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Original article

Neutrophil-to-lymphocyte, monocyte-to-lymphocyte, and platelet-to-lymphocyte ratios in acute hospitalized patients with schizophrenia

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Abstract

Background: Schizophrenia has increasingly been linked to inflammation. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have emerged as potential indicators of systemic inflammation.
Objectives: The objectives of this study were to compare the NLR, MLR, and PLR between patients with schizophrenia and healthy controls and to investigate the factors associated with NLR.
Methods: This retrospective study included 102 sex- and age-matched patients hospitalized with schizophrenia and 102 healthy control subjects. The NLR, MLR, and PLR were calculated from the complete blood count results and compared between the groups. Sociodemographic data and clinical characteristics were analyzed using multiple linear regression to identify factors associated with the NLR in patients with schizophrenia.
Results: The NLR and MLR of patients with acute schizophrenia were found to be significantly higher compared to those of the control group (3.0 ± 2.0 *vs.* 1.8 ± 0.8, $P < 0.01$; 0.3 ± 0.1 *vs.* 0.2 ± 0.1, $P < 0.01$, respectively). However, the PLR was not significantly different between the two groups (152.1 ± 70.8 *vs.* 143.1 ± 49.1, $P = 0.29$). First-episode illness was the only identified factor associated with a higher NLR in patients with schizophrenia ($P < 0.05$).
Conclusion: The higher NLR and MLR values found in hospitalized patients with schizophrenia support the inflammatory hypothesis of schizophrenia.

Keywords: Neuroinflammation, neutrophil-to-lymphocyte ratio, NLR, schizophrenia.

Schizophrenia is a chronic mental disorder that presents with the distortion of thought, perception, and behavior. The pathophysiology of this disorder is unclear; however, it is believed to be multifactorial, including genetic and environmental factors. Moreover, genetic areas that code for immune-related functions are hypothesized to be related to this disorder.[1] Studies focusing on the immune system in schizophrenia, including the increase in c-reactive protein (CRP) levels in patients with greater disease severity,[2] and the increase in serum interleukin-6 levels in schizophrenia and its decrease after treatment with antipsychotic medication.[3] Furthermore, maternal infection has been identified as a risk factor for the development of schizophrenia[4] as well as an increase in oxidative stress products.[5]

Inflammation occurs as a response to endogenous and exogenous factors. This physiological response includes an increase in the number of neutrophils with a left shift and a decrease in the number of lymphocytes; therefore, the ratio of these two leukocytes is used as an indicator of inflammation.[6] The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are also used to predict inflammation. In addition, the CRP level as an indicator of inflammation has been found to be positively correlated with NLR.[7]

As the NLR, MLR, and PLR are easily measured and inexpensive, they have recently been used as

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indicators of inflammation, and their utility has been investigated in numerous diseases. The NLR is used as a marker for ongoing cancer-related inflammation. [8] Evidence suggests that the pretreatment NLR may serve as a valuable prognostic marker in various cancers, including renal cell carcinoma, hepatocellular carcinoma, melanoma, and non-small cell lung cancer. [9] Furthermore, serious critical conditions, including acute pancreatitis, multiple traumas, hemorrhagic shock, and septic shock, have been linked to a high NLR. [6] In addition, the PLR was found to predict outcomes in advanced cancer, [10] while a high MLR has been used to predict the prognosis of coronary artery disease after percutaneous coronary intervention. [11]

In mental disorders, the NLR was found to be significantly higher in patients with bipolar and major depressive disorders than in the control group. [12] Furthermore, patients with attention-deficit/hyperactivity disorder had considerably higher NLR and PLR compared to those of the control group. [13]

In schizophrenia, an increased NLR—as well as MLR and PLR—is also used as a systemic immune response marker. [14] NLR values were found to be higher in patients with first-episode psychosis [15] and patients with acute schizophrenia. [16] Moreover, the NLR and MLR were found to be higher in hospitalized patients with schizophrenia than in those with bipolar disorders. [17] However, one study found that NLR had no significant correlation with the number of hospitalizations, duration of disease, and disease severity. [15]

From the literature review, there is an under-representation of studies evaluating the NLR in patients with schizophrenia in Thailand and within Asian populations. To bridge this gap, our study addressed this limitation by establishing a sample composed of individuals of Thai ethnicity. Moreover, the current body of literature has presented conflicting findings on three specific biomarkers. To enhance clarity, the current study aimed to compare the NLR, MLR, and PLR in acute hospitalized patients with schizophrenia with those of a healthy control group and investigate the factors associated with NLR. Specifically, this study considers the hypothesis that patients with schizophrenia would exhibit higher NLR, MLR, and PLR values compared to those of the control group.

