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Evaluation of Anterior and Posterior Corneal Higher Order Aberrations for the Detection of Keratoconus and Suspect Keratoconus

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Abstract: Aim: To investigate the application of anterior and posterior corneal higher order aberrations (HOAs) in detecting keratoconus (KC) and suspect keratoconus (SKC). **Method:** This is a retrospective, case-control study which evaluated non-ectatic (normal) eyes, SKC eyes, and KC eyes. The Sirius Scheimpfug (CSO, Italy) analyzer was used to measure HOAs of the anterior and posterior corneal surfaces. Sensitivity, specificity and area under receiver operating characteristic curve (AUC) were calculated. **Results:** Two-hundred and twenty eyes were included in the analysis (normal n = 108, SKC n= 42, KC n= 70). Receiver operating characteristic (ROC) curve analysis revealed a high predictive ability for anterior corneal HOAs parameters: Root mean square (RMS) total corneal HOAs, RMS trefoil and RMS coma to detect keratoconus (AUC > 0.9 for all). RMS Coma (3, ±1) derived from the anterior corneal surface was the parameter with the highest ability to discriminate between suspect keratoconus and normal eyes (AUC = 0.922; cutoff > 0.2). All posterior corneal HOAs parameters were insufficient in discriminating between SKC and normal eyes (AUC < 0.8 for all). In contrast, their ability to detect KC was excellent with AUC of > 0.9 for all except RMS spherical aberrations (AUC = 0.846). **Conclusion:** Anterior and posterior corneal higher order aberrations can differentiate between keratoconus and normal eyes, with a high level of certainty. In suspect keratoconus disease however, only anterior corneal HOAs, and in particular coma-like aberrations, are of value. Corneal aberrometry may be of value in screening for keratoconus in populations with a high prevalence of the disease.

Keywords: higher-order aberrations; sensitivity; keratoconus suspect; Sirius topography; Scheimpflug

1. Introduction

Keratoconus (KC) is a progressive corneal disease characterized by stromal thinning and protrusion, resulting in irregular astigmatism and visual impairment (1). Ectasia may initially be present unilaterally, however due to the progressive nature of the disease, both eyes are often affected (2). Advanced signs of KC can be detected clinically using slit-lamp biomicroscopy as well as keratometry. Visual impairment in such cases is common. Screening can lead to early detection of the early stages of the disease. Split or scissoring retinscopic reflex, or the "Charleaux" oil droplet sign are clinical indicators that may be seen in early keratoconus (3).

The use of videokeratography-derived indices is the most sensitive and sophisticated way of detecting KC. However, some corneal anomalies induced by corneal scarring, dry eye or hard contact lenses, may yield false positives on videokeratoscopy and findings ordinarily seen in early keratoconus. Similarly, a negative videokeratography may not rule out absence of an early form of KC (4). Several studies have suggested that the addition of corneal aberrometery data may allow for better sensitivity and specificity for the detection of keratoconus in comparison to topographical evaluation alone (5, 6, 7).

The aim of this study was to determine the diagnostic accuracy of the anterior and posterior corneal wavefront aberrations in differentiating between keratoconus, suspect keratoconus (SKC) and normal corneas, and to ascertain the parameters with the highest sensitivity and specificity.

2. Material and Methods

This single-centre retrospective, case-controlled study was conducted at the department of ophthalmology, Tishreen University Hospital (Latakia, Syria). Study participants underwent comprehensive ocular assessment and included: uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), auto-refracto-keratometry (SEIKO CO., GR-3500KA, Japan), slit-lamp examination to detect the presence or absence of signs of KC (apical scar or thinning, Fleischer rings and Vogt's striae), Goldmann applanation tonometry, dilated funduscopy and retinoscopic examination.

Corneal topography and aberrometery was conducted using the Sirius Sheimpflug-Placido topographer (Costruzioni Strumenti Oftalmici, Florence, Italy; software version: Phoenix v.2.6). Anterior corneal higher order aberrations (HOAs) were measured over the central 6.0 mm. Three well-focused, centered images were obtained for both eyes. Tear-film was optimized in dry eye patients with topical lubricants or spontaneous repeated blinking. A quality threshold of 16 continuous Placido disc mires was set to maintain image acquisition quality and subsequent calculation of the Zernike coefficients for a 6.0 mm simulated pupil. All subjects with a history of contact lens-use were asked to discontinue wearing their lenses for 3 weeks and 1 week for rigid lenses and soft lenses, respectively.

