Influence of corneal diameters on the accuracy of Scheimpflug-derived corneal tomographic indices in Chinese patients with forme fruste keratoconus or thin corneas

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Research Article

Keywords: corneal biomechanics, tomography, corneal diameter, forme fruste keratoconus, corneal thickness

Posted Date: April 6th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1508464/v1

Abstract

Background

To investigate the influence of corneal diameters (CD) on the diagnostic accuracy of Pentacam tomographic indices in eyes with forme fruste keratoconus (FFKC) or thin corneas (TC).

Methods

One hundred and one eyes of 101 patients with FFKC (FFKCG), 104 eyes of 104 patients with corneal thickness < 490μm (TCG), and 200 eyes of 200 normal subjects (NG) were analyzed in the study. Pentacam ectasia indices were compared between different groups.

Results

The results for the multiple linear regression analysis between CD groups and corneal indices adjusted for flat central power (Kf), steep central power (Ks) and maximum corneal power (Kmax) showed that, compared with ≤ 11.9mm, back corneal elevation (BE) decreased 2.35 per unit, deviation of normality of the back elevation (Db) decreased 0.45 per unit (P = 0.007) and overall deviation of normality (BAD-D) decreased 0.26 per unit (P = 0.027) on average for subjects with CD > 11.9 in the FFKCG. The comparisons for the classifications (normal/abnormal) of the individual indices showed that for CD ≤ 11.9mm, the rates of abnormal cases in the FFKCG were significantly higher than NG for seven indices; for CD > 11.9mm, the rates of abnormal cases were higher than NG only for two indices. For CD ≤ 11.9mm, the rates of abnormal cases in the TCG were higher than NG for nine indices; for CD > 11.9mm, the rates of abnormal cases were higher than NG for seven indices.

Conclusion

BAD indices could underestimate the risk of ectasia in patients with large cornea, especially those with FFKC.

Introduction

As the most widely employed technique in the early diagnosis of corneal etasia, Scheimpflug tomography provides accurate data of corneal elevations for both the front and back cornea, as well as several standardized indices for ectasia detection including the Belin/Ambrosio Enhanced Ectasia display (BAD display) [1]. For all the standardized indices, the typical dimension of analysis is 8 mm in diameter and could not be adjusted according to the dimensions of individual cornea[2]. In our past study[3], we explored the performance of these descriptors in a sample of tomographically normal patients with different horizontal corneal diameters (CDs and found that CD has an influence on the BAD parameters, especially Db, BE, and BAD-D. The rates of suspect or abnormal cases were significantly higher in eyes with CD < 11mm and lower in eyes with CD ≥ 12 mm. In a retrospective study with a large sample of Chinese patients (n = 6744), Cao et al [4] also found that the false positive rate of BAD was higher in eyes with small cornea. These studies all indicated that BAD indices could overestimate the risk of ectasia in small cornea [2–4]. However, whether BAD indices underestimate the risk of ectasia in large cornea is still to be verified because all the subjects were tomographically normal in those studies. To address this issue, the performance of BAD indices on tomographically abnormal eyes should be evaluated in different CD-based groups.

The purpose of this study was to investigate the influence of corneal diameters on the diagnostic accuracy of Pentacam corneal tomographic indices in eyes of forme fruste keratoconus or thin corneas and furtherly to verify whether BAD indices underestimate the risk of ectasia in large cornea.

Materials And Methods

Patients were enrolled from the Ophthalmology Department of Eye and ENT Hospital of Fudan University (Shanghai, China) between January 2016 and September 2020. The criteria for clinical diagnosis of ectasia included topographic characteristics (eg, skewed asymmetric bowtie or inferior steepening) and at least one slit-lamp finding (eg, Munson's sign, Vogt's striae, Fleischer's ring, apical thinning, or Rizutti's sign). Patients were considered to be very asymmetric ectasia (VAE) if the diagnosis of ectasia was confirmed in one eye based on the previously described criteria and the fellow eye (the forme fruste keratoconus, FFKC) conformed to the following criteria for the FFKC [5]: 1) unremarkable slit-lamp examination; 2) Stage 0 for ABCD classification system: ARC (anterior radius of curvature for a 3.0 mm zone centered on the thinnest point) > 7.25 mm (< 46.5D), PRC (posterior radius of curvature for a 3.0 mm zone centered on the thinnest point) > 5.9 mm, TP (the thinnest pachymetry) > 490 μm, BDVA (the best documented visual acuity) ≥ 1.0, and absence of corneal scarring; 3) index of height decentration (IHD) less than 0.014. IHD [6, 7] is the absolute value of decentration of elevation data in the vertical direction (expressed in μm). An IHD value larger than 0.014 is considered abnormal, and larger than 0.016 is pathological. The FFKC eyes comprised of the FFKC group (FFKCG). And the fellow ectatic eyes in this group were not assessed because they all had moderate or advanced stages of the disease, which was not the focus of the present study. The thin cornea group (TCG) comprised of one eye of patients with normal tomography as mentioned above, except that the TP is less than 490μm. A group of patients with normal tomography for both eyes (Stage 0 for ABCD system and IHD ≤ 0.014) served as controls (normal group, NG).

Those cases with any pathological ocular conditions or relevant systemic diseases or any previous ocular procedures (eg, corneal cross-linking or intracorneal ring segments implantation) were excluded. Wearing soft contact lenses was discontinued for at least 7 days prior to the examination, and rigid or hybrid contact lenses were discontinued for a minimum period of 4 weeks. This study was approved by the Ethics Committee of the Eye and ENT Hospital of Fudan University (Shanghai, China) (2021118-1), and was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in this study.

