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Evaluation of systemic immune-inflammation index, systemic inflammatory response index and hematologic inflammatory parameters in generalized anxiety disorder: a controlled study

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ABSTRACT

Aims: The current study aimed to examine the values of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) in generalized anxiety disorder (GAD).

Methods: In this retrospective study, 147 GAD patients who did not receive treatment and 154 healthy controls with similar characteristics to the patient group were included. NLR, PLR, MLR, SII, and SIRI values calculated from the complete blood count values of the GAD group were compared with age- and sex-matched healthy controls.

Results: Neutrophil, lymphocyte, monocyte, platelet counts and NLR, MLR, SII, and SIRI values were significantly higher in the GAD group compared to healthy controls ($p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.003$, $p<0.001$, $p<0.001$, respectively). The logistic regression analysis revealed that SII and SIRI were identified as significant variables associated with receiving a diagnosis of GAD.

Conclusion: Inflammatory markers such as NLR, MLR, SII, and SIRI are thought to play an important role in the evaluation of inflammatory activity in GAD. However, larger and more comprehensive studies are needed.

Keywords: Generalized anxiety disorder, inflammatory biomarker, systemic immune-inflammation index, systemic inflammatory response index

INTRODUCTION

Generalized anxiety disorder (GAD) is a common mental disorder characterized by persistent worry, restlessness, tension, and somatic symptoms associated with many various events, situations, and activities. These symptoms significantly impact daily life, and individuals with GAD often experience difficulty controlling their apprehensions.[1] Symptoms must persist for at least 6 months for diagnosis. GAD is the most prevalent among anxiety disorders.[2] Although there is no single cause of GAD, a combination of multiple risk factors may influence the development of the disorder. There is increasing evidence that neuroinflammation is also involved in the etiology of psychiatric disorders and that inflammatory processes play a role in psychiatric disorders.[3,4] Evidence for the role of inflammation in GAD is also increasing.[2]

Although there are various blood biomarkers such as cytokines to evaluate inflammation, most of them are difficult and expensive tests. Therefore, there is a growing interest in blood biomarkers that are more accessible, cost-effective, and suitable for routine practice. NLR, PLR, and MLR are biomarkers used to show systemic inflammation in many diseases. These markers have also been investigated in different psychiatric diseases.[5] These ratios, calculated from a complete blood count, are more useful in indicating the status and severity of inflammation compared to a single parameter.

In addition to these markers, newer parameters have come to the forefront in recent years. These are SII and SIRI values. In recent studies, SII and SIRI have been defined as more sensitive markers.[6] Various studies have been conducted in recent years on complete blood count parameters in psychiatric disorders. Studies related to complete blood count data in panic disorder (PD) and GAD, two psychiatric disorders included in the DSM-5 Anxiety Disorders section, have been observed.[7,8] It is thought that the results obtained from this study may contribute to clinical practice in the diagnosis and follow-up of GAD and the evaluation

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of response to treatment by using a combination of systemic inflammation parameters that can be obtained from complete blood count and can be easily calculated. As far as the literature review reveals, there is no study specifically focusing on the role of SII and SIRI in GAD. Therefore, this study aimed to evaluate SII and SIRI along with lymphocyte-related ratios in GAD and compare them with healthy controls.

METHODS

The study was carried out with the permission of the Amasya University Non-interventional Clinical Researches Ethics Committee (Date: 04.01.2024, Decision No: 2023/162). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was planned retrospectively. The files of the patients were examined through the patient record system of our hospital. The patient record system shows patients' past treatments and comorbidities. The files of 324 patients admitted to our hospital between January 2022 and January 2023 and diagnosed with GAD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by a specialist psychiatrist were examined. 21 individuals with a diagnosis of GAD using medication, 33 individuals with comorbid psychiatric disorders, 96 individuals with comorbid organic diseases, and 27 individuals with both comorbid psychiatric and organic diseases were excluded from the study. Considering the inclusion criteria, 147 patients were included in the study. The patient group was composed of individuals who were seeking help for the first time and were not taking medication. The control group consisted of hospital staff who were sent for routine psychiatric examination by the workplace physician, who were not diagnosed with any psychiatric illness as a result of the psychiatric examination performed by the psychiatry specialist, and who did not have any organic disease.

