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The Role of Systemic Inflammation and Haematological Parameters in Autism

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by challenges in social communication and repetitive behaviors. Emerging evidence suggests that ASD may also involve systemic inflammatory processes. This study aimed to assess systemic inflammation in children with ASD using hematological biomarkers and to investigate the association between these markers and autism severity. A total of 75 children with ASD (mean age: 4.37±1.01 years) and 75 age- and sex-matched healthy controls (mean age: 4.41±1.06 years) were included. Complete blood count data were used to calculate neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). Compared to controls, the ASD group showed significantly higher levels of leukocytes (p=0.011), neutrophils (p=0.001), monocytes (p<0.001), NLR (p=0.005), SII (p=0.001), and SIRI (p<0.001). Moreover, CARS scores, indicating autism severity, were positively correlated with these inflammatory markers (e.g., SIRI: r=0.403, p<0.001; monocyte: r=0.362, p<0.001). These findings suggest that systemic inflammation may contribute to the pathophysiology of ASD and that hematological indices could serve as accessible biomarkers for clinical evaluation.

Keywords: ASD, SII, SIRI, Inflammation, Haematological biomarkers.

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Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder that affects social communication and interaction, accompanied by repetitive and restrictive behavioral patterns [1]. Recent epidemiological research has indicated a notable rise in the prevalence of ASD [2]. Although its precise etiology remains unclear, genetic, neurophysiological, neuroanatomical, immunological, and environmental factors are thought to contribute to its pathogenesis [3]. Growing evidence suggests that, beyond being a neurodevelopmental disorder, ASD may also be associated with immunological and inflammatory processes [4, 5].

Inflammation serves as a defense mechanism of the immune system against infections, tissue damage, and stress [6]. Low-grade systemic inflammation has been implicated in various psychiatric disorders, including psychotic, mood, and personality disorders [7]. While blood-based biomarkers are commonly used to investigate inflammation in psychiatric research, many of these markers are costly and not suitable for routine clinical application. Consequently, there is a need for more cost-effective and practical alternatives. Among these, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple and efficient marker for assessing systemic inflammation and has recently been investigated in psychiatric populations [8]. Similarly, the platelet-to-lymphocyte ratio (PLR) has been explored as an indicator of subclinical inflammation, with studies demonstrating elevated PLR levels in individuals with bipolar disorder and schizophrenia [9].

Serum inflammation biomarkers are increasingly recognized as valuable tools for the early identification and etiological investigation of psychiatric disorders. In addition to NLR and PLR, several novel hematological indices, including the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) have been proposed [10]. These indices, derived from complete blood count and biochemical analyses, provide cost-effective and practical measures of systemic inflammation and immune response [11].

SII, a novel inflammatory biomarker, is calculated as (platelet count × neutrophil count) / lymphocyte count, while SIRI is determined using the formula (neutrophil count × monocyte count) / lymphocyte count. These indices are considered comprehensive indicators of inflammation, reflecting both neutrophil-mediated inflammatory activity and the suppression of lymphocyte-driven immune responses [12-14]. Despite their potential utility, the diagnostic value of these biomarkers in psychiatric disorders remains insufficiently explored.

The present study aims to assess systemic inflammation in individuals with ASD through hematological biomarkers and to investigate the

association between these parameters and autism severity. Current literature lacks sufficient data on the use of novel hematological markers such as SII and SIRI in evaluating ASD severity. Therefore, this study seeks to compare these markers between individuals with ASD and healthy controls and to examine their potential correlations with autism severity. These results are anticipated to improve insights into the immunological mechanisms involved in ASD and support the assessment of inflammation-related biomarkers in both diagnostic and clinical decision-making.

Materials and Methods

In this study, the records of patients who applied to the Child and Adolescent Mental Health and Diseases Outpatient Clinic of Sivas Cumhuriyet University Faculty of Medicine Hospital between January 2023 and January 2024 were retrospectively analysed. The study included children diagnosed with autism spectrum disorder (ASD) as a result of clinical interviews based on DSM-5 diagnostic criteria, family interviews and diagnostic psychiatric evaluation performed in the infant/child play observation room. The study group consisted of 75 children diagnosed with ASD, aged between 3 and 6 years, who did not have any accompanying psychiatric, neurological or medical disease and whose haemograms were performed. The control group consisted of 75 healthy children who did not have any psychiatric diagnosis, who underwent haemogram examinations and were matched with the patient group in terms of age and gender. In order to support the diagnosis and differential diagnosis, routine blood tests were requested from all participants to evaluate their current metabolic status and to monitor drug side effects in case of possible need for pharmacological treatment. Children with recent infections, chronic medical conditions, recent vaccinations, or current medication use were excluded from both groups in order to minimize potential confounding effects on inflammatory parameters. The Childhood Autism R ating Scale (CARS) was used to assess the severity of autism and the relevant data were retrospectively scanned from the patient files. Sociodemographic data of the children in the study were obtained from the hospital registration system. Complete Blood Count (CBC) analyses were performed in the hospital biochemistry laboratory using a MINDRAY BC-6200 device. From the CBC parameters, two systemic inflammatory indices were calculated: the SII, defined as (Platelet × Neutrophil) / Lymphocyte, and the SIRI, defined as (Neutrophil × Monocyte) / Lymphocyte. These indices were used to assess systemic inflammatory status based on peripheral blood parameters. Approval for this study was obtained from Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee dated 17.10.2024 and numbered 2024-10/17.

