Molecular Vision 2026; 32:143-153 <http://www.molvis.org/molvis/v32/143>
Received 19 May 2025 | Accepted 1 March 2026 | Published 27 February 2026

The role of corneal epithelial thickness parameters with different degrees of keratoconus in the diagnosis of keratoconus

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Purpose: To assess the diagnostic value of corneal epithelial thickness parameters measured by RTVue XR OCT in different stages of keratoconus.

Methods: This is a cross-sectional study of 64 patients (64 eyes) with keratoconus who visited from January 2021 to December 2023. The control group randomly had 46 patients (46 eyes) with refractive errors. The RTVue XR OCT was used to measure the distribution and parameter indicators of corneal epithelial thickness in various regions of the normal corneal group. We measured parameters with statistically significant differences and calculated cutoff points, sensitivity, specificity, the area under the receiver operating characteristic curve, and the Youden index for the parameter indicators in the preclinical, mild, moderate, and severe keratoconus groups during the clinical period and in the normal control group.

Results: The normal corneal epithelial thickness was unevenly distributed in various regions within the range of 0 to 5 mm. The cornea was thinner above and below the nose, as well as thicker above and below the temporal area, and the central area of the cornea was the thinnest. The Min-Max parameter showed the highest diagnostic value for preclinical keratoconus. For mild, moderate, and severe keratoconus, parameters including superior-inferior (S-I), supranasal (SN)-infranasal (IT), Max, and standard deviation showed high diagnostic value. SN-IT and standard deviation demonstrated high specificity and sensitivity in distinguishing the clinical keratoconus groups from the normal control group.

Conclusions: Corneal epithelial thickness parameters are valuable for diagnosing various stages of keratoconus. The Min-Max parameter is particularly valuable for preclinical diagnosis, while SN-IT and standard deviation are highly valuable for diagnosing clinical stages.

Corneal keratoconus is an eye disease of unknown origin that can cause the cornea to become thinner and protrude forward [1]. Highly irregular astigmatism often occurs, and most people have binocular onset, which can also be asymmetric. Most people develop corneal keratoconus in their youth, and the condition gradually worsens, leading to decreased vision and blurred vision. The condition can lead to severe visual impairment and, in severe cases, vision loss [2]. In addition, the incidence rate of myopia remains high in China [3]. Corneal refractive surgery is an important correction method for adult refractive errors such as myopia, astigmatism, and hyperopia, and the number of patients undergoing the procedure is increasing each year [4]. Corneal keratoconus is an absolute contraindication for corneal refractive surgery. If no potential keratoconus lesions are detected, corneal refractive surgery can accelerate pathological corneal dilation, leading to decreased vision. Therefore, the diagnosis of keratoconus is of great significance [5]. At present, the diagnostic criteria for keratoconus are based on three-dimensional morphological changes, with corneal tomography as the main indicator, and the abnormality of the corneal posterior surface height in early keratoconus has also been recognized and valued. However, once corneal morphology changes, it is no longer the early stage of the disease. For early diagnosis, existing corneal topographic maps have limitations and cannot distinguish abnormal corneal topographic changes in normal eyes from those in early keratoconus, posing a challenge to early diagnosis [6]. Current diagnostic criteria predominantly rely on corneal topography, which has limitations in distinguishing early-stage keratoconus from normal corneal variations. This study aims to address this gap by investigating the diagnostic value of corneal epithelial thickness parameters measured by RTVue XR OCT (Optovue, Fremont, CA, USA) across various stages of keratoconus. Fourier-domain optical coherence tomography (OCT) (RTVue XR OCT) is an anterior segment technique that follows the principles of coherent optical tomography. It has high scanning speed and resolution and can measure corneal cross sections, providing accurate corneal epithelial thickness values and related parameters [7]. At present, no relevant study uses RTVue XR OCT to measure and compare corneal epithelial thickness in preclinical keratoconus, across

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different clinical stages (mild, moderate, severe) of keratoconus, and in normal corneas. The purpose of this study is to utilize a cross-sectional research design and RTVue XR OCT technology to measure and analyze corneal epithelial thickness parameters in patients with various stages of keratoconus, with the aim of providing a more accurate diagnostic tool for clinical use and serving as a reference for subsequent research and clinical practice.

METHOD

General information: To ensure the study's statistical power, we conducted an a priori sample size calculation. Assuming a power of 80%, a significance level of 0.05, and based on preliminary data indicating a mean difference in epithelial thickness parameters between keratoconus and control groups, we estimated that a sample size of 64 eyes with keratoconus and 46 eyes in the control group would be sufficient to detect a clinically significant difference. This calculation was performed using statistical software specifically designed for sample size estimation in diagnostic studies. The study used a cross-sectional design, and participants were consecutively recruited from our clinic's database between January 2021 and December 2023. Random sampling was employed, and 64 patients (64 eyes) with keratoconus who visited from January 2021 to December 2023 were selected as research participants. The age range of patients with keratoconus was 20 to 32 years, with a total of 34 men and 30 women. This includes 21 cases of preclinical keratoconus, 19 cases of mild keratoconus, 11 cases of moderate keratoconus, and 13 cases of severe keratoconus. The control group randomly selected 46 patients (46 eyes) with refractive errors who visited the same period, aged 21 to 33 years, including 20 men and 26 women. This study complies with the Declaration of Helsinki and has been reviewed and approved by the hospital's Medical Ethics Committee. All patients in the case and control groups were provided with detailed explanations and informed of their testing status, and they voluntarily agreed and cooperated to sign an informed consent form with clear intentions.