Corneal Tomography

All patients underwent a comprehensive ophthalmic examination, including the slit-lamp examination, objective and subjective refractions, and Pentacam HR (OCULUS Optikgerate GmbH, Wetzlar, Germany) examination. Pentacam imaging was performed by the same experienced examiner for all participants with three measurements averaged for each individual. Only scans registered as "OK" by the Examination Quality Specification of the instrument were saved and analyzed.

The horizontal corneal diameter was measured for each patient (Pentacam, Oculus, Germany). In the current study, we defined those eyes with CD > 11.9mm as large cornea. The following corneal descriptors were obtained by the Pentacam software: flat central power (Kf), steep central power (Ks), mean central power [Km = (Kf + Ks)/2], maximum corneal power (Kmax); corneal astigmatism (Ka = Ks - Kf); anterior radius of curvature for a 3.0 mm zone centered on the thinnest point (ARC); posterior radius of curvature for a 3.0 mm zone centered on the thinnest point (PRC); the best fit sphere for the anterior cornea (BFSa) and the best fit sphere for the posterior cornea (BFSp); thinnest pachymetry (TP); front and back corneal elevations at TP (FE and BE); pachymetric progression index (PPI, minimum, average, and maximum); Ambrosio's maximum relational thickness index (ARTmax); normalized indices: Df (deviation of normality of the front elevation), Db (deviation of normality of the back elevation), Dp (deviation of normality of pachymetric progression), Dt (deviation of normality of corneal thinnest point), Da (deviation of normality of relational thickness), and BAD-D (overall deviation of normality). The analyzing dimensions for these indices are all 8mm in diameter. PPI represents the change in corneal thickness from TP to periphery and can be calculated over all 360 degrees of the cornea. The average of these meridians is represented as PPI-Avg, whereas the meridian with maximal pachymetric increase is PPI-Max, and minimal pachymetric increase is PPI-Min. Upon request, the manufacturer informed that the deviation-based indices can be classified by the software as normal (< 1.6 standard deviation [SD] from the population mean, shown in white), suspect (> 1.6 SD and < 2.6

SD, highlighted in yellow), and abnormal (> 2.6 SD, highlighted in red), according to data reported by Ambrosio et al. [8], and this scheme was followed throughout the present study. FE was classified as normal (< 5.01), suspect (≥ 5.01 and < 7.14) and abnormal (≥ 7.14), and BE (for myopia only) was classified as normal (< 11.77), suspect (≥ 11.77 and < 16.42), and abnormal (≥ 16.42). For PPI and ARTmax, each observation was categorized as normal or abnormal according to the cutoff values reported by the manufacturer or Ambrosio et al. [9]: PPI-Min (abnormal: ≥ 0.79); PPI-Avg (abnormal: ≥ 1.15); PPI-Max (abnormal: ≥ 1.44), and ARTmax (abnormal: ≤ 313).

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 software (IBM, Armonk, NY, USA). Comparisons between groups were carried out using one-way analysis of variance (ANOVA). Linear regression analyses were undertaken for indices. The percentages of abnormality between groups were compared by chi-squared test. A P value of less than 0.05 was considered statistically significant.

Results

One hundred and one eyes of 101 patients with FFKC (FFKCG), 104 eyes of 104 patients with corneal thickness < 490μm (TCG), and 200 eyes of 200 normal subjects (NG) were included in the study. The demographic characteristics and the means for individual Pentacam corneal descriptors are shown in Table 1. The values of CD were higher in the FFKCG (ANOVA, P = 0.002). The distributions of CD in individual groups are presented in Fig. 1. For the FFKCG, no significant difference was found in CD between the keratoconic eye and the FFKC eye (KC: 11.88 ± 0.37mm, FFKC: 11.88 ± 0.35mm, paired-samples t-test, P = 0.804).

Table 1

Demographic characteristics and Pentacam corneal descriptors of three groups[a].

	FFKCG (n = 101)	TCG (n = 104)	NG (n = 200)	*P*[b]
Age (years)	23.6 ± 7.4 (9, 44)	25.6 ± 6.3 (14, 45)	25.5 ± 5.5 (13, 40)	> 0.05
Sphere (D)	-5.52 ± 1.75 (-10.25, -1.25)	-5.31 ± 1.23 (-8.5, -0.5)	-5.7 ± 1.05 (-10.0, -1.0)	> 0.05
Cylinder (D)	-1.30 ± 0.71 (-3.5, -0.25)	-1.35 ± 0.91 (-4.5, 0)	-1.21 ± 0.68 (-3.0, -0.5)	> 0.05
TP (μm)	530.0 ± 25.0 (490, 593)	476.7 ± 12.0 (442, 489)	540.6 ± 26.4 (491, 623)	**< 0.001**
CD (mm)	11.9 ± 0.3 (10.9, 12.7)	11.8 ± 0.5 (10.6, 12.9)	11.7 ± 0.4 (10.5, 12.9)	**0.002**
IHD	0.008 ± 0.003 (0.002, 0.013)	0.010 ± 0.006 (0, 0.032)	0.008 ± 0.003 (0, 0.013)	**0.006**
Kf (D)	42.24 ± 1.36 (38.0, 44.8)	42.73 ± 1.41 (39.6, 46.2)	42.43 ± 1.44 (38.6, 46.1)	**0.044**
Ks (D)	43.55 ± 1.58 (39.1, 47.1)	44.08 ± 1.45 (41.5, 48.0)	43.69 ± 1.52 (39.6, 48.0)	**0.031**
Kmax (D)	44.12 ± 1.65 (39.8. 48.6)	44.61 ± 1.53 (41.6, 49.4)	44.20 ± 1.55 (39.8, 48.8)	**0.046**
Ka (D)	1.30 ± 0.71 (0.20, 3.50)	1.35 ± 0.82 (0, 4.50)	1.26 ± 0.72 (0.5, 3.5)	0.58
ARC (mm)	7.86 ± 0.26 (7.40, 8.74)	7.78 ± 0.25 (7.17, 8.30)	7.83 ± 0.26 (7.20, 8.61)	0.067

