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ORIGINAL AND RESEARCH ARTICLE

Corneal Biomechanical Properties in Keratoconic, Myopic, and Hyperopic Eyes as Measured with a Scheimpflug-based Tonometer

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ABSTRACT

Aim: To evaluate corneal biomechanical properties in myopic (MY), hyperopic (HY), and keratoconic (KCN) eyes as measured with the Corvis ST, a newly developed Scheimpflug-based noncontact tonometer with features of visualization and measurement of the corneal deformation response to an air impulse.

Materials and methods: Corneal biomechanical properties measurements were obtained for 34 KCN, 109 MY, and 12 HY patients. Statistical analysis was performed using logistic regression in order to control for confounders (intraocular pressure, pachymetry, and first applanation time) and to identify optimal combinations of parameters for KCN detection.

Results: No single parameter was significantly different between KCN and either MY or HY after controlling for cofounders. The two combinations of parameters that were assessed achieved low specificity and sensitivity values.

Conclusion: The parameters and their combinations overlapped significantly between the groups and could not provide an adequate means to differentiate KCN from healthy corneas. Therefore, with regard to KCN, the Corvis ST can only be used as an adjunct to the clinical examination and customary diagnostic tools.

Keywords: Biomechanical, Cornea, Keratoconus, Scheimpflug based tonometer.

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INTRODUCTION

Keratoconus is a progressive, asymmetric ectatic disease of the cornea that causes decreased vision as a result of irregular astigmatism and corneal scarring.[1] Preliminary signs of KCN include focally reduced corneal radius of curvature, abnormal corneal wavefront aberrations, and localized reduction in thickness. In KCN corneas, it was found that the native collagen fiber network is disorganized. Biochemical studies have demonstrated increased collagenolysis, keratocyte loss, and reduced collagen cross-links with KCN.[2,3] Clinical, pachymetric, and topographic signs exhibit a wide spectrum of severity; hence, early disease with no fulminant complications can be easily missed.[4,5]

The ocular response analyzer (ORA) has been widely used to study biomechanics of KCN corneas. It utilizes an air puff to produce a dynamic bidirectional indentation process, resulting in a biomechanical waveform, from which corneal hysteresis (CH) and corneal resistance factor (CRF) are derived. The ORA CH and CRF are decreased in advanced and mild KCN patients. However, the distribution of these variables presents a high degree of overlap between normal corneas and KCN corneas. Therefore, many early KCN cases, such as "forme fruste keratoconus," can be mistaken for normal corneas and vice versa. It is clear that the CH and the CRF values cannot be used alone, but as a combination with other parameters to facilitate identifying and diagnosing the subtle forms of preclinical KCN.[6-9]

The Corvis ST (OCULUS Optikgeräte GmbH)[10] is a novel noncontact tonometer that utilizes a high-speed Scheimpflug-camera (4330 frames/sec within a 100 ms period) to record the dynamic reaction of the cornea to an air impulse. The ultra-slow motion recording allows for the calculation of various parameters, including the applanation time, length, and velocity, as well as highest concavity. Presumably, such measurements can allow further assessment of corneal biomechanical properties and may help identify early forms of KCN.

The aim of the current study was to identify a significant parameter, or a combination of parameters, that will allow a more sensitive and specific diagnosis of KCN. This was conducted by comparing the various parameters obtained by the Corvis ST measurements

of KCN patients with the measurements of a group of otherwise-healthy MY and hypermetropic candidates for a corneal refractive surgery.

MATERIALS AND METHODS

This retrospective study included 195 eyes of 195 patients divided into three groups: 46 KCN patients, 135 MY patients, and 14 HY patients. One eye from each subject was randomly selected.

The local Medical Ethics Committee approved the study protocol before data collection began. The research complied with the tenets of the Declaration of Helsinki. A waiver of written informed consent was granted by the committee.

We excluded patients who had any known ocular pathology other than refractive error, patients who underwent any previous eye surgery including collagen cross-linking, and all cases of examinations not meeting the quality standards set by the Corvis ST software (quality standards score other than "OK" or "alignment").

After exclusion, 34 KCN eyes as well as 109 MY and 12 HY eyes were included in the study.

