

# Femtosecond LASIK with Corneal Cross-Linking (FS-LASIK Xtra) for Myopic Astigmatism in Eyes with Asymmetric Cornea: A Retrospective Comparative Study of UVA Energy Protocols

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## Research Article

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# Abstract

## Purpose

To evaluate the safety, efficacy, and refractive outcomes of femtosecond laser-assisted in situ keratomileusis combined with prophylactic corneal collagen cross-linking (FS-LASIK Xtra) using different total ultraviolet-A (UVA) energy protocols in patients with myopic astigmatism and asymmetric cornea.

## Methods

This retrospective comparative study included 114 eyes from 114 patients who underwent FS-LASIK Xtra at Beijing Mingshiguang Ophthalmology Hospital between January 2022 and January 2025. Patients were divided into two groups according to total UVA energy: Group A (3.6 J/cm<sup>2</sup>, 58 eyes) and Group B (2.7 J/cm<sup>2</sup>, 56 eyes). Preoperative and postoperative evaluations at 1, 6, and 12 months included uncorrected visual acuity (UCVA), corrected distance visual acuity (CDVA), spherical equivalent (SE), astigmatism, average keratometry (AveK), central corneal thickness (CCT), and corneal endothelial cell density. Statistical analyses were conducted using linear mixed models and other appropriate tests.

## Results

At 12 months postoperatively, UCVA  $\geq$  20/20 was achieved in 98.3% and 94.6% of eyes in Groups A and B, respectively. The proportion of eyes within  $\pm$  0.50 D of target SE was 89.7% in Group A and 80.4% in Group B. Both groups demonstrated stable postoperative refraction, mean keratometry, and central corneal thickness. No significant differences in visual or refractive outcomes were observed between groups. Mild, transient grade 1 corneal haze occurred in 4 eyes (Group A) and 2 eyes (Group B) and resolved with corticosteroid therapy. No cases of ectasia or other severe complications were reported.

## Conclusions

FS-LASIK Xtra using either 3.6 J/cm<sup>2</sup> or 2.7 J/cm<sup>2</sup> UVA energy demonstrates excellent efficacy, predictability, stability, and safety in eyes with myopic astigmatism and asymmetric cornea over a 1-year follow-up. The higher-energy protocol (3.6 J/cm<sup>2</sup>) showed slightly improved refractive and corneal curvature stability, although differences were not statistically significant. Longer-term studies with larger sample sizes are warranted to confirm these findings.

## Introduction

Femtosecond laser-assisted in situ keratomileusis (FS-LASIK) is among the most widely performed refractive surgical procedures, offering excellent postoperative visual rehabilitation and refractive outcomes[1–3]. However, the creation of a corneal flap and excimer laser stromal ablation inherently

reduces corneal biomechanical integrity[4, 5], increasing the risk of postoperative regression and iatrogenic corneal ectasia. These risks are particularly relevant in patients with recognized predisposing factors, including younger age, high myopia, reduced corneal thickness, and corneal morphological asymmetry[6–10].

Corneal collagen cross-linking (CXL) has been shown to enhance corneal biomechanical stability by reinforcing stromal collagen fibrils, effectively halting or slowing the progression of keratoconus and other ectatic corneal disorders[11–14]. Incorporating prophylactic CXL into keratorefractive procedures has led to the concept of “xtra surgery”, aimed at improving postoperative biomechanical stability and reducing ectasia risk[15–18].

While excimer laser in situ keratomileusis combined with prophylactic corneal collagen cross-linking (LASIK Xtra) has been investigated primarily in patients with high myopia or thin corneas, limited data exist for individuals with asymmetric corneas—a significant risk factor for postoperative ectasia. To address this gap, we conducted a retrospective comparative study to evaluate femtosecond laser-assisted in situ keratomileusis combined with prophylactic corneal collagen cross-linking (FS-LASIK Xtra) in eyes with asymmetric cornea, comparing two different total ultraviolet-A (UVA) irradiation energy protocols. The primary objective was to assess safety and efficacy, providing evidence to optimize surgical planning and refractive outcomes in this high-risk population.

# 1. Materials and Methods

## 1.1 Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Beijing Ming Vision Ophthalmology Hospital (Ethics Approval No.: 2023yh-007) and adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants after detailed preoperative counseling.

## 1.2 General Information

This study was designed as a retrospective comparative investigation. We collected a total of 114 eyes that underwent FS-LASIK Xtra surgery at Beijing Mingshiguang Ophthalmology Hospital (Teaching Base of Optometry, Eye Institute of Chengdu University of Traditional Chinese Medicine) between January 2022 and January 2025. The cases were divided into two groups based on the total corneal cross-linking energy: FS-LASIK Xtra Group A (total energy 3.6 J/cm<sup>2</sup>, 58 eyes) and FS-LASIK Xtra Group B (total energy 2.7 J/cm<sup>2</sup>, 56 eyes).

**Inclusion Criteria: 1) Indication for Surgery:** Patients with moderate to high myopia (spherical equivalent (SE) > −3.0 D) and/or thin corneas (central corneal thickness (CCT) ≤ 500 μm) who underwent FS-LASIK Xtra. **2) Corneal topography showed non-progressive, non-keratoconus-related morphological asymmetry (images acquired using a Tomey TMS-4 corneal topography analyzer, with an 8 mm corneal analysis diameter, confirmed by at least two repeated measurements, with artifacts such as eyelid**

pressure and tear film instability excluded), including: **a. Asymmetric bow-tie pattern: the axial curvature map of the cornea shows an asymmetrical bow-tie configuration. b. Inferior steepening: the axial curvature map of the cornea shows localized steepening in the inferior region.**

**Exclusion Criteria:** 1) Severe intraoperative complications (e.g., flap creation failure, free flap, decentered ablation). 2) Intended residual refraction (target spherical equivalent  $\neq 0$ ). 3) Findings suggestive of keratoconus or ectatic disease (pentacam **corneal topography analyzer, with an 8 mm corneal analysis diameter**): a. Belin/Ambrósio deviation index (BAD-D)  $\geq 2.6$ ; b. topographic keratoconus classification (TKC)  $\geq$  grade 2; c. maximum keratometry (Kmax)  $> 48.7$  D; d. back elevation at the thinnest location (BELE)  $> +15$   $\mu\text{m}$ ; e. inferior–superior (I-S) value  $> 1.9$  D.

### 1.3 Examination Methods

All patients underwent standard preoperative examinations, including uncorrected visual acuity (UCVA), corrected distance visual acuity (CDVA), intraocular pressure (IOP), manifest and cycloplegic refraction, CCT (LS900, Switzerland), corneal topography (Tomey-4, Japan; Pentacam, Germany), slit-lamp biomicroscopy, and fundus evaluation. Postoperative follow-up examinations were conducted at 1, 6, and 12 months to assess UCVA, CDVA, SE, astigmatism, average keratometry (AveK), CCT and corneal endothelial cell count. Corneal condition was evaluated using slit-lamp biomicroscopy.

### 1.4 Surgical Procedure

All patients instilled levofloxacin eye drops four times daily for three days before surgery. All procedures were performed by the same experienced surgeon (Y.H. ZHOU) to ensure consistency.