Inclusion and exclusion criteria: Inclusion criteria: (1) Preclinical keratoconus group: contralateral eye of patients with clinical keratoconus [8], and no features of keratoconus were found in the clinical manifestations and corneal topography screening of the eye. (2) Corneal conus patients: (a) met the diagnostic criteria agreed upon by keratoconus experts [9]; (b) soft contact lenses could not be worn for more than 2 weeks, while hard contact lenses could not be worn for 3 months. (3) Normal corneal group: (a) clinical manifestations of the eye and corneal topography screening did not reveal any features of keratoconus; (b) no history of wearing contact lenses; (c) slit-lamp examination eliminated other eye diseases; (d) equivalent spherical mirror degree not higher than −10.0 D and astigmatism less than 2 D; (e) tear film rupture time greater than 5 s; (f) Schirmer 1 test for 5 min above 10 mm; (g) no history of eye surgery or trauma. Exclusion criteria: (1) accompanied by other eye diseases; (2) accompanied by systemic diseases; (3) a history of eye surgery; (4) pregnancy or lactation.

Diagnostic criteria for clinical stage keratoconus: The standards are as follows [9]: (1) a history of myopia and astigmatism; (2) a history of visual impairment; (3) corrected visual acuity less than 1.0; (4) at least one of the following signs positive for slit-lamp microscopy examination: conical protrusion, Vogt line, epithelial or subcutaneous scar, Fleischer's ring, thinning of corneal stroma, corneal topography examination showing the central refractive index of the anterior surface of the cornea greater than 47 D; (5) difference in refractive power between 3 mm below and 3 mm above the center of the cornea greater than 3 D; and (6) difference in refractive power between the central and anterior surfaces of both corneas greater than 1 D.

The standard classification of mild, moderate, and severe keratoconus is based on the Amsler-Krumeich keratoconus grading system [10]: (1) Mild: corneal eccentricity becomes steeper, myopic astigmatism is less than 5.0 D, and the average K value is less than 48.00 D. (2) Moderate: myopia with astigmatism greater than 5.0 D but less than 8.0 D, with an average K value less than 53.00 D, no scars on the cornea, and a thinnest corneal vertex thickness greater than 400 μm. (3) Severe: myopic astigmatism greater than 8.0 D but less than 10.0 D, with an average K value greater than 53.0 D, no scars on the cornea, and the thinnest thickness of the corneal apex greater than 300 μm but less than 400 μm, or corneal refractive index, with an average K value greater than 55.0 D and a thinnest corneal vertex thickness less than 300 μm.

Detection instruments RTVue XR OCT:

Testing methods—All participants were first tested for naked eye vision, diagnostic optometry, intraocular pressure, slit lamp examination, corneal topography examination, fundus examination, and so on to rule out other eye diseases. Then, the same skilled examiner used RTVue XR OCT to examine the participants separately. Each participant underwent this examination three or more times, with an interval of 3 to 5 min between each scan. Specific steps: Install a wide-angle corneal adaptor lens, verify the patient's identity information, and input the patient's basic information, with the patient sitting in front of the instrument in a normal and natural state, with the lower jaw resting steadily on the lower

Table 1. Distribution of corneal epithelial thickness in different regions of the normal corneal group.

0–5 mm 9 area	Center area	S area	SN area	N area	IN area	I area	IT area	T area	ST area
Corneal epithelial value (X±SD)μm	54.11 ±3.09	52.87 ±2.45	53.41 ±2.83	54.04 ±2.95	54.59 ±2.87	54.63 ±3.11	54.30 ±3.15	53.61 ±2.94	53.26 ±2.63
Parameter indicators		S-I		SN-IT		N-T		IN-ST	
numerical value (X±SD) μm		−1.76±2.17		- 0.89±2.16		0.43±1.47		1.33±1.66	

S area, upper area; SN area, supranasal area; N area nasal side area; IN area, infranasal area; I area, lower area; IT area, infratemporal area; T area, temporal area; ST area, superior temporal area.

jaw support. The patient had their eyelids opened and looked ahead. The examiner used the computer screen to assess the patient's gaze and scanning situation; adjusted the distance between front and back, as well as left and right; and formed a clear image on the monitor. The Pachymetry scanning mode was used, and the participants were informed to focus on the center of the lens. The center of the pupil was taken as the scanning center to obtain a corneal epithelial thickness map within the range of 0 to 6 mm.

Detection parameter indicators—As shown in Figure 1, the results showed numerical maps of corneal epithelial thickness (CET) in the central area of the cornea (0-2 mm center area), eight areas within the 2- to 5-mm range, and eight areas within the 5- to 6-mm range: upper area (S area), upper nasal area (SN area), nasal side area (N area), lower nasal area (IN area), lower area (I area), lower temporal area (IT area), temporal side area (T area), and upper temporal area (ST area). Simultaneously, six parameter indicators were displayed: average epithelial thickness (S value) above the 2- to 5-mm range of the cornea, average epithelial thickness (I value) below the 2- to 5-mm range of the cornea, thinnest corneal thickness (Min), difference between thinnest and thickest corneal thickness (Min-Max), thickest corneal thickness (Max), and standard deviation (SD).