FFKCG = Forme fruste keratoconus group; TCG = thin cornea group; NG = normal group; TP = thinnest pachymetry; CD = corneal diameter; IHD = Index of height decentration. Kf = flat central power; Ks = steep central power; Kmax = maximum corneal power; Ka = corneal astigmatism; ARC = anterior radius of curvature for a 3.0 mm zone centered on the thinnest point; PRC = posterior radius of curvature for a 3.0 mm zone centered on the thinnest point; BFSa = the best fit sphere for the anterior cornea; BFSp = the best fit sphere for the posterior cornea; FE = front elevation at TP; BE = back elevation at TP; PPI = pachymetric progression indices (min = minimum, avg = average, max = maximum); ARTmax = Ambrosio's maximum relational thickness index; Df = deviation of normality of the front elevation; Db = deviation of normality of the back elevation; Dp = deviation of normality of pachymetric progression; Dt = deviation of normality of corneal thinnest point; Da = deviation of normality of relational thickness; BAD-D = overall deviation of normality.

[a]Values are presented as mean ± standard deviation (range).

[b]P values for analysis of variance analysis.

	FFKCG (n = 101)	TCG (n = 104)	NG (n = 200)	P^b
PRC (mm)	6.34 ± 0.26 (5.90, 7.25)	6.40 ± 0.25 (5.94, 7.09)	6.36 ± 0.25 (5.72, 7.04)	0.211
BFSa	7.97 ± 0.27 (7.47, 8.84)	7.87 ± 0.23 (7.34, 8.32)	7.93 ± 0.26 (7.27, 8.73)	**0.019**
BFSp	6.51 ± 0.24 (5.97, 7.28)	6.47 ± 0.20 (6.05, 6.85)	6.45 ± 0.24 (5.83, 7.19)	0.121
FE (μm)	2.38 ± 1.33 (-3, 6)	2.77 ± 1.49 (-1, 8)	2.03 ± 1.17 (-2, 5)	**< 0.001**
BE (μm)	6.87 ± 3.47 (0, 16)	5.03 ± 3.47 (-2, 16)	4.93 ± 3.29 (-2, 17)	**< 0.001**
PPImin	0.76 ± 0.13 (0.46, 1.05)	0.79 ± 0.16 (0.38, 1.18)	0.75 ± 0.12 (0.43, 1.05)	0.044
PPImax	1.40 ± 0.22 (0.87, 1.94)	1.47 ± 0.21 (0.93, 2.21)	1.29 ± 0.15 (0.92, 1.78)	**< 0.001**
PPIavg	1.08 ± 0.14 (0.64, 1.43)	1.14 ± 0.15 (0.70, 1.56)	1.04 ± 0.11 (0.75, 1.39)	**< 0.001**
ARTmax	389.0 ± 71.1 (265, 669)	329.8 ± 48.1 (215, 521)	424.8 ± 62.7 (284, 614)	**< 0.001**
Df	0.20 ± 0.97 (-1.72, 2.67)	0.51 ± 0.98 (-1.67, 3.16)	0.14 ± 0.92 (-1.79, 3.33)	**0.005**
Db	0.12 ± 0.80 (-1.36, 2.35)	-0.25 ± 0.82 (-1.39, 2.42)	0.03 ± 0.95 (-1.39, 2.97)	**0.007**
Dp	1.18 ± 0.93 (-1.78, 3.64)	1.62 ± 1.02 (-1.39, 4.44)	0.89 ± 0.76 (-1.04, 3.26)	**< 0.001**

FFKCG = Forme fruste keratoconus group; TCG = thin cornea group; NG = normal group; TP = thinnest pachymetry; CD = corneal diameter; IHD = Index of height decentration. Kf = flat central power; Ks = steep central power; Kmax = maximum corneal power; Ka = corneal astigmatism; ARC = anterior radius of curvature for a 3.0 mm zone centered on the thinnest point; PRC = posterior radius of curvature for a 3.0 mm zone centered on the thinnest point; BFSa = the best fit sphere for the anterior cornea; BFSp = the best fit sphere for the posterior cornea; FE = front elevation at TP; BE = back elevation at TP; PPI = pachymetric progression indices (min = minimum, avg = average, max = maximum); ARTmax = Ambrosio's maximum relational thickness index; Df = deviation of normality of the front elevation; Db = deviation of normality of the back elevation; Dp = deviation of normality of pachymetric progression; Dt = deviation of normality of corneal thinnest point; Da = deviation of normality of relational thickness; BAD-D = overall deviation of normality.

[a]Values are presented as mean ± standard deviation (range).

[b]P values for analysis of variance analysis.