The complete blood count parameters examined during the initial visit were analyzed. Patients with additional psychiatric or organic diseases that might affect complete blood count data were not included in the study. Thus, those with a diagnosis of GAD who were taking medication, those with comorbid psychiatric diseases, and those with comorbid organic diseases (chronic liver or kidney disease, autoimmune disease, diabetes mellitus, hypertension, heart disease, respiratory system disease, cancer, anemia, endocrine diseases, etc.), and those with active infection were excluded from the study.

The NLR, PLR, and MLR were calculated using the following formula: NLR=neutrophil count/lymphocyte count, PLR=platelet count/lymphocyte count, and MLR=monocyte count/lymphocyte count.[9-11] SII and SIRI values were also calculated using neutrophil, lymphocyte, and monocyte counts. SII="(platelet count x neutrophil count)/lymphocyte count" formula, SIRI="(neutrophil count x monocyte count)/lymphocyte count" formula.[12,13]

Statistical Analysis

IBM SPSS version 22.0 (IBM Corp., Released 2013; IBM SPSS Statistics for Windows, Version 22.0; Armonk, NY: IBM Corp.) was used for statistical analysis. Descriptive statistics and continuous variables were given as mean±standard deviation. Compliance with normal distribution was evaluated by the Kolmogorov-Smirnov/Shapiro-Wilk test. Parametric values were evaluated using the t-test, and non-parametric values were evaluated using the chi-square test. The Student's t-test was employed for comparing groups with data conforming to a normal distribution, and the Mann-Whitney U test was used for data not conforming to a normal distribution. Numerical variables were presented as mean±Standard deviation, and categorical variables were presented as numbers and percentages. Receiver operating characteristic (ROC) analyzes were conducted to evaluate the ability of the NLR, PLR, MLR, SII, and SIRI to predict the diagnosis of GAD. The area under the ROC curve (AUC) values of NLR, PLR, MLR, SII, and SIRI to predict the diagnosis of GAD were given with 95% confidence interval (CI) and with sensitivity and specificity. Variables associated with the diagnosis of GAD were investigated using logistic regression analyses. Since the formulas for SII and SIRI among the variables included the NLR, PLR, and MLR variables, SII and SIRI variables were included in the analysis as variables that could be associated with the diagnosis of GAD. The statistical significance level was determined to be 0.05 and below.

RESULTS

The GAD group consisted of 147 (74 females and 73 males) patients, and the control group consisted of 154 (77 females and 77 males) healthy individuals. The mean age was 40.44±0.84 years in the patient group and 40.19±0.96 years in the control group. There was no significant difference between the groups in terms of mean age, gender, and marital status (p=0.847, p=0.953, p=0.854, respectively) (**Table 1**).

Table 1. Characteristics of patients with generalized anxiety disorder and the control group participants

Characteristics	Patients (n=147) mean±SD	Controls (n=154) mean±SD	p value
Age (years)	40.44±0.84	40.19±0.96	
Gender, n (%)			0.847
Female	74 (50.3)	77 (50.0)	
Male	73 (49.7)	77 (50.0)	
Marital status			0.953
Married	96 (65.3)	99 (64.3)	
Single	51 (34.7)	55 (35.7)	
Occupational status			0.854
Working	70 (47.6)	154 (100.0)	
Not working	77 (52.4)		

mean±SD: mean±standard deviation

Neutrophil, lymphocyte, monocyte, platelet counts, NLR, MLR, SII, and SIRI values were found to be significantly higher in GAD patients than in the control group, while there was no statistically significant difference between the groups in terms of PLR values. The pairwise comparisons of laboratory findings are presented in **Table 2**.

Table 2. Comparison of complete blood count values and some laboratory findings of generalized anxiety disorder and control group

Variables	GAD (N=147) mean±SD	Control (N=154) mean±SD	p value
Neu (10^3/μl)	5.19±0.08	3.57±0.06	<0.001*
Lym (10^3/μl)	2.44±0.05	2.23±0.04	0.001*
Mono (10^3/μl)	0.63±0.02	0.50±0.01	<0.001*
Plt (10^3/uL)	279.67±5.10	245.51±4.23	<0.001*
NLR	2.27±0.06	1.68±0.04	<0.001*
PLR	192.45±54.35	114.52±2.44	0.444
MLR	0.27±0.01	0.23±0.01	0.003*
SII	637.17±22.93	408.73±11.10	<0.001*
SIRI	1.42±0.05	0.84±0.03	<0.001*
Alanine amino transferase (U/L)	18.56±4.28	19.36±4.97	0.137
Aspartate amino transferase (U/L)	21.42±4.64	22.34±4.87	0.094
Blood urea nitrogen (mg/dL)	23.01±10.10	25.17±10.08	0.065
Creatinine (mg/dL)	0.83±0.16	0.80±0.17	0.097

