

# Application of Scheimpflug-Based Biomechanical Analyzer and Tomography in Early Detecting of Subclinical Keratoconus in Chinese Patients

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## Research article

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# Abstract

## Purpose

To evaluate the value of Scheimpflug-based biomechanical analyzer combined with tomography in detecting early keratoconus by distinguishing normal eyes from frank keratoconus (KC) and forme frusta keratoconus (FFKC) eyes in Chinese patients.

## Methods

This study included 31 bilateral frank keratoconus patients, 27 unilateral clinical manifest keratoconus patients with very asymmetric eyes, and 79 control subjects with normal corneas. Corneal morphological and biomechanical parameters were measured using the Pentacam HR and Corvis ST (OCULUS, Wetzlar, Germany). The diagnostic capacity of computed parameters reflecting corneal biomechanical and morphological traits [including Belin-Ambrósio deviation index (BAD\_D), Corvis biomechanical index (CBI) and tomographic and biomechanical index (TBI)] was determined using receiver operating characteristic (ROC) curves and compared by DeLong test. Additionally, the area under the curve (AUC), the best cutoff values, and Youden index for each parameter were reported. The novel corneal stiffness parameter (Stress-Strain Index or SSI) was also compared between KC, FFKC and normal eyes.

## Results

Every morphological and biomechanical index analyzed in this study was significantly different between KC, FFKC and normal eyes ( $p=0.000$ ). TBI was most valuable for detecting subclinical keratoconus (FFKC eyes) with an AUC of 0.928 ( $P=0.000$ ), and any forms of corneal ectasia (FFKC and frank KC eyes) with an AUC of 0.966 ( $P=0.000$ ). The sensitivity and specificity of TBI for detecting FFKC was 97.5% and 77.8%, for detecting any KC was 97.5% and 89.7%, with a cut-off value of 0.375. Morphological index BAD\_D and biomechanical index CBI were also very useful in distinguishing any KC eyes from normal eyes with an AUC of 0.965 and 0.934, respectively. SSI was significantly different between KC, FFKC and normal eyes ( $P=0.000$ ), indicating an independent decrease in corneal stiffness in KC eyes.

## Conclusion

Combination of Scheimpflug-based biomechanical analyzer and tomography could increase the accuracy of detecting early keratoconus in Chinese patients. TBI was the most valuable index for detecting subclinical keratoconus with high sensitivity and specificity. Evaluation of corneal biomechanical property in refractive surgery candidates is helpful to recognize potential keratoconic eyes and increase surgical safety.

## Introduction

Laser vision correction (LVC) surgery has gained increasing attention and become quite widespread due to soaring prevalence of myopia in China<sup>[1,2]</sup>. As postoperative iatrogenic corneal ectasia is a very severe

surgical complication that would cause irreversible loss of corrected visual acuity, screening early phase of corneal ectasia and predisposition of keratoconus (KC) is crucial in preoperative assessment<sup>[3]</sup>. Previous study indicated that iatrogenic keratoectasia was related to preoperative corneal topographic abnormalities, thin corneal thickness, percentage tissue altered (PTA) in the surgery, low residual stromal bed thickness and other risk factors like eye rubbing, young age, and pregnancy<sup>[3]</sup>. It is of paramount importance to discover corneal ectatic possibility to avoid potential LVC surgery complication and improve vision prognosis.

Placido-disk based topography has been used as a classic method to screen corneal ectasia for a long time. Corneal topography is a non-contact imaging technique that maps the shape and features of the corneal anterior surface<sup>[4]</sup>. In recent decades, Scheimpflug-based tomography is introduced to evaluate corneal morphology<sup>[5]</sup>. Scheimpflug-based tomography is a non-contact optical device with a rotating Scheimpflug camera that takes up to 50 slit-images of the anterior segment of the eye in less than 2 seconds, which allows for the measurement of both anterior and posterior corneal surfaces<sup>[5]</sup>. The latest global consensus on KC in 2015 proposed that KC initiated from the posterior surface of cornea<sup>[6]</sup>, thus Scheimpflug-based tomography is more superior to detect suspect or early KC than traditional topography. Pentacam HR (OCULUS Optikgeräte GmbH; Wetzlar, Germany) is one kind of widely used Scheimpflug-based tomography, and BAD\_D is a computed index used to assess the predisposition of keratoconus using Pentacam parameters, which is a combination of 'D' values using a logistic regression analysis to optimize ectasia detection<sup>[7]</sup>. Different studies have found the BAD-D is a very accurate parameter to detect ectasia with relatively high sensitivity and specificity<sup>[8-10]</sup>. Recently, Pentacam Random Forest Index (PRFI), based on artificial intelligent computation, was introduced to improve the detection of corneal ectasia susceptibility, which reported a higher AUC than BAD\_D<sup>[11]</sup>. Although many novel instruments have been put into application to detect potential ectasia predisposition, it still remains a challenge for refractive surgeons. There were still sporadic reports of patients with relatively normal topography progressing to corneal ectasia after LVC surgeries<sup>[12,13]</sup>. Therefore, new screening method is imperative to increase the diagnostic accuracy, especially for those topography-normal eyes.

In recent years, in vivo corneal biomechanical assessment has emerged for detecting suspect or early keratoectasia. It was reported corneal biomechanical properties are mainly determined by extracellular matrix (ECM) components, hydration pressure, conreal layers and their interactions<sup>[14]</sup>. Corvis ST (OCULUS Optikgeräte GmbH; Wetzlar, Germany) is a novel non-contact biomechanical measurement device using a consistent air puff to deform the cornea, along with an ultra-high speed camera utilizing Scheimpflug geometry to capture images of the horizontal meridian at greater than 4,300 frames per second, resulting in 140 images during the 30ms air puff<sup>[15]</sup>. Corvis biomechanical index (CBI) is an integration of several dynamic corneal response parameters measured by Corvis ST, reflecting the comprehensive corneal biomechanical property<sup>[16]</sup>. Recently, Ambrósio and coworkers developed a combined parameter based on tomographic data and biomechanical parameters using artificial intelligence (AI) technology, introducing a novel index for enhanced ectasia detection, the tomographic/biomechanical index (TBI),

which enables a robust integration of corneal morphology by Pentacam HR and corneal biomechanics by Corvis ST. The TBI is calculated using a regression formula to optimize ectasia detection taking both corneal morphological and biomechanical characteristics into consideration, which further improved the accuracy of mild keratoectasia detection<sup>[17]</sup>.

