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RESEARCH

Markers of inflammation in patients with generalized anxiety disorder

Yaygın anksiyete bozukluğu tanılı hastalarda inflamasyon belirteçleri

Sevler Yıldız[1], Aslı Kazgan Kılıçaslan[2], Burcu Sırlıer Emir[1], Muhammed Fatih Tabara[3], Osman Kurt[4], Şeyma Sehlikoğlu[5], Kerim Uğur[6]

[1]Elazığ Fethi Sekin City Hospital, Elazığ, Türkiye
[2]Basaksehir Cam Sakura City Hospital, İstanbul, Türkiye
[3]Fırat University, Elazığ, Türkiye
[4]İnönü University, Malatya, Türkiye
[5]Adıyaman University, Adıyaman, Türkiye
[6]Malatya Turgut Özal University, Malatya, Türkiye

Abstract

Purpose: The aim of this study was to analyze the systemic immune response index, systemic immune inflammation index, neutrophil/HDL, lymphocyte/HDL, platelet/HDL, and monocyte/HDL ratio, used as inflammatory markers in patients with generalized anxiety disorder (GAD).

Materials and Methods: A total of 864 participants, including 432 healthy controls and 432 patients diagnosed with GAD, were included in this study. High-density lipoprotein (HDL-c) levels, neutrophil, monocyte, lymphocyte, and platelet counts; systemic inflammatory response index (SIRI), systemic immune-inflammatory index (SII), neutrophil/high-density lipoprotein ratio (NHR), lymphocyte/high-density lipoprotein ratio (LHR), monocyte/high-density lipoprotein ratio (MHR), and platelet/high-density lipoprotein ratio (PHR) were calculated.

Results: The median age of the case group was 35.50 (interquartile range: 28.00-44.00), while the median age of the control group was 35.00 (interquartile range: 28.00-44.00). In the GAD group, neutrophils, monocytes, SII, SIRI, NHR, LHR, MHR, and PHR were significantly higher, while platelets and HDL were significantly lower.

Conclusions: This study highlights that elevated systemic inflammation markers, such as SII and SIRI, along with altered HDL ratios, may be associated with GAD. The findings support the hypothesis that inflammation plays a role in the etiopathogenesis of GAD, potentially contributing to both diagnosis and management.

Keywords: Generalized anxiety disorder, SIRI, SII, NHR, LHR, MHR, PHR, inflammation

Öz

Amaç: Bu çalışmada yaygın anksiyete bozukluğu (YAB) hastalarında inflamasyon belirteçleri olarak kullanılan sistemik immün cevap indeksi, sistemik immün inflamasyon indeksi, nötrofil/HDL, lenfosit/HDL, platelet/HDL ve monosit/HDL oranını incelemeyi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya 432 sağlıklı kontrol ve 432 YAB tanılı hasta olmak üzere toplam 864 katılımcı dahil edildi. Yüksek yoğunluklu lipoprotein (HDL-c) seviyeleri, nötrofil, monosit, lenfosit ve trombosit sayıları; sistemik inflamatuar yanıt indeksi (SIRI), sistemik immün-inflamatuar indeks (SII), nötrofil/yüksek yoğunluklu lipoprotein oranı (NHR), lenfosit/yüksek yoğunluklu lipoprotein oranı (LHR), monosit/yüksek yoğunluklu lipoprotein oranı (MHR), trombosit/yüksek yoğunluklu lipoprotein oranı (PHR) hesaplandı.

Bulgular: Vaka grubunun ortanca yaşı 35.50 (çeyrekler arası aralık: 28.00-44.00), kontrol grubunun ortanca yaşı ise 35.00 (çeyrekler arası aralık: 28.00-44.00) idi. GAD grubunda nötrofil, monosit, SII, SIRI, NHR, LHR, MHR ve PHR değeri kontrol grubundan anlamlı şekilde yüksek; trombosit ve HDL değeri ise anlamlı şekilde düşük bulunmuştur.