All patients were examined by a cornea specialist (DZ, IB). The diagnosis of KCN was made based on slit-lamp biomicroscopy findings and confirmed by corneal topography. All eyes were examined by Placido disk-based corneal topography and rotating Scheimpflug corneal topography (Pentacam HR; Oculus, Wetzlar, Germany).

The Corvis ST was used by a qualified and experienced technician to obtain a record of the dynamic reaction of the patients' corneas to a short, reproducible air puff. The patients were seated comfortably and fixated on a dedicated fixation light within the instrument, and the examination was carried out after automatic alignment of the instrument with the patient's cornea. A puff of air was blown a single time for each examination, and the corneal deformation was recorded by the instrument's high-speed Scheimpflug camera. The parameters obtained from each examination are presented in Table 1.

Table 1: Corvis ST parameters

Parameter	*Definition*
IOP	Intraocular pressure (mm Hg)
Pachy	Corneal thickness (μm)
Def. amp. max	Maximal amplitude of deflection, from resting state (mm)
A1 time	Elapsed time until first applanation of the cornea was achieved (ms)
A1 length	Applanation length (linear length of flat cornea) at first applanation (mm)
A1 velocity	Corneal velocity at first applanation (m/s)
A2 time	Elapsed time until second applanation (upon recoil of the cornea) (ms)
A2 length	Applanation length (linear length of flat cornea) at second applanation (mm)
A2 velocity	Corneal velocity at second applanation (m/s)
HC time	Elapsed time until highest concavity was achieved (ms)
Peak dist	Maximal distance between two peaks of corneal surface while the cornea is maximally concave (mm)
Radius	Radius of curvature at maximum deformation calculated using parabolic function fitted to the cornea (mm)
Radius (3P)	Radius of curvature at maximum deformation calculated based on a simple three-point fit (mm)
A1 deformation amp	Movement of the corneal apex to first applanation (mm)
HC deformation amp	Movement of the corneal apex to highest concavity (mm)
A2 deformation amp	Movement of the corneal apex to second applanation (mm)
A1 deflection length	Length of a line at first applanation between two points where the cornea differs from resting shape (mm)
HC deflection length	The length of a line at the maximum deformation between two points where the cornea differs from the resting shape (mm)
A2 deflection length	Length of a line at second applanation between two points where the cornea differs from resting shape (mm)
HC deflection amp.	The difference between whole eye movement and deformation amplitude (the movement of the cornea itself) at the maximum deformation (mm)
A1 deflection amp.	The difference between whole eye movement and deformation amplitude at the first applanation (mm)
A2 deflection amp.	The difference between whole eye movement and deformation amplitude at the second applanation (mm)
Deflection amp. max	The maximum difference between whole eye movement and deformation amplitude during measurement (mm)
Deflection amp. max time	Elapsed time until maximum deflection amplitude was achieved (ms)
Whole eye movement	Movement of the whole eye, calculated based on the edge point in the periphery of the captured images (mm)
Whole eye movement max time	Elapsed time until maximum whole eye movement was achieved (ms)
NTSim A1 time	Simulation of a conventional noncontact tonometer first applanation time (ms)
NTSim A2 time	Simulation of a conventional noncontact tonometer second applanation time (ms)

The following information was obtained for each patient: Age, sex, and data related to the Corvis ST readings.

Statistical Analysis

Statistical analysis was performed using GNU R version 2.15.2-1 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). A Student's *t*-test was used to compare variables between groups. In order to control for the intraocular pressure, corneal thickness, and first applanation time (a parameter used by the Corvis ST to calculate the intraocular pressure), we used a logistic regression model (selection based on $p < 0.05$ using the *t*-test). All variables were checked for colinearity using Pearson correlation.

Later, two predicting formulae were developed using logistic regression based on randomly selected two-thirds of the study population and validated on the remaining third.

A p-value <0.05 was considered significant.

RESULTS

The age and gender characteristics of the three groups are presented in Table 2. The mean age of the HY patients was significantly higher compared with the KCN and MY patients (p = 0.02). The KCN group comprised predominantly male patients (74%), while other groups had similar proportions of males and females. This difference was found to be statistically significant (p = 0.001).

