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Key words

Grading system, Cornea, Machine learning, Keratoconus, Refractive surgery, Progression, Severity.

Running title

Logistic Index for Keratoconus identification and severity scoring.

Declaration of interests

None

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Logistic index for keratoconus detection and severity scoring (Logik)

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Abstract

Purpose

To develop an objective severity scoring system for keratoconus for the use in clinical practice.

Methods

Corneal elevation and minimum thickness data of 812 subjects were retrospectively collected and divided into two groups: one control group with normal topography in both eyes (304 eyes), and one keratoconus group (508 eyes). Keratoconus cases ranged from suspect to moderate and had at least 1 examination in 1 of 2 recruiting centres. The elevation data were fitted to Zernike

polynomial functions up to 8th order. An adapted machine learning algorithm was then applied to derive a platform-independent severity scoring and identification system for keratoconus.

Results

The resulting logistic index for keratoconus (Logik) provided consistent and progressing scoring that reflected keratoconus severity. Moreover, the system provided an accurate classification of suspect keratoconus versus normal (sensitivity of 85.2%, specificity of 70.0%) when compared with Belin/Ambrosio Display Deviation (BAD_D) (sensitivity of 75.0%, specificity of 74.4%) and the Pentacam Topographical Keratoconus Classification (TKC) (sensitivity of 9.3%, specificity of 97.0%). Logik also showed better accuracy for grading keratoconus stages with an average accuracy of 99.9% versus (98.2%, 94.7%) with BAD_D and TKC respectively.

Conclusion

Logik is a reliable index to identify suspect keratoconus and to score the severity of the disease. It shows an agreement with existing approaches while achieving better performance.

Key words

Grading system, Cornea, Machine learning, Keratoconus, Refractive surgery, Progression, Severity.

1. Introduction

Keratoconus (KC) is a bilateral ectatic disease, characterized by a progressive thinning in the corneal stroma, resulting in an irregular astigmatism and a decrease of visual acuity [1]. The convex aspherical shape of healthy corneas is distorted in conditions such as keratoconus, causing the weaker stromal tissue to form a progressive protrusion at the anterior surface that looks like an inferior conical shape (Figure 1).

The reported prevalence of keratoconus in the general population is 1:2000 [2], though a recent study reported that it could be as high as 1:375 [3]. While methods of optical correction, such as specialty contact lenses, may improve vision, they do not halt keratoconus progression. The only treatment known to stabilize the disease clinically is corneal collagen crosslinking (CXL) which was introduced in the early 2000s. In corneal refractive surgery, early diagnosis of keratoconus is of great importance to identify, and thereby avoid postoperative corneal ectasia [4]. There is no consensus among clinicians, however, on what constitutes progression, nor is there consensus on a valid detection and grading system [1]. This indicates a need for sensitive early diagnostic and scoring tools.

Many studies have suggested efficient techniques for early identification [5–7], yet none have been universally accepted. In addition, various diagnostic scores and indices have been suggested, both to detect as well as to assess keratoconus progression [7–15]. Unfortunately, most did not correlate continuously with the disease severity [15–20], which reduced their usefulness in clinical practice. A more reliable and consistent system is needed if it is to be

utilised in the clinic. Topographical Keratoconus Classification (TKC) [12] and Belin-Ambrosio Deviation [21–25] (BAD_D) are considered high sensitive systems for keratoconus detection, therefore, a comparation with the implemented system is suggested.

Recently, several mathematical and computational techniques were used to develop computer aided keratoconus diagnosis systems, from which machine learning (ML) algorithms have shown high performance [26,27]. ML consists of artificial intelligence algorithms capable of learning and extracting meaningful knowledge from data and has been used in the development of most keratoconus grading systems mentioned above. The ML outputs are often assigned as categorical variables associated with each KC group, which impairs its ability to score the severity of the condition continuously. However, an enhanced data design strategy to regulate the machine learning's output, followed by a feedforward neural network could enable to continuous scoring the disease severity and provide a reliable identification system.

This study therefore introduces a novel score-based machine learning system, named Logistic Index for Keratoconus (Logik), capable to (1) correctly classify keratoconus according to its severity, (2) to objectively discriminate suspect keratoconus from healthy eyes, and (3) to provide a consistent, time-continuous scoring system for keratoconus progression.