Sonuç: Bu çalışma, SII ve SIRI gibi yüksek sistemik inflamasyon belirteçlerinin, değişmiş HDL oranları ile birlikte, YAB ile ilişkili olabileceğini vurgulamaktadır. Bulgular, inflamasyonun YAB'nin etiyopatogenezinde rol oynadığı hipotezini desteklemekte ve potansiyel olarak hem tanıya hem de tedaviye katkıda bulunmaktadır.

Anahtar kelimeler: Yaygın anksiyete bozukluğu, SIRI, SII, NHR, LHR, MHR, PHR, inflamasyon

Address for Correspondence: Kerim Uğur, Malatya Turgut Özal University Faculty of Medicine, Department of Psychiatry, Malatya, Türkiye E-mail address: premirek@gmail.com
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INTRODUCTION

Generalized anxiety disorder (GAD) is a mental disorder that includes symptoms such as insomnia, fatigue, muscle aches, and a state of constant anxiety that significantly distress the individual[1]. The lifetime incidence of GAD becoming chronic if left untreated is 6%[2]. The prevalence of generalized anxiety disorder varies in different countries[3]. In the "Mental Health Profile of Turkey" report, mental illness was determined in 17.2% of the population, and the most frequent diagnoses were anxiety and depression[4]. It shows that if left untreated, generalized anxiety disorder is a chronic disease that can cause patients to suffer for many years and cause a decrease in the person's functionality[5]. In conjunction with genetic, biological, and environmental determinants, inflammation is implicated in the etiopathogenesis of anxiety disorders, notably GAD[6, 7]. Stress may increase proinflammatory cytokine levels because it stimulates the hypothalamic-pituitary-adrenal axis, increases sympathetic nervous system activity, and decreases parasympathetic nervous system activity[8-10]. Anxiety symptoms are known to exert neurotoxic effects on the brain through these cytokines[11]. Recently, the relationship between GAD and inflammation has been investigated. In a meta-analysis study of GAD patients, peripheral inflammatory markers such as C-reactive protein (CRP), interferon-γ, and tumor necrosis factor-α were examined, and CRP, in particular, was found to be significantly higher in GAD patients than in the control group[12].

Neutrophils, lymphocytes, platelets, and monocytes are important cells in the immune system, and the neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and platelet/lymphocyte ratio are used as indicators of inflammation in psychiatric disorders[13,14]. The systemic immune inflammation index (SII), defined as platelet count × monocyte/lymphocyte, and the systemic inflammation response index (SIRI), calculated using the formula neutrophil count × monocyte/lymphocyte count, also indicate inflammation [15, 16]. Wei et al. have shown that SIRI and SII levels can be used as indicators of inflammation in patients with schizophrenia and bipolar disorder[17]. High-density lipoprotein (HDL-c) alleviates endothelial damage by demonstrating anti-inflammatory, antioxidant, and antithrombotic characteristics in inflammatory conditions [18]. Neutrophil/HDL ratio (NHR), lymphocyte/HDL ratio (LHR), monocyte/HDL ratio (MHR), and platelet/HDL ratio (PHR) are investigated as new markers of inflammation in psychiatric diseases [19]. These inflammation markers have been shown to increase acute mania [20]. However, no large-scale study has investigated the differences in NHR, LHR, MHR, PHR, SII, and SIRI indicators of inflammation and the relationship between these factors and GAD in GAD patients. We hypothesized that these indicators of inflammation may be associated with GAD at different levels. We wondered whether hemogram and biochemical parameters, which are simple and applicable, show changes in patients diagnosed with generalized anxiety disorder. We thought that clarification of this situation may give an idea about the diagnosis of generalized anxiety disorder, the severity of the disease during follow-up, and affect the treatment modality. Therefore, we examined some laboratory tests and their relationship with the related formulas in patients with GAD.