Statistical methods: Data were analyzed using SPSS 22.0 software (SPSS, Inc., Chicago, IL). Normality of the data was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were calculated as mean ± SD. Comparisons between groups were made using either the independent samples *t* test or the Mann-Whitney *U* test, depending on the distribution of the data. Receiver operating characteristic (ROC) curves were generated to assess the diagnostic accuracy of the corneal epithelial thickness parameters. The area under the ROC curve (AUC), sensitivity, specificity, and Youden's index were calculated to determine the optimal cutoff points for diagnosing keratoconus at various stages.

RESULTS

Normal corneal group corneal epithelial thickness value: The normal corneal epithelial thickness was unevenly distributed within the 0- to 5-mm range. The epithelium was thinner in the S and SN areas, but thicker in the I and IT areas. Notably, the thinnest epithelium was observed in the S area (S: 52.87 ± 2.45 μm), while the central region (54.11 ± 3.09 μm) was thicker than the S area but thinner than the I and IT areas. Data are summarized in Table 1.

Comparative analysis and ROC curve of two parameter indicators: For Min-Max and SD in corneal epithelial parameters

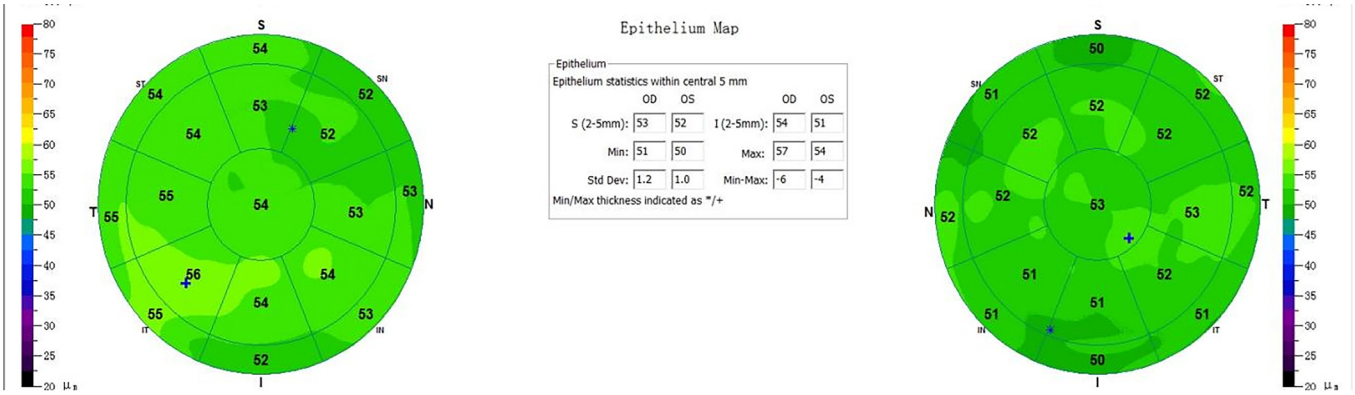

Figure 1. Results and parameter values of RTVue XR OCT measurement of corneal epithelium in the 0- to 6-mm area.

Table 2. Comparison of epithelial thickness differences in different corneal regions between the normal corneal group and the preclinical and clinical stages of keratoconus groups.

Group	S-I (μm)	SN-IT (μm)	Min(μm)	Min-Max (μm)	Max (μm)	Std.Dev
Normal corneal	−1.76±2.17	- 0.89±2.16	50.33±3.25	−5.33±1.38	55.65±3.68	1.22±0.33
Preclinical keratoconus	−1.67±2.50	- 0.19±2.46	50.14±2.97	−7.24±2.57	57.38±3.97	1.70±0.69
P1 value	0.88	0.07	0.83	0.00	0.09	0.00
Mild keratoconus	4.42±5.55	9.21±6.59	42.53±4.01	−19.68±6.24	62.21±4.10	5.16±2.03
P2 value	0.00	0.00	0.00	0.00	0.00	0.00
Moderate keratoconus	2.55±5.77	9.27±7.82	37.18±4.79	−26.19±7.88	63.36±6.33	6.93±2.43
P3 value	0.00	0.00	0.00	0.00	0.00	0.00
Severe keratoconus	8.23±7.28	13.85±6.72	33.69±4.25	−32.54±7.89	66.23±4.64	8.92±2.52
P4 value	0.00	0.00	0.00	0.00	0.00	0.00

between the preclinical keratoconus and normal control groups, the deviation (Dev) comparison showed statistically significant differences ($p < 0.05$). For Min, Min-Max, S-I, supranasal-infratemporal [SN-IT], and SD of corneal epithelial parameters in the mild keratoconus group and normal control group, the difference in Dev comparison was statistically significant ($p < 0.05$). In the clinical stage, the corneal epithelial parameter values of Min, Min-Max, S-I, SN IT, Max, and SD in the moderate and severe keratoconus groups and the normal control group were compared. The differences in Dev comparison were statistically significant ($p < 0.05$), as shown in Table 2.

ROC curve analysis was performed on parameter indicators for the preclinical keratoconus group; the clinical mild, moderate, and severe keratoconus groups with differences ($p < 0.05$); and the normal control group. The Min-Max and SD in the preclinical keratoconus group and the normal control group corresponded to the area under the ROC curve, tangent, specificity, sensitivity, and Youden index, which were 0.27 and 0.71, respectively. The cutoff values were −2.00 and 1.65, respectively, with a sensitivity of 0.00 and 0.48, a specificity of 1.00 and 0.94, and a Youden index of 0.00 and 0.41 (see Figure 2 and Table 3).