	FFKCG (n = 101)	TCG (n = 104)	NG (n = 200)	P^b
Dt	0.26 ± 0.73 (-1.43, 1.62)	1.99 ± 0.45 (1.51, 3.33)	-0.03 ± 0.74 (-2.11, 1.93)	**< 0.001**
Da	0.91 ± 0.66 (-1.65, 2.04)	1.45 ± 0.44 (-0.30, 2.49)	0.58 ± 0.57 (-1.15, 1.87)	**< 0.001**
BAD-D	1.35 ± 0.60 (-0.05, 2.69)	1.79 ± 0.60 (0.54, 3.62)	1.03 ± 0.58 (-0.27, 2.78)	**< 0.001**

FFKCG = Forme fruste keratoconus group; TCG = thin cornea group; NG = normal group; TP = thinnest pachymetry; CD = corneal diameter; IHD = Index of height decentration. Kf = flat central power; Ks = steep central power; Kmax = maximum corneal power; Ka = corneal astigmatism; ARC = anterior radius of curvature for a 3.0 mm zone centered on the thinnest point; PRC = posterior radius of curvature for a 3.0 mm zone centered on the thinnest point; BFSa = the best fit sphere for the anterior cornea; BFSp = the best fit sphere for the posterior cornea; FE = front elevation at TP; BE = back elevation at TP; PPI = pachymetric progression indices (min = minimum, avg = average, max = maximum); ARTmax = Ambrosio's maximum relational thickness index; Df = deviation of normality of the front elevation; Db = deviation of normality of the back elevation; Dp = deviation of normality of pachymetric progression; Dt = deviation of normality of corneal thinnest point; Da = deviation of normality of relational thickness; BAD-D = overall deviation of normality.

[a]Values are presented as mean ± standard deviation (range).

[b]P values for analysis of variance analysis.

Relationship Between Cd And Individual Corneal Indices In Different Groups

The results for the multiple linear regression analysis between CD groups and individual corneal indices adjusted for Kf, Ks and Kmax are summarized in Table 2. Compared with ≤ 11.9mm, BE decreased 2.35 per unit on average for subjects with CD > 11.9 after adjustment for Kf, Ks and Kmax in the FFKCG (P = 0.001). Db decreased 0.45 per unit (P = 0.007) and BAD-D decreased 0.26 per unit (P = 0.027) on average for subjects with CD > 11.9 after adjustment for Kf, Ks and Kmax when compared with ≤ 11.9mm.

Table 2
Multiple linear regression analysis between corneal diameters and individual corneal indices in different groups when adjusted for Kf, Ks and Kmax.

	FFKCG (n = 101)		TCG (n = 104)		NG (n = 200)	
	Coefficient	P	Coefficient	P	Coefficient	P
FE (μm)	-0.29	0.329	-0.37	0.231	0.19	0.357
BE (μm)	-2.35	**0.001**	-1.87	**0.013**	-1	0.093
PPImin	-0.02	0.54	-0.17	**< 0.001**	-0.06	**0.003**
PPImax	-0.06	0.225	-0.09	**0.036**	-0.03	0.238
PPIavg	-0.04	0.136	-0.13	**< 0.001**	-0.04	**0.015**
ARTmax	6.25	0.69	20.7	0.053	16.18	0.126
Df	-0.19	0.389	-0.36	0.058	-0.12	0.461
Db	-0.45	**0.007**	-0.54	**0.002**	-0.69	**< 0.001**
Dp	-0.31	0.119	-0.88	**< 0.001**	-0.29	**0.018**
Dt	0.13	0.43	0.11	0.267	0.03	0.835
Da	-0.07	0.638	-0.19	0.051	-0.15	0.131
BAD-D	-0.26	**0.027**	-0.37	**< 0.001**	-0.27	**0.003**

FFKCG = forme fruste keratoconus group; TCG = thin cornea group; NG = normal group; CD = corneal diameter; Kf = flat central power; Ks = steep central power; Kmax = maximum corneal power; FE = front elevation at TP; BE = back elevation at TP; PPI = pachymetric progression indices (min = minimum, avg = average, max = maximum); ARTmax = Ambrosio's maximum relational thickness index; Df = deviation of normality of the front elevation; Db = deviation of normality of the back elevation; Dp = deviation of normality of pachymetric progression; Dt = deviation of normality of corneal thinnest point; Da = deviation of normality of relational thickness; BAD-D = overall deviation of normality.

In the TCG, BE decreased 1.87 per unit on average for subjects with CD > 11.9 after adjustment for Kf, Ks and Kmax when compared with CD ≤ 11.9mm (P = 0.013). PPImin decreased 0.17 per unit (P < 0.001), PPImax decreased 0.09 per unit (P = 0.036), PPIavg decreased 0.13 per unit (P < 0.001), Db decreased 0.54 per unit (P = 0.002), Dp decreased 0.88 per unit (P < 0.001), and BAD-D decreased 0.37 per unit (P < 0.001) on average for subjects with CD > 11.9 after adjustment for Kf, Ks and Kmax when compared with CD ≤ 11.9mm.

In the NG, PPImin decreased 0.06 per unit (P = 0.003), PPIavg decreased 0.04 per unit (P = 0.015), Db decreased 0.69 per unit (P < 0.001), Dp decreased 0.29 per unit (P = 0.018) and BAD-D decreased 0.27 per unit (P = 0.003) for subjects with CD > 11.9 after adjustment for Kf, Ks and Kmax when compared with CD ≤ 11.9mm.