MATERIALS AND METHODS

Sample

The medical records of individuals who attended the Mental Health and Diseases Clinic at Fethi Sekin City Hospital from January 2020 to January 2024 were reviewed using the hospital's registration system. Patients' previous treatment and comorbidities were analyzed using the patient record system. Patients who presented within the analyzed date range were included in the study. The patient's medical history, anamnesis, and other systemic diseases were examined in detail from the hospital record system by a mental health and diseases specialist. G*Power 3.1.9.2 program was used to calculate the sample of the study and the study "Evaluation of Simple Inflammation Markers and Systemic Immune Inflammation Index in Schizophrenia Patients, Bipolar and Healthy Control Group" was taken as reference. Accordingly, it was determined that a total of at least 232 participants, including at least 116 patient groups and 116 control groups, should be reached with a 95% confidence interval and 99% power.

Procedure

The ethical approval of our study was obtained from the Non-Interventional Research Ethics Committee of Fırat University (05.12.2022-12647).

The medical records of patients diagnosed by a specialized psychiatrist following the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) were analyzed. After excluding 27 patients with missing data, the study included data from 432 patients with GAD. The data of healthy people with similar characteristics to the patients who came to our hospital for a routine annual check-up and who had no known systemic or mental illness were included in the study as a control group.

The patient's laboratory values were analyzed at the psychiatric clinic's first visit. Patients with alcohol and substance abuse in the last 6 months were not included in the study. Patients with chronic diseases such as diabetes, hypertension, chronic kidney and liver disease, heart disease, respiratory diseases, cancer, anaemia, autoimmune diseases, endocrine diseases, etc., in addition to the diagnosis of GAD in the registry system and patients with active infections, were excluded from the study.

Measures

Sociodemographic data form

The sociodemographic and clinical data form developed by the researchers was used. This form includes demographic information such as age and marital status, as well as clinical assessment questions such as history of psychiatric treatment.

Laboratory analysis

In our Mental Health and Disease Clinic, blood is routinely taken from the antecubital vein in the morning and when patients are fasting. In our hospital, a complete blood count is performed using the DXH-800 (Beckman Coulter, Inc., Miami, FL, USA), and biochemical parameters are analyzed using the Beckman AU-5800 (Beckman Coulter Diagnostics, Indianapolis, IN, USA). Neutrophil, platelet, lymphocyte, and monocyte counts and HDL-c levels were measured in the patient groups. Neutrophil count/HDL-c, platelet count/HDL-c, and monocyte count/HDL-c were calculated, respectively. SIRI and SII were calculated using the formulas SIRI = neutrophil count x monocyte/lymphocyte count and SII = platelet count x monocyte/lymphocyte count.

Statistical analysis

The analyses were conducted using the SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL) version 22 software package. Categorical variables such as gender, active psychiatric treatment, and previous psychiatric treatment were compared by the Pearson Chi-square test. In the study, descriptive statistics were reported using frequencies (n) and percentages (%) for categorical variables and median with interquartile range (25th-75th percentile values) for continuous variables. The Kolmogorov-Smirnov test was utilized to evaluate the normal distribution suitability of continuous variables. The Mann-Whitney U test was used to compare the blood parameters and related indices of the groups. The relationship between age and inflammation indices was investigated by the Spearman correlation test. A significance level of $p<0.05$ was adopted for all analyses.

RESULTS

A total of 864 participants, 432 cases and 432 controls, were included in the study. In the case group, 55.1% were female, 44.9% were male, and in the control group, 60.9% were female and 39.1% were male. There was no significant difference in gender between the groups ($p=0.085$). The median age of the case group was 35.50 (interquartile range: 28.00-44.00), while the median age of the control group was 35.00 (interquartile range: 28.00-44.00). There was no statistically significant difference in age between the groups ($p=0.939$). The rate of active psychiatric treatment ($p<0.001$) and the rate of previous psychiatric treatment ($p<0.001$) were significantly higher in the case group than in the control group. Neutrophils ($p<0.001$), monocytes ($p<0.001$), SII ($p<0.001$), SIRI ($p<0.001$), NHR ($p<0.001$), LHR ($p<0.001$), MHR ($p<0.001$), and PHR ($p=0.002$) exhibited significantly higher levels in the case group. In contrast, platelets ($p=0.01$) and HDL-c ($p<0.001$) were significantly lower (Table 1).

