

SIMPLE BIOMARKER ANALYSIS OF SYSTEMIC INFLAMMATION IN AGITATION AMONG SCHIZOPHRENIA PATIENTS: CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: Schizophrenia is a serious mental disorder characterized by reality distortion and psychomotor disorganization, with agitation as a common symptom that increases the risk of rehospitalization. Systemic inflammation, measured by biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), has been identified as being associated with the pathophysiology of schizophrenia. This study aims to investigate the relationship between agitation and inflammation, as indicated by elevated NLR, MLR, PLR, and SII values, in schizophrenia patients.

Methods: A retrospective cross-sectional study was conducted involving 314 schizophrenia patients hospitalized at Dr. Amino Gondohutomo Mental Hospital, Semarang, from December 2023 to July 2024. Data was collected from medical records, including NLR, MLR, PLR, and SII values calculated from routine hematological exams, and the degree of agitation measured with the PANSS-EC scale.

Results: The majority of patients (65.3%) were aged 18-37 years, with a mean age of 34.07 years. Most patients were male (52.5%) and exhibited moderate agitation (66.6%). Regression analysis showed that NLR, MLR, and SII values were significantly positively correlated with agitation levels. NLR had a regression coefficient of 0.122 ($p=0.001$), MLR of 0.293 ($p=0.046$), and SII of 0.000 ($p=0.035$), indicating that increases in these inflammatory biomarkers correlated with higher agitation levels in schizophrenia patients.

Discuss: Hematological biomarkers such as Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Immune-Inflammation Index (SII) hold significant potential in psychiatric emergency settings as simple, cost-effective, and accessible tools for early identification and risk stratification of acute agitation in schizophrenia and other severe mental disorders.

Conclusion: This study found that elevated NLR, MLR, and SII values were closely associated with increased agitation levels in schizophrenia patients, supporting the hypothesis that systemic inflammation plays a role in the pathophysiology of schizophrenia. These findings suggest the potential for using inflammatory biomarkers as predictive tools for assessing agitation severity in schizophrenia patients, which could aid in clinical management and rehospitalization prevention.

Keywords: Schizophrenia, NLR, MLR, PLR, SII.

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INTRODUCTION

Schizophrenia is a mental disorder characterized by reality distortion, disorganization, and psychomotor poverty, which can create significant burdens for both affected individuals and healthcare systems.¹ According to the Basic Health Research (Riskesdas) by Indonesia's Ministry of Health in 2018, schizophrenia prevalence in individuals over 15 years old

reached 7%, equating to around 470,000 individuals.² In 2023, the national prevalence of schizophrenia in Indonesia was recorded at 4%, with Central Java Province having one of the highest prevalence rates at 6.5%.³

One major challenge in managing schizophrenia is the high rehospitalization rate following discharge from acute inpatient care. Rehospitalization not only strains healthcare systems but also indicates worsening clinical conditions and instability

among patients.⁴ Agitation, commonly observed in schizophrenia patients, is a factor that can significantly increase the risk of rehospitalization.⁵ Agitation is marked by intense restlessness, irritability, and aggressive behavior, often requiring immediate medical intervention. This condition can be triggered by various factors, including neurochemical imbalances, environmental stress, and non-compliance with treatment.⁶

Recent studies have suggested a link between inflammatory processes and the pathophysiology of schizophrenia.⁷ Hematological parameters such as NLR, MLR, PLR, and SII have been identified as important indicators of systemic inflammation status.⁸ Elevated levels of these ratios often reflect immune activation and inflammatory responses, which have been associated with various medical conditions, including mental disorders.⁹

Studies in Beijing Huilongguan Hospital showed that individuals with schizophrenia had higher NLR and MLR levels than healthy individuals, supporting the hypothesis of an inflammatory process in schizophrenia.¹⁰ Research at Kars Harkani Hospital, Turkey, found that schizophrenia patients had higher NLR, PLR, and SII values and lower lymphocyte counts than the control group. These findings suggest low-grade systemic inflammation in schizophrenia patients.¹¹

Agitation in schizophrenia patients is marked by excessive, often disruptive, motor and verbal behaviors that complicate further assessment. The Positive and Negative Syndrome Scale Excited Component (PANSS-EC) is an effective tool for detecting agitation-related changes in emergency psychiatric units.⁶ The relationship between NLR and agitation levels in acute psychotic patients has also been reported, with findings showing that higher NLR correlates with higher agitation levels. Chronic inflammation is thought to influence neurotransmission and brain function, which, in turn, may trigger or exacerbate psychotic symptoms and agitation.¹²

