· Clinical Research ·

Outcomes of different lines of keratoconus management in a tertiary eye center in north China

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Abstract
● **AIM:** To evaluate the treatment selections and outcomes of keratoconus and discuss the grading treatment of keratoconus.
● **METHODS:** Medical records of 1162 patients (1863 eyes) with keratoconus treated with rigid gas permeable (RGP), corneal collagen crosslinking, and keratoplasty were reviewed. The patients were grouped according to the CLEK Study. The advanced group was further divided into a <60 D group and >60 D group. The best-corrected visual acuity (BCVA) and topographic data before and after treatment were recorded.
● **RESULTS:** In the 761 eyes with steep K<52 D, nonsurgical management accounted for 83.4%, while in the 735 eyes with steep K>60 D, surgical management accounted for 90.6%. A total of 618 eyes had improved BCVA at the final follow-up point (>18mo, *P*<0.001). When steep K was <52 D, the BCVA in the RGP group was better than those with lamellar keratoplasty (LKP; *P*=0.028). When steep K was >52 D, the BCVA and topographic astigmatism outcomes showed no differences among the treatment groups. When steep K was >60 D, the BCVA in eyes treated with LKP was worse than those with steep K<60 D (*P*=0.025). The incidence of steep K progression in the RGP group was higher in advanced group (20.0% *vs* 10.8%, *P*=0.019). The probability of future keratoplasty in RGP was higher in advanced group (14.8% *vs* 7.0%, *P*=0.027). The incidence of steep K progression in the corneal collagen crosslinking (CXL) group was higher in advanced group (32.3% *vs* 8.5%, *P*=0.007). Multivariate logistic regression revealed the following related factors for treatment options: steep K [odds ratio (OR)=1.208, 95%CI: 1.052-1.387], TA (OR=1.171, 95%CI: 1.079-1.270), and TCT (OR=0.978, 95%CI: 0.971-0.984). The level of steep K, TA, and TCT all relates to the treatment choices of both keratoplasty and non-keratoplasty, while steep K provided the highest diagnostic accuracy (AUC=0.947, *P*<0.001).
● **CONCLUSION:** Steep K is an important grading treatment indicator. When steep K is <52 D, RGP lenses should be recommended. It is the best time for LKP when the steep K ranges from 52 to 60 D.
● **KEYWORDS:** keratoconus; management; rigid gas permeable; corneal collagen crosslinking; keratoplasty
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INTRODUCTION
The description of keratoconus was first published 150 years ago. During the past two decades, the diagnosis and management of keratoconus has undergone a revolution of technological advances in surgical options and equipment. Experts reached a global consensus on keratoconus in 2015: abnormal posterior ectasia, abnormal corneal thickness distribution, and clinical noninflammatory corneal thinning are now mandatory findings for diagnosis of keratoconus. True unilateral keratoconus is exceedingly rare or non-existent[1].

At present, rigid gas permeable (RGP) lens wear, corneal collagen crosslinking (CXL) and keratoplasty are the main treatments for keratoconus[2]. However, there has been no adequate clinical classification system developed for keratoconus; the historical Amsler-Krumeich classification does not incorporate current information and technological advances[1-2]. Many studies have explored and establishing a new classification system for keratoconus, but no scheme has involved therapeutic classification[3-4]. A therapeutic classification that is reasonably accurate and readily adoptable could help us to answer the challenging question regarding which treatment is most appropriate for different stages of keratoconus. Shandong Eye Institute is a tertiary eye center in north China capable of providing a variety of treatment options for keratoconic patients, such as RGP, CXL, and corneal transplantation. We retrospectively studied our population of keratoconic patients over a 20-year period to evaluate the outcomes of different treatment approaches and to provide data to inform further research.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee of Shandong Eye Institute and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects in this study. None participants received a stipend. Medical records of patients with keratoconus treated with RGP lens wear, CXL, and corneal transplantation at Shandong Eye Institute between January 1997 and December 2017 were reviewed. Patients with other concurrent eye diseases or previous eye surgeries were excluded.

A total of 1162 patients (1863 eyes) with keratoconus who fit the following inclusion criteria were included: clinically evident keratoconus defined by the evidence of one or more of the following clinical findings using the slit-lamp microscopy in at least one eye: corneal stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt's striae, and anterior corneal scarring[5]. Contralateral eyes of patients with clinical keratoconus in one eye were also included. Patients with keratoconus who did not receive any treatment were excluded.

