A predictive model for early diagnosis of keratoconus

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Research article

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Abstract

Background: The diagnosis of keratoconus in the early stages of the disease is necessary to initiate an early treatment of keratoconus. Furthermore to avoid possible refractive surgery that could produce ectasias. This study aims to describe the topographic, pachymetric and aberrometry characteristics in patients with keratoconus, subclinical keratoconus and normal corneas. Additionally to propose a diagnostic model of subclinical keratoconus based in binary logistic regression models Methods: The design was a cross-sectional study. It included 205 eyes from 205 patients distributed in 82 normal corneas, 40 subclinical keratoconus and 83 established keratoconus The rotary Scheimpflug camera (Pentacam® type) analyzed the topographic, pachymetric and aberrometry variables. It performed a descriptive and bivariate analysis of the recorded data. A diagnostic and predictive model of subclinical keratoconus was calculated with the statistically significant variables Results: Statistically significant differences were observed when comparing normal corneas with subclinical keratoconus/ in variables of the vertical asymmetry to 90º and the central corneal thickness. The binary logistic regression model included the minimal corneal thickness, the anterior coma to 90º and posterior coma to 90º. The model properly diagnosed 92% of cases Conclusions: The differential diagnosis between normal cases and subclinical keratoconus depends on the mínimum corneal thickness, the anterior coma to 90º and the posterior coma to 90º.

Background

Keratoconus is an asymmetrical bilateral eye disease [1] in which corneal thinning and protrusion occurs in the form of a generally lower temporal cone. This corneal deformation produces a significant decrease in visual quality.

It usually appears in adolescence, progressing into the third or fourth decade [1]. Although of unknown etiology, it has been related to genetic factors [2] such as environmental factors [3-4].

The incidence and prevalence of keratoconus are very variable. It has been seen that in Europe, the frequency would be between 5 and 23 per 100,000 people/year and the average prevalence would be 54 per 100,000 [5]. In a recent study, it was observed that the prevalence of keratoconus in southern Spain was 30 per 100,000 [6].

The diagnosis of keratoconus is clinical. Therefore, it is established when a patient presents progressive loss of vision that is not corrected with glasses and is accompanied by biomicroscopic findings in the exploration.

Subclinical Keratoconus is defined as early stages of the disease, where visual acuity is usually preserved.[5]

Throughout history, several classifications of clinical keratoconus have been used; the Amsler-Krumeich classification has been the most widely used. Alió-Shabayek modified it including coma-like corneal

aberrations.[8]. However, there is no adequate classification to determine the stage of this pathology at an early stage.

Corneal topography is a non-invasive diagnostic test that allows knowing the surface of the cornea. It was established that this is the best method of diagnosis in incipient keratoconus [9] The Oculus Pentacam® system provides the anterior and posterior topographic, pachymetric and aberrometry maps.

The anterior corneal surface is the most important refractive component of the eye, and its aberrations are very useful in the diagnosis of the corneal disease.[8-12]However, studies of aberrations of the posterior surface are discordant and inconclusive.[9-14]

The study of corneal aberrations in incipient stages has allowed us to affirm that the anterior coma to 90º is the one that most discriminates them from healthy corneas.[15].Parameters as minimum corneal thickness, posterior coma,[16]trefoil[17] and spherical aberration[14]would also have an influence.

It has been analyzed that corneal aberrations, especially the anterior coma to 90º and its influence in the visual quality of patients with keratoconus [16]

The study of the wavefront has great importance for the early diagnosis of keratoconus and the determination of variables that influence visual acuity. The main objective of this study is to establish a predictive model of early diagnosis in keratoconus with topographic variables obtained by Pentacam®.

Methods

A cross-sectional study was carried out to analyses the topographic, pachymetric and aberrometry variables obtained by rotary Scheimpflug camera (Pentacam® type) from patients diagnosed with keratoconus, subclinical keratoconus and normal corneas in the Ophthalmology Service at the Torrecárdenas University Hospital (Almería, Spain) between February 2018 and February 2019. The data have been collected from the Pentacam® clinical database.

Participants have been previously informed of the data to be taken and have signed an informed consent authorizing the use of their data anonymously. The ethical principles for medical research on human beings of the Declaration of Helsinki have been followed.

