

One-year structural and functional outcomes of accelerated epithelium-off corneal cross-linking in keratoconus

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Received: 2025-10-27 Accepted: 2026-04-21

Abstract

• **AIM:** To evaluate the structural and functional outcomes of accelerated epithelium-off corneal collagen cross-linking (CXL) in patients with keratoconus (KC) 1y after treatment.

• **METHODS:** This retrospective study included patients who underwent an accelerated epi-off CXL for progressive KC at the Department of Ophthalmology, Sveti Duh University Hospital, Zagreb, Croatia, between January and December 2023. The protocol consisted of epithelial removal, riboflavin 0.1% instillation for 3min, and ultraviolet-A (UVA) irradiation at 9 mW/cm² for 10min. Pentacam HR was used to assess keratometric parameters (Kmax, Kmean), curvature-based indices [index of surface variance, index of vertical asymmetry, keratoconus index, central keratoconus index, index of height asymmetry (IHA), index of height decentration, minimum sagittal curvature (Rmin)], pachymetry-based indices [central corneal thickness (CCT), average pachymetric progression index, maximum Ambrósio relational thickness], Belin/Ambrósio deviation, and the ABCD progression system preoperatively and at 12mo.

• **RESULTS:** A total of 45 eyes from 45 patients (mean age: 29.1±6.2y) were included in the study. One year after CXL treatment, only Kmax front (55.20 to 55.00 D) showed a statistically significant decrease among the keratometric parameters. A statistically significant reduction was observed in all curvature-based indices, except for

IHA, which did not reach statistical significance, whereas Rmin (6.11 to 6.14 mm) showed a statistically significant increase. Additionally, CCT, anterior radius of curvature (ARC), and best-corrected distance visual acuity (BCVA) also demonstrated statistically significant increase.

• **CONCLUSION:** Accelerated epi-off CXL results in significant structural and functional improvements in KC at the 1-year follow-up. Decreased Kmax and curvature indices, increased Rmin, CCT, and ARC, and improved BCVA indicate better corneal regularity, biomechanical stability, and functional vision, with ABCD analysis confirming disease stabilization.

• **KEYWORDS:** keratoconus; corneal cross-linking; corneal topography; corneal tomography; accelerated epithelium-off

DOI:10.18240/ijo.2026.10.10

Citation: Čubela I, Miletić D, Kuzmanović Elabjer B, Ramić S, Pavlović I, Šarić D, Bušić M. One-year structural and functional outcomes of accelerated epithelium-off corneal cross-linking in keratoconus. *Int J Ophthalmol* 2026;19(10):1964-1970

INTRODUCTION

Keratoconus (KC) is a form of corneal ectasia characterized by progressive thinning and cone-like protrusion of the cornea, resulting in irregular astigmatism, myopia, and reduced visual acuity^[1]. In advanced stages, corneal hydrops and scarring may require more aggressive treatment, such as a corneal transplantation^[2]. The only method that has been proven to be safe and effective treatment for slowing or stopping the progression of KC is corneal cross-linking (CXL) with riboflavin and ultraviolet-A (UVA) light^[3]. The accelerated epithelium-off (epi-off) CXL protocol involves applying UVA light at 370 nm with an intensity of 9.0 mW/cm² for 10min with comparable efficacy and safety profile to the standard protocol. Clinically, this approach provides the benefits of reduced treatment time, improved patient comfort, and faster visual recovery^[4-6].

Modern corneal tomography systems, such as the Pentacam HR, based on Scheimpflug imaging, enable early detection and longitudinal monitoring of KC.

Among the most clinically relevant anterior surface parameters are mean keratometry (Kmean) and maximum keratometry (Kmax), which provide insight into the steepening of the cornea during disease progression and after therapeutic intervention such as CXL^[7-8].