While research on the relationship between inflammation and schizophrenia has grown, studies specifically exploring the link between inflammatory biomarkers and agitation in schizophrenia patients remain limited. This study aims to investigate the relationship between agitation and inflammation, as indicated by elevated NLR, MLR, PLR, and SII values, in schizophrenia patients at Dr. Amino Gondohutomo Psychiatric Hospital, Semarang. The urgency of this research lies in its potential to aid in screening agitation in schizophrenia patients, thereby reducing morbidity and hospitalization rates.

METHOD

This study used a cross-sectional design with a retrospective approach. Samples were collected using consecutive sampling. Data were sourced from secondary data recorded at Dr. Amino Gondohutomo Psychiatric Hospital between December 2023 and July 2024. The study began by collecting PANSS-EC scores assessed at the initial emergency department examination, using the highest score on the 0-7 scale across its five components. Agitation levels were categorized as mild (PANSS-EC 5-10), moderate (PANSS-EC 11-20), and severe (PANSS-EC 21-35). NLR was calculated based on neutrophil

and lymphocyte percentages from routine hematology tests conducted at the first examination. MLR was obtained by dividing the absolute monocyte count by the absolute lymphocyte count, while PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. SII was calculated by multiplying the absolute neutrophil count by the absolute platelet count, then dividing by the absolute lymphocyte count. The dependent variable was the PANSS-EC score (ratio scale), while the independent variables were the NLR, MLR, PLR, and SII values (ratio scale). Inclusion criteria included patients with schizophrenia (PPGDJ III or ICD-10 F20.0 - F20.3), aged 18-59, of either gender, with at least primary school education, first-time inpatients, and who had not received antipsychotic therapy. Exclusion criteria included patients with more than one prior hospitalization, incomplete laboratory data, signs of severe infection, or other serious medical conditions like chronic diseases, fever, or anti-inflammatory drug use within four weeks prior to the study. Patients with organic brain disorders, substance abuse, or no family support were also excluded. Statistical analysis was conducted using SPSS Version 27 to evaluate the relationships between variables.

This research has been presented in front the Ethics Committee of Dr. Amino Gondohutomo Psychiatric Hospital with No. 420/7251/RSJDAGH and has been approved for implementation. The research protocol includes attached information provided to respondents, including the reasons for participation, research objectives, required time, as well as the risks and benefits of the study. All consequences arising from the implementation of this research, particularly regarding intervention actions on respondents, are the responsibility of the researcher.

RESULT

This study involved 314 schizophrenia patients who met the inclusion and exclusion criteria and were hospitalized at RSJD Amino Gondohutomo Semarang from December 2023 to July 2024. The majority of the sample were aged between 18-37 years (65.3%), with a mean age of 34.07 years (SD $\pm$ 10.00). Most participants were male (52.5%), unemployed (58.3%), unmarried (58.6%), and had a primary school education as their highest level of education (42.4%). Analysis of variance also showed significant differences between marital status and employment in relation to agitation levels ($p < 0.05$) (Table 1). The majority of patients were diagnosed with unspecified schizophrenia (48.1%) and experienced moderate agitation (66.6%) (Table 2).

Based on multivariate analysis with regression testing, it was found that the NLR value has a significant positive relationship with the degree of agitation, with a regression coefficient (B) of 0.122 ($p = 0.001$). The MLR and SII Index values also showed a significant positive relationship with the degree of agitation, with regression coefficients (B) of 0.293 ($p = 0.046$) and 0.000 ($p = 0.035$), respectively. These results indicate that increases in NLR, MLR, and SII values are associated with higher degrees of agitation in schizophrenia patients (Table 3).

