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Predicting Refractive Outcome of Small Incision Lenticule Extraction for Myopia Using Corneal Properties

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Purpose: To investigate whether preoperative corneal topographic and biomechanical parameters (CTBPs) predict postoperative residual refractive error (RRE).

Methods: We retrospectively included 151 eyes from 151 patients of small-incision lenticule extraction (SMILE) with target RRE of plano and 3-month measurements of refractive error from Tianjin Eye Hospital. Multivariate linear/logistic regressions were performed to associate age, gender, preoperative refractive error, lenticule thickness, and CTBPs with postoperative RRE/the occurrence of myopic RRE ≤ -0.25 diopter (D). Stepwise regression was used for feature selection. Leave-one-cross-validation was used for model evaluation by the area under the receiver operating characteristic curve (AUC).

Results: From linear regression, more myopic RRE was associated with higher preoperative myopia, intraocular pressure (IOP), flattest curvature of anterior cornea (AC), and highest concavity deformation (HCD), and was associated with lower anterior elevation, anterior asphericity, steepest curvature of AC, and second applanation velocity. The occurrence of ≤ -0.25 D RRE was associated with higher myopia, IOP, posterior elevation and asphericity, flattest curvature of AC, first applanation velocity and HCD, and was associated with lower first applanation stiffness parameter, central corneal thickness, anterior elevation and asphericity, steepest curvature of AC, and second applanation velocity as well as thinner lenticule thickness. Compared to the baseline model using age, gender, and preoperative refractive error, adding CTBPs significantly ($P < 0.001$) improved the AUC performance to 0.771 from 0.615.

Conclusions: Postoperative outcomes of SMILE can be predicted by individual CTBPs.

Translational Relevance: Our findings could be used to customize a refractive nomogram based on individual corneal properties improving outcomes and patient satisfaction.

Introduction

Small-incision lenticule extraction (SMILE) has been developed as a new flap-free technique for corneal refractive surgery.[1] In SMILE, a femtosecond laser is used to cut an intrastromal lenticule, which is then extracted manually through a peripheral corneal tunnel incision.[2] Compared to conventional laser-assisted in situ keratomileusis (LASIK), SMILE promises to reduce a number of potential LASIK side effects including flap dislocation,[3,4] reduced corneal sensitivity,[5,6] corneal ectasia,[7,8] dry eye,[9,10] epithelial ingrowth,[11,12] etc.

In previous studies, refractive predictability, safety, and patient satisfaction for SMILE were high and comparable to LASIK[13–15]; however, the factors associated with the postoperative visual and refractive

outcomes of SMILE remain largely unexplored in comparison to LASIK. For example, in LASIK, higher preoperative myopia, residual astigmatism, and older age were identified as risk factors for retreatment.[16,17] In addition, environmental factors such as procedure room humidity, 2-week preoperative mean outdoor humidity, outdoor temperature, and room temperature were associated with enhancement after LASIK.[18] For SMILE, steeper corneal curvature and increasing age have been associated with undercorrection of myopia,[19] while higher preoperative myopia and greater intraoperative suction loss were associated with enhancement after SMILE.[20] To date, the postoperative visual and refractive outcomes of LASIK and SMILE have not been associated with corneal biomechanical properties, which have been shown to be related to refractive error and to be weaker after LASIK/SMILE in previous studies.[21–25] Furthermore, no studies have been performed associating the extensive available topographic parameters apart from the simple summary index of corneal curvature with the outcome of refractive surgery, while it is known that corneal topography is related to refractive error[26] and is altered by refractive surgery.[27,28] More importantly, the corneal biomechanical properties are also interactively related to the relevant topographic parameters.

In this work, we aim to elucidate the relationship between the refractive outcome after SMILE and corneal topographic and biomechanical parameters (CTBPs). In addition, a predictive model will be developed to predict the occurrence of myopic residual refractive error (RRE) after SMILE for myopia correction. In particular, we are interested in predicting the occurrence of myopic RRE ≤ -0.25 diopter (D) with a target RRE of plano. Our model aims to improve the correction precision based on individual corneal properties.

Methods

This retrospective cohort study was approved by the Tianjin Eye Hospital Ethics Committee. A written informed consent was obtained from all participants before enrollment. This study adheres to the Declaration of Helsinki.