Evaluation of corneal thickness, including central corneal thickness (CCT) and the thinnest point of the cornea, remains essential for staging KC and identifying progression^[9]. Topometric indices such as the index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central KI (CKI), index of height asymmetry (IHA), and index of height decentration (IHD) are sensitive indicators of corneal irregularity and asymmetry that support the diagnosis of subclinical and clinical KC^[7,10]. In addition, minimum sagittal curvature (Rmin) reflects central steepening and is commonly used in progression analyses^[10].

Pachymetric progression indices, such as the average pachymetric progression index (PPIavg) and the maximum Ambrósio relational thickness (ARTmax), are essential for identifying focal corneal thinning patterns. Belin/Ambrósio deviation (BAD_D) integrates anterior and posterior elevation with pachymetric data to detect ectatic changes by comparing corneal elevations to both a standard best-fit sphere (8.0 mm zone) and an “enhanced reference surface”, which excludes the 3.0–4.0 mm zone around the thinnest point to better highlight localized ectatic deformation^[9,11].

The Belin-Ambrósio ABCD progression system provides a robust framework for disease classification. Parameter A represents the anterior radius of curvature (ARC, mm), parameter B the posterior radius of curvature (PRC, mm), parameter C the thinnest corneal thickness (TCT, μm), and parameter D the best-corrected distance visual acuity (BCVA, Snellen lines). The latter is not machine-generated and must be entered manually by the user. These are all measured within a 3.0 mm zone centered on the corneal thinnest location (CTL), and together they capture both morphological and functional aspects of the disease. The ABCD progression display enables sensitive tracking of corneal changes over time and is particularly valuable for monitoring stability after CXL^[10-13].

Monitoring a comprehensive range of parameters provides a robust and objective framework for the assessment of KC. Given the multifactorial and complex nature of the disease, reliance on a single parameter may not fully capture subtle structural and functional changes. Therefore, the combined evaluation of keratometric values, curvature-based indices, pachymetric measurements, and composite indices allows for a more sensitive detection of disease progression and

a more accurate assessment of treatment response. This multidimensional approach enhances the ability to identify early changes, improves the reliability of follow-up, and supports more informed and individualized clinical decision-making in the management of KC^[7-13].

PARTICIPANTS AND METHODS

Ethical Approval The study adhered to the principles of the 1964 Declaration of Helsinki and its subsequent revisions for research involving human participants. All patient information was managed in strict compliance with confidentiality and data protection regulations. Ethical approval was obtained from the Institutional Review Board of Sveti Duh University Hospital (approval number 03-549, from 27 January 2025). Due to the retrospective design and the utilization of anonymized data obtained during standard clinical care, the ethics committee waived the necessity for patient informed consent. No identifying patient data was utilized, and no experimental procedures were conducted.

Participants A retrospective study included patients who underwent the CXL procedure for progressive KC at the Department of Ophthalmology, Sveti Duh University Hospital, Zagreb, Croatia, between January and December 2023. Inclusion criteria were age older than 18y and progressive KC, defined as an increase in Kmax of ≥ 1.0 diopter (D) and/or corneal thinning of ≥ 10 μm over a 6–12-month follow-up period^[14]. The exclusion criteria were pregnancy, corneal opacity, a history of any eye surgery, previous ophthalmic herpes infection, a past diagnosis of uveitis, diabetes mellitus, collagen vascular diseases, and corneal stromal thickness below 400 μm .

Methods The preoperative evaluation included anamnesis, distance visual acuity assessment, slit lamp examination, and imaging utilizing the Scheimpflug imaging system Pentacam HR (Oculus, Germany).