Childhood Autism Rating Scale (CARS)

The ASRS is a behavioural rating scale developed by Schopler et al. (1980) and is used for screening and differential diagnosis of autism spectrum disorders [15]. The scale consists of 15 items and classifies the severity of autism as 'mild-moderate' and 'severe'. The severity of 15 behaviours such as 'Relationship with People', 'Imitation', 'Emotional Reactions', 'Use of Body', 'Object Use', 'Visual Reaction', 'Adaptation to Change', 'Listening Reaction', 'Taste, Smell, Touch Reaction and Use', 'Verbal Communication', 'Fear or Irritability', 'Nonverbal Communication', 'Activity Level', 'Level and Consistency of Mental Reactions', 'General Impressions' are evaluated. The severity of each behaviour is evaluated on a 1-4, half-point scale. The total score obtained from the scale varies between 15-60, and 30 points and above support the diagnosis of autism. According to the scoring, autism symptoms are not present in children between 15-29.5 points. Children with a score range of 30-36.5 are considered 'mild-moderately autistic'; children with a score range of 37-60 are considered 'severely autistic'. The Turkish validity and reliability study of the CARS was conducted by Gassaloğlu, Baykara et al. (2016) [16].

Statistical Analysis

SPSS software (IBM SPSS, Version 22.0, IBM Corporation, Armonk, NY, USA) was used for the statistical analyses of the data. The Kolmogorov-Smirnov test was performed to determine normality. The numerical and categorical data were given as mean ± standard deviation (SD), medians (25th, 75th), number (n), and percentage (%) as appropriate. Normally distributed data were analyzed using Independent Samples t-test and non-normally distributed data were analyzed using the Mann-Whitney U test. The comparison of categorical variables between the groups was analysed by Chi-square (χ^2) test. Correlations were evaluated using Pearson correlation analysis. A p-value of <0.05 was considered statistically significant in all analyses.

Results

Socio-demographic and Familial Characteristics of Participants

The mean age of the ASD group was 4.37±1.01 years and the mean age of the control group was 4.41±1.06 years. Age, gender, family income, place of residence, parental age and education did not differ significantly between the ASD and control groups (all p values >0.05). Table 1 shows the sociodemographic and familial characteristics of the participants.

Table 1. Socio-demographic and familial characteristics of participants. Data were given as mean±standard deviation or number (percent%).

	ASD group (n=75)	Control group (n=75)	p-value*
Age (mean-years±SD)	4.37±1.01	4.41±1.06	0.935
Gender (n, %)			0.119
Male	62 (82.7)	54 (72.0)	
Female	13 (17.3)	21 (28.0)	
Family income level (n, %)			0.577
The minimum wage/less than minimum wage	18 (24)	21 (28)	
Above the minimum wage	57 (76)	54 (72)	
Place of residence (n, %)			0.666
Urban	61 (81.3)	63 (84)	
Rural	14 (18.7)	12 (16)	
Maternal age (mean-years±SD)	30.73±3.45	30.56±4.08	0.356
Level of education of the mother (n, %)			0.578
Primary and secondary school	13 (17.3)	18 (24)	
High school	51 (68)	48 (64)	
University	11 (14.7)	9 (12)	
Paternal age (mean-years±SD)	35.47±4.19	34.96±4.02	0.757
Level of education of the father (n,%)			0.733
Primary and secondary school	9 (12)	12 (16)	
High school	41 (54.7)	41 (54.7)	
University	25 (33.3)	22 (29.3)	

Notes: *The chi-square test for categorical variables and the Mann-Whitney U for continuous variables were used to test group differences. Bold font indicates statistical significance: $p< 0.05$.
Abbreviations: ASD, Autism Spectrum Disorder; SD, Standard Deviation.

Comparison of CBC, Systemic Inflammatory Indices and Scale Scores Used between ASD and Control Groups

In the evaluation of blood parameters, no statistically significant difference was found between ASD and control groups in terms of haemoglobin, lymphocyte, platelet and PLR values. On the other hand, leucocyte, neutrophil, monocyte, NLR, SII and SICI values were significantly higher in the ASD group compared to the control group (p=0.011, p=0.001, p<0.001, p=0.005, p=0.001, p<0.001, respectively). Similarly, it was determined that the mean scores of the CARS were statistically significantly higher in the ASD group compared to the control group (p<0.001). The results are displayed in Table 2.