Participants and Data

Two hundred seventy-nine eyes of 163 patients received SMILE for myopia correction at Tianjin Eye Hospital between January 2015 and March 2016 were initially enrolled in this study. The enrollment criteria of patients were detailed as follows: age $\geq$ 18 years, stable refraction for at least 2 years, central corneal thickness (CCT) more than 480 μm, target postoperative refraction of plano and without a history of corneal trauma or past surgery, corneal diseases, and systemic diseases such as diabetes mellitus or connective tissue disorders.

The preoperative corneal topographic parameters measured by Scheimpflug tomography system (Pentacam, Oculus GmbH, Wetzlar, Germany) and biomechanical parameters measured by Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany) were extracted, respectively. The Corvis ST is a noncontact tonometer that assesses corneal dynamic response to a puff of air using an ultra-high speed Scheimpflug camera.[29] All measurements of CTBPs for each eye were repeated three times by the same technician. The measurements with signal quality that passed the machine threshold were used for statistical analysis. In addition, preoperative manifest refractions were extracted. Manifest refractive error measured at 3-month follow-up was considered to be stable and was used to analyze the efficacy of the SMILE.

Eyes with missing CTBPs were excluded from our data analyses. To avoid the biases from correlated measurements, we randomly selected one eye per patient.

SMILE Procedure

All surgeries were performed by an experienced surgeon (Yan Wang). Preoperatively, two drops of 0.4% oxybuprocaine hydrochloride (Benoxil; Santen, Osaka, Japan) were used for topical anesthesia. Patient was positioned under the curved contact glass and asked to fixate on a blinking target light. Once appropriate centration was achieved, suction was applied to contact glass. The VisuMax femtosecond laser system (Carl Zeiss Meditec AG, Jena, Germany) was used to create the stromal refractive lenticule with a laser pulse frequency of 500 kHz and pulse energy 130 to 160 nJ. The cap thickness was between 110 and 120 μm, the diameter of stromal lenticule varied from 6.0 to 7.0 mm, and the corneal cap diameter was 1.0 mm larger than the lenticule. The lenticule was scanned in the following sequence: the posterior surface of the lenticule (periphery to center), the border, the anterior surface of lenticule (center to periphery), and the side-cut incision located at 12 o'clock position. A blunt spatula was used to first separate the anterior surface of stromal lenticule and

then the posterior surface. The surgeon grasped and removed the lenticule through the small incision with forceps. The refractive nomogram was increased by 5% based on individual preoperative manifest refraction. Postoperative medications included 0.5% levo-floxacin (Cravit; Santen, Osaka, Japan) four times a day for 3 days and 0.1% fluorometholone (Flumetholon; Santen) four times a day. The fluorometholone eye drops were tapered every 2 weeks.

Feature Description

The 3-month postoperative refraction was associated with 15 features of preoperative CTBPs in addition to demographics (age, gender), preoperative refraction (sphere and cylinder), and lenticule thickness. The 15 preoperative CTBPs include: anterior and posterior elevations of central cornea, anterior and posterior asphericities of cornea, anterior and posterior astigmatisms of cornea, biomechanically corrected intraocular pressure (bIOP), IOP, flattest curvature of anterior surface, steepest curvature of anterior surface, stiffness parameter at first applanation, CCT, first and second applanation velocities, and highest concavity deformation (HCD).

Statistical Modeling

All statistical analyses were performed using R language.[30] Multivariate linear regression was performed to associate postoperative 3-month spherical equivalent (SE) with the CTBPs in addition to demographics, preoperative refraction, and lenticule thickness. Variance inflation factor was calculated to detect potential multicollinearity issue. To remove the redundant features that might cause the multicollinearity issue, stepwise regression was used to select the optimal feature combination that predicts the postoperative RRE based on Akaike information criterion.[31] In addition, logistic regression was applied to predict the occurrence of myopic RRE after SMILE for myopia correction. Specifically, we are particularly interested in predicting the occurrence of myopic RRE ≤ -0.25 D. Similarly, stepwise regression was used for feature selection. Leave-one-cross-validation[32] was used to evaluate the model on testing data by the area under the receiver operating characteristic curve (AUC).[33] Jackknife resampling[34] was applied to obtain the confidence interval (CI) of the AUC performance.

