ORIGINAL

Increased neutrophil-to-lymphocyte ratio is associated with symptom severity in patients with schizophrenia

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Abstract : Objective : We investigated the relationship between neutrophil-to-lymphocyte ratio (NLR) and symptom severity, clinical and socio-demographic variables in patients with schizophrenia. Methods : One hundred and ten patients with schizophrenia were compared with 110 healthy subjects matched by gender, age, body mass index, and smoking status. The NLR was determined after obtaining full blood counts by calculating the ratio of absolute neutrophil count and the absolute lymphocyte count. The Positive and Negative Syndrome Scale (PANSS) was used to determine the severity of symptoms in patients. Results : In patients with schizophrenia, neutrophil count and NLR were significantly higher ($p < 0.001$), while lymphocyte count ($p = 0.035$) was significantly lower compared to healthy controls. A significant positive correlation was found between NLR and the PANSS negative, general psychopathology, and total scores (all $p < 0.05$). The NLR was also positively correlated with PANSS negative, cognitive, excitement, and depression factor scores (all $p < 0.05$). Regression analysis revealed that NLR was a predictor for the clinical symptoms. No significant correlations were found between NLR and clinical and demographic characteristics in patients. Conclusion : Increased NLR is associated with the severity of symptoms in patients with schizophrenia, and may be a state marker in schizophrenia. J. Med. Invest. 72 : 408-418, August, 2025

Keywords **:** *neutrophils, lymphocytes, schizophrenia, immune system, psychopathology*

INTRODUCTION

Schizophrenia is a severe, chronic, and disabling mental disorder that affects approximately 1% of people worldwide (1). It is characterized by considerable heterogeneity in terms of etiopathogenesis, clinical presentation, course trajectory, treatment response, and long-term prognosis among patients. A mixture of diverse psychopathology, including positive, negative, cognitive, disorganization, psychomotor, and mood symptoms, is the hallmark of schizophrenia (2). The pathophysiology of schizophrenia is not fully understood, although research has suggested that a complex interaction between genetic, environmental, and neurobiological factors plays a role in the development of schizophrenia (3, 4). A growing body of evidence suggests that immune system dysfunction and inflammatory mechanisms are involved in the pathogenesis of schizophrenia (5, 6). It has been shown that schizophrenia is associated with several common variants within the major histocompatibility complex (MHC) (7), increased microglial activation (8), increased frequency of activated lymphocytes (9), abnormal levels of cytokines (10), increased prevalence of autoantibodies (11), and increased levels of C-reactive protein (CRP) (12). Recent evidence for efficacy of anti-inflammatory agents on symptom severity in schizophrenia has further supported the immune hypothesis in schizophrenia (13).

Among numerous inflammatory indicators, the neutrophil-to-lymphocyte ratio (NLR) has received increasing attention in recent years (14). NLR is inexpensive and easy-to-obtain marker of systemic inflammation (15). Since its introduction, elevated NLR has been associated with poor prognosis in a wide range of non-psychiatric disorders (16-18). Additionally, elevated NLR has been found in a number of psychiatric disorders, including schizophrenia (19). Steiner *et al*. (2020) reported a significantly elevated NLR in first-episode psychosis (FEP) and chronic schizophrenia patients compared to healthy controls (20). A meta-analysis conducted by Karageorgiou *et al*. (2019) reported elevated NLR, both in chronic disease and in first-episode patients with schizophrenia (15). Another meta-analysis reported that patients with non-affective psychosis had significantly increased NLR values compared to the healthy controls (21). Higher NLR was also found in adolescents with early-onset (EO) schizophrenia compared to age- and sex-matched healthy controls (22). Özdin *et al*. (2019) found increased NLR in the remission phase of schizophrenia patients compared to healthy subjects, but lower than during relapse (23).

Although the majority of the studies suggest that NLR is elevated in patients with schizophrenia, it remains unclear whether NLR is associated with symptom severity and other clinical variables, such as antipsychotic drugs (24). To date, the few studies investigating the relationship between NLR and symptom severity in patients with schizophrenia have yielded inconclusive results (25-28). Possible explanations for the inconsistent findings may include : 1) recruiting patients at different stages of schizophrenia ; 2) different type and dose of antipsychotic drugs ; 3) different treatment duration ; 4) small sample sizes ; and 5) heterogeneous patient populations (29, 30).