The S-I, SN-IT, Min, Min-Max, SD, and Max parameters of the mild keratoconus group and the normal control group corresponded to the area under the ROC curve, tangent, specificity, sensitivity, and Youden index, which were 0.86, 0.97, 0.05, 0.03, 0.97, and 0.89, respectively. The tangent points were −0.50, 1.50, 66.00, −2.00, 2.20, and 58.50, respectively. The sensitivity was 0.84, 0.95, 0.00, 0.00, 0.95, and 0.90, respectively. The specificity was 0.78, 0.85, 1.00, 1.00, 1.00, and 0.83, respectively. The Youden index was 0.62, 0.80, 0.00, 0.00, 0.95, and 0.73, respectively (see Figure 3 and Table 4).

The S-I, SN-IT, Min, Max, Min-Max, and SD parameters corresponded to the ROC curve area, tangent point, specificity, sensitivity, and Youden index for the moderate keratoconus group during the clinical stage and the normal control group. The area under the ROC curve was 0.76, 0.94, 0.00, 0.00, 0.88, and 1.00, respectively. The tangent points were 0.50, 0.50, 66.00, −2.00, 60.50, and 2.65, respectively. The sensitivity was 0.64, 1.00, 0.00, 0.00, 0.82, and 1.00, respectively. The specificity was 0.83, 0.74, 1.00, 1.00, 0.96, and 1.00, respectively. The Youden index was 0.47, 0.74, 0.00, 0.00, 0.78, and 1.00, respectively (see Figure 4 and Table 5).

The S-I, SN-IT, Min, Max, Min-Max, and SD parameters of the severe keratoconus group and the normal control group during the clinical period corresponded to the area under the ROC curve, tangent, specificity, sensitivity, and Youden index, which were 0.92, 1.00, 0.00, 0.00, 0.97, and 1.00, respectively. The tangent points were 1.50, 3.50, 66.00, −2.00, 59.5, and 3.90, respectively. The sensitivity was 0.92, 1.00, 0.00, 0.00, 0.92, and 1.00, respectively. The specificity was 0.89, 1.00, 1.00, 1.00, 0.94, and 1.00, respectively. The Youden index was 0.81, 1.00, 0.00, 0.00, 0.86, and 1.00, respectively (see Figure 5 and Table 6).

As a result, the ROC results showed that compared with normal corneas, the Min-Max parameter demonstrated the highest diagnostic value for preclinical keratoconus (AUC = 0.71), while the SD showed limited utility in this stage (AUC = 0.27). For mild, moderate, and severe clinical keratoconus, parameter indicators, including S-I, SN-IT, Max, and SD, showed high diagnostic value, among which SN-IT and SD achieved the highest diagnostic accuracy.

Table 3. RTVue XR OCT distinguishes Std between preclinical keratoconus group and normal control group Dev and Min-Max values correspond to the area, tangent, specificity, sensitivity, and Youden index under the ROC curve.

Parameter	Preclinical keratoconus and normal control group					
	cut-off point	sensitivity	specificity	AUC	Youden index	P value
Std.Dev	−2.00	0.00	1.00	0.27	0.00	0.00
Min-Max	1.65	0.48	0.94	0.71	0.42	0.01

Note: Youden Index=Sensitivity + Specificity - 1.

DISCUSSION

We propose that the epithelial thickness variations may serve as a compensatory response in the early stages of the disease, where subtle corneal shape changes are initially masked by the epithelium. As keratoconus progresses, these changes become more pronounced and can be detected through OCT imaging, providing a valuable diagnostic indicator.

The corneal epithelial layer serves as the external protective barrier of the cornea and, together with the tear film, affects the changes in corneal refractive power [11]. The measurement of corneal epithelium plays an important role in the diagnosis and treatment of ophthalmic diseases such as glaucoma, refractive error, and keratoconus [12,13]. In the early stage of keratoconus, subtle thickness and morphological changes in the cornea are compensated for by the corneal epithelium. Therefore, corneal epithelium with changes in partial epithelial thickness can provide sensitive diagnostic evidence for early diagnosis of keratoconus [14-16]. Nowadays, the research and measurement of corneal epithelium are receiving increasing attention.

Noncontact corneal measurement has recently received widespread attention due to its multiple advantages compared

