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# Refractive Lenticule-Assisted Accelerated Corneal Cross-linking: A Three-Year Clinical Observation in Patients with Thin Keratoconus

Ying Li[1], Mingyan Wang[1], Linxin Guo[1], Dian Zhao[1] and Chunyang Zhou[1,2*]

## Abstract

**Background:** Accelerated corneal cross-linking (A-CXL) is unsuitable for thin keratoconus treatment. We developed refractive lenticule-assisted A-CXL by overlaying lenticules during A-CXL to optimize therapy for thin keratoconus. This retrospective study evaluates its 3-year efficacy and safety.

**Methods:** This study retrospectively included 63 eyes (42 cases) with progressive keratoconus who underwent A-CXL in our hospital from September 2017 to December 2020. The surgical method is determined based on the patients' corneal thickness. Patients received refractive lens-assisted A-CXL (10 cases with 18 eyes) were designated as Group A, while those underwent A-CXL alone (32 cases with 45 eyes) were classified

*Correspondence:
Chunyang Zhou, Ph.D.
zhouchunyang@cdutcm.edu.cn
Tel: +86139 8205 9090
Fax: +86139 8205 9090
Eye School of Chengdu University of Traditional Chinese Medicine, Ineye Hospital of Chengdu University of TCM, Chengdu, Sichuan, China

[1]Eye School of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China
[2]Ineye Hospital of Chengdu University of TCM, Chengdu, Sichuan, China



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as Group B. The follow-up duration for both groups was 3 years. Preoperative and postoperative evaluation (6 months, 12 months, 24 months, and 36 months) included best corrected visual acuity (BCVA), endothelial cell density (ECD), thinnest corneal thickness (TCT), keratoconus vertex back (Kvb) and corneal curvature. Any adverse events like delayed corneal healing, corneal infections, haze, etc. that occurred during this period should be recorded.

**Results:** During the follow-up period, no significant changes were observed in TCT, Kmax, K1, K2, or Kvb in Group A, while BCVA significantly improved at 36 months postoperatively ($P = 0.006$), and ECD significantly increased at 12 months postoperatively ($P = 0.016$). Over the same period, Group B showed decreases in TCT and ECD compared to baseline ($P < 0.05$), increases in anterior surface K1 and K2 values, and improvements in BCVA and Kmax ($P < 0.05$), with no significant change in Kvb. Both groups exhibited uneventful healing with no adverse events. Parameter Change Magnitude Comparison: i) During the 12-month postoperative period, Group A demonstrated more pronounced thickening of Kvb, decreases in TCT and K1, and ECD recovery compared to Group B. ii) During the 36-month postoperative period, Group A exhibited more substantial improvements in BCVA and more pronounced elevation in Kvb.

**Conclusion:** Over the 3-year follow-up period, the refractive lenticule-assisted A-CXL and A-CXL showed similar efficacy and safety in controlling the progression of keratoconus.

***Keywords:*** *Progressive keratoconus, ultrathin cornea, accelerated corneal cross-linking, A-CXL, refractive lenticule, Small Incision Lenticule Extraction, SMILE, Refractive Lenticule-assisted A-CXL*

## 1. Background

Keratoconus (KC) is an ocular disorder characterized by central or para-central expansion and thinning of the cornea, resulting in a conical protrusion of the corneal tissue anteriorly [1]. It usually onset during adolescence, often affecting both eyes simultaneously, with a subtle and insidious presentation. and be considered one of the significant causes of blindness in our country. Corneal cross-linking (CXL) is a common and effective method for treating KC [2]. It induces a chemical cross-linking reaction between the amino groups of collagen fibers, triggered by riboflavin and ultraviolet A (UVA) rays, to enhance the biomechanical stability of collagen fibers, reinforcing the cornea's structural integrity against ectatic deformation, and thereby halting the progression of KC [3-5]. Conventional CXL, adhering to the Dresden protocol [6], involves the removal of corneal epithelium followed by exposure of the treated eye to UVA radiation at an intensity of 0.36 mW/cm² for a duration of 30 minutes. The process resulted in

cytotoxic effects on endothelial cells within a depth of 400 μm. Consequently, this approach is not suitable for KC with a thickness of less than 400 μm following epithelial debridement [7, 8]. Furthermore, long time of radiation elevates the risk of epithelial complications, infection, and other potential injury to the corneal endothelium and other intraocular structures.