Subclinical or early keratoconus recognition was always a challenge for ophthalmologists. In some cases, subclinical keratoconus is so difficult to identify, that the diagnosis could only be confirmed by follow-ups for years. Fortunately, there are some unilateral clinical manifest keratoconus patients with very asymmetric eyes (VAE). According to the 2015 KC global consensus, “*true unilateral keratoconus does not exist*”<sup>[6]</sup>. Although the corneal topography of the other eye (FFKC eye) is relatively normal, early corneal disease has quietly occurred. To analyze the morphology and biomechanics of FFKC eyes could provide precious information for subclinical KC diagnosis.

Considering that previous studies mostly focused on non-Chinese population<sup>[16-20]</sup>, the purpose of the current study is to evaluate the accuracy of KC and subclinical KC detection in Chinese patients by comparing the morphological and biomechanical parameters between frank KC, subclinical KC (FFKC) and normal eyes.

## Methods

### Study Design

This study is a diagnostic test to compare instrument accuracy.

### Participants

This study enrolled 137 subjects from Jun. 2019 to Jun. 2020 in Peking University Eye Center, Beijing, China. Among those 31 patients were diagnosed as binocular keratoconus, 27 patients were unilateral frank keratoconus with very asymmetric eyes and 79 participants were with no signs of keratoconus who underwent both topography and tomography examinations before laser vision correction surgeries. Informed consent was obtained from the subjects. This study followed the tenets of the Declaration of Helsinki and the study protocol was approved by Medical Science Research Ethics Committee of Peking University Third Hospital.

All the participants were divided into three groups: binocular KC group, very asymmetric eye (VAE) group and control group. The clinical diagnosis of KC was based on slit-lamp findings (i.e. stromal thinning, conical protrusion of corneal apex, Fleischer ring, Vogt striae or anterior stromal scar), abnormal topographic patterns on the sagittal (axial) front curvature map, disregarding tomographic and biomechanical findings, confirmed by an experienced specialist majoring in cornea and LVC surgery. Very asymmetric eyes (VAE) included the frank ectasia eyes (VAE-E) and the fellow eyes with normal topography (VAE-NT) or forme fruste keratoconus (FFKC) eyes. FFKC eyes were diagnosed by a specialist as following criteria:

1. Eyes with normal topography (Allegro Topolyzer; WaveLight Technologie AG, Alcon Laboratories, Erlangen, Germany), with a KC grading of KC0.
2. Mean keratometry (K) value < 47 Diopters (D) and inferior–superior (I-S) value  $\leq 1.4$  D according to the Rabinowitz and McDonnell criteria<sup>[21]</sup>;
3. No signs of KC under slit lamp examination;
4. Confirmed KC in the fellow eye.

The exclusion criteria included previous ocular surgery or trauma history, significant corneal scarring or associated ocular pathology. All participants were asked to stop wearing contact lens 2 weeks or longer before examinations.

## Procedure

All the participants underwent basic eye examination including visual acuity, slit lamp examination, indirect ophthalmoscope fundus examination, refraction and corneal topography (WaveLight Allegro Topolyzer, Alcon Surgical). Furthermore, all eyes were examined by rotating Scheimpflug corneal tomography (Pentacam HR). Scans that were registered as “OK” or “model deviation” on the Examination Quality Specification were included for analysis.

Corneal biometric parameters were measured using Corvis ST II. The Corvis ST II is a novel-developed tool to measure corneal deformation in a non-contact mode by a released air puff (60 mmHg of pressure, diameter of air puff 3.05 mm). Video footage of the corneal deformation is achieved by a Scheimpflug camera angled at 45° towards the apex of the cornea. A total of approximately 140 cross-sectional images of the cornea are collected over a collimated air puff for 30ms. Biomechanical parameters are measured at the end of this process by a built-in software (Version 1.4r1755). All examinations were performed by one single experienced technician in a same examining room (Pentacam under low light condition and Corvis under normal light condition) to avoid bias.

## Data Collection

Corneal morphological parameters were obtained from Pentacam examination, including simulated keratometry in the flat and steep meridians in the central 3 mm of the front and back corneal surfaces; maximum keratometry (Kmax) of front corneal surface; central corneal thickness (CCT) at the apex and the thinnest corneal point; Ambrósio relational thickness to the horizontal profile (ARTh), inferior-superior difference value (I-S), and Belin–Ambrósio enhanced ectasia total deviation index (BAD-D).

The following biomechanical parameters were obtained from Corvis: applanation lengths (AL1 and AL2: the flattened corneal length in the first and second applanations), applanation velocities (AV1 and AV2: velocity of the corneal apex at the first and second applanations), and the highest concavity (HC) parameters [peak distance (PD): distance between the 2 peaks, radius (R): central corneal radius of curvature and DA: the largest axial displacement at the corneal apex at the HC phase]. In addition, the new Corvis ST parameters were SPA\_1 (resultant pressure divided by the deflection amplitude at A1),

integrated radius (IR, area under the inverse concave radius curve), and DA ratio\_2 (the ratio between DA at the apex and the average of DAs at 2 mm around the center in temporal and nasal directions). The novel parameters, the CBI (a combination of dynamic corneal response parameters and corneal thickness profile in the horizontal meridian) and the TBI were analyzed for assessing their discrimination ability. A new in vivo biomechanical parameter Stress-Strain Index (SSI) was introduced and collected in this study<sup>[22]</sup>.

In KC group and control group, a randomly selected eye was included in data analysis to avoid bias. In VAE group, eyes with normal topography (FFKC eyes) were included in analysis. When coming to data analysis, KC group included one eye from bilateral KC group and the ectasia eye in the VAE group (35 eyes in total). FFKC group included the opposite eye (VAE-NT eye) in the VAE group (22 eyes). And the control group included one eye from control group as mentioned (56 eyes).

## Statistical Analysis

Data were analyzed using SPSS.22 software (SPSS Inc., Chicago, IL, USA). The data distribution was assessed with the Kolmogorov-Smirnov goodness-of-fit test. Data following normal distribution were compared by one-way Analysis of Variance (ANOVA), otherwise were compared by non-parametric test (Kruskal-Wallis test) between groups. Bonferroni test and Post hoc test for Kruskal-Wallis analysis was used for pairwise comparison. Receiver operating characteristic (ROC) curves were used to illustrate the sensitivity and specificity for different cut-off points of the corneal morphological and biomechanical parameters in KC, FFKC and control eyes. Moreover, the best cut-off value, the area under the ROC curve (AUC), and the Youden index for BAD\_D, CBI and TBI were determined. An AUC value of 1.0 indicates perfect discrimination, whereas values less than 0.5 show that the assessed parameter has no diagnostic ability. The pairwise comparison of the AUCs was performed using the method of DeLong test<sup>[23]</sup>.  $P < 0.05$  was considered statistically significant for all tests.