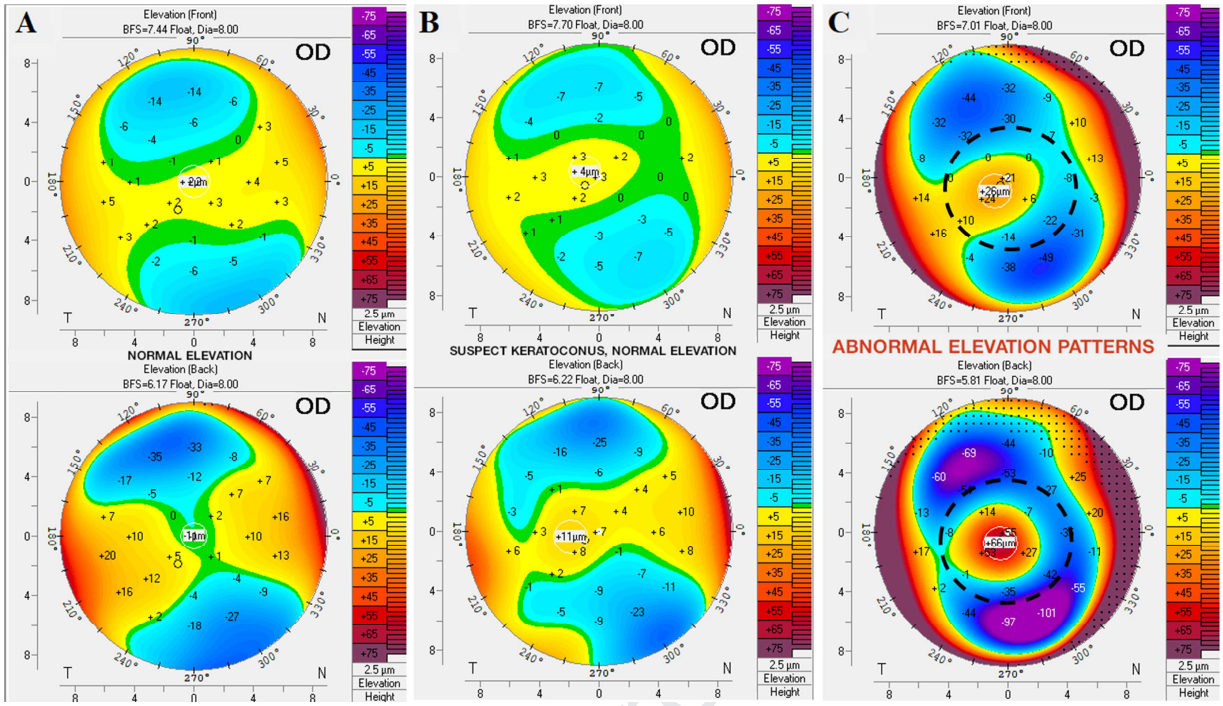

Figure 1: Example of the right (OD) corneal elevation maps (anterior surface (upper), posterior surface (lower)) of a healthy cornea (A), suspect KC (B), and moderate KC (C). The inferior distortion is visible in moderate KC (black circle).

2. Subjects and Methods

2.1 Patient data

Schiempflug tomographic measurements obtained using the Pentacam HR (Oculus GmbH, Wetzlar, Germany) of 812 subjects (aged 33.9 ± 9.5 years) were used to create the Logik index. These Scheimpflug measurements were retrospectively collected from two centres, Antwerp University Hospital (UZA; Edegem, Belgium) and Ghent University Hospital (UZG, Ghent, Belgium). The UZA data consisted of 304 healthy control cases and 449 keratoconus cases and

the UZG data consisted of 59 keratoconus subjects. All keratoconus subjects had at least one measurement, with possible follow-up examinations spaced 6 months apart. Subjects with a self-reported history of ocular surgery, relevant systemic or ocular diseases were excluded.

The study was approved by the UZA and UZG Ethical Committees and adhered to the tenets of Declaration of Helsinki. The keratoconus subjects from UZG provided written informed consent before inclusion, while the UZA ethical committee deemed informed consent unnecessary for retrospective analysis, in accordance with prevalent Belgian law. The Scheimpflug measurements were screened by an experienced ophthalmologist and an optometrist for quality and validity.

In this study five groups were considered: normal, suspect keratoconus, early, mild, and moderate to advanced keratoconus [6,28], defined as follows:

- **Normal** *(n=304):* eyes without slit-lamp findings suggestive of corneal ectasia and normal tomography.
- **Suspect keratoconus (forme fruste keratoconus)** *(n=117):* the contralateral, asymptomatic eye of a subject with clinical keratoconus in one eye, showing no clinical signs of ectasia or tomographic changes.
- **Early keratoconus** *(n=34):* eyes with a subtle sign of keratoconus, such as localized steeping in anterior or posterior surface, without significant changes of the cornea in the slit lamp.
- **Mild keratoconus** *(n=158):* eyes with tomographic changes consistent with keratoconus (anterior and/or posterior corneal steepening, corneal thinning, stromal thinning),

Fleischer rings at the cone base, partial or circular Fleisher rings, but no visible Vogt's striate.