**Group A:** Patients underwent standard preoperative disinfection, followed by topical anesthesia with 0.4% oxybuprocaine hydrochloride eye drops. Corneal flaps were created using the VisuMax femtosecond laser system (Carl Zeiss Meditec, Germany) with a target flap thickness of 90  $\mu\text{m}$ , a diameter of 8 mm, a flap edge cut angle of 90°, and a hinge positioned at 90°. After flap creation, the flap was lifted, and excimer laser ablation was performed using the VISX Star S4 IR excimer laser system (VISX, USA). Following laser ablation, 0.22% Vibex Xtra riboflavin solution was applied to completely cover the exposed stromal bed and allowed to soak for 90 seconds, after which the stromal bed was rinsed with balanced salt solution and the flap was repositioned. Corneal cross-linking was then performed using a keratoconus cross-linking (KXL) corneal cross-linking system (Avedro, USA) with continuous UVA irradiation at a wavelength of 365 nm for 120 seconds, an irradiance of 30 mW/cm<sup>2</sup>, and a total UVA energy dose of 3.6 J/cm<sup>2</sup>. At the end of the procedure, a bandage contact lens was applied.

**Group B:** Corneal cross-linking was performed using the KXL system (Avedro, USA) with continuous UVA irradiation at a wavelength of 365 nm for 90 seconds, an irradiance of 30 mW/cm<sup>2</sup>, and a total UVA energy dose of 2.7 J/cm<sup>2</sup>. All other surgical steps were identical to those in Group A.

### 1.5 Statistical Analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS, version 26.0, IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution were compared between groups using independent-samples t-tests, while variables not following a normal distribution were analyzed using the Mann-Whitney U test. Categorical variables, such as sex, were compared using the chi-square test or Fisher's exact test, as appropriate. Linear regression analysis was conducted to assess the relationship between attempted and achieved SE correction at 12 months postoperatively.

Linear mixed models (LMM) were used to analyze five continuous outcome measures separately: UCVA (logMAR), SE, astigmatism, AveK, and CCT. The models included random intercepts for individual subjects, with a first-order autoregressive (AR1) covariance structure to account for repeated measurements across eyes and time points within the same subject. Fixed effects included group (Group A, Group B), time (preoperative, 1 month, 6 months, and 12 months postoperatively), eye laterality (right eye, left eye), and all two-way interactions. Parameter estimation was performed using restricted maximum likelihood (REML). Multiple comparisons were adjusted using the Bonferroni method. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

## 2. Results

### 2.1 Baseline Characteristics

A total of 58 eyes in the FS-LASIK Xtra Group A and 56 eyes in Group B were included. Baseline characteristics of all patients are presented in **Table 1**, and representative preoperative corneal topography images are shown in **Figure 1**. Independent-samples t-tests showed that there were statistically significant differences in age and CCT between the two groups preoperatively ( $P = 0.010$  and  $0.013$ , respectively), with Group A having higher values than Group B. No significant differences were observed between the two groups in preoperative UCVA, CDVA, SE, sphere, astigmatism, AveK, ablation depth, or percentage of tissue altered (PTA) ( $P > 0.05$ ).

### 2.2 Statistical Analysis Results

The results of fixed effects from the linear mixed model analyses for all outcome measures are summarized in **Table 2**. Estimated marginal means, standard errors (SE), and 95% confidence intervals (CI) for each measure across different groups and time points are shown in **Table 3**.

The analysis showed that the main effect of group, the group  $\times$  eye interaction, and the time  $\times$  eye interaction were not statistically significant for any of the outcome measures ( $P > 0.05$ ).

**Eye Laterality Main Effect:** A significant main effect of eye laterality was observed for CCT: the estimated marginal mean CCT was  $436.07 \mu\text{m}$  for the right eye and  $438.84 \mu\text{m}$  for the left eye, with a difference of  $-2.77 \mu\text{m}$  ( $F = 4.03$ ,  $P = 0.047$ ), indicating that the left eye was slightly thicker than the right eye. Although statistically significant, this difference is much smaller than the clinically acceptable measurement error for CCT (typically  $5\text{--}10 \mu\text{m}$ ) and is therefore considered clinically negligible, likely

reflecting physiological variation or random sampling. No significant eye laterality differences were observed for the other four outcome measures ( $P > 0.05$ ).

**Group × Time Interaction:** A significant group × time interaction was observed for CCT ( $F = 11.46$ ,  $P < 0.001$ ). Simple effects analysis showed that in Group A, CCT decreased by  $95.07 \mu\text{m}$  at 1 month postoperatively compared with preoperative values ( $P < 0.001$ ), increased by  $7.02 \mu\text{m}$  at 6 months compared with 1 month ( $P = 0.003$ ), and increased by  $5.39 \mu\text{m}$  at 12 months compared with 1 month ( $P = 0.084$ ). In Group B, CCT decreased by  $80.32 \mu\text{m}$  at 1 month postoperatively compared with preoperative values ( $P < 0.001$ ), with no significant changes at 6 or 12 months relative to 1 month ( $P > 0.05$ ). These results indicate that postoperative CCT thickening was more pronounced in Group A than in Group B. No other significant group × time interactions were observed for the remaining outcomes ( $P > 0.05$ ).

**Time Main Effect:** All outcome measures demonstrated highly significant main effects of time ( $P < 0.001$ ), indicating that each postoperative time point differed significantly from baseline. Pairwise comparisons of time points (Bonferroni-adjusted) yielded the following:

1. **UCVA, SE, and Astigmatism:** In both groups, all postoperative time points differed significantly from preoperative values ( $P < 0.001$ ), whereas differences between postoperative time points were not significant ( $P > 0.05$ ), suggesting stabilization by 1 month postoperatively.
2. **CCT:** In both groups, postoperative CCT values were significantly lower than preoperative values ( $P < 0.001$ ). In Group A, CCT increased significantly at 6 months compared with 1 month ( $7.02 \mu\text{m}$ ,  $P = 0.003$ ), whereas in Group B the increase was negligible ( $-0.47 \mu\text{m}$ ,  $P = 1.000$ ). At 12 months relative to 1 month, Group A showed an increase of  $5.39 \mu\text{m}$  ( $P = 0.084$ ) and Group B  $3.43 \mu\text{m}$  ( $P = 0.748$ ).
3. **AveK:** In both groups, postoperative AveK was significantly lower than preoperative values ( $P < 0.001$ ). In Group A, AveK increased significantly at 6 months compared with 1 month ( $0.492 \text{ D}$ ,  $P < 0.001$ ), whereas in Group B the increase was not significant ( $0.303 \text{ D}$ ,  $P = 0.052$ ). At 12 months relative to 1 month, AveK increased by  $0.315 \text{ D}$  in Group A ( $P = 0.076$ ) and  $0.487 \text{ D}$  in Group B ( $P = 0.001$ ), indicating slightly less curvature regression in Group A.

## 2.3 Visual Acuity and Refractive Outcome

At 12 months postoperatively, the proportion of eyes achieving UCVA of 20/20 or better was 98.3% in Group A and 94.6% in Group B. Compared with preoperative CDVA, the proportion of eyes losing one line of UCVA at 12 months was 1.7% in Group A and 5.4% in Group B, with no eyes in either group losing two or more lines. At 12 months, the proportion of eyes within  $\pm 0.50 \text{ D}$  of SE was 89.7% in Group A and 80.4% in Group B, with residual astigmatism  $\leq 0.50 \text{ D}$  in both groups, demonstrating high efficacy and refractive stability. At 12 months postoperatively, the proportions of eyes in both groups achieving UCVA of 20/20 or better and 20/25 or better are shown in **Figure 2**. **Figure 3** shows the changes in UCVA at 12 months postoperatively compared to preoperative CDVA. **Figure 4** shows the proportions of eyes in both groups within  $\pm 0.50 \text{ D}$  and  $\pm 1.00 \text{ D}$  of the target SE at 12 months postoperatively. At 12 months postoperatively,

the proportions of eyes in both groups with postoperative astigmatism within  $\pm 0.25$  D and  $\pm 0.50$  D are shown in **Figure 5**. The correlation coefficients ( $R^2$ ) for both groups are shown in **Figure 6**, indicating a strong linear relationship between achieved SE and intended SE, which supports the consistency of the surgical nomogram. The  $R^2$  values of 0.9629 and 0.9113 suggest that the intended SE explains a substantial proportion of the variance in achieved SE. The trend of SE and AveK changes during the 12-month follow-up period is shown in **Figure 7**.