2.1. Study participants

Participants were divided into three study groups: normal, SKC and KC. The normal group was composed of individuals who had undergone previous laser-assisted in situ keratomileusis (LASIK) at least 3 years prior with no evidence of postoperative ectasia. All eyes in the normal group had a corrected distance Snellen(feet) visual acuity of 20/20 or better.

Suspect KC was defined as anterior or posterior corneal steepening, absence of clinical (keratometric, retinscopic, or biomicroscopic) signs of keratoconus in either eye, and best corrected visual acuity of 20/20 or better (8, 9). Only one eye (right eye) was included if both eyes were suspect.

A diagnosis of KC was made if (a) there was an irregular cornea, determined by distorted keratometry mires or distortion of the dilated retinoscopic reflex (or a combination of both) (10,11), in addition to (b) at least two of the following tomographic/topographic findings: Abnormal posterior ectasia, abnormal thickness distribution, or symmetry index front (SIf) of > 1.17 D (4); or one of the following slit lamp findings: Vogt striae, 2-mm arc of Fleisher ring, or corneal scarring consistent with KC (12). The data of one eye (right) was included if both eyes had evidence of KC or SKC.

Exclusion criteria included patients with a history of previous corneal or ocular surgery (e.g., cataract, glaucoma, corneal cross-linking, excimer laser surgery, intra stromal corneal rings, phakic intraocular lens), any disease that could possibly interfere with the readings/results (e.g., dry eye disease, keratitis, glaucoma, uveitis Fuch’s dystrophy), corneal scarring not consistent with KC, autoimmune disease, lactation or pregnancy. Individuals with ocular or systemic disease (e.g., uveitis, glaucoma, atopic dermatitis, connective tissue disorders) were also excluded from the normal group.

2.2. Mean Outcomes Measures:

Anterior and posterior corneal HOAs were obtained from the Sirius topographer at a 6 mm diameter. Normalized coefficients were used, expressed in microns of wavefront error (root mean square [RMS]), and labeled with International Organization for Standardization (ISO) standardized double-index Zernike (Z) symbols (13). The collected data included: RMS total HOAs, RMS trefoil Z (3, ±3), RMS coma Z (3, ±1) and RMS primary spherical aberrations (SA) Z (4, 0).

2.3. Statistical Analysis

The study was approved by the research committee of Tishreen University in accordance with the ethical standards stated in 1964 Declaration of Helsinki, with informed consent of participants. Statistical analysis was performed using MedCalc Statistical Software, version 19.5.3 (MedCalc Software bv, Ostend, Belgium) and SPSS software (version, 17, SPSS Inc, Chicago, IL, USA). A two-tail t-test was used to compare means between each two groups. Receiver operating characteristic (ROC) curves were used to distinguish KC and SKC from normal corneas. These curves were obtained by plotting sensitivity against 1-specificity, calculated for each value observed. The area under the ROC curve (AUC) measures discrimination, which is the ability of the test to accurately classify eyes with and without disease. An area of 1.0 represents a perfect test, whereas an area of 0.5 represents a poor test. P-values less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Two-hundred and twenty eyes of 196 patients were included and separated into three groups; normal, SKC, and KC. Demographic characteristics for the respective groups are presented in Table 1. The normal group included 108 eyes of 108 subjects (60% males). The Mean age was 24.17 ± 5.58 years. Mean sphere was -1.33 ± 2.83 dioptres (D) and mean cylinder was -1.14 ± 0.95 D. The SKC group included 42 eyes of 42 patients (55% males). Mean patient age was 26.62 ± 6.2 years. Mean sphere was -1.04 ± 1.81 D and cylinder was -1.07 ± 0.71 D. The KC group included 70 eyes of 46 patients (23% males). Mean patient age was 24.87 ± 5.98 years. Mean sphere was -1.25 ± 2.02 D and mean cylinder was -2.67 ± 1.61 D.

Table 1. Demographic Characteristics of Each Group.

	Normal	SKC	KC
Patients (n)	108	34	46
Eyes (n)	108	42	70
Sex			
F	77	17	24
M	31	17	22
Age, (mean±SD)	24.17±5.58	26.62±6.2	24.87±5.98
Sphere (D), (mean±SD)	-1.33±2.83	-1.04±1.81	-1.25±2.02
Cylinder (D), (mean±SD)	-1.14±0.95	-1.07±0.71	-2.67±1.61

n: number; F: female; M male; SD: standard deviation; D: diopter.