*p<0.05 statistically significant; The data were compared using Student's t-test and Mann-Whitney U-test .
Abbreviations: mean±SD: mean±standard deviation, GAD: Generalized anxiety disorder, Neu: Neutrophil count, Lym: Lymphocyte count, Mono: Monocyte count, NLR: Neutrophil-to-lymphocyte ratio, PLR; Platelet-to- lymphocyte ratio, MLR; Monocyte-to- lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index

ROC curve analyses for NLR, PLR, MLR, SII, and SIRI to predict the diagnosis of GAD are demonstrated in **Figure 1**. The AUC values for NLR, PLR, MLR, SII, and SIRI to predict diagnosis of GAD were 0.75 (95% CI: 0.69-0.80, p<0.001), 0.53 (95% CI: 0.46-0.59, p=0.444), 0.60 (95% CI: 0.53-0.66, p=0.003), 0.80 (95% CI: 0.75-0.85, p<0.001) and 0.82 (95% CI: 0.77-0.87, p<0.001), respectively. The cut-off value of SIRI (1.01) was associated with 74.0% sensitivity and 75% specificity. The cut-off value of SII (472.38) was associated with 75.0% sensitivity and 75% specificity.

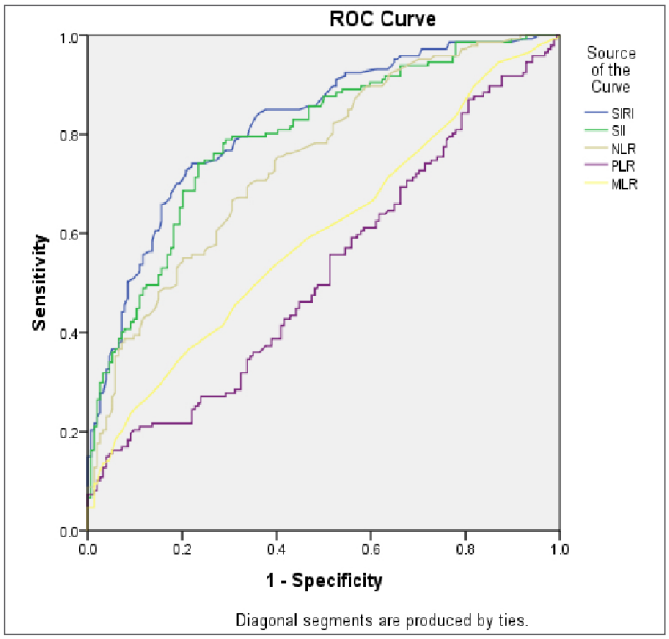

Figure 1. ROC curve analyses for NLR, PLR, MLR, SII and SIRI to predict diagnosis of GAD
ROC: Receiver operating characteristic, GAD: Generalized anxiety disorder, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR; Monocyte-to- lymphocyte ratio, SIRI: Systemic inflammatory response index, SII: Systemic immune-inflammation index,

Logistic regression analysis was performed separately for the SII and SIRI variables, which were the most comprehensive among the significant parameters obtained. According to the results of the analysis, it was determined that when the SIRI variable value increased by one unit, the probability of being diagnosed with GAD increased 26.687 times, and when the SII variable value increased by one unit, the probability of being diagnosed with GAD increased 1.007 times. According to the data obtained, SIRI was found to be an important variable in the diagnosis of GAD. The logistic regression analysis conducted to assess the predictors of GAD diagnosis is presented in **Table 3**.

