• Clinical Research •

Diagnostic value of OCT-based temporal macular retinal thinning in children with hereditary glomerular diseases

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Received: 2025-07-29 Accepted: 2025-12-23

Abstract

● **AIM:** To determine the differences in temporal macular thinning among children with Alport syndrome (AS), thin basement membrane nephropathy (TBMN), and age-matched healthy controls and to clarify its diagnostic and differential diagnostic significance.

● **METHODS:** This was a case-control study. Children with AS and TBMN diagnosed at our hospital between January 2021 and December 2024 were enrolled. All participants underwent comprehensive ophthalmic assessments, including visual acuity, refraction, slit-lamp biomicroscopy with dilated pupils, color fundus photography, biometry, and optical coherence tomography (OCT). Refractive error, lens thickness, axial length, macular retinal thickness in all sectors, and temporal thinning index (TTI) values were compared using one-way analysis of variance (ANOVA) or an independent samples *t*-test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic efficacy of the TTI for AS in males.

● **RESULTS:** The cohort consisted of 40 patients with genetically confirmed AS [33 with X-linked Alport syndrome (XLAS): 16 males, 17 females; 7 with autosomal recessive Alport syndrome (ARAS): 4 males, 3 females], 40 patients with TBMN (male:female=1:1, 40 eyes), and 40 age-matched healthy controls (male:female=1:1, 40 eyes). The standard deviations of the mean TTI values were 12.08±3.18 in the AS group, 6.60±1.88 in the TBMN group, and 6.42±1.14 in the control group. The TTI was significantly greater in the AS group than in both the TBMN and control groups (P<0.001). A statistically significant difference in TTI was observed between sexes in the XLAS subgroup but not in the ARAS subgroup. ROC analysis for males with XLAS revealed an area under the curve of 0.897 (95% confidence interval: 0.844–0.949, P<0.001) for the TTI in the diagnosis of AS. The optimal cutoff value was 9.67, yielding a sensitivity of 0.875 and specificity of 0.826.

● **CONCLUSION:** Children with AS exhibit greater temporal macular retinal thinning than do those with TBMN and healthy controls. The TTI shows potential as an auxiliary diagnostic marker for AS in male patients.

● **KEYWORDS:** Alport syndrome; thin basement membrane disease; optical coherence tomography; retinal thinning index

DOI:10.18240/ijo.2026.07.16

Citation: Wang J, Feng Y, Lin P, Chen L. Diagnostic value of OCT-based temporal macular retinal thinning in children with hereditary glomerular diseases. *Int J Ophthalmol* 2026;19(7):1351-1356

INTRODUCTION

Alport syndrome (AS) is an inherited multisystem disorder characterized by hematuria, proteinuria, progressive renal failure, sensorineural hearing loss, anterior lenticonus, and dot-and-fleck retinopathy[1-3]. It arises primarily from abnormalities in type IV collagen α-chains, leading to basement membrane pathology[4-5]. Type IV collagen, a major constituent of basement membranes throughout the body, is prominently distributed in ocular structures, including the corneal epithelial basement membrane, the lens capsule, the retinal pigment epithelium, Bruch's membrane, and the internal limiting membrane (ILM)[6]. Mutations in these collagen chains underlie the various forms of AS.

AS is a rare disease, with an estimated prevalence ranging from 1 in 5000 people to 1 in 50 000 people worldwide[7]. Approximately 85% of cases exhibit X-linked inheritance, predominantly caused by mutations in the collagen type IV alpha-5 chain (*COL4A5*)[8-10] gene. The remaining 15% consist of autosomal recessive forms and rare autosomal dominant forms, primarily resulting from mutations in the collagen type IV alpha-3 chain (*COL4A3*) and collagen type IV alpha-4 chain (*COL4A4*) genes[11-12]. Mutations in *COL4A5*

or *COL4A3*/*COL4A4*[13-14] lead to the loss of the collagen IV α3α4α5 network within the corneal basement membrane, lens capsule, and retina[4]. This molecular defect is associated with ocular manifestations such as corneal opacities, anterior lenticonus, dot-and-fleck retinopathy[15], and temporal retinal thinning[16].