## 2.4 Corneal Endothelial Cell Density and Complications

In FS-LASIK Xtra Group A, corneal endothelial cell density was  $2533.49 \pm 249.14$  cells/mm<sup>2</sup> preoperatively and  $2504.29 \pm 209.90$  cells/mm<sup>2</sup> at 12 months postoperatively. In Group B, corresponding values were  $2577.54 \pm 231.29$  cells/mm<sup>2</sup> preoperatively and  $2560.57 \pm 237.40$  cells/mm<sup>2</sup> at 12 months postoperatively. No statistically significant differences were observed between preoperative and postoperative values within either group ( $P = 0.559$  for Group A,  $P = 0.702$  for Group B).

During the 1-year follow-up, 4 eyes in Group A and 2 eyes in Group B developed grade 1 corneal haze at 1 month postoperatively. Following corticosteroid treatment, the haze completely resolved on follow-up examinations at 3–6 months postoperatively. No cases of postoperative corneal ectasia or other severe complications, such as diffuse lamellar keratitis, infection, or flap-related complications, were observed in either group.

## 3. Discussion

Iatrogenic corneal ectasia is a rare but severe complication following refractive surgery, also referred to as secondary keratoconus. Alterations in corneal biomechanical properties may lead to abnormalities in corneal optics and morphology, ultimately resulting in significant visual impairment[19, 20].

Kanellopoulos et al. [21] reported that prophylactic CXL is a safe and effective adjunctive strategy in high-risk LASIK cases, reducing the risk of refractive regression and postoperative ectasia. Patients with preoperative corneal topographic asymmetry are at increased risk of postoperative biomechanical instability and ectasia, highlighting the clinical value of combining refractive surgery with prophylactic CXL.

However, current evidence regarding LASIK Xtra in patients with asymmetric cornea remains limited. Although some studies have included topographic irregularities as part of eligibility criteria[22, 23], these were not strictly required for inclusion. In contrast, the present study specifically enrolled patients with asymmetric cornea, thereby focusing on a higher-risk population. At present, no standardized protocol exists for refractive surgery combined with CXL, and the minimum UVA energy required for adequate biomechanical reinforcement remains undetermined. Insufficient energy may fail to achieve sufficient cross-linking effects, whereas excessive energy may increase the risk of corneal haze or persistent flattening[24]. A total UVA energy of  $2.7 \text{ J/cm}^2$  has been widely used in LASIK Xtra procedures[22, 23, 25–27]. The present study compared two UVA energy protocols ( $3.6 \text{ J/cm}^2$  vs.  $2.7 \text{ J/cm}^2$ ) in FS-LASIK Xtra

for the correction of myopic astigmatism with asymmetric cornea, focusing on visual outcomes, refractive stability, and corneal morphological changes.

The visual and refractive outcomes in this study indicate that both groups demonstrated good efficacy, safety, stability, and predictability. In a retrospective comparative study by Li et al.[28] comparing LASIK Xtra versus LASIK, 29 eyes in the LASIK Xtra group were evaluated at 2 years postoperatively. In this group, 90% of eyes achieved an uncorrected visual acuity (UCVA) of 20/20 or better, 93% were within  $\pm 0.50$  D of the intended spherical equivalent, and 100% had postoperative residual astigmatism  $\leq 0.50$  D, with a coefficient of determination ( $R^2$ ) of 0.9379. Similarly, in a retrospective study of LASIK Xtra by Alonso-Aliste et al.[25], 100 eyes were assessed at 4 years postoperatively. In this cohort, 87% of eyes achieved UCVA of 20/20 or better, 93% were within  $\pm 0.50$  D of the intended spherical equivalent, and 84% had postoperative residual astigmatism  $\leq 0.50$  D, with an  $R^2$  of 0.9682. These findings are consistent with the results of the present study.

Postoperative visual acuity improved progressively, reaching optimal levels at 12 months. Early visual recovery was slightly delayed, consistent with previous studies reporting transient visual fluctuations within the first postoperative week or month[22, 23, 26, 27, 29]. These early fluctuations are likely associated with CXL-induced stromal edema and inflammatory responses, including transient subepithelial haze and diffuse lamellar keratitis (DLK), which resolve with time.

A mild postoperative regression in SE was observed in both groups, consistent with previous studies[26, 27, 29]. Di et al. [30] reported a SE change of -0.81 D from 1 to 12 months following LASIK Xtra, suggesting a more pronounced regression. In contrast, Kaiser et al. [31] reported a long-term SE change of -0.15 D over 8 years, indicating long-term stability. Variations among studies may be related to differences in preoperative refractive status and patient selection.

A mild steepening trend in anterior AveK was observed in both groups during follow-up, consistent with previous studies[27-29]. Corneal ablation flattens the central and paracentral cornea; however, subsequent biomechanical remodeling may lead to partial reversal and gradual steepening of the treated zone[32, 33]. The magnitude of this change may correlate with the attempted correction, with higher corrections resulting in greater postoperative curvature changes. In the present study, no significant differences in AveK changes were observed between groups, possibly due to the relatively short follow-up period, during which the full biomechanical effect of CXL may not yet have manifested[34], and the relatively small difference in total UVA energy between protocols.

CCT remained stable with slight postoperative thickening in both groups. This finding is consistent with previous reports and may reflect epithelial hyperplasia and stromal remodeling during wound healing.

Corneal haze (grade 1) occurred in 4 eyes in Group A and 2 eyes in Group B at 1 month postoperatively and resolved completely after corticosteroid therapy within 3–6 months. No other severe complications were observed. Previous studies have identified corneal haze as a common early complication after LASIK Xtra[31, 35], potentially related to transient keratocyte activation and inflammatory responses

induced by cross-linking[36]. Corneal endothelial cell density showed no significant change postoperatively in either group, indicating that FS-LASIK Xtra maintains a favorable safety profile.

This study has several limitations. The relatively small sample size and 1-year follow-up may not fully capture late-onset corneal ectasia, which can occur years after surgery. In addition, due to incomplete postoperative Pentacam data, key ectasia-related parameters such as Kmax, thinnest corneal thickness (TCT), and BELE could not be analyzed. Corneal biomechanical measurements were also not available. Future prospective studies with larger cohorts, longer follow-up, and comprehensive biomechanical assessments are required to further validate long-term safety and efficacy.

## 4. Conclusion

FS-LASIK Xtra using different UVA energy protocols demonstrated excellent efficacy, predictability, stability, and safety in patients with myopic astigmatism and asymmetric cornea over a 1-year follow-up period. Both energy regimens yielded comparable clinical outcomes, suggesting that the 3.6 J/cm<sup>2</sup> protocol is safe and effective. Although slightly improved refractive and corneal curvature stability was observed with the higher-energy protocol, the differences were not statistically significant. Further studies with longer follow-up periods and larger sample sizes are warranted to confirm long-term outcomes and optimize energy settings in this high-risk population.

## Declarations

**Authors' Contributions:** M.W. contributed to drafting the manuscript, acquiring and interpreting the data, and undertaking the literature review. C.L. contributed to editorial changes and provided photos. L.W. contributed to interpreting the data. X.Y. and H.W. provided statistical analysis of data. M.W. and Y.Z. contributed to the statistical analyses and participated in the interpretation of results. All authors have read and agreed to the published version of the manuscript.

**Data Availability Statement:** The data used for this manuscript are available upon reasonable request of the corresponding author: Yuehua Zhou (Email: YH0623667@163.com).

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**Conflicts of Interest:** The authors declare that they have no competing interests.