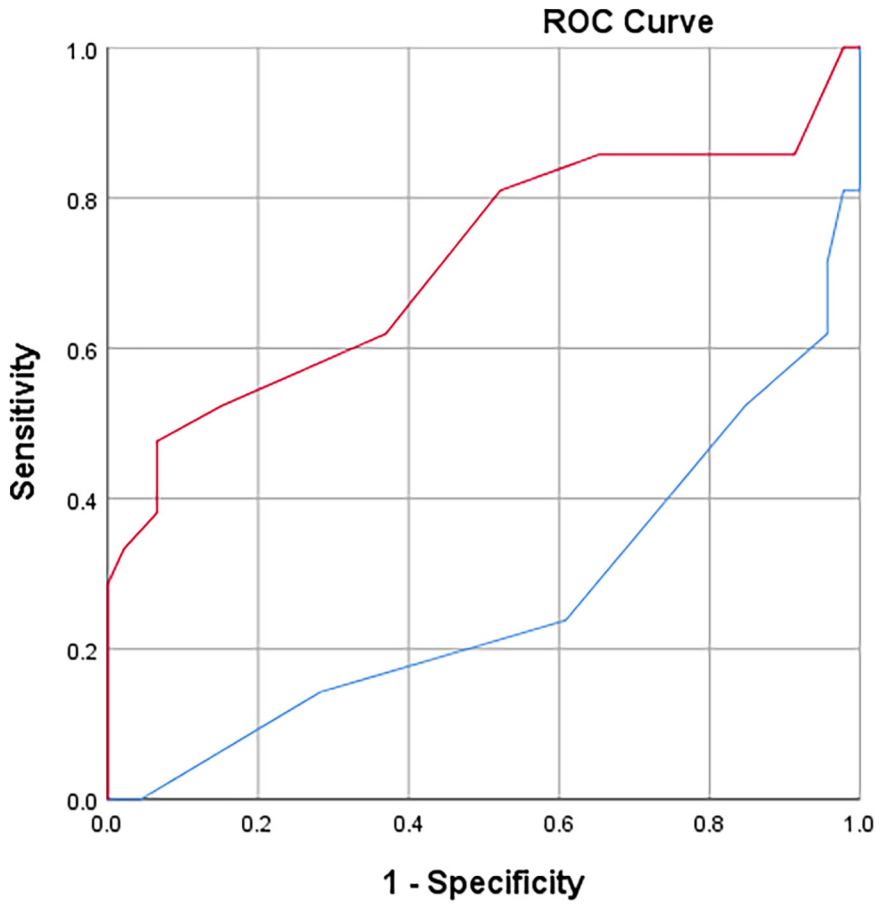

Figure 2. Distinguishing Min-Max and SD between the preclinical keratoconus group and the normal control group. Dev value corresponds to the ROC curve. Curve colors: Min-Max: red; SD: blue.

Table 4. RTVue XR OCT distinguishes the S-I, SN-IT, MIN, MAX, MIN-MAX, Std.

Parameter	Mild keratoconus and normal control group					
	cut-off point	sensitivity	specificity	AUC	Youden index	P value
S-I	−0.50	0.84	0.78	0.86	0.62	0.00
SN-IT	1.50	0.95	0.85	0.97	0.80	0.00
Min	66.00	0.00	1.00	0.05	0.00	0.00
Min-Max	−2.00	0.00	1.00	0.03	0.00	0.00
Std.Dev	2.20	0.95	1.00	0.97	0.95	0.00
Max	58.50	0.90	0.83	0.89	0.73	0.00

Dev values corresponding to the area under the ROC curve, cut-off point, specificity, sensitivity, and Youden index between the mild keratoconus group and the normal control group in the clinical stage

to contact methods [17]. The coherent light tomography (OCT) scanner, founded in the past century, was initially used to observe retinal diseases. With the development of medical technology, it has gradually been applied to anterior segment examination, and its scanning speed has increased, reducing artifacts caused by eye movement and enabling higher resolution, richer image details, and greater measurement accuracy [18,19]. The measurement of corneal epithelial thickness has good repeatability and accuracy [18,20,21]. In previous literature on Fourier OCT research, the RTVue XR 100 OCT was most commonly used for corneal examination [22]. In this study, the RTVue XR OCT demonstrated significantly improved scanning speed compared to earlier Fourier OCTs, and the reliability of the results was also enhanced. RTVue