The biomechanical parameters measured in each group are shown in Table 3. For the MY group, we found the following parameters to differ significantly from the KCN group: IOP (14.03 ± 2.00, 12.79 ± 1.55 mm Hg myopia and KCN respectively; p = 0.0003), pachy (527.92 ± 39.97,

Table 2: Demographic data

	Myopia (n = 109)	*Hyperopia (n = 12)*	*KCN (n = 34)*
Age (years)	29.8 ± 9.3	42.1 ± 13.9*	31 ± 8.8
Gender (% female)	56**	50	26

*Hyperopia *vs* KCN p = 0.02; **Myopia *vs* KCN p = 0.001

Table 3: Biomechanical parameters

	KCN	*Myopia*		*Hyperopia*	
	Average ± SD	*Average ± SD*	*p-value*	*Average ± SD*	*p-value*
IOP (mm Hg)	12.79 ± 1.55	14.03 ± 2.00	0.0003	14.08 ± 2.07	0.07
Pachy (μm)	502.19 ± 34.92	527.92 ± 39.97	0.001	556.70 ± 43.88	0.003
Def. amp. max (mm)	1.13 ± 0.09	1.12 ± 0.12	0.89	1.11 ± 0.10	0.56
A1 time (ms)	7.02 ± 0.19	7.16 ± 0.26	0.001	7.16 ± 0.26	0.11
A1 length (mm)	1.69 ± 0.37	1.76 ± 0.31	0.28	1.75 ± 0.25	0.54
A1 velocity (m/s)	0.16 ± 0.06	0.16 ± 0.03	0.93	0.15 ± 0.02	0.28
A2 time (ms)	22.20 ± 0.31	22.06 ± 0.38	0.03	22.12 ± 0.49	0.59
A2 length (mm)	1.88 ± 0.50	1.84 ± 0.50	0.69	1.83 ± 0.38	0.72
A2 velocity (m/s)	−0.43 ± 0.09	N/A	N/A	N/A	N/A
HC time (ms)	17.08 ± 0.49	16.90 ± 1.09	0.17	17.19 ± 0.69	0.62
Peak dist (mm)	3.80 ± 1.29	3.60 ± 1.24	0.42	3.56 ± 1.15	0.54
Radius (mm)	6.71 ± 0.81	7.04 ± 0.82	0.04	7.17 ± 0.87	0.12
Radius (3P) (mm)	6.77 ± 0.82	7.08 ± 1.18	0.10	7.55 ± 0.96	0.02
A1 deformation amp. (mm)	0.12 ± 0.02	0.12 ± 0.02	0.18	0.13 ± 0.02	0.13
HC deformation amp. (mm)	1.13 ± 0.09	1.12 ± 0.12	0.90	1.11 ± 0.10	0.56
A2 deformation amp. (mm)	0.38 ± 0.06	0.38 ± 0.08	0.89	0.46 ± 0.06	0.0004
A1 deflection length (mm)	2.26 ± 0.20	2.23 ± 0.26	0.53	2.27 ± 0.25	0.95
HC deflection length (mm)	5.84 ± 0.21	5.78 ± 0.43	0.23	5.76 ± 0.30	0.37
A2 deflection length (mm)	2.68 ± 0.34	2.59 ± 0.46	0.20	2.61 ± 0.51	0.63
HC deflection amp. (mm)	0.92 ± 0.09	0.90 ± 0.11	0.20	0.83 ± 0.08	0.002
A1 deflection amp. (mm)	0.09 ± 0.02	0.10 ± 0.04	0.04	0.10 ± 0.02	0.08
A2 deflection amp. (mm)	0.12 ± 0.03	0.12 ± 0.05	0.81	0.12 ± 0.03	0.96
Deflection amp. max (mm)	0.94 ± 0.08	0.91 ± 0.11	0.11	0.84 ± 0.08	0.001
Deflection amp. max time (ms)	16.15 ± 0.71	16.12 ± 1.17	0.84	16.22 ± 0.81	0.80
Whole eye movement max (mm)	0.27 ± 0.06	0.29 ± 0.10	0.35	0.36 ± 0.07	0.001
Whole eye movement max time (mm)	21.52 ± 1.36	21.25 ± 1.69	0.3	21.63 ± 1.35	0.81
NTSim A1 time (ms)	7.41 ± 0.34	7.66 ± 0.74	0.01	7.79 ± 0.53	0.04
NTSim A2 time (ms)	21.99 ± 0.37	21.87 ± 0.83	0.25	21.67 ± 0.65	0.13

p-values represent comparison of the MY group *vs* the KCN group or HY group *vs* the KCN group; p < 0.05 was considered significant; SD: Standard deviation