Table 2. Comparison of CBC, systemic inflammatory indices and scale scores used between ASD and control groups

	ASD group (n=75)	Control group (n=75)	p-value*
Hemoglobin mean ± SD	13.2±0.9	12.9±1.2	0.060
Leukocyte mean ± SD	8.6±2.4	7.6±2.1	**0.011**
Neutrophil median (25th-75th)	3.9 (2.8-4.8)	3.2 (2.5-4.1)	**0.001**
Lymphocyte median (25th-75th)	3.3 (2.8-4.2)	3.3 (2.7-3.8)	0.549
Monocyte mean ± SD	0.5±0.2	0.4±0.1	**<0.001**
Platelet mean ± SD	358.3±94.2	354.2±66.4	0.754
NLR median (25th-75th)	1.1 (0.8-1.7)	1.0 (0.7-1.1)	**0.005**
PLR mean ± SD	110.2±44.5	108.0±32.6	0.721
SII mean ± SD	514.2±441.5	338.4±131.7	**0.001**
SIRI median (25th-75th)	0.6 (0.4-0.9)	0.4 (0.3-0.5)	**<0.001**
CARS median (25th-75th)	38.5 (35.5-47.5)	17 (16-17)	**<0.001**

Notes: * The chi-square test was used for categorical variables, while the Mann-Whitney U test or the Independent Samples t-test was applied to continuous variables, depending on their distribution, to test group differences. **Bold font** indicates statistical significance: $p< 0.05$.
Abbreviations: ASD, Autism Spectrum Disorder; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-inflammation İndex; SIRI, Systemic Inflammation Response Index; CARS, Childhood Autism Rating Scale; SD, Standard Deviation

Correlations between CARS Mean Score and CBC and Systemic Inflammatory Indices

According to the correlation analysis, there was a significant positive correlation between the mean of the CARS total score and the values of leukocyte, neutrophil, monocyte, NLR, Sİİ and SİCİ (p=0.01, p=0.008, p<0.001, p<0.001, p=0.001, p<0.001, respectively). The results are shown in Table 3.

Table 3. Correlations between CARS mean score and CBC and systemic inflammatory indices

	CARS- Total Scores	
	r*	p*
Hemoglobin	0.120	0.143
Leukocyte	0.210	**0,01**
Neutrophil	0.215	**0,008**
Lymphocyte	0.019	0.819
Monocyte	0.362	**<0.001**
Platelet	-0.021	0.795
NLR	0.285	**<0.001**
PLR	0.037	0,656
SII	0.264	**0,001**
SIRI	0.403	**<0.001**

*Pearson correlation analysis was used. **Bold font** indicates statistical significance: $p < 0.05$.

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-inflammation İndex; SIRI, Systemic Inflammation Response Index; CARS, Childhood Autism Rating Scale; SD, Standard Deviation

Notes: * The chi-square test was used for categorical variables, while the Mann-Whitney U test or the Independent Samples t-test was applied to continuous variables, depending on their distribution, to test group differences. Bold font indicates statistical significance: $p< 0.05$.

Abbreviations: ASD, Autism Spectrum Disorder; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-inflammation İndex; SIRI, Systemic Inflammation Response Index; CARS, Childhood Autism Rating Scale; SD, Standard Deviation

Discussion

In this study, systemic inflammatory markers were analysed in children with ASD and the relationship between these markers and autism severity was evaluated. Results showed that leukocyte, neutrophil, monocyte, NLR, SII and SRI values were significantly higher in children with ASD compared to healthy control group. In addition, a positive correlation was found between CARS scores and these inflammatory markers.

Recent studies suggest that ASD should not only be considered as a neurodevelopmental disorder, but may also be closely related to immunological and inflammatory mechanisms. Indeed, postmortem analyses have demonstrated elevated levels of proinflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and monocyte chemotactic protein-1 (MCP-1), in the cerebellum and frontal cortex of individuals with autism. It has been reported that IL-6 in particular is associated with a decrease in dentritic branching and granule cell number and may contribute to excitatory-inhibitory synaptic imbalances [17-19]. TNF-α has been suggested to be a potential biomarker in the early diagnosis of autism [20]. Meta-analyses on this topic indicate that individuals with ASD exhibit significantly higher proinflammatory cytokine levels compared to healthy controls [21]. These findings support that inflammation may interact with the neurodevelopmental processes of ASD.