- **Moderate to advanced keratoconus** *(n=199)* Clear cornea, corneal thinning at the apex, visible Vogt striae, clearly visible circular Fleischer ring) and corneal tomography findings compatible with keratoconus.

Anterior and posterior corneal elevation data were exported as Pentacam CSV files, and imported into MATLAB (MathWorks, USA, version R2017a) as 141×141 matrices, corresponding with an area of 8 *mm*. Moreover, the minimum pachymetry value was extracted from the pachymetry map and imported into MATLAB as a scalar value.

2.2 Methods

2.2.1 Data pre-processing

The Pentacam anterior and posterior elevation maps were fit to an 8^{th} order Zernike polynomial expansion (equivalent to 45 coefficients) for each subject. These polynomials are orthonormal functions and widely used to represent optical abnormalities [29]. For both the anterior and posterior elevation maps, 45 Zernike polynomial coefficients were used without additional measures. Apart from these Zernike polynomial-derived features, the minimum corneal thickness was the only non-elevation-based value added to both the anterior and to the posterior polynomial fit. Therefore, each of the anterior and posterior elevation maps were structured into 2 vectors of 46 anterior (*anterior predictors*) and 46 posterior (*posterior predictors*) parameters

(Figure 2). Finally, all features were normalized using Euclidian normalization procedure to optimize the computational cost later on.