3.2. Anterior and Posterior Corneal HOAs Data

The anterior corneal HOA values were statistically significant between the normal group and the SKC group, between the normal group and the KC group, and between the SKC group and the KC group (P < 0.0001, for all). The posterior corneal RMS HOA values were statistically different between the normal group and the SKC group, between the normal group and the KC group, and between the SKC group and the KC group for the total RMS HOAs, RMS trefoil and RMS coma (P < 0.0001, for all). However, the RMS spherical HOAs values were only statistically significant between the normal group and

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the SKC group (P < 0.0001). RMS mean values of the anterior and posterior corneal HOAs are shown in Table 2.

Table 2. Corneal Higher-Order Aberrations Parameters in Normal, Suspect Keratoconus and Normal Groups.

Indices	**Normal (n=108)**		**SKC (n=42)**		KC (n=70)		P value		
	Mean	**SD**	**Mean**	SD	Mean	SD	Normal vs. SKC	Normal vs. KC	SKC vs. KC
					Anterior HOAs				
Total HOAs	0.28	0.14	0.73	0.34	2.11	0.90	<0.0001	<0.0001	<0.0001
Trefoil Z(3,±3)	0.12	0.07	0.30	0.23	0.56	0.27	<0.0001	<0.0001	<0.0001
coma Z(3,±1)	0.15	0.13	0.55	0.29	1.90	0.88	<0.0001	<0.0001	<0.0001
Spherical Z(4,0)	0.02	0.15	-0.15	0.18	0.16	0.35	<0.0001	<0.0001	<0.0001
					Posterior HOAs				
Total HOAs	0.21	0.12	0.27	0.16	0.85	0.48	0.609	<0.0001	<0.0001
Trefoil Z(3,±3)	0.13	0.10	0.18	0.14	0.60	0.38	0.82	<0.0001	<0.0001
coma Z(3,±1)	0.08	0.09	0.11	0.08	0.38	0.26	0.883	<0.0001	<0.0001
Spherical Z(4,0)	0.04	0.06	-0.02	0.04	-0.08	0.11	<0.0001		

n: number; SKC= suspect keratoconus; KC= Keratoconus; HOAs= higher-order aberrations; Z= Zernike; statistically significant values (P < 0.05).

3.3. Discriminant Analysis and ROC Curves

Table 3 demonstrates the sensitivity, specificity and AUC values identified by cut-off points of different anterior corneal RMS HOA parameter sets, to differentiate pathological corneas with SKC and KC from normal corneas.

Table 3. Sensitivity, Specificity and Area Under the Curve Values identified by Cut-off Points of Different Anterior Corneal Parameters Sets to Differentiate Eyes with Suspect Keratoconus from Normal Corneas and Keratoconus from Normal ones.

Indices	**Cut-off value**		**ROC AUC**		Sensitivity (%)		Specificity (%)	
	Normal vs. SKC	**Normal vs. KC**	**Normal vs. SKC**	Normal vs. KC	Normal vs. SKC	Normal vs. KC	Normal vs. SKC	Normal vs. KC
Total HOAs	>0.4	>0.65	0.918	1	90.48	100	81.48	99.07
Trefoil Z(3,±3)	>0.2	>0.34	0.756	0.959	59.52	82.86	87.96	100
coma Z(3,±1)	>0.2	>0.57	0.922	1	95.24	100	75	100
Spherical Z(4,0)	≤-0.01	>0.16	0.767	0.594	83.33	40	73.15	90.74

ROC AUC= receiver operating characteristic area under the curve; vs= versus; SKC= suspect keratoconus;.

KC= Keratoconus; HOAs= higher-order aberrations; Z= Zernike .

In distinguishing between SKC and normal corneas, the sensitivity was 90.48%, 59.52%, 95.24% and 83.33% for RMS total HOAs, RMS trefoil, RMS coma and RMS spherical aberrations, respectively. The highest specificity was seen for RMS trefoil (87.96%). As indicated, AUC of RMS total HOAs and RMS coma were strong enough to identify SKC (AUC > 0.9) and the highest strength was seen for RMS coma (0.92).

