

# The Hemoglobin-to-Red Cell Distribution Width Ratio and Systemic Inflammatory Response Index in Children with Autism Spectrum Disorder

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## WHAT IS ALREADY KNOWN ON THIS TOPIC?

- The utilization of peripheral biomarkers in the investigation of various psychiatric and neurodevelopmental disorders, including autism spectrum disorder (ASD), is a growing area of research.
- The systemic inflammatory response index (SIRI) has been associated with many psychiatric conditions; studies investigating its role in ASD are emerging and report inconsistent results.
- Hemoglobin-to-red blood cell distribution width ratio (HRR) has been investigated as a hematologic biomarker in adults with depression resulting from psychiatric disorders, but not in children with ASD.

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## ABSTRACT

**Objective:** Inflammation is reported to play an important role in the etiology of autism spectrum disorder. The purpose of this study was to investigate hemoglobin-to-red blood cell distribution width ratio (HRR) and systemic inflammatory response index (SIRI) levels, which may indicate immunological mechanisms involved in the etiopathogenesis of autism spectrum disorder.

**Methods:** One hundred forty-eight participants (74 diagnosed with autism spectrum disorder and 74 healthy controls) aged 24-72 months were included in the study. The Childhood Autism Rating Scale was applied to measure disease severity. The Denver Developmental Screening Test-2 was applied to the children in the autism spectrum disorder group.

**Results:** Hemoglobin-to-red blood cell distribution width ratio and lymphocyte values were significantly low in the children with autism spectrum disorder group compared to the healthy controls ( $P=.031$  and  $P=.003$ , respectively). No significant difference was determined between the healthy children and those with autism spectrum disorder in terms of systemic inflammatory response index. Low HRR and maternal age were determined to predict autism spectrum disorder ( $B=-4.963$ ,  $P=.003$  and  $B=0.176$ ,  $P=.011$ , respectively). Receiver-operating curve analysis showed that HRR had limited discriminative ability for autism spectrum disorder ( $AUC=0.602$ ).

**Conclusion:** Although HRR values were statistically lower in children with autism spectrum disorder, the observed difference was small. The small statistical difference observed in HRR may represent a preliminary finding that requires cautious interpretation and validation in larger, prospective studies.

**Keywords:** Autism spectrum disorder, biomarkers, hemoglobin-to-red blood cell distribution width ratio, inflammation, systemic inflammatory response index

## INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficiencies in social communication and the presence of limited and repetitive behaviors.<sup>1</sup> Recent studies of the

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## WHAT THIS STUDY ADDS ON THIS TOPIC?

- *This study provides the first direct evidence that the HRR is significantly lower in children with ASD compared to healthy controls.*
- *The significant but limited discriminatory power observed in HRR (AUC=0.602) warrants further investigation in the future.*
- *The SIRI levels may not be elevated in all pediatric ASD cohorts, suggesting heterogeneity in the immunological response in ASD.*

prevalence of ASD have reported an increase, with a worldwide figure of 1%.<sup>2</sup> Although genetic and epigenetic factors play a role, increasing attention has been directed toward environmental and immunological influences on ASD pathophysiology.<sup>3,4</sup>

The immune system is closely associated with the nervous system and affects neurogenesis, neuronal migration and differentiation, and synaptic formation and plasticity. The associations between inflammation and ASD have attracted increasing interest in current research.<sup>5</sup> Studies investigating the etiology of ASD have shown that several cytokines may be involved, but measuring biomarkers such as cytokines and chemokines is both costly and complex.<sup>6</sup> However, the evaluation of inflammatory markers obtained from routine peripheral blood counts during health screening is rapid and low-cost. One of the inflammatory markers obtained from peripheral blood is the systemic inflammation response index (SIRI).

Systemic inflammation response index was first reported to be used for the evaluation of inflammation and prognosis by Qi et al.<sup>7</sup> The index was calculated from neutrophil, monocyte, and lymphocyte counts. Neutrophils affect the inflammatory response by producing cytokines that trigger inflammation and other inflammatory mediators in the immune system.<sup>8</sup> Lymphocytes and monocytes are responsible for regulatory and protective functions in the immune system. In addition to hematological disorders, a change in lymphocyte numbers is also regarded as a marker of general inflammation.<sup>9</sup> Recent studies have examined the relationship between SIRI and mental disorders in adults, and SIRI has been shown to be associated with anxiety,<sup>10</sup> depression,<sup>11,12</sup> and bipolar disorder.<sup>13</sup> However, findings in ASD remain limited,<sup>14,15</sup> necessitating further research to clarify the role of SIRI in this population.