No statistically significant difference was noted between genders in terms of blood values ($p>0.05$) (Table 2). Likewise, no significant difference was observed between previous and active psychiatric treatment statuses concerning blood values ($p>0.05$) (Table 3). No significant correlation was observed

between age and blood parameters in the case group (Table 4).

Table 1. Comparison of all characteristics of the groups

Variables		Case		Control		p
		n	%	n	%	
Gender	Female	238	55.1	263	60.9	0.085*
	Male	194	44.9	169	39.1	
Age, median (IQR)		35.50 (28.00-44.00)		35.00 (28.00-44.00)		0.939**
Active psychiatric treatment	Yes	253	58.6	0	0	**<0.001***
	No	179	41.4	432	100.0	
Previous psychiatric treatment	Yes	209	48.4	21	4.9	**<0.001***
	No	223	51.6	411	95.1	
Neutrophil, median (IQR)		5.09 (3.94-6.55)		3.78 (3.17-4.70)		**<0.001****
Lymphocyte, median (IQR)		2.10 (1.57-2.61)		2.09 (1.59-2.50)		0.583**
Monocyte, median (IQR)		0.60 (0.48-0.70)		0.53 (0.42-0.66)		**<0.001****
Plt, median (IQR)		242.00 (210.00-283.50)		253.50 (220.50-291.50)		**0.01****
HDL, median (IQR)		43.00 (36.50-48.00)		50.00 (42.00-57.00)		**<0.001****
SII, median (IQR)		577.07 (399.70-902.22)		467.88 (355.52-652.75)		**<0.001****
SIRI, median (IQR)		1.38 (0.94-2.15)		1.00 (0.71-1.46)		**<0.001****
NHR, median (IQR)		0.12 (0.09-0.16)		0.08 (0.06-0.10)		**<0.001****
LHR, median (IQR)		0.05 (0.04-0.07)		0.04 (0.03-0.06)		**<0.001****
MHR, median (IQR)		0.011 (0.010-0.020)		0.010 (0.009-0.011)		**<0.001****
PHR, median (IQR)		5.73 (4.80-6.98)		5.22 (4.10-6.28)		**<0.001****

*Chi-square analysis, **Mann Whitney U test were conducted.

Table 2. Comparison of some parameters according to gender in the case group

	Female	Male	p*
	Median (IQR)	Median (IQR)	
SII	553.71 (391.25-886.88)	631.46 (413.30-918.34)	0.214
SIRI	1.31 (0.99-2.05)	1.44 (0.90-2.31)	0.553
NHR	0.12 (0.09-0.16)	0.12 (0.09-0.16)	0.876
LHR	0.05 (0.04-0.07)	0.05 (0.04-0.06)	0.379
MHR	0.010 (0.010-0.020)	0.010 (0.010-0.020)	0.498
PHR	5.65 (4.73-7.13)	5.82 (4.85-6.92)	0.965

*Mann Whitney U test was applied.

Table 3. Comparison of some parameters according to previous and active psychiatric treatment

	Active psychiatric treatment			Previous psychiatric treatment		
	Yes	No	p*	Yes	No	p*
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
SII	576.80 (408.18-918.34)	581.14 (397.50-879.48)	0.497	576.80 (430.26-895.42)	580.53 (361.89-918.34)	0.591
SIRI	1.36 (0.94-2.18)	1.39 (0.93-2.01)	0.887	1.40 (0.97-2.13)	1.34 (0.91-2.18)	0.741
NHR	0.12 (0.09-0.16)	0.12 (0.09-0.16)	0.553	0.12 (0.09-0.16)	0.12 (0.09-0.16)	0.856
LHR	0.05 (0.04-0.06)	0.05 (0.04-0.07)	0.080	0.05 (0.04-0.07)	0.05 (0.04-0.07)	0.493
MHR	0.010 (0.010-0.020)	0.010 (0.010-0.020)	0.438	0.010 (0.010-0.020)	0.010 (0.010-0.020)	0.118
PHR	5.67 (4.83-6.90)	5.88 (4.74-7.09)	0.602	5.67 (4.75-6.92)	5.85 (4.85-7.06)	0.497

*Mann Whitney U test was applied.

