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Cingulin, Claudin-5 And Tricellulin As A Novel Biomarker For Autism Spectrum Disorder

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Abstract

Background: Autism spectrum disorder is a complex, heterogeneous developmental disorder, typically diagnosed in early childhood. Genetic, prenatal, and environmental factors all play a role in the development of autism. It can present at various levels of severity, from mild to severe, and has a male preponderance. Key symptoms of ASD include deficits in social communication, restricted interests, and repetitive behaviors.

In recent years, the prevalence of ASD has been steadily increasing, raising significant concerns regarding its causes, diagnosis, and effective management. In ASD, the word (spectrum) stands for a wide range of symptoms and to what extent these symptoms progress, and the degree of symptoms development.

Given that ASD is associated with neurological dysfunction, this study highlights the importance of analyzing specific tight junction proteins therefore; Cingulin, Claudin-5, and Tricellulin proteins were examined to explore their potential role in the pathogenesis of ASD.

Aim of the study: The study aims to determine whether there is a difference in serum levels of Cingulin, Claudin-5, and Tricellulin between children diagnosed with Autism Spectrum Disorder and healthy controls.

Materials and methods: The research was conducted as a case-control study over four months from November 2024 to February 2025 at specialized autism centers and a pediatric hospital and included a total of 88 participants aged 3-12 years. The participants were categorized into 56 autistic children (41 males, 15 females) and 32 healthy controls (23 males, 9 females). Blood samples were collected and analyzed for biochemical markers (CGN, CLDN-5, and TRIC) alongside certain vitamins and minerals. Official approval was obtained from the autism centers before the commencement of the study, and verbal consent was secured from the families of autistic children, who voluntarily participated in the study by completing the questionnaire form.

Data analysis employed the Mann-Whitney U tests, Pearson's chi-squared test, Spearman's correlation test, Univariate and multivariable logistic regression, and ROC analysis. All *P* values less than 0.05 were considered statistically significant.

Results: Among the total 88 participants—ASD group (n = 56) and control group (n = 32)—the median age (IQR) was 6 years (4–8). The median age at symptom onset was 2 years (IQR: 1.5–4).

The median (IQR) concentration of Cingulin (ng/mL) was lower in the ASD group compared to the healthy control group, but this difference was not statistically significant (0.13 [0.08–0.24] vs. 0.15 [0.09–0.30]; p = 0.3). Claudin-5 (pg/mL) showed a significantly lower median (IQR) in the ASD group compared to the healthy control group (32.22 [16.85–48.70] vs. 60.93 [40.93–96.30]; p < 0.001).

Similarly, Tricellulin (ng/mL) also showed a significantly lower median (IQR) in the ASD group compared to healthy controls (0.23 [0.09–0.47] vs. 0.42 [0.22–0.69]; p = 0.027).

Conclusion and Recommendations: Claudin-5, Cingulin, and Tricellulin levels were significantly lower in the ASD group compared to the control group, suggesting a potential association between tight junction protein dysfunction and ASD pathophysiology. Further detailed and comprehensive longitudinal studies are needed to determine whether altered levels of Claudin-5, Cingulin, and Tricellulin are a cause or consequence of the disease process in ASD.

Keywords: Claudin-5, Cingulin, and Tricellulin, Autism spectrum disorder

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous, behaviorally defined neurodevelopmental disorder. Over the past two decades, the prevalence of autism spectrum disorders has progressively increased, however, no clear diagnostic markers and specifically targeted medications for autism have emerged [(1,2)].

ASD consists of a genetically heterogeneous group of neurobehavioral disorders characterized by impairment in three behavioral domains, including communication, social interaction, and stereotypic repetitive behaviors [(3,4)].

Children with autism spectrum disorder (ASD) often exhibit behavior problems, with more severe ASD symptomatology relating to more severe behavior problems. Behavior problems are correlated with parenting behaviors [(5)].

The increase in ASD prevalence has been attributed to an increase in public awareness, changing diagnostic standards, earlier diagnosis of autism, and the development of treatment targets [6)].Both genetics and environmental factors play a vital role in the etiology of autism early in development.

