Journal homepage: **https://medicinskiglasnik.ba**

Med Glas (Zenica) 2026;23(2)
https://doi.org/10.17392/medglas-2197-23-2

Med Glas (Zenica)

ORIGINAL ARTICLE

Neutrophil-to-lymphocyte ratio and metabolic syndrome in patients with schizophrenia spectrum disorders

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ABSTRACT

Aim To investigate the differences in neutrophil-to-lymphocyte ratio (NLR) between patients with schizophrenia spectrum disorders (SSD) and healthy controls, and their association with metabolic syndrome (MS) in SSD patients.

Methods A cross-sectional study was conducted involving 70 SSD patients and 55 healthy controls. NLR was calculated using absolute neutrophil and lymphocyte counts (WBC) after obtaining complete blood counts. MS was diagnosed using ATP III criteria, and SSD patients were divided into two subgroups with and without MS.

Results Patients with SSD had significantly higher total WBC (p = 0.001), as well as neutrophil counts and NLR (both p 0.05).

Conclusion The findings suggest that inflammation, as indicated by elevated NLR, is linked to SSD independent of MS.

Keywords: biomarkers, inflammation, leukocytes, psychotic disorders, waist circumference

INTRODUCTION

Schizophrenia spectrum disorders (SSD) encompass a group of phenotypically heterogeneous psychotic disorders that may be transient or chronic and present with a wide range of clinical symptoms, ranging from mild psychotic features to severe schizophrenia, which is considered the core disorder within this spectrum (1–3). Schizophrenia is a severe mental disorder characterized by diverse psychopathology, primarily manifested through positive, negative, and cognitive symptoms (4). It has long been recognized that patients with schizophrenia experience increased mortality compared to the general population, largely due to cardiovascular diseases associated with a higher prevalence of metabolic syndrome (MS) in this population (5). MS is a cluster of metabolic abnormalities, including visceral obesity, hyperglycaemia, dyslipidaemia, and hypertension. It is multifactorial in origin, with chronic low-grade inflammation playing a central role in its pathogenesis (6).

Although extensively investigated for decades, the pathophysiology of schizophrenia remains incompletely understood (7). Among the various proposed mechanisms, abnormalities in the immune system and inflammatory processes are increasingly recognized as important contributors to the pathophysiology of schizophrenia and other psychotic disorders (8,9). Given the significant role of inflammation in both schizophrenia and MS, a shared inflammatory process may underlie metabolic dysfunction and neurobiological alterations in schizophrenia (10).

The neutrophil-to-lymphocyte ratio (NLR), calculated from routine complete blood count (CBC) parameters, is a widely accessible and cost-effective marker of systemic inflammation, as first described by Zahorec in critically ill patients (11). Elevated NLR has been linked to both the presence and severity of MS in general population studies and has been identified as a predictor of increased cardiovascular and all-cause mortality, highlighting its potential as a clinically relevant marker of systemic inflammation (12,13). Additionally, a growing body of evidence indicates that patients with schizophrenia exhibit elevated NLR compared to healthy controls, reflecting an increased inflammatory state; furthermore, elevated NLR has been associated with increased symptom severity in patients with schizophrenia (14,15). Although NLR is increasingly recognized as a common underlying factor in both schizophrenia and MS, only one study has specifically investigated the link between NLR and MS in schizophrenia, suggesting that NLR elevation may occur independently of metabolic factors (16). This points to a significant gap in the literature, as the exact role of NLR in linking systemic inflammation to both SSD and MS is not clear yet.

Therefore, this study aimed to determine whether NLR differs between patients with SSD with and without MS, as well as healthy controls, and to assess its relationship with individual components of MS.

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Submitted: 10 October 2025; **Revised:** 21 May 2026; **Accepted:** 25 May 2026

PATIENTS AND METHODS

Patients/participants and study design

A total of 125 participants were included in this cross-sectional study. The study group consisted of 70 patients/participants diagnosed with SSD, recruited from the University Clinical Hospital (UCH) Mostar, while the control group included 55 physically and mentally healthy employees from the same institution. The study was performed between January and May 2025. The SSD group included patients with diagnoses of schizophrenia, delusional disorder, acute psychotic disorder, schizoaffective disorder, and unspecified psychosis. All psychiatric diagnoses were established based on the International Classification of Diseases, 10th Revision (ICD-10) criteria (17), following assessment with the Mini-International Neuropsychiatric Interview (M.I.N.I.) (18). Subjects in both groups were within the age range of 18 to 65 years, with groups matched according to age and sex. Subjects in the SSD group did not have any comorbid psychiatric disorders but could have diagnoses related to MS. The diagnosis of MS was established based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (19). Control subjects had no history of psychiatric disorders, MS, or any of its components. Additionally, all control subjects were screened using the M.I.N.I. to ensure the absence of any current or past psychiatric disorders. The general exclusion criteria for both groups were as follows: elevated C-reactive protein (CRP) levels (> 5 mg/L); autoimmune diseases, malignancies, degenerative diseases, rheumatic diseases, or acute and chronic infectious diseases; pregnancy or lactation; substance abuse/dependence other than tobacco; treatment with immunomodulatory medications, including nonsteroidal anti-inflammatory drugs.