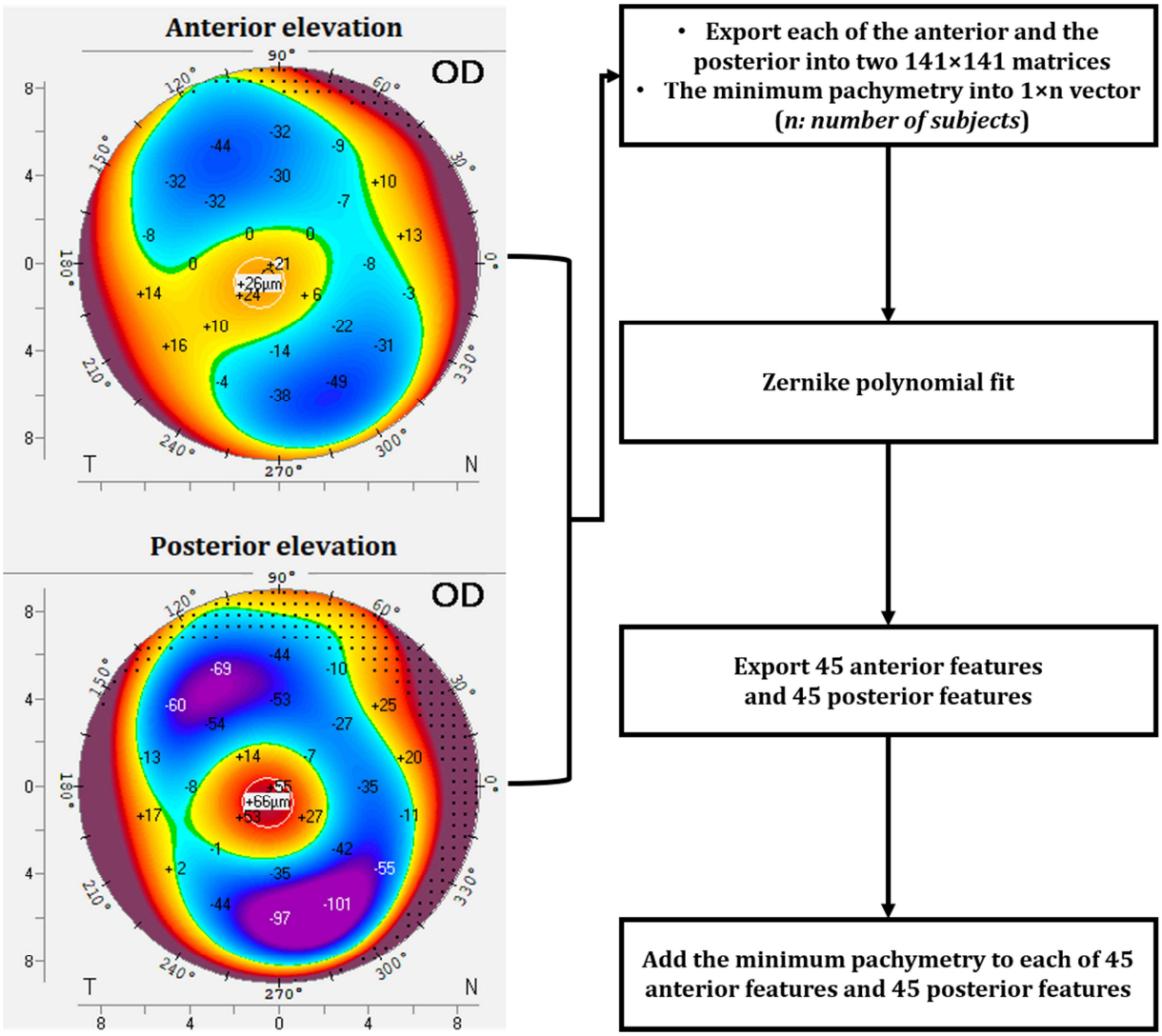

Figure 2: Representative example of feature extraction from anterior (upper) and posterior KC elevation maps (lower).

2.2.2 Feedforward neural network algorithm

Feedforward Neural Network (FNN) is a supervised machine learning (ML) algorithm characterized by the capabilities of intelligent systems. Due to its ability to learn from data, as well as adapting to data and generalizing from new results, FNN is able to detect patterns within large amounts of data, map complex input/output relationships and is often used for classification and prediction problems. One major advantage of this algorithm is its ability to classify in continuous ranges, making it a good candidate for scoring keratoconus progression. In this work FNN was configured in MATLAB with one hidden layer (60 neurons), logistic activation function, learning rate of *0.001* and Levenberg-Marquardt training algorithm for the training.

2.2.3 Training & validation sets

A common standard for the training and the validation of a machine learning model consists of dividing data into 70% training and into 30% validation. Therefore, 70% of each of the control (212/304) and keratoconus (314/449) subjects from UZA were used to train the ML model. Meanwhile, a validation set was used based on 30% of data from UZA. The validation was based on 10 repetitive holdouts. Each time, the training and the validation sets were randomly selected to ensure the model reproducibility. The results were presented in term of averages of accuracies. The data collected from UZG (n =59) were never included in the training of the model, instead used to perform an additional, external validation using data collected at an external center under slightly different clinical protocols (Figure 3). The output of the machine learning system was set

as -1 to normal, 0 to suspect keratoconus, 1 to early, 2 to mild, and 3 to moderate-advanced keratoconus.

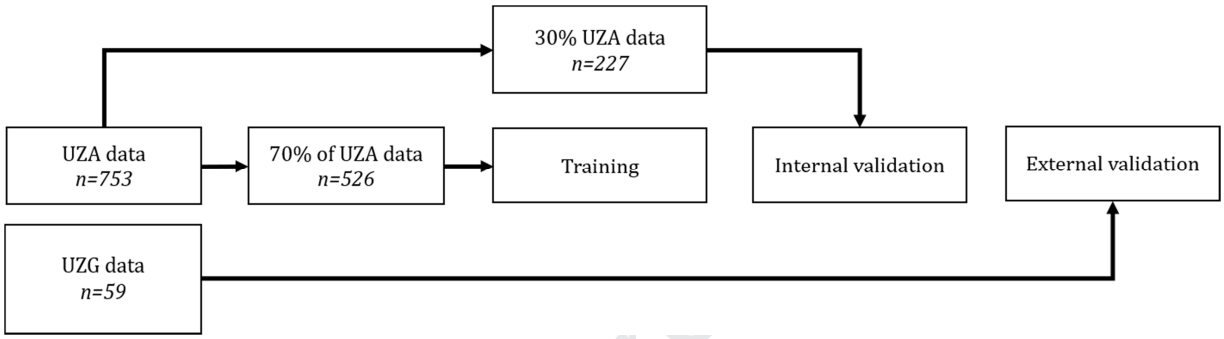

Figure 3: Diagram of the training and the validations process based on UZA d UZG data.

2.2.4 Implementation

The implementation of the keratoconus grading and detection system was based on a combination of a FNN and a Moving Average Filter (MAF) algorithm [30]. MAF is an engineering technique for data regulation that adjusts data by creating a series of averages of subsets of the full data set. The implementation of the system is based on two steps, combine a hybrid FNN with MAF to design a new *desired output*, and a second step consists of retraining the hybrid FNN for KC scoring and detection. First, two FNNs were trained separately, one using the anterior predictors and the other using the posterior predictors. Next, the estimated anterior and posterior FNNs outputs were used as an input to train a third FNN and estimate a

combined final score. This score vector of the examinations of each keratoconus subject is regulated using MAF. The adjusted scores of each KC were used as a new desired output for the ML model, rather than the categorical outputs previously mentioned. The output regulation step was done one time, and no validation data were included. Finally, the FNNs were retrained for a second time to compute both the new anterior and the posterior score values, and subsequently the combined overall score. Training the ML model with the corrected desired outputs and a sigmoid logistic activation function resulted in the **Log**istic **I**ndex for **K**eratoconus (**Logik**). An implementation diagram is provided in Figure 4.