The patients were grouped into a mild-moderate group and an advanced group according to the CLEK (the Collaborative Longitudinal Evaluation of Keratoconus) Study[6]. The advanced group was further divided into a steep K<60 D group and steep K>60 D group. Relevant patient details were documented, including gender, age, time of first consultation at our institute, treatment selections, best corrected visual acuity (BCVA), corneal curvature, topographic astigmatism (TA), and thinnest corneal thickness (TCT) before treatment. For all eyes with follow-up>18mo after treatment, the corneal curvature, BCVA, TA, and TCT at the final follow-up point were recorded. The occurrence, timing, and treatment of related complications were also recorded.

As the time span of this study was large, only the results from the same type of corneal topography systems for individual patients were included to avoid any errors caused by instrument difference. The corneal topography equipment included the Tomey screening system (Tomey Corp, Nagoya, Japan), the Obscan II (Bausch & Lomb, Rochester, NY, USA), and the Oculus Pentacam (Oculus Optikgerate GmbH, Wetzlar, Germany).

Statistical analyses were performed using SPSS (version 22.0, IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics were reported as means±standard deviation (SD). Normality of data distribution was tested using the 1-sample Kolmogorov-Smirnov test. Differences between before and after treatment were assessed with the paired-samples *t*-test if variables had a normal distribution and with the Wilcoxon signed-rank test if the variables did not have a normal distribution. Differences in steep K groups were assessed with the one-way analysis of variance (ANOVA) if variables had a normal distribution with equal variance and with the Mann-Whitney *U* test or the Kruskal-Wallis test if the variables did not have a normal distribution or had unequal variance. The endothelial cell density (ECD) between the lamellar keratoplasty (LKP) and penetrating keratoplasty (PKP) groups at different time points was assessed with the Mann-Whitney *U* test. Frequency analyses were performed using the Fisher's exact Chi-square test. Basic characteristic differences between the treatment groups were compared using ANOVA. Logistic regression analysis was used to detect the related factors for keratoplasty options. The receiver operating characteristic (ROC) curve analysis was performed to test the ability of analysed variables to distinguish between keratoplasty and non-keratoplasty. The area under the receiver operating characteristic curve (AUC) with 95% confidence interval (95%CI) was estimated, and the optimal cut-off values were determined. Comparison of the area under the AUCs was performed using the z-test. Two-tailed *P* values less than 0.05 were considered statistically significant.

RESULTS

The patients were 913 males and 249 females, with a gender ratio of 3.7:1. The average age at initial diagnosis was 20.9±6.0y (range, 6-58y). The average age was 20.5±5.5y (range, 6-48y) in males and 22.3±7.5y (range, 11-58y) in females (*P*<0.001).

Among the keratoconic eyes, 50.5% (941/1863) of the eyes wore RGP lenses, 6.9% (129/1863) underwent CXL, 11.7% (218/1863) had lamellar keratoplasty (LKP), and 30.9% (575/1863) had penetrating keratoplasty (PKP). In the eyes with steep K<52 D, nonsurgical management (RGP) accounted for 83.4%, while in the eyes with steep K>60 D, surgical management (CXL, LKP, and PKP) accounted for 90.6% (Figure 1).

There were 618 eyes for which the follow-up was more than 18mo after treatment. The 348 (56.3%) eyes wore RGP lenses, for which the follow-up was 54.0±31.9mo (range, 18.1-172.1mo). Totally 90 eyes (14.6%) underwent CXL, for which the follow-up was 22.3±3.7mo (range, 18.1-32.3mo). The 75 eyes (12.1%) had LKP, for which the follow-up was 47.9±30.5mo (range, 18.2-156.1mo) and 105 eyes (17.0%) had PKP, for which the follow-up was 57.3±45.9mo (range, 18.3-241.9mo). The steeper curvature was accompanied by worse BCVA, greater TA, and thinner corneal thickness before treatment (Table 1).

Table 1 Best corrected visual acuity, topography astigmatism, and thinnest corneal thickness before treatment in different K subgroups

mean (95%CI)

Steep K subgroup	Best corrected visual acuity (logMAR)	Topographic astigmatism (D)	Thinnest corneal thickness (μm)
Steep K<52 D	0.13 (0.10-0.16)	1.9 (1.7-2.1)	494.7 (487.1-502.4)
52 D<Steep K<60 D	0.48 (0.43-0.54)	4.7 (4.3-5.1)	443.2 (433.4-453.0)
Steep K>60 D	1.20 (1.12-1.29)	8.0 (7.5-8.6)	363.7 (351.8-375.6)
P[a]	<0.001	<0.001	<0.001

[a]Comparison between different K groups. *P* value calculated with Kruskal-Wallis test.

