Biomechanical effects of tPRK, FS-LASIK and SMILE on the cornea

Yue Xin[1], Bernardo T. Lopes[2], Junjie Wang[1], Jie Wu[1], ManMan Zhu[1], MuChen Jiang[1], YuanYuan Miao[1], HuiNi Lin[3], Si Cao[4], XiaoBo Zheng[1], Ashkan Eliasy[2], ShiHao Chen[1], QinMei Wang[1], YuFeng Ye[1*], FangJun Bao[1*], Ahmed Elsheikh[2]

[1]Affiliated Eye Hospital of Wenzhou Medical College, China, [2]University of Liverpool, United Kingdom, [3]Joint Shantou International Eye Center, Shantou University & the Chinese University of Hong Kong, China, [4]Wuhan Puren Hospital, China

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Prof Elsheikh is a consultant to Oculus Optikgeräte GmbH

Author contribution statement

Ye YF and Bao FJ proposed the idea and designed the experiment; Ye YF, Bao FJ and Elsheikh A built initial constructs and supervised the project; Xin Y, Lopes BT, Wang JJ, Wu J, Zhu MM, Jiang MC, Miao YY, Lin HN, Cao S, Zheng XB, Eliasy A, Chen SH, Wang QM and Bao FJ collected and analyzed data. Xin Y, Lopes BT, Wang JJ, Wu J, Zhu MM, Jiang MC, Miao YY, Lin HN, Cao S, Zheng XB, Eliasy A, Chen SH, Wang QM and Bao FJ drafted the manuscript. Ye YF, Bao FJ and Elsheikh A revised the draft. All authors have read and approved the final manuscript.

Keywords

biomechanical response, in-vivo, TprK, FS-LASIK, smile

Abstract

Word count: 239

Purpose: To evaluate the in-vivo corneal biomechanical response to three laser refractive surgeries

Methods: Two hundred and twenty-seven patients submitted to tPRK, FS-LASIK or SMILE were included in this study. All cases were examined with the Corvis ST preoperatively (up to 3 months) and postoperatively at 1 month, 3 months and 6 months and the differences in the main device parameters were assessed. The three groups were matched in age, gender ratio, corneal thickness, refractive error corrections, optical zone diameter and intraocular pressure. They were also matched in the preoperative biomechanical metrics provided by the Corvis ST including SP-A1, IIR, DA and DARatio2mm.

Results: The results demonstrated a significant decrease post operation in SP-A1 and significant increases in IIR, DA and DARatio2mm ($p < 0.05$), all of which indicated reductions in overall corneal stiffness. Inter-procedure comparisons provided evidence that the smallest overall stiffness reduction was in the tPRK group, followed by the SMILE, and then the FS-LASIK group ($p < 0.05$). These results remained valid after correction for the change in CCT between pre and 6 months post operation, and for the percentage tissue altered. In all three surgery groups, higher degrees of refractive correction resulted in larger overall stiffness losses based on most of the biomechanical metrics.

Conclusions: The corneal biomechanical response to the three surgery procedures varied significantly. With similar corneal thickness loss, the reductions in overall corneal stiffness were highest in FS-LASIK and lowest in tPRK.

Contribution to the field

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Ethics statements

Studies involving animal subjects

Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects

Generated Statement: The studies involving human participants were reviewed and approved by the Eye Hospital, Wenzhou Medical University (WMU). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Inclusion of identifiable human data

Generated Statement: Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Data availability statement

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Yue Xin and Bernardo T Lopes are co-first authors of the article.

Affiliations

[1] Eye Hospital, Wenzhou Medical University, Wenzhou 325027, China

[2] School of Engineering, University of Liverpool, Liverpool L69 3GH, UK

[3] The Institute of Ocular Biomechanics, Wenzhou Medical University, Wenzhou 325027, China

[4] STU-CUHK Joint Shantou International Eye Center, Shantou 510000, China

[5] Wuhan Puren Hospital, Wuhan 430080, China

[6] National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK

[7] Beijing Advanced Innovation Center for Biomedical Engineering, Beihang University, Beijing, 100083, China

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Short Title

Corneal stiffness changes after surgeries

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Co-Corresponding author

Professor ShiHao Chen

No. 270 Xueyuan West Road, WenZhou City, ZheJiang Prov, 325027, China

e-mail: chenshihao73@126.com

Tel: 86-577-88068862

Fax: 86-577-88824115

Co-Corresponding author

Dr YuFeng Ye

No. 618 Fengqidong Road, HangZhou City, ZheJiang Prov, 310000, China

e-mail: yeyufeng2000@126.com

Tel: 86-571-88193999

Fax: 86-571-86795926

Corresponding author

Dr. FangJun Bao

No. 270 XueYuan West Road, WenZhou City, ZheJiang Prov, 325027, China

e-mail: bfjmd@126.com

Tel: 86-577-88067937

Fax: 86-577-88832083

Highlights:

The stiffness losses were smallest in tPRK, followed by SMILE, and then FS-LASIK

Abstract

Purpose: To evaluate the *in-vivo* corneal biomechanical response to three laser refractive surgeries

Methods: Two hundred and twenty-seven patients submitted to tPRK, FS-LASIK or SMILE were included in this study. All cases were examined with the Corvis ST preoperatively (up to 3 months) and postoperatively at 1 month, 3 months and 6 months and the differences in the main device parameters were assessed. The three groups were matched in age, gender ratio, corneal thickness, refractive error corrections, optical zone diameter and intraocular pressure. They were also matched in the preoperative biomechanical metrics provided by the Corvis ST including SP-A1, IIR, DA and DARatio2mm.

Results: The results demonstrated a significant decrease post operation in SP-A1 and significant increases in IIR, DA and DARatio2mm ($p < 0.05$), all of which indicated reductions in overall corneal stiffness. Inter-procedure comparisons provided evidence that the smallest overall stiffness reduction was in the tPRK group, followed by the SMILE, and then the FS-LASIK group ($p < 0.05$). These results remained valid after correction for the change in CCT between pre and 6 months post operation, and for the percentage tissue altered. In all three surgery groups, higher degrees of refractive correction resulted in larger overall stiffness losses based on most of the biomechanical metrics.

Conclusions: The corneal biomechanical response to the three surgery procedures varied significantly. With similar corneal thickness loss, the reductions in overall corneal stiffness were highest in FS-LASIK and lowest in tPRK.