Power analysis for multivariate linear and logistic regressions were performed to calculate the statistical power of detecting a medium effect size of Cohen's f^2

(0.15) and odds ratio 3.47 with a type I error of 0.05, with adjusted effects of covariates of age, gender, sphere, and cylinder. G*Power and R package were used for our power analysis.[30,35]

Results

Twenty-two eyes from 12 patients are excluded due to missing lenticule thickness measurements from the initial 279 eyes of 163 patients enrolled in this study. As we only included one eye per patient randomly, 151 eyes from 151 patients including 75 males and 76 females were finally selected for our data analyses. The statistical power for multivariate linear regression to detect a medium effect size of Cohen's f^2 (0.15) with a type I error of 0.05 was 0.83. For logistic regression, there were eight parameters out of the 16 CTBPs possessing the statistical power (mean $\pm$ standard deviation: 0.97 ± 0.03) of at least 0.8 to detect a medium size of odds ratio 3.47 with a type I error of 0.05. The eight parameters include: CCT, anterior and posterior elevations, anterior and posterior asphericities, posterior astigmatism, and first and second applanation velocities.

The mean $\pm$ standard deviation of age was 23.24 $\pm$ 5.40 years. The preoperative SE (-5.38 ± 1.69 D), which was also the attempted SE correction, was significantly ($r = 0.29$, $P < 0.001$) correlated to the postoperative SE (-0.07 ± 0.21 D) as shown in Figure 1(a). As shown in Figure 1(b), 94 eyes achieved the target fraction of plano, while 43 and 14 eyes had myopic and hyperopic RRE, respectively. For eyes with myopic and hyperopic RRE, -0.25 and 0.25 D were the most frequent (32 and 10 eyes) values of RRE, respectively.

Table 1 shows (1) the summary statistics of age, gender, preoperative refraction, lenticule thickness, and preoperative CTBPs, (2) the correlation statistics (correlation coefficients and P values) between aforementioned features and postoperative SE, and (3) the summary of multivariate linear regression (r^2: 0.31) from aforementioned features to predict postoperative SE. In particular, the preoperative sphere ($r = 0.29$, $P < 0.001$), lenticule thickness ($r = -0.29$, $P < 0.001$), and HCD ($r = -0.25$, $P = 0.01$) were significantly correlated to postoperative SE after P value adjustment for multiple comparisons. Second applanation velocity ($r = -0.17$, $P = 0.03$) and anterior asphericity ($r = 0.17$, $P = 0.03$) were also significantly correlated to postoperative SE without multiple comparison adjustment. From the multivariate linear regression, it was observed that the postoperative SE
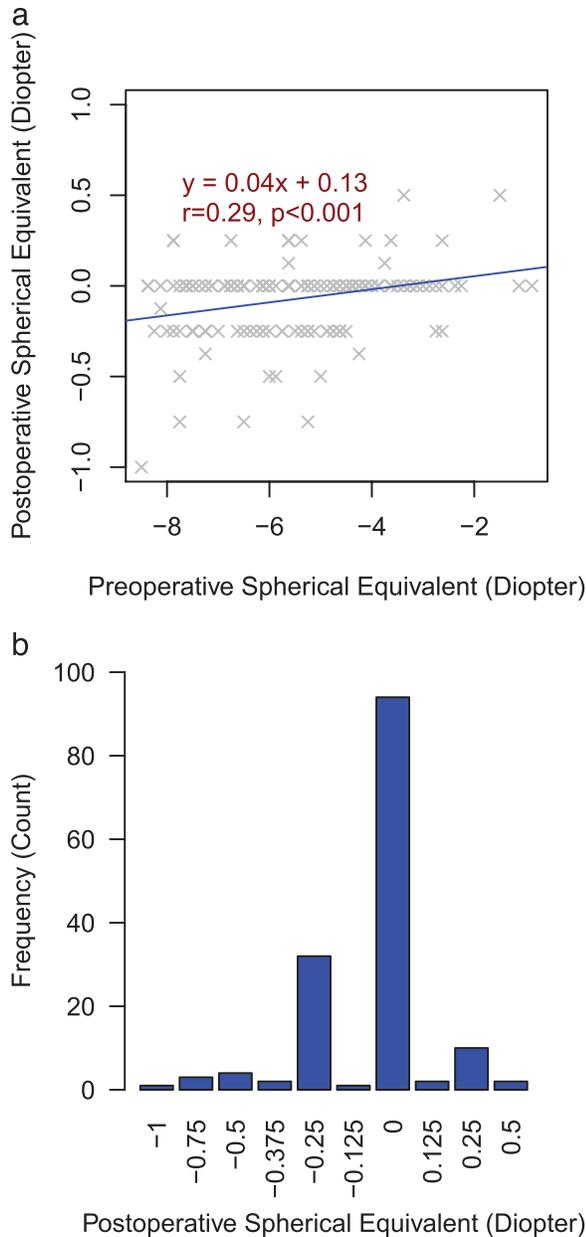
Figure 1. (a) Linear regression from the preoperative SE to the postoperative SE and (b) the postoperative SEs of all eyes. Note that the SE of attempted correction was the same as the postoperative SE. All eyes had target refractions of plano.