Table 3. Logistic resgresion analysis model for the effect of SIRI and SII values on generalized anxiety disorder

Variables	B (S.E.)	df	Sig.	95% C.I.for Exp(B)		
				Lower	Exp(B)	Upper
Constant	-3.540 (0.455)	1	0.000			
SIRI*	3.284 (0.426)	1	0.000	11.584	26.687	61.483
Constant	-3.511 (0.480)	1	0.000			
SII**	0.007 (0.001)	1	0.000	1.005	1.007	1.009

A p-value less than 0.05 was considered significant for statistical analysis.
* Nagelkerke R square: 0.394; Hosmer-Lemeshow test's chi-square value: 5.590
** Nagelkerke R square: 0.344; Hosmer-Lemeshow test's chi-square value: 6.101
SIRI: Systemic inflammatory response index, SII: Systemic immune-inflammation index, C.I.: Confidence interval

DISCUSSION

In this study, ratios related to neutrophils, lymphocytes, monocytes, and platelets were compared between the GAD and control groups. While there are studies evaluating NLR and PLR levels in GAD patients, this is the first study in which the newer parameters SII and SIRI values were examined together. In our study, it was determined that untreated patients with GAD had higher neutrophil, lymphocyte, monocyte, platelet counts, NLR, MLR, SII, and SIRI values compared to healthy controls.

Recently, the usability of complete blood count parameters to examine inflammatory processes in psychiatric diseases has been the subject of research. Especially schizophrenia, schizoaffective disorder, bipolar disorder, depression, and substance use disorders are the most studied psychiatric disorders.[14-17] These parameters have also been investigated in obsessive-compulsive disorder (OCD) and PD, which are anxiety-related psychiatric disorders.[8,18,19]

White blood cells and their subtypes along with platelets are significant biomarkers that play an important role in inflammation, and the activation of these cells results in the release of inflammatory cytokines. Neutrophils are important components of innate immunity and are the first line of defense against tissue inflammation. They lead to the release of various cytokines that induce oxidative stress and inflammation. Lymphocytes play a key role in the adaptive immune response, primarily contributing to functions like antibody production.[16,20] On the other hand, monocytes are vital for the innate immune response, releasing pro-inflammatory and pro-oxidant cytokines during inflammation.[21] Platelets, akin to neutrophils, produce and release cytokines influencing inflammation.[22] These cell parameters are easily accessible through a complete blood count. The combined evaluation of these cells and ratios such as NLR, PLR, MLR, SII, and SIRI calculated based on these cells is thought to be more valuable in evaluating inflammation.[23]

The pathophysiology of GAD is complex, and the role of systemic inflammation has not yet been fully elucidated. However, although it has not yet been proven, it has been shown that inflammatory activation increases in GAD patients independently of the accompanying depression.[24] In their study, Hou et al.[25] reported a relatively increased pro-inflammatory response, a decrease in anti-inflammatory response, and a change in cytokine balance in GAD patients.

It has been shown that stress induction in humans leads to an increase in the neutrophil count.[26] Additionally, NLR is an important indicator reflecting the activation of inflammatory cells. Therefore, NLR may be an indicator of inflammatory response reflecting stress intensity and systemic inflammation.[27] The relationship between NLR and inflammatory markers such as inflammatory cytokines and CRP has also been reported.[28] Therefore, studies especially on NLR, have been intensified. Higher NLR levels have been linked to higher mortality in psychiatric patients, suggesting a potential role of neuroinflammation in the development of psychiatric diseases.[23,29,30] Platelets play a modulatory role in activating neutrophils and monocytes. PLR is a value calculated based on the ratio of platelet to lymphocyte counts. This value is being researched for its utility in monitoring individual immune processes through changes in the number of platelets, which have a modulatory role in the immune system, and the ratio of changes in lymphocytes, which are elements of acquired and innate immune responses. Activated monocytes play a role in paracrine signaling and are involved in the release of various proinflammatory cytokines and chemokines. MLR provides an understanding of the relationship between acquired and innate immune responses. There are a limited number of studies related to MLR.[5]