A total of 205 eyes of 205 patients (only one eye per patient) was distributed in 3 groups

Group 1: Healthy patients without corneal pathology,

Group 2 Patients with subclinical keratoconus. This group included patients with any altered corneal topography but without clinical signs of disease and clinical keratoconus in the contralateral eye

Group 3 Patients with keratoconus. They must present at least one biomicroscopic alteration of the anterior segment (central thinning with Fleischer's ring and Vogt's striae) and the topography compatible with corneal ectasia. In patients with bilateral keratoconus, one of the eyes had been taken randomly.

The exclusion criteria were to have any systemic or ocular pathology and any ocular surgical intervention, including intrastromal rings and cross-linking.

A complete ophthalmological examination was performed in all cases.

Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were collected with Snellen's chart (decimal scale). Objective refraction obtained by an autorefractometer (KR8900, Topcon, Japan) biomicroscopy (Carl Zeiss Meditec AG, Jena, Germany) and fundus were examined.

A corneal topographic analysis was performed on all patients by the same trained physician, under the same dark conditions and a pupil diameter of 6 mm. Patients with soft contact lenses didn´t wear them for three weeks and the gas-permeable rigid lenses for at least five weeks before the test. The examination was performed with the rotary camera Scheimpflug (Pentacam® AXL, Oculus Optikgeräte, Wetzlar, Germany).

The following variables were collected:

Corneal topography of the anterior face: minor curvature (K1), major curvature (K2), mean curvature (Km), maximum curvature (KMAX), asphericity (Q), vertical asymmetry index (VAI); corneal topography of the posterior face: minor curvature (K1), major curvature (K2), mean curvature (Km) and asphericity (Q), central corneal thickness (CCT), minimum corneal thickness (MCT) with its coordinates (x,y) mean square root of total aberrations (Total RMS), mean square root of high order aberrations (HOA RMS), secondary corneal astigmatism to 0º ($Z2^{2}$) and 45º ($Z2^{-2}$), anterior horizontal coma to 0º, posterior horizontal coma to 0º, total horizontal corneal coma to 0º ($Z3^{1}$), anterior vertical coma to 90º, posterior vertical comato90º, total vertical corneal coma to 90º ($Z3^{-1}$), trefoil to 0º ($Z3^{-3}$), trefoil to 30º ($Z3^{3}$), tetrafoil to 0º ($Z4^{4}$), tetrafoil to 22.5º ($Z4^{-4}$) and spherical aberration ($Z4^{0}$).

Statistical analysis was performed using the software for Windows SPSS (version 25.0, SPSS, Chicago, Illinois, USA) and R (version 3.5.1).

Results

The study compared 205 eyes divided into three study groups, the distribution of which is shown in Table 1. There were no statistically significant differences in laterality or sex between the groups.

There were statistically significant differences between the three groups ($p < 0.05$, Kruskal-Wallis) for the sphere, cylinder, spherical equivalent and BCVA (decimal scale). Also, there were statistically significant differences between group 1 and 2 for the sphere ($p = 0.012$, U Mann-Whitney), (Table 1).

Means and standard deviations were calculated for the different variables. Those of more considerable clinical significance are presented in Table 2.

able 1: Demographic characteristics

		Normal	SCKC	KC	SCKC Vs Controls P Value*	Controls Vs KC P Value*
atients	n (%)	82 (39.8)	40 (19.4)	83 (40.3)		
ye	Right	41 (50.0)	19 (47.5)	54 (65.1)		0.078
	Left	41 (50.0)	21 (52.5)	29 (34.9)		
ex	Male	36 (43.9)	23 (57.5)	40 (48.2)		0.369
	Female	46 (56.1)	17 (42.5)	43 (51.8)		
phere (D)		-0.36 ± 3.02 [-8; 4.50]	-1.06 ± 1.71 [-5.50; 3]	-3.71 ± 4.71 [-16;6]	0.012	< 0.01
linder (D)		-1.82 ± 2.15 [-6; 3.75]	-1.19 ± 0.99 [-2.50; 2.75]	-2.95±1.46 [-6;1]	0.059	< 0.01
pherical equivalent D)		-1.38 ± 3.23 [-10; 5.50]	-1.73 ± 1.62 [-5.50; 2.25]	-4.84 ± 4.61 [-18; 4.50]	0.251	< 0.01
CVA (decimal ale)		0.97 ± 0.07 [0.7;1]	0.99 ± 0.06 [0.7;1]	0.6 ± 0.29 [0.05; 1]	0.219	< 0.01