Table 4. Correlation of age and blood parameters in the case group

	Age	
	r	p
SII	-0.015	0.753
SIRI	-0.019	0.693
NHR	-0.001	0.983
LHR	0.033	0.496
MHR	-0.019	0.701
PHR	-0.024	0.622

DISCUSSION

In this retrospective study, we evaluated some hemogram values and the relationship between HDL-c and blood lipids in patients with generalized anxiety disorder. Our findings suggest that high levels of neutrophils, monocytes, SII, SIRI, NHR, LHR, MHR, and PHR and low levels of platelets and HDL-c may be important indicators of inflammation in generalized anxiety disorder.

Recently, biomarkers have been used in many diseases for their diagnostic value and to predict prognosis [21]. Among these markers, hemogram and biochemical parameters come to the fore because they are cheap and applicable[22]. Neutrophil, lymphocyte, platelet, and monocyte levels, HDL-c ratios, SII, and SIRI values are investigated as markers of inflammation in many diseases[23]. In a study of 200 patients with schizophrenia, the relationship between neutrophil-lymphocyte, platelet-lymphocyte, and monocyte-lymphocyte ratios and immune inflammation index and negative symptoms was investigated, and it was reported that there was a positive correlation between neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) and negative symptoms[24]. Another retrospective study found that platelet and lymphocyte counts in patients with schizophrenia were low, NLR and MLR ratios were significantly high, and monocyte count, lymphocyte count, NLR, and MLR showed gender differences[25]. In patients with depression, especially the neutrophil-lymphocyte ratio was significantly associated with an increased risk of depression [26]. Uzun et al. found that white blood cell and neutrophil counts, NLR, MLR, and PLR values were significantly higher in children and adolescents with anxiety disorders compared to the control group [27]. Blood lipids and psychiatric disorders are known to be causally related. It is thought that blood lipid levels may be a reliable biological marker of psychiatric disorders [28]. Low serum HDL-c levels have been suggested as an indicator of the development of postnatal depressive symptoms [29]. Torsvik et al. have shown that patients with schizophrenia and bipolar disorder have high levels of immature neutrophils about lipid changes with the genes that cause this condition [30]. In another study, high MHR was reported as an independent marker of inflammation in patients with stable coronary artery disease in schizophrenia[31]. The systemic immune inflammation index and systemic inflammatory response index are much more important markers of inflammation[16]. Inaltekin et al. observed high NLR, PLR, and SII values and low mean platelet volume (MPV) and lymphocyte counts in patients with schizophrenia compared to the control group. In bipolar disorder patients, elevated values of NLR, PLR, and SII, as well as increased neutrophil counts, were observed compared to those in the control group. It was shown that there were lower MPV values in patients with schizophrenia compared to bipolar disorder patients, and it was concluded that these significant values indicated the presence of low-grade systemic inflammation in patients with schizophrenia and bipolar disorder[15]. A study conducted among patients with depression suggested that elevated SII values were indicative of moderate to severe depression[32]. A study conducted in 2023 among patients diagnosed with bipolar disorder revealed notable disparities in SII, SIRI, NHR, LHR, MHR, PHR, neutrophils, and monocytes. These findings underscored the involvement of systemic inflammation in the pathophysiology of bipolar disorder, as well as the association between inflammation and criminal behaviour[33]. Canlı et al. found that neutrophil, lymphocyte, monocyte, and thrombocyte counts and NLR, MLR, SII, and SIRI values were high in 147 GAD patients who did not receive treatment, and SII and SIRI parameters predicted the diagnosis of GAD[34]. Similar to most of the studies in the literature, we found that neutrophil, monocyte, SII, SIRI, NHR, LHR, MHR, and PHR values were high,