Keywords: biomechanical response, in-vivo, tPRK, FS-LASIK, SMILE

Introduction

The current growth in interest in the evaluation of corneal biomechanics and the changes caused by laser vision correction (LVC) surgeries is driven mainly by the emergence of cases that developed iatrogenic ectasia [1]. This complication is multifactorial and some of its risk factors are still to be elucidated [2, 3]. The corneal instability leading to irregular astigmatism and vision impairment in this complication can be triggered in susceptible corneas by the tissue alterations and the subsequent stiffness reductions associated with the surgical procedures [4]. Bohac et al. found that corneal thickness (a major contributing factor to cornea's overall stiffness) below 500 µm was present in 50% of the ectatic cases [3]. Other researchers further noted that corneal instability can develop in previously stiff and stable corneas when the tissue alteration caused by the procedure was large [5, 6]. In connection with this observation, Bohac et al. identified risk factors related to the tissue alteration induced by the procedures such as a low residual stromal bed (≤ 300µm) in 30% of the cases and high percentage tissue thickness alteration (≥40%) in 20% [3]. Interestingly, these studies have shown that the majority of LASIK cases with these risk factors remained stable for a period between 2 to 8 years before developing ectasia, suggesting that still unknown factors affecting the corneal biomechanical behaviour were involved in this complication.

Over the years, and with more cases of iatrogenic ectasia reported [7], there was a search for procedures that would have a low impact on corneal biomechanics – this search led to an increased use of surface ablation surgeries including transepithelial PRK, and the introduction of the small-incision lenticule extraction (SMILE) surgery. However, recent case reports of iatrogenic ectasia post SMILE have highlighted the need to carefully evaluate the biomechanical advantage of this procedure over LASIK [8-13]. Even though there is experimental and numerical evidence of the reduced biomechanical effect of SMILE compared to LASIK [14, 15], this expected reduced effect was not evident in clinical studies [16, 17]. The same is true for comparisons between LASIK and SMILE on one hand, and PRK on the other. Although PRK did not involve tissue separation, or the formation of a cap or a flap, its expected reduced biomechanical effect compared to both LASIK and SMILE was not consistently seen in earlier clinical studies [14, 18-20].

With the fast growth in popularity of laser vision correction surgeries worldwide [21], the increased recognition of the effect of corneal biomechanics on surgery outcomes [22, 23] , and the continued concern about post-surgery ectasia, it is important to reach a definitive answer concerning the mechanical effect of different LVCs. This study is part of our efforts to evaluate clinically the *in vivo* biomechanical impact of the three most common forms of LVCs, namely FS-LASIK, SMILE and tPRK, while controlling for potential confounding factors.

Materials and Methods

Patient Inclusion

This prospective comparative cases series was approved by the Ethics Committee of the Eye Hospital, Wenzhou Medical University (WMU). Two hundred and twenty-seven Chinese patients, who had undergone corneal refractive surgery for myopia and astigmatism at the Eye Hospital of WMU were included in this study. All the patients belong to east Asian race and the Han nationality. The patients had myopia between -1.00 and -9.75 D (mean -4.82 ±1.57 D) and astigmatism between 0 and -3.00 D (mean -0.76 ±0.59 D). Among these patients, 74 received transepithelial PRK (tPRK), 81 accepted Femtosecond laser-assisted LASIK (FS-LASIK) and 72 underwent SMILE. Informed consent was provided by all participants to use their data in research. Only one eye, randomly selected per patient, was included in analysis. All the LVC was operated by the same operator and only patients with no systemic or ocular condition apart from the refractive error, and with complete records of the surgical procedure, clinical examination and Corvis ST (CVS, software version 1.6r2031, OCULUS Optikgeräte, Wetzlar, Germany) results up to 3 months on preoperative (pre), 1 month (pos1m), 3 months (pos3m) and 6 months postoperative (pos6m) were included. Those did not complete the 6 months postoperative follow-up were excluded from the study.

Surgical Technique

In the tPRK procedure, the epithelium and stroma were ablated with a central ablated epithelium thickness of 55 μm in a single step using the aberration-free mode of the Schwind Amaris 750Hz excimer laser (Schwind eye-tech-solutions, Kleinostheim, Germany). In the FS-LASIK procedure, the lamellar flap was created with a femtosecond laser (Ziemer Ophthalmic Systems AG, Port, Switzerland). The flaps had a superior hinge, their thickness ranged from 95 to 110 μm and diameter from 8.5 to 9.0mm. The FS-LASIK ablation was then performed using the Schwind Amaris 750Hz excimer laser. The SMILE procedure was performed using the VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany). A stromal lenticule was removed leaving a cap whose thickness ranged from 115 to 140 μm.

The postoperative care was similar for the three procedures starting with one drop of tobramycin/dexamethasone (Tobradex; Alcon, TX, USA) instilled at the surgical site. This was followed by placing on the cornea a bandage contact lens (Acuvue Oasys; Johnson & Johnson, FL, USA) and keeping it for one day in FS-LASIK and for 3 to 7 days in the tPRK group until complete corneal re-epithelisation. Fluorometholone 0.1% (Flumetholon; Santen, Osaka, Japan) and topical levofloxacin 0.5% (Cravit; Santen, Osaka, Japan) were then applied 4 times a day in all three groups. In the tPRK group, the fluorometholone dosage was tapered each subsequent 2-3 weeks and stopped 2-3 months after surgery, while for FS-LASIK and SMILE, the fluorometholone dosage was tapered each subsequent week until 1 month after surgery.

Surgical parameters including optical zone diameter (OZD) and manifest refractive error correction (MRx) were recorded from surgery planning/treatment printouts. The MRx was recorded with spherical (MRxSph) and cylindrical parts (MRxCyl) and was converted into spherical equivalent (SE). Central corneal thickness (CCT) and mean corneal curvature (Km) was measured with a Pentacam (software version: 1.21r65, OCULUS Optikgerate GmbH, Wetzlar, Germany), and used to calculate the difference in CCT (CCT_{dif}) between the values obtained before and 6 months after surgery. The CCT measurements also allowed calculation of the tissue altered (TA) as TA = CCT_{dif} in the tPRK group, TA = flap thickness + CCT_{dif} in the FS-LASIK group, and TA = cap thickness + CCT_{dif} in the SMILE group. PTA was defined as percentage tissue altered (PTA) as PTA= TA/CCT_{pre}. According to SE measured pre-surgery, participants were divided into two groups with low to moderate myopia

(-0.50D > SE ≥ -5.00D, LM group) and high myopia (-5.00D > SE, HM group) as we did in a previous study [24]. No patients experienced complications related to the surgical procedures.

Biomechanical evaluation

All Corvis ST exams were taken in the sitting position with undilated pupils by two experienced examiners. They were taken in the same half-day session to minimize diurnal effects. Five Corvis ST biomechanical metrics that had been linked to corneal stiffness [25, 26] were recorded pre and post-surgery. The parameters included the stiffness parameter at first applanation (SP-A1) [26], calculated as the difference between the adjusted air puff pressure at first applanation (AdjAP1) and biomechanically-corrected intraocular pressure (bIOP) divided by the defection amplitude at the first applanation (A1DeflAmp).

$$\text{SP-A1} = (\text{adjAP1} - \text{bIOP}) / (\text{A1DeflAmp}) \qquad \text{Equation 1}$$

The metrics also included the integrated inverse radius (IIR) – the integrated sum of the inverse concave radii between the first and second applanation events, the deformation amplitude (DA), which measures the corneal apex maximum displacement under air-puff, and the ratio between the deformation amplitude 2mm away from apex and the apical deformation (DARatio2mm). These parameters have been described as suitable parameters to evaluate corneal biomechanics in vivo [25].