Classification Results For The Corneal Indices

Comparisons between CD groups (≤ 11.9mm or > 11.9mm)

The results of classifications (normal or abnormal) for the individual indices for each group are summarized in Table 3. For the FFKCG, the differences in the classifications between CD groups were statistically significant for BE (Continuity correction of chi-squared test, χ^2 = 4.50, P = 0.034), Db (Continuity correction of chi-squared test, χ^2 = 4.50, P = 0.044), BAD-D (Pearson's chi-squared test, χ^2 = 10.36, P = 0.001) and PPImax (Pearson's chi-squared test, χ^2 = 6.57, P = 0.01). For the TCG, the differences in the classifications between CD groups were statistically significant for Dp (Pearson's chi-squared test, χ^2 = 9.87, P = 0.002), BAD-D (Pearson's chi-squared test, χ^2 = 11.82, P = 0.001), PPImin (Pearson's chi-squared test, χ^2 = 19.42, P <

0.001), and PPIavg (Pearson's chi-squared test, $\chi^2 = 8.96$, P = 0.003). For the NG, the differences in the classifications between CD groups were statistically significant for Dp (Pearson's chi-squared test, $\chi^2 = 3.96$, P = 0.047), BAD-D (Pearson's chi-squared test, $\chi^2 = 6.86$, P = 0.009), PPImin (Pearson's chi-squared test, $\chi^2 = 10.01$, P = 0.002).

Table 3
Results of classification for the keratoconus indices.

		FFKCG (n = 101)			TCG (n = 104)			NG (n = 200)		
		Normal	abnormal	P [a]	Normal	abnormal	P [a]	Normal	abnormal	P [a]
FE	CD ≤ 11.9	56 (98.2%)	1 (1.8%)	> 0.05	61 (93.8%)	4 (6.2%)	> 0.05	148 (100%)	0 (0%)	NA
	CD > 11.9	43 (97.7%)	1 (2.3%)		38 (97.4%)	1 (2.6%)		52 (100.0%)	0 (0%)	
BE	CD ≤ 11.9	47 (82.5%)	10 (17.5%)	0.034	60 (92.3%)	5 (7.7%)	> 0.05	142 (95.9%)	6 (4.1%)	> 0.05
	CD > 11.9	43 (97.7%)	1 (2.3%)		39 (100%)	0 (0%)		50 (96.2%)	2 (3.8%)	
Df	CD ≤ 11.9	51 (89.5%)	6 (10.5%)	> 0.05	54 (83.1%)	11 (16.9%)	> 0.05	139 (93.9%)	9 (6.1%)	> 0.05
	CD > 11.9	40 (90.9%)	4 (9.1%)		38 (97.4%)	1 (2.6%)		51 (98.1%)	1 (1.9%)	
Db	CD ≤ 11.9	50 (87.7%)	7 (12.3%)	0.044	62 (95.4%)	3 (4.6%)	> 0.05	135 (91.2%)	13 (8.8%)	> 0.05
	CD > 11.9	44 (100%)	0 (0%)		39 (100%)	0 (0%)		50 (96.2%)	2 (3.8%)	
Dp	CD ≤ 11.9	36 (63.2%)	21 (36.8%)	> 0.05	26 (40%)	39 (60%)	0.002	119 (80.4%)	29 (19.6%)	0.047
	CD > 11.9	33 (75%)	11 (25%)		28 (71.8%)	11 (28.2%)		48 (92.3%)	4 (7.7%)	
Dt	CD ≤ 11.9	56 (98.2%)	1 (1.8%)	> 0.05	8 (12.3%)	57 (87.7%)	> 0.05	147 (99.3%)	1 (0.7%)	> 0.05
	CD > 11.9	44 (100%)	0 (0%)		9 (23.1%)	30 (76.9%)		52 (100%)	0 (0%)	
Da	CD ≤ 11.9	46 (80.7%)	11 (19.3%)	> 0.05	38 (58.5%)	27 (41.5%)	> 0.05	145 (98.0%)	3 (2.0%)	> 0.05

FFKCG = Forme fruste keratoconus group; TCG = thin cornea group; NG = normal group; FE = front elevation; BE = back elevation; Df = deviation of normality of the front elevation; Db = deviation of normality of the back elevation; Dp = deviation of normality of pachymetric progression; Dt = deviation of normality of corneal thinnest point; Da = deviation of normality of relational thickness; BAD-D = overall deviation of normality. PPI = pachymetric progression indices (min = minimum, avg = average, max = maximum); ARTmax = Ambrosio's maximum relational thickness index. NA = not applicable.

[a] P *value of Pearson's chi-squared test or Continuity correction of chi-squared test for the comparisons between CD groups.*

	FFKCG (n = 101)				TCG (n = 104)			NG (n = 200)		
	CD > 11.9	41 (93.2%)	3 (6.8%)		28 (71.8%)	11 (28.2%)		51 (98.1%)	1 (1.9%)	
BAD-D	CD ≤ 11.9	29 (50.9%)	28 (49.1%)	0.001	15 (23.1%)	50 (76.9%)	0.001	120 (81.1%)	28 (18.9%)	0.009
	CD > 11.9	36 (81.8%)	8 (18.2%)		22 (56.4%)	17 (43.6%)		50 (96.2%)	2 (4.0%)	
PPImin	CD ≤ 11.9	31 (54.4%)	26 (45.6%)	> 0.05	21 (32.3%)	44 (67.7%)	< 0.001	83 (56.1%)	65(43.9%)	0.002
	CD > 11.9	30 (68.2%)	14 (31.8%)		30 (76.9%)	9 (23.1%)		42 (80.8%)	10 (19.2%)	
PPImax	CD ≤ 11.9	27 (47.4%)	30(52.6%)	0.01	29 (44.6%)	36 (55.4%)	> 0.05	122 (82.4%)	26 (17.6%)	> 0.05
	CD > 11.9	32 (72.7%)	12(27.3%)		24 (61.5%)	15 (38.5%)		45 (86.5%)	7 (13.5%)	
PPIavg	CD ≤ 11.9	37(64.9%)	20 (35.1%)	> 0.05	27 (41.5%)	38 (58.5%)	0.003	124 (83.8%)	24 (16.2%)	> 0.05
	CD > 11.9	34 (77.3%)	10 (22.7%)		28 (71.8%)	11 (28.2%)		48 (92.3%)	4 (7.7%)	
ARTmax	CD ≤ 11.9	47 (82.5%)	10 (17.5%)	> 0.05	41 (63.1%)	24 (36.9%)	> 0.05	145 (98.0%)	3 (2.0%)	> 0.05
	CD > 11.9	41 (93.2%)	3 (6.8%)		28 (71.8%)	11 (28.2%)		51 (98.1%)	1 (1.9%)	