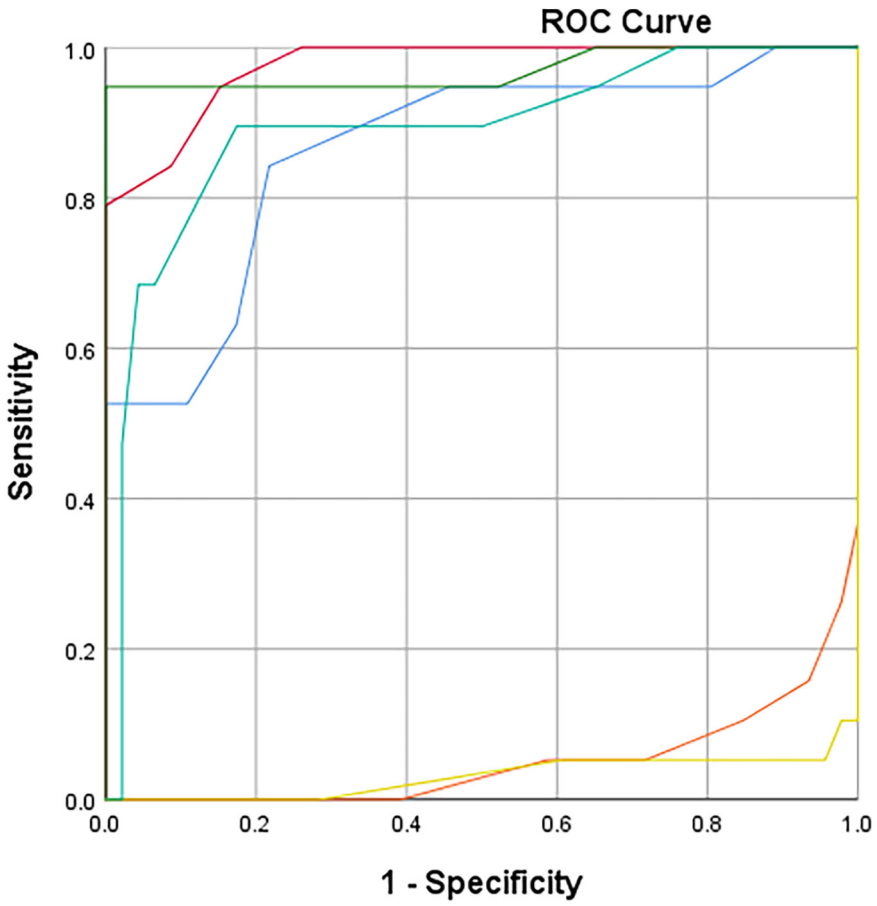

Figure 3. ROC curves corresponding to S-I, SN-IT, Min, Max, Min-Max, and SD values for distinguishing mild keratoconus in the clinical stage from the normal control group. Curve colors: S-I: blue; SN-IT: red; Min: orange; Max: cyan; Min-Max: yellow; SD: green.

Table 5. RTVue XR OCT distinguishes the S-I, SN-IT, MIN, MAX, MIN-MAX, Std.

Parameter	Moderate keratoconus and normal control group					
	cut-off point	sensitivity	specificity	AUC	Youden index	P value
S-I	0.50	0.64	0.83	0.76	0.47	0.01
SN-IT	0.50	1.00	0.74	0.94	0.74	0.00
Min	66.00	0.00	1.00	0.00	0.00	0.00
Min-Max	−2.00	0.00	1.00	0.00	0.00	0.00
Max	60.50	0.82	0.96	0.88	0.78	0.00
Std.Dev	2.65	1.00	1.00	1.00	1.00	0.00

Dev values corresponding to the area under the ROC curve, cut-off point, specificity, sensitivity, and Youden index between the clinical moderate keratoconus group and the normal control group

XR OCT can provide up to 16-mm long B-scans, with a scanning speed of 70,000 times per second and an axial resolution of 5 µm. It records measurements across different areas of the cornea and displays measurement images and analysis values for each area. This study used RTVue XR OCT to detect corneal epithelial thickness and other parameters as research indicators to observe the distribution characteristics of normal corneal epithelial thickness. Then, by comparing the preclinical, mild, moderate, and severe keratoconus groups with the normal control group, the distribution characteristics of normal corneal epithelial thickness and its role in the diagnosis of different severities of keratoconus were explored, providing guidance and assistance for clinical applications.

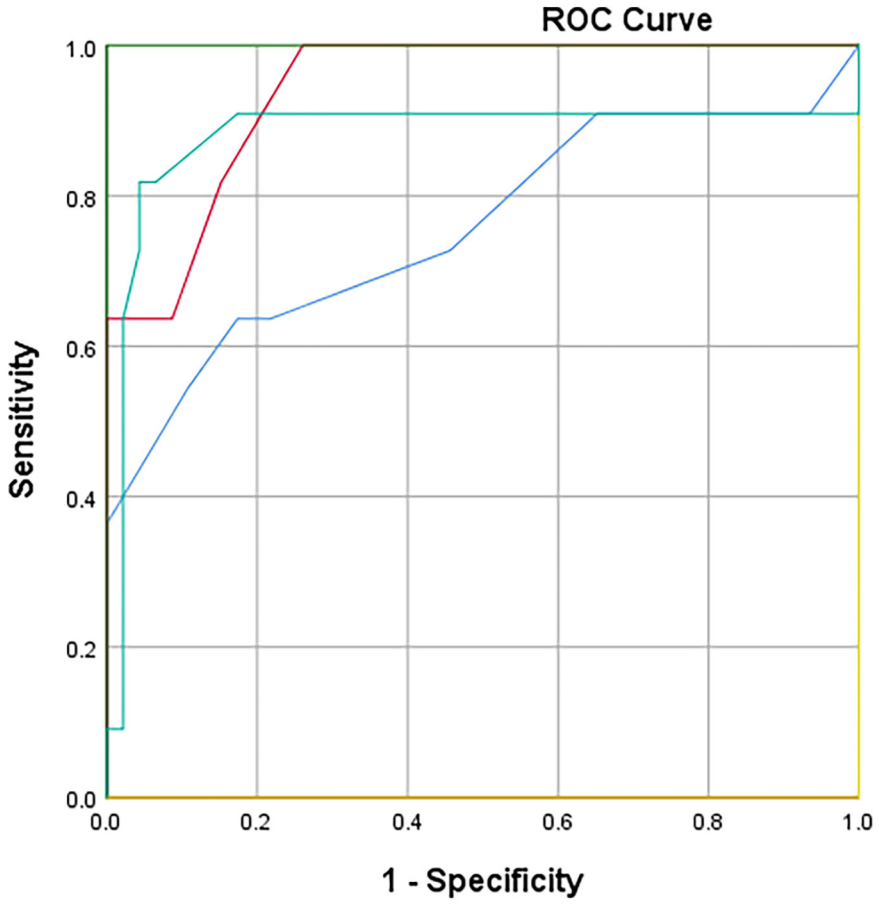

Figure 4. S-I, SN-IT, Min, Max, and Min-Max between the clinical moderate keratoconus group and the normal control group. SD value corresponds to ROC curve. Curve colors: S-I: blue; SN-IT: red; Min: orange; Max: cyan; Min-Max: yellow; SD: green.