## References

1. Ahluwalia A, Manche EE. Comparing femtosecond LASIK and small-incision lenticule extraction (SMILE). *Curr Opin Ophthalmol*. 2025;36(4):276–81.
2. Humayun S, Ishaq M, Fawad A, Arzoo S. Refractive Outcome of Femtosecond Assisted Laser in situ Keratomileusis in 1564 cases of Myopia and Compound Myopic Astigmatism. *J Coll Physicians Surg Pak*. 2024;34(1):42–7.

3. Susanna BN, Mohan N, Santhiago MR, Randleman JB. Laser in Situ Keratomileusis Outcomes and Complications: 2016 to 2023. *J Refract Surg.* 2025;41(4):e391–403.
4. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal refractive surgery. *Ophthalmology.* 2008;115(1):37–50.
5. Wang C, Li X, Guo Y, He R, Guo H, Chen W. Effects of Laser In Situ Keratomileusis and Small-Incision Lenticule Extraction on Corneal Biomechanical Behavior: A Finite Element Analysis. *Front Bioeng Biotechnol.* 2022;10:855367.
6. Ambrósio R Jr., Salomão MQ, Barros L, da Fonseca Filho JBR, Guedes J, Neto A, et al. Multimodal diagnostics for keratoconus and ectatic corneal diseases: a paradigm shift. *Eye Vis.* 2023;10(1):45.
7. Brar S, Roopashree CR, Ganesh S. Incidence of Ectasia After SMILE From a High-Volume Refractive Surgery Center in India. *J Refract Surg.* 2021;37(12):800–8.
8. Huang TZ, Jin HY. Case Report: Bilateral Corneal Ectasia Developed during Pregnancy after Small-incision Lenticule Extraction. *Optom Vis Sci.* 2022;99(6):528–33.
9. Salomão MQ, Hoffling-Lima AL, Sena NJ, Lopes BT, Guedes J, Ambrósio RJ. Enhanced Screening for Ectasia Risk: Multimodal Refractive Imaging Observations From the Fellow Unoperated Eye of Patients With Post-Laser In Situ Keratomileusis Ectasia. *Cornea.* 2024;3(1):e0023.
10. Soundarya B, Sachdev GS, Ramamurthy S, Dandapani R. Ectasia after keratorefractive surgery: Analysis of risk factors and treatment outcomes in the Indian population. *Indian J Ophthalmol.* 2020;68(6):1028–31.
11. Bao F, Chen W, Zheng X, Miao Y, Zhu M, Akiti S, et al. Changes in Corneal Biomechanical Properties in PRK Followed by Two Accelerated CXL Energy Doses in Rabbit Eyes. *J Refract Surg.* 2021;37(12):853–60.
12. Chen W, Bao F, Roberts CJ, Zhang J, Wang C, Li X, et al. Effect of corneal cross-linking on biomechanical changes following transepithelial photorefractive keratectomy and femtosecond laser-assisted LASIK. *Front Bioeng Biotechnol.* 2024;12:1323612.
13. Gurnani B, Kaur K. Recent Advances in Refractive Surgery: An Overview. *Clin Ophthalmol.* 2024;18:2467–72.
14. Li L, Zhang B, Hu Y, Xiong L, Wang Z. Comparison of safety and efficiency of corneal topography-guided photorefractive keratectomy and combined with crosslinking in myopic correction: An 18-month follow-up. *Med (Baltim).* 2021;100(2):e23769.
15. Brar S, Gautam M, Sute SS, Ganesh S. Refractive surgery with simultaneous collagen cross-linking for borderline corneas - A review of different techniques, their protocols and clinical outcomes. *Indian J Ophthalmol.* 2020;68(12):2744–56.
16. Lu NJ, Hafezi F, Torres-Netto EA, Assaf JF, Aslanides IM, Awwad ST, et al. Effect of fluence levels on prophylactic corneal cross-linking for laser in situ keratomileusis and transepithelial photorefractive keratectomy. *Acta Ophthalmol.* 2023;101(2):e185–96.
17. Yang SA, Liou SW, Chen CC. Corneal stability comparison between prophylactic cross-linking with laser refractive surgery technique versus laser refractive surgery technique alone for myopia: a

- meta-analysis. Graefes archive for clinical and experimental ophthalmology. 2025; 263:3037–52.
18. Zu P, Gong Y, Zhang X, Ren C, Wang X, Bi H. Clinical outcomes of femtosecond laser-assisted laser in situ keratomileusis combined with accelerated corneal cross-linking versus standard femtosecond laser-assisted laser in situ keratomileusis for the correction of myopia and myopic astigmatism. *Int Ophthalmol*. 2025;45(1):491.
  19. Huang G, Melki S. Small Incision Lenticule Extraction (SMILE): Myths and Realities. *Semin Ophthalmol*. 2021;36(4):140–8.
  20. Moshirfar M, Tukan AN, Bundogji N, Liu HY, McCabe SE, Ronquillo YC, et al. Ectasia After Corneal Refractive Surgery: A Systematic Review. *Ophthalmol Ther*. 2021;10(4):753–76.
  21. Kanellopoulos AJ. Long-term safety and efficacy follow-up of prophylactic higher fluence collagen cross-linking in high myopic laser-assisted in situ keratomileusis. *Clin Ophthalmol*. 2012;6:1125–30.
  22. Seiler TG, Fischinger I, Koller T, Derhartunian V, Seiler T. Superficial corneal crosslinking during laser in situ keratomileusis. *J Cataract Refract Surg*. 2015;41(10):2165–70.
  23. Xu W, Tao Y, Wang L, Huang Y. Evaluation of Biomechanical Changes in Myopia Patients with Unsatisfactory Corneas After Femto Second-Laser In Situ Keratomileusis (FS-LASIK) Concurrent with Accelerated Corneal Collagen Cross-Linking Using Corvis-ST: Two-Year Follow-Up Results. *Med Sci Monit*. 2017; 23:3649–3656.
  24. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. 2014;121(4):812–21.
  25. Alonso-Aliste F, Amián-Cordero J, Rachwani-Anil R, De-Hita-Cantalejo C, Borroni D, Rocha-de-Lossada C, et al. Prophylactic Corneal Cross-Linking in Myopic Femtosecond Laser-Assisted In Situ Keratomileusis: Long-Term Visual and Refractive Outcomes. *Optics*. 2021;2(1):55–62.
  26. Dong R, Zhang Y, Yuan Y, Liu Y, Wang Y, Chen Y. A prospective randomized self-controlled study of LASIK combined with accelerated cross-linking for high myopia in Chinese: 24-month follow-up. *BMC Ophthalmol*. 2022;22(1):280.
  27. Kohnen T, Lwowski C, Hemkepler E, de'Lorenzo N, Petermann K, Forster R, et al. Comparison of Femto-LASIK With Combined Accelerated Cross-linking to Femto-LASIK in High Myopic Eyes: A Prospective Randomized Trial. *Am J Ophthalmol*. 2020;211:42–55.
  28. Li JX, Shen D, Zhou K, Sun XY, Wang YN, Wei W. Corrective effect of femtosecond laser assisted in situ keratomileusis Xtra on patients with moderate to high myopia after 2a postoperatively. *Int J Ophthalmol*. 2024;24(02):295–300.
  29. Tomita M, Yoshida Y, Yamamoto Y, Mita M. Waring Gt. In vivo confocal laser microscopy of morphologic changes after simultaneous LASIK and accelerated collagen crosslinking for myopia: one-year results. *J Cataract Refract Surg*. 2014;40(6):981–90.
  30. Di Y, Mo F, Li Y. Comparison of the Clinical Outcomes between Combined Femtosecond Laser-Assisted In Situ Keratomileusis and Corneal Cross Linking versus Combined Small-Incision Lenticule Extraction and Corneal Cross Linking. *J Ophthalmol*. 2022; 2022:6994355.