Hemoglobin-to-red blood cell distribution width ratio (HRR), obtained from peripheral blood counts, has been identified as a novel marker.<sup>16</sup> Recent studies examining the relationship between HRR and mental disorders have only examined its relationship with depression. These studies have noted lower HRR values in individuals diagnosed with depression, suggesting that reduced HRR may represent a biomarker in depression.<sup>17,18</sup> Studies conducted to date have shown a decrease in hemoglobin (Hb) levels and an increase in red cell distribution width (RDW) in ASD.<sup>19,20</sup> In consideration of the role of HRR in depression and the observed alterations in its components in ASD, HRR warrants investigation as a potential biomarker in the diagnostic and assessment processes of ASD.

The early detection of neurodevelopmental disorders or the identification of factors affecting disease severity can assist the development of rapid interventions capable of reducing the social and economic consequences of the condition. Therefore, markers with appropriate costs that can be rapidly used in the diagnosis and screening of ASD are highly important. The HRR and SIRI are currently the subjects of wide-ranging investigation as biomarkers by psychiatry and other medical disciplines.<sup>7,10,13,16,17</sup> To the best of the present author's knowledge, HRR has never been examined in ASD, despite prior reports of alterations in its components (Hb and RDW) in this population. In addition, extant evidence on SIRI in ASD is both scarce and inconsistent, particularly in young children. These gaps underscore the need to evaluate HRR and SIRI as potential peripheral markers in this population.

This study was designed to compare the HRR and SIRI values of children diagnosed with ASD with those of healthy children. It was hypothesized that HRR values would be lower and SIRI values would be higher in children with ASD than in healthy children.

## MATERIAL AND METHODS

### Study Design and Participants

The research was conducted as a cross-sectional/retrospective study. One hundred-nine aged 24-72 months presented for the first time to the Child and Adolescent Psychiatry Clinic of a training and research hospital between January and November 2024 and were diagnosed with ASD as a result of The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5) based evaluations. These patients' medical records were re-evaluated by 3 pediatric psychiatrists working in that hospital and making initial diagnoses of ASD. Following a comprehensive re-evaluation of the medical records, 35 children were excluded from the original case group, thereby establishing a new case group consisting of 74 children (Figure 1). Complete blood counts, Childhood Autism Rating Scale (CARS), and Denver Developmental Screening Test-2 (DDST-2) results for the initial diagnosis were retrieved from medical records. The control group was selected from among children who attended the hospital for routine check-ups in order of admission. All participants underwent psychiatric and medical screening using medical records to rule out any disorder. Children in the control group underwent the DDST-2 as part