Typically, these features do not impair visual acuity; anterior lenticonus, for example, is correctable. In contrast, rare ophthalmological complications, such as posterior polymorphous corneal dystrophy, giant macular holes, and maculopathy, can result in significant vision loss[17]. Ocular abnormalities have been reported in approximately 10% to 90% of AS patients. Anterior lenticonus and dot-and-fleck retinopathy represent the earliest described and most characteristic ocular findings.

Clinically, both AS and thin basement membrane nephropathy (TBMN) are hereditary glomerular basement membrane disorders. TBMN, which is typically an autosomal dominant condition caused by heterozygous mutations in *COL4A3* or *COL4A4*, shares significant genotypic and phenotypic overlap with AS. This substantial overlap in genetic variants and clinical manifestations poses considerable challenges for differential diagnosis in clinical practice[18-19].

With the widespread application of optical coherence tomography (OCT), the temporal thinning index (TTI) has emerged as a significant diagnostic marker for AS[20-21]. Notably, TTI has been associated with the development of renal failure before the age of 30y in males with X-linked disease. However, existing research on temporal macular thinning has focused primarily on adult populations. Data regarding its earliest age of onset, prevalence, and relationship with other ocular abnormalities in pediatric patients remain scarce. This study enrolled 40 pediatric patients with AS (40 eyes; 20 males, 20 females) to characterize ocular biometric features, with a specific focus on analyzing the characteristics of temporal macular thinning in children with AS.

PARTICIPANTS AND METHODS

Ethical Approval This study conformed to the principles of the Declaration of Helsinki and was reviewed and approved by the Hospital Ethics Committee (No.20231228-01). Written informed consent was obtained from the guardians of all participants.

Participants This was a case-control study. Children were diagnosed with AS or TBMN at our hospital between January 2021 and December 2024. Inclusion criteria: 1) Confirmed diagnosis of AS or TBMN by renal biopsy and/or genetic screening in the Department of Nephrology; 2) age<18y; 3) the completion of comprehensive ophthalmic examinations, including visual acuity testing, refraction testing, slit-lamp biomicroscopy, color fundus photography, and macular OCT. Exclusion criteria: 1) Diagnosis other than AS or TBMN; 2) presence of other systemic or ocular comorbidities. Study groups: AS group: Forty patients [40 eyes; 33 with X-linked Alport syndrome (XLAS): 16 males, 17 females; 7 with autosomal recessive Alport syndrome (ARAS): 4 males, 3 females]. The mean age was 9.39y. TBMN group: Forty patients (40 eyes; male-to-female ratio, 1:1). The mean age was 8.43y. Control group: Forty age-matched healthy children (40 eyes; male-to-female ratio, 1:1). The mean age was 8.60y. Refractive error range: -3.00 to +3.00 D (spherical equivalent) across all groups. No history of ocular or significant systemic disease was present in the control group.

Ophthalmic Imaging Procedures Color fundus photography was performed using a nonmydriatic retinal camera (Canon, Japan). Two independent retinal specialists assessed the images for the presence of dot-and-fleck retinopathy. Discrepancies were adjudicated by a third senior retinal expert. Macular OCT scans were acquired using a standardized protocol. A 6 mm×6 mm early treatment diabetic retinopathy study (ETDRS) grid centered on the fovea was applied. The software automatically delineated Bruch's membrane and the ILM. The mean thickness within each sector was defined as the distance between the ILM and Bruch's membrane. Three consecutive measurements were taken per sector, and the average value was recorded. The macular sectors were designated as follows: inner temporal (T1), outer temporal (T2), inner nasal (N1), and outer nasal (N2).

TTI Calculation The TTI was calculated according to the method described by Ahmed *et al*[22]. This index quantifies the degree of temporal retinal thinning by expressing the difference between nasal and temporal retinal thickness relative to temporal retinal thickness. The formula is as follows: TTI=[(Nasal thickness-Temporal thickness)/Nasal thickness]×100% (Figure 1).

Statistical Analysis SPSS 22.0 software was used for statistical analysis and processing. Normal analysis and homogeneity tests of variance were first performed on all the data. The quantitative data are expressed as the means±standard deviations (SD). Univariate analysis of variance was performed for TTI, age, diopter, eye axis, and crystal thickness. The optimal diagnostic threshold was determined on the basis of the receiver operating characteristic (ROC) curve, and the effectiveness of the TTI in the diagnosis of children with AS was evaluated on the basis of the area under the ROC curve (AUC). Pearson analysis was used to evaluate the relationship between age and TTI, and $P<0.05$ was considered statistically significant.