Antipsychotics appear to exert complex immunomodulatory effects by influencing the levels of anti- and pro-inflammatory cytokines (31), while animal studies indicate that antipsychotics such as clozapine may also reduce myeloid and T cell activation (32). However, the precise mechanism by which antipsychotics exert these effects remains unclear. Previous studies found no significant difference in NLR between medicated and drug-free patients with schizophrenia (23, 33). On the other hand, the

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aforementioned meta-analysis showed a modest increase in NLR associated with higher use of antipsychotics, which may imply that antipsychotic-medicated patients may exhibit a higher NLR irrespectively of schizophrenia diagnosis (15), while another study reported a higher NLR in drug-free patients compared to antipsychotic-medicated patients with schizophrenia (30). Further research is necessary to clarify the effect of antipsychotic on NLR in patients with schizophrenia.

Finally, several confounders such as gender, age, smoking, and body mass index (BMI) may modulate NLR, and many previous studies have not taken these potential confounding factors into account (34). The effect of these confounding factors on NLR in patients with schizophrenia thus requires further investigation.

The present study aimed to investigate whether NLR was associated with symptom severity evaluated by the PANSS in patients with schizophrenia after controlling for confounding variables. We also sought to determine if there was an association between NLR and clinical and socio-demographic characteristics and antipsychotic therapy in patients with schizophrenia.

PATIENTS AND METHODS

Subjects

One hundred and ten patients with schizophrenia (69 males, 41 females) were recruited from the University Clinical Hospital Mostar (UCH) (Mostar, Bosnia and Herzegovina), by using a cross-sectional design. We included both inpatients and outpatients. The recruitment criteria included : 1) age 18-65 years ; 2) ICD-10 diagnosis of schizophrenia which was confirmed by two psychiatrists following the Mini-International Neuropsychiatric Interview (M.I.N.I.) (35) ; 3) receiving stable doses of oral antipsychotics for > 1 month prior to study entry. Patients with a psychiatric diagnosis other than schizophrenia were excluded. The age of onset was defined as the age at which the first symptoms of schizophrenia appeared as reported by the patients or family members. The duration of antipsychotic treatment was defined as the total duration of treatment with any antipsychotic from the onset of illness. The mean antipsychotic dose was calculated using chlorpromazine equivalence.

One hundred and ten healthy subjects matched by gender, age, BMI, and smoking status to the patients with schizophrenia were recruited from the staff of UCH Mostar. The M.I.N.I. questionnaire was used to rule out psychiatric disorders in healthy subjects.

A complete medical history, socio-demographic data, physical examination, and laboratory tests were obtained from all subjects. The general exclusion criteria for all subjects included : 1) age < 18 or > 65 years ; 2) elevated CRP serum concentration (> 5 mg/L) ; 3) central nervous system diseases ; 4) obesity (BMI ≥ 30 kg/m^2) ; 5) the presence of an autoimmune, allergic, degenerative, rheumatic, acute or chronic inflammatory disease, metabolic disease, or malignancy ; 6) pregnancy or breastfeeding ; 7) substance abuse/dependence other than tobacco ; 8) treatment with antibiotics, antivirals, anti-inflammatory and immunosuppressive drugs.

The study was conducted in accordance with the Declaration of Helsinki and the principles of high-quality clinical practice, with the approval of the Ethics Committee of the School of Medicine, University of Mostar (No. 01.197.20/11). All subjects provided signed, informed consent to participate in the study.

Clinical assessment

The patient's psychopathology was assessed within 24 hours after blood sampling using the Positive and Negative Syndrome Scale (PANSS) (36). The assessment was performed by two psychiatrists who attended the PANSS training session before the study began. The PANSS is a 30-item scale that measures the severity of symptoms of schizophrenia across multiple domains. Each item is rated on a seven-point severity scale that represents increasing levels of psychopathology : 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe, and 7 = extreme. The original PANSS is composed of three subscales : positive scale (7 items), negative scale (7 items), and general psychopathology scale (16 items). Possible PANSS score ranges are 7-49 for the positive and negative scales, and 16-112 for the general psychopathology scale. The total PANSS score is obtained by summing the subscale scores. Some factor-analytic studies have suggested that there are five independent factors that can describe distinct symptom domains in schizophrenia, commonly labelled as „positive", „negative", „cognitive", „depression", and „excitement" (37, 38). Given that the PANSS five-factor structure represents a more valid distribution of the items compared to the original three-subscale classification, the consensus PANSS five-factor model proposed by Wallwork *et al*. (2012) was also used in this study (39).