Statistical Analysis

All statistical analyses were performed using PASW Statistics 20.0 (SPSS Inc., Chicago, USA). Baseline characteristics among the three surgery groups were paired using propensity density scores in order to reduce the influence of confounding factor. Comparisons among the three surgery groups were made using the MANOVA of repeated measurements. One-way ANOVA and ANCOVA (Analysis of Covariates) with a general linear model were used to compare the changes in biomechanical metrics in the three surgery groups, where CCT_{dif} or PTA was considered a covariate.

The frequencies of the categorical variable gender were arranged in a 3x2 contingency table, and the Chi-square test of independence was used to compare them. A p-value of less than 0.05 was considered statistically significant.

Results

The three groups (tPRK, FS-LASIK and SMILE) were matched in age (27.2±5.2 yeas vs 26.1±4.8 years and 26.3±6.0 years, $F = 0.876$, $p = 0.418$), gender ratio (Male/Female: 22/52 vs 37/44 and 33/39, $\chi^2 = 5.312$, $p = 0.070$), CCT (540.1±29.3 μm vs 545.0±27.2 μm and 546.6±21.5 μm, $F = 1.838$, $p = 0.162$), MRxSph (-4.69±1.57 D vs -5.04±1.58 D and -4.72±1.57 D, $F = 1.151$, $p = 0.318$), MRxCyl (-0.81±0.57 D vs -0.66±0.57 D and -0.83±0.63 D, $F = 1.776$, $p = 0.172$), OZD (6.59±0.37 mm vs 6.61±0.34 mm and 6.61±0.18 mm, $F = 0.133$, $p = 0.876$) and bIOP (13.90±1.83 mmHg vs 14.17±1.91 mmHg and 13.67±1.68 mmHg, $F = 1.456$, $p = 0.235$). Record matching was also applied for the LM group and HM group individually except for CCT_{dif} (Table 1).

Km decreased at pos1m compared with the pre-surgery stage in all surgery groups (all $p < 0.01$). During follow up, Km values at pos3m and pos6m were significantly different in the tPRK group ($p = 0.007$) although there was little change from pos1m to pos3m ($p > 0.05$). In contrast, in the FS-LASIK group, Km experienced significant fluctuations during follow up (pos1m vs pos3m: $p < 0.01$; pos1m vs pos6m: $p < 0.01$; pos3m vs pos6m: $p = 0.019$). Km values at pos1m and pos6m were also significantly different in the SMILE group ($p = 0.020$), but the changes were not significant within shorter follow-up stages ($p > 0.05$).

Figures 1 to 4 and Table 2 show the corneal biomechanical metrics measured by Corvis ST for the three groups both pre and post operation, which represent the effect of the surgical procedure in each patient group. While there were no significant differences (all p> 0.05) in SP-A1, IIR, DA and

DARatio2mm among the three surgery groups before surgery, uneven shifts towards overall softening were observed after all three surgery procedures (at pos1m) with small, inconsistent and insignificant stiffness changes taking place between pos1m and pos6m in most situations.

SP-A1 decreased at pos1m compared with the pre surgery stage in all surgery groups (all $p < 0.01$), indicating overall stiffness reduction, then experienced non-significant ($p > 0.05$) fluctuations during follow up except for the LM-tPRK subgroup ($p = 0.039$, pos3m vs pos6m). Comparing pos6m and pre, the change in SP-A1 was larger in FS-LASIK (-34.15±13.17 mmHg/mm, significant when compared with tPRK, $p = 0.008$), smaller in SMILE (-32.40±10.42 mmHg/mm, non-significant when compared with tPRK, $p = 0.090$) and smallest in tPRK (-27.40±16.91 mmHg/mm), Figure 1. After correction for CCT_{dif}, the changes in SP-A1 between pre and pos6m in tPRK were statistically lower than in FS-LASIK ($p = 0.001$) and SMILE ($p = 0.022$). Further, the decrease in SP-A1 from pre to pos6m in FS-LASIK was statistically higher than in SMILE ($p = 0.022$) after correction for TA. However, after correction for PTA, the changes in SP-A1 between pre and pos6m became non-significant among the three groups ($p > 0.05$). The SP-A1 changes from pre to pos6m were also significantly higher in the HM group than in the LM group after tPRK ($t = 2.715$, $p = 0.008$), FS-LASIK ($t = 3.876$, $p <0.001$), and SMILE ($t = 2.626$, $p = 0.011$).

IIR exhibited a significant increase from pre to pos1m ($p < 0.01$), demonstrating overall stiffness reduction, and continued to undergo increases, albeit at a much reduced rate, from pos1m to pos6m in the three groups, Figure 2. The differences between pre and pos6m were statistically significant, being smallest in tPRK (2.40±0.94 mm^{-1}) and relatively higher in SMILE (2.84±1.03 mm^{-1}) when compared with tPRK ($p = 0.020$). The IIR changes were also higher in FS-LASIK (2.85±0.96 mm^{-1}) compared with tPRK ($p = 0.014$). After correction for CCT_{dif}, the changes in IIR between pre and pos6m in tPRK remained lower than in FS-LASIK ($p = 0.004$) and SMILE ($p = 0.002$). Also, after correction for TA, the growth in IIR from pre to pos6m was similar in FS-LASIK and SMILE ($p = 0.248$). However, after correction for PTA, the changes in IIR between pre and pos6m became non-significant among the three groups ($p > 0.05$). The IIR increases from pre to pos6m were further significantly higher in the HM subgroup than in the LM subgroup (tPRK: t = -4.678, p < 0.001, FS-LASIK: t = -4.438, p < 0.001, SMILE: t = -3.417, p = 0.001).

Another evidence of overall stiffness reduction was seen in the significant increases observed in DA at pos1m compared with the pre surgery stage in all groups (p > 0.05 except in the HM subgroup of tPRK). DA then continued to increase in most follow up stages from pos1m to pos6m. With tPRK, this trend was more obvious from pos1m to pos3m, Figure 3. The change in DA from pre to pos6m in FS-LASIK was significantly higher than in tPRK (0.134±0.057 mm vs 0.101±0.086 mm, p = 0.009) but was not significantly different from the change in SMILE (0.118±0.063 mm, p = 0.409). Meanwhile, the changes in tPRK and SMILE were similar (p = 0.448). After correction for CCT_{dif}, the changes in DA between pre and pos6m in tPRK remained statistically lower than in FS-LASIK (p = 0.024), but not different from SMILE (p = 0.750). Meanwhile, the increase in DA from pre to pos6m after FS-LASIK and SMILE were similar (p = 0.277) after correction for TA. However, after correction for PTA, the changes in DA between pre and pos6m were larger in FS-LASIK compared with tPRK (p = 0.038), but remained similar in SMILE and tPRK (p = 1.000). In contrast, the corresponding changes in DA from pre to pos6m were similar in the LM and HM subgroups of tPRK (t = -0.855, p = 0.396) and SMILE (t = 0.084, p = 0.934), but not FS-LASIK (t = -2.470, p = 0.016).