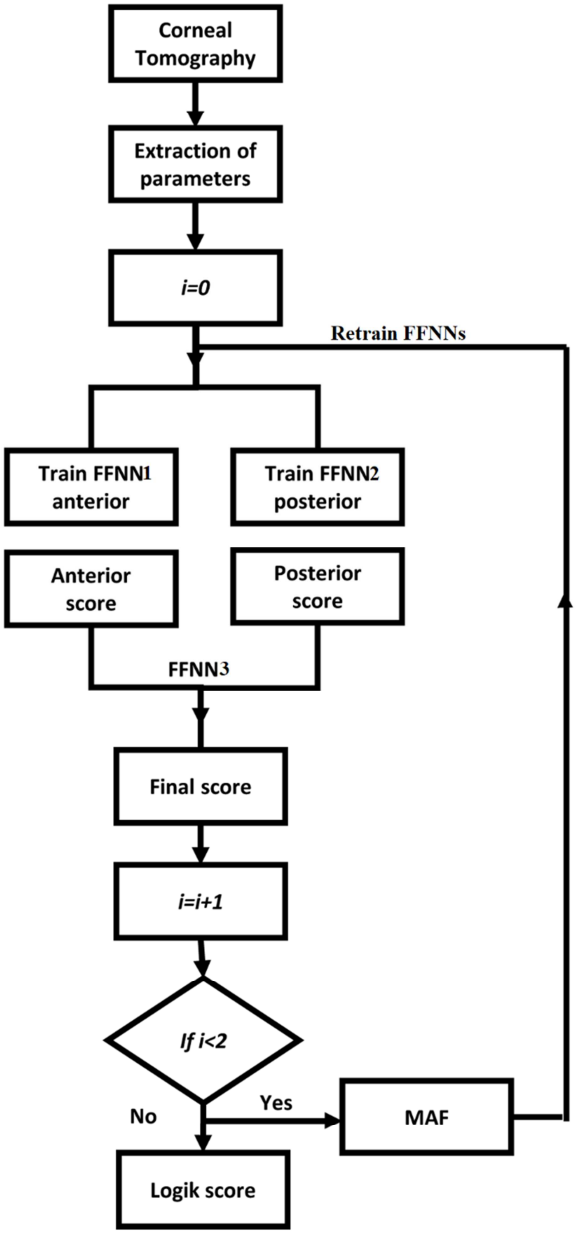

Figure 4: Diagram of Logik implementation algorithm. For each subject the process of training the network is repeated twice before obtaining the corresponding final Logik score. The number of iterations is represented by 'i' in the diagram.

2.2.5 Validation criteria

Receiver Operating Characteristic (ROC) curves in terms of the Area Under the Curve (AUC) were used to determine the discriminative ability of the system for normal (*negative class:-1*) versus suspect keratoconus (*positive class:0*), and for normal versus early-advanced KC (*positive class:1*). The hold out validation technique was used to validate independently each time, and the average accuracies were computed in terms of sensitivity, specificity and validation standards as defined in Table 1.

Table 1: Validation standards

Hold out validation		
True positive	*TP*	*Rate of keratoconus correctly identified*
True negative	*TN*	*Rate of healthy correctly identified*
False positive	*FP*	*Rate of keratoconus detected as healthy*
False negative	*FN*	*Rate of normal detected as keratoconus*
Accuracy	*(TP+TN) / (TP + FP + FN + TN)*	*Percentage of individuals correctly classified in the data set.*
Sensitivity	*TP / (TP + FN)*	*Percentage of keratoconus cases correctly classified.*
Specificity	*TN / (TN + FP)*	*Percentage of normal cases correctly classified*
Receiver operating characteristic (ROC) curve		
AUC	*The performance of the machine learning to apply a binary classification between healthy and keratoconus*	

Cut-off *Thresholds between the negative and the positive group.*

3. Results

Logik index was evaluated for its ability to detect suspect keratoconus, its reproducibility, and its consistency. Moreover, the performance of the system was compared to existing approaches, such as BAD_D and TKC.

3.1 Baseline Data description

The results of ocular biometry of different study groups (normal, suspect KC, early KC, mild KC, and moderate to advanced KC) provided in Table 2 are in agreement with previous clinical studies for subgroup classification [7,31].