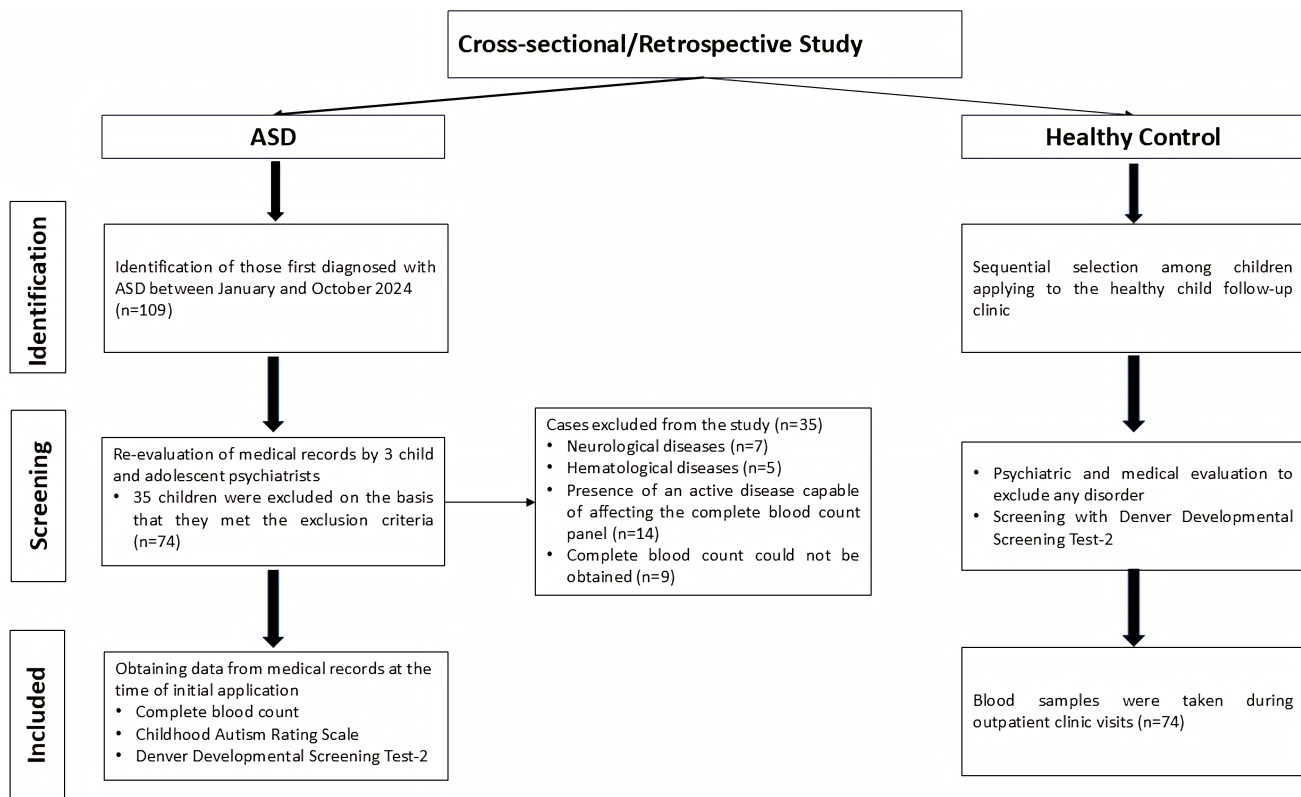


Figure 1. Process of case and control group formation.

of routine clinical assessment. Only children demonstrating typical development on the DDST-2 were included in the control group. Blood samples were collected during outpatient visits (Figure 1).

Exclusion criteria for case and control groups were applied solely to identify documented diagnoses or conditions that met exclusion criteria based on retrospective review of electronic medical records. Exclusion criteria for the case and control groups were the presence of neurodevelopmental disorder (other than ASD in the case group), neurological, hematological, metabolic disorders, the presence of medical drug and/or nutritional supplement use in medical records, the presence of an immune system disease, obesity (body mass index (BMI) >30 kg/m<sup>2</sup>), and the presence of an active disease capable of affecting the complete blood count panel during blood collection (C-reactive protein >10 mg/L, erythrocyte sedimentation rate >20 mm/hour, and WBC >11,000/mm<sup>3</sup>). Acute infections were ruled out based on medical records, documented clinical diagnoses, and laboratory records found in electronic medical files at the time the blood sample was taken (C-reactive protein >10 mg/L, erythrocyte sedimentation rate >20 mm/hour, and WBC >11.000/mm<sup>3</sup>).

The study was approved by the Alaaddin Keykubat University Medical Faculty Clinical Research Ethical Committee (ALKÜ-KAEK) (no. 25-01 dated November 20, 2024). All procedures were conducted in accordance with local laws and regulations and with the principles of the Declaration of Helsinki. Both the ASD and control groups were formed through retrospective review of anonymized medical records. Due to the retrospective nature of the study and the use of de-identified data, written informed consent was waived by the ethics committee.