Laboratory measurements

Peripheral blood samples were extracted from each subject between 8:00 and 9:00 a.m. after a 12-hr overnight fast. Complete blood count with differential was determined from full blood samples taken with K3-EDTA anticoagulant using the SYSMEX XN-3100 automated hematology system (Sysmex Corporation, Japan). The absolute numbers of white blood cells (WBC), neutrophils, and lymphocytes were measured. Reference values were established by the Department of Laboratory Diagnostics of the UCH Mostar. The NLR was calculated manually by dividing the neutrophil count by the lymphocyte count.

Anthropometric measurements

Weight was measured using a spring scale with subjects wearing light clothing and no shoes on. Height was measured using a telescopic measuring rod without the subjects wearing footwear. BMI was calculated as body weight in kilograms divided by the height in meters squared (kg/m^2). A BMI < 18.5 was taken as underweight, BMI of 18.5-24.9 indicated normal weight, and values of 25-29.9 implied overweight.

Statistical analyses

The statistical analyses were performed using SPSS statistics software, ver. 20.0 (IBM Corp., Armonk, NY). Data were analyzed using descriptive statistics methods. Categorical variables are presented as the frequency and percentage, and continuous variables are presented as arithmetic mean ± standard deviation (SD). The normality of the distributions was tested with the Shapiro–Wilk test. The Mann–Whitney U-test was used to analyze differences between pairs of groups, and the Kruskal–Wallis test was used for multiple-group comparisons. Spearman's correlation test was used to assess the correlations between variables. Multiple linear regressions were performed to examine the predictive value of socio-demographic and clinical variables for NLR and the PANSS scores in the patients with schizophrenia. The probability level $p < 0.05$ was considered significant.

RESULTS

Socio-demographic data of the study participants are presented in Table 1. Statistically significant differences were found between patient and control groups in terms of employment and marital status ($p < 0.001$). There were no differences between patients and controls with regard to age, gender, BMI, education

level, residence, or smoking status.

The mean age at onset, duration of illness, and duration of antipsychotic treatment in the patient group were 24.41 ± 7.19 years, 19.35 ± 12.01 years, and 13.84 ± 11.21 years, respectively. Nearly half of patients with schizophrenia were being treated with a combination of typical and atypical antipsychotics (46.4%). The mean PANSS total score was 77.01 ± 20.01, indicating a markedly ill status in the patients. Detailed clinical characteristics of patients with schizophrenia are summarized in Table 2.

Table 1. Socio-demographic data of the patients with schizophrenia and healthy controls

	Group				test	p
	Schizophrenia		Control			
Age ($\bar{X}$±SD)	43.84±12.01		43.45±12.01		t=0.241	0.810
Gender N (%)					χ^2=0	0.555*
Male	69	62.7	69	62.7		
Female	41	37.3	41	37.3		
BMI ($\bar{X}$±SD)	24.75±3.29		24.72±2.78		t=0.079	0.937
Education level N (%)					χ^2=0.916	0.822
Elementary school	9	8.2	7	6.4		
High school	82	74.5	79	71.8		
College	6	5.5	7	6.4		
University degree	13	11.8	17	15.5		
Employment N (%)					χ^2=136.841	<0.001
Unemployed	65	59.1	5	4.5		
Employed	10	9.1	94	85.5		
Student	2	1.8	4	3.6		
Retired persons	33	30.0	7	6.4		
Marital status N (%)					χ^2=70.425	<0.001
Married	14	12.7	74	67.3		
Unmarried	78	70.9	31	28.2		
Divorced	11	10.0	5	4.5		
Widow/er	7	6.4	0	0.0		
Residence N (%)					χ^2=1.639	0.128*
Urban area	68	61.8	77	70.0		
Countryside	42	38.2	33	30.0		
Smoking status N (%)					χ^2=0	0.556*
Smoker	70	63.6	70	63.6		
Non smoker	40	36.4	40	36.4		

