

## Accelerated corneal collagen cross-linking in progressive keratoconus: Five-year results and predictors of visual and topographic outcomes

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**Purpose:** To analyze the 5-year results of accelerated corneal collagen crosslinking (CXL) for progressive keratoconus and identify preoperative characteristics predictive of visual and topographic outcomes. **Methods:** A prospective interventional case series. Nineteen eyes of 19 patients receiving accelerated CXL with settings of 18 mW/cm<sup>2</sup> for 5 min were included. Clinical and topographic parameters were assessed. Linear regression and logistic regression were used to compare the R<sup>2</sup> and odds ratio (OR), respectively, between baseline characteristics and postoperative outcomes. **Results:** Corrected distance visual acuity (CDVA) remained stable from 0.28 ± 0.21 to 0.25 ± 0.18 logMAR (*P* = 0.486). The mean cylindrical refraction was stable (*P* = 0.119). The maximal keratometry (Kmax) decreased from 61.99 ± 10.37 to 59.25 ± 7.75 D (*P* < 0.001), flattening in the flattest and steepest meridians and mean keratometry were also observed (*P* ≤ 0.040). The mean anterior elevation at the apex reduced from 21.42 ± 16.69 to 18.53 ± 12.74 μm (*P* = 0.013) and changes in posterior elevation were non-significant (*P* = 0.629). Preoperative Kmax best predicted the postoperative change in Kmax (R<sup>2</sup> = 0.55, *P* < 0.001) compared to the other baseline characteristics (*P* ≤ 0.028), whereas preoperative CDVA was the only significant predictor of postoperative change in CDVA (R<sup>2</sup> = 0.41, *P* = 0.003). Accelerated CXL is less likely to fail in eyes with a steeper preoperative Kmax (OR = 0.74, *P* = 0.040) or greater posterior elevation at the apex (OR = 0.91, *P* = 0.042). **Conclusion:** Kmax significantly decreased following accelerated CXL. Eyes with worse preoperative CDVA and higher Kmax were more likely to have an improvement in visual acuity and corneal flattening.

**Key words:** Collagen crosslinking, keratoconus, keratometry, topography

Corneal collagen crosslinking (CXL) has become a common and effective treatment for progressive keratoconus in recent years.<sup>[1-3]</sup> Although the definition of progression remains variable among different studies, characteristics of progressive disease include irregular steepening and changes in manifest refraction. CXL aims to increase the corneal biomechanics to strengthen corneal stability and stiffness, which ultimately arrest progression. In corneal CXL, the photochemical reaction between ultraviolet A (UVA) irradiation and photosensitizer riboflavin induces interfibrillar and intrafibrillar covalent crosslinks between collagen fibers.<sup>[4]</sup> The conventional CXL, often referred to as the Dresden protocol, was first reported by Wollensak *et al.*,<sup>[5]</sup> which uses a 3 mW/cm<sup>2</sup> intensity over an irradiation time of 30 min.

Based on the Bunsen–Roscoe law of reciprocity, an equal photochemical reaction can be achieved with higher intensity over a shorter duration provided that the cumulative dose remains constant. Given the long treatment duration in the Dresden protocol, studies have adopted various accelerated CXL protocols with shorter illumination durations of

3, 5, or 10 min by using 30, 18, or 9 mW/cm<sup>2</sup> irradiance, respectively.<sup>[6-9]</sup> A recent meta-analysis comparing standard and accelerated CXL from 22 studies of 1,158 eyes reported that standard CXL was better than accelerated CXL with a greater demarcation line depth and superior minimum keratometry, whereas accelerated CXL should be favored when considering the minimal corneal thickness. Other outcomes including visual, refractive, topographic, corneal biomechanical properties, time of re-epithelialization, and endothelial cell density, were comparable between the two protocols.<sup>[10]</sup>

However, there is limited evidence regarding the long-term outcomes of accelerated CXL. Limited results are available beyond 2 years of follow-up,<sup>[11,12]</sup> whereas data for standard CXL are available beyond 5 years.<sup>[2,13]</sup> Prognostic factors predicting the long-term effects of accelerated CXL also remain to be elucidated. We previously reported that accelerated CXL seems to be effective in preventing progression and causing topographic flattening in advanced cases of keratoconus; however, not as effective in the less progressed counterparts.<sup>[14]</sup>

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In the current study, we report the visual, refractive, topographic, and tomographic outcomes and identify their prognostic factors following accelerated CXL from 2 to 5 years.