Biomarkers used in the evaluation of systemic inflammation are generally expensive and not suitable for routine clinical use. Therefore, the need for affordable and accessible inflammatory markers is increasing. NLR, a low-cost and reliable parameter, was initially developed to measure the level of inflammation and stress in critically ill patients. Later studies have indicated that NLR is linked to unfavorable outcomes in conditions such as pancreatitis, cardiovascular diseases, and liver disorders. Elevated NLR levels have also been found to correlate with increased C-reactive protein (CRP) and cytokine concentrations [22]. Similarly, PLR is an important marker used to evaluate the level of inflammation [8]. Studies have reported that NLR and PLR show significant changes in various neuropsychiatric diseases such as mood disorders, schizophrenia and Parkinson's disease [23, 24].

Although studies examining inflammatory biomarkers in childhood and adolescence are limited, high NLR and PLR levels have been shown to be associated with major depressive disorder and obsessive-compulsive disorder in adolescents [25, 26]. Higher NLR and PLR levels were reported in children with attention deficit hyperactivity disorders (ADHD) compared to healthy controls, but lymphocyte counts were found to be lower [27, 28]. Studies conducted in individuals with ASD have revealed similar findings. For example, it has been reported that neutrophil counts and NLR values were significantly higher compared to the healthy control group, but PLR levels remained similar and lymphocyte counts were lower [29]. It was also reported that monocyte levels increased and there was a positive correlation between autism severity and NLR [30]. The findings of our study, consistent with the existing literature, suggest that inflammation may be an important component in understanding the neurodevelopmental mechanisms of autism.

SII and SIRI, which are among the biomarkers of systemic inflammation, are inflammatory markers calculated using neutrophil, platelet, monocyte and lymphocyte from peripheral blood parameters . In the literature, SII and SIRI have been shown to have higher prognostic value compared to other inflammatory markers such as NLR and PLR [12, 13]. These parameters, which were first evaluated as a prognostic indicator in neurological and cardiovascular diseases, have started to be examined in the context of psychiatric disorders in recent years [14, 31]. It has been reported that SII and SIRI levels are significantly higher in individuals diagnosed with schizophrenia, bipolar disorder and anxiety disorder compared to healthy controls. However, studies addressing the role of these inflammatory markers in childhood psychiatric disorders are quite limited [32-34]. This study revealed that individuals with ASD had significantly elevated SII and SIRI levels compared to healthy controls. These results suggest that inflammation could be involved in the etiology of ASD and highlight the potential of these inflammatory markers as biomarkers in the assessment of ASD

The relationship between neurodevelopmental disorders and inflammatory processes has been addressed especially through the role of proinflammatory cytokines such as IL-6. Monocytes may contribute to neuroinflammation by producing high levels of IL-6 with the activation of inflammatory processes [35]. Studies in the literature indicate that IL-6 levels are significantly elevated in individuals with ASD compared to healthy controls. Additionally, higher IL-6 levels have been found to be positively correlated with repetitive behaviors and behavioral issues, which are core symptoms of ASD. In addition, it was found that not only IL-6 but also other proinflammatory cytokines increased in individuals with ASD and this was associated with more severe behavioural symptoms [35, 36].

In a study using the CARS, the relationship between ASD severity and inflammatory markers was examined and it was reported that IL-12p40 levels were higher in individuals with mild ASD and TNF-α levels were higher in individuals with moderate ASD [37]. In addition, it was discovered that there was a strong positive link between NLR and social interaction issues, and that this ratio tended to correlate with the overall severity of ASD symptoms [38]. Other studies in the literature also indicates that in people with neurodevelopmental issues, inflammatory markers may be linked to significant attention and social difficulties, as well as an increase in aggressive behaviors and hostility [39, 40]. In this study, a significant positive correlation was found between inflammatory markers and autism severity. This finding suggests that systemic inflammation may be associated not only with the presence of ASD but also with the clinical severity of the disease. In particular, the relationship between inflammatory response and autism symptom severity was observed to be significant.

Although our findings emphasise the role of inflammatory processes in ASD, our study has some limitations. Due to the retrospective design of the study, temporal changes of inflammatory markers could not be evaluated. Furthermore, cytokine analyses assessing specific immune responses in individuals with ASD were not performed. In addition, the relatively small sample size may limit the generalisability of our findings. Future prospective and longitudinal studies with larger populations are needed to examine the impact of inflammation on the course of ASD symptoms in more detail.

In conclusion, this study shows that markers of systemic inflammation are increased in children with ASD and that these markers are positively associated with autism severity. Our findings suggest that ASD is not only a neurodevelopmental disorder, but may also be linked to immunological mechanisms. In the future, we emphasise the need for large-scale studies investigating the potential role of inflammation-targeted therapeutic approaches in the management of ASD.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval Statement

This study was approved by the local Ethics Committee of the Medical Faculty of Sivas Cumhuriyet University. (Date: 17.10.2024, No: 2024-10/17).

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