Materials and methods

Participants

This retrospective cross-sectional observational study collected data from Thai patients with schizophrenia who were admitted to the hospital because of a psychotic episode and a control group at the King Chulalongkorn Memorial Hospital, a tertiary hospital in Bangkok, Thailand, between 2015 and 2020. The participants were between the ages of 18 and 70 years. The exclusion criteria included psychiatric comorbidities; medical illnesses that are related to inflammation or affect white blood cell or platelet levels (such as diabetes mellitus, chronic obstructive pulmonary disease, rheumatoid arthritis, dementia, leukemia, lymphoma, multiple myeloma, and immune thrombocytopenic purpura); taking drugs (such as non-steroidal anti-inflammatory drugs, steroids, and immunosuppressive agents); having a fever (body temperature >37.9°C) during the 24-h period before and after admission; suspected infection (such as urinary tract infection and respiratory tract infection); being pregnant; being treated with electroconvulsive therapy within 1 week before admission; recent trauma or surgery; recent blood donors or recipients; recently received vaccinations; and having an absolute neutrophil count <1,500 cell/mm^3. A total of 102 patients (49 males and 53 females) diagnosed with schizophrenia were included in this study.

The control group included 102 routine health check-up participants who were age- and sex-matched without underlying medical or psychiatric conditions or a history of substance use. Pregnant women were excluded from the study.

Variables and measurements

Demographic data were collected from the admission records, including sex, age, education level, marital status, medical illness, smoking and alcohol history, and history of substance use. Furthermore, clinical characteristics were collected, including age of onset, duration of illness, first-episode psychosis (defined as the first occurrence of a psychotic episode), incidence of self-harm, psychiatric drug history, and previous psychiatric hospitalization. The complete blood count (CBC) results were collected from the routine laboratory tests performed within 24 h of psychiatric admission. Controls underwent standard laboratory screening, including CBC, during their routine health check-ups. The NLR, MLR, and PLR were calculated from the CBC results.

This study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand (IRB No. 490/64).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 22.0 program. Demographic data, clinical characteristics, and CBC results were presented as the count and percentage, mean ± standard deviation (SD), or median (interquartile range, IQR), as appropriate. The unpaired *t*-test and Mann-Whitney U test were used to determine the difference in the CBC data between the groups. Factors associated with the NLR in the schizophrenia group were assessed using multiple linear regression analysis. Statistical significance was set at $P < 0.05$.

Results

Of the 204 individuals included in the study, 102 (50.0%) had schizophrenia and 102 (50.0%) had healthy controls. Age and gender did not differ significantly between the patients and control groups. Twenty-nine patients had first-episode psychosis, and the other findings are shown in **Table 1**.

The NLR and MLR and the number of white blood cells, including neutrophils and monocytes, were significantly higher in patients with schizophrenia than in the control group ($P < 0.05$). Moreover, the PLR, platelet count, and lymphocyte count did not differ significantly between the two groups **(Table 2).**

Although there was a significant association between the NLR and patients with first-episode psychosis ($\beta = 0.423$, $P = 0.024$), no significant association was found between the NLR and age, sex, medical illness, duration of illness, number of previous episodes, self-harm, and antipsychotic use **(Table 3).**

Table 1. Demographic and clinical characteristics of patients and control group.

	Patients (n = 102) n (%) or mean ± SD	Controls (n = 102) n (%) or mean ± SD
Demographic data		
Male	53 (51.9)	53 (51.9)
Age		
18 to 40 years old	61 (59.8)	61 (59.8)
41 to 60 years old	29 (28.4)	29 (28.4)
61 to 70 years old	12 (11.8)	12 (11.8)
Mean ± SD (years)	39.1 ± 13.9	40.9 ± 12.3
Married	26 (25.5)	
Smoking	20 (19.6)	
Alcohol	14 (13.7)	
Other substances	8 (7.8)	
Year of education > 12 years	44 (43.1)	
Clinical characteristics		
Age of onset	27.0 ± 11.5	
First episode	29 (28.4)	
Duration of illness (years), median (IQR)	4 (1, 12)	
Number of previous psychiatric hospitalizations, median (IQR)	1 (0, 3)	
Previous treatment		
Typical antipsychotic	24 (23.5)	
Atypical antipsychotic	52 (50.9)	
Free of antipsychotic	26 (25.5)	

IQR, interquartile range; SD, standard deviation.

Table 2. Complete blood count parameters between groups presented as mean ± SD.