*p<0.05

Table 2. Main Pentacam indices and bivariate analysis

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*diopters, ** µm

Early diagnosis of Keratoconus:

Our main objective in the study was to differentiate between healthy patients (group 1) and patients with SCKC (group 2). To achieve our goal we have designed a binary logistic regression model in which the dependent variable is qualitative with two categories: normal patient or subclinical keratoconus. The independent variables included are those in the bivariate analysis have a statistically significant relationship with the dependent variable. The independent variables included MCT, anterior coma to 90° and posterior coma to 90°

Table 3 analyzed the coefficients of the equation accompanied by their statistical significance and their OR (Exp (B)) with the 95% confidence interval and the variance inflation factor to evaluate the collinearity between the variables. Taking the normal patient as a reference category, we can diagnose the patient

	Controls	SCKC	KC	SCKC Vs Controls p Value	KC Vs Controls p Value
Anterior surface topography					
Km*	43.55±1.43	43.37±1.55	48.26±4.64	0.616	
KMAX*	45.49±1.92	45.91±1.97	55.14±7.66	0.285	<0.01
VAI	0.16±0.08	0.28±0.14	0.79±0.51	<0.01	<0.01
Posterior surface topography					
Km	-6.246±0.22	-6.148±0.34	-7.15±0.9	0.067	<0.01
Pachymetry					
CCT**	543.76±36.42	515.20±27.59	466.92±55.94	<0.01	<0.01
MCT**	538.52±37.03	503.67±26.62	456.93±50.65	<0.01	<0.01
Corneal Aberrometry**					
RMS HOA	0.52±0.23	0.69±0.31	1.74±1.02	<0.01	<0.01
Ant Coma 90º	0.01±0.20	0.49±0.43	-2.06±1.51	<0.01	<0.01
Post Coma 90º	-0.01±0.05	0.11±0.10	0.53±0.39	<0.01	<0.01
Coma 90º	0.01±0.21	-0.40±0.32	-1.88±1.41	<0.01	<0.01
Trefoil 0º	0.03±0.18	0.08±0.22	0.09±0.34	0.396	<0.01
Spherical aberration	0.20±0.14	0.18±0.16	-0.279±0.75	0.204	<0.01

with subclinical keratoconus with the data contained in Table 3. The posterior coma to 90º is the most important variables to diagnose the presence of SCKC; Curiously, the increase with a positive sign of the anterior coma to 90º reduces the probability of SCKC (characterized by an increase with a negative sign of the anterior coma 90º). Increased the minimum central corneal thickness decreases the probability of SCKC. The model expressed in the form of an algorithm is:

$\ln(p/1-p) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3$

Then our model is:

$\ln (p/1-p) = 19.258 - 0.04x_1 + 19.92x_2 - 2.63x_3$

where p is the probability of the subclinical keratoconus and (p/1-p) is the Odds Ratio (OR) that means the probability of the diagnosis of SCKC divided by the probability of the diagnosis of normal cases (1-p).

$OR = e^{19.258 - 0.04x1 + 19.92x2 - 2.63x3}$

for each patient with data from MCT, anterior coma to 90º and posterior coma to 90 º

The increased minimum corneal thickness(x_1) and the anterior coma to 90º(x_2) with positive sign decrease the probability of SCKC. On the other hand, the probability of SCKC is greatly increased with the posterior coma to 90º and the anterior coma to 90º with the negative sign

Table 3: Regression model coefficients for the diagnosis of subclinical keratoconus

	Estimate β	Exp β (OR)	Std. Error	P value	VIF
(Intercept)	19.25789	2.31E+08	6.20707	0.001918	
MCT	-0.04001	0.961	0.01198	0.000838	1.25
COMA.POST.90	19.92046	4.48E+08	6.90491	0.003915	1.82
COMA.ANT.90	-2.62811	0.072	1.53268	0.086397	1.53

The Hosmer and Lemeshow goodness of fit test (GOT) (p=0.566) indicated that the proposed model was correctly calibrated.

Table 4 shows a contingency table of observed cases versus predicted cases. The sensitivity defined as the percentage of true positives among all those diagnosed as subclinical keratoconus was 91.2% (31/34=0.912*100) and the specificity, percentage of true negatives among all negatives was 89.8% (79/88=0.898*100)

Table 4: Contingency table of observed cases versus predicted cases

	predicted	
outcome	Normal	SCKC
Normal	79	3
SCKC	9	31

The AUC (Area Under Curve) of the ROC (Receiver Operating Characteristics) curve for the binary logistic regression model was 0.92 (IC 95% 0.86 – 0.98) in the diagnosis of subclinical keratoconus (Figure 1) which means that 92% of the cases were well classified

Discussion

Detection of SCKC has always been a challenge for ophthalmologists, especially when there are no clinical signs or symptoms in the patient.