## Methods

This was a 5-year prospective interventional case series of consecutive patients undergoing accelerated CXL for progressive keratoconus at Hong Kong Eye Hospital between June 2012 and September 2015. The study was approved by the Kowloon Central/Kowloon East Cluster Research Ethics Committee and was performed following the tenets of the Declaration of Helsinki. Informed written consent was obtained from all patients or their parents. The inclusion criteria included patients age 14 years and above, documented progressive keratoconus indicating the need for treatment defined as  $\geq 1$  D increase in the maximum keratometry (Kmax),  $\geq 1$  D increase in the manifest cylinder, or  $\geq 0.5$  D increase in the manifest spherical equivalent (SEQ) confirmed by two consecutive examinations over 9 to 12 months.<sup>[15]</sup> Patients with any of the following were excluded from the study: corneal thickness at the thinnest point (TCT)  $< 400$   $\mu\text{m}$ , endothelial cell density  $< 2000$  cells/ $\text{mm}^2$ , severe corneal scarring, or ocular surface diseases, autoimmune disease, or pregnancy.

Uncorrected (UDVA) and corrected distance visual acuity (CDVA), objective and manifest refractive error, slit-lamp evaluation, elevation-based topography (Pentacam HR, OCULUS Optikgeräte GmbH, Wetzlar, Germany) were analyzed preoperatively, 2 years and 5 years after accelerated CXL. Specular microscopy utilizing the center method (Konan SP-9000; Konan, Hyogo, Japan) before and 1 year after accelerated CXL was performed. Visual acuity was recorded using the Snellen chart and converted to logMAR. The topographic corneal analysis included the measurements of the flattest (Kflat) and steepest (Ksteep) meridian keratometry, mean keratometry (Kmean), Kmax, TCT, central corneal thickness (CCT), anterior and posterior elevations at the apex. Contact lens wearers were asked to discontinue their contact lens before corneal imaging (rigid contact lens  $\geq 4$  weeks and soft contact lens  $\geq 2$  weeks). For subgroup analysis, eyes were divided at baseline into two subgroups: mild-to-moderate keratoconus with Kmax  $< 58$  D, and advanced keratoconus with Kmax  $\geq 58$  D.<sup>[14]</sup>

Accelerated CXL was performed under the same setting using a standard technique. Corneal anesthesia was achieved using proparacaine 0.5% eyedrops. The central 9 mm corneal epithelium was debrided using a flat-edged knife. Topical 0.1% riboflavin with 20% dextran solution (MedioCROSS D; Kronen-Apotheke, Kiel, Germany) was instilled every 2 min for 30 min. Residual corneal thickness was measured using sterile handheld ultrasonic pachymetry (DGH 500; DGH Technology Inc, Exton, PA) under the aseptic technique. The cornea was then exposed to 370 nm UVA light (CCL-HE; PeschkeMeditrade GmbH, Huenenberg, Switzerland) for 5 min at an irradiance of 18 mW/ $\text{cm}^2$  (fluence of 5.4 J/ $\text{cm}^2$ ). Riboflavin solution was reapplied every 2 min during the irradiation. A bandage contact lens was inserted after the procedure and was removed at 1 week postoperatively. Oral analgesic was given for the first 2 days, and topical 0.5% levofloxacin was given four times daily until complete epithelial healing. Topical 0.1% dexamethasone four times daily was prescribed for 1 week postoperatively and tapered over 2 months (three times daily for 2 weeks, twice daily for 2 weeks, and once daily for the remaining 3 weeks).<sup>[14]</sup>