was positively and significantly associated with anterior elevation ($P = 0.049$) and anterior asphericity ($P = 0.008$), and was negatively and significantly associated with HCD ($P < 0.001$). The multicollinearity was high as there were seven parameters with variance inflation factor > 10 including sphere,[36] lenticule thickness, bIOP, IOP, anterior astigmatism, flattest curvature, and steepest curvature.

Figure 2 shows the best predict model (r^2: 0.29)

with the optimal feature combination to predict the postoperative SE. Redundant features were removed by stepwise regression to resolve the multicollinearity issue. More myopic RRE was associated with higher preoperative myopia, IOP, flattest curvature of anterior cornea (AC) and HCD, and was associated with lower anterior elevation and asphericity, steepest curvature of AC, and second applanation velocity.

Forty-two out of 151 eyes had ≤ -0.25 D RRE. Figure 3 shows the best predictive model with optimal feature combination selected by stepwise regression to predict the occurrence of RRE ≤ -0.25 D. The occurrence of RRE ≤ -0.25 D was associated with higher myopia, IOP, posterior elevation and asphericity, flattest curvature of AC, first applanation velocity and HCD, and was associated with lower first applanation stiffness parameter, CCT, anterior elevation and asphericity, steepest curvature of AC and second applanation velocity as well as thinner lenticule thickness. Compared to the baseline model using the known predictors of preoperative sphere and cylinder in the literature in addition to age and gender, the AUC performance of our optimal model with additional CTBPs was significantly higher ($P < 0.001$) than the baseline model (0.771 [95% CI: 0.770, 0.772]) compared to 0.615 (95% CI: 0.614, 0.615). The AUC to predict the occurrence of RRE < 0 D with respective optimal model selected by stepwise regression was 0.790 (95% CI: 0.788, 0.793).

Discussion

In this study, we systematically examined the risk factors that potentially affect the postoperative refractive outcome after SMILE for myopia correction from a large set of features including demographics, preoperative refraction, lenticule thickness, and CTBPs. To our best knowledge, this paper is the first of its kind to systematically investigate the impact of CTBPs on the postoperative RRE.

Through bivariate correlation study in this work, we demonstrated that more negative preoperative sphere and thicker lenticule thickness (highly correlated to preoperative sphere) were significantly correlated to more myopic RRE after SMILE, which were also reported in multiple studies in the literature.[16,19,20] Beyond that, we are the first to show that corneal dynamic biomechanical parameters are significantly correlated to postoperative RRE. Specifically, higher HCD and lower second applanation velocity were correlated to more myopic RRE. In following multivariate linear regression study includ-

Table 1. (a) The mean ± standard deviation of the age, preoperative refraction, lenticule thickness, and preoperative CTBPs as well as the gender distribution, (b) the correlation statistics (correlation coefficients and P values) between aforementioned features and postoperative SE, and (c) the summary of multivariate linear regression from aforementioned features to predict postoperative SE.