In all cases, an accelerated epi-off CXL protocol was used. All patients received preoperative treatment with tetracaine hydrochloride 0.5% (Tetrakain 0.5%, Gradska ljekarna Zagreb, Croatia) and periocular povidone-iodine 10% (Betadine[®] 10%, Alkaloid AD Skopje, Skopje, Republic of North Macedonia). Epithelial ablation was performed with a hockey knife, creating an 8- to 9-mm diameter area. The 0.1% riboflavin with 20% dextran (MedioCROSS D[®], Glaukos Corporation, Germany) was instilled every 2min for 30min. UVA irradiation (IROC Innocross UV-X[™] 2000, Zug, Switzerland) was then administered using a 9-mW/cm² lamp for 10min. Riboflavin was reapplied twice during irradiation. Postoperatively, a bandage contact lens was applied with ciprofloxacin hydrochloride 0.3% drops (Ciloxan, Novartis, Croatia). Additionally, tobramycin/dexamethasone eye drops (Tobradex, Novartis, Croatia) were initiated on postoperative day 3 and prescribed 5 times daily for 1wk.

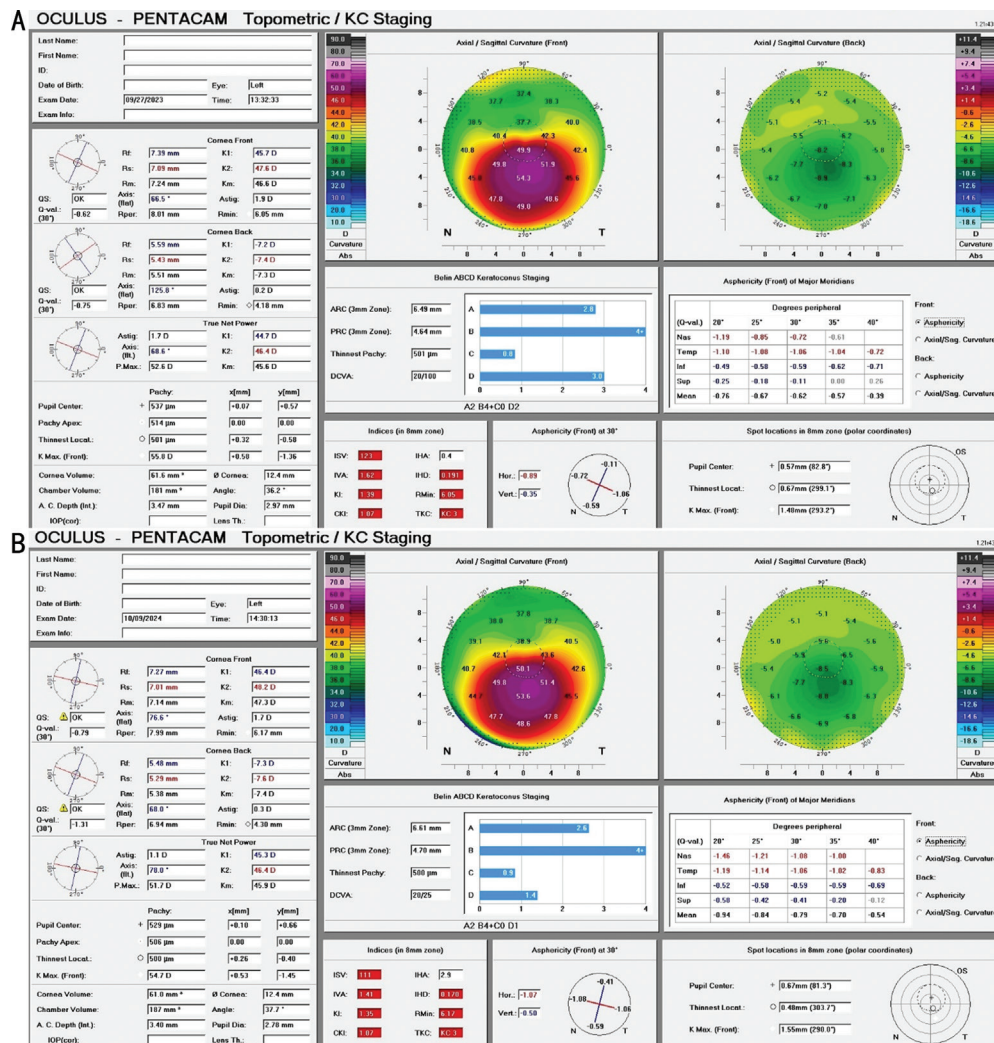


Figure 1 Keratometric parameters and curvature-based indices A: Preoperatively; B: 1y after CXL. KC: Keratoconus; ARC: Anterior radius of curvature; PRC: Posterior radius of curvature; DCVA: Distance-corrected visual acuity; ISV: Index of surface variance; IVA: Index of vertical asymmetry; KI: Keratoconus index; CKI: Central keratoconus index; IHA: Index of height asymmetry; IHD: Index of height decentration; Rmin: Minimum sagittal curvature; TKC: Topographic keratoconus classification; Kmax: Maximum keratometry; CXL: Corneal cross-linking.

Keratometric parameters (Kmax and Kmean), curvature-based indices (ISV, IVA, CKI, KI, IHA, IHD, Rmin; Figure 1), pachymetry-based indices (CCT, PPIavg, ARTmax), the BAD_D (Figure 2), and the ABCD progression system (Figure 3) were obtained using Pentacam HR. Preoperative and one-year postoperative values of all assessed parameters, including BCVA, were systematically collected and analyzed.