Statistical analysis was performed with linear mixed models with repeated measures. A Mann-Whitney *U* test was used to compare the quantitative variables between the subgroups. The association between the changes in Kmax and CDVA with the preoperative factors was evaluated using a linear regression model. To better identify patients who might do poorly after accelerated CXL, logistic regression was performed for baseline characteristics predictive of failure, which was defined as an increase in Kmax  $> 1$  D or worsening of CDVA by  $> 1$  Snellen line postoperatively.<sup>[16]</sup> Multivariable analyses were not performed due to the multicollinearity between the baseline characteristics. To compare the strength of association and predictors of failure, bootstrap resampling ( $n = 1,000$ ) was performed to generate the 95% bias-corrected confidence intervals of coefficients of determination and odds ratio. All *P* values were two-tailed. Statistical analyses were performed with Stata version 14.0 (StataCorp LLC, College Station, TX, USA).

## Results

In the original study, 25 eyes of 24 patients were included.<sup>[14]</sup> Of those, 19 eyes of 19 patients returned for evaluation 5 years after

**Table 1: Visual and topographic outcomes at baseline, 2 years, and 5 years following accelerated corneal collagen crosslinking**

Parameters	Baseline	2 years	<i>P</i> <sup>#</sup>	5 years	<i>P</i> <sup>#</sup>	<i>P</i> <sup>%</sup>
UDVA (logMAR)	0.62 $\pm$ 0.26	0.61 $\pm$ 0.40	0.239	0.72 $\pm$ 0.41	0.522	0.651
CDVA (logMAR)	0.28 $\pm$ 0.21	0.29 $\pm$ 0.24	0.814	0.25 $\pm$ 0.18	0.486	0.365
Manifest cylinder (D)	3.97 $\pm$ 1.70	3.57 $\pm$ 2.11	0.151	3.62 $\pm$ 1.66	0.199	0.880
SEQ (D)	-10.3 $\pm$ 4.56	-11.36 $\pm$ 7.11	0.317	-10.09 $\pm$ 6.43	0.606	0.628
Flattest keratometry (D)	48.74 $\pm$ 4.58	48.61 $\pm$ 4.40	0.687	47.98 $\pm$ 4.24	0.020*	0.055
Steepest keratometry (D)	52.38 $\pm$ 5.59	52.01 $\pm$ 5.47	0.328	51.61 $\pm$ 4.80	0.040*	0.282
Mean keratometry (D)	50.46 $\pm$ 4.94	50.22 $\pm$ 4.78	0.357	49.72 $\pm$ 4.44	0.006*	0.065
Maximum keratometry (D)	61.99 $\pm$ 10.37	60.12 $\pm$ 8.42	0.010*	59.25 $\pm$ 7.75	$< 0.001$ *	0.236
Thinnest pachymetry ( $\mu\text{m}$ )	467.05 $\pm$ 38.59	454.84 $\pm$ 47.21	0.064	452.68 $\pm$ 60.12	0.029*	0.743
Central pachymetry ( $\mu\text{m}$ )	485.16 $\pm$ 35.92	473.58 $\pm$ 41.62	0.035*	472.42 $\pm$ 54.14	0.020*	0.833
Anterior elevation ( $\mu\text{m}$ )	21.42 $\pm$ 16.69	19.84 $\pm$ 13.32	0.177	18.53 $\pm$ 12.74	0.013*	0.261
Posterior elevation ( $\mu\text{m}$ )	42.79 $\pm$ 31.95	43.79 $\pm$ 31.08	0.541	43.58 $\pm$ 31.72	0.629	0.898

Mean values are presented in mean $\pm$ standard deviation (SD). CDVA=Corrected distance visual acuity; UDVA=uncorrected distance visual acuity; SEQ=spherical equivalent. <sup>#</sup>*P* between baseline and respective postoperative time points. <sup>%</sup>*P* between postoperative 2-years and postoperative 5-years. \**P* $< 0.05$