Cingulin (CGN) is a cytoskeleton-associated protein localized at the apical junctions of epithelial cells. CGN interacts with major cytoskeletal filaments and regulates RhoA activity. However, the physiological roles of CGN in development and human diseases are currently unknown [(7)].Serum cingulin levels are significantly higher in children with ASD compared to healthy controls, indicating a potential disruption in BBB integrity [(8)].

The claudin family of membrane proteins plays central roles in TJ structure and function. Claudin-5 (CLDN5) is an essential component of tight junctions (TJs) and is critical for the integrity of the blood-brain barrier (BBB), ensuring homeostasis and protection from damage to the central nervous system (CNS). Alterations in CLDN-5 levels have been linked to psychiatric disorders, suggesting its potential as a biomarker for BBB dysfunction in these conditions. [(9,10)]. Tricellulin is an integral component of tricellular tight junctions (tTJs), but the molecular mechanism of its contribution to the epithelial barrier function remains unclear. mobilizes actomyosin contractility to close the lateral gap between the TJ strands of the three proximate cells that converge on tricellular junctions [(11,12)].

The study aims to determine whether there is a difference in serum levels of Cingulin, Claudin-5 and Tricellulin levels between children diagnosed with ASD and healthy controls.

MATERIALS AND METHODS

A case-control study was performed at children's autism centers (Al-Irada Center for Autism and Al-Tammauz Center for Autism) and the Pediatrics Hospital in Kirkuk City-Iraq from November 2024 to February 2025.

The study was conducted in Kirkuk City, which is located in northern Iraq, approximately 238 kilometers north of the capital, Baghdad. The city is known for its diverse population and significant economic importance.

The total number of ASD patients is (56). Forty-one of them were males, while fifteen were females. Their ages ranged from 3 to 12 years.

The present study contained a control group of thirty-two subjects who were healthy. Twenty-three of them were males and nine of them were females. Their ages ranged from 3 to 12 years. These individuals were attending different clinics of a pediatric hospital and were evaluated by a clinician.

INCLUSION CRITERIA

1- Previously diagnosed with ASD (for SG). 3- Within the specified age group.

Exclusion criteria: Has a chronic illness or a hematological disorder., and children outside the specified age group.

A volume of approximately 5 milliliters of venous blood was collected from both patient and control participants and transferred into a gel tube containing No EDTA to allow for clotting for 30 minutes at room temperature. Subsequently, the tubes were centrifuged at a speed of 4000 rpm for 15 minutes. After first centrifugation, the clot was removed and re- centrifuged at 4000 rpm for 10 minutes. Then, the acquired sera were aspirated by using an automatic micropipette, transported separately to two microtubes (Eppendorf), and stored at a temperature of -20℃ for late serological examination.

RESULTS & DISCUSSION

Among the 88 participants, the median age (IQR) was **6 years (4–8)**. The median age was lower in the ASD group than in the control group (5.00 **years [IQR: 4.00, 8.00] vs.** 7.00 **years [IQR: 4.75, 9.50]; p** =0.058).

There were no significant differences in gender distribution between the groups (p = 0.7), with males comprising 73% of the ASD group and 69% of the control group. ASD is more common in males (13). (14) suggested that girls who meet the criteria for ASD are at higher risk of not receiving a clinical diagnosis. Among ASD group, positive family history of autism was reported in **11 (20%)**. The median age at symptom onset was **2 years (IQR: 1.5 – 4)**. Additionally, **8 (14%)** had comorbid conditions other than autism. Regarding the symptoms in autistic children, speech difficulties were the most prevalent (91.1%). Attention deficits were reported in 82.1% of the children, and social interaction problems were reported in 67.9%. The core features of autism spectrum disorders (ASD) are communication impairments, social skills deficits, and the presence of repetitive or overly restricted behaviors (15).

In the present study, the median (IQR) of Cingulin (ng/mL) was lower in ASD group compared to healthy control group but this difference was not statistically significant (0.13 (0.08, 0.24) **vs.** 0.15 (0.09, 0.30)**; p** = 0.3) **(Fig.1). in contrast, a case – control study in Turkey among 40 ASD children and 40 healthy control children, showed that** Cingulin levels were higher in ASD group compared to healthy control group ($p < 0.05$) (16).