## Results

The mean age of participants in bilateral KC group, VAE group and control group was  $23.81 \pm 6.98$ ,  $22.00 \pm 6.26$  and  $24.87 \pm 7.62$  years, respectively. ANOVA analysis showed there was no significant difference of age between the three groups (ANOVA,  $p=0.203$ ) to ensure comparability. And the male/female ratio was 25/6, 16/11 and 47/32 in each group (Chi-squared test,  $P < 0.05$ ). Figure 1 presents a case of patient with VAE-E (Figure 1a) in the right eye and VAE-NT (Figure 1b) in the left eye.

### Corneal Morphological Parameters Using the Pentacam and Biomechanical Parameters Using the Corvis

The main morphological and biomechanical parameters were demonstrated in Table 1. Morphological parameters included Pachy (corneal thickness of the thinnest point), ARTh and BAD\_D, biomechanical parameters included IR, SP\_A1, DA-ratio\_2mm, SSI and CBI, and combined index included TBI. Statistical analysis showed there was significant difference between groups for each parameter showed in the table ( $P=0.000$ ). Bonferroni and Post hoc tests indicated that between KC and control eyes, all morphological

and biomechanical parameters were significantly different ( $P<0.05$ ). But between FFKC and control eyes, BAD\_D, SSI and TBI was found to be not significantly different ( $p=0.121$ ,  $p=0.465$ ,  $p=0.096$ , respectively), while other parameters all demonstrated significant difference ( $p<0.05$ ). And between KC and FFKC eyes, SSI was not significantly different ( $p=0.132$ ), while other parameters were all significantly different ( $p<0.05$ ).

### **ROC Curves and the Best Cut-off Points Distinguishing Abnormal Eyes with Control Eyes**

To improve the diagnostic efficacy, we chose three combined parameters computed by Pentacam and Corvis parameters to evaluate its receiver operating characteristic (ROC) curves and the best cut-off points<sup>[17]</sup>. ROC curves of BAD\_D, CBI and TBI when separating abnormal eyes (both KC eyes and FFKC eyes) and control eyes were demonstrated in Figure 2. Areas Under the Curve (AUC), best cut-off points, Youden index (Youden index= sensitivity+specificity-1), sensitivity and specificity were showed in Table 2. From these results, we found out that TBI had the highest values of AUC, reaching 0.966 (0.936~0.997,  $p=0.000$ ), followed by BAD\_D (0.965, 0.939~0.992,  $p=0.000$ ) and CBI (0.934, 0.886~0.982,  $p=0.000$ ).

### **ROC Curves and the Best Cut-off Points Distinguishing FFKC Eyes with Control Eyes**

Furthermore, ROC curves and the best cut-off points were determined to diagnose FFKC from control eyes as demonstrated in Figure 3 and Table 3a. As illustrated above, FFKC could be considered as potential or early form of keratoconus and might progress into clinical manifest KC in the future. Therefore, the ability to distinguish FFKC from normal eyes is of great importance and is quite valuable in clinical practice. We found all 3 parameters had good diagnostic values in detecting subclinical KC, among which TBI had the best distinguishing ability with an AUC of 0.928 ( $p=0.000$ ).

### **ROC Curves and the Best Cut-off Points Distinguishing KC Eyes with Control Eyes**

BAD\_D, CBI and TBI had an excellent performance in detecting frank KC eyes. The AUCs reached 1.000, 1.000 and 0.998, with a cut-off value of 2.82, 0.71 and 0.28, respectively. Table 3b showed ROC curves and the best cut-off points to diagnose frank KC from control eyes.

### **Pairwise Comparisons of the Areas Under the Curve (AUC)**

The comparison of AUCs showed that although the Yoden index of TBI was highest, TBI and BAD-D had a similar AUC of 0.966 and 0.965 (DeLong test,  $p=0.617$ ) in distinguishing abnormal eyes from control eyes. There was significant difference between TBI and CBI (AUC 0.966 vs. 0.934,  $p=0.003$ ), and between BAD\_D and CBI (AUC 0.965 vs. 0.934,  $p=0.014$ ), indicating a better diagnostic accuracy TBI and BAD\_D. As for detecting FFKC and control eyes, TBI also had a similar AUC with BAD\_D (0.928 vs. 0.926,  $p=0.826$ ). Similarly, AUC of CBI was significantly lower than that of TBI (0.860 vs. 0.928,  $p=0.005$ ) and BAD\_D (0.860 vs. 0.926,  $p=0.014$ ). However, CBI, TBI and BAD\_D showed no significant difference in the ability to differentiate KC from control eyes (0.998, 1.000 vs. 1.000,  $p>0.05$ ).

## Discussion

This current study found the diagnostic capacity of Scheimpflug-based tomography combined with biomechanical examination for distinguishing normal eyes from frank KC and FFKC in Chinese population. Our results indicated that the Scheimpflug-derived morphological and biomechanical examinations were very useful to accurately distinguish normal from abnormal corneas (including both clinical and potential ectatic eyes). Previous studies using these measuring instruments reported similar outcomes that the combined parameters, especially TBI, was more effective<sup>[17-20, 24]</sup>. In this study, we found that TBI had the highest diagnostic capacity in detecting corneal ectasia (AUC 0.966, Youden index 0.872), in accordance with many previous studies which found TBI was very accurate and valuable index to detect ectasia with high sensitivity and specificity in European, Middle East, South American, even Japanese population<sup>[17-20, 24]</sup>. In this study, TBI cut-off value of 0.38 had a sensitivity of 97.5% with a specificity of 89.7% for detecting any corneal ectasia, which confirmed its high diagnostic efficacy in Chinese patients. This result was different from a previous study in Chinese myopic patients, which found CBI was most sensitive factor for the diagnosis of FFKC eyes (AUROC: 0.909 (0.828–0.989);  $P < .001$ ) with a very low cut-off value 0.019<sup>[25]</sup>. This divergence might be due to different inclusion criteria: in that study, the participants were all refractive surgery candidates, which might implicate less severe corneal ectasia.