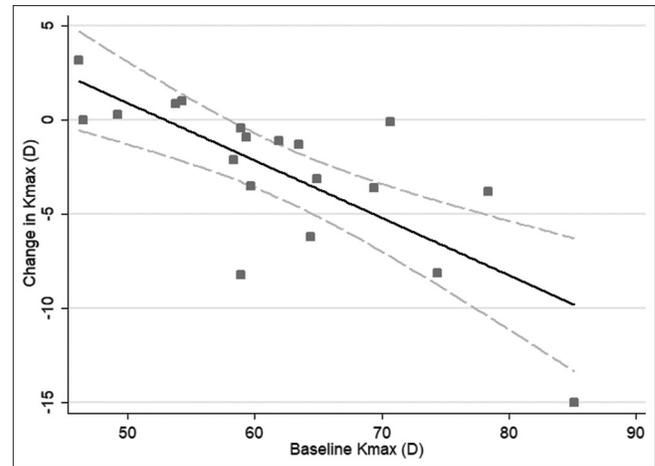
accelerated CXL. The mean age of all patients (five women and 14 men) was  $28.63 \pm 11.11$  years. 73.68% of eyes had baseline Kmax  $\geq 58$  D. Based on the Amsler–Krumeich classification, two (10.53%), eight (42.11%), seven (36.84%), and two (10.53%) were of stage 1, stage 2, stage 3, stage 4 keratoconus at baseline, respectively. Five years after treatment, the mean UDVA, CDVA, manifest cylinder, and objective SEQ remained stable, and the improvements were non-significant [Table 1,  $P \leq 0.606$ ]. Significant corneal flattening was identified in all topographic parameters: Kflat, Ksteep, Kmean, and Kmax at the fifth year of follow-up compared to baseline (0.76, 0.77, 0.74, and 2.74 D, respectively,  $P \leq 0.040$ ), only the flattening in Kmax was significant compared to baseline at the second year of follow-up ( $P = 0.010$ ). Both pachymetric parameters, CCT and TCT, decreased by 12.74  $\mu\text{m}$  and 14.37  $\mu\text{m}$ , compared with baseline ( $P \leq 0.029$ ). The anterior elevation at the apex decreased by 2.89  $\mu\text{m}$  ( $P = 0.013$ ) at the end of the fifth year, where the posterior elevation remained stable ( $P = 0.629$ ). No significant changes in any of the parameters were reported between the second year and fifth year [Table 1]. The endothelial cell density remained stable ( $P = 0.834$ ) at first year ( $2795 \pm 258$  cells/ $\text{mm}^2$ ) as compared to the baseline ( $2783 \pm 258$  cells/ $\text{mm}^2$ ). Relevant complications such as delayed re-epithelialization, stromal scarring, infection, and endothelial decompensation were not observed throughout the 5-year follow-up.

Comparing the changes at the fifth year of follow-up to baseline between the mild-to-moderate keratoconus eyes (baseline Kmax  $< 58$  D) and the advanced keratoconus eyes (baseline Kmax  $\geq 58$  D), the former group reported an increase in Kflat, Kmean, Kmax, and anterior elevation at the apex of 0.78 D, 0.52 D, 1.08 D, and 2.80  $\mu\text{m}$ , respectively, where the latter group showed a reduction of 1.31 D, 1.19 D, 4.10 D, and 4.93  $\mu\text{m}$  in these corresponding parameters [ $P \leq 0.007$ , Table 2]. Changes in UDVA, CDVA, manifest cylinder, objective SEQ, Ksteep, TCT, CCT, and posterior elevation at the apex were not significantly different between the subgroups.