#### Method of Measurement

**Blood Indicators and Novel Systemic Inflammatory Markers (HRR, SIRI):** Results retrieved from the hospital database included white blood cell count (WBC, 1000 cells/μL), lymphocyte count (1000 cells/μL), monocyte count (1000 cells/μL), segmented neutrophil count (1000 cells/μL), red blood cell count (RBC, million cells/μL), hemoglobin (Hb, g/dL), and RDW (%). The novel systemic inflammatory markers, HRR and SIRI, were obtained from blood counts during the initial diagnosis of ASD. The HRR values were calculated as Hb / RDW.<sup>16</sup> The SIRI was calculated as neutrophils × monocytes / lymphocytes.<sup>7</sup>

**Childhood Autism Rating Scale (CARS):** This behavioral rating scale was developed to evaluate the severity of symptoms in children with ASD.<sup>21</sup> The Turkish-language version of the CARS was validated by Incekas et al.<sup>22</sup> It was one of the first diagnostic rating scales for autism and is still used. It consists of 15 items investigating the following areas: relationships with people, mimicking behaviors, emotional response, use of own body, use of objects, adaptation to change, visual response, auditory response, response to and use of taste, smell, and touch, fear or nervousness, verbal communication, non-verbal communication, activity levels, level and consistency of intellectual response, and general impression. The total scale score indicates disease severity.<sup>21</sup> In the present study, the CARS assessment was administered during the initial diagnostic phase, and the results obtained from the medical records.

**Denver Developmental Screening Test-2 (DDST-2):** This scale was developed by Dodds and Frankenburg for application to children aged 0-6 years for the purpose of examining children's development and detecting deficits in the early period.<sup>23</sup> It was subsequently revised by Anlar et al, who also validated the Turkish version.<sup>24</sup> This

standardized developmental test evaluated 4 basic areas of development: fine motor, gross motor, personal-social, and language, based on 134 skills. The DDST-2 is routinely applied to all children diagnosed with ASD in the clinic, and the results were retrieved from medical records during the initial diagnostic process. A developmental quotient (DQ) is calculated separately for each developmental subheading from the test results obtained using the formula (developmental age / chronological age) × 100.<sup>25</sup>

**Statistical Analysis**

Statistical analysis was applied to compare demographic, clinical, and laboratory parameters between the ASD and control groups and to construct relational and predictive models. Normality of distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and graphical methods (Q-Q plot and histogram). Non-normally distributed continuous variables were expressed as median (min-max) values and normally distributed continuous variables as mean ± standard deviation, while categorical variables were presented as frequency (%) values. Normally distributed laboratory parameters were compared between the 2 groups using the *t*-test, and others by means of the Mann–Whitney *U*-test. The relationships between HRR and SIRI parameters, DQ subscales, and CARS scores were examined using Pearson (normal distribution) and Spearman (non-normal distribution) correlation coefficients. A multivariate logistic regression model was created to determine factors predicting diagnosis of ASD. The goodness of fit of this model was evaluated using the Hosmer & Lemeshow test and Omnibus test. Regression coefficients, odds ratios (OR), and 95% CI were calculated. The variance explained by the model was reported using Cox & Snell *R*<sup>2</sup> and Nagelkerke *R*<sup>2</sup>. A receiver-operating curve (ROC) was produced to assess the performance of the HRR parameter in predicting diagnosis of ASD, and area under the curve (AUC), sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated. The optimal cut-off point was determined using Youden’s index. The analysis was performed on IBM SPSS Statistics version 27 software, and *P* values < .05 were regarded as significant.

**RESULTS**

The study was carried out with 148 participants, 74 patients with ASD and 74 controls. Girls constituted 51.4% of the ASD group and

48.6% of the control group, the difference being statistically insignificant (*P* = .742). No significant age difference was also determined between the 2 groups (*P* = .994). However, the mean ages of the mothers and fathers in the ASD group were significantly higher than those in the control group (*P* = .002 and *P* = .016, respectively). All children included in the control group demonstrated age-appropriate development on the DDST-2. The ASD group had significantly lower coefficients of improvement on all subdimensions of the DQ compared to the control group (*P* < .001). Childhood Autism Rating Scale results were calculated for the ASD group (Table 1).

No statistically significant differences were observed between the ASD and control groups in terms of mean Hb levels and RBC, WBC, neutrophil, lymphocyte, eosinophil, basophil, monocyte, RDW-CV, SIRI, or platelet values (*P* > .05). However, the mean HRR value in the control group (0.93 ± 0.13) was significantly higher than that in the ASD group (0.88 ± 0.15) (*P* = .031). Lymphocyte value (3.38 ± 0.97) in the ASD group was significantly lower than that in the control group (3.95 ± 1.30) (*P* = .003) (Table 2).