All participants provided written informed consent after receiving a detailed explanation of the study and prior to their inclusion. 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. 01-1-707/25).

Methods

Socio-demographic data were collected using a structured questionnaire designed specifically for this study. A complete medical history, physical examination, and laboratory tests were obtained from all subjects. Anthropometric parameters included height, weight, and waist circumference. Height and weight were measured using a multifunctional scale (SECA 223). Waist circumference was measured with a tailor's measuring tape at the level of the umbilicus, with participants standing upright, on bare skin, and during expiration. All measurements were taken three times, and the mean value was calculated for analysis. Body mass index (BMI) was calculated based on height and weight data, by dividing body mass (in kilograms) by the square of height (in meters). Arterial blood pressure was measured using a mercury sphygmomanometer.

Blood samples were collected from the cubital vein of all study participants into vacuum tubes, both with and without anticoagulants, at 8:30 a.m. following an overnight fast. The serum biochemical parameters measured included glucose, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and CRP. Analyses were conducted using enzymatic methods on an automated Olympus AU 600 analyser (Olympus Corporation, Tokyo, Japan).

The haematological parameters measured included total white blood cells (WBC), neutrophils, and lymphocytes. The differential blood counts were performed on whole blood samples collected in K3-EDTA anticoagulant tubes using an automated haematology analyser SYSMEX XN-3100 (Sysmex Corporation, Japan). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The reference values applied were those provided by the Department of Laboratory Diagnostics at UCH Mostar.

Statistical analysis

Categorical data are presented as absolute and relative frequencies, while numerical data are expressed as mean ± standard deviation or median with interquartile range. Statistical comparisons for categorical variables were conducted using the chi-square test or Fisher's exact test. Normality of numerical data was assessed with the Kolmogorov-Smirnov test, and appropriate parametric or non-parametric methods were selected accordingly. Comparisons between two groups were performed using Student's t-test or the Mann-Whitney U test, whereas analyses involving three or more groups were conducted with one-way ANOVA (with Bonferroni post hoc correction) or the Kruskal-Wallis test (with Dunn's post hoc). Correlations between numerical data were evaluated using Pearson's or Spearman's correlation coefficients. Statistical significance was set at $p < 0.05$.

RESULTS

Statistically significant differences between patients and controls were observed with respect to education level, employment status, marital status, and smoking status. No significant differences were observed between the patient and control groups with respect to age, gender, or BMI (Table 1).

Within the SSD group, schizophrenia was the predominant diagnosis, accounting for 47 cases (67.1%). This was followed by acute psychotic disorder, in 12 cases (17.1%), schizoaffective disorder in 8 cases (11.4%), unspecified psychosis in 2 cases (2.9%), and delusional disorder in 1 case (1.4%). A total of 31 patients (44.3%) were diagnosed with MS, while 39 patients (55.7%) did not meet the diagnostic criteria of MS (Table 2).

Total WBC, neutrophil counts, and NLR were significantly higher in patients with SSD compared to healthy controls. No significant differences were observed in lymphocyte count or CRP levels between the groups (Table 3).

NLR did not differ significantly between male and female patients with SSD ($Z = 0.870$, $p = 0.384$) nor between smokers and non-smokers ($p = 0.633$) (Table 4, Table 5).

NLR values were significantly higher in patients with schizophrenia and acute psychotic disorder compared to controls. No significant differences in NLR values were found among the diagnostic subgroups within the SSD group. Due to insufficient numbers, patients with unspecified psychosis and delusional disorder were excluded from the statistical analysis and are not presented in the table (Table 6).

NLR values were significantly higher in patients with SSD, both with and without MS, compared to healthy controls. No significant difference in NLR was observed between the SSD subgroups (Table 6). There were no significant correlations between NLR and BMI, or MS components in patients with SSD (Table 7, Table 8).