502.19 ± 34.92 µm; p = 0.001), A1 time (7.16 ± 0.26, 7.02 ± 0.19 ms; p = 0.001), A2 time (22.06 ± 0.38, 22.20 ± 0.31 ms; p = 0.03), radius (7.04 ± 0.82, 6.71 ± 0.81 mm; p = 0.04), A1 deflection amp (0.10 ± 0.04, 0.09 ± 0.02 mm; p = 0.04), and NTSim A1 time (7.66 ± 0.74, 7.41 ± 0.34 ms; p = 0.009). All other parameters presented in Table 3 did not differ significantly between the two groups.

For the HY group, we found the following parameters to differ significantly from the KCN group: Pachy (556.70 ± 43.88, 502.19 ± 34.92 µm hyperopia and KCN respectively; p = 0.003), radius 3P (7.55 ± 0.96, 6.77 ± 0.82 mm; p = 0.02), A2 deformation amp (0.46 ± 0.06, 0.38 ± 0.06 mm; p = 0.0004), HC deflection amp (0.83 ± 0.08, 0.92 ± 0.09 mm; p = 0.002), deflection amp max (0.84 ± 0.08, 0.94 ± 0.08 mm; p = 0.001), whole eye movement max (0.36 ± 0.07, 0.27 ± 0.06 mm; p = 0.001), and NTSim A1 time (7.79 ± 0.53, 7.41 ± 0.34 ms; p = 0.04). All other parameters did not differ significantly. It is noteworthy that the Corvis ST was not able to measure the A2 velocity for all the patients in the MY and HY groups.

The parameters found to be different significantly were further analyzed using a logistic regression model, in order to control for the influence of the IOP and pachymetry as possible cofounders. The results of the logistic regression are presented in Tables 4 and 5. During the analysis, we found that there was significant colinearity between the IOP and A1 time (r = 0.99), thus preventing the model from discriminating the influence of IOP and A1 time (therefore, A1 time was considered as a cofounder as well).

For the myopia *vs* KCN analysis, three parameters were found significantly different (Table 4): IOP [odds ratio (OR) 6.69 e-02 (95% confidence interval [CI]: 9.75 e-03–4.59 e-01)], pachymetry [OR 9.81 e-01 (95% CI: 9.65 e-01–9.98 e-01)], and A1 time [OR 5.94 e+07 (95% CI: 7.12–4.95 e+14]). Two parameters showed a possible association with KCN (0.05 < p < 0.1): A1 deflection amp [OR 3.44 e-08 (95% CI: 7.36 e-16–1.61)] and NTSim A1 time [OR 3.96 (95% CI: 8.12 e-01–1.94 e+01)].

Table 4: Logistic regression—myopia *vs* KCN

	p-value	*OR*	*CI*
IOP	0.006	6.69 e-02	9.75 e-03–4.59 e-01
Pachymetry	0.03	9.81 e-01	9.65 e-01–9.98 e-01
A1 time	0.03	5.94 e+07	7.12–4.95 e+14
A2 time	0.96	1.08	7.13 e-02–1.63 e+01
Radius	0.99	1.01	4.83 e-01–2.10
A1 deflection amp.	0.06	3.44 e-08	7.36 e-16–1.61
NTSim A1 time	0.08	3.97	8.12 e-01–1.94 e+01

Positive outcome defined as KCN; p-value for the model: 0.0003

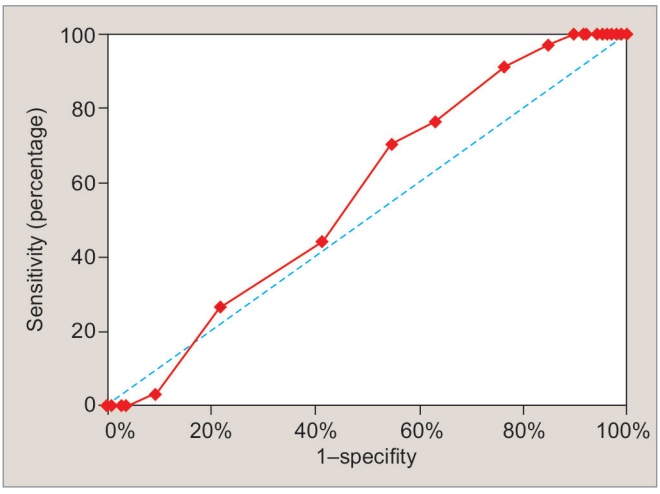
Table 5: Logistic regression hyperopia *vs* KCN