In the current study, Claudin-5 (pg/ml) showed a significantly lower median (IQR) in the ASD group compared to the healthy control group (32.22 (16.85, 48.70) vs. 60.93 (40.93, 96.30); $p < 0.001$) (Fig.

4.2.b). Similarly, Tricellulin (ng/ml) also showed a significantly lower median (IQR) in the ASD group compared to the healthy controls (0.23 (0.09, 0.47) vs. 0.42 (0.22, 0.69); p = 0.027) (Fig. 1). These findings contribute to the growing, yet conflicting, body of literature on the role of tight junction (TJ) proteins in neurodevelopmental disorders. While our results align with certain studies, they contrast with others, underscoring the complexity of barrier dysfunction in ASD pathophysiology and emphasizing the need for further investigation.

Table 1. Comparisons of Biomarkers level Between ASD and Control Group

Biomarker	Total (N = 88)	Study Groups		p-value[1]
		ASD (N = 56)	Healthy Control (N = 32)	
Cingulin (ng/mL)				0.3
Median (Q1, Q3)	0.13 (0.08, 0.26)	0.13 (0.08, 0.24)	0.15 (0.09, 0.30)	
Claudin-5 (pg/mL)				**<0.001**
Median (Q1, Q3)	40.37 (21.30, 65.00)	32.22 (16.85, 48.70)	60.93 (40.93, 96.30)	
Tricellulin (ng/mL)				**0.027**
Median (Q1, Q3)	0.30 (0.12, 0.51)	0.23 (0.09, 0.47)	0.42 (0.22, 0.69)	

[1] Mann- Whitney U test

Significant results ($p < 0.05$) are bolded.

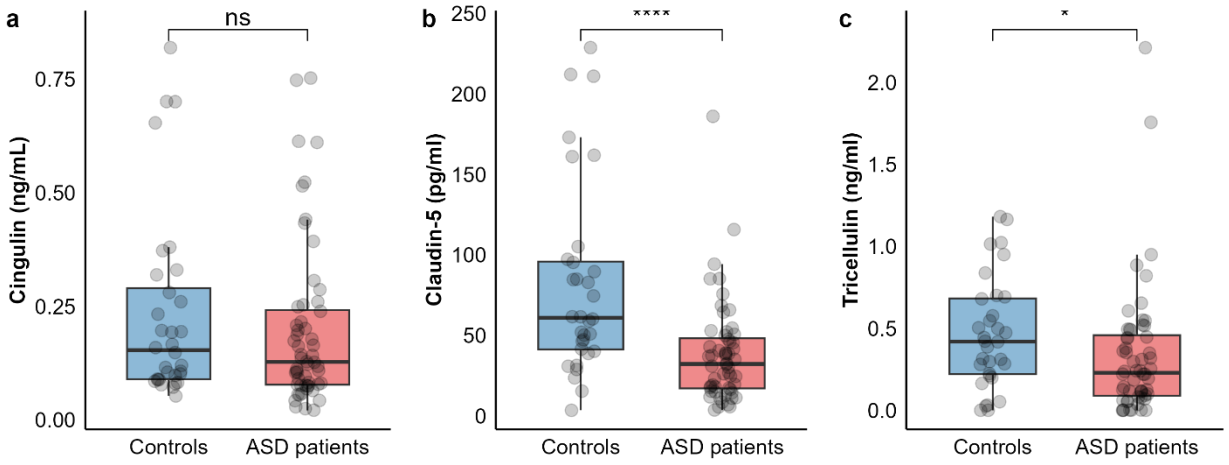

Figure 1. a-boxplot of cingulin by study groups, b-boxplot of claudin by study groups, c- boxplot of Tricullin by study groups. Significance was assessed using the Mann-Whitney U test; ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, ns = not significant ($p \geq 0.05$).

Eroğlu et al., 2024 (17) have reported varying results regarding the role of TJ proteins in neurodevelopmental disorders. For instance, a study involving 40 children with ASD and 40 controls aged 2–12 years aimed to determine whether serum levels of Zonulin, Occludin, Claudin-5, Junctional Adhesion Molecule-A (JAM-A), and Tricellulin differed between individuals with ASD and healthy controls. The study revealed no significant differences between the groups, and no relationship was found between the severity of ASD symptoms and the biochemical parameters. These findings suggest that blood-brain barrier (BBB) permeability may not play a significant role in the etiology of ASD.