No significant correlations were observed between HRR or SIRI values and DQ subdimensions or CARS scores (Table 3).

A logistic regression model was created in order to test the effects of age, sex, mother’s age, father’s age, and HRR parameters on the likelihood of ASD. This model exhibited good goodness-of-fit results (Hosmer & Lemeshow test *X*<sup>2</sup> = 3.977, *P* = .859 and Omnibus tests *X*<sup>2</sup> = 27.932, *P* < .001). The results showed that the model was capable of differentiating ASD. It was capable of explaining between 21% (Cox & Snell *R* Square) and 29% (Nagelkerke *R* Square) of the variance concerning ASD. The HRR emerged as a significant predictor of ASD (odds ratio: 0.007 (95% CI: 0.0003-0.182), *B* = -4.963, *P* = .003). Maternal age was also a significant predictor of ASD (odds ratio: 0.838 (95% CI: 0.731-0.961), *B* = 0.176, *P* = .011). The age of the child, sex, and paternal age exhibited no significant predictive power. These results show that low HRR values are associated with a slightly increased probability of ASD (Table 4).

The ROC analysis was applied to calculate which HRR value best predicted ASD. The cut-off point was determined using Youden’s index, with a maximum value of 0.217. The best HRR value for predicting HSD

**Table 1. General Characteristics of the Study Groups**

	ASD (N = 74)		Control (N = 74)		t/Z/X <sup>2</sup>	P
	Mean ± SD/Median (Min-Max)	N (%)	Mean ± SD/Median (Min-Max)	N (%)		
Age (month)	46.48 (24-72)		46 (24-72)		-0.008	.994 <sup>b</sup>
Sex	Female	38 (51.4%)	36 (48.6)		0.108	.742 <sup>c</sup>
	Male	36 (48.6%)	38 (51.4)			
Maternal age	39 (24-60)		34.50 (21-47)		-3.060	.002 <sup>b</sup>
Paternal age	42.22 ± 6.82		39.07 ± 6.85		-2.435	.016 <sup>a</sup>
DQ PSD	48.87 ± 25.35		99.7 ± 3.90		-19.68	<.001
DQ FMD	63.70 ± 25.77		94.0 ± 6.0		-23.53	<.001
DQ LD	42.90 ± 22.50		99.3 ± 4.27		-10.79	<.001
DQ GMD	76.92 (14.50-100)		97.1 ± 5.43		-9.49	<.001
CARS	49.50 (27-60)		N/A		-	-

Values with *P* < .05 are written in bold.

CARS, Childhood Autism Rating Scale; DQ, developmental quotient; FMD, fine motor domain; GMD, gross motor domain; LD, language domain; PSD, personal-social domain.

<sup>a</sup>Independent *t*-test (mean ± SD), <sup>b</sup>Mann–Whitney *U*-test [median (min-max)], <sup>c</sup>Chi-square test.

**Table 2. A Comparison of Laboratory Parameters between the ASD and Control Groups**

	ASD (N=74)		Control (N=74)		t/Z	ES	P
	Mean ± SD/Median (Min-Max)	Mean ± SD/Median (Min-Max)	Mean ± SD/Median (Min-Max)	Mean ± SD/Median (Min-Max)			
WBC (x10 <sup>3</sup> /mm <sup>3</sup> )	7.96 ± 1.73	7.49 ± 1.46	1.755 <sup>a</sup>	0.24	.081		
HGB	12.09 ± 1.20	12.44 ± 1.01	-1.926 <sup>a</sup>	-0.40	.056		
PLT (x10 <sup>3</sup> /mm <sup>3</sup> )	334.15 ± 81.37	332.64 ± 70.26	0.921 <sup>a</sup>	0.09	.358		
Neutrophils (x10 <sup>3</sup> /mm <sup>3</sup> )	3.39 (1.09-6.10)	2.81 (1.24-5.38)	-1.879 <sup>b</sup>	-0.13	.060		
Lymphocytes (x10 <sup>3</sup> /mm <sup>3</sup> )	3.38 ± 0.97	3.95 ± 1.30	-3.022 <sup>a</sup>	0.31	<b>.003</b>		
Eosinophil (x10 <sup>3</sup> /mm <sup>3</sup> )	0.24 (0-0.86)	0.19 (0-1.10)	-0.840 <sup>b</sup>	0.11	.401		
Monocyte (x10 <sup>3</sup> /mm <sup>3</sup> )	0.53 (0.26-1.17)	0.60 (0.01-1.66)	-1.903 <sup>b</sup>	-0.02	.057		
Basophil (x10 <sup>3</sup> /mm <sup>3</sup> )	0.02 (0-0.26)	0.03 (0-0.30)	-1.053 <sup>b</sup>	0.10	.292		
RDW (%)	13.50 (11.6-19.30)	13.20 (11.08-18.37)	-1.141 <sup>b</sup>	0.31	.150		
HRR	0.88 ± 0.15	0.93 ± 0.13	-2.179 <sup>a</sup>	-0.42	<b>.031</b>		
SIRI	0.54 (0.13-1.52)	0.47 (0.01-1.86)	-1.396 <sup>b</sup>	0.05	.163		