Over the past two decades, a variety of modified CXL protocols have been developed and implemented in clinical. A-CXL is generated based on the Bunsen-Roscoe law, which employs high-intensity UVA irradiation to reduce the duration of ultraviolet exposure [9]. This approach minimizes patient discomfort associated with prolonged irradiation and decreases the risks of corneal infection, dehydration, and thinning. Extensive research has demonstrated its efficacy and safety [10, 11]. However, it is still not suitable for patients with thin keratoconus. For Asian and African populations, who inherently have thinner corneas [12, 13]. It is particularly urgent to develop modified surgical techniques for the treatment of thin keratoconus. There are several modified CXL procedures have been developed in clinical for the treatment of KC with thin corneal, such as the use of hypotonic riboflavin to swell the corneal stroma [14], transepithelial CXL (TE-CXL) [15], contact lens-assisted CXL (CACXL) [16, 17], etc.

In 2015, Sachdev *et al*. first reported a technique utilizing SMILE-derived donor lenticules to augment traditional CXL by expanding stromal thickness in thin corneas [18]. Subsequently, in 2024, they published 5-year follow-up results of this procedure [19], demonstrating an average reduction in Kmax of 4.30D in the treated eyes, with significant improvements in UDVA and CDVA without any complications or significant endothelial cell loss observed during the follow-up period. Cagini *et al*. similarly reported favorable outcomes [20]. Refractive lens-assisted CXL augments stromal depth via SMILE-derived allogenic lenticule overlay to minimize radiation-induced damage to corneal endothelium and intraocular tissues in thin KC. While preliminary studies show encouraging results, long-term clinical data are required to fully validate its safety and efficacy.

In an effort to minimize damage to the corneal endothelium and other intraocular tissues from radiation while shortening surgical time, we attempted to cover the refractive lenticule on the eyes undergoing A-CXL surgery (refractive lenticule-assisted A-CXL) to provide a novel surgical option for patients with thin keratoconus. Herein, we report a retrospective clinical study to evaluate the efficacy and safety of refractive lenticule-assisted A-CXL over a 3-year follow-up period.

## 2. Materials and Methods

This retrospective study enrolled 63 eyes from 42 patients who underwent A-CXL for keratoconus at the Refractive Surgery Department of Ineye Hospital of Chengdu University of TCM in China between September 2017 and December 2020. Patients with a predicted corneal stromal thickness of less than 400 μm following epithelial debridement were treated with refractive lenticule-assisted A-CXL and assigned to Group A (10 cases with 18 eyes). The rest of the patients, who had a thicker stroma, received conventional A-CXL only and were assigned to Group B (32 cases with 45 eyes). The study adhered to the tenets of declaration of Helsinki. Ethics committee approval was taken (protocol number 2021yh-016), and written informed consent was obtained from all participants.

### 2.1. Inclusion Criteria

i) A definitive diagnosis of progressive keratoconus. ii) No history of contact lens wear within the past month. iii) Age between 9 and 37 years. iv) No other corneal diseases expect keratoconus. v) No family history of hereditary diseases.

### 2.2. Exclusion Criteria

i) Acute keratoconus. ii) History of poor epithelial healing after corneal trauma. iii) Severe ocular comorbidities. iv) Systemic conditions affecting corneal health or surgical recovery. v) Previous corneal surgery. vi) Allergic reactions during treatment. vii) Female patients who are lactating or pregnant. viii) Severe psychological or psychiatric disorders. ix) Inability to complete the required follow-up.

Preoperative and postoperative evaluation (6 months, 12 months, 24 months, and 36 months) included the assessments of BCVA, slit lamp examination of the anterior segment, fundus examination, ECD measurement, and corneal topography. Visual acuity was assessed using the International Standard Visual Acuity Chart and recorded in logMAR. Fundus examination was performed by Dayton. ECD were obtained by TOMEYEM-400. Topography and curvature of the anterior and posterior corneal surfaces were captured using the Sirius System (Schwind, CSO SpA, Italy). All measurements were taken by a trained ophthalmologist with over 10 years of experience.