DARatio2mm also significantly increased, denoting overall stiffness reduction, in all three groups from pre to pos1m (all p < 0.01). DARatio2mm then experienced a gradual, slight decrease through the rest of the follow up period in the three groups, Figure 4. The increases in DARatio2mm between pre and pos6m were statistically significant, being smallest in tPRK (0.79±0.55), higher in SMILE (1.15±0.83) compared with tPRK (p < 0.01) and also higher in FS-LASIK (1.28±0.53) when compared with tPRK (p < 0.01). After correction for CCT_{dif}, the changes in DARatio2mm between pre and pos6m in tPRK were statistically lower than in FS-LASIK (p = 0.000) and in SMILE (p = 0.001). Further, the increase of DARatio2mm from pre to pos6m in FS-LASIK were statistically higher than in SMILE (p = 0.020) after correction for TA. However, after correction for PTA, the changes in DARatio2mm between pre and pos6m were larger in FS-LASIK compared with tPRK (p < 0.01), and remained similar in SMILE and tPRK (p = 0.416). The DARatio2mm increases from pre to pos6m were further significantly higher in the HM subgroup than in the LM subgroup (tPRK: t = -3.309, p = 0.001, FS-LASIK: t = -2.104, p = 0.039), SMILE: t = -2.087, p = 0.040).

Discussion

In this study, the biomechanical impact of the three most-common LVC procedures was evaluated by monitoring the changes in the *in vivo* biomechanical parameters obtained by the Corvis ST over a 6 month follow up period. A significant shift in parameter values towards softening was observed following all three surgery forms. After correction for corneal thickness loss (CCT_{Diff}) or percentage tissue altered (PTA), the changes in the four biomechanical metrics (SP-A1, IIR, DA and DARatio2mm) with strong correlation to cornea's overall stiffness, showed significant stiffness reductions in all three surgery groups. The metrics' values also indicated that FS-LASIK was associated with the largest stiffness reduction, followed by SMILE, and then tPRK. The results also illustrated continued biomechanical changes during the postoperative period, but these changes were small, inconsistent and insignificant.

The *in vivo* measurement of corneal biomechanics with air-puff systems like the Corvis ST used in this study was assessed in earlier publications [27]. Among the several parameters that Corvis ST offers, four were selected for being closely associated with corneal overall stiffness, namely SP-A1, IIR, DA and DARatio2mm. In earlier studies, SP-A1 was correlated with removed corneal tissue in refractive surgery procedures [28], DA was influenced by changes in bIOP [29], and IIR and DARatio2mm had the highest correlation with CCT [25]. All four parameters were also able to detect corneal softening in keratoconus [26, 30].

In order to minimise the effect of confounding factors that may have an effect on the four biomechanical parameters selected, the groups were paired for age, gender, baseline CCT, IOP and biomechanical parameter readings. The additional pairing for surgical parameters was more challenging since different ablation profiles and depths were obtained with different techniques, even with no statistically significant differences being observed in the corrected manifest equivalent and treated optical zones. Moreover, the difference in the planned tissue removal and achieved stromal reduction could be up to 12 μm in SMILE while in LASIK it is as small as less than 1 μm [31, 32].

When SMILE was introduced, it was theorised to be the procedure with the least impact on corneal stiffness [33]. Seven et al. observed less impact on anterior stromal collagen mechanics in SMILE compared to flap-based procedures in numerical modelling [15]. Several clinical studies were conducted to evaluate the difference between the procedures. Guo et al carried out a meta-analysis of *in vivo* evaluation of corneal biomechanical properties after the procedures [16]. They observed using the corneal hysteresis (CH) and corneal resistance factor (CRF) from the Ocular Response Analyzer (ORA), that SMILE was superior to FS-LASIK and comparable to PRK. Raevdal et al, in a systematic review comparing SMILE with flap-based procedures, did not find significant differences between the procedures using CH or CRF [17]. Both systematic reviews included only a limited number of randomised clinical trials and detected a serious risk of bias due to the presence of confounding factors.

Parameters of the relatively new Corvis ST were evaluated in recent studies on refractive surgeries. Cao et al studied the effect of FS-LASIK and SMILE using two of the parameters evaluated in this study; DARatio2mm and integrated Inverse Radius[34]. Although FS-LASIK showed higher post-surgery values of both parameters, indicating higher reductions in stiffness, no significant differences were observed between FS-LASIK and SMILE. The bIOP was also significantly reduced by a similar amount at the postoperative of both procedures. Khamar et al also reported no significant differences between the procedures in DARatio2mm and integrated Inverse Radius in a contralateral study with up to 1 month follow-up [35]. They also found no significant differences in SP-A1 or bIOP postoperatively, even though the median value of bIOP was 1.1 mmHg lower in SMILE than FS-LASIK at the postoperative stage. In another study, Lee et al observed significantly higher increases in DARatio2mm and IIR after FS-LASIK compared to tPRK up to 6 months follow-up [36]. Meanwhile, there were no significant differences between FS-LASIK and tPRK in the reduction of SP-A1 or bIOP readings.

In this study, with a view to uniformize the data analysis and reduce the confounding factors, the three procedures were evaluated together using data from a single centre and a single surgeon. All exams were taken at the same period of the day in order to avoid diurnal variance [37]. Baseline age, CCT, bIOP and biomechanical parameters were paired along with surgical parameters including optical zone dimeter and refractive corrections. The main trends reported in the literature that tPRK and FS-LASIK were the procedures with the least and highest effects on corneal biomechanics, respectively, were observed in this study. The SMILE procedure, on the other hand, presented intermediate effects.

Considering the pairwise analysis, the three procedures showed significant shifts towards softening at pos1m in all biomechanical metrics considered (SP-A1, IIR, DA and DARatio2mm). The increases in DARatio2mm were not significantly different between FS-LASIK and SMILE, but were larger than those recorded after tPRK. This was also observed by Cao et al [34] in which the SE and the baseline bIOP values were the closest to the ones in this study, but not by Khamar et al or by Lee et al [35, 36] in which the SE was lower and the baseline bIOP values higher than corresponding values in this study.