* Fisher's exact test

Table 2. Clinical characteristics of the patients with schizophrenia

Variable	Mean ± SD or N (%)
Age of onset	24.41 ± 7.19
Duration of illness	19.35 ± 12.01
Duration of antipsychotic treatment	13.84 ± 11.21
Antipsychotic dose	641.36 ± 385.19
PANSS	
Total score	77.01 ± 20.01
Positive subscale	16.62 ± 5.92
Negative subscale	24.85 ± 8.94
General psychopathology subscale	35.55 ± 9.82
Antipsychotic type	
Typical	33 (30.0%)
Atypical	26 (23.6%)
Typical+Atypical	51 (46.4%)

Total WBC, neutrophil counts, and NLR were significantly higher (for WBC : $p = 0.040$; for neutrophils : $p < 0.001$; for NLR : $p < 0.001$), while lymphocyte counts ($p = 0.035$) were significantly lower in patients with schizophrenia compared with the healthy controls (Table 3). Compared to healthy controls, patients with schizophrenia also had significantly higher CRP levels ($Z = -2.094$, $p = 0.036$).

The NLR did not differ significantly according to the type of antipsychotics used ($p = 0.837$) (Table 4). The NLR did not differ significantly between the male and female patients ($Z = -0.522$, $p = 0.601$), or between the smokers and non-smokers ($Z = -0.155$, $p = 0.877$). There were no significant differences in NLR values among the underweight, normal weight, and overweight patients ($p = 0.632$).

As presented in Table 5, there was a significant positive correlation between NLR and CRP levels in patients with schizophrenia. There were no significant correlations between NLR and age, age of onset, duration of illness, duration of antipsychotic treatment, antipsychotic dose, or BMI. The associations between patients' demographic and clinical characteristics and NLR were initially examined using bivariate Spearman correlation analyses due to the non-normal distribution of NRL. Subsequently, a multiple regression analysis with 2000 bootstrap samples using bias-corrected and accelerated (BCa) method was conducted to assess the unique contributions of these characteristics to NLR. The bootstrap approach was chosen because it does not assume normality of residuals and is robus to violations of parametric assumptions. Three variables (age of onset,

Table 3. Comparison of blood count parameters between patients with schizophrenia and healthy controls

	Group				Z	p
	Schizophrenia		Control			
	C	Q	C	Q		
WBC	7.54	2.36	6.91	2.02	−2.050	0.040
Neutrophils	4.56	1.90	3.65	1.24	−4.002	<0.001
Lymphocytes	2.18	0.79	2.43	0.90	−2.111	0.035
NLR	2.32	1.22	1.63	0.68	−4.898	<0.001

Mann–Whitney U-test.

Table 4. Comparison of NLR values among individuals with schizophrenia being treated with a typical antipsychotic, an atypical antipsychotic, or a typical/atypical antipsychotic combination

	Antipsychotics						$\chi 2$	p
	Typical		Atypical		Typical+Atypical			
	C	Q	C	Q	C	Q		
NLR	2.24	1.03	2.44	1.33	2.31	1.30	0.356	0.837

Kruskal–Wallis test.

Table 5. Correlations between the demographic and clinical characteristics of patients with schizophrenia and their NLR values

	NLR	
	ρ	p
Age	0.061	0.529
Age of onset	0.077	0.423
Duration of illness	0.022	0.816
Duration of antipsychotic treatment	0.070	0.461
Antipsychotic dose	0.005	0.960
BMI	0.031	0.745
CRP	0.200	0.036

Spearman correlation coefficients.

duration of illness and duration of antipsychotic treatment) were excluded from the regression model due to high multicollinearity with age (VIF values exceeding 2.5). The model with four predictors (age, antipsychotic dose, BMI, CRP) was not statistically significant ($p > 0.05$). While the p-value associated with CRP was statistically significant, the corresponding bootstrap confidence interval included zero, suggesting that CRP does not contribute uniquely to NLR in full regression model. Although none of the predictors showed a significant unique contribution in the regression analysis, the bivariate (Spearman) correlations indicate that CRP is positively associated with NLR. These results suggest that there is a bivariate association, but that the contribution of this variable is not independent when other variables are controlled for (Table 6).