31. Kaiser KP, Wend J, Davidova P, Jandewerth T, Omerovic ZH, Hemkeppler E, et al. Eight-year results of laser in-situ keratomileusis with or without combined accelerated cross-linking in highly myopic eyes. *J Cataract Refract Surg.* 2025;52:245–52.
32. Bao F, Cao S, Wang J, Wang Y, Huang W, Zhu R, et al. Regional changes in corneal shape over a 6-month follow-up after femtosecond-assisted LASIK. *J Cataract Refract Surg.* 2019;45(6):766–77.
33. Zhang J, Chen T, Wang J, Bao F, Chen W, Stojanovic A, et al. Laser In Situ Keratomileusis (LASIK) Combined with Prophylactic Corneal Cross-Linking for Correction of Myopia: Regional Analysis of Corneal Morphology. *Ophthalmol Ther.* 2022;11(4):1423–39.
34. Kanellopoulos AJ, Asimellis G. Keratoconus management: long-term stability of topography-guided normalization combined with high-fluence CXL stabilization (the Athens Protocol). *J Refract Surg.* 2014;30(2):88–93.
35. Lim L, Lim EWL, Rosman M, Koh JCW, Htoon HM. Three-Year Outcomes of Simultaneous Accelerated Corneal Crosslinking and Femto-LASIK for the Treatment of High Myopia in Asian Eyes. *Clin Ophthalmol.* 2020;14:2865–72.
36. Ng AL, Kwok PS, Wu RT, Jhanji V, Woo VC, Chan TC. Comparison of the Demarcation Line on ASOCT After Simultaneous LASIK and Different Protocols of Accelerated Collagen Crosslinking: A Bilateral Eye Randomized Study. *Cornea.* 2017;36(1):74–7.

## Tables

| <b>Table 1</b> Baseline demographics and clinical characteristics of the two groups                                                                                                                                                                                                                                                   |                         |                         |        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--------|
|                                                                                                                                                                                                                                                                                                                                       | Group A                 | Group B                 | P      |
| Male/Female                                                                                                                                                                                                                                                                                                                           | 7/22                    | 5/29                    | -      |
| Age(years)                                                                                                                                                                                                                                                                                                                            | 29.14±6.96 18~45        | 26.02±5.64 18~43        | 0.010* |
| UDVA (log MAR)                                                                                                                                                                                                                                                                                                                        | 1.42±0.25 0.70~2.00     | 1.38±0.17 1.00~1.70     | 0.324  |
| CDVA (log MAR)                                                                                                                                                                                                                                                                                                                        | 0.00±0.00 0.00~0.00     | 0.00±0.01 0.00~0.05     | 0.322  |
| SE(D)                                                                                                                                                                                                                                                                                                                                 | -7.48±1.76 -10.50~-3.63 | -7.44±1.55 -11.38~-4.88 | 0.886  |
| Sphere(D)                                                                                                                                                                                                                                                                                                                             | -6.75±1.78 -10.50~-3.00 | -6.69±1.58 -11.00~-3.75 | 0.833  |
| Astigmatism(D)                                                                                                                                                                                                                                                                                                                        | -1.45±0.91 -3.50~0.00   | -1.50±0.97 -4.25~0.00   | 0.804  |
| CCT (um)                                                                                                                                                                                                                                                                                                                              | 508.00±25.92 454~566    | 495.68±26.49 458~553    | 0.013* |
| AveK(D)                                                                                                                                                                                                                                                                                                                               | 44.27±1.15 41.37~46.72  | 44.33±1.32 41.70~46.99  | 0.808  |
| Ablation depth (um)                                                                                                                                                                                                                                                                                                                   | 87.76±17.69 48~124      | 81.59±15.96 48~122      | 0.053  |
| RST (um)                                                                                                                                                                                                                                                                                                                              | 330.07±23.25 287~395    | 323.38±19.54 282~371    | 0.099  |
| PTA(%)                                                                                                                                                                                                                                                                                                                                | 0.35±0.03 0.29~0.41     | 0.35±0.02 0.30~0.40     | 0.580  |
| UDVA=uncorrected distance visual acuity; CDVA=corrected distance visual acuity; SE=spherical equivalent; D=dioptr; CCT=central corneal thickness; AveK=average keratometry; RST=residual stromal thickness; PTA=percentage of tissue altered. Data are presented as the mean ± SD.* p < 0.05 is considered statistically significant. |                         |                         |        |

Table 2 Type III tests of fixed effects for each outcome variable

| Parameters      | Effect       | Num. df | Den. df | F        | P       |
|-----------------|--------------|---------|---------|----------|---------|
| UCVA (log MAR)  | Group        | 1       | 102.643 | 0.381    | 0.538   |
|                 | Time         | 3       | 277.317 | 4559.818 | <0.001* |
|                 | Eye          | 1       | 159.034 | 0.315    | 0.576   |
|                 | Group × Time | 3       | 275.978 | 0.285    | 0.836   |
|                 | Group × Eye  | 1       | 178.046 | 0.724    | 0.396   |
|                 | Time × Eye   | 3       | 282.683 | 0.254    | 0.858   |
| SE (D)          | Group        | 1       | 58.473  | 1.459    | 0.232   |
|                 | Time         | 3       | 272.716 | 2333.383 | <0.001* |
|                 | Group × Time | 1       | 152.521 | 0.154    | 0.695   |
|                 | Group × Time | 3       | 273.468 | 0.878    | 0.453   |
|                 | Group × Eye  | 1       | 141.496 | 0.656    | 0.419   |
|                 | Time × Eye   | 3       | 271.277 | 0.092    | 0.965   |
| Astigmatism (D) | Group        | 1       | 60.299  | 0.912    | 0.343   |
|                 | Time         | 3       | 273.811 | 198.578  | <0.001* |
|                 | Group × Time | 1       | 153.389 | 3.529    | 0.062   |
|                 | Group × Time | 3       | 274.253 | 0.788    | 0.502   |
|                 | Group × Eye  | 1       | 146.521 | 0.052    | 0.820   |
|                 | Time × Eye   | 3       | 273.283 | 1.289    | 0.279   |
| AveK (D)        | Group        | 1       | 59.892  | 0.277    | 0.601   |
|                 | Time         | 3       | 292.263 | 2562.645 | <0.001* |
|                 | Group × Time | 1       | 96.431  | 0.403    | 0.527   |
|                 | Group × Time | 3       | 292.179 | 2.307    | 0.077   |
|                 | Group × Eye  | 1       | 115.224 | 0.141    | 0.708   |
|                 | Time × Eye   | 3       | 259.907 | 0.081    | 0.970   |
| CCT (μm)        | Group        | 1       | 60.895  | 0.784    | 0.379   |
|                 | Time         | 3       | 297.107 | 1621.79  | <0.001* |
|                 | Group × Time | 1       | 115.497 | 4.031    | 0.047*  |

|              |   |         |        |         |
|--------------|---|---------|--------|---------|
| Group × Time | 3 | 296.834 | 11.462 | <0.001* |
| Group × Eye  | 1 | 133.91  | 0.707  | 0.402   |
| Time × Eye   | 3 | 273.982 | 0.921  | 0.431   |

UCVA=uncorrected visual acuity; SE= spherical equivalent; AveK= average keratometry; CCT=central corneal thickness; Num. df=numerator degrees of freedom; Den. df=denominator degrees of freedom. \* p < 0.05 is considered statistically significant.