As a further observation, biomechanical changes induced by the surgical operations were generally larger in the high myopia group compared to the low to moderate myopia group. This was evident in the postoperative changes in SPA1, IIR, DA and DARatio2mm observed after all three procedures. This outcome is expected as higher degrees of myopic correction typically require more tissue removal and hence can introduce larger reductions in corneal biomechanics. This particular observation was also found in several previous studies [33, 36, 38-40].

By conducting a continuous follow-up, the study also revealed an overall softening trend (although the changes were small and insignificant) in the postoperative stages (pos1m to pos6m) in addition to the immediate effects caused by the surgery (pre to pos1m), similarly with results in an animal test using rabbit done by Raghunathan et al [41]. The results demonstrated that this trend did not show signs of stopping by the time of pos6m which was most evident in IIR (Figure 2) and DA (Figure 3). The DARatio2mm however appeared to show an opposite trend with a further decrease from pos1m to pos6m following the immediate increase after surgery at pos1m. At first glance, this finding contradicted the further softening trend suggested by IIR and DA; however, because DARatio2mm is defined as the ratio of deformation amplitude between the corneal apex and location 2mm away from it, the results in fact indicated that the cornea deformation amplitude 2mm away from the apex increased more than that at the apex (DA), which in turn showed non-uniform biomechanical changes (softening) across the cornea. The continuous changes in biomechanical parameters over time and asynchronization of these changes in different regions are believed to be related to the wound healing process after surgery, and they may be the cause of the continuous shape changes after surgery reported above and observed in Bao et al [42]. Corneal curvature changed statistically significant during the follow-up consisted with that, especially in FS-LASIK group.

Combined with the correction for corneal thickness loss and percentage tissue altered, which considered the thickness of separated tissue in the FS-LASIK flap and the SMILE cap, the four biomechanical metrics (SP-A1, IIR, DA and DARatio2mm) showed the largest overall stiffness reductions in FS-LASIK, followed by SMILE, and the lowest stiffness losses in tPRK. These results indicate the negative biomechanical effects of the tissue separation in FS-LASIK flap and SMILE cap, in addition to the tissue ablation in all three procedures. Nevertheless, the decreases in SP-A1 and increases in DARatio2mm from pre to pos6m in FS-LASIK were statistically higher than in SMILE ($p = 0.022$ and 0.020, respectively). These trends illustrate that the SMILE cap was able to contribute to post-surgery corneal stiffness more than an FS-LASIK flap with equal thickness. Separating the tissue flap in LASIK effectively means losing completely this part of the cornea, and along with the tissue ablation, the tissue loss in LASIK is therefore much more than that in tPRK. In SMILE, an attempt is made to maintain some connection between the cap and the rest of the cornea, but this connection is not perfect, as it is affected by the incision and the loss of support on the posterior side. for these reasons, it is expected that tPRK would have a smaller (or much smaller) biomechanical effect on the cornea than both LASIK and SMILE.

Stress-Strain index (SSI) was recently introduced as a measure of the material stiffness of corneal tissue [43]. Material stiffness is part of overall stiffness, alongside geometric stiffness, which is dominated by corneal thickness, but also influenced by corneal curvature and diameter. With refractive surgery, it is expected that the large thickness loss (due to both tissue ablation and separation) would lead to substantial geometric stiffness loss, and significant reductions in corneal overall stiffness. On the other hand, the material stiffness would not be expected to undergo notable changes, as these would be limited to the small effects of wound healing following surgery [44]. For these reasons, the SSI (measure of material stiffness) would not be expected to demonstrate significant changes, unlike those taking place in the overall stiffness parameters like the SP and IIR. Presenting these small changes in SSI alongside the large changes in overall stiffness metrics could therefore be confusing – and in any case not relevant to the subject of this study, and for this reason, SSI was not included in the present comparisons.

The study included a number of limitations, one of which was the diurnal fluctuations of the IOP that were reported to influence the values of the four Corvis ST metrics considered [29]. The variations observed between the pre and post-surgery stages could have been affected by this change. Further, the use of different femtosecond lasers in FS-LASIK and SMILE, which was necessary due to the Wenzhou Eye Hospital surgical routine, may have led to different flap and cap architectures although the differences were not significant [45].

In conclusion, the biomechanical impact of tPRK, FS-LASIK and SMILE varied significantly in this study where the data was paired for the main confounding factors. The SMILE procedure induced less corneal biomechanical degradation than FS-LASIK but more than tPRK in cases with comparable corrected refractive errors and optical zone diameter.

References

1. Randleman JB. Ectasia After Corneal Refractive Surgery: Nothing to SMILE About. *J Refract Surg* 2016;32:434-435.
2. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. *J Cataract Refract Surg* 2007;33:1530-1538.
3. Bohac M, Koncarevic M, Pasalic A, et al. Incidence and Clinical Characteristics of Post LASIK Ectasia: A Review of over 30,000 LASIK Cases. *Semin Ophthalmol* 2018;33:869-877.
4. Ambrosio R, Jr., Dawson DG, Salomao M, Guerra FP, Caiado AL, Belin MW. Corneal ectasia after LASIK despite low preoperative risk: tomographic and biomechanical findings in the unoperated, stable, fellow eye. *J Refract Surg* 2010;26:906-911.