The rotary camera Scheimpflug (Pentacam®) topography is usually used to diagnose keratoconus in daily clinical practice [13-14, 20-26, 30]. The topographic parameters of clinical keratoconus are recognizable. However, it is not easy to diagnose subclinical keratoconus based on topographic variables. This study calculates a diagnostic model based on the aberrometry data of the anterior and posterior corneal surface provided by the Pentacam

The selection of the sample was made that there were no differences between the age groups [12-15, 17-19, 21, 24, 29], sex [14, 21-22, 29], and eye [21-22]. This is an advantage when interpreting results that aren´t biased by age and sex. As reported by Koçamis et al. [22], there are significant differences for age between keratoconus (26.19 ± 7.90) and healthy (30.88 ± 7.57)

Pupillary dilatation is another parameter that can modify the aberrometry results [27]. In this study, it was prefixed in 6 mm. In previous studies [8, 12-14, 20-23, 29] like Hondur et al [27] established it in 5 mm.

Many studies have been made between healthy patients with Keratoconus [8-10, 12-14, 20-27] or healthy patients with SCKC [15-19, 21-23, 26, 28-31]. The purpose in most of them was to analyze the topographic parameters to find differences between a healthy patient and an incipient corneal ectasia without symptoms. However in all of them, many different classification methods have been used: Amsler-Krumeich [24, 27- 28], Alió and Shabayek [13, 20], KISA % index [21] or KSS [29]. All this methodological variability leads to an outstanding selection and classification bias when making comparisons between studies.

If we analyze the refractive parameters of our study, statistically significant differences were obtained between the three groups analyzed for the sphere, the cylinder and the spherical equivalent ($p < 0.05$, Kruskal-Wallis), as in other studies[19, 30]. However, when comparing normal corneas with SCKC, we

obtained statistically significant differences only for the sphere (p = 0.012, U Mann-Whitney). Saad and Gatinel [17] obtained that the mean of the sphere was significantly higher in their normal group than in their SCKC group (p < 0.001). Reddy et al [19] observed statistically significant differences for the cylinder (p < 0.001) not for the sphere (p = 0.08). However, Naderan et al [29] didn´t find statistically significant differences for sphere (p = 0.136) or cylinder (p = 0.108). In our study, we found statistically significant differences between the visual acuity of the three groups, but it wasn´t differences between normal corneas and SCKC. These values are consistent with previous studies [8, 20-22, 27, 30-31]. When we analyzed a bivariate analysis between normal corneas and SCKC, statistically significant differences were only obtained for variables of vertical asymmetry, total coma to 90º and corneal thickness (p < 0.05). Bührenet al [15], found that the anterior coma to 90º would be the most useful parameter to differentiate normal corneas from SCKC. Other parameters such as the posterior coma to 90º and the minimum corneal thickness didn't exceed the value of the anterior surface for this author. In our study, when the total corneal coma to 90º was analyzed in absolute value, we found that it was higher in SCKC (|-0.404| ± 0.319) than in normal (0.0123 ± 0.209), but lower than in keratoconus (|-1.877| ± 1.413). This value indicates that the parameter total corneal coma to 90º had increased with the natural history of the disease [17]. The negative sign of the corneal coma to 90º refers to the lower decentration of the cone in the y-axis [17]. More recently, Naderan et al [29] and Xu et al [30] indicated the importance of posterior surface aberrations to differentiate normal from SCKC corneas. In the first study, they obtained that the values for posterior coma to 90º of the healthy group were 0.032 ± 0.363 and for the SCKC group were 0.193 ± 0.264 with statistically significant differences between groups (p = 0.003, U Mann-Whitney). In our database, the posterior coma to 90º for normal corneas were -0.008±0.049 and for SCKC were 0.112±0.103, (p < 0.05, U Mann-Whitney). The relationship between coma-like aberrations of the anterior surface and the degree of manifest keratoconus is well known [8, 12, 22, 24-27]. Piñero et al [13] were the first to attempt to characterize the posterior corneal surface and its aberrations in patients with normal corneas and keratoconus, finding results that were not concordant by the optical theory of the corneal surface. In Piñero´s study, have obtained values of anterior coma to 90º of 0.001 ± 0.225 and posterior coma to 90º of 0.319 ± 0.372 from the healthy patients. In keratoconus were -1.754 ± 0.976 and -3.692 ± 1.81 respectively.