Notably, (18) reported increased Claudin-5 expression in ASD brain tissues, suggesting compartment-specific dysregulation—serum levels may not directly reflect cerebral expression. Reduced serum Claudin-5 could indicate systemic barrier leakage, allowing translocation into tissues. whereas brain-specific increases might reflect compensatory mechanisms aimed at restoring BBB integrity. Similarly, lower Tricellulin levels in our cohort align with Fiorentino's observation of intestinal barrier dysfunction in ASD but contrast with their findings of increased cortical Tricellulin expression. This highlights the importance of distinguishing between systemic and CNS-specific TJ protein dynamics.

Moreover, (19) conducted a case-control study involving 24 patients with obsessive–compulsive disorder (OCD) (13 boys and 11 girls) and 24 healthy controls matched for age and sex. They found that serum Claudin-5 levels were significantly higher in the OCD group. Similarly, a study by Aydoğan Avşar et al. 2021(20) reported elevated serum Claudin-5 levels in individuals with attention-deficit/hyperactivity disorder (ADHD) compared to controls. These findings contrast with our results in ASD. However, (21) reported that serum Claudin-5 and Tricellulin levels were significantly lower in the ADHD group compared to the control group, which aligns with our findings in ASD.

A systematic review by [22] reported increased Claudin-5 levels in the blood of individuals with schizophrenia, bipolar disorder, and depression. Conducted a case-control study involving 80 children with ASD and 40 healthy controls aged 18–60 months, suggesting that Claudin-11, Occludin, and β-catenin may play a role in the pathogenesis of ASD. These proteins may impact brain function by disrupting intestinal or BBB permeability or through other, yet unknown, mechanisms (23).

Cingulin (ng/mL) showed statistically significant positive correlations with **Tricellulin** ($r = 0.32$, $p < 0.05$)**.** Additionally, **Claudin-5** exhibited a significant positive correlation with **Tricellulin** ($r = 0.39$, $p < 0.05$). Similarly, **Tricellulin** demonstrated statistically significant positive correlations with **Zinc** ($r = 0.22$, $p < 0.05$).

Table 2. Spearman correlation of characteristic

	Age	**Cingulin**	**Claudin-5**	**Tricellulin**
Age	1			
Cingulin	-0.10	1		

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	Age	Cingulin	Claudin-5	Tricellulin
Claudin-5	0.03	0.17	1	
Tricellulin	-0.15	**0.32*****	**0.39*****	1
Significant results ($p < 0.05$) are bolded. ***p < 0.001, **p < 0.01, *p < 0.05.				

Cingulin showed statistically significant positive correlations with claudin-5 (r = 0.18, p < 0.05). similarly, claudin-5 showed statistically significant positive correlation with tricellulin (r = 0.347, p < 0.05).