5. Santhiago MR, Smadja D, Gomes BF, et al. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. *Am J Ophthalmol* 2014;158:87-95 e81.
6. Santhiago MR, Smadja D, Wilson SE, Krueger RR, Monteiro ML, Randleman JB. Role of percent tissue altered on ectasia after LASIK in eyes with suspicious topography. *J Refract Surg* 2015;31:258-265.
7. Ambrosio R, Jr. Post-LASIK Ectasia: Twenty Years of a Conundrum. *Semin Ophthalmol* 2019;34:66-68.
8. El-Naggar MT. Bilateral ectasia after femtosecond laser-assisted small-incision lenticule extraction. *J Cataract Refract Surg* 2015;41:884-888.
9. Wang Y, Cui C, Li Z, et al. Corneal ectasia 6.5 months after small-incision lenticule extraction. *J Cataract Refract Surg* 2015;41:1100-1106.
10. Mattila JS, Holopainen JM. Bilateral Ectasia After Femtosecond Laser-Assisted Small Incision Lenticule Extraction (SMILE). *J Refract Surg* 2016;32:497-500.
11. Voulgari N, Mikropoulos D, Kontadakis GA, Safi A, Tabibian D, Kymionis GD. Corneal Scarring and Hyperopic Shift After Corneal Cross-linking for Corneal Ectasia After SMILE. *J Refract Surg* 2018;34:779-782.
12. Pazo EE, McNeely RN, Arba-Mosquera S, Palme C, Moore JE. Unilateral ectasia after small-incision lenticule extraction. *J Cataract Refract Surg* 2019;45:236-241.
13. Shetty R, Kumar NR, Khamar P, et al. Bilaterally Asymmetric Corneal Ectasia Following SMILE With Asymmetrically Reduced Stromal Molecular Markers. *J Refract Surg* 2019;35:6-14.
14. Spiru B, Kling S, Hafezi F, Sekundo W. Biomechanical Properties of Human Cornea Tested by Two-Dimensional Extensiometry Ex Vivo in Fellow Eyes: Femtosecond Laser-Assisted LASIK Versus SMILE. *J Refract Surg* 2018;34:419-423.
15. Seven I, Vahdati A, Pedersen IB, et al. Contralateral Eye Comparison of SMILE and Flap-Based Corneal Refractive Surgery: Computational Analysis of Biomechanical Impact. *J Refract Surg* 2017;33:444-453.
16. Guo H, Hosseini-Moghaddam SM, Hodge W. Corneal biomechanical properties after SMILE versus FLEX, LASIK, LASEK, or PRK: a systematic review and meta-analysis. *BMC Ophthalmol* 2019;19:167.
17. Raevdal P, Grauslund J, Vestergaard AH. Comparison of corneal biomechanical changes after refractive surgery by noncontact tonometry: small-incision lenticule extraction versus flap-based refractive surgery - a systematic review. *Acta Ophthalmol* 2019;97:127-136.
18. Yildirim Y, Olcucu O, Basci A, et al. Comparison of Changes in Corneal Biomechanical Properties after Photorefractive Keratectomy and Small Incision Lenticule Extraction. *Turkish journal of ophthalmology* 2016;46:47-51.
19. Yu M, Chen M, Dai J. Comparison of the posterior corneal elevation and biomechanics after SMILE and LASEK for myopia: a short- and long-term observation. *Graefes Arch Clin Exp Ophthalmol* 2019;257:601-606.
20. Chen M, Yu M, Dai J. Comparison of biomechanical effects of small incision lenticule extraction and laser-assisted subepithelial keratomileusis. *Acta Ophthalmol* 2016;94:e586-e591.
21. Kim TI, Alio Del Barrio JL, Wilkins M, Cochener B, Ang M. Refractive surgery. *Lancet* 2019;393:2085-2098.
22. Roberts CJ. Importance of accurately assessing biomechanics of the cornea. *Curr Opin Ophthalmol* 2016.
23. Esporcatte LPG, Salomao MQ, Lopes BT, et al. Biomechanical diagnostics of the cornea. *Eye and vision* 2020;7:9.
24. Bao F, Huang W, Zhu R, et al. Effectiveness of the Goldmann Applanation Tonometer, the Dynamic Contour Tonometer, the Ocular Response Analyzer and the Corvis ST in Measuring Intraocular Pressure following FS-LASIK. *Curr Eye Res* 2020;45:144-152.

25. Vinciguerra R, Elsheikh A, Roberts CJ, et al. Influence of Pachymetry and Intraocular Pressure on Dynamic Corneal Response Parameters in Healthy Patients. *J Refract Surg* 2016;32:550-561.
26. Roberts CJ, Mahmoud AM, Bons JP, et al. Introduction of Two Novel Stiffness Parameters and Interpretation of Air Puff-Induced Biomechanical Deformation Parameters With a Dynamic Scheimpflug Analyzer. *J Refract Surg* 2017;33:266-273.
27. Miki A, Maeda N, Ikuno Y, Asai T, Hara C, Nishida K. Factors Associated With Corneal Deformation Responses Measured With a Dynamic Scheimpflug Analyzer. *Invest Ophthalmol Vis Sci* 2017;58:538-544.
28. Fernandez J, Rodriguez-Vallejo M, Martinez J, Tauste A, Salvestrini P, Pinero DP. New parameters for evaluating corneal biomechanics and intraocular pressure after small-incision lenticule extraction by Scheimpflug-based dynamic tonometry. *J Cataract Refract Surg* 2017;43:803-811.
29. Ye Y, Li Y, Zhu Z, et al. Effect of Mydriasis-Caused Intraocular Pressure Changes on Corneal Biomechanical Metrics. *Front Bioeng Biotechnol* 2021;9:751628.
30. Sedaghat MR, Momeni-Moghaddam H, Ambrosio R, Jr., et al. Diagnostic Ability of Corneal Shape and Biomechanical Parameters for Detecting Frank Keratoconus. *Cornea* 2018;37:1025-1034.
31. Ryu IH, Kim BJ, Lee JH, Kim SW. Comparison of Corneal Epithelial Remodeling After Femtosecond Laser-Assisted LASIK and Small Incision Lenticule Extraction (SMILE). *J Refract Surg* 2017;33:250-256.
32. Reinstein DZ, Archer TJ, Gobbe M. Lenticule thickness readout for small incision lenticule extraction compared to artemis three-dimensional very high-frequency digital ultrasound stromal measurements. *J Refract Surg* 2014;30:304-309.
33. Reinstein DZ, Archer TJ, Randleman JB. Mathematical model to compare the relative tensile strength of the cornea after PRK, LASIK, and small incision lenticule extraction. *J Refract Surg* 2013;29:454-460.
34. Cao K, Liu L, Yu T, Chen F, Bai J, Liu T. Changes in corneal biomechanics during small-incision lenticule extraction (SMILE) and femtosecond-assisted laser in situ keratomileusis (FS-LASIK). *Lasers in medical science* 2020;35:599-609.
35. Khamar P, Shetty R, Vaishnav R, Francis M, Nuijts R, Sinha Roy A. Biomechanics of LASIK Flap and SMILE Cap: A Prospective, Clinical Study. *J Refract Surg* 2019;35:324-332.
36. Lee H, Roberts CJ, Kim TI, Ambrosio R, Jr., Elsheikh A, Yong Kang DS. Changes in biomechanically corrected intraocular pressure and dynamic corneal response parameters before and after transepithelial photorefractive keratectomy and femtosecond laser-assisted laser in situ keratomileusis. *J Cataract Refract Surg* 2017;43:1495-1503.
37. Ariza-Gracia MA, Piñero DP, Rodriguez JF, Pérez-Cambrodí RJ, Calvo B. Interaction between diurnal variations of intraocular pressure, pachymetry, and corneal response to an air puff: Preliminary evidence. *JCRS Online Case Reports* 2015;3:12-15.
38. Lee H, Roberts CJ, Ambrosio R, Jr., Elsheikh A, Kang DSY, Kim TI. Effect of accelerated corneal crosslinking combined with transepithelial photorefractive keratectomy on dynamic corneal response parameters and biomechanically corrected intraocular pressure measured with a dynamic Scheimpflug analyzer in healthy myopic patients. *J Cataract Refract Surg* 2017;43:937-945.
39. Fernandez J, Rodriguez-Vallejo M, Martinez J, Tauste A, Pinero DP. Corneal Thickness After SMILE Affects Scheimpflug-based Dynamic Tonometry. *J Refract Surg* 2016;32:821-828.
40. Wang D, Liu M, Chen Y, et al. Differences in the corneal biomechanical changes after SMILE and LASIK. *J Refract Surg* 2014;30:702-707.
41. Raghunathan VK, Thomasy SM, Strom P, et al. Tissue and cellular biomechanics during corneal wound injury and repair. *Acta biomaterialia* 2017;58:291-301.
42. Bao F, Cao S, Wang J, et al. Regional changes in corneal shape over a 6-month follow-up after femtosecond-assisted LASIK. *J Cataract Refract Surg* 2019;45:766-777.