If we analyze the results of our study, in healthy patients the anterior coma to 90º was 0.01 ± 0.20 and posterior coma to 90º was -0.01 ± 0.05 (the same mean but opposite sign) and in keratoconus, we obtained -2.06 ± 1.51 and 0.53 ± 0.38 respectively. In our case, the anterior coma to 90º, in absolute value, were higher than the posterior ones. In subclinical keratoconus, the anterior coma to 90º was 0.49±0.43 and the posterior coma to 90º was 0.11±0.10. Comparing the results, we observed that both anterior and posterior coma at 90º increase with the appearance of the corneal alterations of keratoconus from early stages but with opposite signs, while the anterior coma to 90º becomes negative, the posterior coma to 90º becomes positive

Attempted to other parameters, several studies like Buhrenet al [15] observed that the MCT was the most discriminating parameter between normal corneas and SCKC. However, they concluded that the posterior surface was not discriminate as to the anterior surface, and this surface was not sufficient for the

diagnosis of the subclinical keratoconus. Otherway Safarzadeh et al [28] reflected that minimum corneal thickness and posterior corneal elevation would be the best parameters for differentiating suspicious keratoconus from healthy eyes in concordance with our results.

Finally, we propose a binary logistic model to predictive the subclinical keratoconus. Other authors [17, 21, 30] have established binary logistic models for keratoconus diagnosis but not for subclinical keratoconus. Our results analyze the probability of subclinical keratoconus using three variables: MCT, anterior coma to 90º and posterior to 90º. The validation of this model with Hosmer Lemeshow test and the AUC (Area Under Curve of the sensibility vs specificity graphic), suggest a good calibration in 92% of cases The main limitation of our results is the population size of the subclinical keratoconus. We need to increase the number of subclinical keratoconus to improve the sensibility of the model

Conclusions

The most important aberrometry parameters in the diagnosis of keratoconus are those related to vertical asymmetries: specifically the anterior coma to 90º and the posterior coma to 90º, and the minimum corneal thickness. In the case of the diagnosis of subclinical keratoconus, the main parameter is the increase with a positive sign of the posterior coma to 90º.

Abbreviations

SCKC = Subclinical Keratoconus

MCT=Minimum Corneal Thickness

UCVA= Uncorrected Visual Acuity

BCVA=Best Corrected Visual Acuity

Km= Mean curvature (Km),

Kmax= maximum curvature (KMAX),

Q= asphericity

VAI= vertical asymmetry index

Total RMS = mean square root of total aberrations

HOA RMS = mean square root of high order aberrations

AUC= Area Under Curve

ROC curve = Receiver Operating Characteristics curve

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its comparable ethical standards. Ethical approval by Ethics Committee Torrecárdenas University Hospital. The committee's reference number is 19/2019

Informed consent: Informed consent was obtained from all individual participants included in the study

Consent for publication

Not Applicable

Availability of data and material

The datasets generated and/or analysed during the current study are available in the KERATOCONUS repository, Castro de Luna, Gracia; Perez Rueda, Antonio (2020), "KERATOCONUS", Mendeley Data, V2, doi: 10.17632/t2yzmb4c7s.2

Competing interests
The authors declare no competing interests

Fundings

No funding was obtained for this study

Authors' contributions

GCL has contributed to the design of this study and has calculated the statistical data

APR has collected the data

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Not Applicable

References

1. Mas Tur V, MacGregor C, Jayaswal R, O'Brart D, Maycock N. A review of keratoconus: Diagnosis, pathophysiology, and genetics. SurvOphthalmol. 2017 Nov; 62(6):770–83.
2. Moussa S, Grabner G, Ruckhofer J, Dietrich M, Reitsamer H. Genetics in Keratoconus – What is New? Open Ophthalmol J. 2017; 11(Suppl-1, M4):201–10.