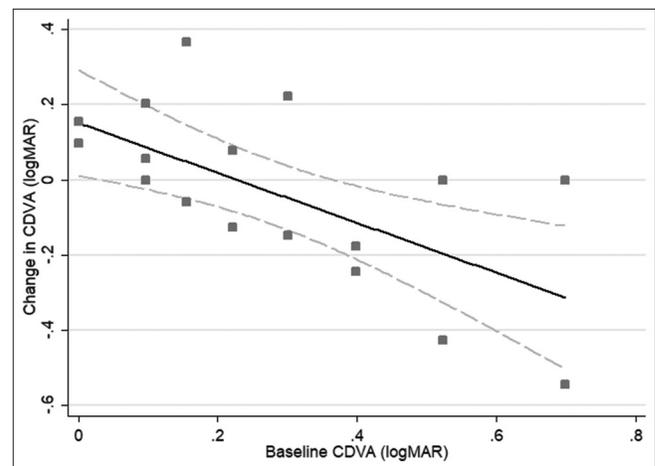
The association between the 5-year change in Kmax/CDVA and the baseline parameters is shown in Table 3. Greater baseline topographic parameters (Kflat, Ksteep, Kmean, and Kmax), higher elevation at the apices (anterior and posterior), and larger manifest cylinder were significantly associated with a greater reduction of KMax [Table 3]. In contrast, the baseline CDVA and pachymetric parameters were not. Baseline Kmax demonstrated the greatest strength of association with the 5-year change in Kmax [ $R^2 = 0.55$ ,  $\beta$ -coefficient =  $-0.30$ , Fig. 1] and was stronger than all other baseline parameters ( $P \leq 0.028$ ). Likewise, in the association between 5-year change in CDVA and preoperative characteristics, preoperative CDVA was the only significant predictor of the CDVA changes [ $R^2 = 0.41$ ,  $\beta$ -coefficient =  $-0.66$ ,  $P = 0.003$ , Fig. 2]. A steeper preoperative Kmax and greater posterior elevation at the apex were significantly less likely (OR = 0.74 and 0.91, respectively,  $P \leq 0.042$ ) to fail after accelerated CXL [Table 3], where baseline Kmax was a stronger predictor of treatment failure ( $P = 0.001$ ). The other baseline characteristics were not predictive of worsening of visual acuity or corneal topography ( $P \geq 0.054$ ).

## Discussion

Studies have consistently found a stabilization effect after accelerated CXL, with a variable degree of corneal flattening.<sup>[6-9]</sup> There is a paucity of data evaluating the long-term outcomes beyond 2 years after accelerated CXL.<sup>[11,12]</sup> In our study, we



**Figure 1:** Scatterplot and linear regression between the change in the maximum keratometry (Kmax) at 5-year and baseline Kmax; dash lines indicate the 95% confidence interval



**Figure 2:** Scatterplot and linear regression between the change in corrected distance visual acuity (CDVA) at 5-year and baseline CDVA; dash lines indicate the 95% confidence interval

observed significant flattening of 0.76 D, 0.77 D, 0.74 D, and 2.74 D in Kflat, Ksteep, Kmean, and Kmax, respectively, over 5 years. The significant flattening across all topographic measurements conclusively documents the progressive flattening of the ectatic cornea following accelerated CXL. Our results are in agreement with another recently published study using a different accelerated CXL protocol (30 mW/ $\text{cm}^2$  with a total dose of 7.2 J/ $\text{cm}^2$ ), which reported a significant reduction in the Kmean and Kmax at 5 years in mild-to-moderate keratoconus eyes (Amsler–Krumeich grades I to III).<sup>[17]</sup> Long-term results for standard CXL are available with up to 10 years of follow-up. The Siena eye cross study reported a 2 D in Kmean reduction after 48 months.<sup>[18]</sup> Hashemi *et al.*<sup>[12]</sup> reported the stability of Kmean and Kmax over 5-years with a non-significant reduction of 0.11 D and 0.24 D, respectively. The 10-year results reported by Raiskupet *et al.*<sup>[13]</sup> found a significant reduction in the maximum K, minimum K, and K value at the apex following standard CXL. In a recent letter to the editor, Kato *et al.*<sup>[19]</sup> compared the 5-year outcome between conventional and accelerated CXL, they found that the change in steep K was comparable up to 6 months

following CXL. However, continuous flattening was observed in conventional CXL but not accelerated CXL from 6 months onward up to the fifth year. Nonetheless, either stabilization or improvement in Kmax would indicate a beneficial effect of CXL. The variable outcomes among the CXL studies may result from the differences in age and ethnicity of the patients, the severity of keratoconus, riboflavin products, and irradiation protocols.<sup>[10,20,21]</sup>