### 2.3. Surgical Technique

#### 2.3.1. Refractive Lenticule-assisted A-CXL

##### 2.3.1.1. Lenticule Acquisition

Refractive lenticules were obtained from patients underwent SMILE correction for myopia. The donor cases for lenticules were checked preoperatively for no infectious diseases. The thickness of the lenticules was determined by the actual need for stromal expansion in patients receiving A-CXL. After extraction, the micro-lenticules were placed in a balanced salt solution.

##### 2.3.1.2. Surgical Technique

The procedure was performed under topical anesthesia and aseptic conditions. After removing the central 9 mm area of corneal epithelium using 20% ethanol and an epithelial scraper, VibeX Rapid riboflavin solution (0.1% riboflavin salt solution with hydroxypropyl methylcellulose) was applied every 30 seconds for a total of 10 minutes. The eye was then flushed with balanced salt solution, and the allogeneic corneal stromal lenticule was placed on the stromal bed of the operative eye, centered and spread evenly. Subsequently, the UV Crosslinking Accelerator (Avedro Inc, USA) was used to irradiate the surgical eye with UV-A pulsed mode for 8 minutes (UV wavelength 365 nm, irradiance 30 $mW/cm^2$, total irradiation energy 7.2 $J/cm^2$). Balanced salt solution drops were administered during the procedure to keep the cornea moist. After UV exposure, the corneal stromal lenticule was removed, the cornea was rinsed with balanced salt solution, and a bandage contact lens was placed on the operative eye to conclude the surgery.

#### 2.3.2. Conventional A-CXL

Surgical Technique: The procedure was performed under topical anesthesia and aseptic conditions. Initially, the central 9 mm area of the corneal epithelium was debrided using 20% ethanol solution and an epithelial scraper. Subsequently, VibeX Rapid riboflavin solution was applied every 30 seconds for a total of 10 minutes. After rinsing with balanced salt solution, the UV Crosslinking Accelerator (Avedro Inc, USA) was used to irradiate the surgical eye with continuous mode for 4 minutes (UV wavelength 365 nm, irradiance 30 mW/cm², total irradiation energy 7.2 J/cm²). Balanced salt solution drops were used to maintain corneal hydration during the UV exposure. Following the irradiation, the conjunctival sac was washed with balanced salt solution again, and a bandage contact lens was placed on the operative eye to complete the surgery.

### 2.4. Statistical Analysis

Data analysis was performed using SPSS 26.0. Normality and variance homogeneity were assessed for all variables. Normally distributed and variance-homogeneous continuous data are expressed as mean ± standard deviation ($\bar{x} \pm s$). Repeated measures ANOVA was used to assess within-group changes over time, with LSD-t tests for post-hoc analysis if significant differences were found. Independent samples t-tests were utilized for between-group comparisons. Non-normally distributed or variance-heterogeneous data are presented as median [interquartile range, M (P25, P75)], with Friedman tests for within-group comparisons and Bonferroni-adjusted post-hoc tests following significant findings. Wilcoxon rank-sum tests were employed for between-group contrasts. A $P$-value < 0.05 denoted statistical significance.

## 3. Results

### 3.1. Study Subjects

In this study, patients were allocated to different surgical methods based on corneal thickness, resulting in baseline differences between two groups that precluded intergroup comparisons. The baseline characteristics in the two groups are as follows in (Table 1 & Table 2).