Outcome	Schizophrenia (n = 102)	Controls (n = 102)	*P* - value
NLR	3.0 ± 2.0	1.8 ± 0.8	< 0.001*†
MLR	0.3 ± 0.1	0.2 ± 0.1	< 0.001*†
PLR	152.1 ± 70.8	143.1 ± 49.1	0.987†
WBC	7.8 ± 2.3	6.0 ± 1.4	< 0.001*
Neutrophil	5.1 ± 2.1	3.4 ± 1.1	< 0.001*
Lymphocyte	2.0 ± 0.8	2.0 ± 0.6	0.885
Monocyte	0.5 ± 0.1	0.4 ± 0.1	< 0.001*
Platelet	273.8 ± 75.7	273.3 ± 57.4	0.954

MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; WBC, white blood cell.
Neutrophils, lymphocytes, monocytes, and platelets are shown as 1000 cells/μL
*Significantly different $P < 0.05$
†Mann-Whitney U test.

Table 3. Multiple linear regression analysis of log NLR† with other variables in the schizophrenia group

	Unstandardized β	Coefficients standard error	*P* - value
Sex	0.165	0.121	0.175
Age	0.004	0.006	0.443
Medical illness	0.075	0.146	0.607
Duration of illness	0.008	0.007	0.278
First episode	0.423	0.184	0.024*
Number of previous episodes	0.007	0.021	0.744
Self-harm	0.154	0.194	0.428
Antipsychotic use	0.063	0.172	0.717

NLR, neutrophil-to-lymphocyte ratio
*Significantly different $P < 0.05$
†The log NLR is the natural logarithm of the NLR.

Discussion

This study compared the NLR, MLR, and PLR between patients with schizophrenia and healthy controls. The age and sex differences between the two groups were not statistically significant. We acknowledge that age related inflammation can increase the baseline NLR, MLR, and PLR values in otherwise healthy older adults, which may potentially lead to false positives. To address this, we matched the cases and controls and adjusted for age in the regression model. Our results showed that the NLR, MLR, and white blood cell, neutrophil, and monocyte counts in the hospitalized patients with schizophrenia were significantly higher than those in the control group. However, the PLR, platelet count, and lymphocyte count did not differ significantly between groups. There was a significant relationship between the NLR values and first-episode psychosis. Nevertheless, there was no significant relationship between the NLR, age, sex, smoking, alcohol consumption, duration of illness, previous psychiatric hospitalization, and previous use of antipsychotics **(Figure 1).**

Recent studies have suggested that inflammation may play a role in the pathogenesis of schizophrenia. In addition, there have been reports of elevated peripheral cytokine levels, such as interleukin (IL)-2, IL-6, IL-8, tumor necrosis factor-α,[18] autoantibodies,[19] and oxidative stress, in the plasma of individuals with schizophrenia.[5] The NLR is determined by the ratio of absolute neutrophil to absolute lymphocyte count and serves as a marker of systemic inflammation.[6] Previous studies have shown that NLR values were higher in patients with schizophrenia than in controls.[14-17, 20] Our study was conducted specifically within the Thai ethnicity, and our findings align with this established trend, which further underlines the