Statistical Analysis Statistical analysis was performed using SPSS Statistics version 27.0 (IBM Corp, USA). All data were investigated for normal distribution with the Shapiro-Wilk test. Rank-Biserial correlation was used for effect sizes, and the Wilcoxon signed-rank test for comparison of preoperative and postoperative data. $P \leq 0.05$ was considered statistically significant.

RESULTS

The study included 45 eyes from 45 patients, with a mean age of 29.1 ± 6.2 y (range 18–42 y). Of the participants, 26.67% (12/45) were female and 73.33% (33/45) were male.

Descriptive statistical data before and after CXL are presented in Tables 1, 2, 3, and 4.

One year after accelerated CXL, median value of Kmean front showed a slight increase of 0.30 D (from 47.00 to 47.30 D), while median Kmean back remained unchanged at 7.10 D. The median Kmax front decreased by 0.20 D (from 55.20 to 55.00 D; Table 1).

Table 2 demonstrated an overall improvement in corneal regularity, with median ISV decreasing by 5 units (86 to 81), IVA by 0.07 (0.90 to 0.83), IHA by 1.5 (26.2 to 24.7), and IHD by 0.012 (0.118 to 0.106). Median KI remained stable at 1.20, whereas CKI showed a minimal increase from 1.06 to 1.07. In addition, Rmin increased by 0.03 mm (6.11 to 6.14 mm).

Table 3 showed an increase in median CCT from 491 to 498 μ m. Both PPIavg and CTL (Table 4) remained unchanged. In contrast, ARTmax decreased by 8 μ m. The Belin/Ambrosio deviation value showed minimal changes, with a median of 8.7 (IQR 5.1) preoperatively and 8.8 (IQR 4.9) 1-year post-CXL.