Table 1. Socio-demographic data of patients with schizophrenia spectrum disorders (SSD) and healthy controls

Variable	Group		p
	SSD	Control	
Age (mean ± SD)	44.61±12.99	42.80±12.69	0.424*
BMI (mean ± SD)	24.9±3.92	24.42±2.57	0.521*
No(%) of patients			
Gender			0.776
Male	45 (64.3%)	34 (61.8%)	
Female	25 (35.7%)	21 (38.2%)	
Education level			0.001†
Elementary school	10 (14.3%)	0 (0.0%)	
High school	52 (74.2%)	37 (67.2%)	
College	2 (2.9%)	4 (7.3%)	
University degree	6 (8.6%)	14 (25.5%)	
Employment			<0.001†
Unemployed	38 (54.3%)	3 (5.5%)	
Employed	11 (15.7%)	42 (76.3%)	
Student	2 (2.9%)	3 (5.5%)	
Retired persons	19 (27.1%)	7 (12.7%)	
Marital status			<0.001†
Married	14 (20%)	33 60.0	
Unmarried	47 (67.1%)	16 29.1	
Divorced	7 (10.0%)	2 3.6	
Widower	2 (2.9%)	4 7.3	
Smoking status			0.035
Smoker	45 (64.3%)	25 (45.5%)	
Non-smoker	25 (35.7%)	30 (54.5%)	

* Mann–Whitney U test; † Fisher's exact test. BMI, body mass index.

Table 2. Prevalence of metabolic syndrome (MS)

	n	%	χ^2	p
MS			0,914	0,339
Yes	31	44,3		
No	39	55,7		

Metabolic syndrome (MS).

Table 3. Comparison of blood count parameters and C-reactive protein (CRP) levels between patients with schizophrenia spectrum disorders (SSD) and healthy controls

Variable	Group		p*
	SSD	Controls	
WBC ($\times 10^9$/L)	7.58 [2.46]	6.3 [2.0]	**0.001**
Neutrophils ($\times 10^9$/L)	4.25 [1.87]	3.3 [1.30]	<**0.001**
Lymphocytes ($\times 10^9$/L)	2.11 [0.85]	2.22 [1.21]	0.158
NLR (%)	2.25 [1.36]	1.31 [0.94]	<**0.001**
CRP (mg/L)	2.5 [2.8]	1.4 [2.0]	0.099

* Mann–Whitney.
WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

DISCUSSION

The current study identified two main findings. First, patients with SSD had significantly elevated NLR values compared to healthy controls. Second, the presence of MS did not affect NLR values in SSD patients.

NLR is increasingly recognized as a reliable immunological marker of inflammation and an independent prognostic factor across a broad spectrum of somatic diseases (20). Growing evidence also suggests a potential role for NLR in psychiatric disorders, in which systemic inflammation is increasingly implicated in the pathophysiology of various conditions such as depression, schizophrenia, and bipolar disorder (21). Although most research on NLR in psychotic disorders has focused on schizophrenia (22), elevated NLR has also been documented in related spectrum and other psychiatric disorders (14,23). Consistent with our results, several previous studies have reported increased NLR in patients with SSD (14,16,24–26). Similarly, Üstün et al. (2025) found no significant differences in NLR across various psychosis spectrum disorders, suggesting that peripheral inflammation may be a common biological mechanism across these conditions (27). In the present study, the observed increase in NLR was attributed to a higher neutrophil count, while lymphocyte counts remained unchanged, suggesting an enhanced inflammatory response characterised by up-regulated neutrophil-driven processes. This finding may reflect dysregulated innate immune activation involving neutrophils, contributing to the pathogenesis of schizophrenia (15). Elevated neutrophil counts and increased NLR in schizophrenia are indicative of systemic inflammation and a shift towards a pro-inflammatory state (28). Supporting this, a meta-analysis of prior studies demonstrated immune dysregulation in individuals with schizophrenia, evidenced by elevated inflammatory markers such as interferon-gamma (IFN-γ), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), highlighting the role

Table 4. Differences in neutrophil-to-lymphocyte ratio (NLR) values among genders in patients with schizophrenia spectrum disorder (SSD)

	Gender		Mann–Whitney
	Male	Female	p
NLR	2,44 [1,65]	1,94 [1,35]	0,384

NLR, neutrophil-to-lymphocyte ratio.
Data are presented as median [interquartile range].

Table 5. Differences in neutrophil-to-lymphocyte ratio (NLR) values according to smoking status in patients with schizophrenia spectrum disorder (SSD)

	Smoking status		Mann–Whitney
	Yes	No	p
NLR	2,38 [1,53]	2,16 [1,28]	0,633

Neutrophil-to-lymphocyte ratio (NLR).
Data are presented as median [interquartile range].