In this study, there was a significant reduction in the anterior elevation at the apex from 21.42 to 18.53 μm; however, the change in posterior elevation was non-significant at the end of the fifth year compared to the baseline. This is similar to the 5-years results after standard CXL reported by Hashemi *et al.*<sup>[2]</sup> who observed a significant reduction in the front elevation from

13.92 to 11.45 μm; however, not the back elevation in the apex. Both CCT and TCT at the end of the fifth year were thinner than the preoperative measurements in our study. This corroborates with previous studies reporting a decrease in CCT or TCT following standard CXL.<sup>[22-24]</sup> TCT measured using the Orbscan throughout 3 years of follow-up was significantly lower than baseline, where the thinning was comparable between standard CXL and placebo.<sup>[1]</sup> In a comparative case series between standard and accelerated CXL in pediatric keratoconus patients, TCT in both groups was reduced at 2 years compared to the baseline, with a more significant thinning in the accelerated group.<sup>[25]</sup> Significant reduction in TCT has also been observed following transepithelial accelerated CXL.<sup>[26,27]</sup> Keratocyte apoptosis, changes in corneal hydration, collagen fibril, and extracellular matrix remodeling may explain the small; however, persistent corneal thinning that is observed not only after conventional CXL,<sup>[23]</sup> but conceivably, could account for the similar corneal thinning observation in accelerated and transepithelial CXL. The observed thinning could also be related to post-CXL stromal reflectivity changes detected using Scheimpflug imaging.<sup>[28]</sup>

In agreement with other published evidence, stabilization in CDVA was observed in our study.<sup>[7,12,29]</sup> Despite the significant flattening in all keratometric parameters and anterior elevation after accelerated CXL, CDVA showed non-significant improvement in the present study. Lang *et al.*<sup>[30]</sup> found that changes in a number of keratometric variables, pachymetry, and keratoconus indices correlated poorly with CDVA in both standards and accelerated CXL. They postulate that these measurements are an indirect reflection of the actual biomechanical disease process, which could partially explain the poor correlation. The relatively good baseline CDVA in our study (0.28 logMAR) might also explain why the improvement in CDVA was non-significant. Previous studies identified that eyes with CDVA of 0.3 logMAR or worse were more likely to have an improvement in CDVA after CXL.<sup>[31,32]</sup> Our regression analysis revealed that preoperative CDVA was the only factor associated with the amount of CDVA improvement. The negative association

**Table 2: Changes in parameters from baseline after accelerated corneal collagen crosslinking in mild-to-moderate and advanced keratoconus at 5 years**

Changes in	Mild moderate (n=5)	Advanced (n=14)	P
UDVA (logMAR)	0.19±0.71	-0.24±0.32	0.857
CDVA (logMAR)	0.07±0.30	-0.07±0.19	0.13
Manifest cylinder (D)	-0.58±1.14	-0.28±1.15	0.754
SEQ (D)	-1.91±2.59	0.14±5.44	0.260
Flattest keratometry (D)	0.78±0.58	-1.31±1.63	0.005*
Steepest keratometry (D)	0.24±0.89	-1.14±2.19	0.156
Mean keratometry (D)	0.52±0.50	-1.19±1.61	0.003*
Maximum keratometry (D)	1.08±1.26	-4.10±4.10	<0.001*
Thinnest pachymetry (μm)	-4.60±16.52	-17.86±46.19	0.754
Central pachymetry (μm)	-3.40±15.29	-16.07±37.85	0.444
Anterior elevation (μm)	2.80±0.84	-4.93±6.17	0.007*
Posterior elevation (μm)	4.20±1.92	-0.43±9.28	0.087

Mean values are presented in mean±standard deviation (SD). CDVA=Corrected distance visual acuity; UDVA=uncorrected distance visual acuity; SEQ=spherical equivalent. \*P<0.05

**Table 3: Univariable linear and logistic regressions of preoperative characteristics on postoperative outcomes and treatment failure following accelerated corneal collagen crosslinking**