Examining the effect of potential influencing factors on NLR values in healthy subjects, we found no significant differences in relation to gender ($Z = -1.122$, $p = 0.262$) or smoking status ($Z = -1.075$, $p = 0.282$). Additionally, there were no significant correlations between NLR and age ($\rho = -0.124$, $p = 0.197$) or BMI ($\rho = -0.004$, $p = 0.964$) in healthy subjects.

We found significant positive correlations between NLR and negative, general psychopathology, and total PANSS scores. The NLR was not correlated with positive PANSS scores (Table 7). Additionally, we found that NLR was positively correlated with PANSS negative, cognitive, excitement, and depression factor scores (Table 8).

After controlling for demographic (i.e., age, gender, education level, smoking status, and BMI) and clinical confounding variables (i.e., antipsychotic dose and type), multiple regression analysis revealed that NLR was a predictor for PANSS negative ($\beta = 0.308$, $t = 3.701$, $p < 0.001$), general psychopathology ($\beta = 0.439$, $t = 5.263$, $p < 0.001$), and total scores ($\beta = 0.402$, $t = 4.734$, $p < 0.001$). In addition, NLR was also a significant factor for predicting PANSS negative factor ($\beta = 0.278$, $t = 3.171$, $p = 0.002$), cognitive factor ($\beta = 0.219$, $t = 2.629$, $p = 0.01$), and depression factor scores ($\beta = 0.195$, $t = 2.178$, $p = 0.032$).

Table 6. Bootstrap multiple regressions predicting NLR

Predictor	NLR			
	b	SE (boot)	95% BCa CI	p
Age	-0.002	0.010	[-0.024 ; 0.020]	0.835
Antipsychotic dose	-0.000	0.000	[-0.001 ; 0.001]	0.695
BMI	-0.046	0.040	[-0.130 ; 0.023]	0.227
CRP	0.164	0.117	[-0.025 ; 0.342]	0.031

b- unstandardized regression coefficient ; SE (boot) = bootstrap standard error (2000 samples) ; Model $R^2 = 0.045$; Adjusted $R^2 = 0.021$; $\chi^2(4, 105) = 7.440$; $p > 0.05$

Table 7. Correlations between PANSS scores and NLR

PANSS	NLR	
	ρ	p
Positive score	0.132	0.170
Negative score	0.295	0.002
General psychopathology score	0.336	<0.001
Total score	0.362	<0.001

Spearman correlation coefficients.

Table 8. Correlations between scores of the PANSS five-factor model and NLR

PANSS five-factor model	NLR	
	ρ	p
Positive factor	-0.006	0.951
Negative factor	0.266	0.005
Cognitive factor	0.195	0.041
Excitement	0.275	0.004
Depression	0.286	0.002

Spearman correlation coefficients.

DISCUSSION

The main findings of this study were : 1) compared with the healthy subjects, patients with schizophrenia had significantly higher neutrophil counts and NLR, while the lymphocyte count was significantly decreased ; 2) the correlation analysis revealed a positive correlations of NLR with the total PANSS, negative, and general psychopathology scores as well as with the PANSS negative, cognitive, excitement, and depression factor scores ; 3) there were no significant correlations between NLR and clinical and demographic variables in patients.

NLR reflects the balance between innate and adaptive immune response during various pathological states (40). In the present study, increased NLR was characterized by an increase in neutrophils and a decline in lymphocytes, indicating an imbalance in leukocyte distribution in patients with schizophrenia (41). In agreement with our present results, previous studies also reported increased neutrophil counts and NLR in patients with schizophrenia (27, 29, 33 ,42, 43). These findings suggest the existence of enhanced immune activation and inflammatory response in patients with schizophrenia (44) and may be related to pathogenic mechanisms in schizophrenia (45). On the other hand, low NLR was found to be protective against schizophrenia (27). The role of neuroinflammation in the pathophysiology of several psychiatric disorders, including schizophrenia, has gained substantial attention in recent years (44). Neuroinflammation is associated with white matter pathology and impaired connectivity, and thus, it may be involved in the manifestation of schizophrenia symptoms (46). The mechanisms through which neutrophils contribute to this process include the disruption of the blood—brain barrier (BBB) and the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS) (44). Enhanced lymphocyte apoptosis has been suggested as a mechanism for explaining lymphocyte depletion in inflammatory conditions (47). Additionally, elevated cortisol levels in chronic schizophrenic patients contribute to a decrease in the number of lymphocytes (48). A decline in total lymphocyte count is associated with the early neuroinflammation and suggests a deterioration of immune function. Therefore, NLR is a more sensitive biomarker and better reflects systemic inflammation than neutrophils or lymphocytes alone (49). Although it has been suggested that a disruption of the cytokine system is a potential mechanism underlying the increased NLR (29), the exact cause of elevated NLR in patients with schizophrenia is still unclear (42).