Table 6. RTVue XR OCT distinguishes the S-I, SN-IT, MIN, MAX, MIN-MAX, Std.

Parameter	Severe keratoconus and normal control group					
	cut-off point	sensitivity	specificity	AUC	Youden index	P value
S-I	1.50	0.92	0.89	0.92	0.81	0.00
SN-IT	3.50	1.00	1.00	1.00	1.00	0.00
Min	66.00	0.00	1.00	0.00	0.00	0.00
Min-Max	−2.00	0.00	1.00	0.00	0.00	0.00
Max	59.5	0.92	0.94	0.97	0.86	0.00
Std.Dev	3.90	1.00	1.00	1.00	1.00	0.00

Dev values corresponding to the area under the ROC curve, cut-off point, specificity, sensitivity, and Youden index between the clinical severe keratoconus group and the normal control group

Our findings indicate that variations in corneal epithelial thickness are not merely a consequence of keratoconus but may also reflect an adaptive response to underlying stromal changes, potentially contributing to the disease's clinical presentation. The corneal epithelium, while traditionally viewed as a passive barrier, is now recognized for its active involvement in corneal homeostasis. In keratoconus, the epithelium's adaptive changes could be an early response to subclinical biomechanical alterations within the stroma. These changes may represent an attempt to maintain the corneal surface regularity and refractive power, thus masking the early signs of the disease. The epithelium's thickness adjustments could be mediated through several mechanisms [22]. First, the epithelial cells might alter their proliferation

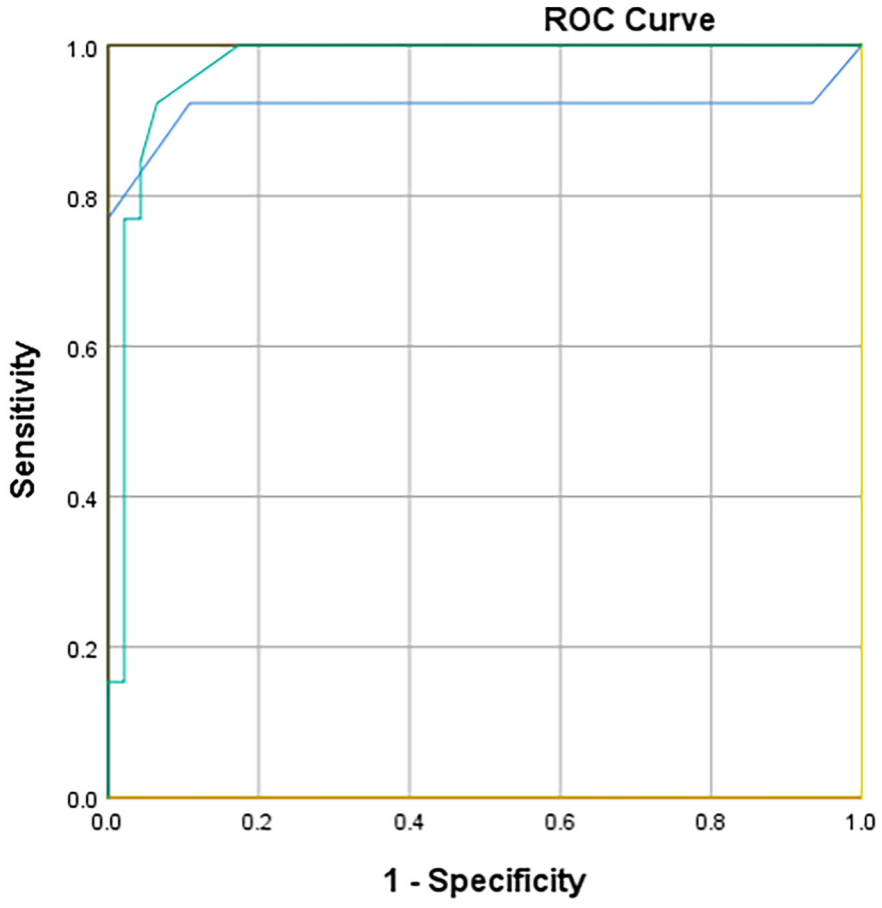

Figure 5. S-I, SN-IT, Min, Max, and Min-Max between the clinical severe keratoconus group and the normal control group. SD value corresponds to ROC curve. Curve colors: S-I: blue; SN-IT: red; Min: orange; Max: cyan; Min-Max: yellow; SD: green.

and differentiation rates in response to the stromal changes, leading to regional thickening or thinning. Second, the epithelium might modulate the expression of extracellular matrix components, affecting its own thickness and the overall corneal shape. Additionally, the epithelium's interaction with the underlying stroma is regulated by a complex network of cytokines and growth factors, which could be disrupted in keratoconus, contributing to the observed thickness changes [5]. By using RTVue XR OCT to measure the corneal epithelial thickness in different areas within the 0- to 6-mm range of the normal cornea group, it was found that the thickness of each area showed uneven distribution, and the thickness below was thicker. This is consistent with the study by Reinstein et al., which also showed that the thickness of the lower epithelium of the normal human cornea is thicker than that of the upper epithelium [23]. The latest research also suggests that the distribution of corneal epithelial thickness in patients with refractive errors measured by RTV OCT within the range of 0 to 6 mm is uneven, with gradually increasing changes in thickness from top to bottom and from temporal to nasal sides [24]. By comparing the corneal thickness and corneal epithelial thickness of nine regions pairwise, the *p* values were all greater than 0.05, and there was no significant difference in measured thickness values between the regions. The corneal epithelial thickness value did not change significantly in the range of 0 to 5 mm. By comparing the epithelial thickness and parameters S-I and SN-IT between the normal corneal group and the preclinical and clinical corneal groups, it was found that as the severity of keratoconus progresses, the trend of thinning below the cornea and on the temporal side increases the difference in corneal epithelial thickness, which is particularly evident in clinical keratoconus. Previous studies have suggested that compared to normal corneas, the corneal epithelial thickness of keratoconus is significantly thinner [25]. Reinstein et al. also believe that as the condition worsens, the lower corneal epithelium in keratoconus gradually becomes thinner, and its thickness is even lower than that of the upper corneal epithelium [23].