To distinguish between keratoconus and normal corneas, the highest sensitivity (100%) was seen for RMS total HOAs and RMS coma. RMS trefoil and RMS coma demonstrated the highest specificity (100%). The parameters with the highest AUC (1.0) to identify keratoconus was seen for RMS total HOAs and RMS coma. Table 4 illustrates the sensitivity, specificity and AUC values identified by cut-off points of different posterior corneal RMS HOAs parameter sets to differentiate corneas with suspect KC and KC from normal corneas.

Table 4. Sensitivity, Specificity and Area Under the Curve Values identified by Cut-off Points of Different Posterior Corneal Parameters Sets to Differentiate Eyes with suspect Keratoconus from Normal Corneas and Keratoconus from Normal ones.

Indices	**Cut-off value**		**ROC AUC**		Sensitivity (%)		Specificity (%)	
	Normal vs. SKC	**Normal vs. KC**	**Normal vs. SKC**	Normal vs. KC	Normal vs. SKC	Normal vs. KC	Normal vs. SKC	Normal vs. KC
Total HOAs	>0.33	>0.37	0.629	0.963	33.33	91.43	89.81	93.52
Trefoil Z(3,±3)	>0.23	>0.25	0.588	0.93	30.95	84.29	88.89	91.67
coma Z(3,±1)	>0.03	>0.18	0.667	0.929	88.1	81.43	43.52	87.96
Spherical Z(4,0)	≤0.05	≤-0.03	0.753	0.846	100	67.14	36.11	94.44

ROC AUC= receiver operating characteristic area under the curve; vs= versus; SKC= suspect keratoconus; KC= Keratoconus; HOAs= higher-order aberrations; Z= Zernike.

To distinguish between suspect keratoconus and controls, the highest sensitivity was seen for RMS total HOAs (100%), with the highest specificity was seen for RMS total HOAs (89.81%). However, no parameters were strong enough to identify suspect keratoconus (AUC < 0.8, for all). In identifying keratoconus, the highest sensitivity was seen for RMS total HOAs (91.43%) with the highest specificity for RMS spherical aberrations (94.44%). All parameters were strong enough to identify keratoconus (AUC > 0.9) except for RMS spherical aberrations (AUC = 0.846).

Figures 1 and 2 show the ROC curves of the different anterior RMS HOAs parameters to differentiate suspect KC from normal eyes, and KC from normal eyes.

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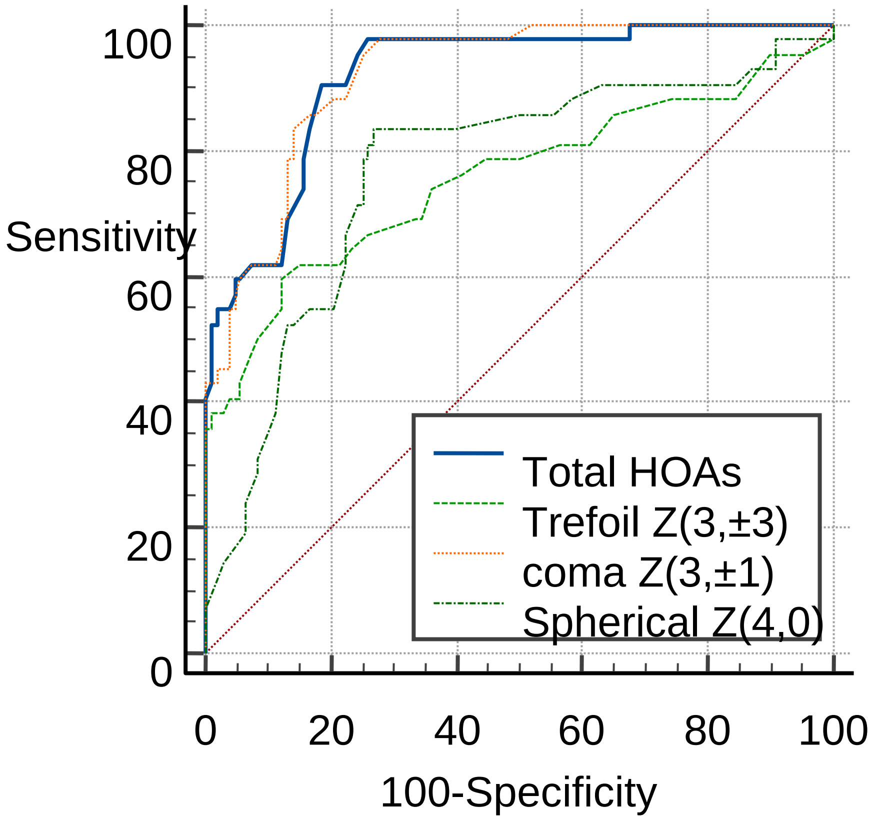