For detecting FFKC eyes, TBI also had the highest detecting capacity (AUC 0.928), similar with BAD\_D (AUC 0.926,  $p=0.826$ ), better than CBI (AUC 0.860,  $p=0.005$ ). These results indicated TBI was superior to discover mild or subclinical KC. The analyses of VAE patients provided vital information to detect potential KC eyes at a relatively early stage. Global Consensus on Keratoconus and Ectatic Diseases in 2015<sup>[6]</sup> mentioned that “*real unilateral keratoconus does not exist*”. Accordingly, we could think VAE-NT eyes already have some early biomechanical abnormality in spite of its relatively normal topography appearance. In this case, Scheimpflug-derived biomechanical evaluation could help to discover early forms of KC or potential ectatic eyes, which was crucial in refractive surgery screening. In theory, corneal biomechanical property changes might occur before shape change in subclinical KC<sup>[26]</sup>. So biomechanical parameters might be more sensitive than morphological ones. Interestingly, although the AUC of BAD\_D was larger, the sensitivity of CBI was higher than BAD\_D (97.5% vs. 87.3%), which indicated a better screening capacity of biomechanical index.

BAD\_D alone was also very useful parameters to detect corneal ectasia, which was in consistent with some other previous studies using Scheimpflug-based tomography only for early diagnosis of KC<sup>[7-10]</sup>. The AUC of BAD\_D for detecting any KC or FFKC was very close to TBI (0.965 vs. 0.966, 0.926 vs. 0.928,  $p>0.05$ ). Pencatam alone could detect corneal ectasis with satisfactory efficacy, however, combination of corneal shape information and biomechanical property could further improve the diagnostic accuracy, which was of great value in screening of any signs of keratoconus before refractive surgery. Considering TBI had higher sensitivity and BAD\_D had better specificity, TBI was of higher value for KC or subclinical

KC screening and BAD\_D was more useful for treatment decision-making. Users could choose a preferred index according to different application purpose.

The novel in vivo biomechanical parameter, SSI was explored in this study. SSI is a material stiffness parameter, which is independent of corneal thickness (CCT) and intraocular pressure (IOP), but only significantly correlated with age<sup>[22]</sup>. SSI was taken as 1.0 for the average experimental behavior obtained for corneal tissue with age=50 years<sup>[27]</sup>. In this study, we found for normal eyes in their 20s, the average SSI was  $0.83\pm 0.11$ , in accordance with previous finding that SSI is positively correlated with age<sup>[22]</sup>. Moreover, we found SSI decreased in KC eyes, indicating a reduce in corneal stiffness in corneal ectasia. To our knowledge, there were few reports of SSI changes in keratoconic eyes. Further studies are needed to investigate this issue.

The main limitation of this current study is that it was a cross-sectional diagnostic test. Because of its cross-sectional nature, it was impossible to know how many FFKC corneas would develop to frank KC, or how corneal biomechanical property would change subsequently. Longitudinal study is needed to illustrate the odds of VAE-NT eyes with beyond cut-off BAD\_D, CBI or TBI values progressing into frank corneal ectasia. Another limitation is that the number of inclusion cases in this study was relatively small, which could be addressed in a future study including more eligible cases.

In summary, Scheimpflug-based morphological and biomechanical examination is of great value to detect and diagnose KC, especially early or subclinical KC in Chinese patients. TBI is the most accurate parameter with both high sensitivity and specificity. Combination of Scheimpflug-based tomography and biomechanical analyzer can play an essential role in screening potential corneal ectasia and could maximize LVC surgical safety.

## Declarations

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Author contributions: Yan Liu conducted the experiments, analyzed data, wrote the paper and edited the manuscript.

Yu Zhang conducted the experiments, reviewed and edited the manuscript.

Yueguo Chen conceived and designed the study, conducted the experiments and reviewed the manuscript.

Each author believed that the manuscript represented honest work, and this manuscript has been approved for publication by all the authors.

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## Tables

**Table 1 Morphological and biomechanical parameters in KC eyes, FFKC eyes and control eyes**

	KC eyes	FFKC eyes	Control eyes	<i>p</i>
Pachy (μm)	467.3±59.1	519.4±28.4	554.1±31.3	0.000 <sup>#</sup>
ARTh	199.44±121.01	470.67±109.69	607.65±118.30	0.000 <sup>#</sup>
IR (mm <sup>-1</sup> )	12.20±2.75	8.81±1.14	7.94±0.82	0.000 <sup>#</sup>
SP_A1(Hg/mm)	57.69±23.71	87.62±15.45	118.45±14.87	0.000 <sup>#</sup>
DA-ratio_2mm	6.47±1.98	4.70±0.63	3.92±0.29	0.000 <sup>#</sup>
SSI	0.67±0.13	0.77±0.16	0.83±0.11	0.000 <sup>#</sup>
CBI	0.92±0.18	0.48±0.33	0.09±0.08	0.000 <sup>&amp;</sup>
BAD_D	11.05±5.16	2.04±0.57	0.89±0.59	0.000 <sup>#</sup>
TBI	0.99±0.03	0.67±0.34	0.13±0.14	0.000 <sup>&amp;</sup>

KC represents keratoconus; FFKC represents forme frusta keratoconus; Kmax represents the maximum value of corneal curvature; I-S value represents the inferior-superior value; Pachy represents the thinnest corneal thickness; ARTh represents Ambrósio relational thickness horizontal; IR represents integrated radius; SP\_A1 represents stiffness parameter at first applanation; DA-ratio\_2mm represents deformation amplitude at 2 mm around the center; BAD\_D represents Belin-Ambrósio deviation index; CBI represents Corvis biomechanical index; And TBI represents tomographic and biomechanical index. *P* was calculated to determine the difference between the three groups.

<sup>#</sup> means comparisons of Pachy, ARTh, IR, SP\_A1, DA-ratio\_2mm, SSI and BAD\_D were using ANOVA, and <sup>&</sup> means comparisons of CBI and TBI were using Kruskal-Wallis test.

**Table 2 AUC and Best cut-off values of Combined Parameters for Distinguishing any KC Eyes (KC+FFKC, n=58) from Normal Eyes (n=79)**

	AUC	Best Cut-off Values	Youden Index	Sensitivity (%)	Specificity (%)
BAD_D	0.965	1.48	0.804	87.3	93.1
CBI	0.934	0.27	0.820	97.5	84.5
TBI	0.966	0.38	0.872	97.5	89.7

AUC represents area under the curve; KC represents keratoconus; FFKC represents forme frusta keratoconus; BAD\_D represents Belin-Ambrósio deviation index; CBI represents Corvis biomechanical index; And TBI represents tomographic and biomechanical index.