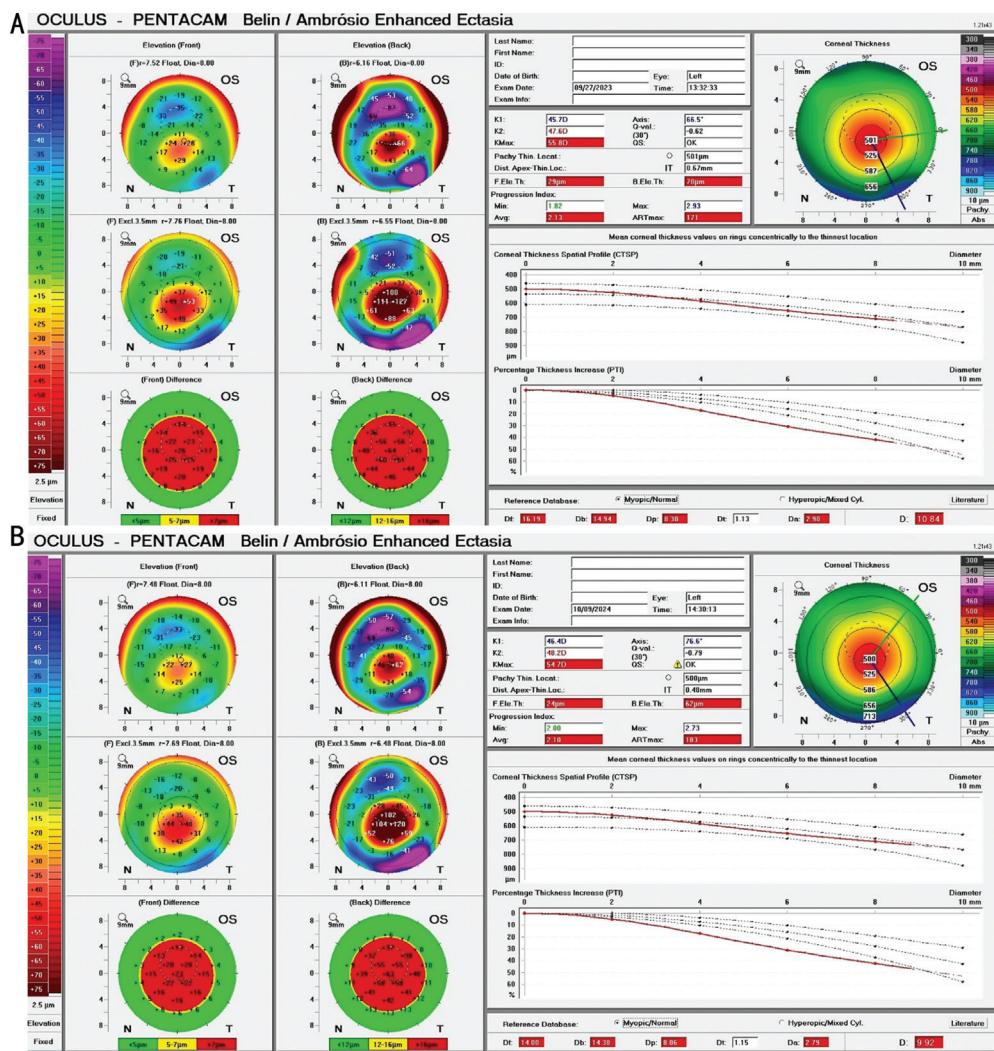


Figure 2 Pachymetry-based indices, Belin/Ambrósio deviation value A: Preoperatively; B: 1y after corneal cross-linking.

Table 1 Keratometry indices			
Parameters	Median	IQR	Range
Kmean front (D)			
Pre-CXL	47.00	3.70	42.40–52.30
Post-CXL	47.30	3.70	42.70–52.50
Kmean back (D)			
Pre-CXL	7.10	0.70	6.00–8.20
Post-CXL	7.10	0.70	5.90–8.20
Kmax front (D)			
Pre-CXL	55.20	8.00	47.00–64.50
Post-CXL	55.00	6.50	45.70–62.10

D: Diopters; Kmean: Mean keratometry; Kmax: Maximal keratometry; CXL: Corneal cross-linking; IQR: Interquartile range.

Table 4 showed the PRC decreased from 4.91 to 4.87, while the ARC increased (6.68 to 6.73). Table 5 revealed significant changes with large effect sizes in several parameters following CXL, with increases observed in Rmin, CCT, and ARC, and decreases in Kmax, ISV, IVA, KI, CKI, and IHD. Additionally, BCVA significantly improved. A and D showed extremely large effect sizes among the custom parameters.

DISCUSSION

The results of our study indicate that accelerated CXL produces meaningful structural and functional alterations in patients with KC 1y postoperatively. The noted decrease in Kmax, along with improvements in various curvature-based indices (ISV, IVA, KI, CKI, and IHD), signifies a movement towards corneal surface regularization and biomechanical stabilization. Despite the modest absolute change in Kmax, its statistical significance reinforces the established role of CXL in arresting disease progression rather than producing substantial refractive alterations.