Our present analyses demonstrated that NLR correlates with the clinical state of patients with schizophrenia. Previous investigations reported on relationships between NLR and schizophrenia symptom severity, but with inconsistent findings. A positive correlation of NLR with the PANSS negative, total, and general score was observed in first-episode medication-naïve patients (29). In individuals with chronic schizophrenia a positive correlation was found between NLR and the PANSS total, positive and general score (25) as well as between NLR and the PANSS total score (26). Recently, significant positive correlations between NLR and all PANSS scores were also reported (50). In contrast, some studies reported no significant correlation between NLR and disease severity as assessed by the Brief Psychiatric Rating Scale (BPRS) in first-episode medication-naïve patients (28) as well as in patients with chronic schizophrenia, with and without antipsychotic treatment (33). A recent longitudinal study in first episode patients found no significant correlations between NLR and PANSS scores (51). Moreover, Yüksel *et al*. (2018) reported that NLR was not correlated with the PANSS and clinical global impression – severity scale (CGI-S) scores in individuals with schizophrenia in the acute exacerbation phase (27). A discrepant correlation of NLR with the severity of disease in patients with or without antipsychotic therapy was described in another study. Specifically, NLR was positively correlated with the BPRS total score and CGI-S score in drug-free patients and it was negatively correlated with the BPRS negative symptoms score in drug-therapy patients. Consequently, antipsychotic treatment has been suggested to influence the relationship between NLR and disease severity (30). Given the inconsistent findings of previous investigations regarding the relationship between NLR and symptom severity in schizophrenia, reaching definitive conclusions is limited.

Cognitive impairment is one of the core symptoms of schizophrenia and an important contributor to disability and poor clinical outcomes in these patients (52). Possible underlying mechanisms of cognitive impairment include microglial activation, monoaminergic imbalance, structural brain abnormalities, and the changes in the kynurenine pathway (53). Our present analyses revealed that NLR was positively correlated with the PANSS cognitive factor score, and NLR was also a significant factor for predicting PANSS cognitive factor score after we controlled for confounding variables. In agreement with our findings, a positive correlation of NLR with the PANSS cognitive factor score was reported in patients with first-episode adolescent-onset schizophrenia (45). Recently, increased NLR was found to be associated with poorer cognitive functioning in first-episode medication-naïve patients (54) and in patients with chronic schizophrenia (55). The NLR has also been reported to be negatively correlated with verbal working memory capacity in female patients, but not in male patients (56). These findings suggest that cognitive deficits in schizophrenia are related to immune system dysregulation.

We also observed significant correlations between negative symptoms and NLR. In agreement with our findings, previous studies also reported a positive correlation between NLR and PANSS negative score (57, 58). Negative symptoms are also closely related to disability and poor functional outcomes in schizophrenia, where they occur in up to 60% of patients (59). Furthermore, neurodegeneration has been suggested to be involved in the pathophysiology of schizophrenia for decades (60-62). Although most evidence indicates that schizophrenia is not a neurodegenerative disease, but a complex syndrome characterized by biological and clinical heterogeneity, it may involve some neurodegenerative processes (30). Considering that there is a substantial relationship between cognitive and negative symptoms of schizophrenia (63), our results support the possible role of neurodegenerative processes in these patients.

Previous research has not sufficiently investigated the association between NLR and depressive symptom severity in patients with schizophrenia. Conversely, this association was documented in patients with depression (64, 65). To the best of our knowledge, only a single study reported a positive correlation of NLR with the PANSS depressive factor score (57), which is consistent with our findings.