FFKCG = Forme fruste keratoconus group; TCG = thin cornea group; NG = normal group; FE = front elevation; BE = back elevation; Df = deviation of normality of the front elevation; Db = deviation of normality of the back elevation; Dp = deviation of normality of pachymetric progression; Dt = deviation of normality of corneal thinnest point; Da = deviation of normality of relational thickness; BAD-D = overall deviation of normality. PPI = pachymetric progression indices (min = minimum, avg = average, max = maximum); ARTmax = Ambrosio's maximum relational thickness index. NA = not applicable.

[a] P *value of Pearson's chi-squared test or Continuity correction of chi-squared test for the comparisons between CD groups.*

Comparisons between FFKCG, TCG, and NG

For eyes with CD ≤ 11.9mm, the comparison of classification results between the FFKCG and the NG showed that the rates of abnormal cases were statistically higher in the FFKCG for BE (Continuity correction of chi-squared test, $\chi^2 = 8.62$, P = 0.003), Dp (Pearson's chi-squared test, $\chi^2 = 6.34$, P = 0.01), Da (Continuity correction of chi-squared test, $\chi^2 = 16.67$, P < 0.001), BAD-D (Pearson's chi-squared test, $\chi^2 = 18.91$, P < 0.001), PPImax (Pearson's chi-squared test, $\chi^2 = 25.48$, P < 0.001), PPIavg (Pearson's chi-squared test, $\chi^2 = 8.69$, P = 0.003), and ARTmax (Continuity correction of chi-squared test, $\chi^2 = 14.17$, P <

0.001). For eyes with CD > 11.9mm, the rates of abnormal cases were statistically higher in the FFKCG for Dp (Pearson's chi-squared test, $\chi^2 = 5.42$, P = 0.02) and PPIavg (Pearson's chi-squared test, $\chi^2 = 4.33$, P = 0.038).

For eyes with CD ≤ 11.9mm, the comparison of classification results between the TCG and the NG showed that the rates of abnormal cases were statistically higher in the TCG for Df (Pearson's chi-squared test, $\chi^2 = 6.24$, P = 0.012), Dp (Pearson's chi-squared test, $\chi^2 = 33.93$, P < 0.001), Dt (Pearson's chi-squared test, $\chi^2 = 172.6$ P < 0.001), Da (Pearson's chi-squared test, $\chi^2 = 58.27$, P < 0.001), BAD-D (Pearson's chi-squared test, $\chi^2 = 65.47$, P < 0.001), PPImin (Pearson's chi-squared test, $\chi^2 = 10.22$, P = 0.001), PPImax (Pearson's chi-squared test, $\chi^2 = 31.30$, P < 0.001), PPIavg (Pearson's chi-squared test, $\chi^2 = 39.06$, P < 0.001) and ARTmax (Pearson's chi-squared test, $\chi^2 = 49.69$, P < 0.001). For eyes with CD > 11.9mm, the abnormal rates were statistically higher in the TCG for Dp (Pearson's chi-squared test, $\chi^2 = 6.81$, P = 0.009), Dt (Pearson's chi-squared test, $\chi^2 = 59.67$, P < 0.001), Da (Pearson's chi-squared test, $\chi^2 = 13.45$, P < 0.001), BAD-D (Pearson's chi-squared test, $\chi^2 = 21.31$, P < 0.001), PPImax (Pearson's chi-squared test, $\chi^2 = 7.60$, P = 0.006), PPIavg (Pearson's chi-squared test, $\chi^2 = 6.81$, P = 0.009) and ARTmax (Pearson's chi-squared test, $\chi^2 = 13.45$, P < 0.001).

Discussion

In the present study, we explored the performance of BAD parameters in a sample of Chinese patients with forme fruste keratoconus and those with corneal thickness less than 490um. Our results showed that the influence of CD on the BAD parameters, which had been proved in tomographically normal cornea [2–4], may also affect the FFKC and thin cornea. Then, we found that for eyes with CD ≤ 11.9mm, the rates of abnormal cases in the FFKCG were significantly higher than in the NG for seven indices: BE, Dp, Da, BAD-D, PPImax, PPIavg, and ARTmax. Meanwhile, for eyes with CD > 11.9mm, the rates of abnormal cases in the FFKCG were significantly higher than in the NG only with Dp and PPIavg. For eyes with CD ≤ 11.9mm, the rates of abnormal cases in the TCG were significantly higher than in the NG for nine indices: Df, Dp, Dt, Da, BAD-D, PPImin, PPImax, PPIavg, and ARTmax. For eyes with CD > 11.9mm, the rates of abnormal cases in the TCG were significantly higher than in the NG for seven indices: Dp, Dt, Da, BAD-D, PPImax, PPIavg, and ARTmax. The above data suggest that BAD indices might underestimate the risk of ectasia in the large cornea of Chinese patients, especially for eyes with FFKC.