Our results demonstrate both consistency and variability when juxtaposed with existing literature, likely attributable to disparities in study design, disease stage, patient characteristics, and CXL protocols. Although studies have indicated enhancements in indices such as ISV, IVA, and KI, variations in parameters like CKI and IHD underscore the heterogeneity of KC progression and treatment response^[15-18].

The elevation of Rmin further substantiates the notion of corneal flattening and enhanced geometric regularity after treatment. This parameter is particularly relevant as it denotes

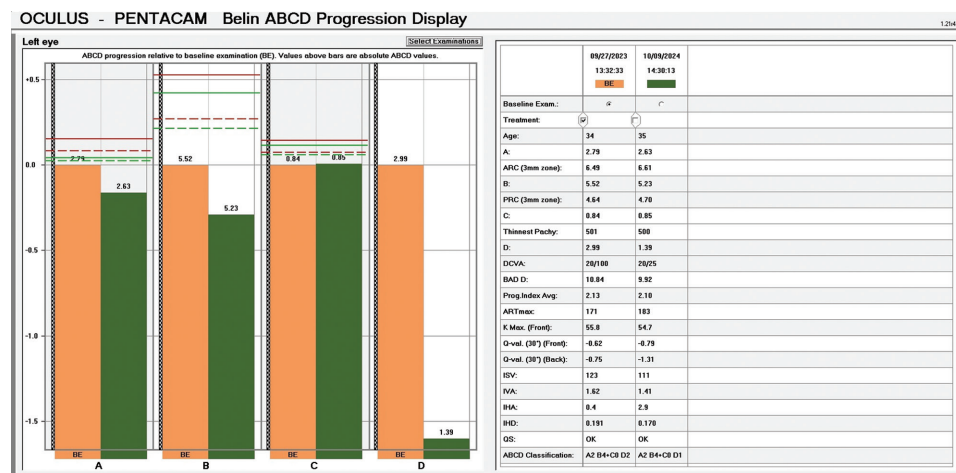


Figure 3 ABCD progression system Preoperatively and 1y after CXL. ARC: Anterior radius of curvature; PRC: Posterior radius of curvature; DCVA: Distance-corrected visual acuity; BAD_D: Belin/Ambrósio deviation value; ARTmax: Maximum Ambrósio relational thickness; Kmax: Maximum keratometry; ISV: Index of surface variance; IVA: Index of vertical asymmetry; IHA: Index of height asymmetry; IHD: Index of height decentration; QS: Quality specification; CXL: Corneal cross-linking.

Table 2 Curvature-based indices

Parameters	Median	IQR	Range
ISV			
Pre-CXL	86	44	24–165
Post-CXL	81	40	24–135
IVA			
Pre-CXL	0.90	0.68	0.25–2.15
Post-CXL	0.83	0.61	0.24–1.74
KI			
Pre-CXL	1.20	0.14	1.06–1.44
Post-CXL	1.20	0.13	1.06–1.38
CKI			
Pre-CXL	1.06	0.06	0.98–1.14
Post-CXL	1.07	0.06	0.99–1.16
IHA			
Pre-CXL	26.2	32.4	0.2–76.5
Post-CXL	24.7	41.6	1.0–77.7
IHD			
Pre-CXL	0.118	0.092	0.018–0.241
Post-CXL	0.106	0.085	0.017–0.212
Rmin (mm)			
Pre-CXL	6.11	0.88	5.23–7.18
Post-CXL	6.14	0.74	5.44–7.39

ISV: Index of surface variance; IVA: Index of vertical asymmetry; KI: Keratoconus index; CKI: Central keratoconus index; IHA: Index of height asymmetry; IHD: Index of highest decentration; Rmin: Minimum sagittal curvature; CXL: Corneal cross-linking; IQR: Interquartile range.

the radius of the steepest curvature and may serve as a more sensitive indicator of morphological change than keratometry alone^[15-16]. The reduction in asymmetry indices and the elevation of Rmin indicate a transition towards a more uniform corneal structure, aligning with the biomechanical fortification caused by CXL.