WBC, white blood cell count; HGB, hemoglobin; PLT, platelet; RDW, red cell distribution width; HRR, hemoglobin-to-red blood cell distribution width ratio; SIRI, systemic inflammatory response index; ES, Effect size. Values with *P* < .05 are written in bold. ES, Effect size; HGB, hemoglobin; HRR, hemoglobin-to-red blood cell distribution width ratio; PLT, platelet; RDW, red cell distribution width; SIRI, systemic inflammatory response index; WBC, white blood cell count. <sup>a</sup>Independent *t*-test (mean ± SD), <sup>b</sup>Mann-Whitney *U*-test (median (min-max)).

**Table 3. Correlations between HRR and SIRI Results and CARS and DQ Sub-Dimensions**

		DQ PSD	DQ FMD	DQ LD	DQ GMD	CARS
HRR	Corr. Coeff.	0.052 <sup>a</sup>	0.20 <sup>a</sup>	0.07 <sup>a</sup>	0.117 <sup>b</sup>	-0.084 <sup>b</sup>
	<i>P</i>	0.688	0.112	0.561	0.363	0.476
SIRI	Corr. Coeff.	-0.003 <sup>b</sup>	-0.001 <sup>b</sup>	-0.127 <sup>b</sup>	0.109 <sup>b</sup>	0.077 <sup>b</sup>
	<i>P</i>	0.982	0.992	0.322	0.394	0.514

Values with *P* < .05 are written in bold. CARS, Childhood Autism Rating Scale; Corr. Coeff., Correlation Coefficient; DQ, developmental quotient; PSD, Personal-social domain; LD, Language domain; FMD, Fine motor domain; GMD, Gross motor domain; CARS, Childhood Autism Rating Scale; HRR, hemoglobin-to-red blood cell distribution width ratio; LD, Language domain; PSD, Personal-social domain; SIRI, systemic inflammatory response index. <sup>a</sup>Pearson Correlation, <sup>b</sup>Spearman's rho.