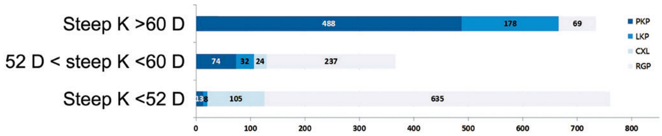

Figure 1 The distribution of different treatments in different K subgroups PKP: Penetrating keratoplasty; LKP: Lamellar keratoplasty; CXL: Corneal collagen crosslinking; RGP: Rigid gas permeable.

Outcomes of Treatments

Rigid gas permeable lens wear group At the last time of follow-up, the best contact lens corrected visual acuity (BCLVA) after RGP lens wear was better than the best spectacle corrected visual acuity (BSCVA) before treatment (0.12±0.22 logMAR, 0.32±0.32 logMAR, respectively, *P*<0.001, *n*=348). Higher steep K values were associated with lower BCLVA after treatment (*P*<0.001). The mean steep K value improved from 50.9±5.9 to 51.4±6.9 D (*P*=0.009). The mean TA decreased from 3.5±2.4 to 3.1±2.3 D (*P*<0.001). The mean TCT decreased from 480.1±46.1 to 466.2±48.4 μm (*P*<0.001; Table 2).

The incidence of steep K progression in the eyes with RGP lenses was 14.4% (50/348). In the setting of larger initial steep K (>52 D) 20.0% (27/135) had progression, while 10.8% (23/213) progressed in the setting of lower initial steep K (<52 D; *P*=0.019). The 10.1% (35/348) of the eyes underwent keratoplasty after 29.6±20.1mo (range, 3.2-82.5mo) of RGP lens wear, with a significant difference between steep K>52 D subgroup and steep K<52 D subgroup (14.8% and 7.0%, respectively, *P*=0.027). In the 135 eyes in which steep K was >52 D, the probability of future keratoplasty was significantly higher in the steep K>60 D subgroup versus steep K<60 D subgroup (32.0% and 10.9%, respectively, *P*=0.008; Table 3).

Corneal collagen crosslinking group As of the last follow-up, BCVA improved from 0.21±0.19 logMAR to 0.10±0.11 logMAR after CXL (*P*<0.001, *n*=90). Higher steep K values were associated with lower BCVA after treatment (*P*=0.003). The steep K, TA and TCT after treatment showed no significant difference compared to preoperative among all K subgroups (Table 2).

The incidence of steep K progression in the eyes that underwent CXL was 16.7% (15/90), with a significantly higher incidence in the steep K>52 D subgroup compared to the steep K<52 D subgroup (32.3% and 8.5%, respectively, *P*=0.007; Table 3).

Lamellar keratoplasty group At the last follow-up, the BCVA had improved from 0.94±0.57 to 0.24±0.21 logMAR after LKP (*P*<0.001, *n*=75). The BCVA after LKP was 0.27±0.22 logMAR in the steep K>60 D subgroup, and 0.15±0.12 logMAR in the subgroup in which steep K was between 52 to 60 D (*P*=0.025). The mean steep K value decreased from 62.7±5.3 to 46.6±2.7 D (*P*<0.001). The mean TA decreased from 8.4±3.9 to 4.4±2.4 D (*P*<0.001). The mean TCT increased from 380.5±62.5 to 545.6±42.5 μm (*P*<0.001; Table 2).

Penetrating keratoplasty group At the last follow-up, the BCVA had improved from 1.22±0.53 to 0.27±0.32 logMAR after PKP (*P*<0.001, *n*=105). The BCVA after PKP showed no significant difference among different curvature subgroups (*P*=0.611). The mean steep K value decreased from 67.3±6.7 to 47.8±4.1 D (*P*<0.001). The mean TA decreased from 6.6±3.3 to 4.6±3.1 D (*P*<0.001). The mean TCT increased from 356.8±75.3 to 504.2±37.4 μm (*P*<0.001; Table 2).

Other Conditions after Corneal Transplantation The rate of immune rejection was 1.3% (1/75) after LKP and 8.6% (9/105) after PKP (*P*=0.047). After PKP rejection, the BCVA decreased to 0.53±0.42 logMAR (*P*=0.012).