Baseline characteristics	Change in Maximum Keratometry (D)			Change in CDVA (logMAR)			Treatment Failure		
	R <sup>2</sup>	β-Coefficient	P	R <sup>2</sup>	β-Coefficient	P	Odds ratio	P	95% CI
Age	0.001	-0.01	0.897	0.0003	-0.0003	0.948	0.92	0.221	0.81-1.05
Male sex	0.06	-2.38	0.293	0.003	-0.03	0.815	0.41	0.425	0.05-3.68
UDVA (logMAR)	0.003	0.79	0.855	0.005	0.05	0.823	13.47	0.94	0.06-3085.73
CDVA (logMAR)	0.12	-6.77	0.152	0.41	-0.66	0.003*	0.11	0.441	0.00-28.71
Manifest cylinder (D)	0.25	-1.25	0.029*	0.0001	-0.001	0.965	0.24	0.063	0.05-1.08
SEQ (D)	0.38	0.36	0.015*	0.02	-0.006	0.637	1.06	0.400	0.80 -1.39
Flattest keratometry (D)	0.35	-0.55	0.008*	0.005	-0.003	0.775	0.73	0.128	0.48-1.10
Steepest keratometry (D)	0.34	-0.44	0.009*	0.001	-0.001	0.895	0.67	0.077	0.43-1.04
Mean keratometry (D)	0.36	-0.51	0.007*	0.003	-0.002	0.836	0.66	0.104	0.40-1.09
Maximum keratometry (D)	0.55	-0.30	<0.001*	0.02	-0.003	0.525	0.74	0.040*	0.56-0.99
Thinnest pachymetry (μm)	0.16	0.04	0.086	0.02	-0.001	0.568	1.02	0.116	0.99-1.05
Central pachymetry (μm)	0.19	0.05	0.065	0.04	-0.001	0.443	1.02	0.226	0.99-1.05
Anterior elevation (μm)	0.41	-0.16	0.003*	0.05	-0.003	0.373	0.83	0.054	0.68-1.00
Posterior elevation (μm)	0.37	-0.08	0.006*	0.09	-0.002	0.216	0.91	0.042*	0.83-1.00

CDVA=Corrected distance visual acuity; UDVA=uncorrected distance visual acuity; SEQ=spherical equivalent. \*P<0.05

indicates that the improvement in visual acuity increases in those with worse preoperative CDVA, which is consistent with earlier studies in both conventional and accelerated CXL.<sup>[31-33]</sup>

We selected the change in Kmax as the dependent variable for corneal topography in our regression analysis because it is an informative biomarker of keratoconus progression and is consistently reported by randomized controlled trials comparing standard versus accelerated CXL for progressive keratoconus.<sup>[1,21]</sup> Kmax measured using the Pentacam is objective, quantitative, repeatable, and well represents the severity of the topographic distortion in keratoconus.<sup>[3]</sup> We found that in the preoperative manifest cylinder, all topographic and elevation parameters were associated with the postoperative change in Kmax. Baseline Kmax; however, had the greatest strength of association with the change in Kmax compared to the other preoperative characteristics. The prognostic value of preoperative Kmax on the effect of CXL remains controversial. Ting *et al.*<sup>[34]</sup> reported that a higher baseline Kmax was associated with progression after accelerated CXL; however, statistical significance was not achieved. Consistent with previous case series on standard and accelerated CXL,<sup>[33,35,36]</sup> our results also demonstrated a more pronounced effect in the advanced keratoconus subgroup despite the small subgroup sample size. Greenstein *et al.*<sup>[31]</sup> reported that the only independent predictor of improvement in Kmax following standard CXL was preoperative Kmax, where eyes with Kmax of more than 55 D were 5.4 times more likely to have 2 D more of flattening. This is particularly important for patients with advanced keratoconus eyes as they would be indicated for keratoplasty, thus accelerated CXL could be a potential treatment to delay keratoplasty. As reported in previous studies, accelerated CXL not only halts progression but results in significant corneal flattening.<sup>[12,29,34]</sup> In our study, we reported a mean corneal flattening of 2.74 D in the Kmax, with 11 of the 19 eyes (57.89%) experiencing a flattening of  $\geq 1$  D. It remains unclear why a greater flattening effect occurs in advanced keratoconus eyes; however, we hypothesize that the looser collagen fibers and a higher proportion of stroma get crosslinked in these thinner eyes and might account for this phenomenon. Furthermore, the effect of CXL is more deeply located in the corneal stroma in these advanced eyes due to the inherent thinner cornea.