43. Eliasy A, Chen KJ, Vinciguerra R, et al. Determination of Corneal Biomechanical Behavior in-vivo for Healthy Eyes Using CorVis ST Tonometry: Stress-Strain Index. *Front Bioeng Biotechnol* 2019;7:105.
44. Dupps WJ, Jr., Wilson SE. Biomechanics and wound healing in the cornea. *Exp Eye Res* 2006;83:709-720.
45. Riau AK, Liu YC, Lwin NC, et al. Comparative study of nJ- and muJ-energy level femtosecond lasers: evaluation of flap adhesion strength, stromal bed quality, and tissue responses. *Invest Ophthalmol Vis Sci* 2014;55:3186-3194.

Figure Captions:

Figure 1 Changes in SP-A1 throughout all follow up stages in tPRK, FS-LASIK and SMILE patient groups (mean and standard deviation)

Figure 2 Changes in IIR throughout all follow up stages in tPRK, FS-LASIK and SMILE patient groups (mean and standard deviation)

Figure 3 Changes in DA throughout all follow up stages in tPRK, FS-LASIK and SMILE patient groups (mean and standard deviation)

Figure 4 Changes in DARatio2mm throughout all follow up stages in tPRK, FS-LASIK and SMILE patient groups (mean and standard deviation)

Table Captions:

Table 1 Basic information for the three surgery groups

Table 2 Biomechanical metrics provided by Corvis ST before and after three forms of corneal refractive surgery