**Table 3a AUC and Best cut-off values of Combined Parameters for Distinguishing FFKC (n=27) from Control Eyes (n=79)**

	AUC	Best Cut-off Values	Youden Index	Sensitivity (%)	Specificity (%)
BAD_D	0.926	1.48	0.725	87.3	85.2
CBI	0.860	0.27	0.642	97.5	66.7
TBI	0.928	0.38	0.753	97.5	77.8

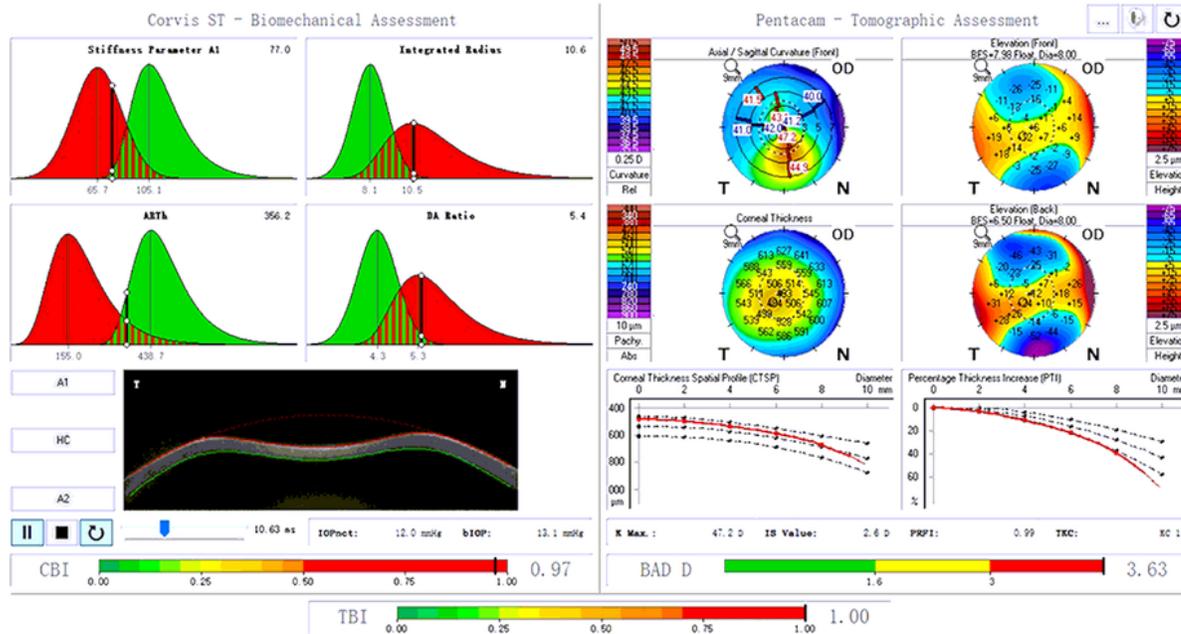
AUC represents area under the curve; KC represents keratoconus; FFKC represents forme frusta keratoconus; BAD\_D represents Belin-Ambrósio deviation index; CBI represents Corvis biomechanical index; And TBI represents tomographic and biomechanical index.

**Table 3b AUC and Best cut-off values of Combined Parameters for Distinguishing frank KC (n=31) from Control Eyes (n=79)**

	AUC	Best Cut-off Values	Youden Index	Sensitivity (%)	Specificity (%)
BAD_D	1.000	2.82	1.000	100.0	100.0
CBI	0.998	0.28	0.975	97.5	100.0
TBI	1.000	0.71	1.000	100.0	100.0

AUC represents area under the curve; KC represents keratoconus; FFKC represents forme frusta keratoconus; BAD\_D represents Belin-Ambrósio deviation index; CBI represents Corvis biomechanical index; And TBI represents tomographic and biomechanical index.

## Figures



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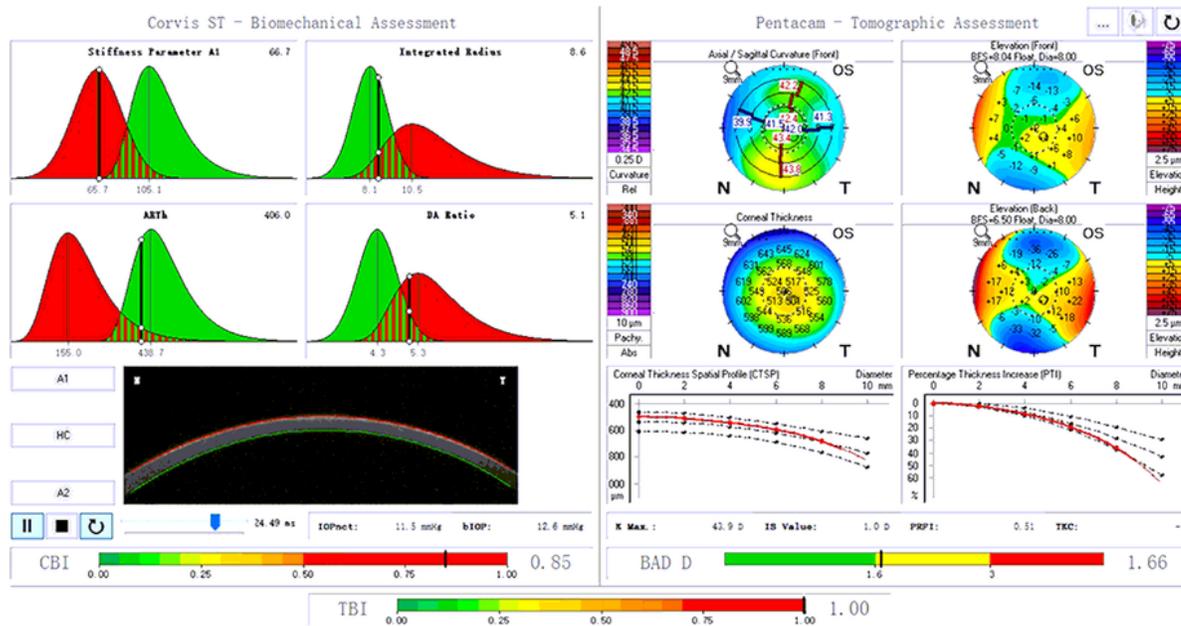
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Fig 1a