Table 3 Estimated marginal means  $\pm$  standard errors (95% CI)

| Parameters      | Time          | Group A                           | Group B                           |
|-----------------|---------------|-----------------------------------|-----------------------------------|
| UCVA (log MAR)  | Preop.        | 1.39 $\pm$ 0.02 (1.36, 1.42)      | 1.41 $\pm$ 0.02(1.38, 1.44)       |
|                 | 1 mo postop.  | -0.00 $\pm$ 0.02(-0.03, 0.03)     | 0.01 $\pm$ 0.02(-0.02, 0.04)      |
|                 | 6 mo postop.  | 0.01 $\pm$ 0.02(-0.02, 0.04)      | 0.00 $\pm$ 0.02(-0.03, 0.03)      |
|                 | 12 mo postop. | -0.02 $\pm$ 0.02(-0.05, 0.01)     | -0.02 $\pm$ 0.02(-0.05, 0.01)     |
| SE (D)          | Preop.        | -7.48 $\pm$ 0.13(-7.74, -7.23)    | -7.43 $\pm$ 0.13(-7.69, -7.18)    |
|                 | 1 mo postop.  | 0.20 $\pm$ 0.13(-0.05, 0.45)      | 0.06 $\pm$ 0.13(-0.19, 0.31)      |
|                 | 6 mo postop.  | 0.15 $\pm$ 0.13(-0.10, 0.40)      | -0.13 $\pm$ 0.13(-0.39, 0.12)     |
|                 | 12 mo postop. | 0.11 $\pm$ 0.13(-0.14, 0.36)      | -0.10 $\pm$ 0.13(-0.35, 0.16)     |
| Astigmatism (D) | Preop.        | -1.45 $\pm$ 0.07(-1.59, -1.31)    | -1.50 $\pm$ 0.07(-1.64, -1.36)    |
|                 | 1 mo postop.  | -0.33 $\pm$ 0.07(-0.47, -0.19)    | -0.24 $\pm$ 0.07(-0.37, -0.10)    |
|                 | 6 mo postop.  | -0.28 $\pm$ 0.07(-0.42, -0.15)    | -0.21 $\pm$ 0.07(-0.35, -0.07)    |
|                 | 12 mo postop. | -0.32 $\pm$ 0.07(-0.46, -0.19)    | -0.20 $\pm$ 0.07(-0.34, -0.06)    |
| AveK (D)        | Preop.        | 44.28 $\pm$ 0.26(43.75, 44.80)    | 44.34 $\pm$ 0.25(43.85, 44.83)    |
|                 | 1 mo postop.  | 37.85 $\pm$ 0.26(37.33, 38.38)    | 38.08 $\pm$ 0.25(37.59, 38.57)    |
|                 | 6 mo postop.  | 38.35 $\pm$ 0.26(37.83, 38.87)    | 38.38 $\pm$ 0.25(37.89, 38.87)    |
|                 | 12 mo postop. | 38.17 $\pm$ 0.26(37.65, 38.69)    | 38.57 $\pm$ 0.25(38.08, 39.05)    |
| CCT ( $\mu$ m)  | Preop.        | 508.02 $\pm$ 4.11(499.83, 516.22) | 494.59 $\pm$ 3.87(486.89, 502.29) |
|                 | 1 mo postop.  | 412.95 $\pm$ 4.12(404.75, 421.15) | 414.26 $\pm$ 3.87(406.55, 421.98) |
|                 | 6 mo postop.  | 419.97 $\pm$ 4.12(411.77, 428.17) | 413.79 $\pm$ 3.87(406.08, 421.50) |
|                 | 12 mo postop. | 418.34 $\pm$ 4.11(410.14, 426.54) | 417.69 $\pm$ 3.87(409.99, 425.40) |

UCVA=uncorrected visual acuity; SE= spherical equivalent; AveK= average keratometry; CCT=central corneal thickness. There were no statistically significant differences between groups (Group A vs. Group B) at any time point ( $P > 0.05$ ). See Table 2 for the fixed effects test results.

## Figures

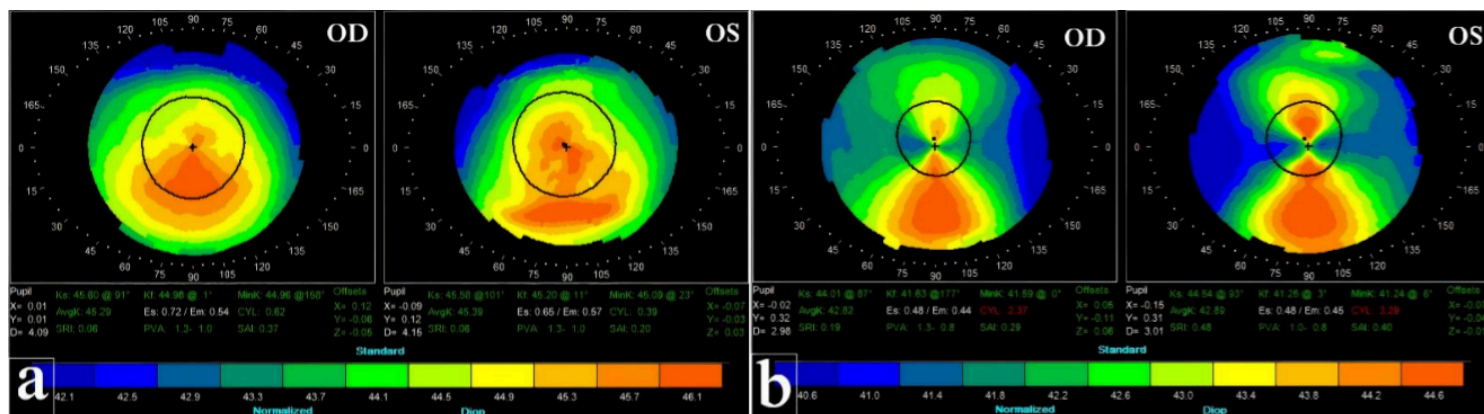


**Figure 1**

Preoperative corneal topography in some patients (Panel a: inferior steepening; Panel b: asymmetric bow-tie pattern. )

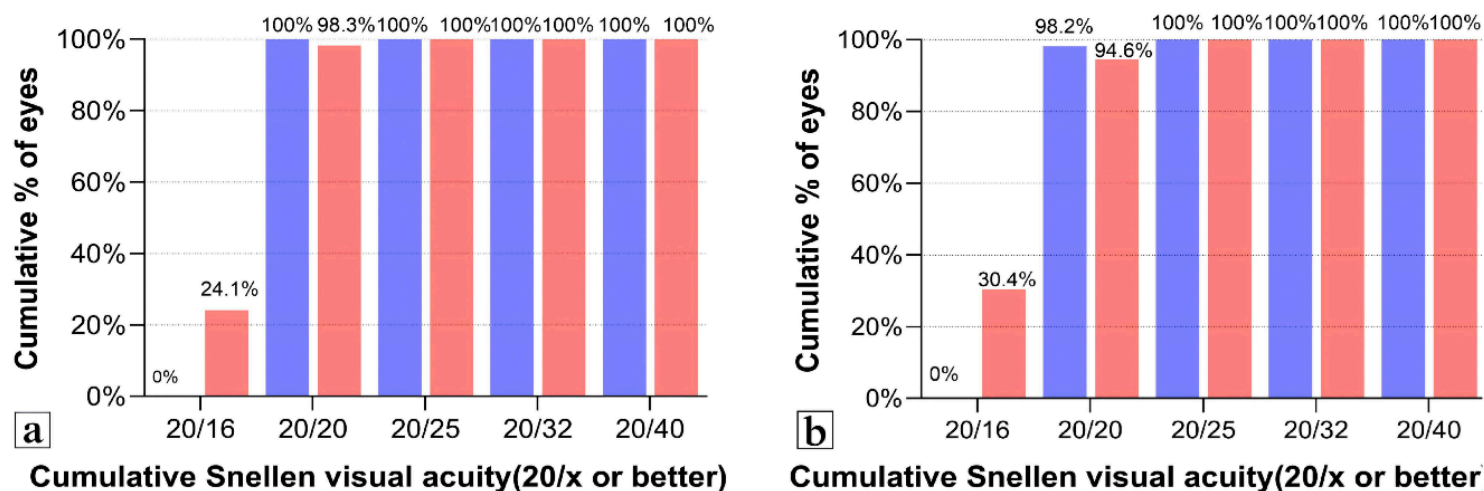


**Figure 2**

Postoperative UCVA vs preoperative CDVA at 12 months in Groups A and B (Panel a (Group A) and panel b (Group B): In both panels, blue represents preoperative CDVA; red represents UCVA at 12 months postoperatively.)