	p-value	*OR*	*CI*
IOP	0.77	2.72 e-01	4.34 e-05–1.70 e+03
Pachymetry	0.13	9.17 e-01	8.21 e-01–1.02
A1 time	0.79	4.90 e-04	1.14 e-28–2.10 e+21
Radius (3P)	0.20	1.11 e+02	8.70 e-2–1.41 e+05
A2 deformation amp.	0.39	7.39 e-22	1.37 e-69–3.97 e+26
HC deflection amp.	0.52	2.07 e-15	3.13 e-60–1.37 e+30
Deflection amp. max	0.46	2.46 e+19	1.87 e-32–3.23 e+70
Whole eye movement max	0.90	8.55 e+1	1.80 e-29–4.07 e+32
NTSim A1 time	0.34	8.37 e+1	9.42 e-03–7.45 e+05

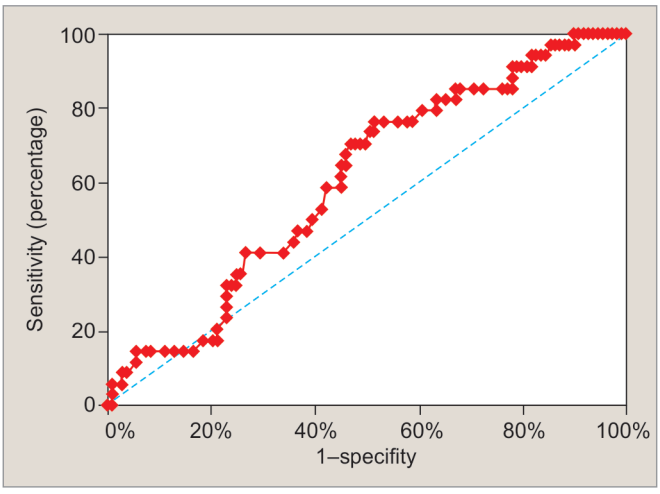
Positive outcome defined as KCN; p-value for the model: 0.0007

We produced receiver operator characteristic (ROC) curve analysis for these two variables (Graphs 1 and 2). Using a cutoff of 0.08 mm for A1 deflection amp results in a specificity of 58.5% and sensitivity of 44.1%. The area under the curve (AUC) is 0.568. Using a cutoff of 7.31 ms for NTSim A1 time results in a specificity of 73.4% and sensitivity of 41.2%. The AUC is 0.606.

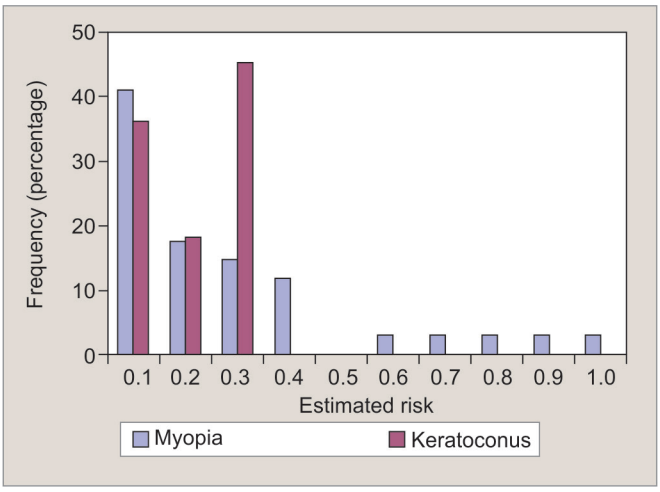
In the hyperopia *vs* KCN analysis, shown in Table 5, no parameter was found to be different statistically significant using the logistic regression model.