Table 6. Comparison of neutrophil-to-lymphocyte ratios (NLR) values among diagnostic subgroups of patients with metabolic syndrome (MS)

	Diagnosis				Kruskal-Wallis	
	Schizophrenia	Acute psychotic disorder	Schizoaffective disorder	Healthy controls	H(3)	p
NLR	2,16 [1,63–2,94]	2,68 [1,59–3,36]	1,74 [1,48–2,37]	1,31 [1,03–1,97]	19,912	<0,001

Neutrophil-to-lymphocyte ratio (NLR)
Data are presented as median [interquartile range]

Table 7. Comparison of neutrophil-to-lymphocyte ratio (NLR) values among patients with schizophrenia spectrum disorders (SSD) with and without metabolic syndrome (MS) and healthy controls

	SSD+MS	SSD–MS	Healthy controls	Kruskal-Wallis	
				H(2)	p
NLR	2,18 [1,05]	2,32 [1,81]	1,31 [0,94]	22,914	<0,001

Data are presented as median [interquartile range].

Table 8. Correlation of body mass index (BMI) and metabolic syndrome (MS) components with neutrophil-to-lymphocyte ratios (NLR) in patients with schizophrenia spectrum disorders (SSD)

Variable	NLR	
	Correlation coefficient (ρ/r)	p
BMI	-0.179^{*}	0.138
Number of MS components	$0.064^{\dagger}$	0.596
Systolic blood pressure	$0.121^{\dagger}$	0.320
Diastolic blood pressure	$0.116^{\dagger}$	0.337
Fasting glucose	$0.094^{\dagger}$	0.441
Triglycerides	$-0.162^{\dagger}$	0.182
HDL-C	$-0.101^{\dagger}$	0.405
Waist circumference	-0.118^{*}	0.330

* Spearman correlation coefficients; † Pearson correlation coefficients.
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

of inflammation in the disorder (29). Following this systemic immune activation, neuroinflammation has emerged as a key and complex contributor to the pathogenesis of schizophrenia, characterized by microglial activation, immune gene dysregulation, altered kynurenine pathway metabolites, and peripheral cell infiltration, all of which collectively contribute to disease development (30). Neutrophils play an important role in this process by releasing pro-inflammatory and cytotoxic mediators that promote endothelial injury, increase vascular permeability and form neutrophil extracellular traps (NETs), thereby amplifying inflammation and potentially causing neuronal injury (31). However, although elevated neutrophil counts have been consistently reported in patients with schizophrenia, possibly reflecting inflammation involving cytokines such as interleukin 1 beta (IL-1β), as well as effects of antipsychotic medication, stress, disease stage, and symptom severity, the precise cause of neutrophil elevation remains unknown (32).

Our analysis showed that NLR was not associated with metabolic abnormalities in patients with SSD. Previous studies have not adequately investigated this association in this patient population. Consistent with our findings, Yüksel et al. (2018) observed that NLR levels in patients with schizophrenia were not associated with MS or its individual components (16). While research on the relationship between NLR and metabolic abnormalities in patients with SSD remains limited, substantial evidence suggests that total WBC count is positively associated with metabolic abnormalities in this population (33). In line with this, Karakaş Uğurlu et al. (2016) found that total WBC count was significantly higher in patients with schizophrenia who had MS, compared to those without (34). Additionally, total WBC count has been shown to predict MS in both the general population (35,36) and patients with schizophrenia (37). Babio et al. (2013) also demonstrated that WBC count is significantly associated with the incidence of MS and several of its individual components (38). Furthermore, NLR has been reported to increase with the severity of MS in affected patients, exhibiting a strong positive correlation with the number of MS components (39). However, our study found no such correlation between NLR and individual components of MS or their number. Although research on NLR and metabolic abnormalities in SSD is limited, studies in non-psychiatric populations have identified NLR as a predictive biomarker of MS (40). Taken together, while NLR is associated with MS in the general population, it does not appear to be associated with MS in patients with SSD. Total WBC, however, shows a clear link to metabolic abnormalities in both populations.

The limitations of the study should be acknowledged. First, because of the cross-sectional design, causal inferences between variables could not be established. Second, the relatively small sample size may have limited the detection of actual relationships between NLR and MS. Third, we did not assess other markers of inflammation, such as cytokines. Fourth, we did not account for the effects of antipsychotic treatment, disease stage, or symptom severity on NLR. Fifth, the impact of stress, diet, and physical exercise on NLR was not investigated.

In conclusion, our study demonstrated that patients with SSD have elevated NLR compared to healthy controls, regardless of the presence of MS, suggesting that systemic inflammation is associated with SSD independently of metabolic status.

FUNDING

No specific funding was received for this study.

CONFLICTS OF INTEREST

None to declare.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Ethical Committee of the Faculty of Medicine, University in Mostar (approval number: 01-I-707/25).

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request and with permission of the institution.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: S.H., M.P.; **Formal analysis:** M.K.Ć.; **Investigation:** S.H., M.K.Ć., I.S.; **Methodology:** S.H., M.P.; **Project administration:** M.K.Ć., I.S.; **Visualization:** I.S.; **Writing – original draft:** S.H., M.P.; **Writing – review & editing:** S.H., M.P. All authors have read and agreed to the published version of the manuscript.

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