3. Naderan M, Shoar S, Rezagholizadeh F, Zolfaghari M, Naderan M. Characteristics and associations of keratoconus patients. Contact Lens Anterior Eye. 2015; 38(3):199–205.
4. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The Genetic and Environmental Factors for Keratoconus. Biomed Res Int. 2015.
5. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: A review. Contact Lens Anterior Eye. 2010; 33 (4):157–66.
6. Fernández-Barrientos Y, Gismero-Moreno S, Lorenzo-Soto M. Estimated prevalence and clinical characteristics of keratoconus in the healthcare setting of the Hospital Costa del Sol, Spain. J Emmetropia. 2014; 5: 15–21.
7. Huseynli S, Abdulaliyeva F. Evaluation of Scheimpflug Tomography Parameters in Subclinical Keratoconus, Clinical Keratoconus and Normal Caucasian Eyes. TürkOftalmolDerg. 2018; 48(3):99–108.
8. Alió JL, Shabayek MH. Corneal higher-order aberrations: a method to grade keratoconus. J Refract Surg. 2006; 22(6):539–45.
9. Gomes JAP, Tan D, Rapuano CJ, Belin MW, Ambrósio R, Guell JL, Malecaze F, Nishida K, Sangwan VS.Global Consensus on Keratoconus and Ectatic Diseases. Cornea. 2015; 34(4):359–69.
10. Mounir A, El Saman IS, Anbar M. The Correlation between Corneal Topographic Indices and Corneal High Order Aberrations in Keratoconus. Med Hypothesis Discov Innov Ophthalmol.2019; 8(1):1-6.
11. Oliveira CM, Ferreira A, Franco S. Wavefront analysis and Zernike polynomial decomposition for evaluation of corneal optical quality. J Cataract Refract Surg. 2012; 38(2):343–56.
12. Maeda N, Fujikado T, Kuroda T, Mihashi T, Hirohara Y, Nishida K, Watanabe H, Tano Y.Wavefront aberrations measured with a Hartmann-Shack sensor in patients with keratoconus. Ophthalmology. 2002; 109(11):1996–2003.
13. Piñero DP, Alió JL, Alesón A, Escaf M, Miranda M. Pentacam posterior and anterior corneal aberrations in normal and keratoconic eyes. ClinExpOptom. 2009; 92(3):297–303.
14. Nakagawa T, Maeda N, Kosaki R, Hori Y, Inoue T, Saika M, Mihashi T, Fujikado T, Tano Y. Higher-order aberrations due to the posterior corneal surface in patients with keratoconus. Investig Ophthalmol Vis Sci. 2009; 50(6):2660–5.
15. Bühren J, Kook D, Yoon G, Kohnen T. Detection of subclinical keratoconus by using corneal anterior and posterior surface aberrations and spatial thickness profiles. Investig Ophthalmol Vis Sci. 2010; 51(7):3424–32.
16. Alió JL, Piñero DP, Alesón A, Teus MA, Barraquer RI, Murta J, Maldonado MJ, Castro de Luna G, Gutiérrez R, Villa C, et al. Keratoconus-integrated characterization considering anterior corneal aberrations, internal astigmatism, and corneal biomechanics. J Cataract Refract Surg. 2011; 37(3):552–68.
17. Saad A, Gatinel D. Evaluation of total and corneal wavefront high order aberrations for the detection of forme fruste keratoconus. Investig Ophthalmol Vis Sci. 2012;53(6):2978–92.