The ECD gradually declined after keratoplasty. The corneal endothelial cell loss rate slowed down over time and endothelial dysfunction did not appear. During the postoperative 5y after LKP, the ECD decreased from 2648.9±828.4 cells/mm^2 to 2003.8±574.3 cells/mm^2, and the 5-year loss rate was 24.4%; at 10y after LKP, the ECD was 1925.9±366.9, and the 10-year loss rate was 27.3%; at 15y after LKP, the ECD was 1882.9±285.3 cells/mm^2, and the 15-year loss rate was 28.9%. During the first 5y after PKP, the ECD decreased from 2467.2±513.7 to 1218.1±337.1 cells/mm^2, and the loss rate was 50.6%; at 10y after PKP, the ECD became 924.9±215.8 cells/mm^2, and the 10-year loss rate was 62.5%; at 15y, the ECD decreased to 900.9±240.0 cells/mm^2, and the 15-year loss rate was 63.5%. The ECD between the LKP and PKP groups at the 4 time points showed significant differences (1-week: *P*=0.021; 5-year: *P*<0.001; 10-year: *P*<0.001; 15-year: *P*<0.001). The lowest ECD was 480 cells/mm^2 without

Table 2 Outcomes of treatments in K subgroups mean±SD (range)

Steep K subgroup	Total n (%)	Best corrected visual acuity (logMAR)			Steep K value			Topographic astigmatism (D)			Thinnest corneal thickness (μm)			Follow-up (mo)
		Before treatment	Follow-up >18mo	*P*	Before treatment	Follow-up >18mo	*P*	Before treatment	Follow-up >18mo	*P*	Before treatment	Follow-up >18mo	*P*	
RGP														
Total	348	0.32±0.32 (0.00-1.70)	0.12±0.22 (0.00-2.00)	<0.001[a]	50.9±5.9 (41.0-68.5)	51.4±6.9 (40.3-66.4)	0.009[a]	3.5±2.4 (0.1-15.7)	3.1±2.3 (0.0-15.0)	<0.001[a]	480.1±46.1 (324-677)	466.2±48.4 (295-650)	<0.001[a]	54.0±31.9 (18.1-172.1)
Steep K<52 D	213 (61.2)	0.18±0.20 (0.00-1.30)	0.08±0.19 (0.00-1.70)	<0.001[a]	47.1±2.8 (41.0-51.9)	48.5±5.3 (40.3-65.0)	<0.001[a]	2.6±1.7 (0.1-8.7)	2.3±1.6 (0.0-8.0)	<0.001[a]	491.1±53.2 (356-677)	479.2±43.4 (336-650)	0.004[a]	56.1±33.6 (18.3-172.1)
52 D<steep K<60 D	110 (31.6)	0.51±0.27 (0.05-1.70)	0.16±0.25 (0.00-2.00)	<0.001[a]	55.0±2.3 (52.0-60.0)	55.8±4.2 (45.1-65.5)	0.041[a]	5.2±2.7 (0.1-13)	4.1±2.2 (0.1-12.5)	<0.001[b]	463.6±42.8 (329-559)	455.6±42.3 (321-543)	<0.001[b]	49.7±28.8 (18.1-145.7)
Steep K>60 D	25 (7.2)	0.74±0.50 (0.10-1.70)	0.26±0.29 (0.00-1.00)	0.001[a]	64.7±1.9 (60.4-68.5)	59.8±5.4 (46.3-66.4)	0.001[a]	10.2±3.0 (2.5-15.7)	5.8±3.9 (0.5-15.0)	<0.001[a]	429.6±52.4 (324-527)	404.7±56.1 (295-501)	0.071[b]	55.1±28.9 (18.2-111.6)
P		<0.001[d]	<0.001[d]					<0.001[d]	<0.001[d]		<0.001[d]	<0.001[d]		0.227[e]
CXL														
Total	90	0.21±0.19 (0.00-1.00)	0.10±0.11 (0.00-0.52)	<0.001[a]	50.1±3.7 (41.9-58.6)	50.1±4.1 (41.2-60.8)	0.428[a]	3.6±2.1 (0.4-11)	3.4±2.1 (0.2-11.8)	0.196[b]	481.9±33.4 (395-575)	472.0±41.2 (372-551)	0.004[a]	22.3±3.7 (18.1-32.3)
Steep K<52 D	59 (65.6)	0.15±0.13 (0.00-0.52)	0.07±0.08 (0.00-0.40)	<0.001[a]	48.0±2.7 (41.9-51.9)	47.9±2.9 (41.2-53.5)	0.895[a]	3.1±1.7 (0.5-7.3)	3.0±1.7 (0.2-7.8)	0.421[b]	490.9±28.8 (395-575)	480.5±42.0 (372-551)	0.027[a]	21.4±2.3 (18.1-27.9)