**TABLE 1:** Baseline characteristics of study participants.

| **Group** （n= patients number） | **Gender** Male | Female | **Age** |
|---|---|---|---|
| Group A（n=10） | 6 | 4 | 17（15,29） |
| Group B（n=32） | 19 | 13 | 20（17,25） |

**TABLE 2:** Baseline characteristics of study eyes.

| **Group** （n=eyes number） | **BCVA** | **UCVA** | **ECD** |
|---|---|---|---|
| Group A（n=18） | 1.10(0.72,1.26) | 0.40(0.16,1.16) | 2614.11±341.193 |
| Group B（n=45） | 1.00(0.70,1.30) | 0.30(0.10,0.61) | 2873.36±261.648 |
| *t/Z* | -0.163 | 1.392 | 2.156 |
| *P* | 0.870 | 0.164 | 0.057 |

### 3.2. Outcomes of Efficacy Metrics

In Group A, no statistically significant differences were observed in TCT, Kvb, Kmax, K1 and K2 at all time points before and after surgery ($P > 0.05$). BCVA showed a significant improvement during the follow-up period ($P = 0.030$), with a particularly notable improvement at 36 months postoperatively ($P = 0.006$). Detailed data are presented in (Table 3).

**TABLE 3:** Variations in TCT, corneal curvature, Kvb, and BCVA across time in Group A.

| Group | Parameter | Preoperative | 6mo postoperative | 12mo postoperative | 24mo postoperative | 36mo postoperative | $F/\chi^2, P$ |
|---|---|---|---|---|---|---|---|
| GROUP A (n=18) | BCVA[M(P25,P75), logMAR] | 0.4(0.16,1.16) | 0.10(0.05,0.66) | 0.10(0.00,0.07) | 0.10(0.10,0.61) | 0.10(-0.04,0.61)[a] | 15.807,=0.030 |
| | TCT[M(P25,P75), μm] | 414(385,419) | 388(374,393) | 395(370,403) | 395(383,412) | 399(380,407) | 7.514,=0.111 |
| | $K_{max}$(x±s, D) | 58.43±4.95 | 58.31±4.13 | 56.99±5.64 | 57.75±5.99 | 57.69±6.14 | 1.381,=0.280 |
| | K1(x±s, D) | 49.49±4.83 | 49.26±4.26 | 49.13±4.83 | 49.52±5.22 | 49.13±4.88 | 0.403,0.674 |
| | K2(x±s, D) | 52.20±4.67 | 52.31±4.56 | 51.97±5.48 | 52.70±5.35 | 51.79±5.41 | 0.699,=0.599 |
| | Kvb(x±s, μm) | 91.78±51.36 | 94±48.70 | 104.56±40.78 | 104.56±42.95 | 105.44±43.92 | 5.112,=0.054 |

In Group B, significant changes were detected in BCVA, TCT, Kmax, K1, and K2 at all time points before and after surgery ($P < 0.05$), while Kvb exhibited no statistically significant changes ($P > 0.05$). Postoperative TCT values were significantly lower than preoperative measurements at all time points ($P < 0.001$, $P = 0.011$, $P = 0.001$, $P = 0.003$), with the most substantial reduction observed at 6 months postoperatively; however, a thickening trend was noted from 12 to 36 months postoperatively. Kmax showed a significant decrease at 36 months postoperatively compared to baseline ($P = 0.007$). K1 and K2 values significantly increased at 6 months postoperatively ($P = 0.001$, $P = 0.009$) and then trended downward. BCVA demonstrated significant improvement during follow-up ($P = 0.026$). Detailed data are presented in (Table 4).