| Feature | Mean ± Standard Deviation | Correlation Statistics | | Multivariate Regression (r^2: 0.31) | |
		Correlation	Adjusted P Value (Nonadjusted)	Coefficient	P Value
Age (year)	23.24 ± 5.4	−0.1	0.43 (0.23)	−0.003	0.31
Gender (male/female)	75/76	0.002	0.98 (0.98)	−0.02	0.56
Sphere (D)	−5.05 ± 1.64	0.29	0.004* ($P < 0.001*$)	0.06	0.38
Cylinder (D)	−0.67 ± 0.63	0.08	0.5 (0.32)	0.13	0.09
Lenticule thickness (μm)	103.15 ± 26.81	−0.29	0.004* ($P < 0.001*$)	0.002	0.67
bIOP (mm Hg)	13.55 ± 1.94	0.02	0.93 (0.84)	0.02	0.46
IOP (mm Hg)	12.94 ± 2.28	0.06	0.56 (0.48)	−0.04	0.1
SP-A1 (mm Hg/mm)	89.32 ± 15.68	0.1	0.43 (0.24)	−0.001	0.71
CCT (μm)	553.28 ± 26.8	0.12	0.43 (0.16)	0.001	0.35
Anterior elevation (mm)	2.09 ± 1.02	0.09	0.46 (0.28)	0.04	0.049*
Posterior elevation (mm)	1.66 ± 2.23	0.06	0.56 (0.44)	−0.002	0.87
Anterior asphericity	−0.33 ± 0.11	0.17	0.13 (0.03*)	0.51	0.008*
Posterior asphericity	−0.31 ± 0.11	0.003	0.98 (0.97)	−0.13	0.52
Anterior astigmatism (D)	1.22 ± 0.65	0.06	0.56 (0.46)	0.01	0.91
Posterior astigmatism (D)	0.36 ± 0.14	0.1	0.43 (0.22)	0.08	0.63
Flattest curvature (D)	42.69 ± 1.12	−0.11	0.43 (0.16)	−0.08	0.47
Steepest curvature (D)	43.93 ± 1.24	−0.07	0.53 (0.37)	0.07	0.56
First applanation velocity (m/s)	0.15 ± 0.01	−0.11	0.43 (0.19)	−0.93	0.6
Second applanation velocity (m/s)	0.37 ± 0.05	−0.17	0.13 (0.03*)	0.83	0.13
Highest concavity deformation (mm)	1.03 ± 0.09	−0.25	0.01* (0.002*)	−1.39	$P < 0.001*$

Both P values adjusted for multiple comparisons and original P values of correlation statistics were reported. P values that are less than 0.05 are denoted as significant by asterisk. SP-A1, stiffness parameter at first applanation.

ing 20 available features, the postoperative RRE was positively associated with anterior elevation and asphericity significantly, and was negatively associated with HCD significantly. Note that while the impact of preoperative myopia was dampened to become insignificant due to the strong correlations between features, the impact of the dynamic biomechanical parameter of HCD still remained to be significant, which might suggest that HCD covers a substantially different proportion of variance to predict postoperative RRE compared to preoperative myopia related parameters. We further applied step regression to select the optimal feature combination to predict the postoperative RRE based on Akaike information criterion.[31] In the optimal feature set, more myopic RRE was associated with higher preoperative myopia, IOP, flattest curvature of AC, and HCD, and was associated with lower anterior elevation and aspher-

icity, steepest curvature of the AC, and second applanation velocity. Since intuitively higher IOP, flattest curvature of AC and HCD are all related to weaker corneal biomechanical condition, our results solidly confirmed the speculation in previous studies[19,20] that the age-related corneal biomechanical properties might be related to the outcome of refractive surgery. In addition, from the perspective of biomechanics, higher preoperative myopia also implies greater disturbance of the refractive surgery to the corneal structure, which imposes more difficulty and unpredictability to the postoperative remodeling process and can be also considered as weak biomechanical condition.