52 D<steep K<60 D	31 (34.4)	0.33±0.24 (0.00-1.00)	0.14±0.14 (0.00-0.52)	<0.001[a]	54.1±1.5 (52.2-58.6)	54.2±2.5 (46.2-60.8)	0.195[a]	4.5±2.4 (0.4-11)	4.1±2.5 (0.4-11.8)	0.182[b]	464.7±35.2 (400-532)	455.8±32.5 (399-527)	0.027[b]	24.1±5.0 (18.4-32.3)
P		<0.001[c]	0.003[c]					0.002[d]	0.017[d]		<0.001[e]	0.002[c]		0.104[c]
LKP														
Total	75	0.94±0.57 (0.00-2.00)	0.24±0.21 (0.00-1.30)	<0.001[a]	62.7±5.3 (48.9-68.9)	46.6±2.7 (41.9-52.4)	<0.001[a]	8.4±3.9 (0.3-18.1)	4.4±2.4 (0.0-10.7)	<0.001[b]	380.5±62.5 (260-560)	545.6±42.5 (459-597)	<0.001[a]	47.9±30.5 (18.2-156.1)
Steep K<52 D	5 (6.7)	0.44±0.17 (0.30-0.70)	0.15±0.11 (0.00-0.30)	0.013[b]	50.1±1.0 (48.9-51.4)	45.8±2.5 (42.2-48.4)	0.026[b]	3.1±2.2 (1.0-5.5)	4.3±1.0 (3.3-5.8)	0.331[b]	440.0±19.9 (410-460)	527.4±55.8 (467-588)	<0.001[a]	41.6±26.3 (18.4-85.4)
52 D<steep K<60 D	14 (18.7)	0.46±0.46 (0.10-1.30)	0.15±0.12 (0.00-0.40)	0.033[a]	56.3±2.6 (52.5-60.0)	45.8±2.1 (42.2-48.2)	<0.001[b]	4.8±3.4 (0.3-12.3)	4.0±2.8 (0.0-9.8)	0.573[b]	371.6±64.9 (260-512)	548.4±45.4 (460-596)	<0.001[a]	62.3±45.2 (18.2-156.1)
Steep K>60 D	56 (74.7)	1.10±0.53 (0.00-2.00)	0.27±0.22 (0.00-1.30)	<0.001[a]	65.4±1.8 (62.3-68.9)	46.9±2.8 (41.9-52.4)	<0.001[a]	9.8±3.0 (1.3-18.1)	4.5±2.4 (0.0-10.7)	<0.001[a]	377.5±62.3 (264-560)	546.5±41.1 (459-597)	<0.001[a]	44.9±25.5 (18.2-106.9)
P		<0.001[d]	0.046[d]					<0.001[d]	0.816[e]		0.025[d]	0.745[d]		0.538[d]
PKP														
Total	105	1.22±0.53 (0.30-3.00)	0.27±0.32 (0.00-1.40)	<0.001[a]	67.3±6.7 (53.0-78.5)	47.8±4.1 (33.0-56.9)	<0.001[a]	6.6±3.3 (0.8-16.2)	4.6±3.1 (0.0-13.6)	<0.001[a]	356.8±75.3 (228-573)	504.2±37.4 (437-599)	<0.001[a]	57.3±45.9 (18.6-241.9)
52 D<steep K<60 D	15 (14.3)	0.90±0.50 (0.52-2.00)	0.22±0.28 (0.00-1.00)	0.002[a]	56.4±2.2 (53.0-59.6)	47.6±1.6 (47.6-49.5)	<0.001[b]	4.5±2.1 (0.8-8.4)	4.2±2.0 (1.4-9.0)	0.776[a]	366.8±60.5 (248-445)	513.4±39.3 (450-588)	<0.001[a]	45.8±45.6 (18.6-158.5)
Steep K>60 D	90 (85.7)	1.27±0.52 (0.30-3.00)	0.28±0.33 (0.00-1.40)	<0.001[a]	69.2±5.3 (60.0-78.5)	47.8±4.4 (33.0-56.9)	<0.001[a]	6.9±3.4 (1.3-16.2)	4.6±3.2 (0.0-13.6)	<0.001[a]	355.2±77.7 (228-573)	502.7±37.0 (437-599)	<0.001[a]	59.2±45.9 (20.3-241.9)
P		0.002[c]	0.611[c]					0.008[c]	0.905[c]		0.301[c]	0.27[c]		0.147[c]

RGP: Rigid gas permeable; CXL: Corneal collagen crosslinking; LKP: Lamellar keratoplasty; PKP: Penetrating keratoplasty; BCVA after treatment >18mo in RGP Group is best contact lens corrected visual acuity. [a]Comparing before and after treatment more than 18mo. *P* value calculated with Wilcoxon signed-rank test. [b]Comparing before and after treatment. *P* value calculated with paired-samples *t*-test. [c]Comparing among different K groups. *P* value calculated with Mann-Whitney *U* test. [d]Comparing among different K groups. *P* value calculated with Kruskal-Wallis test. [e]Comparing among different K groups. *P* value calculated with ANOVA.