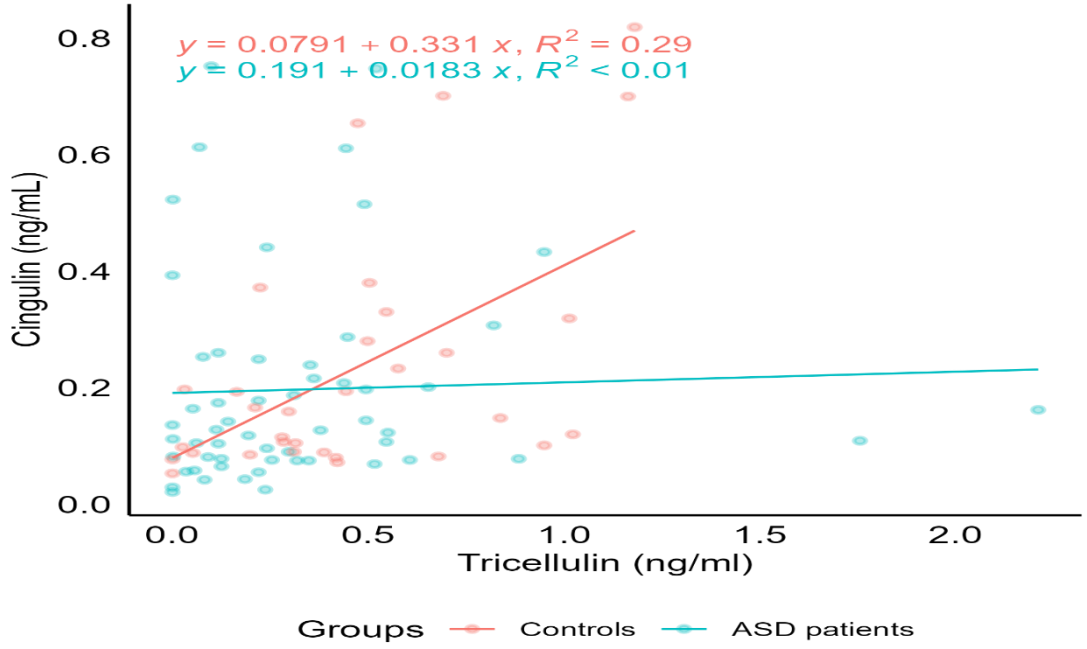

Fig.2. Scatter plot between tricellulin and cingulin among cases and controls.

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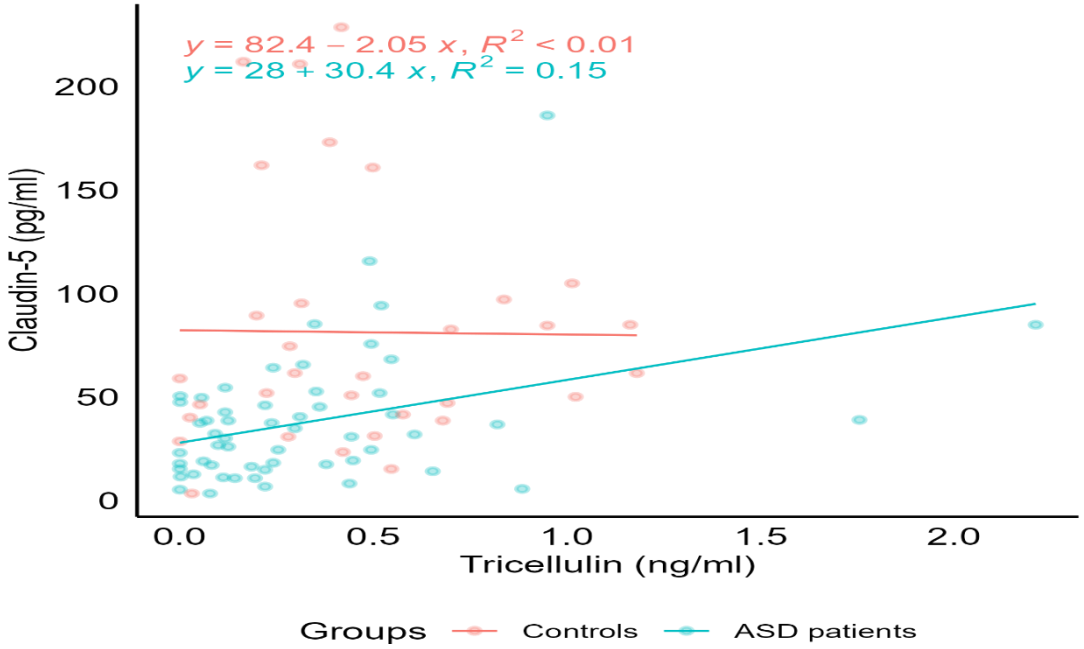

Fig.3. Scatter plot between tricellulin and claudin-5 among the study groups.