Figure 1.JPEG

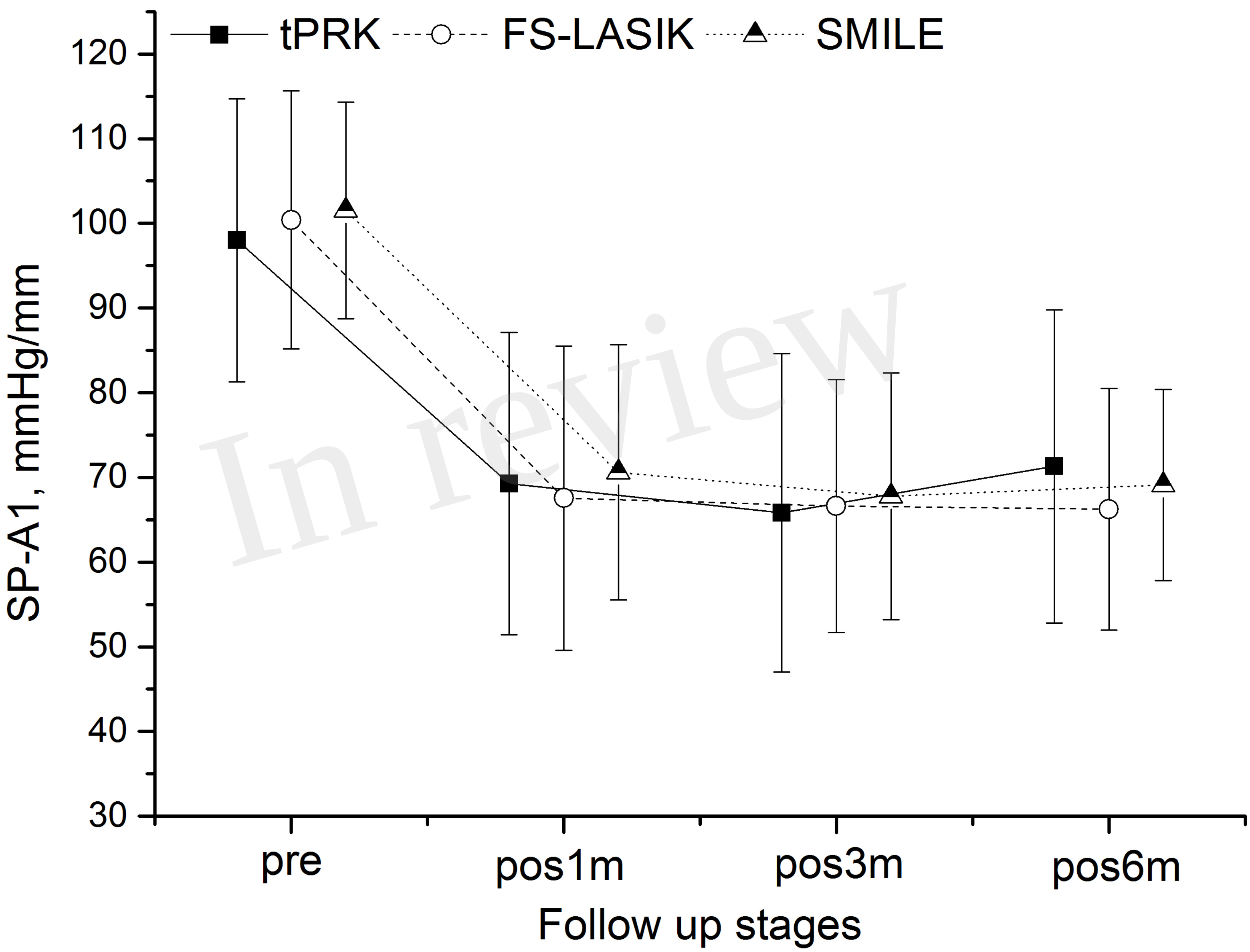

Figure 2.JPEG

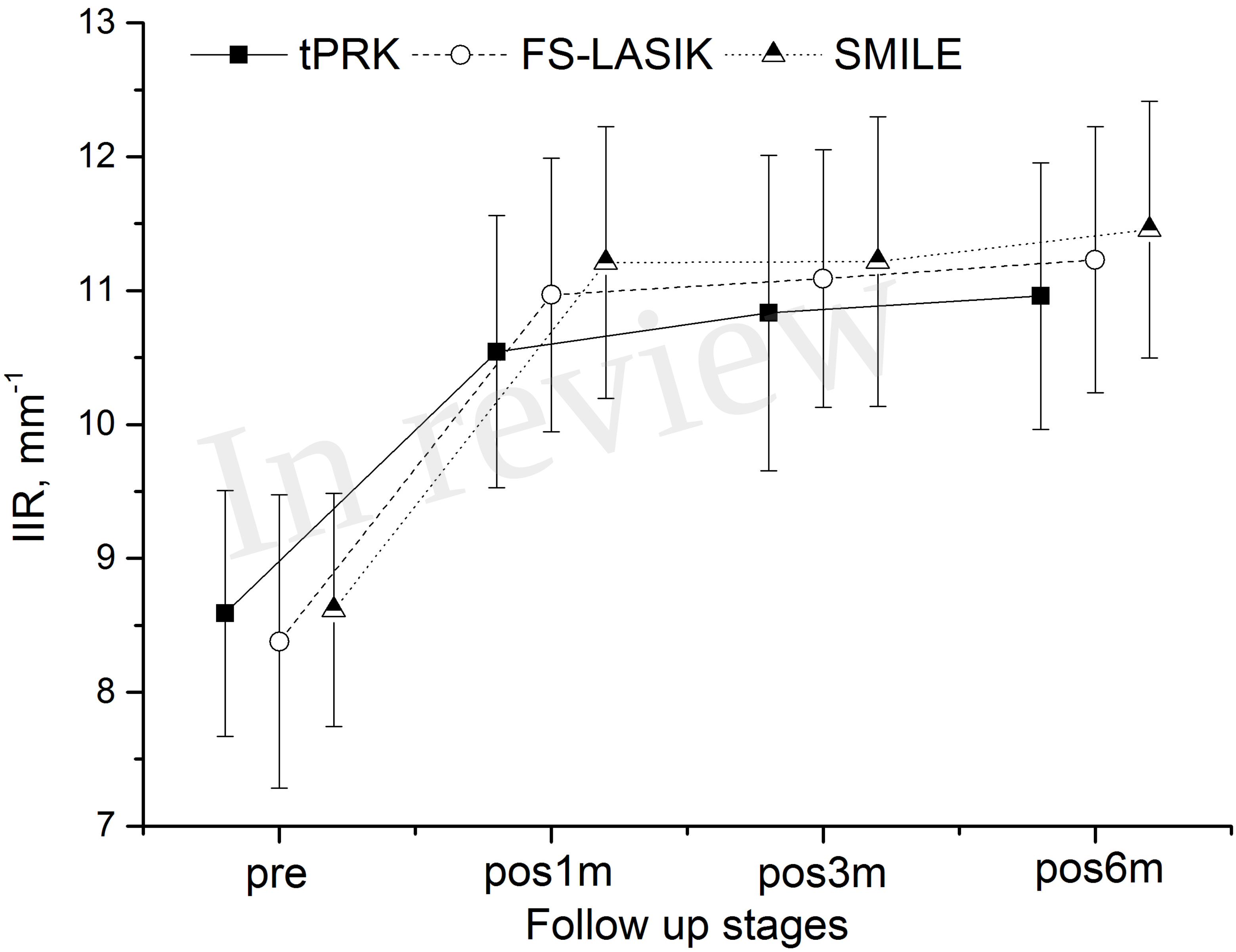

Figure 3.JPEG

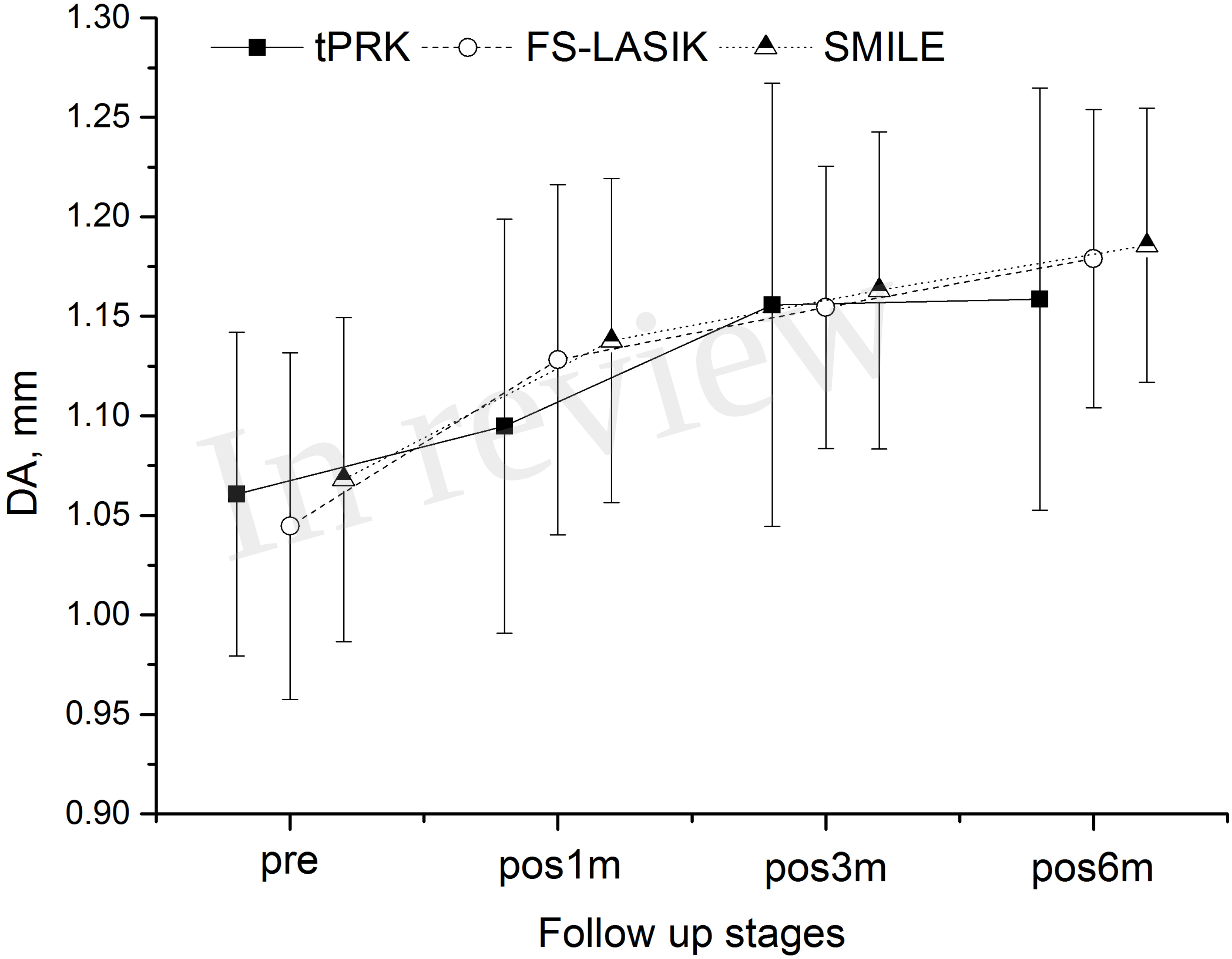

Figure 4.JPEG