We further developed a logistic regression model to predict the occurrence of myopic RRE ≤ −0.25 D. The rational to perform additional modeling of predicting the occurrence of myopic RRE is to further
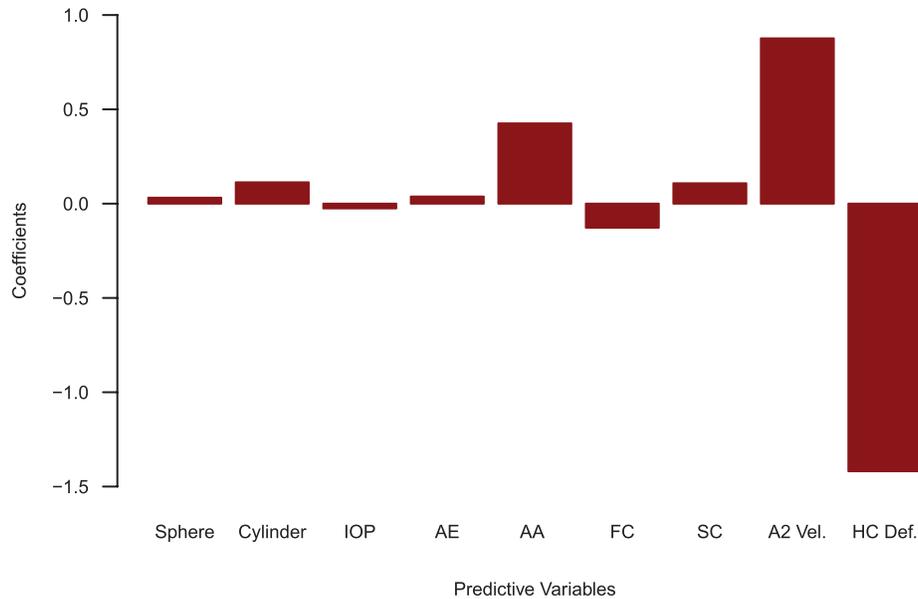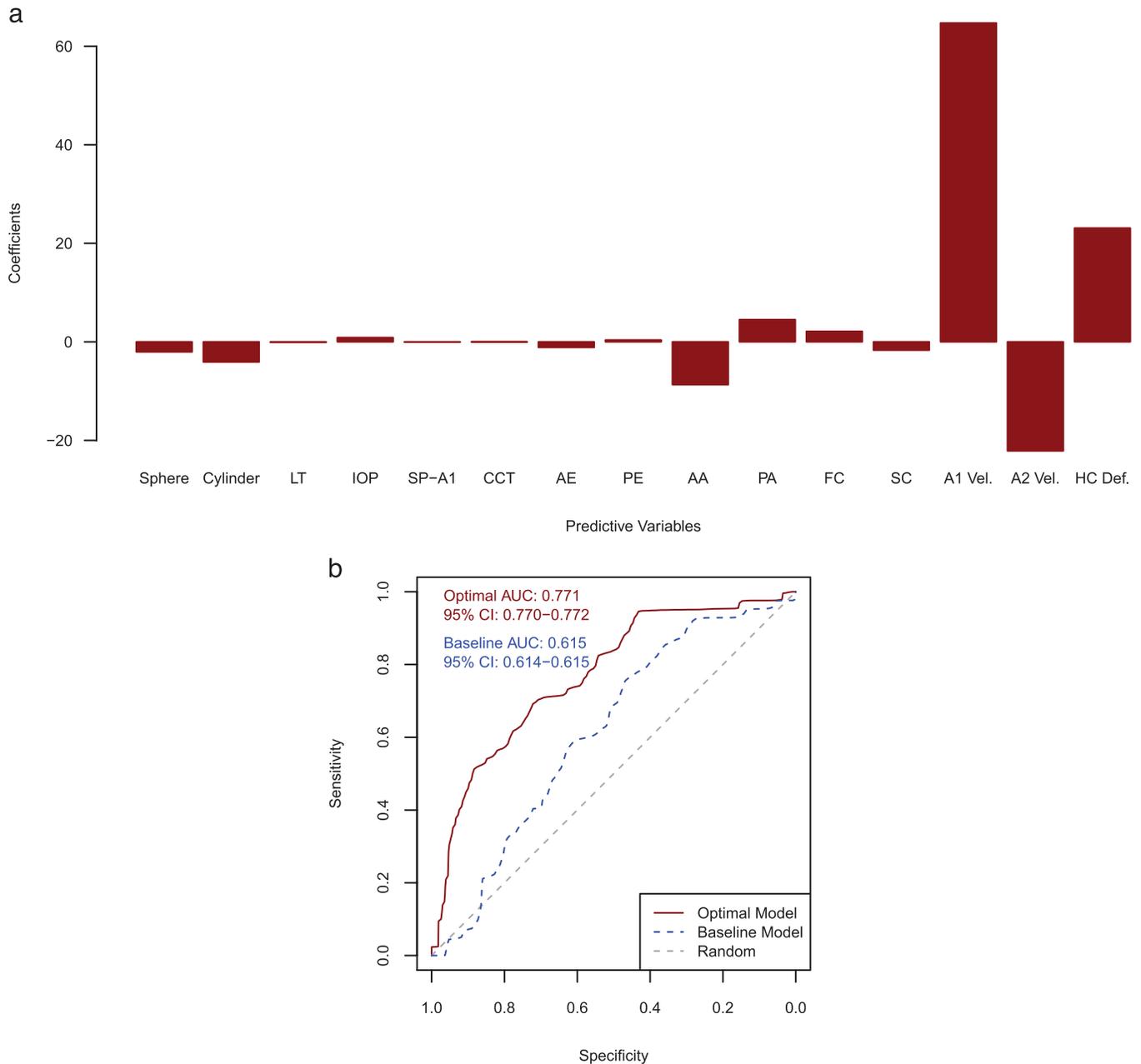
Figure 2. The best predictive model (r^2: 0.29) selected by stepwise regression to predict postoperative SE. AE, anterior elevation of central cornea; AA, anterior asphericity; FC, flattest curvature of AC; SC, steepest curvature of AC; A2 vel., second applanation velocity; HC def., highest concavity deformation.

