·Opinion·

A statistical approach to classification of keratoconus

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INTRODUCTION

The front portion of the eye consists of a transparent layer called the cornea. The cornea is an important optical component for vision and plays a role in the specific refraction of the eye. The cornea normally has convexity but the amount of protrusion progressively increases in patients with keratoconus. In other words, the cornea prolapses forward. Keratoconus is a bilateral, typically asymmetric and non-inflammatory degeneration of the cornea caused by corneal protrusion as a result of progressive thinning of the corneal stroma. Corneal thinning generally occurs in the inferior, inferotemporal or central regions of the cornea [1]. However, corneal thinning in the upper quadrants of the cornea can also occur [2]. Corneal thinning and the following splay can cause high astigmatism and myopia, leading to degradation in visual quality, ranging from mild to severe[3].

Classification of keratoconus is the first step in approaching the disease because the severity of the disease and the stage at which the patient is diagnosed and treated affect treatment results [4]. In the past, there were multiple attempts to reach a reasonable and easily applicable keratoconus staging system, mostly based on the pattern of corneal topography and the morphology of the cone. Most of these attempts shared a common methodological fallacy, taking certain parameters into consideration based on authors' judgement. This caused, the proposed methods for staging of keratoconus were lacking some essential parameters to be incorporated into their methods. Increase and decrease in values that determine the disease may not be associated with each other, and failing to understand and compensate for this may lead to less efficient tracking of the disease. Some researchers classified keratoconus into four groups by looking only at keratometry values or using data on eyesight only, whereas others classified the disease into two groups by looking only at data pertaining to the placido disk. In this study we aimed to define a new classification method for detecting keratoconus based on statistical analysis.

SUBJECTS AND METHODS

Subjects The data used in this study was obtained from Atatürk Education and Research Hospital, Department of Ophthalmology. A total of 301 eyes of 159 patients (85 males, 74 females) with a mean age of 26.19 ±7.90y were enrolled into the study. Keratoconus diagnosis was made with a combination of biomicroscopic findings (Vogt's stria, Fleischer ring, corneal thinning), keratometry readings of corneal topography, paracentral steepening of cornea, and AB/SRAX (Asymmetric Bow Tie/Skewed Radial Axes) pattern on corneal topography maps. Patients' cycloplegic refractive errors on the Snellen chart were recorded. Simulated keratometry 1 (Sim-K1), Simulated keratometry 2 (Sim-K2), average keratometry [(Sim-K1+Sim-K2)/2 (average K)], central keratometry (central K), the cone location and magnitude index (CLMI) magnitude on axial maps (aCLMI), and wavefront aberrations were obtained from corneal topography (Keratron Scout Corneal Topography, Optikon 2000, Germany). The aberrations were measured up to the sixth-order Zernike polynomial at 6.00 mm pupil diameter. Vertical coma (3, -1), horizontal coma (3, 1), coma and coma-like aberrations, spherical aberration (4, 0) and total high-order aberrations (total HOA) were studied. Thinnest corneal thicknesses (TCT) were measured with optical coherence tomography (Optovue, RTVvue, California, USA).

Statistical Analysis All of the statistics were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). A P value of less than 0.05 was considered to be statistically significant. Before beginning the analysis, 17 records containing null-values were deleted. Factor analysis was performed with 16 variables and 284 records. The basic components method was used as a factor differentiation model for factor analysis. To specify the number of factors, factors having eigenvalues greater than 1 were observed. After the factor analysis we used clustering analysis for classification of ungrouped data with unknown group number according to similarity. We used hierarchical methods such as single connection, full connection, average connection and Ward's method, and non-hierarchical methods such as K-average method, in clustering analysis. Squared euclidean distance was used as distance measure and 284 records were classified from 2 groups up to 10 groups.

Table 1 Classification of keratoconus according to the statistical analyses

Severity of keratoconus	Record No.	CLMI		Ho RMS		Central K		Flat SimK		Log BC		Coma	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
First level	150	4.317	2.722	1.339	0.641	46.973	4.373	44.809	2.160	0.150	0.180	1.074	0.600
Second level	65	12.071	5.945	3.267	0.653	49.893	4.406	45.250	2.144	0.327	0.248	2.954	0.618
Third level	55	11.693	3.998	4.018	1.074	59.947	2.822	50.725	2.432	0.665	0.510	3.435	1.096
Fourth level	5	16.762	10.367	7.396	2.121	70.526	7.083	62.658	5.762	3.000	0E-7	5.690	2.547
Fifth level	9	22.422	4.106	7.840	1.284	64.814	4.699	53.963	5.244	0.813	0.428	6.468	0.980

RESULTS

To determine whether the data set was appropriate for factor analysis, the Kaiser-Meyer-Olkin (KMO) and Bartlett tests were used and the result of KMO analysis (0.806) showed that the sample size of 301 entries was sufficient, and the result of Bartlett's test (P <0.01) showed that the distribution of data was normal. In this study, the number of factors to be derived was determined using the eigenvalue criteria. According to these criteria, the number of derived factors was four. According to the eigenvalue criteria, components having eigenvalues greater than 1 determine the total number of factors. In this study, there were four factors having eigenvalues greater than 1, and these four factors accounted for 72.908% of the total variance. According to the results, the variance attributed to the first factor was 44.320%. A variable is in close relationship with the factor under which this variable has higher absolute values. According to the results, steep SimK, coma, high order root mean square (Ho RMS), central K, flat SimK, Log BC and CLMI were the members of first factor.