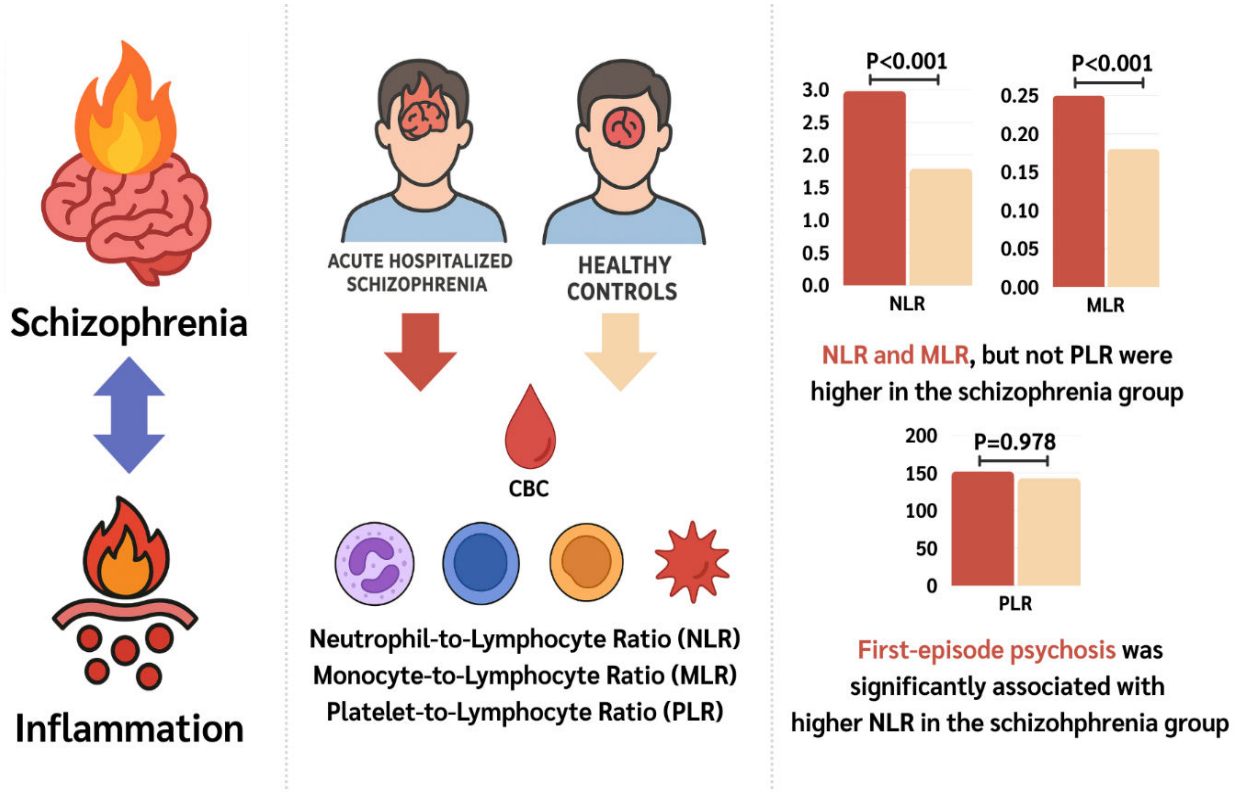

Figure 1. Graphical abstract illustrating the main concept and results of this study.

robust association between elevated NLR values and schizophrenia across varying ethnic backgrounds. Moreover, compared to bipolar individuals, patients with schizophrenia had higher NLR levels. [17] Furthermore, patients with schizophrenia had higher NLR values in the relapse phase of the disease compared to those of the remission phase, as well as higher NLR values in the remission phase than those of the control group. [14] In addition, patients with schizophrenia had higher NLR values than patients with schizoaffective disorder. [21] Significant positive correlations have been found between inflammatory indices and the total, positive, negative, and general psychopathology scores. [22] One study reported that the NLR was negatively correlated with cognitive performance, [23] highlighting the role of systemic inflammation in the severity of schizophrenia. Therefore, it is implied that there is an increase in the inflammatory response in the acute phase of schizophrenia, which presents as an increase in the NLR.

NLR was selected as a representative of inflammation because it reflects systemic inflammation, [24] and it has been widely used in a multitude of previous studies. A higher NLR was found in patients with first-episode psychosis than in the control group, [25-27] which is similar to our results. This may reflect the role of the innate immune response in patients with first-episode psychosis. Previous studies have also reported that NLR values were not correlated with the duration of illness [15, 16] or the number of previous hospitalizations [15], findings that are in agreement with our results.

The PLR is also an inflammatory index that reveals a shift in platelet and lymphocyte counts and has been used as a biomarker for major inflammation and poor prognosis prediction in various diseases, including advanced cancer. [10] PLR values in previous studies [14, 28] differed significantly between the acute schizophrenia and control groups. However, the results of our study did not reveal the same pattern, where the PLR values were not significantly different between acute schizophrenia and healthy control groups. A similar result was found in a previous study in China. [29] This finding may be explained by two reasons. Platelets are non-nucleated cells that are sensitive and fragile, and they tend to undergo apoptosis under stressful conditions, [30] such as schizophrenia. Second, platelets are vulnerable to drugs in circulation, [30] and the platelet counts from participants using antipsychotic drugs may be affected.

The limitations of this study were that we did not exclude patients who used alcohol, cigarettes, or other such substances, which may have affected the NLR values. Moreover, the retrospective nature of the study hindered the assessment of disease severity using a standard scale. The cross-sectional design focused on a sample in the acute stage of schizophrenia, thereby restricting the ability to establish causal relationships and generalize findings to the different phases of the disorder. In addition, the study did not consider the potential impact of body mass index on NLR values, which may have been a pertinent factor.

Conclusion

This study shows that individuals with schizophrenia experiencing psychotic episodes have higher levels of inflammatory markers (NLR and MLR) compared to healthy control participants. Furthermore, we found that individuals with first-episode psychosis had higher NLR values. These results imply that the etiology of schizophrenia may involve inflammatory mechanisms. Further studies should consider inflammatory markers (NLR and MLR) simultaneously with other biological changes, such as brain imaging, disease stage, and response to antipsychotic medication. Over time, pharmacological interventions may target inflammatory markers and pathways to treat schizophrenia.

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Conflict of interest
The authors declare that they have no conflicts of interest.

Data sharing statement
The data sets generated or analyzed during the present study are available from the corresponding author upon reasonable request.

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