Table 3 Percentage of progression with RGP lens and CXL treatment *n* (%)

Steep K subgroup	RGP			CXL	
	Total	Steep K progression	Future keratoplasty	Total	Steep K progression
Steep K<52 D	213	23 (10.8)	15 (7.0)	59	5 (8.5)
52 D<steep K<60 D	110	23 (20.9)	12 (10.9)	31	10 (32.3)
Steep K>60 D	25	4 (16.0)	8 (32.0)	/	/
Total	348	50 (14.4)	35 (10.1)	90	15 (16.7)

RGP: Rigid gas permeable. CXL: Corneal collagen crosslinking.

endothelial dysfunction 13y after PKP, while the ECD of the contralateral eye undergoing LKP in the same year was 2194 cells/mm^2. No keratoconus recurred in any of the corneal allografts.

Results Summary When the steep K was <52 D, the BCVA after treatment in the eyes with RGP lens, CXL and LKP was 0.08±0.19, 0.07±0.08, and 0.15±0.11 logMAR respectively (*P*=0.017). Among them, the RGP group was better than LKP group (*P*=0.028); the difference did not reach significance between CXL group and LKP group (*P*=0.089), and the RGP and LKP group (*P*=0.052). The TA after treatment in the eyes with RGP lens, CXL and LKP was 2.3±1.6, 3.0±1.7, and 4.3±1.0 D, respectively (*P*<0.001). Among them, the RGP group was lower than the LKP group (*P*=0.007) and CXL

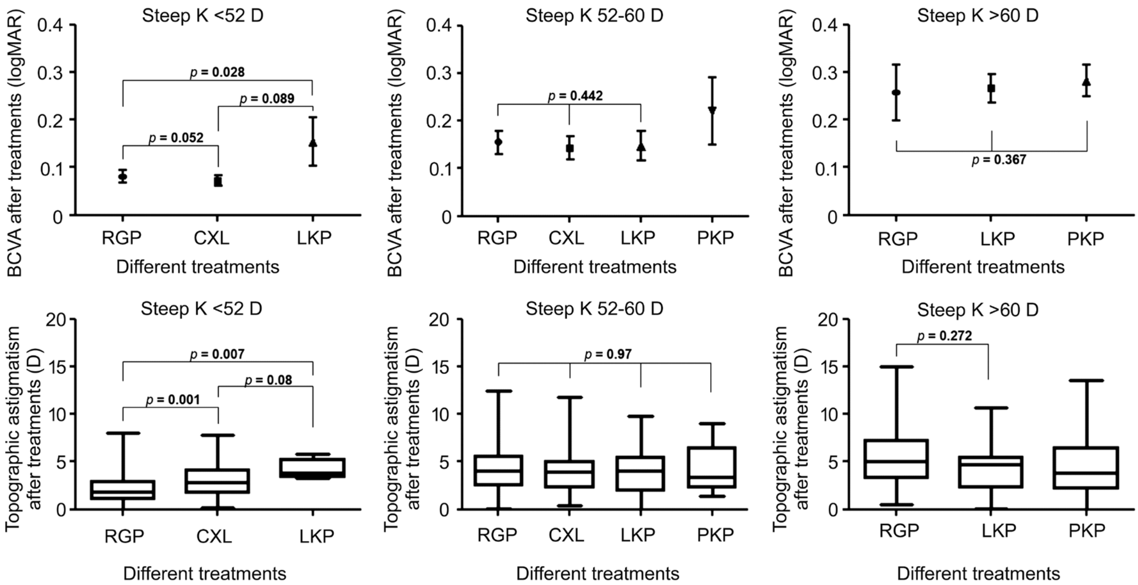

Figure 2 The best corrected visual acuity and topographic astigmatism after different treatments in different K subgroups BCVA: Best-corrected visual acuity; RGP: Rigid gas permeable; CXL: Corneal collagen crosslinking; LKP: Lamellar keratoplasty; PKP: Penetrating keratoplasty.

group (*P*=0.001); the CXL group and LKP group were not significantly different (*P*=0.08).

When the steep K was between 52 to 60 D, the BCVA in the eyes treated with RGP lens, CXL and LKP was 0.16±0.25, 0.14±0.14, and 0.15±0.12 logMAR respectively (*P*=0.442). The TA in the eyes treated with RGP lens, CXL, LKP and PKP was 4.1±2.2, 4.1±2.5, 4.0±2.8, and 4.2±2.0 D, respectively (*P*=0.97).