According to previous research, agitation and aggressive behavior in schizophrenia may also be linked to inflammation. Elevated CRP levels were reported in patients with agitation (66) and in patients with aggressive behavior (67). Plasma levels of tumor necrosis factor-alpha (TNF-α) were found to be positively correlated with the PANSS excitement score in first episode patients (68). Another study found that interferon-gamma (IFN-γ) and interleukin 10 (IL-10) were significantly associated with aggressive behavior in patients with schizophrenia and other psychotic disorders (69). To date, scarce studies have investigated the association of NLR with agitation or aggressive behavior in schizophrenia. The NLR was found to be higher in patients with schizophrenia and aggressive behavior compared

to nonaggressive patients ; therefore, it was proposed as a potential biomarker for assessing aggressive behavior in patients with schizophrenia (70). Bivariate analyses in our study demonstrated significant positive associations between NLR and the PANSS negative, cognitive, excitement, and depression factor scores. After controlling for demographic confounders using multiple regression analysis, these associations remained significant. Interestingly, when clinical variables (i.e. antipsychotic dose and type) were added to the model, the association between NLR and the excitement score lost significance. This suggests that excitement symptoms may be more influenced by confounding clinical variables, while negative, cognitive, and depressive symptoms show a more robust relationship with NLR. Taken together, our results confirm that immune dysregulation is associated with symptom severity and cognitive impairment in patients with schizophrenia. The association of increased NLR with these clinical manifestations of schizophrenia suggests its potential utility as a biomarker for this disorder (44).

Over the years, it has been shown that antipsychotics modulate cytokine networks and cause reduction of peripheral cytokine levels (71). Considering that pro-inflammatory cytokines (e.g., IL-1β, IFN-γ) regulate hematopoiesis primarily through a stimulatory effect on myelopoiesis (72), elevated levels of these cytokines in patients with schizophrenia may increase the number of peripheral blood neutrophils, but not the number of lymphocytes (73). Due to the effect of antipsychotics, the decreasing levels of pro-inflammatory cytokines could reduce the NLR in patients with schizophrenia (73), as shown in previous studies (30, 74). However, due to the design of our study, we were unable to confirm the lowering effect of antipsychotic on NLR values in schizophrenia. The results of our present analyses demonstrated that different types of antipsychotics had no effect on the NLR of the patients with schizophrenia. In agreement with our findings, Zheng *et al*. (2024) found no significant differences in NLR between patients taking typical antipsychotics and atypical antipsychotics (75) and another study detected no differences in NLR among patients taking typical antipsychotics, atypical antipsychotics, or both (23).

No correlation between NLR and the duration of illness was found in the present study, confirming findings from two previous studies (27, 33). In contrast, one study reported negative correlation between NLR and the duration of illness in antipsychotic-medicated patients, but no correlation was found in drug-free patients (30). Furthermore, a recent study reported a positive correlation between NLR and the duration of illness in medicated patients with schizophrenia in the acute exacerbation phase and remission period (75). Given the inconsistent results of these studies, it is difficult to draw a definitive conclusion about the association between the duration of illness and NLR in patients with schizophrenia. Previous studies also reported that NLR in patients with schizophrenia was significantly reduced after long-term antipsychotic treatment (25), while the total WBC count was reduced after short-term but increased after long-term antipsychotic treatment (76). A longer duration of illness often represents a longer time of antipsychotic treatment ; hence, the relationship between NLR and the duration of illness may also be affected by the length of the antipsychotic treatment (75). However, in the present study we found no significant correlation between NLR and the duration of antipsychotic treatment. Further investigations are warranted to determine the association between these clinical variables and NLR.

Earlier age of onset has been found to be linked with increased symptom severity in patients with schizophrenia (77). Significant positive correlations between NLR and PANSS general psychopathology and total scores were reported in patients with EO schizophrenia, suggesting that increased innate immune response may be involved in the development of EO schizophrenia (78). Our study showed no significant correlation between NLR and the age of onset, which is in line with the results of a recent study in first-episode medication-naïve patients with schizophrenia (29). However, our results were inconsistent with previous study, which reported a positive correlation between NLR and the age of onset in patients with chronic schizophrenia (30).

Multiple confounding factors, including gender, age, BMI, and smoking habits have been suggested to influence the NLR (79). In the present study, we matched patients and controls in terms of these variables in order to reduce confounding effects.