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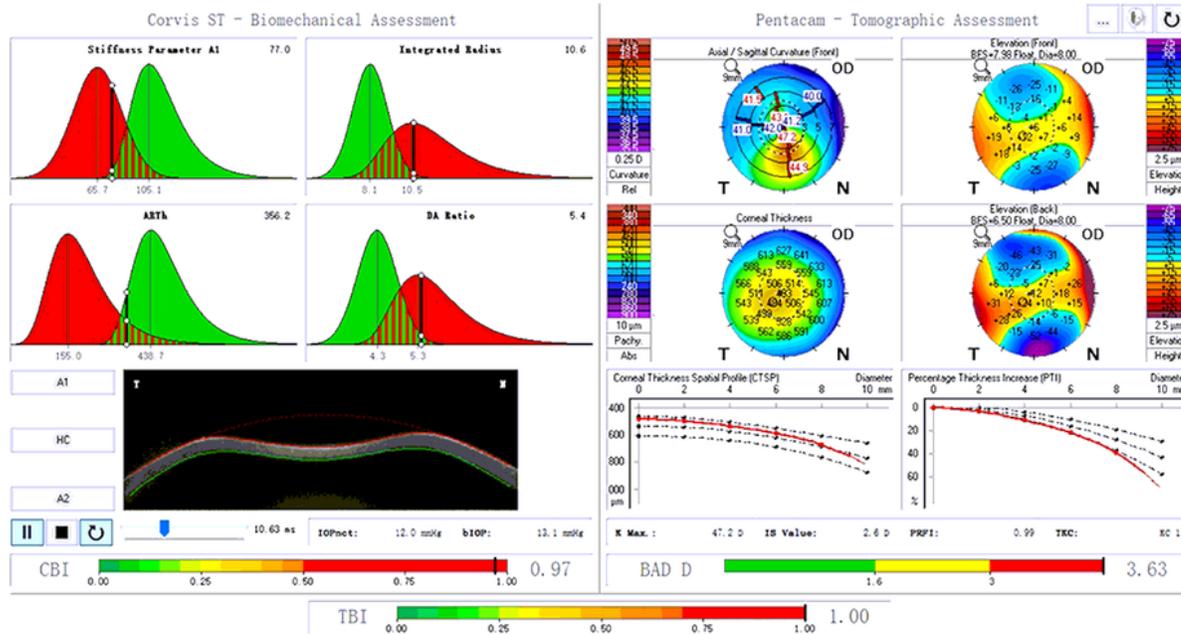
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Fig 1b

Figure 1

One case of VAE patient with VAE-E (Figure 1a) in the right eye and VAE-NT (Figure 1b) in the left eye



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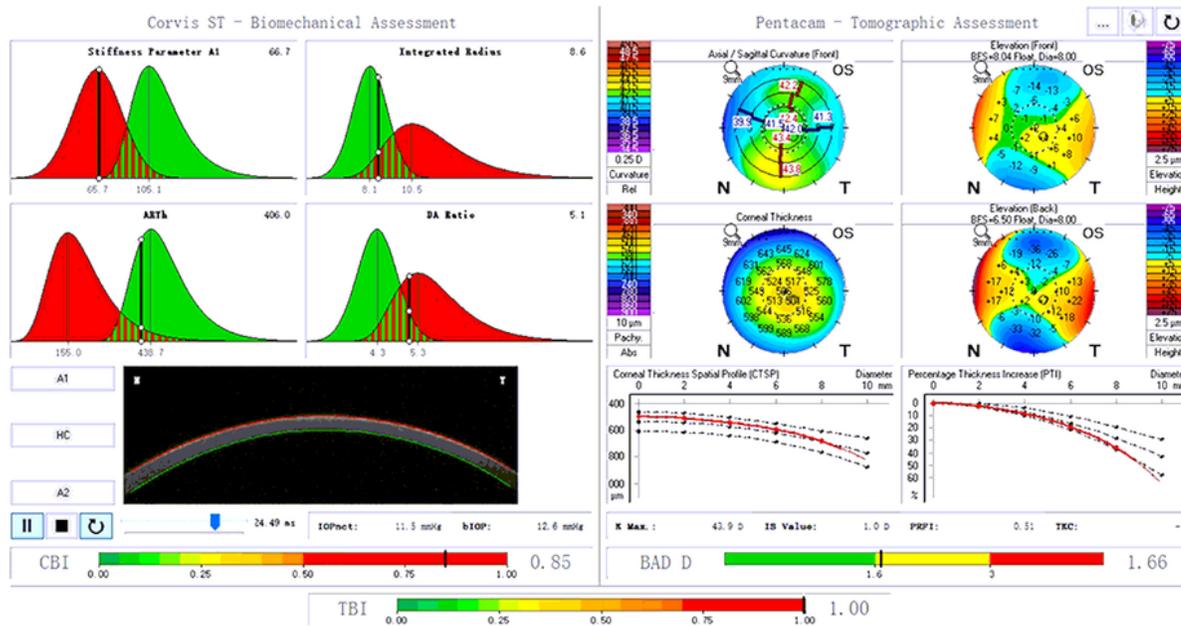
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Fig 1a