18. Bruce AS, Catania LJ. Clinical applications of wavefront refraction. Optom Vis Sci. 2014; 91(10):1278–86.
19. Reddy JC, Rapuano CJ, Cater JR, Suri K, Nagra PK, Hammersmith KM. Comparative evaluation of dual Scheimpflug imaging parameters in keratoconus, early keratoconus, and normal eyes. J Cataract Refract Surg. 2014; 40(4):582–92.
20. Bernal Reyes N, Arias Díaz A, Camacho Rangel LE. Aberraciones corneales anteriores y posteriores medidas mediante imágenes de Scheimpflug en el queratocono en niños. RevMexOftalmol. 2015; 89(4):210–8.
21. Prakash G, Suhail M, Srivastava D. Predictive Analysis between Topographic, Pachymetric and Wavefront Parameters in Keratoconus, Suspects and Normal Eyes: Creating Unified Equations to Evaluate Keratoconus. Curr Eye Res. 2016; 41(3):334–42.
22. Kocamış Sİ, Çakmak HB, Çağıl N, Toklu Y. Investigation of the Efficacy of the Cone Location and Magnitude Index in the Diagnosis of Keratoconus. Semin Ophthalmol. 2016; 31(3):203–9.
23. Bilen NB, Hepsen IF, Arce CG. Correlation between visual function and refractive, topographic, pachymetric and aberrometry data in eyes with keratoconus. Int J Ophthalmol. 2016; 6–7.
24. Colak HN, Kantarci FA, Yildirim A, Tatar MG, Goker H, Uslu H, Gurler B. Comparison of corneal topographic measurements and high order aberrations in keratoconus and normal eyes. Contact Lens Anterior Eye. 2016; 39(5):380–4.
25. Delgado S, Velazco J, Delgado Pelayo RM, Ruiz-Quintero N. Correlación de aberraciones de alto orden en la cara anterior de la córnea y el grado de queratocono medidas con cámara de Scheimpflug. Arch Soc Esp Oftalmol. 2016; 91(7):316–9.
26. Hashemi H, Beiranvand A, Yekta A, Maleki A, Yazdani N, Khabazkhoob M. Pentacam top indices for diagnosing subclinical and definite keratoconus. J CurrOphthalmol.2016;28(1):21–6.
27. Hondur G, Cagil N, Sarac O, Ozcan ME, Kosekahya P. Pupillary Offset in Keratoconus and its Relationship with Clinical and Topographical Features. Curr Eye Res. 2017; 42(5):708–12.
28. Safarzadeh M, Nasiri N. Anterior segment characteristics in normal and keratoconus eyes evaluated with a combined Scheimpflug/Placido corneal imaging device. J Curr Ophthalmol. 2016; 28(3):106–11.
29. Naderan M, Jahanrad A, Farjadnia M. Ocular, corneal, and internal aberrations in eyes with keratoconus, forme fruste keratoconus, and healthy eyes. Int Ophthalmol. 2018; 38(4):1565–73.
30. Xu Z, Li W, Jiang J, Zhuang X, Chen W, Peng M, Wang J, Lu F, Shen M, Wang Y. Characteristic of entire corneal topography and tomography for the detection of sub-clinical keratoconus with Zernike polynomials using Pentacam. Sci Rep. 2017; 7(1):1–10.
31. Aksoy S, Akkaya S, Özkurt Y, Kurna S, Açikalin B, Şengör T. Topography and Higher Order Corneal Aberrations of the Fellow Eye in Unilateral Keratoconus. Turkish J Ophthalmol. 2018; 48(5):274–5.

Figures

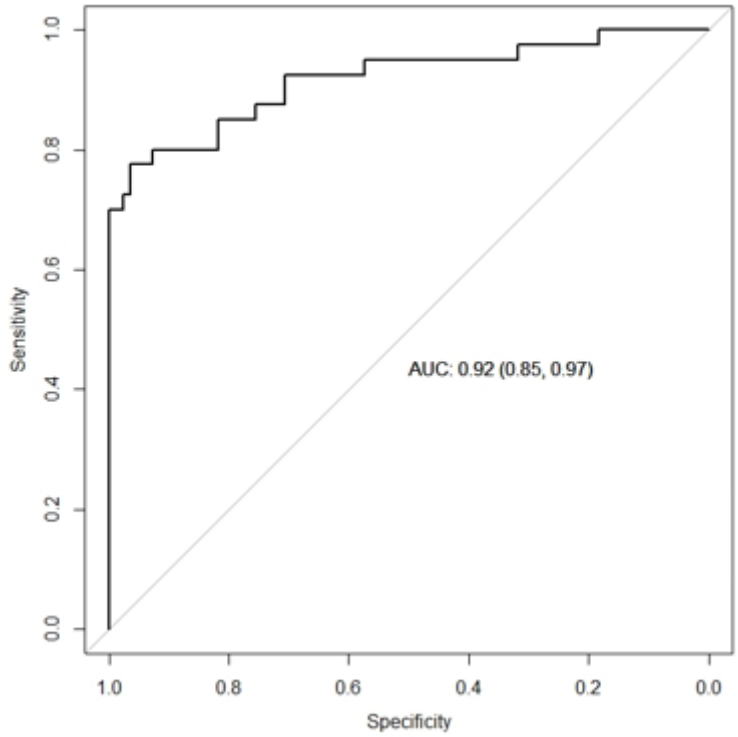

Figure 1

the ROC (Receiver Operating Characteristics) curve for the regression model