**Table 4. The Impact of Predictors on ASD as Determined by Logistic Regression Analysis**

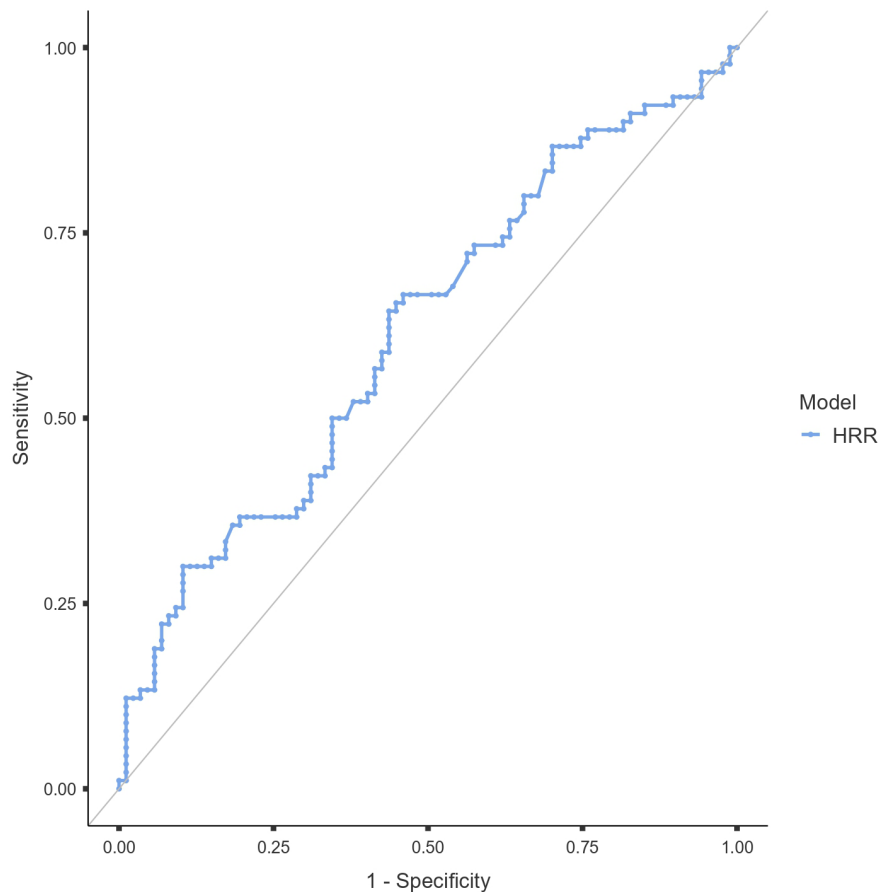
	B	S.E.	Wald	Sig.	Exp(B)	95% CI for EXP(B)	
						Lower	Upper
Constant	7.214	2.226	10.506	0.001	1357.977		
Age	0.354	0.274	1.671	0.196	1.424	0.833	2.436
Sex	0.635	0.441	2.074	0.150	1.887	0.795	4.479
Maternal Age	0.176	0.070	6.446	<b>0.011</b>	0.838	0.731	0.961
Paternal Age	0.068	0.067	1.040	0.308	1.070	0.939	1.220
HRR	-4.963	1.663	8.901	<b>0.003</b>	0.007	0.000	0.182

Values with *P* < .05 are written in bold. HRR: hemoglobin-to-red blood cell distribution width ratio.

was 0.94. The AUC at ROC analysis was 0.602 (0.511-0.693, *P* = .032). The sensitivity of the test at the calculated cut-off point was 55.4%, with specificity of 66.2%. The positive predictive value (PPV) was 62.1% and the negative predictive value (NPV) was 59.8%. The ROC results indicate that HRR has limited discriminative ability and should not be considered a standalone diagnostic tool. The calculated cut-off value may prove to be a valuable source of information for future research endeavors; however, it is important to note that it does not currently possess the requisite level of accuracy for clinical prediction (Figure 2).

**DISCUSSION**

This study was designed to evaluate the HRR and SIRI levels in children with ASD. Few previous studies have examined inflammatory indices obtained from peripheral blood in children with ASD, and the current study is the first to examine HRR and SIRI levels in children with ASD. The study findings show that the HRR was lower in the autistic children than in the healthy controls. However, the results revealed no difference between the 2 groups in terms of SIRI. In addition, logistic regression analysis showed that low HRR values and



**Figure 2. ROC curve analysis of the HRR for ASD**

maternal age predicted a diagnosis of ASD. Furthermore, ROC analysis confirmed the diagnostic potential of HRR, with an AUC value of 0.602. They also corroborate the hypothesis that HRR is lower in children with ASD. However, they did not support the hypothesis of a higher SIRI in these children.

The quest for accessible and cost-effective biological parameters in ASD has given rise to heightened interest in hematological indices. Among these, the HRR emerged as a candidate worthy of investigation in the present study, particularly given the established alterations in its components—Hb and RDW—in the ASD population.<sup>19,20</sup> Studies to date have only examined HRR levels as a biomarker in patients with depression among mental disorders and have suggested that it may represent a biomarker in depressive patients. A previous study on adults compared depressive and healthy individuals and reported lower HRR values in patients diagnosed with depression.<sup>17</sup> Similarly, another recent study reported that individuals with depressive symptoms had lower HRR than those without.<sup>18</sup> The present study compared children with ASD and healthy children and determined lower HRR levels in those with ASD. The absolute value of the observed changes in HRR values was found to be marginal, despite the fact that they were statistically significant (0.88 vs. 0.93). In the present study, the AUC value for HRR was calculated to be 0.602, indicating a weak discriminatory power in distinguishing children with ASD from controls. Given its sensitivity and specificity, HRR alone is unlikely to be a highly accurate diagnostic tool at this stage. Further validation in larger longitudinal cohorts is required to ascertain the clinical value of HRR.