Table 1. Characteristics of Study Sample

Variabel	Frequency (n=314)	Agitation Level
Age, mean±SD	34.07±10.00	
18-37 years, n (%)	205 (65.3)	p=0.57
38-47 years, n(%)	72 (22.9)	
48-58 years, n(%)	37 (11.8)	
Genders		
Male, n(%)	166 (52.9)	P=0.334
Female, n(%)	148 (47.1)	
Employment Status		
employed, n(%)	131 (41.7)	P<0.004*
Unemployed, n(%)	183 (58.3)	
Marital Status		
Married, n(%)	116 (36.9)	P=0.049
Single, n(%)	184 (58.6)	
Divorced (Living or Deceased) , n(%)	14 (4.5)	
Education Level		
Elementary School Graduate, n(%)	133 (42.4)	P=0.173
Junior High School Graduate, n(%)	58 (18.5)	
High School Graduate, n(%)	112 (35.7)	
College Graduate, n(%)	11 (3.5)	

*Analysis was performed using the Chi-square test. Results were considered significant if $p < 0.05$.

Table 2. Diagnosis and Degree of Agitation in Research Sample

Variable	Frequency (n=314)
Diagnosis	
Unspecified Schizophrenia, n (%)	151 (48.1)
Hebephrenic Schizophrenia, n(%)	19 (6.1)
Catatonic Schizophrenia, n(%)	10 (3.2)
Paranoid Schizophrenia, n(%)	134 (42.7)
Degree of Agitation	
Moderate Agitation, n(%)	209 (66.6)
Severe Agitation, n(%)	105 (33.4)

Table 3. Regression Test Results of NLR, MLR, PLR, and SII Values on Degree of Agitation

Variable	Mean±SD	Nilai P	Koefisien Regresi (B)
NLR	3.98±4.62	0.001*	0,122
MLR	0.86±1.19	0.046*	0,293
PLR	14.70±11.09	0.166	-0,022
SII	1472.54±1267.20	0.035*	0,000

*Analysis was conducted using multiple linear regression, with results considered significant if $p \leq 0.05$

DISCUSS

The study found that the total number of inpatients at RSJD Amino Gondohutomo Semarang from December 2023 to 2024 was 2,687. Of these, 314 new schizophrenia patients met the inclusion and exclusion criteria and became the research sample. The study showed that the majority of the sample experienced moderate agitation, approximately 182 (58%). Schizophrenia is often accompanied by agitation, particularly during acute exacerbation phases, and can occur at various stages of the illness course. In the United States, the prevalence of agitation in schizophrenia patients leads to around 900,000 annual visits to psychiatric emergency services, accounting for 21% of total visits. In this study, the prevalence of unspecified schizophrenia was higher (48.2%), with male patients (52.9%) outnumbering other schizophrenia types. Other studies indicate that women may be more vulnerable to psychological

stress, especially if they have experienced past trauma. Women often develop disorders at an older age compared to men, although these disorders can also appear at a younger age.

The prevalence results of schizophrenia in this study are similar to a previous study conducted at the RSKD in South Sulawesi Province, where the highest prevalence of schizophrenia diagnoses was unspecified schizophrenia, at approximately 88.2%. The average age of the sample was 34.07 years, with a standard deviation of ± 10.00 , where the majority age range was 18-37 years, about 65.3%. These results differ from a study at the RSKD in South Sulawesi, where the majority age range of the sample was 41-50 years (26.8%). The majority education level in this sample was elementary school graduation, approximately 42.4%. Age and education level significantly affect the risk of schizophrenia, with this disorder usually emerging in late adolescence to early adulthood, particularly between 18 and 30 years old, a

vulnerable period due to biological and psychosocial changes. Individuals with lower education levels are at higher risk because a lack of education may affect their ability to cope with stress, potentially worsening or triggering schizophrenia. The combination of young age and low education increases vulnerability to this disorder, highlighting the importance of early intervention and educational support to reduce the risk and impact of schizophrenia.¹³

Most of the research sample were unemployed (58.3%), and the majority were unmarried (58.6%). This study supports the theory that employment and marital status affect schizophrenia risk. Individuals who are unemployed or have unstable jobs are more susceptible to schizophrenia, possibly due to economic stress and lack of social support. Marital status plays a role, as those who are unmarried or divorced have a higher risk due to social isolation and lack of emotional support. Stability in employment and marriage can act as protective factors against schizophrenia, whereas instability in both aspects may increase the risk.¹⁴