Previous studies have confirmed the higher rate of false-positive in the BAD parameters in the eyes of the small cornea [2–4]. In the current study, we verified the higher rate of false-negative in the BAD indices in the eyes of CD > 11.9mm with FFKC or thin cornea. The effect of CD on the BAD indices in the large cornea could be attributed to the cornea's asphericity. Compared to the small cornea, the large cornea's curvature flattens more gradually towards the periphery. As a result, a BFS may have a decreased curvature radius (steeper power) in a large cornea. A steeper BFS would result in smaller front and back elevations. For the same reason, the indices of PPIs, which represent the rate of change in corneal thickness from the thinnest point to the periphery, would have a lower rate of change as the overall distance between the thinnest point and periphery is more extended in the large cornea.

We also found that for CD > 11.9mm, the rates of abnormal cases in the FFKCG were significantly higher than in the NG only for Dp and PPIavg. It seemed that the Dp and PPIavg were more sensitive than other indices for detecting subclinical (fruste) ectasia among patients of the large cornea. PPIavg is the average pachymetric progression, and Dp (deviation of normality of pachymetric progression) is the standardized counterpart of PPIavg. According to Ruiseñor et al. [10], PPIavg is the single metric with the highest sensitivity for subclinical keratoconus among all the ten BAD parameters. To date, a limited number of studies have reported on biomechanical characters of the large cornea. Ding et al. [3] found that corneal thickness was negatively correlated with cornea diameter. In addition, Montard et al. [11] demonstrated that corneal diameter was negatively correlated with cornea hysteresis (CH) and corneal resistance factor (CRF), indicating that corneal biomechanics tends to be weaker in the large cornea. Moreover, Shah et al. [12] revealed a negative correlation between the CH/CRF and spur-to-spur distance of the ciliary body. The underestimation of the BAD indices in large cornea should be taken into consideration during the screening of refractive surgical candidates, and additional testing should be applied to these

patients (e.g., corneal biomechanical testing and epithelial thickness analysis) because these cases could be at higher risk for developing iatrogenic ectasia (keratectasia) after corneal laser vision correction [13–15]. Except for BAD parameters, there are several other indices such as the Corneal Biomechanical Index (CBI), the Tomographic and Biomechanical Index (TBI) (Zhang et al. 2020) and the Screening Corneal Objective Risk of Ectasia Analyzer (SCORE, a software linked to the Orbscan topography system) (Saad & Gatinel. 2012; Chan et al. 2015). However, the CD was not incorporated as a variable in all the systems above. Considering the influence of CD on the diagnostic accuracy of BAD indices for FFKC, further studies are needed to test the influence of CD on the performance of these indexes for the large cornea to improve the diagnostic capacity.

The term FFKC was first described by Amsler [16] as an incomplete, abortive form of corneal disease that have subtle topographic characteristics but do not reach the threshold of keratoconus suspect. However, because of the ambiguity of definition there are no definitive criteria to help discriminate subclinical keratoconus from normal. A universally accepted criterion for FFKC has not yet been developed. Most studies defined FFKC as no clinical and topographical signs of keratoconus [17–19]. In the current study, FFKC was defined as 'normal ABCD plus normal IHD' in which ABCD classification system underlies both anterior and the posterior surfaces and the pachymetry at the thinnest point and the IHD index describes the decentration of elevation data in the vertical direction. We used the strict inclusion because we intended to investigate the earliest or mildest form of FFKC. Our study found that the sensitivity for the detection of FFKC was highest with PPImax (41.6%), followed by PPImin (39.6%) and BAD-D (35.7%). The low sensitivity in our study comparing to other studies (52–80% for BAD-D, 76% for PPImin, 78% for PPImax and 46.7% for ARTmax) [5, 20, 21] might be explained by differences in the definition of FFKC and different values of cut-off in different studies. What is added in the current study is that the sensitivity of the KC indices could become even lower in cornea with CD > 11.9mm.

Besides, we also found that the mean CD for the FFKCG, TCG, and NG groups was 11.9mm, 11.8mm, and 11.7mm, respectively, while the proportion of CD > 11.9mm was 43.6%, 37.5%, and 26% for the three groups respectively. According to Edmund [22], the mean CD was 11.8mm, and the proportion of CD > 11.9mm was 35.6% in KC eyes. Meanwhile, we found no significant difference in CD between the keratoconic eyes and the FFKC eyes. There is currently no evidence that keratoconic corneal alterations involve a sideward expansion of the cornea [23, 24]. Consequently, the larger CD in FFKCG could be just a sampling error, and further studies with a larger sample are needed to clarify this question.

In this study we employed the Pentacam HR to measure the cornea diameter [25]. Pentacam measures the horizontal CD with an iris camera optic. It can recognize iris landmarks and determine the pupil's location and shape. Pentacam HR was in agreement with other devices, e.g., Orbscan, and has been widely used to determine the size of phakic posterior chamber intraocular lenses [26, 27].

Our data revealed that the influence of CD on the BAD parameters, which had been proved in tomographically normal cornea, may also affect the FFKC and thin cornea. The BAD indices might underestimate the risk of ectasia in the large cornea of Chinese patients, especially for eyes with FFKC. The analytical dimensions should be individualized for eyes with individual CD. Further studies are required to set up a rule for choosing an appropriate analytical dimension for each CD.