and platelet and HDL-c values were low. Şahpolar et al. found that monocyte counts and MHR values were higher in patients with schizophrenia than in the control group, and there was a positive correlation between age, body mass index, disease severity, and MHR[35]. We did not find any significant correlation between gender, current and past history of psychiatric treatment, age, and blood parameters. Inflammation plays an important role in the etiopathogenesis of GAD. Our findings provide information about the inflammation in GAD disease with the mentioned blood parameters. Prospective studies with large sample sizes are needed. This situation suggests that inexpensive and applicable blood tests may contribute to the subclinical recognition and psychiatric treatment of GAD.

In our study, no significant difference was observed between previous and active psychiatric treatment status in terms of blood values. Dawidowski et al. reported that antipsychotics have a lowering effect on NLR values in psychosis and that NLR may be a potential tool for assessing response to treatment with antipsychotics[36]. Paolini et al. also showed that antidepressant drugs may affect NLR in patients with depression[37]. We can say that psychiatric drugs used in the past may not affect hemogram parameters and HDL levels in patients with generalized anxiety disorder. This suggests that psychiatric medication may not have a permanent effect on blood values. The retrospective nature of our study is an important limitation, and prospective and long-term studies are needed to clarify this situation.

In our research, no statistically significant difference was noted between genders and age in terms of blood values. It is known that age and gender factors are important in terms of psychiatric disorders[38]. In a study examining the effect of gender differences in clinical and biochemical parameters in patients with schizophrenia, it was reported that women showed metabolic changes such as hypercholesterolemia and thyroid dysfunction more frequently[39]. Some studies have also shown that systemic cytokine levels are remodeled with age. This condition, described as inflammaging, is thought to be associated with psychiatric disorders[40, 41]. We observed that the above-mentioned blood parameters were not affected by age and gender variables in patients with generalized anxiety disorder. In this respect, our findings do not support the literature.

This study has several limitations. First, its retrospective design limits the ability to establish causal relationships between inflammation markers and GAD. Second, being a single-center study may restrict the generalizability of our findings to broader populations. Additionally, the control group, selected from individuals attending routine health check-ups, may not be entirely representative of the general population. Some participants were on psychiatric medications, which may influence inflammation markers, although we observed no significant differences in markers between those with previous and current treatment histories. Finally, the study did not account for potential confounding factors such as lifestyle, diet, and comorbid conditions that might impact inflammatory levels. Future prospective, multi-center studies are warranted to address these limitations and further explore the role of inflammation in GAD.

In summary, our study underscores a significant association between GAD and increased levels of inflammation markers, including SII, SIRI, and altered HDL ratios. These findings suggest that systemic inflammation may play a crucial role in the pathophysiology of GAD, potentially offering a new avenue for both diagnostic and therapeutic strategies. The observed correlations indicate that routine blood tests could be valuable, cost-effective tools for assessing inflammation levels in GAD patients, aiding in early identification and intervention. However, further prospective research with larger samples is essential to confirm these relationships and better understand the clinical implications of inflammation markers in GAD.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Washington DC, American Psychiatric Association. 2013.