In this study, all parameters related to neutrophil count were found to be higher in the GAD group compared to the control group. Our study aligns with Orum[8], who found increased neutrophil count and NLR values in patients with GAD compared to healthy controls while investigating inflammatory parameters in GAD patients. The higher NLR levels may have resulted from the higher neutrophil count. In another study, PLR was found to be lower in patients with GAD compared to controls.[31] In a study conducted with children and adolescents with anxiety disorders, it was reported that NLR, MLR, and PLR were higher compared to healthy controls.[32] In children and adolescents with anxiety disorders and depression, high NLR and PLR have also been associated with suicidal behavior.[33] Brinn and Stone[29] reported elevated NLR in nonphobic anxiety disorder. Studies on cells involved in the immune response and lymphocyte-related ratios in PD and OCD, which are anxiety-related disorders, are noteworthy. In a study comparing PD patients with healthy controls, no significant differences were found between the groups in terms of NLR and PLR values, as well as neutrophil and platelet counts, while lymphocyte counts were significantly higher in the PD group.[19] In another study, it was reported that lymphocyte counts were higher in PD patients compared to controls, while there was no difference in terms of neutrophil, monocyte, and platelet counts.[34] When we look at the studies conducted in OCD, which is another anxiety-related disease, it was found that NLR levels were higher in patients diagnosed with OCD compared to healthy controls.[18] Additionally, it was found that NLR levels were higher in adolescent OCD patients with anxiety disorder

compared to controls, and neutrophil count increased when accompanied by anxiety disorder.[35]

In our study, SII and SIRI values were found to be higher in the GAD group compared to healthy controls. SII, a novel biomarker related to inflammation and immunity, is calculated based on neutrophil, platelet, and lymphocyte counts. Studies have reported that SII is a marker reflecting inflammation and immune response. This index includes important components of the immune response, including neutrophils, lymphocytes, and platelets.[36] Previously, SII has been investigated to predict the prognosis and severity of disease in physical conditions such as pancreatitis and ischemic stroke.[37,38] It has been demonstrated that SII can show systemic inflammation and immune response better than NLR, PLR, and MLR.[39] However, SII has been less investigated in psychiatric diseases. There is increasing evidence that SII, NLR, and PLR can be used as markers of disease severity in psychiatric diseases.[40,41] SII has been reported to be significantly associated with depression and anxiety symptoms in patients with tuberculosis.[41]

Dionisie et al.[42] found that SII was higher in patients with bipolar depression than in patients with unipolar depression. Inaltekin and Yağci[43] also reported that NLR, PLR, and SII values were significantly higher in patients with bipolar manic episodes and schizophrenia. Wei et al.[23] reported higher values of NLR, PLR, MLR, SII, and SIRI in patients with schizophrenia and bipolar disorder compared to healthy controls. There is also evidence showing a positive significant relationship between SII and depression and anxiety scores in individuals who have recovered from COVID-19.[44] In addition to the findings of studies that did not find significant differences in SII values between patients with first-episode schizophrenia and healthy controls, there are also study findings reporting that patients with schizophrenia have higher SII values than healthy controls.[23,45] In a study evaluating lymphocyte-related ratios and SII index in sleep-related disorders, sleep-related disorders were shown to have a stronger association with SII than PLR and NLR.[46]

SIRI is a new index of inflammation calculated based on neutrophil, lymphocyte, and monocyte counts. Conceptually, it indicates the ratio of innate immune response cells to adaptive immune response cells. SIRI was initially investigated as a predictor of prognosis in malignancies and later continued to be investigated in different diseases.[47,48] However, it is observed that SIRI is less studied in psychiatric diseases compared to other biomarkers. In the literature, there are reports of abnormal numbers of circulating immune cells in patients with major depressive disorder and bipolar disorder.[49,50] In a study, it has been shown that SII and SIRI significantly influence the risk of depression.[51]

Another finding of our study is the results of logistic regression analysis. With the obtained results, it is considered that SII and SIRI may be associated with the diagnosis of GAD. Therefore, it is believed that calculating SII and SIRI, along with the existing parameters, will be crucial in assessing inflammation. Our findings demonstrate the association of GAD with NLR, MLR, SII, and SIRI.

Limitations

An important limitation of our study is its retrospective nature. In addition, the fact the smoking status, alcohol use, nutrition, and exercise status of the participants could not be evaluated, and the data were not supported by scales are other important limitations. Another limitation of our study is that C-reactive protein (CRP) levels were not available for all participants and this parameter could not be evaluated. Therefore, we need longitudinal studies that evaluate all these parameters together and are supported by scales.

CONCLUSION

In light of the data obtained from the study, it can be suggested that low-grade inflammation is present in GAD. To better understand the role of inflammation GAD's development, we require larger-scale studies with larger sample groups, excluding confounding factors. A better understanding of the role of inflammation in anxiety disorders will shed light on the development of new treatment strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Amasya University Non-interventional Clinical Researches Ethics Committee (Date: 04.01.2024, Decision No: 2023/162).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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