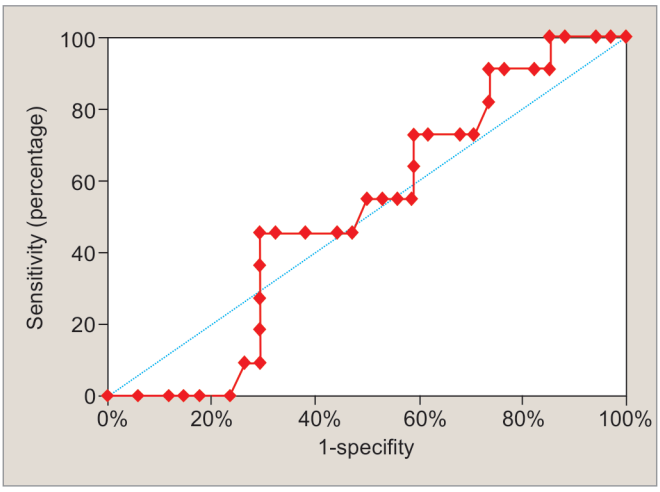
Graph 1: The ROC curve for A1 deflection amp: AUC: 0.568



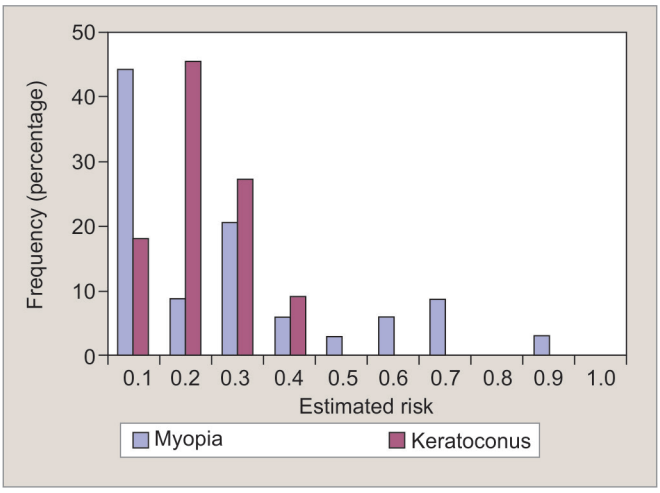
Graph 2: The ROC curve for NTSim A1 time: AUC: 0.606



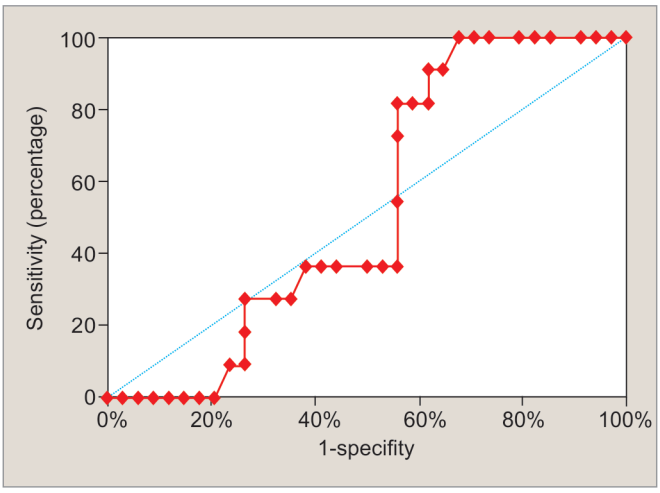
Graph 3: The distribution of the estimated risk, calculated using the first formula, for the MY and KCN patients



Graph 4: The ROC curve for formula 1: AUC: 0.508



Graph 5: The distribution of the estimated risk, calculated using the second formula, for the MY and KCN patients



Graph 6: The ROC curve for formula 2: AUC: 0.527

In order to test the clinical relevance of our findings in the myopia *vs* KCN analysis, we used all parameters that were analyzed in the logistic regression model in order to develop a predicting formula based on randomly selected two-thirds of the study population:

$$t_1 = 30.23707 + (-2.73090 \times \text{IOP}) + (-0.01051 \times \text{pachy}) + (9.86006 \times \text{A1 time}) + (-3.22648 \times \text{A2 time}) + (0.35380 \times \text{radius}) + (-33.77657 \times \text{A1def amp}) + (1.67904 \times \text{NTSim A1 time})$$

$$\text{Estimated risk} = \frac{1}{1+e^{-t_1}}$$

A histogram for the distribution of the estimated risk (ER), calculated using the first formula on the remaining third of the study population, is presented in Graph 3. The ROC curve analysis for the first formula is presented in Graph 4. The AUC is 0.508, using a cutoff of 0.258 results in a specificity of 70.6% and sensitivity of 45.5%.