2. Maron E, Nutt D. Biological markers of generalized anxiety disorder. Dialogues Clin Neurosci. 2017;19:147-58.
3. Ruscio AM, Hallion LS, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J et al. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. JAMA Psychiatry. 2017;74:465-75.
4. Korkut Bayindir S, Ünsal A. Nursing diagnosis and interventions in the common mental diseases. J Duzce Univ Heal Sci Inst. 2016;6:115-19.
5. DeMartini J, Patel G, Fancher TL. Generalized anxiety disorder. Ann Intern Med. 2019;170:9:64.
6. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology. 2017;42:254-70.
7. Munir S, Takov V. Generalized anxiety disorder.. In: StatPearls [Internet]. Treasure Island (FL), StatPearls Publishing; 2024.
8. Yehuda R. Status of glucocorticoid alterations in post-traumatic stress disorder. Ann N Y Acad Sci. 2009;1179:56-69.
9. Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987-2007). Brain Behav Immun. 2007;21:736-45.
10. Won E, Kim YK. Neuroinflammation-associated alterations of the brain as potential neural biomarkers in anxiety disorders. Int J Mol Sci. 2020;21:6546.
11. Felger JC. Imaging the role of inflammation in mood and anxiety-related disorders. Curr Neuropharmacol. 2018;16:533-58.
12. Costello H, Gould RL, Abrol E, Howard R. Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. BMJ Open. 2019;9:e027925.
13. Yıldız S, Kazğan A, Tabara M, Atmaca M. The relationship between impulsivity level and neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and mean platelet volume in individuals diagnosed with gambling disorder. Medical Records. 2021;3:177-83.
14. Inaltekin A, Yağci İ. Evaluation of simple markers of inflammation and systemic immune inflammation index in schizophrenia, bipolar disorder patients and healthy controls. Turk Psikiyatri Derg. 2023;34:11-15.
15. Kong F, Huang J, Xu C, Huang T, Wen G, Cheng W. System inflammation response index: a novel inflammatory indicator to predict all-cause and cardiovascular disease mortality in the obese population. Diabetol Metab Syndr. 2023;15:195.
16. Cheng W, Bu X, Xu C, Wen G, Kong F, Pan H et al. Higher systemic immune-inflammation index and systemic inflammation response index levels are associated with stroke prevalence in the asthmatic population: a cross-sectional analysis of the NHANES 1999-2018. Front Immunol. 2023;14:1191130.
17. Wei Y, Wang T, Li G, Feng J, Deng L, Xu H et al. Investigation of systemic immune-inflammation index, neutrophil/high-density lipoprotein ratio, lymphocyte/high-density lipoprotein ratio, and monocyte/high-density lipoprotein ratio as indicators of inflammation in patients with schizophrenia and bipolar disorder. Front Psychiatry. 2022;13:941728.
18. Bonizzi A, Piuri G, Corsi F, Cazzola R, Mazzucchelli S. HDL dysfunctionality: clinical relevance of quality rather than quantity. Biomedicines. 2021;9:729.
19. Cheng N, Ma H, Zhang K, Zhang C, Geng D. The predictive value of monocyte/high-density lipoprotein ratio (MHR) and positive symptom scores for aggression in patients with schizophrenia. Medicina (Kaunas). 2023;59:503.
20. Korkmaz ŞA, Kızgın S. Neutrophil/high-density lipoprotein cholesterol (HDL), monocyte/HDL and platelet/HDL ratios are increased in acute mania as markers of inflammation, even after controlling for confounding factors. Curr Med Res Opin. 2023;39:1383-90.
21. Bodaghi A, Fattahi N, Ramazani A. Biomarkers: Promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases. Heliyon. 2023;9:13323.
22. Agnello L, Giglio RV, Bivona G, Scazzone C, Gambino CM, Iacona A et al. The value of a complete blood count (CBC) for sepsis diagnosis and prognosis. Diagnostics (Basel). 2021;11:1881.
23. Tekin S, Avcı E, Nar R, Değirmenci E, Demir S, Şenol H. Are monocyte/HDL, lymphocyte/monocyte and neutrophil/lymphocyte ratios prognostic or follow-up markers in ischemic cerebrovascular patients?. J Basic Clin Health Sci. 2020;4:38-43
24. Šagud M, Madžarac Z, Nedic Erjavec G, Šimunović Filipčić I, Mikulić FL, Rogić D et al. The associations of neutrophil-lymphocyte, platelet-lymphocyte, monocyte-lymphocyte ratios and immune-inflammation index with negative symptoms in patients with schizophrenia. Biomolecules. 2023;13:297.
25. Zhu X, Zhou J, Zhu Y, Yan F, Han X, Tan Y et al. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas Psychiatry. 2022;30:95-99.
26. Cheng Y, Wang Y, Wang X, Jiang Z, Zhu L, Fang S. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depression: an updated systematic review and meta-analysis. Front Psychiatry. 2022;13:893097.
27. Uzun N, Akıncı MA. Hemogram parameters in childhood anxiety disorders: Could anxiety disorders be related with inflammation? Med Hypotheses. 2021;146:110440.
28. Li B, Qu Y, Fan Z, Gong X, Xu H, Wu L et al. Causal relationships between blood lipids and major

psychiatric disorders: Univariable and multivariable mendelian randomization analysis. BMC Med Genomics. 2023;16:250.