When the steep K was >60 D, the BCVA and TA after treatment in the eyes with RGP lens, LKP and PKP showed no significant difference (Figure 2).

The results of the univariate and multivariate regression analyses are summarized in Table 4. Univariate analyses revealed that treatment options to keratoconus was significantly associated with the steep K (*P*<0.001), BCVA (*P*<0.001), TA (*P*<0.001), and TCT (*P*<0.001). The following factors in the multivariate analysis remained a significant relation with the different treatments: steep K [odds ratio (OR)=1.208, 95% confidence interval (CI): 1.052-1.387], TA (OR=1.171, 95%CI: 1.079-1.270), and TCT (OR=0.978, 95%CI: 0.971-0.984). A comparative analysis of steep K, TA, and TCT was performed to unveil a predictive index power. Unsurprisingly, the level of steep K, TA, and TCT followed the treatment choice between the keratoplasty and non-keratoplasty, although steep K reached the most significant meaning (AUC=0.947, *P*<0.01) *vs* TA (AUC=0.81, *Z*=6.247, *P*<0.01) and TCT (AUC=0.903, *Z*=2.287, *P*=0.022; Table 5 and Figure 3). While looking for a promising steep K cut-off, we observed that 57.2 D allows for the diversification of whether the keratoplasty should be chosen, and showed a sensitivity of 87.8% with a specificity of 89.5%.

Table 4 Results of the regression analysis of the relative factors for treatment options

Relative factors	Univariate analysis		Multivariate analysis		
	95%CI	*P*	OR	95%CI	*P*
Steep K	54.31-55.70	<0.001	1.208	1.052-1.387	<0.001
BCVA	0.49-0.57	<0.001	2.067	0.778-5.493	0.145
TA	4.40-4.91	<0.001	1.171	1.079-1.270	0.007
TCT	441.48-453.19	<0.001	0.978	0.971-0.984	<0.001

95%CI: 95% confidence interval; OR: Odds ratio; BCVA: Best corrected visual acuity; TA: Topographic astigmatism; TCT: Thinnest corneal thickness.

Table 5 Receiver operating characteristic curve of the ability of analysed variables to distinguish between keratoplasty and non-keratoplasty

Indicators	AUC	Standard error	*P*	95%CI	
				Lower limits	Upper limits
Steep K	0.947	0.009	<0.001	0.929	0.964
TA	0.81	0.02	<0.001	0.77	0.85
TCT	0.903	0.017	0.022	0.87	0.936

AUC: Area under the receiver operating characteristic curve; 95%CI: 95% confidence interval; TA: Topographic astigmatism; TCT: Thinnest corneal thickness.

DISCUSSION

There are racial differences in the presentation of keratoconus[1,7]. Both Asians and Caucasians were studied by Pearson *et al*[8]. Compared with Caucasians, Asians were found to have a fourfold increase in keratoconus incidence, with younger presentation and earlier requirement for corneal grafting. Our current study presents a large-scale Asian population of keratoconic patients. The average age of the patients at the

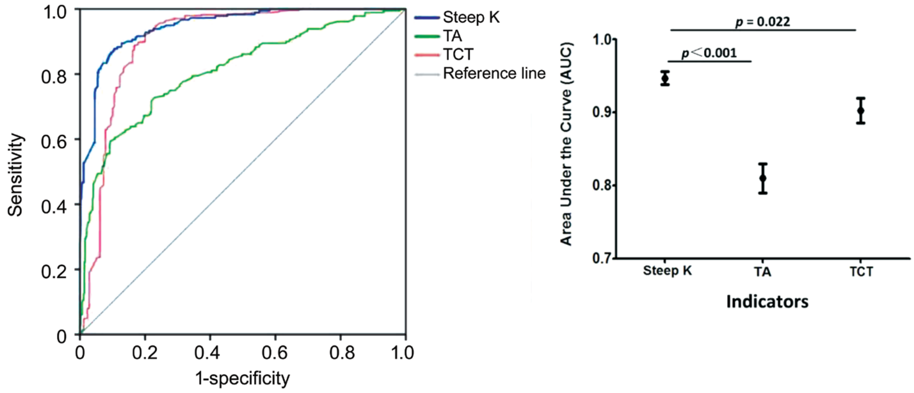

Figure 3 The receiver operating characteristic curve in predicting whether the keratoplasty should be chosen AUC: Area under the receiver operating characteristic curve; TA: Topographic astigmatism; TCT: Thinnest corneal thickness.

initial diagnosis was consistent with previous reports involving Asians[9-10]. The ratio of male to female was 3.7:1, which was consistent with most previous studies.