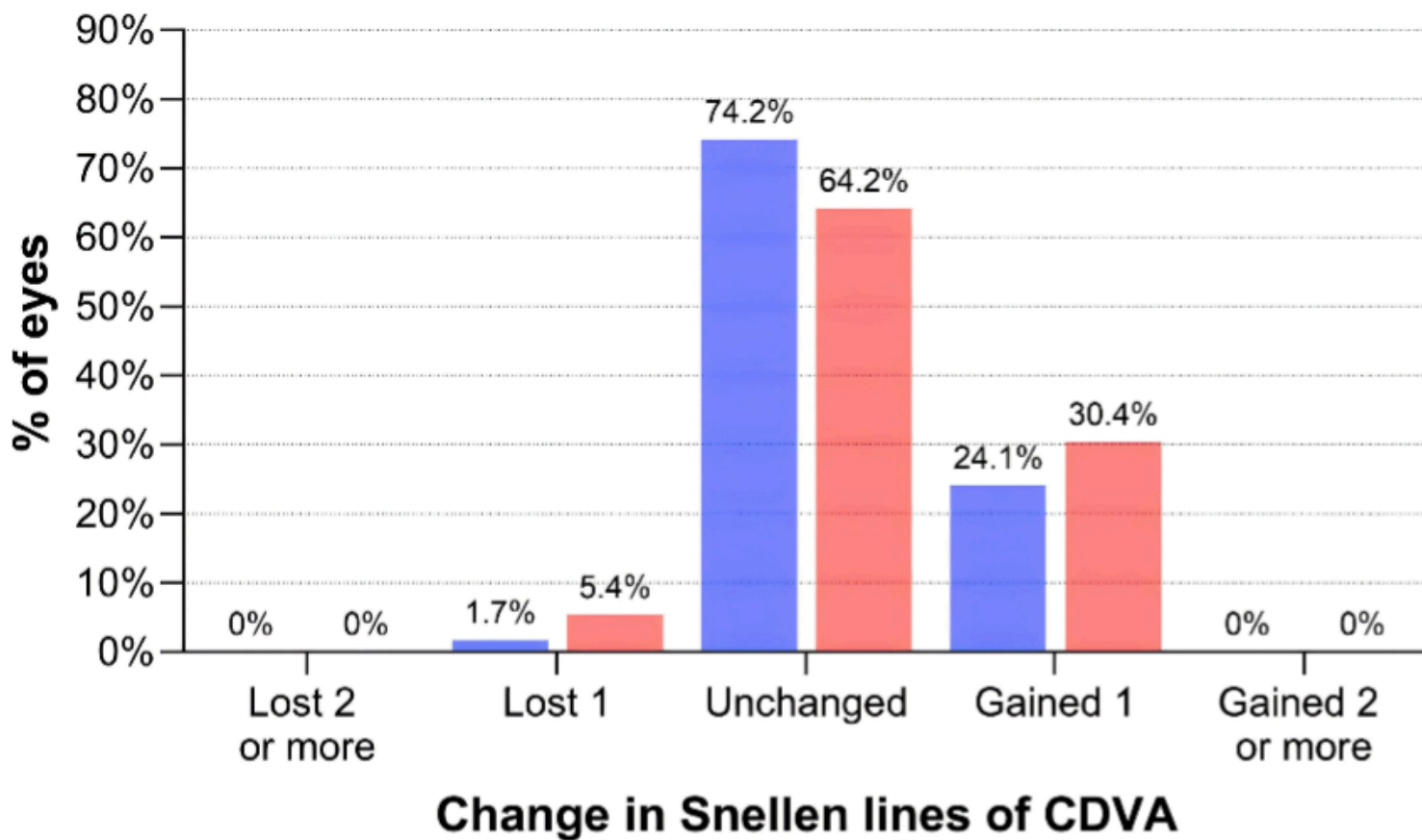


Figure 3

Proportion of eyes with Snellen line gain/loss in UCVA vs preoperative CDVA at 12 months (Blue represents Group A; red represents Group B.)

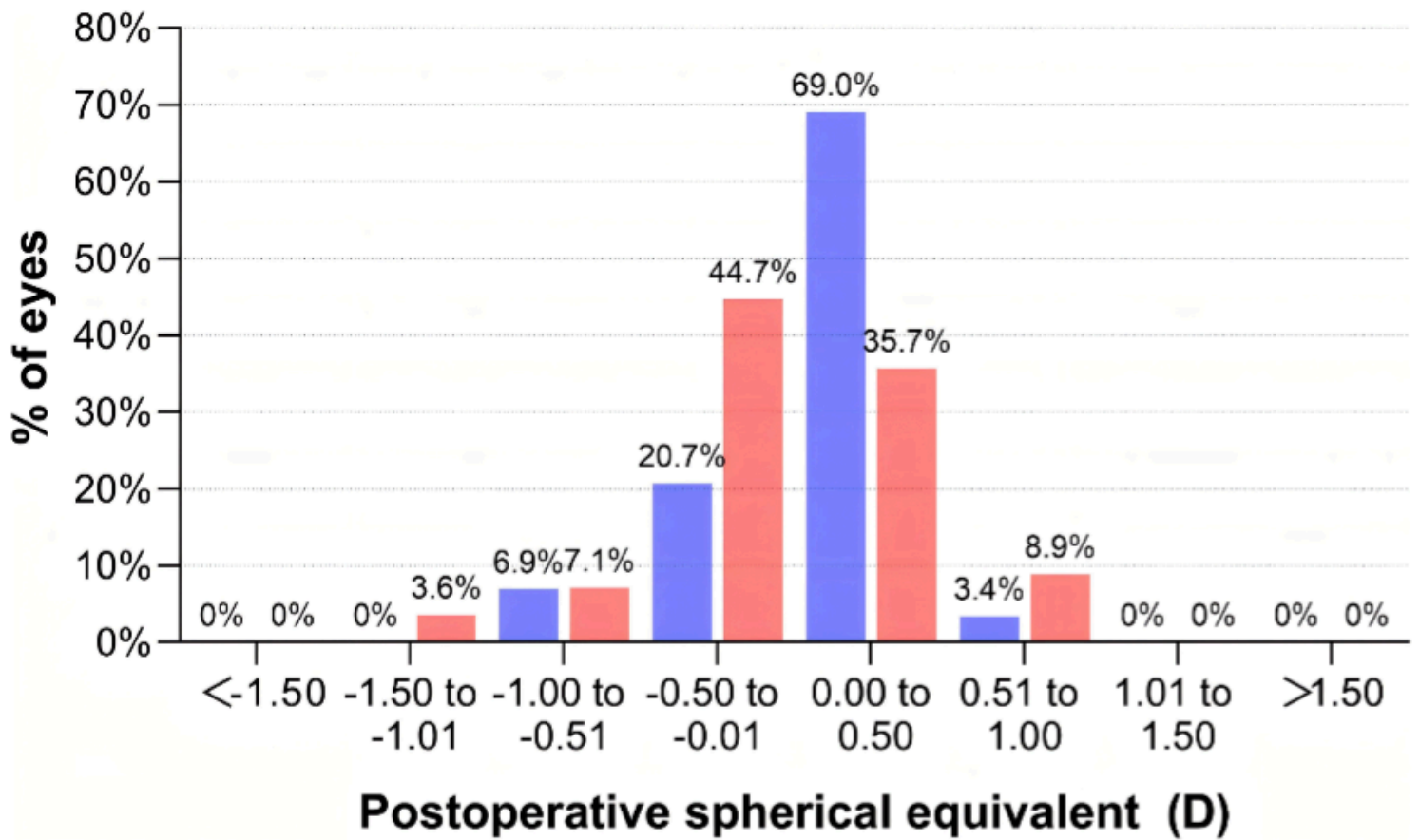


Figure 4

Postoperative SE in both groups at 12 months (Blue represents Group A; red represents Group B.)