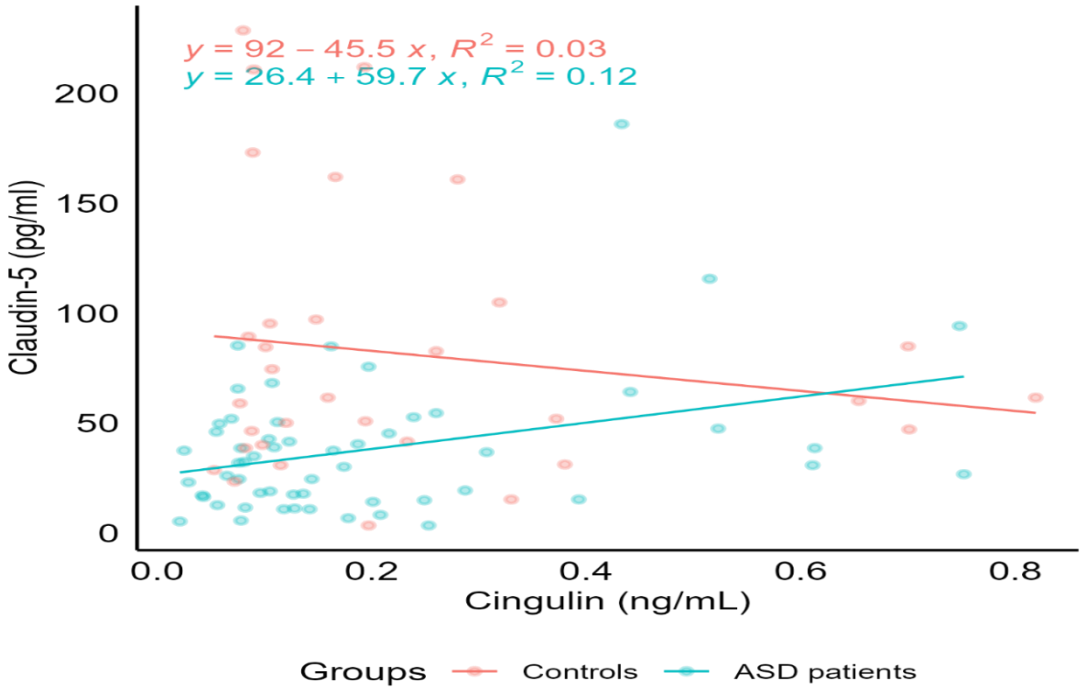

Fig.4. Scatter plot between cingulin and claudin-5 among cases and controls.

Table 3 presents the results of the univariate and multivariable logistic regression analyses. The final multivariable model included all variables.

Age was significantly associated with ASD in both the univariate and multivariable analyses. Each additional year of age was associated with a 16% decrease in the odds of ASD in the univariate model (OR = 0.84; 95% CI: 0.70–0.98; p = 0.035), and a 23% decrease in the multivariable model (aOR = 0.77; 95% CI: 0.58–0.98; p = 0.043).

Gender was not significantly associated with ASD in either model. Female participants had 20% lower odds of being in the ASD group in the univariate analysis (OR = 0.80; 95% CI: 0.31–2.13; p = 0.7), but this association remained non-significant after adjustment (aOR = 1.18; 95% CI: 0.28–5.42; p = 0.8).

Cingulin (ng/mL) showed a non-significant protective effect in the univariate model (OR = 0.38; 95% CI: 0.04–3.68; p = 0.4). Interestingly, in the multivariable model, it was positively associated with ASD (aOR = 1.75; 95% CI: 0.07–53.4; p = 0.7), though not significantly.Claudin-5 (pg/mL) demonstrated a statistically significant inverse association in the univariate analysis, with each unit increase associated with a 2% reduction in odds of ASD (OR = 0.98; 95% CI: 0.96–0.99; p < 0.001). However, this association was not significant in the multivariable model (aOR = 0.99; 95% CI: 0.97–1.00; p = 0.14).

Tricellulin (ng/mL) also showed an inverse relationship with ASD. Although not significant in the univariate model (OR = 0.40; 95% CI: 0.11–1.27; p = 0.13), it became significant in the multivariable model, showing an 88% risk reduction per ng/mL increase (aOR = 0.12; 95% CI: 0.01–0.78; p = 0.030).