The average NLR (Neutrophil-Lymphocyte Ratio) in this study was 3.98 ± 4.62 , MLR (Monocyte-Lymphocyte Ratio) was 0.86 ± 1.19 , PLR (Platelet-Lymphocyte Ratio) was 14.70 ± 11.09 , and the SII Index (Systemic Immune-Inflammation Index) was 1472.54 ± 1267.20 . The NLR, MLR, and SII values in this study were higher compared to a previous study conducted by Zhou (2023) at Beijing HuiLongGuan Hospital, where the NLR value in schizophrenia patients was 1.93 ± 1.00 , the MLR value was 0.20 ± 0.11 , and the SII index value was 452.16 ± 260.62 . The PLR value in this study was lower than Zhou's findings, where the PLR value in schizophrenia patients was 116.90 ± 42.93 (10). Increased NLR and SII index values align with previous findings by Inaltekin (2023), where higher NLR, PLR, and SII values, along with lower MPV (Mean Platelet Volume) and lymphocyte count, were observed in schizophrenia patients compared to control groups.¹¹

The NLR value in this study had a regression coefficient (B) of 0.122 with a p-value of 0.001 ($P < 0.05$), indicating that each increase in NLR is associated with a 0.122 increase in the PANSS EC (Positive and Negative Syndrome Scale for Excitement Component) score. The MLR value had a regression coefficient (B) of 0.293 with a p-value of 0.046 ($P < 0.05$), meaning that each increase in MLR is associated with a 0.293 increase in the PANSS EC score. The SII Index had a regression coefficient (B) of 0.000 with a p-value of 0.035 ($P < 0.05$), indicating that each increase in the SII Index is associated with an increase in the PANSS EC score, albeit a very small or nearly negligible increase. These results are consistent with Zhou's (2023) study at Beijing HuiLongGuan Hospital, which showed that increased NLR, MLR, and SII

index values correlate with a schizophrenia diagnosis. Consistent changes in NLR, MLR, and SII over time suggest that these indicators may serve as stable markers for the disease, unaffected by age and gender.¹⁵

Leukocytes, neutrophils, and C-reactive protein (CRP) are thought to play roles in the inflammatory processes associated with schizophrenia symptoms, with increases in cytokines such as IL-6 and neutrophil counts in peripheral blood, while T cell and monocyte activation triggered by IL-1 and IFN-gamma are associated with increased leukocyte counts.¹⁶ Increased IL-6 is often accompanied by a higher neutrophil-to-leukocyte ratio and elevated CRP. Reduced lymphocyte proliferation, including B and T cells, indicates reduced cellular immunity, reflected in decreased T-helper 4 and increased T-helper 8.¹⁷ Lymphocytopenia may occur due to cellular immunity suppression by cortisol and prolactin, lymphocyte redistribution to the lymphatic system, and accelerated apoptosis triggered by TNF-alpha.¹⁸

The increased Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Immune-Inflammation Index (SII) in this study closely correlate with increased agitation levels in schizophrenia. The hypothesis that systemic inflammation plays a significant role in the pathophysiology of schizophrenia, particularly agitation symptoms, is supported. Hematological biomarkers such as Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Immune-Inflammation Index (SII) hold significant potential in psychiatric emergency settings as simple, cost-effective, and accessible tools for early identification and risk stratification of acute agitation in schizophrenia and other severe mental disorders. Elevated levels of these biomarkers may serve as early warning indicators, enabling timely interventions to prevent escalation into full-blown psychiatric crises, reducing the need for emergency sedation, physical restraints, or involuntary hospitalization. Their quantifiable nature enhances objective assessment of agitation severity, supporting clinical decision-making for personalized treatment approaches, including the potential use of anti-inflammatory agents alongside psychotropic medications. Integrating these biomarkers into routine psychiatric assessments could improve monitoring and management strategies, while their incorporation into predictive models using clinical data and machine learning may enhance early crisis detection. As growing evidence links immune dysregulation to psychiatric symptoms, the utilization of these biomarkers represents a crucial step in bridging psychiatry and immunology, shifting psychiatric care from reactive crisis management to proactive prevention, ultimately improving patient outcomes and reducing the burden on emergency psychiatric services.

CONCLUSION

This study contributes to the understanding of the dynamic interaction between inflammation and agitation symptoms in schizophrenia, which can be assessed through the Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Immune-Inflammation Index (SII). Simple inflammatory biomarkers are expected to serve as an initial screening tool for assessing agitation in schizophrenia that requires further management. Further research with a longitudinal design, a larger sample size, exploration of other inflammatory biomarkers, and genetic analysis is needed to strengthen these findings and improve the effectiveness of clinical interventions as well as the quality of life of patients.

CONFLICT OF INTEREST

There are no conflicts of interest in this research.

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