Variable	AUC	SE	95% CI
Coma Z(3, ±1)	0.922	0.0216	0.866 to 0.959
Total_HOAs	0.918	0.0236	0.862 to 0.957
Spherical Z(4,0)	0.767	0.046	0.691 to 0.832
Trefoil Z(3,±3)	0.756	0.0509	0.680 to 0.823

Figure 1. ROCs of the Different Anterior HOAs Parameters for Discrimination between Suspect Keratoconus and Normal Eyes. (ROC= receiver operating characteristic; HOAs= higher-order aberrations; AUC= area under the curve; Z= Zernike; SE= standard error; CI= confidence interval.)

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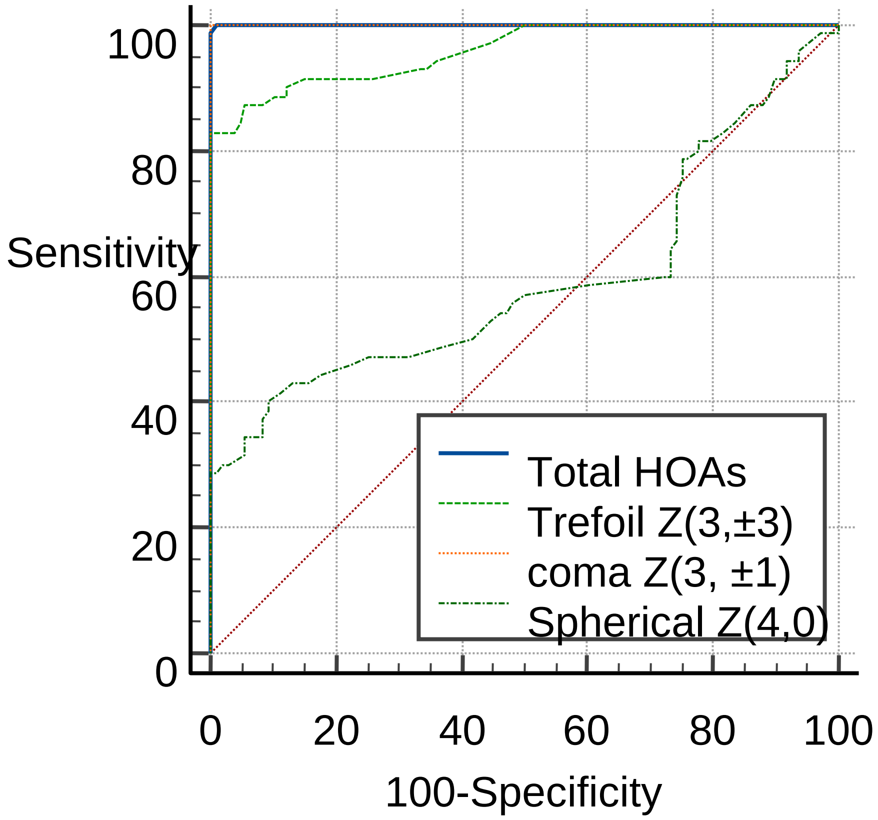

Variable	AUC	SE	95% CI
Coma Z(3, ±1)	1.000	0.000	0.979 to 1.000
Total_HOAs	1.000	0.000142	0.979 to 1.000
Trefoil Z(3,±3)	0.959	0.0146	0.918 to 0.983
Spherical Z(4,0)	0.594	0.0479	0.518 to 0.667

ROC= receiver operating characteristic; HOAs= higher-order aberrations; AUC= area under the curve; Z= Zernike; SE= standard error; CI= confidence interval.

Figure 2. ROCs of the Different Anterior HOAs Parameters for Discrimination between Keratoconus and Normal Eyes.

Figures 3 and 4 show the ROC curves of the different posterior RMS HOAs parameters to differentiate suspect KC from normal eyes and KC from normal eyes.