Table 3. Logistics regression for factors associated with ASD patients

Characteristic	Univariate			Multivariable		
	OR[1]	95% CI[1]	p-value	aOR[1]	95% CI[1]	p-value
Age	**0.84**	0.70, 0.98	**0.035**	**0.77**	0.58, 0.98	**0.043**
Gender						
Male	—	—		—	—	
Female	0.80	0.31, 2.13	0.7	1.18	0.28, 5.42	0.8
Cingulin (ng/mL)	0.38	0.04, 3.68	0.4	1.75	0.07, 53.4	0.7
Claudin-5 (pg/ml)	**0.98**	0.96, 0.99	**<0.001**	0.99	0.97, 1.00	0.14
Tricellulin (ng/ml)	0.40	0.11, 1.27	0.13	**0.12**	0.01, 0.78	**0.030**

[1] **OR = Odds Ratio, aOR = adjusted Odds Ratio, CI = Confidence Interval**

4. Diagnostic efficacy of biomarkers in predicting ASD (Receiver operating characteristic (ROC) analysis)

Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of each study variable as a potential biomarker for ASD. The results are presented in Table 4.7 and illustrated in Figures 5. The performance metrics include the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

The AUC for Cingulin (ng/mL) was 0.567 (95% CI: 0.457–0.672), indicating poor to modest discriminatory ability. At the optimal threshold of ≤0.078 ng/mL, Cingulin showed a sensitivity of 28.57%, specificity of 90.62%, PPV of 84.2%, and NPV of 42.0% (Fig. 4.8).

For Claudin-5 (pg/mL), the AUC was 0.766 (95% CI: 0.664–0.850), suggesting good discriminatory ability. At a threshold of ≤,46.111 pg/mL, Claudin-5 had a sensitivity of 73.21%, specificity of 71.87%, PPV of 82.0%, and NPV of 60.5% (Fig. 4.9).Tricellulin (ng/mL) had an AUC of 0.643 (95% CI: 0.534–0.742). Using a cutoff of ≤0.255 ng/mL, it showed sensitivity of 57.14%, specificity of 71.87%, PPV of 78.0%, and NPV of 48.9% (Fig. 4.10).

The combined model including Cingulin, Claudin-5, and Tricellulin (CGN+CLDN5+Tric) yielded the highest AUC of 0.776 (95% CI: 0.675–0.858), indicating strong diagnostic potential. At a threshold of >0.65, this model had a sensitivity of 78.57%, specificity of 68.75%, PPV of 81.5%, and NPV of 64.7% (Fig. 4.11).

Table 4Area under the curve, sensitivity, specificity, and predictive values of biomarkers

Figure 5. Receiver operating characteristic (ROC) curve for Cingulin (ng/mL).

Biomarker	**AUC**	**AUC 95% CI**	**Threshold**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Cingulin (ng/mL)	0.567	0.457 to 0.672	≤0.078	28.57	90.62	84.2	42.0
Claudin-5 (pg/ml)	0.766	0.664 to 0.850	≤46.111	73.21	71.87	82.0	60.5
Tricellulin (ng/ml)	0.643	0.534 to 0.742	≤0.255	57.14	71.87	78.0	48.9
Combined model (CGN+CLDN5+Tric)	0.776	0.675 to 0.858	> 0.65	78.57	68.75	81.5	64.7

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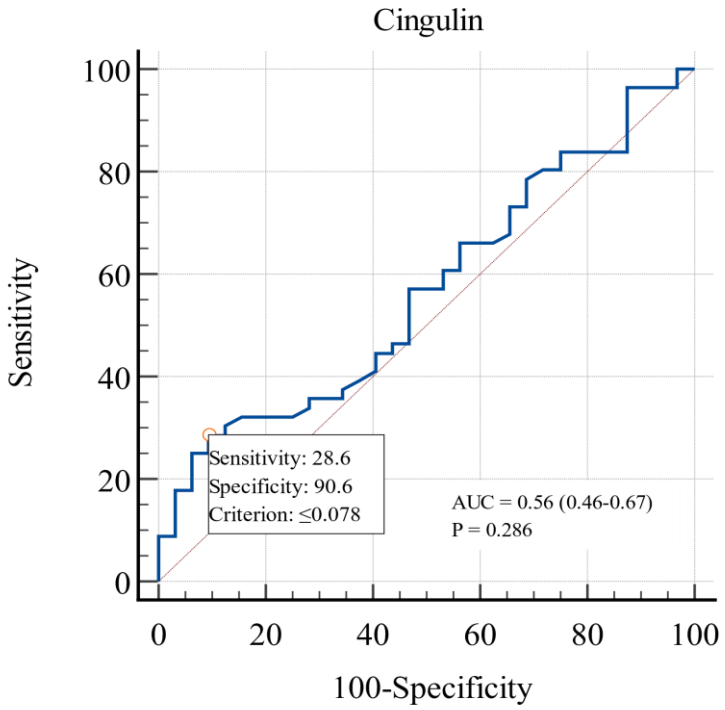