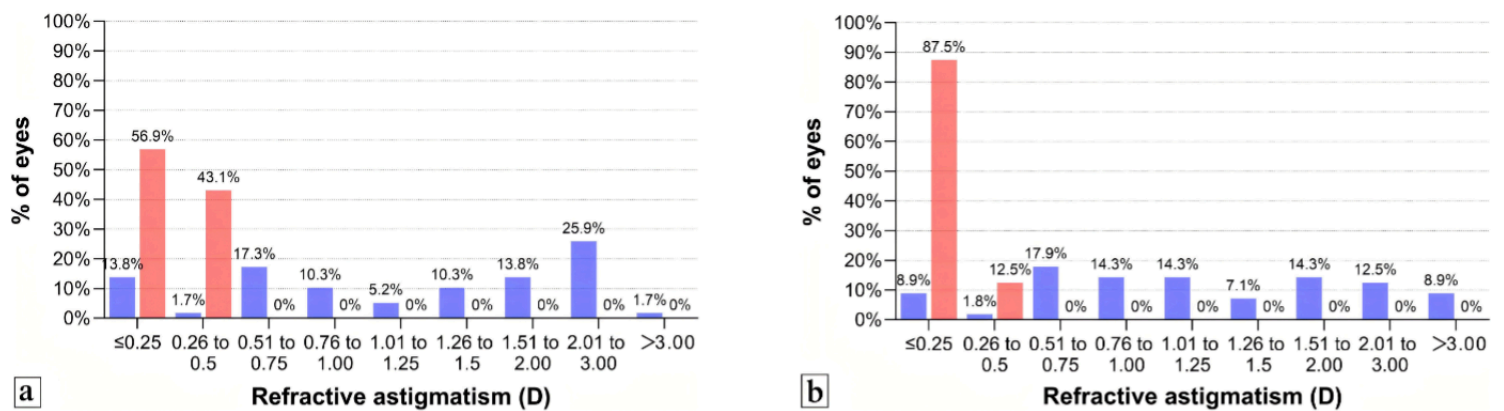


Figure 5

Postoperative astigmatism in Groups A and B at 12 months—Panel a (Group A) and panel b (Group B): In both panels, blue represents preoperative status; red represents 12 months postoperative.

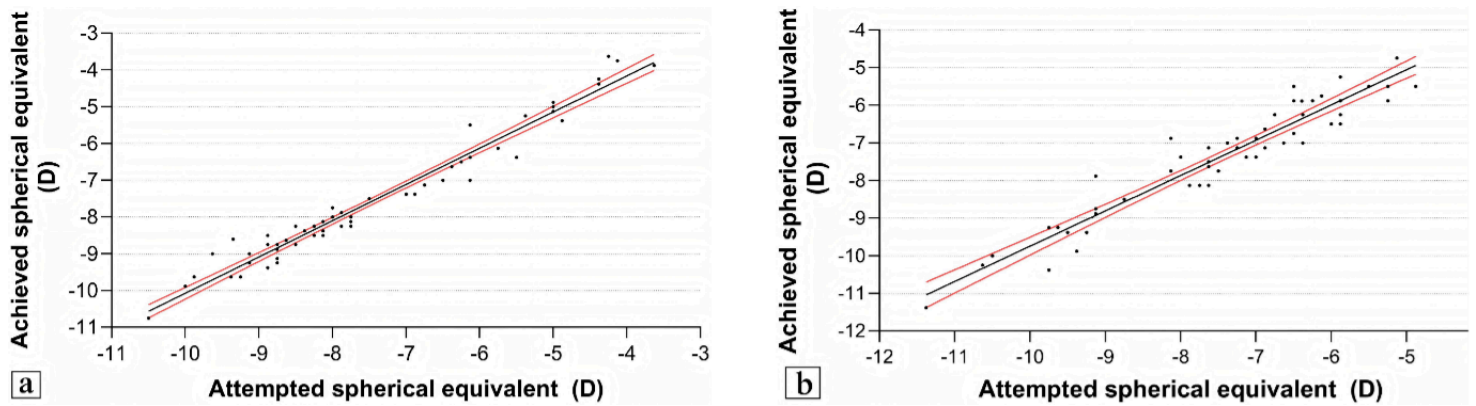


**Figure 6**

Achieved vs attempted SE in Groups A and B at 12 months (Panel a (Group A) and panel b (Group B): black solid line = regression line; red solid line = 95% confidence band; black dots = individual data points. Regression equations – Group A:  $y = -0.2167 + 0.9857x$ ,  $R^2 = 0.9629$ ; Group B:  $y = -0.3599 + 0.9384x$ ,  $R^2 = 0.9113$ .)

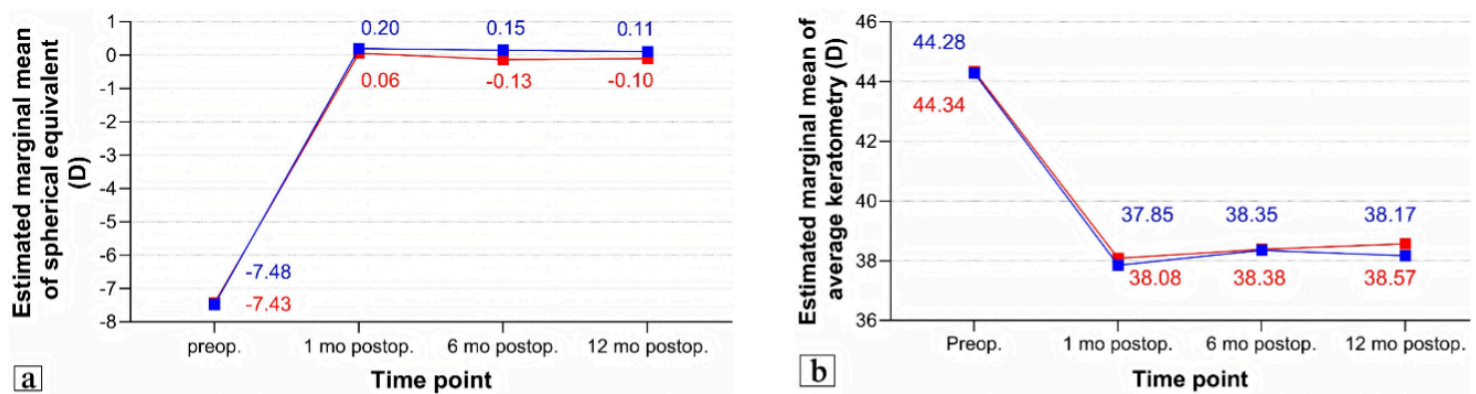


**Figure 7**

Stability of SE and AveK in both groups up to 12 months (Panel a (SE) and panel b (AveK): In both panels, blue represents Group A and red represents Group B.)