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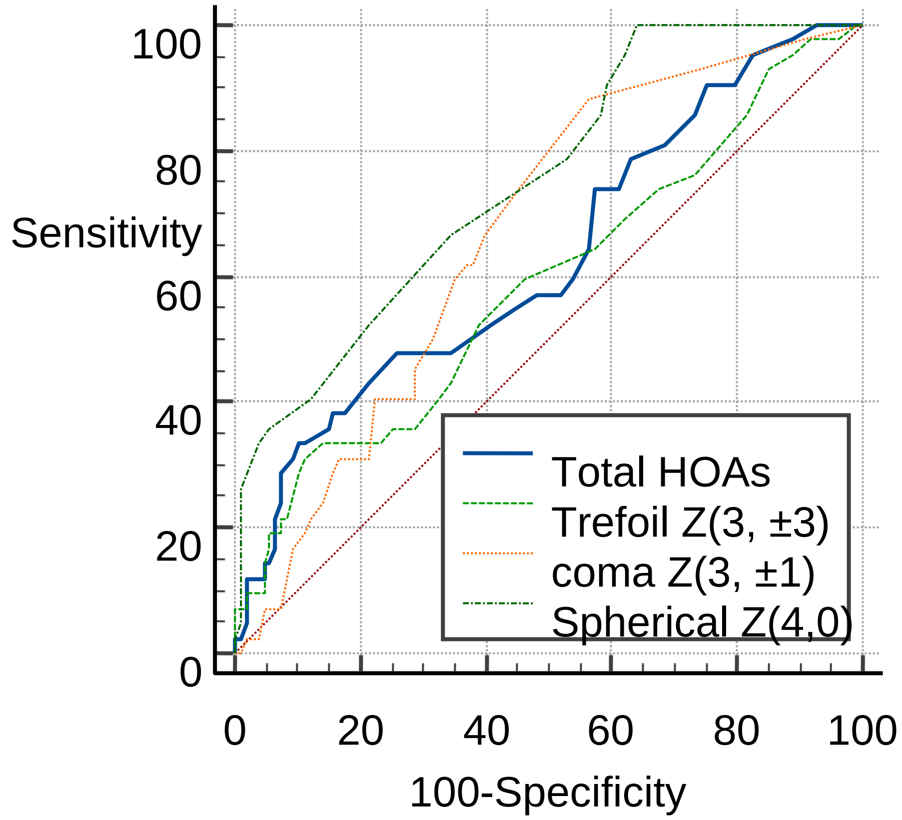
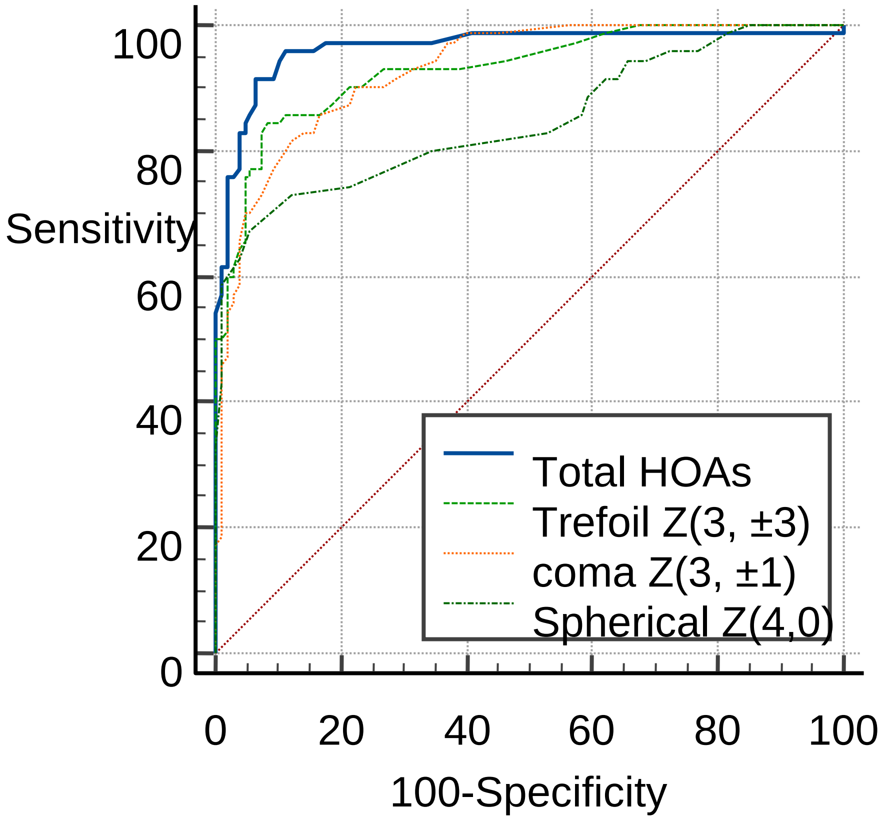