Table 3 Pachymetry-based indices

Parameters	Median	IQR	Range
CCT (μm)			
Pre-CXL	491	46	427–555
Post-CXL	498	42	428–557
PPIavg			
Pre-CXL	2.13	0.82	1.07–3.14
Post-CXL	2.14	0.92	1.06–3.20
ARTmax (μm)			
Pre-CXL	155	89	90–501
Post-CXL	147	70	80–367

CCT: Central corneal thickness; PPIavg: Average pachymetric progression index; ARTmax: Maximum Ambrósio relational thickness; CXL: Corneal cross-linking; IQR: Interquartile range.

Changes in pachymetry-based indices provide additional insight into corneal remodeling after treatment. The documented increase in CCT at 1y corresponds with prior studies indicating an initial postoperative thinning followed by a gradual recovery^[4]. This pattern is believed to indicate stromal repopulation, extracellular matrix remodeling, and keratocyte activity following the initial cytotoxic effects of UVA exposure. The reduction in ARTmax may signify enduring changes in the corneal thickness profile, indicating that although central thickness may recover, the spatial distribution of pachymetry could remain modified. These findings underscore the significance of assessing various pachymetric parameters instead of depending exclusively on CCT.

The improvement in BCVA, evidenced by a substantial effect size, validates that the observed structural changes are clinically significant^[5,17,19]. Visual improvement following CXL is primarily ascribed to the diminishment of higher-order aberrations and the enhancement of corneal symmetry.

Table 4 ABCD progression system

Parameters	Median	IQR	Range
ARC			
Pre-CXL	6.68	0.69	5.98–7.80
Post-CXL	6.73	0.64	6.02–7.75
PRC			
Pre-CXL	4.91	0.80	4.17–6.35
Post-CXL	4.87	0.75	4.24–6.04
CTL			
Pre-CXL	471	50	401–553
Post-CXL	470	48	403–552
A			
Pre-CXL	2	1	0–4
Post-CXL	2	1	0–4
B			
Pre-CXL	4	2	0–4
Post-CXL	4	2	0–4
C			
Pre-CXL	1	1	0–2
Post-CXL	1	1	0–2
D			
Pre-CXL	1	1	0–3
Post-CXL	0	1	0–2

ARC: Anterior radius of curvature; PRC: Posterior radius of curvature;
CTL: Corneal thinnest location; CXL: Corneal cross-linking; IQR:
Interquartile range.

The improvement in BCVA, despite minimal changes in keratometric values, underscores the limitations of relying solely on keratometry to assess visual function.

The analysis of the ABCD progression system further strengthens the interpretation of our findings. The substantial decrease in parameter A suggests a flattening of the anterior corneal surface, whereas the enhancement in parameter D reflects improved visual performance. The stability of parameters B and C indicates that posterior curvature and pachymetric progression remained largely unchanged, suggesting that the primary effect of CXL after 1y is confined to the anterior stromal layers. This observation aligns with the established depth-dependent effect of the CXL procedure^[6,20-24]. This study's primary strength is the concurrent assessment of various tomographic indices in conjunction with the ABCD classification system. Our methodology offers a more thorough and sensitive evaluation of disease progression and treatment efficacy by incorporating keratometric, curvature-based, pachymetric, and composite indices. This comprehensive assessment facilitates the identification of nuanced variations that may remain obscured when employing singular metrics, thus enhancing clinical decision-making and monitoring strategies.