Gender did not significantly affect the NLR values of the patients with schizophrenia, which is consistent with the results of two meta-analyses (15, 21) and several individual studies (23, 25, 30, 33, 73). In contrast, two studies reported lower NLR in the male patients than in the female patients (56, 80) and higher NLR in the male than in the female patients was also reported (78, 81), suggesting gender-related differences in immune response.

The NLR has been proposed as a marker for immunosenescence, an age-related process that affects both myelopoiesis and lymphopoiesis (82). Likewise, NLR has been found to be positively correlated with age in healthy population (83) and higher NLR rates were found in older individuals from general population (79). However, no correlation between NLR and age was found in our control group. Furthermore, no correlation between NLR and age was found in the present schizophrenia group either, as in other studies (29, 80). In contrast, Zhou *et al*. (2020) reported negative correlation between the age and NLR in patients with schizophrenia (30) and a positive correlation between the age and NLR in medicated patients with schizophrenia in the acute exacerbation phase but not in the remission period was also found (75). Thus, the effect of age on NLR in patients with schizophrenia requires further investigation.

Although the association between NLR and BMI has been established in the general population (84), the present investigation found no significant correlation between these variables in either patients with schizophrenia, confirming previous findings (27, 29), nor in the control group. In contrast, Zheng *et al*. (2024) reported negative correlation between NLR and BMI in medicated patients with schizophrenia in the remission period. However, no correlations were found in patients with acutely exacerbated schizophrenia, regardless of antipsychotic use (75).

Smoking has a complex impact on a wide range of immunological functions, affecting both innate and adaptive immunity. It increases inflammatory responses by a variety of mechanisms, including an elevated WBC count and increased numbers of circulating neutrophils and lymphocytes (85). Smoking tobacco has been found to be associated with elevated counts of neutrophils and elevated NLR in healthy population (86, 87) and with NLR in the general population (84) ; however no such association was observed in our study. The smoking status of individuals with schizophrenia has not been taken into account or has not been well defined in most of the previous research related to NLR. Steiner *et al*. (2020) reported that smoking significantly affected neutrophil and monocyte counts, without providing data on the relationship between smoking and NLR (20). In agreement with our results, Bioque *et al*. (2022) found that smoking status did not affect NLR in patients with a first episode of psychosis (51), while the meta-analysis by Karageorgiou *et al*. (2019) revealed that NLR was not associated with smoking in patients with schizophrenia (15). However, we did not collect detailed information about the subjects' smoking data, such as frequency or amount of use, and a history of smoking in the present study. Given that the degree of smoking is related to NLR (86, 88), this can be

considered as a limitation of our study.

Finally, there are several limitations of the present study. First, due to the cross-sectional design, we could not detect the causal relationship between the variables. Second, other biomarkers of inflammation, such as cytokines, were not measured. This is a possible cause of bias. Third, we included patients at different stages of schizophrenia, which could have been a confounding factor (75). Fourth, the patients were taking different antipsychotics and some of them were also taking other psychotropic medications, which could have affected the NLR. Fifth, we did not examine the influence of certain factors that can affect NLR such as diet and physical activity (89), sleep quality (90), and menstrual cycle (91). Sixth, we did not investigate the impact of stress, particularly cortisol level, which is known to increase neutrophil counts while simultaneously decreasing lymphocyte counts (92).

CONCLUSION

In conclusion, this study shows that NLR is increased in patients with schizophrenia compared to healthy controls. Moreover, NLR is positively associated with the severity of symptoms and may be a state marker in schizophrenia. Taken together, these findings support the involvement of inflammatory processes and immune system imbalance in the pathophysiology of schizophrenia. However, longitudinal studies involving a larger sample of drug-naïve patients are necessary to confirm the present findings.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Marko Pavlović : conceptualization, methodology, investigation, writing-original draft, writing-review & editing ; Pejana Rastović : formal analysis, investigation, writing-review & editing ; Martina Krešić Ćorić : investigation, project administration, visualization ; Sanja Burić : methodology, visualization, writing-review & editing ; Tomislav Rajić : project administration, investigation, visualization ; Marko Martinac : conceptualization, formal analysis, writing-review & editing.

All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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