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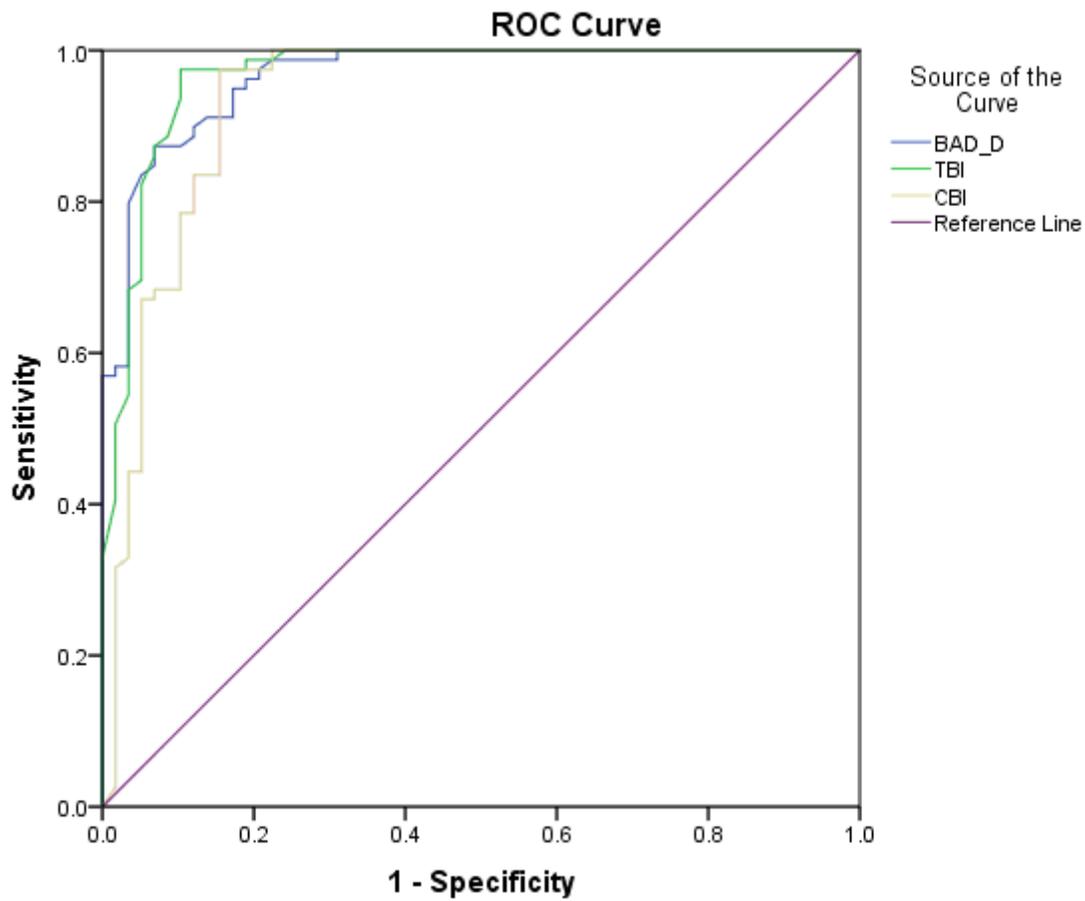
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Fig 1b

Figure 1

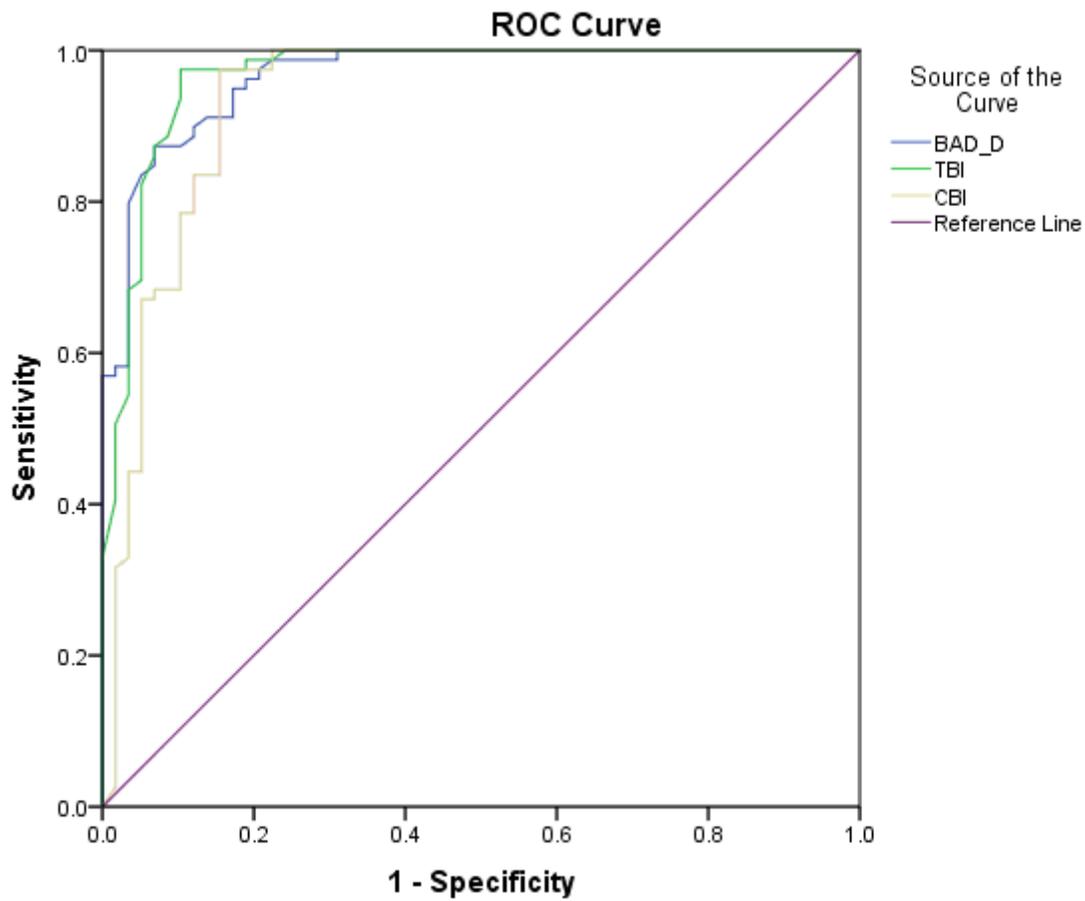
One case of VAE patient with VAE-E (Figure 1a) in the right eye and VAE-NT (Figure 1b) in the left eye



Diagonal segments are produced by ties.