RESULTS

Comparison of Ocular Parameters Between the AS Group and Control Group No corneal abnormalities, anterior

Table 1 Comparison of ocular parameters between the AS group and control group

Parameters	CON (*n*=40)	TBMN (*n*=40)	AS (*n*=40)	*t*1	*P*1	*t*2	*P*2	*t*3	*P*3
TTI	6.42±1.14	6.60±1.88	12.08±3.18	10.750	<0.001	9.860	<0.001	-0.532	0.597
AL, mm	23.22±1.34	23.16±1.24	23.23±0.99	0.003	0.998	0.256	0.812	-0.226	0.808
SE, D	-0.53±1.42	-0.41±1.38	-0.58±1.81	-1.140	0.884	0.872	0.638	-0.399	0.713
Age, y	8.60±2.65	8.43±2.74	9.39±3.24	1.238	0.209	1.421	0.141	-0.287	0.789
LT, mm	3.44±0.21	3.45±0.27	3.41±0.17	-1.184	0.283	-0.861	0.405	-0.195	0.830

*P*1: AS *vs* CON; *P*2: AS *vs* TBMN; *P*3: CON *vs* TBMN. AS: Alport syndrome; TBMN: Thin basement membrane nephropathy; CON: Control group; TTI: Temporal thinning index; AL: Axial length; SE: Spherical equivalent; D: Diopter; LT: Lens thickness.

Table 2 Comparison of macular retinal thickness parameters across ETDRS sectors between AS and control groups mean±SD, μm

Parameters	T2	T1	N1	N2
AS	271.00±15.54	307.38±15.54	336.88±15.95	321.00±11.96
CON	286.22±11.49	324.51±10.54	336.52±12.39	316.14±12.49
TBMN	285.21±15.00	325.21±15.10	337.51±12.90	317.21±15.70
*t*1/*P*1	-4.844/<0.001	-5.561/<0.001	0.111/0.912	1.72/0.089
*t*2/*P*2	-4.162/<0.001	-5.173/<0.001	-0.213/0.834	1.22/0.226
*t*3/*P*3	0.342/0.735	-0.243/0.881	0.342/0.735	0.35/0.727

*P*1: AS *vs* CON; *P*2: AS *vs* TBMN; *P*3: CON *vs* TBMN. ETDRS: Early treatment diabetic retinopathy study; AS: Alport syndrome; TBMN: Thin basement membrane nephropathy; CON: Control group; SD: Standard deviation; T1: Inner temporal; T2: Outer temporal; N1: Inner nasal; N2: Outer nasal.

lenticonus, or dot-and-fleck retinopathy were observed in any AS patient. Mean TTI values were significantly higher in the AS group than in both the TBMN and control groups (P<0.001). Axial length, refractive error, age, and lens thickness did not show statistically significant differences between the AS group and either the TBMN group or the control group (P>0.05; Table 1).

Retinal thickness were observed in the temporal sectors (T2 and T1) were significantly lower in the AS group than in both the TBMN and control groups (P<0.001). However, no statistically significant differences were found in the nasal sectors (N1 and N2) among these groups. Furthermore, retinal thickness measurements across all sectors showed no statistically significant differences between the TBMN group and the control group (P>0.05; Table 2).

Gender difference in mean TTI values were significantly higher in the XLAS subgroup (P<0.05), but there were no significant sex-based differences were found within the control, TBMN, or ARAS subgroups (all P>0.05). Both male and female subgroups of XLAS and ARAS exhibited significantly different mean TTI values compared to both the control and TBMN groups (all P<0.01). No statistically significant differences were detected between male and female subgroups of the control and TBMN groups when compared to each other (all P>0.05). Significant differences in mean TTI values were identified between XLAS and ARAS subgroups when stratified by sex (males: P<0.05; females: P<0.001; Table 3).

ROC curve analysis demonstrated that TTI exhibited significant diagnostic efficacy for AS in male patients, with AUC of 0.897 [95% confidence interval (CI): 0.844–0.949;

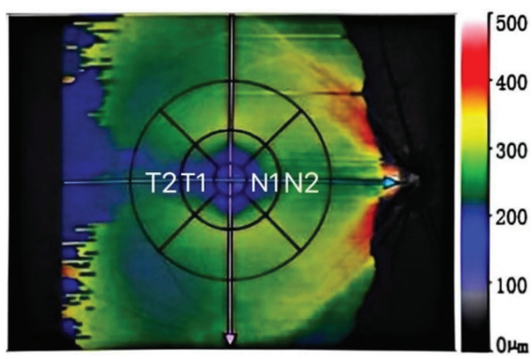

Figure 1 The macular fovea was recorded as inner temporal (T1), outer temporal (T2), inner nasal (N1), or outer nasal (N2).