We identified that flatter preoperative Kmax and smaller posterior elevation at the apex were more likely to have worsening of visual acuity or corneal topography after accelerated CXL. Moreover, the four eyes that lost  $>1$  line in CDVA had a baseline CDVA of 0.30 logMAR or better. The one eye had an increase in Kmax  $>1$  D had a baseline Kmax of 46.1 D and the CDVA improved by 0.43 logMAR by the end of 5 years. Preoperative CDVA was however not an independent predictor of treatment failure in our study. Toprak *et al.*<sup>[32]</sup> observed no change in CDVA in eyes with preoperative CDVA  $<0.3$  logMAR following standard CXL, whereas significant improvement at 1 year was found in eyes with preoperative CDVA  $\geq 0.30$  logMAR, where the change in Kmax was comparable between the groups. Approximately 3% of eyes lost two Snellen lines of CDVA at 1 year following standard CXL in a study by Koller *et al.*<sup>[16]</sup> the authors reported that preoperative CDVA better than 20/25 were identified as risk factors (OR = 18.18). In a large mid-European cohort, no progression was observed when all keratoconus eyes were analyzed; however, subgroup analysis of mild and moderate keratoconus eyes showed progression in the mean posterior keratometry, index of height deviation and TCT after both conventional and accelerated CXL.<sup>[12]</sup> These results suggest that early keratoconus eyes, despite progression, may not necessarily benefit from accelerated

CXL, and could result in worsening of CDVA as a result of topographic steepening in the long term and further add support to our findings that accelerated CXL is more effective in preventing progression in more advanced stages. Thus, patients with early keratoconus, particularly those with good baseline CDVA, should be appropriately counseled before undertaking accelerated CXL.

Our study's limitation includes the study design (non-randomized, non-comparative) and small sample size. Despite significant changes reported between follow-ups and baseline in several topographic, pachymetric, and elevation parameters in our study, these changes could also represent measurement variability of the Pentacam HR, which worsens in moderate to advanced keratoconus.<sup>[37]</sup> However, long-term evidence following accelerated CXL is currently lacking and to our knowledge, this study provides one of the most extended term data after accelerated CXL. Our results further support the long-term significant flattening in Kmax with stabilization of CDVA following accelerated CXL, which was more effective in advanced keratoconus eyes.<sup>[12]</sup> Previous studies reported steeping of  $>1$  D in Kmax following accelerated CXL in 16–17.9% of eyes.<sup>[33,38]</sup> Kuechler *et al.*<sup>[39]</sup> reported treatment failure (defined as Kmax progression of  $>1$  D) in 23% of 61 eyes with a baseline Kmax of  $>58$  D that underwent either standard or accelerated CXL. In our cohort, only one eye (5.3%) had  $>1$  D increase in Kmax postoperatively, which is consistent with published literature. We did not collect endothelial cell density data routinely in the fifth year of follow-up because the endothelial cell density at 1 year was comparable to baseline in our previous study.<sup>[14]</sup> Furthermore, there was no clinically detectable corneal decompensation during follow-up throughout the 5 years.

## Conclusion

In conclusion, accelerated CXL is effective in halting keratoconus progression and flattening the cornea. Topographic flattening was more effective in eyes with higher preoperative Kmax and visual acuity improvement was more substantial in eyes with worse baseline visual acuity. Preoperative Kmax is the strongest predictor of treatment failure. Further studies with larger sample size and different accelerated CXL protocols will help to validate these findings.

## Authors contributions

Conception and design: KHW, TCYC; data collection: RWYT, VWSC, JKML, VWYW, TCYC; analysis and interpretation of data: KHW; writing the manuscript: KHW; critical revision: all authors; supervision: TCYC. All authors read and approved the final manuscript. The requirements for authorship as stated earlier have been met, and each author believes that the manuscript represents honest work.

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## Conflicts of interest

There are no conflicts of interest.

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