**TABLE 4:** Variations in TCT, corneal curvature, Kvb, and BCVA across time in Group B.

| Group | Parameter | Preoperative | 6mo postoperative | 12mo postoperative | 24mo postoperative | 36mo postoperative | $F/\chi^2, P$ |
|---|---|---|---|---|---|---|---|
| GROUP B | BCVA[M(P25,P75), logMAR] | 0.30(0.10,0.61) | 0.30(0.10,0.76) | 0.10(0.00,0.30) | 0.10(0.00,0.30) | 0.10(0.00,0.35) | 11.063,0.026 |
| | TCT(x±s, μm) | 483.29±22.28 | 469.91±24.95 | 478.77±23.97 | 474.93±27.88 | 475.54±25.80 | 13.519,＜0.001 |
| | $K_{max}$ [M(P25,P75), D] | 51.39(48.89,57.83) | 51.23(49.31,56.68) | 50.89(48.81,55.57) | 51.10(48.17,56.30) | 51.41(49.15,55.87)[a] | 22.693,＜0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| （n=45） | K1 [M(P25,P75)，D] | 44.79(43.16,46.50) | 45.02(43.39,47.32) | 44.84(43.19,47.69) | 44.58(43.22,47.82) | 44.62(43.18,47.46) | 16.73,=0.02 |
| | K2 [M(P25,P75)，D] | 47.16(45.75,52.84) | 47.77(46.52,53.41) | 47.79(45.87,51.72) | 46.89(45.73,52.09) | 47.31(45.76,51.70) | 35.88,＜0.001 |
| | Kvb(x±s, μm) | 47.00(27.50,64.50) | 46.00(29.00,66.00) | 45.00(27.50,64.00) | 43.00(31.00,68.00) | 44.00(25.00,65.34) | 5.808,＝0.214 |

### 3.3. Safety Outcomes

During the 3-year follow-up period of this retrospective study, patients in both groups successfully had their corneal contact lenses removed 4 to 7 days postoperatively, and the corneal epithelium of the surgical eyes healed completely. As of the final follow-up, no lens or retinal photodamage was observed in either group. Additionally, there were no complications such as delayed healing of the corneal epithelium, aseptic or infectious stromal infiltration, subepithelial haze, corneal endothelial decompensation, or corneal scarring. The incidence of complications between the two groups showed no statistically significant difference ($P > 0.05$).

The ECD in Group A increased significantly from preoperative to 12 months postoperative ($P = 0.016$), with a mean increase from 2614.11 to 2731.89 cells/mm². In contrast, the ECD of Group B significantly decreased ($P = 0.014$), with a median decrease from 2856 to 2792 cells/mm². Detailed data are presented in (Table 5).

**TABLE 5:** Changes in ECD at 12 months postoperatively in Group A and B.

| Group | Parameter | Preoperative | 12mo postoperative | *t/Z, P* |
|---|---|---|---|---|
| GROUP A | ECD （x±s cells/mm$^2$） | 2614.11±341.19 | 2731.89±309.00 | -3.038, 0.016 |
| GROUP B | ECD [M(P25,P75) cells/mm$^2$] | 2856(2708.5,3031) | 2792(2593,2983.5) | -2.245, 0.014 |

### 3.4. Comparison of the Changes in Indicators between the Two Groups during the Follow-up Period

Define the changes in observation indicators during the 12-month postoperative period as $\Delta_{12}$. We found there were no statistically significant differences between the two groups in terms of $\Delta_{12}$BCVA, $\Delta_{12}$Kmax, and $\Delta_{12}$K2 ($P > 0.05$). Concurrently, we observed Kvb decreased in Group B but increased in Group A ($P = 0.012$). Group B also showed a less pronounced reduction in TCT ($P = 0.013$), while Group A exhibited a greater decline in K1 ($P = 0.036$). Notably, at 12 months postoperatively, ECD declined in Group B but increased significantly in Group A ($P = 0.002$). Detailed data are provided in (Table 6).

Define the changes in observation indicators during the 24-month postoperative period as $\Delta_{24}$. There were no statistically significant differences in the changes of various indicators between the two groups. Detailed data are provided in (Table 7).

**TABLE 6:** Comparison of $\Delta_{12}$BCVA,$\Delta_{12}$TCT, $\Delta_{12}$Kmax, $\Delta_{12}$K1, $\Delta_{12}$K2 $\Delta_{12}$Kvb, and $\Delta_{12}$ECD between the Group A and Group B.