Abbreviations

Belin/Ambrosio Enhanced Ectasia display (BAD display)

corneal diameter (CD)

very asymmetric ectasia (VAE)

the forme fruste keratoconus (FFKC

anterior radius of curvature for a 3.0 mm zone centered on the thinnest point (ARC)

posterior radius of curvature for a 3.0 mm zone centered on the thinnest point (PRC)

the thinnest pachymetry (TP)

the best documented visual acuity (BDVA)

index of height decentration (IHD)

FFKC group (FFKCG)

thin cornea group (TCG)

normal group (NG)

flat central power (Kf),

steep central power (Ks)

mean central power [Km = (Kf + Ks)/2]

maximum corneal power (Kmax)

corneal astigmatism (Ka = Ks - Kf)

the best fit sphere for the anterior cornea (BFSa)

the best fit sphere for the posterior cornea (BFSp)

front and back corneal elevations at TP (FE and BE)

pachymetric progression index (PPI, minimum, average, and maximum)

Ambrosio's maximum relational thickness index (ARTmax)

deviation of normality of the front elevation (Df)

deviation of normality of the back elevation(Db)

deviation of normality of pachymetric progression (Dp)

deviation of normality of corneal thinnest point (Dt)

deviation of normality of relational thickness(Da)

overall deviation of normality (BAD-D)

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Eye and ENT Hospital of Fudan University (Shanghai, China) (2021118-1).This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Written informed consent was obtained from all participants prior to inclusion in this study.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding or sponsorship was received for this study or publication of this article.

Authors' contributions

Conceptualization: YSQ, Responsible for theoretical guidance and conceptual specification; Methodology: LD, Responsible for the guidance of research methods; Formal analysis and investigation: LLN, WRS Analyze the current research status and put forward the research direction; Writing - original draft preparation: LD; Writing - review and editing: LD; Resources: LD; Data collection and collation; Supervision: YSQ, XTZ. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

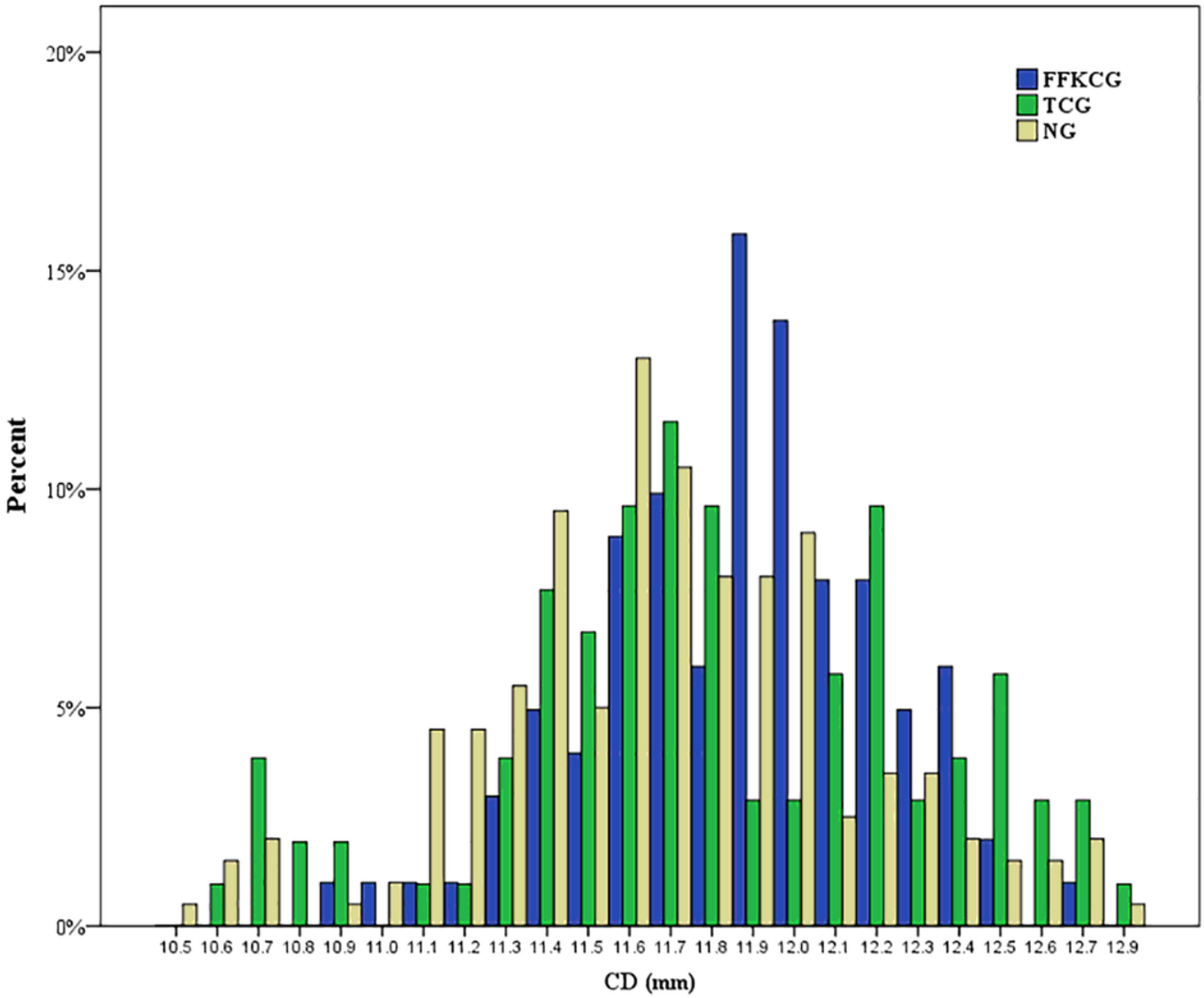

Figure 1

The distributions of corneal diameters (CDs) in individual groups. FFKCG= forme fruste keratoconus group; TCG=thin cornea group; NG=normal group.