Fig 6. Receiver operating characteristic (ROC) curve of Claudin-5 (pg/ml).

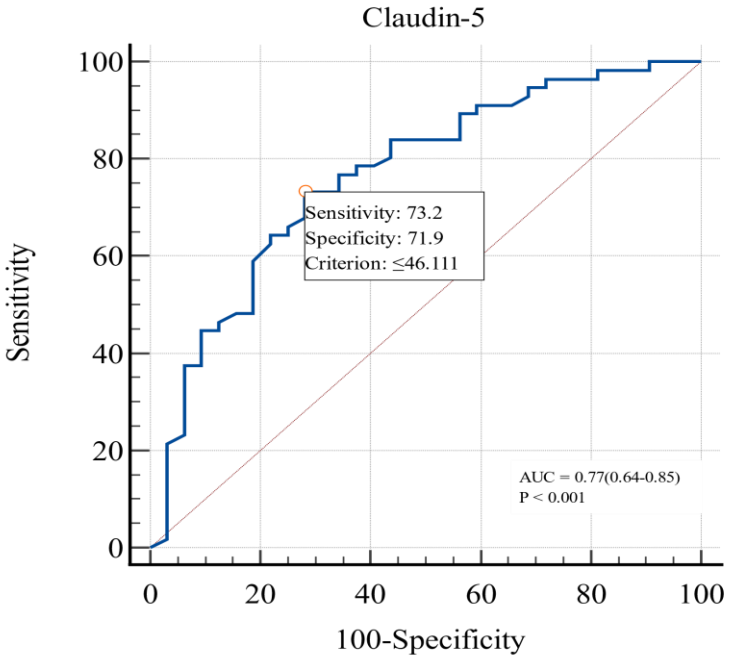

Fig 7. Receiver operating characteristic (ROC) curve of Tricellulin.

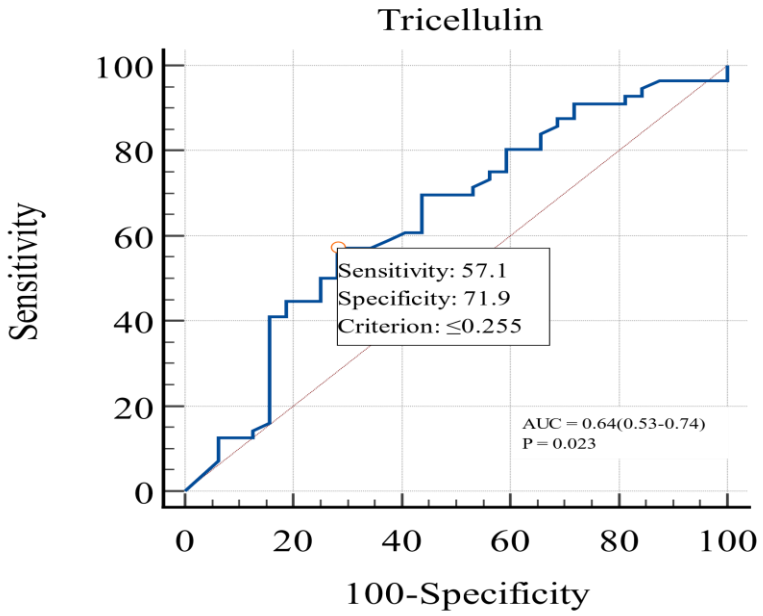

Fig 8. Receiver operating characteristic (ROC) curve of the combined model.

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