| **Group** | **$\Delta_{12}$BCVA** [M(P25,P75), logMAR] | **$\Delta_{12}$TCT** (x±s, μm) | **$\Delta_{12}$Kmax** [M(P25,P75), D] | **$\Delta_{12}$K1** [M(P25,P75), D] | **$\Delta_{12}$K2** [M(P25,P75), D] | **$\Delta_{12}$Kvb** [M(P25,P75), μm] | **$\Delta_{12}$ECD** [M(P25,P75) cells/mm$^2$] |
|---|---|---|---|---|---|---|---|
| Group A | -0.12(-0.40,0) | -16.44±18.53 | -2.00(-2.53,0.36) | -0.55(-0.86,0.48) | -0.77(-1.16,0.82) | 9.00(-0.50,28.50) | 144(41,200) |
| Group B | 0(-0.30,0.10) | -4.52±11.37 | -0.41(-1.56,0.31) | 0.20(-0.24,0.63) | -0.07(-0.74,0.36) | -1.00(-4.50,2.00) | -45(-164,32.5) |
| *Z/t*, *P* | -1.370,0.171 | 2.564,0.013 | -1.079,0.280 | -2.101,0.036 | -1.056,0.291 | 2.510,0.012 | -3.087,0.002 |

**TABLE 7:** Comparison of $\Delta_{24}$BCVA, $\Delta_{24}$TCT, $\Delta_{24}$Kmax, $\Delta_{24}$K1, $\Delta_{24}$K2, and $\Delta_{24}$Kvb between the Group A and Group B.

| **Group** | **$\Delta_{24}$BCVA** [M(P25,P75), logMAR] | **$\Delta_{24}$TCT** (x±s, μm) | **$\Delta_{24}$Kmax** [M(P25,P75), D] | **$\Delta_{24}$K1** [M(P25,P75), D] | **$\Delta_{24}$K2** [M(P25,P75), D] | **$\Delta_{24}$Kvb** (x±s, μm) |
|---|---|---|---|---|---|---|
| Group A | -0.18(-0.40,0) | -9.56±12.40 | -1.46(-2.04,1.10) | -0.27(-0.84,0.92) | -0.97(-1.44,3.05) | 12.78±16.12 |
| Group B | -0.08(-0.30,0.09) | -8.36±16.20 | -0.77(-1.78,0.26) | 0.11(-0.27,0.38) | -0.33(-1.13,0.26) | 0.42±7.09 |
| *Z/t*, *P* | -1.060,0.289 | 0.209,0.835 | -0.499,0.618 | -0.963,0.335 | -0.232,0.816 | -2.257,0.052 |

Define the changes in observation indicators during the 36-month postoperative period as $\Delta_{36}$. There were no statistically significant differences in $\Delta_{36}$TCT, $\Delta_{36}$Kmax, $\Delta_{36}$K1 and $\Delta_{36}$K2 between the two groups ($P > 0.05$). Moreover, we observed Kvb decreased in Group B but increased in Group A ($P = 0.012$). Additionally, Group A exhibited significantly greater changes in BCVA. Detailed data are provided in (Table 8).

**TABLE 8:** Comparison of $\Delta_{36}$BCVA,$\Delta_{36}$TCT, $\Delta_{36}$Kmax, $\Delta_{36}$K1, $\Delta_{36}$K2, and $\Delta_{36}$Kvb between the Group A and Group B.

| **Group** | $\Delta_{36}$**BCVA** [M(P25,P75), logMAR] | $\Delta_{36}$**TCT** (x±s, μm) | $\Delta_{36}$**Kmax** [M(P25,P75), D] | $\Delta_{36}$**K1** [M(P25,P75), D] | $\Delta_{36}$**K2** [M(P25,P75), D] | $\Delta_{36}$**Kvb** (x±s, μm) |
|---|---|---|---|---|---|---|
| Group A | -0.30(-0.48,-0.11) | -11.00±8.94 | -1.15(-2.48,1.605) | -0.47(-0.80,0.38) | -0.77(-1.44,0.60) | 13.67±13.33 |
| Group B | -0.08(-0.30,0.09) | -7.75±16.66 | -0.83(-2.39,0.08) | 0.40(-0.345,0.69) | -0.51(-1.04,0.22) | -0.72±6.22 |
| *Z/t*, *P* | -2.050,0.04 | 0.838,0.412 | -0.244,0.807 | -1.486,0.137 | -0.522,0.601 | -3.170, 0.012 |

## 4. Discussion

In this study, surgical approaches were stratified by corneal thickness, yielding significant baseline disparities in select clinical parameters between groups, which precluded direct intergroup comparisons of the metrics. However, considering that baseline demographic characteristics (age, sex) and preoperative visual parameters (UCVA, BCVA) were statistically balanced between the two groups ($P > 0.05$), we can evaluate the efficacy and safety of refractive lenticule-assisted A-CXL by analyzing longitudinal trends in postoperative observational metrics and comparing within-group changes (Δvalues) in each parameter after surgery.