Another hematological index examined in this study was SIRI, previously investigated in several mental disorders in adults,<sup>11-13</sup> although inconsistent results were observed. Two recent studies have examined SIRI in children diagnosed with ASD. Abanoz et al reported higher SIRI in patients compared to controls and a correlation between SIRI and disorder severity in children with ASD.<sup>14</sup> Conversely, a pilot intervention study in individuals with ASD demonstrated that SIRI decreased following hyperbaric oxygen therapy, suggesting that SIRI may be more responsive to short-term inflammatory changes than it is to being a stable marker.<sup>15</sup> No significant difference in SIRI levels was also determined between healthy children and those with ASD in the present study. In particular, the non-significant lower monocyte counts (which decrease SIRI) in the ASD group, as reported in this study, may provide a rationale for the absence of a significant difference in SIRI levels, in contrast to the findings reported by Abanoz et al.<sup>26</sup> It is of particular significance that this observed reduction in monocyte numbers may itself be indicative of a distinct inflammatory response in the cohort under investigation. Rather than reflecting diminished activity, lower monocyte counts could be a consequence of a hyperresponsive state. This is evidenced by studies showing that monocytes in ASD can produce excess pro-inflammatory cytokines despite numerical changes.<sup>27</sup> This underscores the necessity to transcend the utilization of composite indices and to incorporate functional immune testing in future research endeavors pertaining to ASD.<sup>28</sup>

Lymphocytes are responsible for the regulation of protective functions in the immune system, and a change in lymphocyte counts

is regarded as a marker of general inflammation.<sup>9</sup> The findings of recent studies support the idea of an association between neurodevelopmental disorders and lymphocyte numbers.<sup>29-32</sup> A meta-analysis examining lymphocyte subpopulations in individuals with ASD reported lower lymphocyte subtype T cytotoxic cells in individuals with ASD compared to healthy subjects, but observed no difference in B lymphocyte or T helper cell numbers.<sup>30</sup> In their pediatric study, Arenella et al reported a negative correlation between autistic characteristics and lymphocyte numbers.<sup>31</sup> Another study reported that children with ASD exhibited lower lymphocyte numbers than healthy children.<sup>32</sup> In the present study, lymphocyte counts were found to be significantly lower in the ASD group when compared to healthy controls, thereby corroborating the prevailing body of research.

This study has several limitations. First, because it was a cross-sectional study, a cause-and-effect relationship cannot be established. Second, due to the young age of the participants, the results cannot be generalized to different age groups. Third, the application of exclusion criteria was based solely on medical record review for both groups. Therefore, the lack of additional parental interviews, specialized clinical assessments in the control group, or detailed data on nutritional supplements (e.g., iron or vitamin intake) may have limited the completeness of the health screenings and the control of potential confounders. Furthermore, since retrospective records were examined, it was not possible to completely rule out subclinical or undocumented infections at the time of blood sample collection.

## CONCLUSION

Although HRR values were statistically lower in children with ASD, this small difference should be interpreted with caution and requires confirmation in larger, prospective studies. The lack of a significant difference in SIRI may be indicative of altered monocyte dynamics, rather than a lack of immune involvement. These results highlight the need for further research on the functional properties of monocytes in ASD and their role in immune responses.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of Alanya Alaaddin Keykubat University clinical research (Approval no: 25-01, Date: November 20, 2024).

**Informed Consent:** Written informed consent was obtained from the participants' parents, and verbal consent was obtained from the children themselves.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – O.K., P.A.A.; Design – O.K., T.K., P.A.A.; Supervision – O.K., T.K., P.A.A.; Resources – O.K., T.K., P.A.A.; Materials – O.K., P.A.A.; Data Collection and/or Processing – O.K., P.A.A., T.K.; Analysis and/or Interpretation – T.K., O.K.; Literature Search – O.K., P.A.A.; Critical Review – O.K., T.K., P.A.A.; Other – O.K.

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