Table 3 Intergroup comparisons of TTI values among AS subgroups stratified by sex and genotype versus control and TBMN groups

Group	*n*	TTI		*t*	*P*
		Male	Female		
CON	40	6.08±1.74	6.74±0.54	-1.841	0.074
TBMN	40	6.24±1.85	6.96±1.91	-1.211	0.234
XLAS	33	14.15±4.48	7.99±1.20	5.862	0.002
ARAS	7	12.27±2.77	13.91±4.27	-0.562	0.605
*t*1/*P*1		-0.472/0.641	-0.0712/0.481		
*t*2/*P*2		-11.703/<0.001	-5.213/<0.001		
*t*3/*P*3		-7.111/<0.001	-9.086/<0.001		
*t*4/*P*4		-11.463/<0.001	-3.432/0.001		
*t*5/*P*5		-6.934/<0.001	-8.273/<0.001		
*t*6/*P*6		2.076/0.045	-6.303/<0.001		

*P*1: CON *vs* TBMN; *P*2: CON *vs* XLAS; *P*3: CON *vs* ARAS; *P*4: TBMN *vs* XLAS; *P*5: TBMN *vs* ARAS; *P*6: XLAS *vs* ARAS. TTI: Temporal thinning index; AS: Alport syndrome; CON: Control group; TBMN: Thin basement membrane nephropathy; XLAS: X-linked Alport syndrome; ARAS: Autosomal recessive Alport syndrome.

P<0.001). The optimal cutoff value was determined as 9.67, yielding a sensitivity of 0.875 and specificity of 0.826. Based on these findings, a TTI value>9.67 was defined as clinically significant temporal macular thinning (Figure 2, Table 4).

Pearson correlation analysis performed between TTI values and age in the AS group showed no statistically significant correlation (Table 5).

DISCUSSION

AS affects approximately 1 in 50 000 newborns, with males exhibiting more severe symptoms than females do. An estimated 30 000–60 000 individuals are affected in the United States. Among American children, AS accounts for 3% of all End-Stage Renal Disease (ESRD) cases, whereas this figure is 0.2% in adults[17]. While XLAS, the predominant form causing ESRD, primarily affects males, females with XLAS exhibit comparable prevalence rates. The diagnosis of affected females remains challenging. However, 15%–30% of affected individuals develop renal failure by age 60, with hearing loss often manifesting in middle adulthood[23-24]. Owing to milder symptoms in females, nephrologists often hesitate to perform invasive renal biopsies or genetic testing in pediatric patients. This underscores the critical need for noninvasive auxiliary diagnostic markers[23]. Temporal macular thinning occurs in approximately 80% of AS patients[24-25], exceeding the prevalence of anterior lenticonus and dot-and-fleck retinopathy—the earliest reported characteristic ocular abnormalities. Retinopathy affects approximately 85% of XLAS males but rarely manifests in childhood, typically emerging near renal failure onset. This asymptomatic condition features perimacular yellowish-white flecks with foveal sparing (although peripheral involvement may occur) and a lack of fluorescein angiography hyperfluorescence. While TBMN, which is primarily autosomal dominant, involves mutations in glomerular basement membrane genes, its exact underlying mechanisms remain incompletely understood. Clinical and genetic overlap with AS complicates differential diagnosis. Advances in OCT have identified temporal macular thinning as a characteristic feature of AS. The rapid, noninvasive, operator-independent, and cost-effective nature of OCT make it particularly suitable for evaluating females with suspected AS. Using Ahmed *et al*'s[22] TTI, we quantified retinal thinning in 40 pediatric patients with AS. Notably, no classic signs, corneal abnormalities, anterior lenticonus, or dot-and-fleck retinopathy were observed. Consider that these symptoms may not have manifested due to the young age of the cohort. Its pathogenesis—possibly involving Müller cell dysfunction and abnormal COL4A5 deposition[26-28] requires further investigation. Studies have found that among XLAS male patients (average age 11y), the incidence rates of anterior conical lens and macular lesions were 7% and 27%, respectively, while no such changes were observed in XLAS female patients (average age 8y)[29]. Wang *et al*[30] reported that among XLAS male and female patients, the incidence rates of anterior conical lens and dot-like retinal lesions were 56%, 59% (average age 35.3y) and 0, 18% (average age 43.2y), respectively; among ARAS patients, these rates were 80% and 87% (average age 37.3y). The mean TTI values were 12.08±3.18 (AS), 6.60±1.88 (TBMN), and 6.42±1.14 (CON). The AS group presented significantly greater TTIs than both the TBMN and control groups did (*P*<0.01), indicating that early microstructural changes preceding visible ocular pathology are consistent with prior reports[18]. The presence of thinner temporal maculae in AS children suggests that type IV collagen mutations affect retinal basement membranes, which share underlying pathogenic mechanisms with renal involvement. Thinning may arise from reductions in the ILM/nerve fiber layer and inner nuclear layer[21-22], potentially disrupting retinal nutrition and metabolite clearance[31-32].