Notwithstanding these promising results, specific limitations must be recognized. The retrospective design limited the

Table 5 Wilcoxon signed-rank test between post- and pre-CXL

Parameters	W	Z	P	r	SE
Kmean front (D)	274.500	-1.162	0.248	-0.219	0.186
Kmean back (D)	222.500	0.108	0.922	0.023	0.209
Kmax front (D)	133.000	-3.586	<0.001	-0.659	0.182
ISV	115.000	-3.838	<0.001	-0.705	0.182
IVA	147.500	-3.801	<0.001	-0.673	0.175
KI	212.000	-2.105	0.036	-0.397	0.186
CKI	126.500	-1.968	0.048	-0.418	0.209
IHA	442.500	-0.368	0.717	-0.064	0.173
IHD	136.500	-4.063	<0.001	-0.711	0.173
Rmin (mm)	676.000	3.575	<0.001	0.649	0.179
CCT (μm)	617.000	2.069	0.039	0.367	0.175
PPlavg	574.500	1.226	0.223	0.215	0.173
ARTmax (μm)	403.000	-1.292	0.198	-0.221	0.170
BAD_D	482.000	0.667	0.509	0.120	0.177
ARC	852.500	4.172	<0.001	0.722	0.171
PRC	464.500	-0.356	0.726	-0.062	0.171
CTL	537.500	0.779	0.439	0.136	0.173
BCVA	929.500	5.512	<0.001	0.965	0.173
A	0.000	-3.621	<0.001	-1.000	0.269
B	20.000	0.280	0.821	0.111	0.377
C	24.000	-0.800	0.393	-0.273	0.328
D	19.000	-4.488	<0.001	-0.923	0.203

P values were calculated using the Wilcoxon signed-rank test. Effect sizes (*r*) were calculated using Rank-Biserial correlation. D: Diopters; Kmean: Mean keratometry; Kmax: Maximal keratometry; CXL: Corneal cross-linking; ISV: Index of surface variance; IVA: Index of vertical asymmetry; KI: Keratoconus index; CKI: Central keratoconus index; IHA: Index of height asymmetry; IHD: Index of highest decentration; Rmin: Minimum sagittal curvature; CCT: Central corneal thickness; PPlavg: Average pachymetric progression index; ARTmax: Maximum Ambrósio relational thickness; BAD_D: Belin/Ambrósio deviation; ARC: Anterior radius of curvature; PRC: Posterior radius of curvature; CTL: Corneal thinnest location; BCVA: Best-corrected visual acuity; SE: Standard error.

availability of certain clinically pertinent parameters, such as demarcation line depth, which could offer further insight into treatment efficacy. Moreover, the limited sample size and one-year follow-up period restrict the generalizability of the findings and hinder conclusions about long-term stability. Future prospective studies involving larger cohorts and prolonged follow-up are necessary to corroborate these findings and to elucidate the temporal dynamics of corneal remodeling following CXL.

In conclusion, accelerated CXL seems to be an efficacious intervention for stabilizing KC, resulting in quantifiable enhancements in corneal architecture and visual acuity after 1y. The integration of various tomographic parameters with the ABCD progression system provides a comprehensive

framework for assessing disease progression and treatment efficacy. This thorough approach may improve the accuracy of clinical evaluation and facilitate more personalized management strategies for patients with KC.

ACKNOWLEDGEMENTS

Authors' Contributions: Conceptualization: Ćubela I, Miletić D, Kuzmanović Elabjer B; Data curation: Ćubela I, Ramić S, Pavlović I; Formal analysis: Ćubela I, Miletić D; Investigation: Ćubela I, Miletić D, Ramić S, Pavlović I; Supervision: Miletić D, Kuzmanović Elabjer B, Šarić D, Bušić M; Validation: Miletić D, Kuzmanović Elabjer B, Šarić D, Bušić M; Review and editing: Ćubela I, Miletić D, Kuzmanović Elabjer B.

Data Availability Statement: All data generated or analyzed during this study are included in this published article.

AI-Generated Content Disclosure: No generative AI tools were used in the creation of content for this manuscript.

Conflicts of Interest: Ćubela I, None; Miletić D, None; Kuzmanović Elabjer B, None; Ramić S, None; Pavlović I, None; Šarić D, None; Bušić M, None.

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