provide binary prediction of refractive outcome. In clinical settings, simplified binary evaluation might be preferred in some circumstances of clinical decision. The model performance of AUC with cross validation and nested model selection procedure in training data was 0.771, which was significantly ($P < 0.001$) higher than the AUC (0.615) of the baseline model with risk factors of age, gender, preoperative sphere, and cylinder that were previously identified in the literature.[16,19,20] In the optimal model, the occurrence of myopic RRE ≤ -0.25 D was associated with higher myopia, higher IOP, lower stiffness parameter at first applanation, lower CCT, higher first applanation velocity, and higher HCD, which are all clearly associated with weaker corneal biomechanical conditions. In addition, the occurrence of myopic RRE ≤ -0.25 D was associated with lower anterior elevation and asphericity of cornea but with higher posterior elevation and asphericity of cornea. The different association of the anterior and posterior properties of elevation and asphericity might be related to their respective different impacts on the cornea biomechanical property. Patient-specific finite element modeling might be useful to analyze the sensitivity of those parameters to the corneal mechanical response.

In a previous study,[19] steeper mean corneal curvature was associated with the undercorrection of 0.25 D for myopia. In our results, we demonstrated

that the flattest and steepest curvature of AC were differently associated with postoperative RRE. Our results suggest that it might be not sufficient to only use mean corneal curvature to characterize postoperative RRE. In previous studies,[16,19] older age was also shown to be related to greater myopic RRE after LASIK/SMILE, while we did not find that age was associated with postoperative RRE. The discrepancy between our results and previous findings is likely owing to the younger age of our patients (23.2 ± 5.4 years) compared to the age of 38.3 ± 8.3 years in the work by Hjortdal et al.[19] and the age of 42.8 years in the work by Hersh et al.[16]

Higher second applanation velocity was associated with more myopic RRE in our bivariate analysis, which is consistent with previous finding in the literature that second applanation velocity was lower in healthy eyes than in eyes that underwent myopic photorefractive keratectomy, keratoconus affected eyes, and keratoconus affected eyes that underwent corneal collagen crosslinking,[37] which are all related to weaker biomechanical conditions. However, when accounting the variance explained by other CTBPs in addition to age, gender, and refraction, it became reversely that lower second applanation velocity was associated with more myopic RRE. We suspect that second applanation velocity might be related to viscoelastic properties of the cornea and therefore

Figure 3. The best predictive model selected by stepwise regression to predict the occurrence of ≤ -0.25 D RRE: (a) parameter coefficients of the logistic regression model and (b) receiver operating characteristic (ROC) curve. For comparison purpose, the ROC curve of baseline model using age, gender, sphere, and cylinder was also shown. LT, lenticule thickness; SP-A1, stiffness parameter at first applanation; AE, anterior elevation of central cornea; AA, anterior asphericity; PE, posterior elevation of central cornea; PA, posterior asphericity; FC, flattest curvature of AC; SC, steepest curvature of AC; A1 vel., second applanation velocity; A2 vel., second applanation velocity; HC def., highest concavity deformation.

represents different aspects of the biomechanical properties of the cornea compared to other CTBPs.