Variable	AUC	SE	95% CI
Spherical Z(4,0)	0.753	0.0424	0.676 to 0.820
Coma Z(3, ±1)	0.667	0.0461	0.585 to 0.742
Total_HOAs	0.629	0.0516	0.547 to 0.707
Trefoil Z(3,±3)	0.588	0.0537	0.505 to 0.668

ROC= receiver operating characteristic; HOAs= higher-order aberrations; AUC= area under the curve; Z= Zernike; SE= standard error; CI= confidence interval.

Figure 3. ROCs of the Different Posterior HOAs Parameters for Discrimination between Suspect Keratoconus and Normal Eyes.



Variable	AUC	SE	95% CI
Total_HOAs	0.963	0.0165	0.924 to 0.985
Trefoil Z(3,±3)	0.93	0.0197	0.882 to 0.963
Coma Z(3, ±1)	0.929	0.0183	0.880 to 0.962
Spherical Z(4,0)	0.846	0.0324	0.785 to 0.896

ROC= receiver operating characteristic; HOAs= higher-order aberrations; AUC= area under the curve; Z= Zernike; SE= standard error; CI= confidence interval.

Figure 4. ROCs of the Different Posterior HOAs Parameters for Discrimination between Keratoconus and Normal Eyes.

4. Discussion

Amongst different factors proposed to predict the risk of developing post-LASIK ectasia, early keratoconus was considered as the main risk factor. (14). Detecting corneas with suspect keratoconus is crucial in preventing post-LASIK ectasia. Initially, the term keratoconus suspect was introduced to describe eyes that had demonstrable evidence of subtle Placido-based videokeratography abnormalities without clinical evidence of disease (9).

While Placido-based topography analyzes the central anterior corneal surface, Scheimpflug-based imaging provides data from the anterior and posterior cornea and produces a full corneal thickness map. Several studies have shown that corneal HOAs are higher in keratoconus eyes in comparison to normal eyes. Therefore, the combination of wavefront analysis and videokeratography may help to define keratoconus and increase the sensitivity and specificity for early detection of suspect keratoconus (7, 15).

The aim of this study was to determine the diagnostic ability of anterior and posterior corneal HOAs measured by the Sirius Scheimpflug tomographer in differentiating suspect keratoconus, keratoconus and normal corneas. It also aimed to ascertain the parameters with the highest sensitivity and specificity.

We evaluated corneal HOAs that are most relevant to clinical practice such as coma, trefoil and spherical aberrations. Maeda et al. compared corneal aberrations in normal eyes and eyes with forme-fruste or mild keratoconus, and found that coma-like and spherical-like aberrations were significantly higher in the latter group (16). Our results showed a significant difference between the control and suspect keratoconus group, as well as between the control and keratoconus group for the anterior corneal RMS HOAs (total, trefoil, coma like and spherical HOAs). When comparing our results to the results of Alió and Shabayek who evaluated the anterior corneal RMS HOAs in normal and keratoconic eyes (17), the results confirmed significantly higher anterior corneal aberrations in keratoconic eyes compared to normal eyes. In our study, the mean anterior RMS HOAs values in the keratoconic group were lower (2.11 ± 0.9 µm) than those of Alió and Shabayek (3.14 ± 1.64 µm). This can be explained by the fact that the patients evaluated by Alió and Shabayek had more advanced keratoconus than those evaluated in our study.

The increase in coma-like aberrations in keratoconic eyes is related to the cone decentration resulting in decentration of the visual axis of the eye. Jafri et al. found that RMS coma was 0.229 µm for normal eyes, 0.639 µm for eyes with suspected keratoconus, and 2.034 µm for eyes with early keratoconus (7). Our findings are consistent with this study, despite different acquisition methods, namely Sirius topographer used in our group and the Alcon LADARWave used by Jafri et al.. Moreover, our results are in agreement with Alió and Shabayek, both confirming the increase in the total HOAs in the keratoconic group was primarily due to coma-like aberrations.