Previous studies by Temstet et al. compared the Min, Min-Max, and S-I parameter indicators with normal corneal epithelium in the preclinical stage and showed no statistically significant differences. Catalan et al. studied preclinical corneal epithelial parameter indicators (Center, Superior, Inferior, Min, Min-Max) and found no indicators with significant differences from normal corneal epithelial parameter values [26,27]. In addition, Santhiago et al. found that epithelial measures are useful for identifying eyes with keratoconus that are progressing using spectral-domain OCT imaging [28]. In this RTVue XR OCT measurement, the corneal epithelial thickness parameters obtained from the preclinical, mild, moderate, and severe keratoconus groups, as well as the normal control group, were measured. Different parameter indicators were selected to test the diagnostic value of keratoconus. Among the parameters, the Min-Max of the preclinical keratoconus group and the normal control group had an AUC value of 0.71, indicating moderate to high diagnostic value. In contrast, the SD indicator (AUC = 0.27) showed poor diagnostic performance at this stage. In the clinical stage, the mild, moderate, and severe keratoconus groups and the normal control group had AUC values above 0.7, except for the Min and Min-Max indicators, which were all less than 0.5, especially for SN-IT and SD. The AUC corresponding to Dev was above 0.9, indicating SN-IT and SD. The diagnostic value of Dev parameter indicators was extremely high. Both SN-IT and SD had high sensitivity and specificity, making them important reference indicators for diagnosing clinical keratoconus. Related studies have also shown that using Fourier OCT to measure corneal parameter indicators can improve the diagnostic sensitivity of keratoconus [29].

The shortcomings of this study are that RTVue XR OCT includes tear film thickness when measuring corneal epithelial thickness, which can increase the measured corneal epithelial thickness [30-32]. The measurement of corneal epithelial thickness is influenced by the tear film. Second, the measurement range of the corneal epithelium is not sufficient, and population classification has not been considered.

The limitations of the study include the relatively small sample size, which may affect the generalizability of our findings, and the cross-sectional design, which limits our ability to infer causality. In addition, the RTVue XR OCT has inherent resolution and noise limitations. For keratoconus, which involves subtle microstructural epithelial changes, this can lead to inaccuracies, especially in late-stage disease. Advanced keratoconus often involves scarring/fibrosis, which can make epithelial thickness measurements highly variable and less reliable for diagnostic purposes. We acknowledge that these limitations could influence the interpretation of the results and suggest that future studies employ larger cohorts and longitudinal designs to validate our findings. Upcoming studies should focus on conducting longitudinal studies to monitor changes in corneal epithelial thickness over time in patients with keratoconus, investigating the relationship between epithelial thickness changes and the biomechanical properties of the cornea, and exploring the potential of combining OCT measurements with other diagnostic tools, such as corneal biomechanical assessments, to enhance the accuracy of keratoconus diagnosis.

Conclusion: In summary, the advantages of Fourier RTVue XR OCT, such as high speed, convenience, high resolution, and noninvasiveness, make it particularly useful for distinguishing between those with and without keratoconus. The normal thickness of the cornea and corneal epithelium is unevenly distributed in various regions within the range of 0 to 5 mm. The cornea is thinner above and below the nose, as well as thicker above and below the temporal area, and the central area of the cornea is the thinnest.

RTVue XR OCT measurement of the Min-Max parameter demonstrated the highest diagnostic value for preclinical keratoconus, while SD was not useful in this early stage. For diagnosing mild, moderate, and severe keratoconus, parameters including S-I, SN-IT, Max, and SD showed high diagnostic value. SN-IT and SD have high specificity and sensitivity for distinguishing mild, moderate, and severe keratoconus groups from the normal control group during the clinical stage, and they have high diagnostic value. As the severity of keratoconus progresses, SN-IT and SD diagnostic value of Dev can reach its highest level. The diagnosis of keratoconus at different stages can also be combined with other new instrument detection indicators, such as biomechanics and corneal topography, to make comprehensive judgments and improve diagnostic accuracy.

ACKNOWLEDGMENTS

Declarations/Ethics approval and consent to participate: This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shangqiu Optometric Eye Hospital (NO. SGYK2022–03). Written informed consent was obtained from all participants. Data Availability Statement: All data generated or analyzed during this study are included in this article. Author contributions: Conceptualization: Tao Wang; Methodology: Qixin Cao; Formal analysis and investigation: Tao Wang & Qixin Cao; Writing - original draft preparation: Tao Wang; Writing - review and editing: Tao Wang & Qixin Cao. Funding; This work was sponsored by Huzhou Public Welfare Applied Research Project (Grant Number: 2023GYB44). Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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