Over the course of the 3-year follow-up, we observed that the mean BCVA (LogMAR) in the Group A improved from 0.4 preoperatively to 0.1 postoperatively, with no significant changes in TCT, Kmax, anterior corneal K1 and K2 values, or Kvb. These findings suggest that refractive lenticule-assisted A-CXL effectively and stably controlled the progression of thin keratoconus, demonstrating similar efficacy to that of conventional A-CXL.

The results of this study reveal that refractive lenticule-assisted A-CXL demonstrates better improvement in BCVA at 3 years postoperatively. This effect may be associated with alterations in the arrangement of collagen fibers in the corneal stroma, enhanced biomechanical strength, and improved corneal curvature [21]. Previous studies have indicated that patients with poorer baseline visual acuity and steeper corneal curvature may experience greater improvements following CXL [22]. In this study, the steeper preoperative corneal curvature in Group A may explain the more significant improvement in BCVA compared to Group B. Furthermore, the covering pressure of refractive lenticule can transiently increase epithelial permeability, assisting riboflavin in penetrating into the stromal layer. meanwhile, it reduces tear flushing, prolongs the retention time of riboflavin within the stroma, promotes deep collagen cross-linking, and enhances the cornea's resistance to ectasia [23]. This mechanism may also explain the more significant improvement in BCVA observed in Group A.

In comparison to the patients accepted refractive lenticule-assisted A-CXL, who showed stable TCT levels during the follow-up period, the patients that underwent A-CXL only experienced a decrease in

TCT of approximately 13 μm at 6 months postoperatively, followed by a gradual and fluctuating increase. This pattern of initial decrease and subsequent increase in TCT has also been observed in studies by Konrad and Arbelaez [24, 25]. The early decrease in TCT may be associated with the compression of collagen fiber spacing due to the cross-linking reaction [26], apoptosis of corneal stromal cells, and changes in the composition of glycosaminoglycans and proteoglycans [27]. Over time, as the diameter of the corneal collagen fibers thickens and stromal cell regeneration occurs, the corneal thickness may increase once again. We speculate that refractive lenticule makes the ultraviolet light scatter more uniformly on the corneal surface, avoiding local energy accumulation that may cause thermal damage or excessive collagen contraction, thereby reducing postoperative TCT regression.

Corneal curvature plays a crucial role in the diagnosis, grading and evaluation of the progression of KC [28]. It serves as a critical tool for assessing the efficacy of CXL. Kmax is a pivotal metric for assessing the success of CXL. A progression of Kmax by ≥ 1.0 D within one year can be regarded as indicative of the progression of KC [29]. In our study, both groups effectively controlled the progression of Kmax. However, compared to Group A, which exhibited stable anterior corneal curvature, Group B showed a transient increase in K1 and K2 in the early postoperative period. This temporary elevation was not significant. It may be attributed to corneal edema and epithelial remodeling occurring in the early postoperative phase (1-3 months) after A-CXL, which consequently gives rise to an elevation in irregular astigmatism. There were no significant differences in the changes of K1 and K2 values between the two groups during the 2-year and 3-year postoperative periods. Given the characteristics of KC and its progression, any reduction, stabilization, or deceleration of the increase in corneal curvature after surgery may serve as an indicator of a positive treatment outcome for KC management [30]. Therefore, it can be concluded that during the 3-year follow-up period, the two surgical techniques demonstrated comparable efficacy in inhibiting the progression of corneal curvature on the anterior surface in KC.