Reliability analysis was performed using the values of the first factor. The reliability factor of α=0.884 indicates that the factor is reliable by 88.4%, which can be interpreted as quite reliable. To test whether there was a multiple linear connection issue between obtained variables, simple correlation factors had to be evaluated. If a simple correlation factor between two independent variables is moderately significant (r >75%), this situation can cause multiple linear connection problems, and here, simple correlation factors of steep SimK, flat SimK and central K were observed as moderately significant[5].

However, as significant correlations do not always cause multiple linear connection problems, variance inflation factor (VIF) and tolerance values were also used and according to the results, clustering analysis was performed by excluding steep SimK from the analysis, which had a high VIF and a low tolerance value. It was observed that the grouping performed by Ward's method was better, and finally, discriminant analysis was used to determine the results of the clustering analysis.

The number of clusters with the highest materiality was decided according to Wilks's lambda value, which was calculated by discriminant analysis performed according to the different numbers of clusters. As a result of discriminant analysis, the fifth discriminant function was found to be significant (α=0.087). It was observed that using four discriminant functions for grouping is enough, and it was decided to put these functions into five groups. So, 55 samples were included in the first group, 150 samples in the second, 65 samples in the third, 9 samples in the fourth and 5 samples were included in the fifth group out of 284 in the survey. The level of the disease was determined according to the statistics of groups. The group statistics and statistical classification of keratoconus was shown in Table 1.

DISCUSSION

Early topographic modification of keratoconus was first defined by Amsler in 1938. The introduction of computer-aided videokeratoscopy was a revolution in the diagnosis and follow-up of keratoconus in the early 1980s. Three major patterns specific to keratoconus were defined on corneal topography: a steep corneal region surrounded by concentric regions of decreasing steepness, power asymmetry between the superior and inferior cornea, and skewed steepest radial axes (SRAX) above and below the horizontal meridian of the cornea[6].

In a study performed by Li *et al* [7], it was reported that central K value was not a good predictor for classification of keratoconus. The diagnostic performance of keratoconus percentage index (KISA) was been found to be modest for suspected keratoconus. Some authors [8] have reported better results when relying on posterior corneal elevation measurements, with a sensitivity of 68% and specificity of 90.8% being achieved in the diagnosis of subclinical keratoconus.

In many studies, the researchers have observed that high order aberrations especially coma and coma-like aberrations in eyes with keratoconus were higher than in normal eyes[9]. Mahmoud *et al* [10] developed an index for keratoconus diagnosis that could be used for all corneal front face maps of many topography devices. The possibility of a keratoconus diagnosis is calculated using the CLMI size obtained from an axial map. Percent probability keratoconus (PPK) values below 20% were considered normal while PPK values between 20% and 45% were ranked as suspicious for keratoconus and PPK values above 45% were considered to be keratoconus in this study. Cagıl *et al* [11] compared corneal volume measurements in keratoconus and subclinical keratoconus. It was reported that CV measured with the

Pentacam rotating Scheimpflug camera is lower in eyes with keratoconus or subclinical keratoconus than in normal corneas, and that CV measurements at central 3 mm is useful for discriminating these two conditions.

Fam and Lim [12] showed that anterior corneal elevation parameters are clinically relevant measures for detecting keratoconus and suspected keratoconus eyes. Previous studies reported that anterior and posterior elevation were the most effective parameters for the diagnosis of keratoconus [13-14]. Ambrósio et al [15] compared 44 eyes with keratoconus and 113 normal patients and found that the pachymetric progression indices were better able to differentiate the 2 samples of patients. Uçakhan et al [16] analysed several Pentacam indices (based on both corneal surfaces, curvature elevation and corneal thickness) in normal eyes and patients with subclinical keratoconus and clinically evident keratoconus. Saad and Gatinel [17] performed a discriminant analysis on normal eyes, eyes with forme fruste keratoconus, and eyes affected by keratoconus. They reported that discriminant analysis using data obtained with combined corneal and ocular wavefront data enables the detection of early subclinical keratoconus that may not be detected by placido-based topography analysis (PBTA) with a sensitivity and a specificity of 91% and 94%, respectively. Arbelaez et al [18] analysed the examinations of 877 eyes with keratoconus, 426 eyes with subclinical keratoconus, 940 eyes with a history of corneal surgery and 1259 healthy control eyes. Their study showed that support vector machine (SVM) based algorithm can be successfully used to differentiate normal eyes from eyes with clinical and subclinical keratoconus.

Proposed classification methods and developed indices, summarised above, share a common peculiarity: acceptance of some parameters to be important and taken into the disease diagnosis and staging considerations, solely based on experience and/or subjective judgements. On the other hand, a robust statistical method can separate relevant and irrelevant parameters, when a staging proposal was simulated. For instance, why do we have to accept a four level of staging but not more or less? Our study, indeed, gave a clear answer. Staging keratoconus using a five level is more logical and free of subjective considerations. In addition, results of our study gave a clear answer to an important question: which parameters to choose for classification. These were flat SimK, central K, CLMI, Ho RMS, Log BC and coma.

In conclusion, we showed that looking at only one variable is not sufficient for the classification of the keratoconus and classification based on statistical analyses were used in this study to classify all of the measured values in order to follow up patient progress in a more precise and comprehensive manner. According to the results of our study, it is convenient to stage keratoconus cases in five levels. In future we intend to make a classification by including patients with refractive errors as a control group.

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