**Figure 2**

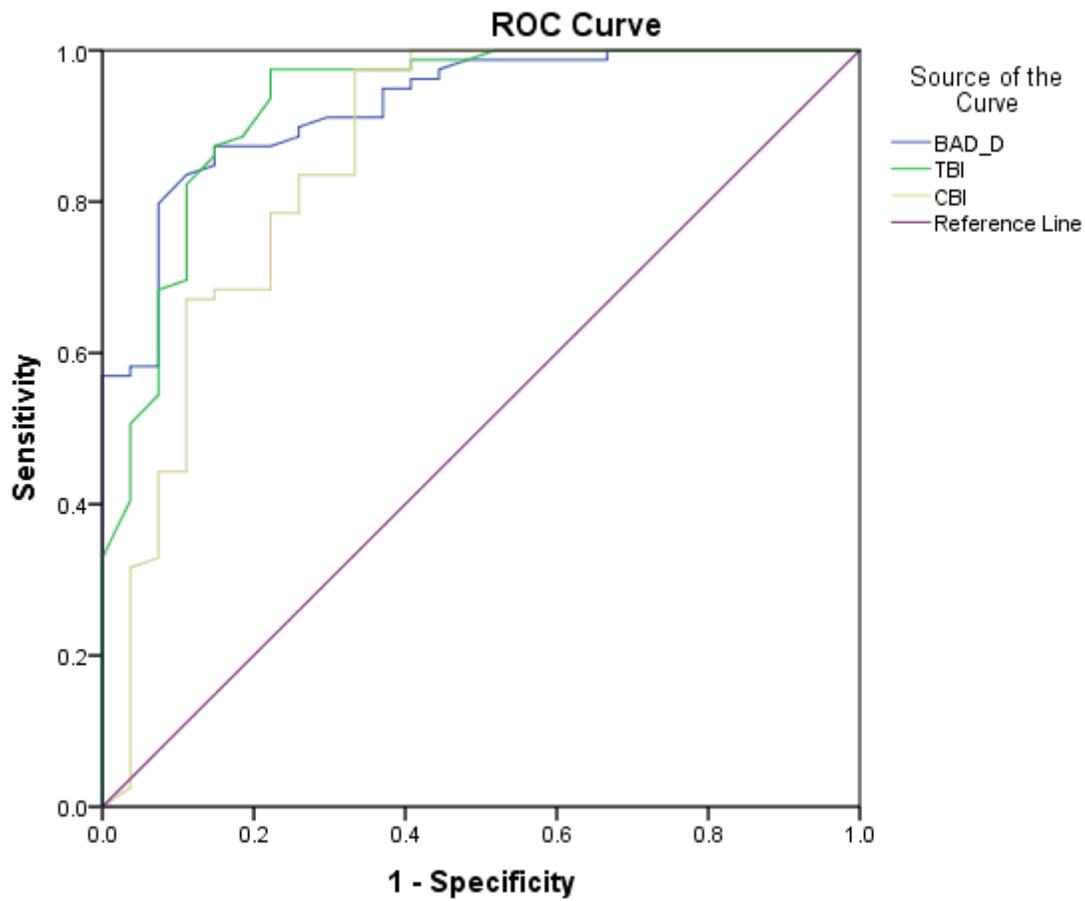
ROC curves of combined parameters for the BAD-D, CBI and TBI in distinguishing corneal ectatic eyes (KC and FFKC, n = 58) and control eyes (n = 79).



Diagonal segments are produced by ties.

**Figure 2**

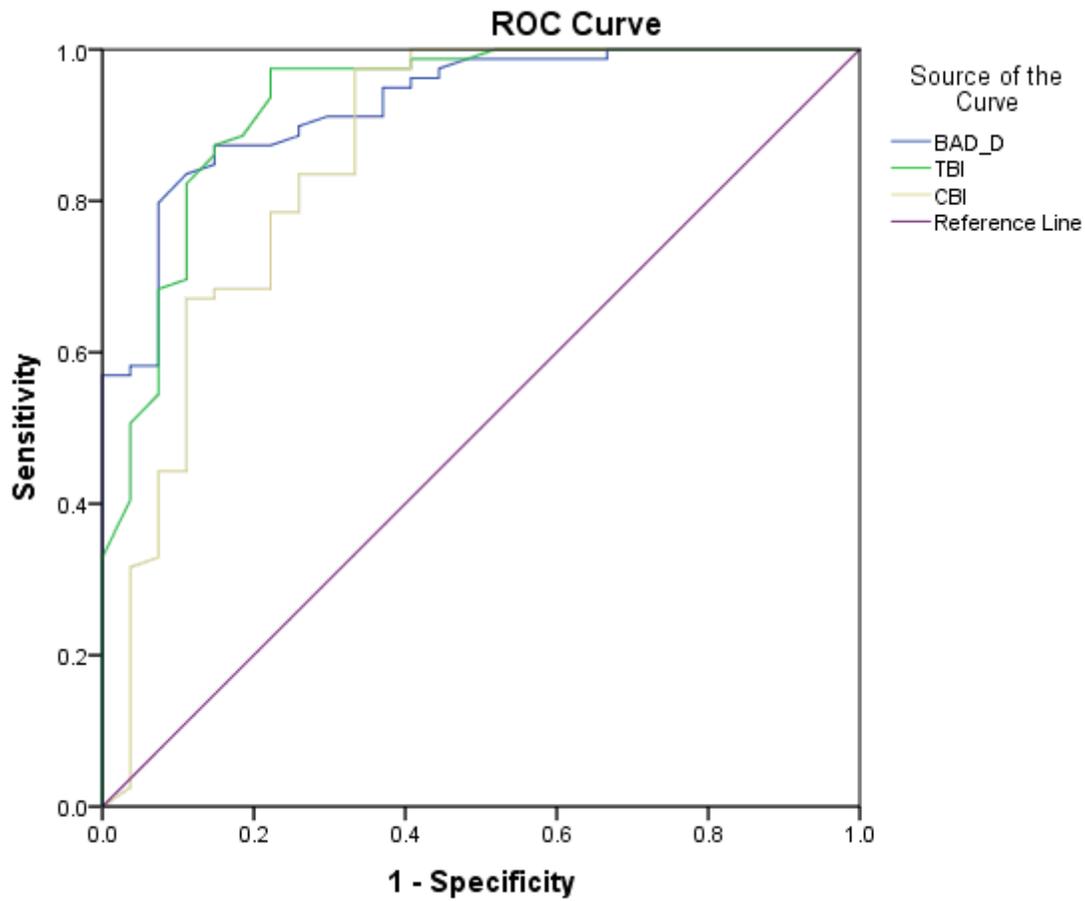
ROC curves of combined parameters for the BAD-D, CBI and TBI in distinguishing corneal ectatic eyes (KC and FFKC, n = 58) and control eyes (n = 79).



Diagonal segments are produced by ties.

**Figure 3**

ROC curves of combined parameters for the BAD-D, CBI and TBI in distinguishing FFKC (n=27) and control eyes (n = 79).



Diagonal segments are produced by ties.

**Figure 3**

ROC curves of combined parameters for the BAD-D, CBI and TBI in distinguishing FFKC (n=27) and control eyes (n = 79).