The expansive changes in KC typically initiate at the posterior corneal surface [31]. Additionally, the data of posterior surface remain unaffected by the ablation of the epithelial flap during surgery or by corneal epithelial healing, providing a more accurate and sensitive reflection of the progression of KC. During the follow-up period of this study, no significant changes in Kvb were observed in both groups, indicating that both approaches effectively mitigated the expansion of the corneal posterior surface. However, the intergroup comparison of changes in Kvb during the follow-up period revealed an increasing trend in Group A, whereas Group B exhibited a slight decrease. This could be attributed to postoperative corneal haze or interference from cross-linking lines, which may have affected the corneal topography measurements, leading to artifacts.

In terms of safety, no complications were observed throughout the follow-up period for both surgical modalities. Furthermore, no significant endothelial cell loss was observed in both groups, demonstrating similar safety profiles for corneal endothelium. Due to the refractive lenticule's coverage, which establishes an optical barrier for endothelial cytoprotection, refractive lenticule-assisted A-CXL may exhibit greater endothelial friendliness [32].

Hypoosmotic riboflavin can cause transient corneal swelling. However, the actual cross-linking depth after dehydration may be less than the cross-linking depth measured during the operation [33]; TE-CXL preserves the corneal epithelium, which can enhance patient comfort and reduce the risk of keratitis. Nevertheless, some researchers have suggested that the riboflavin film and the soaked corneal epithelium may absorb incident ultraviolet light [34], thus leading to attenuation of the cross-linking effect. CACXL employs a contact lens to temporarily augment corneal thickness, which affects oxygen diffusion. Moreover, the ultraviolet transmittance of the contact lens diverges from that of the corneal stroma; this disparity impedes ultraviolet absorption, thereby compromising the cross-linking efficacy [35]. Refractive lenticule-assisted A-CXL augments corneal thickness by using allogeneic refractive lenticules that better match the patient's own corneal characteristics. This approach maintains the cross-linking effect of CXL while improving patient comfort, striking a balance between safety and therapeutic effectiveness.

In summary, refractive lenticule-assisted A-CXL for thin keratoconus demonstrates comparable efficacy and safety to conventional A-CXL in the management of keratoconus over the medium to long term (3 years).

**Limitations**

The study utilized a non-randomized design, and the sample size in Group A was relatively small, which may have introduced selection bias. Additionally, the surgical technique has not undergone statistical comparison with alternative therapeutic modalities for thin keratoconus (e.g., CACXL, TE-CXL). Further investigations are necessary to fully assess its relative benefits and limitations.

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**Author Contributions**

YL: Data curation, Statistical analysis, Writing - original draft, Writing - review& editing. MW: Conceptualization, investigation, data collection. LG: Conceptualization, investigation, data collection. DZ: Statistical analysis, Writing - review & editing. CZ: Conceptualization, supervision, project administration, Writing - review & editing.

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None.

**Data Availability**

In our institutional policy, it is not stated that the data should be made public and a data and material transfer agreement should not allow further transfer of data without the provider’s prior written consent. However, the data can be made available upon request from the corresponding author, who is a member of this team.

**Ethical Approval and Consent to Participate**

The research protocol was approved by the Ethics Committee of Ineye Hospital of Chengdu University of TCM (Ethical Approval Number: 2021yh-026). This study was conducted in strict accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical frameworks. Prior to enrollment, all patients or their guardians provided written informed consent. Additionally, written consent for

both study participation and publication was secured from either the participants themselves or their legal guardians at the time of admission.

## Consent for Publication

Not Applicable.

## Competing Interests

None.

## Abbreviations

**CXL:** Corneal Cross-Linking
**UVA:** Ultraviolet A
**A-CXL:** Accelerated Corneal Cross-Linking
**RLA-ACXL/Refractive Lenticule-Assisted A-CXL:** Refractive Lenticule-assisted Accelerated Corneal Cross-Linking
**KC:** Keratoconus
**BCVA:** Best Corrected Visual Acuity
**ECD:** Endothelial Cell Density
**TCT:** Thinnest Corneal Thickness
**Kvb:** Keratoconus Vertex Back
**Kmax:** Anterior Corneal Surface Vertex K Value
**K1:** Anterior Corneal K1 Value
**K2:** Anterior Corneal K2 Value

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