We also produced a second formula using a stepwise elimination approach (criterion for removal $p > 0.1$). Again, we developed the predicting formula based on the randomly selected two-thirds of the population:

$$t_2 = 2.365817 + (-1.080110 \times \text{IOP}) + (-0.015794 \times \text{pachy}) + (-33.988237 \times \text{A1def amp}) + (2.928363 \times \text{NTSim A1 time})$$

$$\text{Estimated risk} = \frac{1}{1+e^{-t_2}}$$

To test the clinical relevance of the ER calculated using the second formula, we produced a histogram, shown in Graph 5, for the remaining third of the population. We also performed an ROC curve analysis for the second formula shown in Graph 6. The AUC is 0.527. Using 0.235 as a cutoff, a specificity of 61.8% and a sensitivity of 36.4% are achieved.

DISCUSSION

Clinical signs, alongside with topographic and tomographic data,[11] allow detection of the majority of

KCN corneas with high sensitivity and specificity, especially when combining multiple parameters in the data analysis.[12,13] However, the significant implications of ectasias following refractive surgery[14] due to underdiagnosis of early forms of KCN call for even more sensitive and specific methods. With the introduction of computerized videokeratography, corneal biomechanical properties could be tested *in-vivo*, and presumably be used to facilitate diagnosis of early, mild forms of the condition.

Studies performed on the ORA present inconsistent results. Although in some studies, the mean CH and CRF were significantly lower in KCN or KCN suspect corneas,[15-18] the actual values were scattered widely and had significant overlap between groups, limiting the clinical interpretation of the results.[7,19]

In our study, seven parameters were found to differ significantly between the KCN and MY groups, but only three remained significant following the logistic regression models—IOP, pachy, and A1 Time. The HY group consisted of a small number of patients, and, therefore, though seven parameters were found significantly different from the KCN group in single parameter analysis, none retained significance in the logistic regression performed. For this comparison, no regression formula could be developed.

Three parameters were regarded as confounders: Corneal thickness, IOP, and A1 time. The corneal thickness has a well-documented influence on contact and noncontact tonometry results,[20,21] thus has to be taken into consideration when performing applanation measurements. The IOP directly influences all measured applanation parameters, and thereby has been considered a confounder. The A1 time, used to calculate the IOP measurements, naturally presented a strong colinearity with the intraocular pressure and, therefore, was as well regarded as a confounder.

Upon removal of the confounders, no parameters remained significant in distinguishing the MY group from the KCN group. For the two parameters that demonstrated a possible association with KCN (A1deflection amp and NTSim A1), the ROC curves showed poor performance in manners of sensitivity and specificity among various discrimination thresholds.

Though statistically significant, the formulae developed for the detection of KCN corneas, or for risk stratification among patients, also presented low efficacy in ROC curves, with an AUC of 0.508 and 0.594. These values represent nonsatisfactory sensitivity and specificity for detection of KCN among population.

Wolffsohn et al[22] presented a higher AUC in ROC curves for detection of KCN using the ORA. However, only a marginal improvement of the ROC curves could be attributed to the ORA data: Sensitivity was 15% higher compared with keratometry alone, and 5% higher compared with keratometry and pachymetry, with some loss of specificity (3%). Eventually, only 4% of the variance in clinical rating of KCN could be explained by ORA biomechanical parameters. No data were included regarding whether the formula presented in their study was tested on the entire study population or on a distinct subgroup, as the former allows higher specificity and specificity scores.

In conclusion, the Corvis ST was found to be ineffective as a single-examination device in detection of KCN among study population. Better results could possibly be achieved by stepwise modeling, taking into account keratometry and pachymetry prior to addition of the biomechanical data.

Due to insufficient HY patients in the study population, further studies are warranted for conclusions to be drawn for this population.

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