72 (61%)	
Free of medication	13 (15%)	8 (25%)	21 (18%)	
Age (Year)	46.24 ± 13.74	42.34 ± 13.94	45.19 ± 13.84	F = 1.865; $p = 0.175$
BMI (kg/m2)	25.14 ± 5.49	26.46 ± 6.42	25.14 ± 5.50	F = 1.037; $p = 0.311$
White blood cell (10^3 cells/mm^3)	8.01 ± 2.26	7.12 ± 1.91	8.00 ± 2.26	F = 3.887; $p = 0.051$
Neutrophils (10^3 cells/mm^3)	5.00 ± 1.87	3.76 ± 1.44	5.00 ± 1.87	F = 11.532; $p = 0.001$*
Lymphocytes (10^3 cells/mm^3)	2.14 ± 0.68	2.48 ± 0.76	2.14 ± 0.68	F = 5.666; $p = 0.019$*
Monocytes (10^3 cells/mm^3)	0.73 ± 0.26	0.62 ± 0.21	0.73 ± 0.26	F = 4.837; $p = 0.030$*
Platelets (10^3 cells/mm^3)	231.91 ± 55.43	245.56 ± 75.55	231.91 ± 55.43	F = 1.151; $p = 0.285$
Neutrophil/lymphocyte ratio[a]	2.61 ± 1.40	1.65 ± 0.87	2.35 ± 1.35	F = 11.100; $p = 0.001$*
Monocyte/lymphocyte ratio[a]	0.37 ± 0.17	0.26 ± 0.09	0.34 ± 0.16	F = 4.668; $p = 0.033$*
Platelet/lymphocyte ratio[a]	119.43 ± 51.33	108.39 ± 50.49	116.44 ± 51.13	F = 1.320; $p = 0.254$

* Significantly different: $p < 0.05$.
[a] Analysis of covariance (ANCOVA), adjusted for potential confounding factors (age, sex, BMI, smoking and drug therapy).

The main limitation of the present study is that we have included only subjects with an acute exacerbation of the disease. Thus it is not possible to conclude if the observed alterations of the inflammatory ratios could be considered as a state marker of acute exacerbation or could be a trait marker of the disease. Future studies should explore variation in inflammatory ratios corresponding to different types of acute episodes of schizoaffective disorder.

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Declaration of Competing Interest

None.

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