Significant TTI differences existed between sexes for XLAS (*P*<0.05) but not for ARAS. ROC analysis for XLAS males

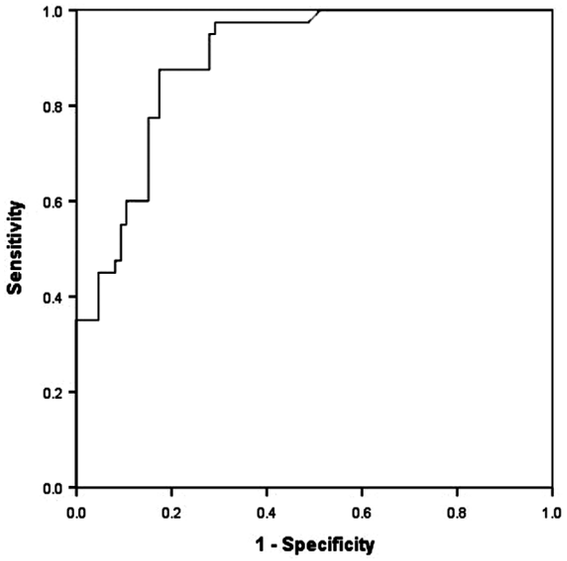

Figure 2 ROC curve analysis of TTI diagnostic AS effectiveness ROC: Receiver operating characteristic; TTI: Temporal thinning index; AS: Alport syndrome.

Table 4 ROC curve analysis of TTI diagnostic AS performance

Area	Std.Error	*P*	Asymptotic 95% confidence interval	
			Lowerbound	Upperbound
0.897	0.027	<0.001	0.844	0.949

ROC: Receiver operating characteristic; TTI: Temporal thinning index; AS: Alport syndrome.

Table 5 Analysis of the correlation between TTI value and age in the AS group

TTI	Age	*r*	*P*
12.08±3.18	9.39±3.24	0.157	0.332

TTI: Temporal thinning index; AS: Alport syndrome.

yielded an AUC of 0.897 (95%CI: 0.844–0.949; P<0.001), with an optimal TTI cutoff of 9.67 (sensitivity: 0.875; specificity: 0.826). Temporal macular thinning precedes anterior lenticonus and retinopathy in AS, enhancing early diagnostic sensitivity. The TTI has significant value in differentiating AS from TBMN. A TTI>9.67 in male children should lead to strong suspicion of XLAS. This is consistent with Zhu *et al*[33] research findings. In this study, the specificity of TTI for diagnosing AS was only 0.826, which did not reach 100%. This indicates that TTI can be used as a diagnostic marker for AS but should be combined with other clinical and genetic findings rather than used as an independent diagnostic marker.

This study has certain limitations. The sample size of children with ARAS included in the study is small, making it difficult to perform effective statistical analysis. The diagnostic efficacy of TTI for patients with ARAS requires further research with a larger sample size.

ACKNOWLEDGEMENTS

Foundations: Supported by Xi'an Municipal Health Commission Scientific Research Project (No.2023yb22); Xi'an Science and Technology Plan Project (No.24YXYJ0108; No.22YXYJ0065).

Conflicts of Interest: Wang J, None; **Feng Y,** None; **Lin P,** None; **Chen L,** None.

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