Table 2: Description of the Study Groups; Normal and Keratoconus at baseline (mean±Standard deviation (range))

	K_{max} (D)	K_{mean} (D)	$Pachy_{min}$ (µm)	Astig (D)	I-S value (D)
UZA data (Center 1)					
Normal (n=304)	*44.31±1.38 (40.65-47.91)*	*43.28±1.29 (39.3-46.6)*	*544.72±31.79 (465-628)*	*0.79±0.48 (0.0-3.4)*	*0.60±0.43 (0,2-78)*
Suspect KC (n=108)	*45.07±1.88 (41.23-50.16)*	*43.47±1.56 (39.6-47.0)*	*519.36±34.57 (448-591)*	*0.98±0.70 (0-4.5)*	*0.97±0.70 (0.06-3.62)*
Early KC	*47.24±1.64*	*43.78±1.53*	*500.38±34.33*	*1.812±0.88*	*2.51±0.74*

(n=34)	*(44.33-53.32)*	*(40.6-49.4)*	*(434-569)*	*(0.5-3.6)*	*(0.52-3.79)*
Mild KC	*51.46±3.44*	*45.18±2.83*	*478.45±38.83*	*2.92±1.53*	*2.92±1.53*
(n=133)	*(43.42-67.88)*	*(39.10-60.8)*	*(278-565)*	*(0.10-7.9)*	*(3.95-8.30)*
Moderate to Advanced	*60.20±5.81*	*49.29±4.34*	*446.11±41.73*	*4.13±2.25*	*10.21±2.88*
KC (n=174)	*(50.72-81.44)*	*(40.1-63.6)*	*(306-535)*	*(0.0-12.6)*	*(2.63-19.52)*
		UZG data (Center 2)			
Suspect KC (n=9)	*46.16±1.16*	*44.26±1.57*	*517.60±45.25*	*1.10±0.36*	*1.49±0.61*
	(45.04-47.45)	*(42.4-45.9)*	*(461-583)*	*(0.5-1.4)*	*(0.83-2.39)*
Early KC (n=0)	-	-	-	-	-
Mild KC	*50.88±2.84*	*45.52±2.25*	*476.16±23.17*	*2.88±1.36*	*4.89±1.76*
(n=25)	*(45.16-56.92)*	*(40.70-50.8)*	*(433-528)*	*(0.5-5)*	*(0.48-7.13)*
Moderate to Advanced	*60.48±7.52*	*51.69±6.81*	*429.00±67.06*	*4.31±2.87*	*9.21±2.88*
KC (n=25)	*(54.30-80.97)*	*(44.70-69.30)*	*(230-505)*	*(0.2-10.9)*	*(4.18-14.14)*

Mean ± SD (range); I-S, inferior-superior value; KC, keratoconus; K_{max}, maximum keratometry; $Pachy_{min}$, minimum pachymetry; Astig, anterior corneal astigmatism.

3.2 Keratoconus detection

Using UZA data, Logik detected suspect keratoconus with an accuracy of 74.0% (AUC = 0.87, sensitivity = 85.2%, specificity = 70.0%). This compared to the 74.8% accuracy of BAD_D (AUC = 0.82, sensitivity = 75.0%, specificity = 74.4%) and the 73.9% accuracy of TKC (AUC = 0.53, sensitivity = 9.3%, specificity = 97.0%) (Table 3-4 and Figure 5a). Moreover, Logik, BAD_D, and TKC were nearly comparable in the identification of other stages of keratoconus, resulting in accuracies of (99.9%, 98.2%, 94.8%) with Logik, BAD_D, and TKC respectively. While Logik and BAD_D performed similarly in detecting early to advanced keratoconus, Logik performed better when identifying suspect keratoconus.

Based on the external validation from UZG data, Logik and BAD_D showed results consistent with the UZA dataset for both suspect KC and other stages of the condition, while TKC demonstrated low accuracies for suspect KC (Table 3-4, Figure 5b). However, the UZG group is not representative and it includes only 9 suspect KC subjects. While this group of data is not descriptive, the detection results were reported but not used to evaluate performances of the three systems. However, the external validation can be considered as a proof of concept of Logik generalizability and repeatability since it includes data collected from a different center.

TKC also performed poorly for classifying suspect keratoconus using UZA data, nonetheless it was better for more advanced stages of the condition (Table 4). This is likely due to the strict definition of our suspect KC group which hampers the identification of the condition according to TKC grading criteria [12].