In their study, to develop a keratoconus detection scheme based on Zernike coefficients, Gobbe and Guillon found that the best anterior HOAs detector at differentiating between suspected keratoconus and normal corneas was vertical coma (C3, -1) with a specificity of 71.9% and sensitivity of 89.3% (18). Saad and Gatinel found that the best cut-off value for anterior corneal RMS coma to differentiate forme fruste keratoconus from normal corneas was 0.157 µm with a sensitivity of 71% and specificity of 78% (15). In contrast, our results showed that RMS coma with a cut-off value of > 0.2 µm was the parameter with the highest AUC (0.992) to distinguish between suspect keratoconus and normal eyes with a sensitivity of 95.24% and a specificity of 75%. The difference in the sensitivity of discrimination of corneal coma between the two studies is due to the fact that our study group objectively selected suspect keratoconus, while Saad and Gatenil selected forme fruste keratoconus eyes (normal fellow eyes of keratoconus patients). Forme fruste keratoconus is the earliest identifiable stage of keratoconus.

Our results showed that all anterior corneal HOAs indices except spherical aberrations had a good ability to detect keratoconus with AUC > 0.9. However, the greatest ability was seen for total HOAs and coma (AUC = 1 for both) with cut-off points of > 0.65 and > 0.57, respectively. Buhren et al. reported that corneal vertical coma (Z3, −1) can be used to distinguish keratoconus from normal eyes (AUC = 0.980; cut-off, - 2.00 µm) (5). However, the cut-off value of these aberrations was not similar to our study. The cut-off value depends on the stage of the disease and on the method of calculation of the aberrations. In the present study, we used the RMS value which represents the sum of horizontal and vertical coma aberrations, regardless of the orientation.

In agreement with the theoretical optical properties of the corneal surface, we found that the posterior corneal surface was less aberrated than the anterior corneal surface. The refractive indices between air (1.0) and the anterior corneal surface (1.376), and between the aqueous (1.336) and the posterior surface (1.376) are not similar. This converts to about 1/14 of refraction occurring posteriorly compared to anteriorly (19). Naderan et al. (20) and Xu et al. (21) indicated the importance of posterior corneal surface aberrations to differentiate normal from suspect keratoconus corneas. They found that the values for posterior coma of the normal group were 0.032 ± 0.363 and for the suspect keratoconus group were 0.193 ± 0.264 with statistically significant differences between groups. Bühren et al.

found that vertical coma (C3, -1) was the only posterior surface parameter with a significant difference between suspect keratoconus and normal eyes (5). However, they found no single posterior-surface coefficient nor RMS value that correctly classified ≥80% of the suspect keratoconus eyes and normal eyes. In the present study, we did not observe significant differences in the RMS of posterior total HOAs, trefoil and coma-like HOAs between the normal group and the suspect keratoconus group. However, spherical aberration was the only parameter with a significant difference between suspect keratoconus and normal eyes ($p < 0.0001$). In addition, these posterior-surface coefficients were not sufficiently able to differentiate between suspect keratoconus and normal eyes (AUC < 0.7 for all except RMS spherical aberrations, 0.75). These findings strongly suggest that posterior surface aberration data is not sufficient for the detection of suspect keratoconus eyes. However, this was not the case when these parameters were used to differentiate between keratoconus and normal eyes. The majority of these parameters were able to differentiate between keratoconus and normal eyes (AUC> 0.9 for all except RMS spherical aberrations, AUC = 0.846).

The present study has some limitations. The retrospective nature of the study is designed to analyse pre-existing data and subject to numerous biases. In addition, the lack of total ocular aberration data as a wavefront device was not used in this study. Future studies that combine total wavefront data, corneal higher order aberrations data and topography data may provide a better approach for the detection of corneas with the earliest stage of keratoconus and to predict corneas susceptible to ectasia.

In conclusion, although anterior and posterior corneal higher order aberrations data measured by the Sirius analyzer are very effective in distinguishing between keratoconus and normal eyes, only coma HOAs derived from the anterior corneal surface can be used to detect suspect keratoconus.

Declarations

Ethics approval and consent to participate: This study was approved by the research ethics committee of Tishreen University in accordance with tents of the Declaration of Helsinki. Informed consent, in Arabic language, to participate in this study was obtained from all participants.

Consent for publication: was obtained from all study subjects

Availability of data and materials: The datasets generated and analysed during the current study are available from the corresponding author (Abdelrahman Salman) on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Author's contributions: AS: Conceptualization: Methodology, Formal analysis, Writing – Original draft, review & editing, Project administration; OK Writing – Original draft, review & editing; JM**:** MG, AAB, TD, AB and HH reviewed the manuscript.

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