There has been no adequate clinical classification system for keratoconus[1-2]. As the most widely used keratoconus classifications, both the Amsler-Krumeich classification and the CLEK Study used corneal curvatures as their only or primary indicators for classification. In the current study, steeper curvature was accompanied by worse BCVA, greater TA, and thinner corneal thickness before treatment. This demonstrates the importance of K values in the severity grading of keratoconus. Sray *et al*[11] reported that, in addition to corneal scarring, the steep corneal curvature was the most relevant risk factor for PKP, and a cut-off level for this higher risk corneal curvature was identified at 55 D (mean K) by Reeves *et al*[12]; the base curve of RGP lens is based on the corneal curvature; a steep curvature is directly related to the probability of RGP lens fitting. In analysis the current study population, as steep K increased, the proportion of surgical treatment became higher, demonstrating the influences of curvature on the selection of treatments for keratoconus. A higher steep K value appeared to have several adverse implications for the various treatment groups: the BCVA after treatment decreased gradually whether treated with RGP lens, CXL or LKP group; the incidence of steep K progression increased in RGP lens and CXL groups; the probability of future keratoplasty increased in the RGP lens group. These data demonstrate the important influences of K values on the outcome of keratoconic treatment.

Halting disease progression and recovering vision are two major goals in the management of keratoconus[1]. When steep K was >52 D, RGP lenses lost their advantage in vision correction. The longest follow-up of keratoplasty was 20y in this study, which showed that the current corneal transplantation can provide patients with long-term satisfactory vision correction.

The incidence of keratoconus is a slowly increasing[10]. Recently, more research has focused on the role of CXL in improving vision and halting the progress of keratoconus[13-14]. In these studies, almost all failed cases (progression of disease or repeated CXL) occurred in eyes with corneal curvature over 55 D or 58 D, with a failure rate ranging from 7.6% to 12.36%[15-16]. In the current study, as the steep K value increased, the incidence of keratoconus progression increased, while the steep K and TA showed no changes after CXL. It is necessary to assess the longer-term results of CXL in steep curvature.

In contrast to CXL, corneal transplantation is the traditional treatment for keratoconus. Keratoplasty can provide a satisfactory visual acuity for keratoconic patients of varied races[17-19]. LKP has been recognized as superior to PKP, and this finding is reinforced by our data[1,20]. Our group successfully modified deep LKP and employed it for the treatment of advanced keratoconus with steep curvature[21].

Concerns about keratoplasty have focused on rejection of allografts and long-term graft survival. The rate of rejection after keratoplasty, particularly LKP, for keratoconus is much lower than for other diseases. The corneal endothelial cell loss rate slowed down over time[22-23]. It is worth noting that even if ECD dropped to 1000 cells/mm^2 or less, endothelial dysfunction did not appear in the current study. This suggests that the occurrence of endothelial dysfunction requires some additional stimulating factors, such as inflammation and rejection, to disrupt the balance of corneal endothelial compensation mechanisms. Absent such stimuli, the corneal endothelium can maintain its own homeostasis for extended periods.

It is important to achieve a global consensus on the management of keratoconus. We propose that when steep K is <52 D, RGP lenses should be recommended because of their better BCVA. When steep K is between 52 to 60 D, the BCVA and TA after treatment in the eyes with RGP lens, CXL and LKP showed no significant difference, but the risk of curvature progression became higher. So, the patients should be monitored more closely in order to best time LKP. In the current study, when steep K is 57.2 D, LKP should be required. If LKP is delayed, BCVA may be worse, and PKP may even be required, followed by the risk of corneal endothelial dysfunction[24]. Further research of a promising steep K cut-off for the diversification of whether the CXL should be chosen in steeper K group is needed. At the same time, we also pay attention to the treatment progress of RGP and CXL to continuously update our grasp of the treatment boundary[25].

The existing keratoconus therapies include corneal surgery, refractive surgery, and optical correction, which may involve multiple subspecialties. Long-term goal-directed therapy is needed for the treatment of keratoconus. Steep K, which can reflect the severity of keratoconus and has a major impact on treatment options and outcomes, appears to be a reasonably accurate and readily adoptable classification scheme to assist in treatment decisions. We speculate that improvements may be achievable by adjusting the grading point of steep K, or designing a more accurate therapeutic classification based on the steep K by introducing BCVA and corneal thickness as sub-indicators. However, the steep K is an undoubtedly important therapeutic classification indicator in the current retrospective study.

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