Table 3: Holdout validation of Logik

		UZG data (Center 2)		**UZA data (Center 1)**	
		Suspect KC vs Normal	**KC vs Normal**	**Suspect KC vs Normal**	**KC vs Normal**
Logik	**Accuracy**	*73.3%*	*99.1%*	*74.0%*	*99.9%*
	Sensitivity	*99.9%*	*94.0%*	*85.2%*	*99.1%*
	Specificity	*75.5%*	*99.9%*	*70.0%*	*99.9%*
	Cut-off	*-0.9810*	*0.5*	*-0.9839*	*0.5*
BAD_D	**Accuracy**	*63.0%*	*57.0%*	*74.6%*	*98.2%*
	Sensitivity	*88.9%*	*99.9%*	*75.00%*	*97.0%*
	Specificity	*62.9%*	*50.0%*	*74.4%*	*99.7%*

	Cut-off	*0.8150*	*2.11*	*0.824*	*2.95*
TKC	**Accuracy**	*93.7%*	*99.9%*	*73.9%*	*94.8%*
	Sensitivity	*0.0%*	*99.9%*	*9.3%*	*90.0%*
	Specificity	*96.3%*	*99.9%*	*97.0%*	*99.9%*
	Cut-off	*0.25*	*1.25*	*0.25*	*1.25*

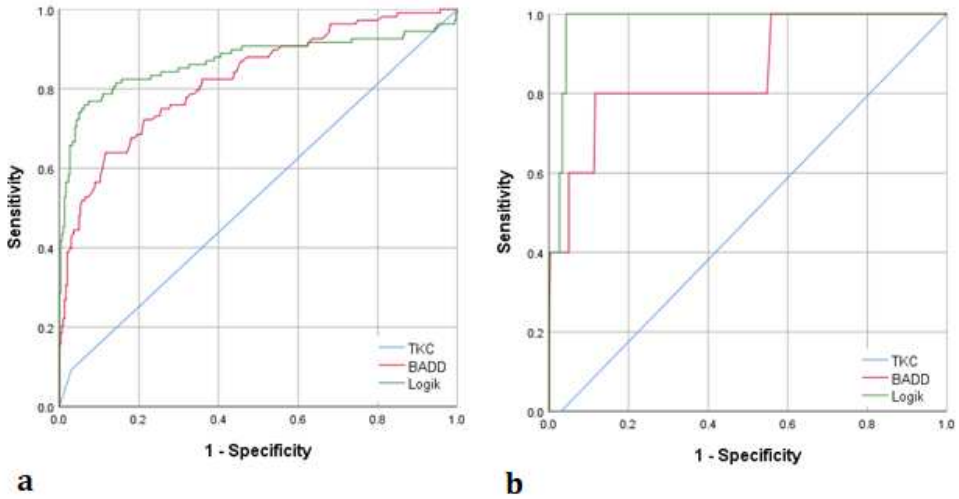

Figure 5: ROC curves for suspect KC detection based on UZA (a) and UZG (b) data.

Table 4: Area under Curves of TKC, BAD_D, Logik for suspect KC versus Normal

	Suspect KC versus Normal		***KC versus Normal***	
	AUC (UZA)	***AUC (UZG)***	***AUC (UZA)***	***AUC (UZG)***
Logik	*0.87*	*0.97*	*0.99*	*0.99*
BAD_D	*0.82*	*0.85*	*0.99*	*0.98*
TKC	*0.53*	*0.48*	*0.99*	*0.97*

3.3 Consistency of Logik for Keratoconus Progression

A consistent quantitative system for keratoconus progression remains lacking. As BAD_D is a performant system for suspect keratoconus detection, and it correlates with the most widely used markers of progression such as minimum pachymetry, [21] maximum anterior sagittal curvature, and mean keratometry, posterior ectasia, it can be used as an index for keratoconus staging. Therefore, BAD_D was considered as a reference system and it was compared with Logik for keratoconus severity grading. Since based on our data TKC was less reliable for the detection of suspect keratoconus and it provides categorical rather than continuous scoring, this was not assessed.

In addition to the accurate classification of normal versus keratoconus at different stages, Logik was found to be a consistent scaling system (Figure 6). The index is following a nearly constant horizontal curve $y = -1$ for controls, whilst it tends to follow a continuous and logistic progressive trend for keratoconus subjects. Figure 6 displays a discrete cut-off of keratoconus severity such that, Logik $\leq$ -0.8 corresponds to a normal eye, >-0.8 and $\leq$ 0.5 corresponds to suspect KC, >0.5 and $\leq$1.5 is early KC, >1.5 and $\leq$2.5 is mild KC, >2.5 and $\leq$3.5 is moderate KC and Logik >3.5 represents advanced keratoconus. Logik therefore showed good agreement for the staging of early, mild, moderate and advanced keratoconus of the original data classification, and most keratoconus subjects ranging, from suspect to moderate, were classified correctly according to severity.