Different from several previous studies focusing on predicting the retreatment after refractive surgery,[16–18,20] the major clinical relevance and importance of this work is that we are the first to demonstrate that the postoperative refractive outcome after refractive surgery (herein, SMILE) is predictable by CTBPs in addition to the previously known risk factors of age and preoperative SE, such that the refractive surgery nomogram can be adapted based on individual corneal parameters to finally improve the precision

of refractive surgery. Note that although most of our patients with myopic RRE were only slightly undercorrected, which typically is not considered to have significant clinical consequence of visual function, it is still strongly valuable to improve the refractive surgery precision and make the outcome more predictable. More importantly, unexpected postoperative RRE (especially myopic RRE) for the patients with target refraction of plano typically reduces the satisfaction of patients and sometimes causes anxiety of patients. Moreover, the purpose of some patients to take the refractive surgery is occupationally relevant, for example, to qualify the physical examination of the recruitment of airline pilot or military service. In such case, perfect postoperative vision is even more demanded by patients. Therefore, it is necessary to improve the precision of current refractive surgery based on individual corneal anatomy and properties. We recognized that the measurements of −0.25 D undercorrection can be disturbed by measurement noise; however, the systematical associations between the occurrence of −0.25 D undercorrection and CTBPs were not likely to be due to the measurement bias. Whatsoever, our results suggest that the preoperative CTBPs are predictive of postoperative refractive outcomes of SMILE, which can be further explored to test whether those CTBPs are also predictive of clinically significant myopic outcomes (postoperative RRE $\leq$ −0.5 D) in future studies.

We are aware that the postoperative RRE at 3-month follow-up might not be stable due to the varying period of remodeling process. Limited to the data availability in this retrospective study, only 58 and 20 eyes out of the total 151 eyes had 6-month and 12-month measurements of postoperative RRE. The 3-month RREs (mean ± standard deviation: −0.07 ± 0.21 D) were not significantly different from the RREs at 6-month (mean ± standard deviation: −0.09 ± 0.20 D, $P = 0.35$, paired t-test) and the RREs of 12-month (mean ± standard deviation: −0.08 ± 0.22 D, $P = 0.33$, paired t-test) follow-ups. Moreover, at least two previous studies[38,39] have reported that there was no significant difference of postoperative SE between 3-month and 12-month follow-ups.

This study had limitations in several respects. First, our subjects were all Han Chinese ethnicity, and it is not clear whether these results can be generalized to other ethnicities, as previous studies have shown that corneal properties are race dependent.[40,41] Second, the model performance of r^2 and AUCs to predict RRE and the occurrence of myopic RRE $\leq$ −0.25 D were not very high (0.29 and 0.771). This is partly because our data sample size was not large (151 eyes from 151 patients) with a relatively large candidate feature size (20 features) to be considered to select the optimal relevant feature combination. Small sample size with large feature size can cause substantial overfitting problem, which can deteriorate the model performance. We envision that our model performance will be improved with more data collected. Though the currently model has not reached the accuracy level that can be directly used to personalize individual nomogram yet, we anticipate that those corneal parameters that are associated with postoperative refractive outcome could be combined with other possible related parameters together to improve the nomogram at individual level ultimately. More investigations will be needed. Lastly, with our limited data sample size, we do not have the capacity to further investigate whether the CTBPs are systematically associated with undercorrection (postoperative RRE $\leq$ −0.5 D) with severe clinical consequence, since we had so few such cases (8 cases out of 151 eyes) that did not allow us to attain meaningful statistical modeling and results. More data will be needed to investigate this valuable aspect.

To summarize, our study promisingly demonstrates that the postoperative refractive outcome of SMILE can be predicted by using individual CTBPs in addition to the known risk factors of age and preoperative refractive error. Those novel findings might be used to customize a refractive nomogram based on individual corneal properties to improve refractive surgery outcomes and achieve better patient satisfaction.

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