29. Ramachandran Pillai R, Wilson AB, Premkumar NR, Kattimani S, Sagili H, Rajendiran S. Low serum levels of high-density lipoprotein cholesterol (HDL-c) as an indicator for the development of severe postpartum depressive symptoms. PLoS One. 2018;13:0192811.
30. Torsvik A, Brattbakk HR, Trentani A, Holdhus R, Stansberg C, Bartz-Johannessen CA et al. Patients with schizophrenia and bipolar disorder display a similar global gene expression signature in whole blood that reflects elevated proportion of immature neutrophil cells with association to lipid changes. Transl Psychiatry. 2023;13:147.
31. Candemir M, Cansız A. Predictive value of monocyte to high-density lipoprotein cholesterol ratio (MHR) in schizophrenia patients with stable coronary artery disease. Genel Tıp Dergisi. 2022;32:77-83.
32. Cui S, Li J, Liu Y, Yao G, Wu Y, Liu Z et al. Correlation of systemic immune-inflammation index and moderate/major depression in patients with depressive disorders: a large sample cross-sectional study. Front Psychiatry. 2023;14:1159889.
33. Sırlıer Emir B, Yıldız S, Kazğan Kılıçaslan A, Kurt O, Uğur K, Tabara MF et al. Inflammation markers in patients with bipolar disorder who have committed offenses and their relationship with criminal behavior. Medicina (Kaunas). 2023;59:1725.
34. Canlı D. Evaluation of systemic immune-inflammation index, systemic inflammatory response index and hematologic inflammatory parameters in generalized anxiety disorder: a controlled study. Anadolu Current Medical Journal. 2024;6:161-67.
35. Sahpolat M, Ayar D, Ari M, Karaman MA. Elevated monocyte to high-density lipoprotein ratios as an inflammation markers for schizophrenia patients. Clin Psychopharmacol Neurosci. 2021;19:112-16.
36. Dawidowski B, Grelecki G, Bilgorajski A, Podwalski P, Misiak B, Samochowiec J. Effect of antipsychotic treatment on neutrophil-to-lymphocyte ratio during hospitalization for acute psychosis in the course of schizophrenia-a cross-sectional retrospective study. J Clin Med. 2021;11:232.
37. Paolini M, Harrington Y, Raffaelli L, Poletti S, Zanardi R, Colombo C et al. Neutrophil to lymphocyte ratio and antidepressant treatment response in patients with major depressive disorder: Effect of sex and hippocampal volume. Eur Neuropsychopharmacol 223;76:52-60.
38. Watkins DC, Johnson NC. Age and gender differences in psychological distress among african americans and whites: findings from the 2016 National Health Interview Survey. Healthcare (Basel). 2018;6:6.
39. Esposito CM, De Cagna F, Caldiroli A, Capuzzi E, Ceresa A, Di Paolo M et al. Gender differences in clinical and biochemical parameters among patients hospitalized for schizophrenia: towards precision medicine. Eur Arch Psychiatry Clin Neurosci. 2024;274:1093-103.
40. Wong GCL, Ng TKS, Lee JL, Lim PY, Chua SKJ, Tan C et al. Horticultural therapy reduces biomarkers of immunosenescence and inflammaging in community-dwelling older adults: A feasibility pilot randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2021;76:307-17.
41. Liu Y, Zhao W, Lu Y, Zhao Y, Zhang Y, Dai M et al. Systematic metabolic characterization of mental disorders reveals age-related metabolic disturbances as potential risk factors for depression in older adults. MedComm (2020). 2022;3:165.