The BAD_D cut-offs values proposed in the literature [23], (i.e., BAD_D < 1.65 corresponds to normal , 1.65 ≤ BAD_D ≤ 3.5 to suspect keratoconus and BAD_D >3.5 to abnormal) lead to a lower sensitivity and specificity. Therefore, other optimum cut-offs were suggested in this paper based on the statistical analysis results (Table 3-4) and ROC curves (Figure 5), by maximizing the sensitivities and specificities and keeping a balance superior of 50% for all BAD_D, TKC and Logik. Consequently, the discrete cut-offs of BAD_D were set such that BAD_D ≤ *0.8* was normal, >0.8 and <2.95 was suspect keratoconus, and BAD_D ≥ 2.95 was abnormal.

Even though BAD_D demonstrated nearly similar results to Logik index for early to advanced keratoconus detection, it was found that BAD_D was less consistent in describing keratoconus severity, because it showed larger overlaps between early stage and more advanced stages (Black boxes in Figure 6). Even though both systems showed some degree of overlap between suspect keratoconus and normal, (circles on Figure 6), this was less in the case of Logik than for BAD_D. The number of misclassifications for suspect keratoconus (Table 3) was 14.8% for Logik (blue circle in Figure 6) and 25% for BAD_D (red circle in Figure 6). The misclassifications area included the overall examinations of KC follow ups, while the misclassification percentages in Tables 3-4 are associated with undetected subjects at the baseline. These misclassifications can result from the limited data sets for suspect keratoconus (*n=108*) versus (*n=304*) for early-advanced keratoconus. The big similarities between normal and suspect keratoconus, require a larger data set which could reduce the number of misclassifications. Moreover, 35% of UZA suspect keratoconus data (*n=38*) with more than 4 measurements were detected normal with both Logik and BAD_D and remained stable for 2 years as apparently suspect KC.

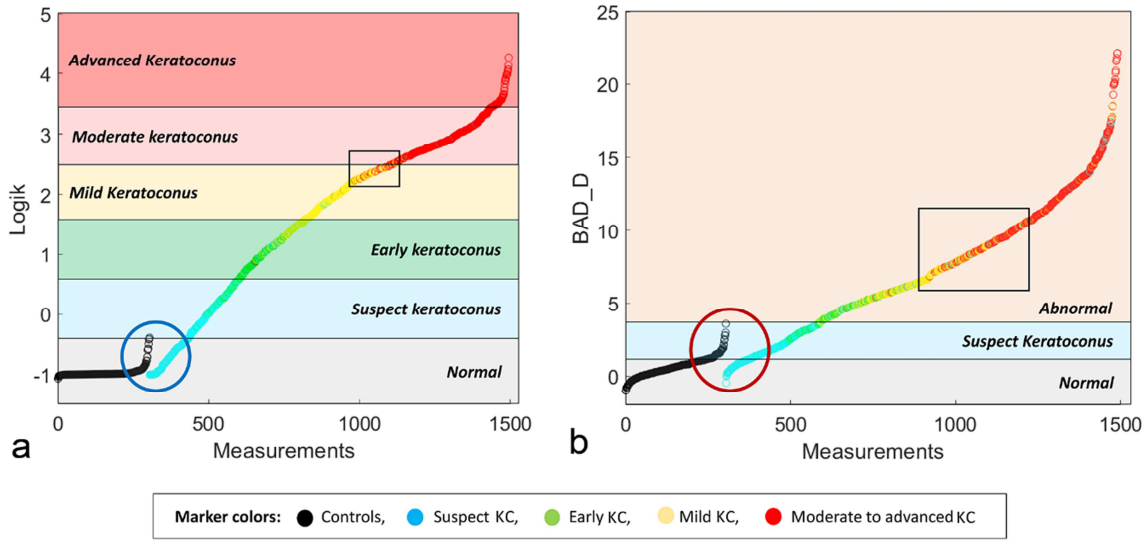

Figure 6: Distribution of data samples of normal and baseline KC according to the detected severity (UZA datasets). Blue and red circles indicate the area of overlap between healthy and suspect keratoconus eyes, the larger the circle, the larger the number of misclassified suspect cases. Black boxes indicate the overlap between early and more advanced KC cases, the larger the area the more misclassifications

3.4 Longitudinal follow-up

For the longitudinal assessment, 308 keratoconus patients with at least 4 measurements were assessed, each spaced 6 months apart. Here, an index (Logik or BAD_D) was considered to increase if the last visit showed a higher score than the first visit and was considered to decrease otherwise. A reliable keratoconus follow-up system, in absence of treatment, would not show a decrease over time. The Logik increased over time for 220 subjects and decreased for 88 subjects, compared to 93 decreasing with BAD_D (Table 5). Logik showed a progressively

increasing trend over time, with mostly positive and steeper slopes than BAD_D between sequential values (Figure 7). Consequently, Logik was more discriminative over time. The confusion matrix (Table 5) demonstrated that generally both systems agree, if the slow (nearly constant) trend of BAD_D is considered progression.

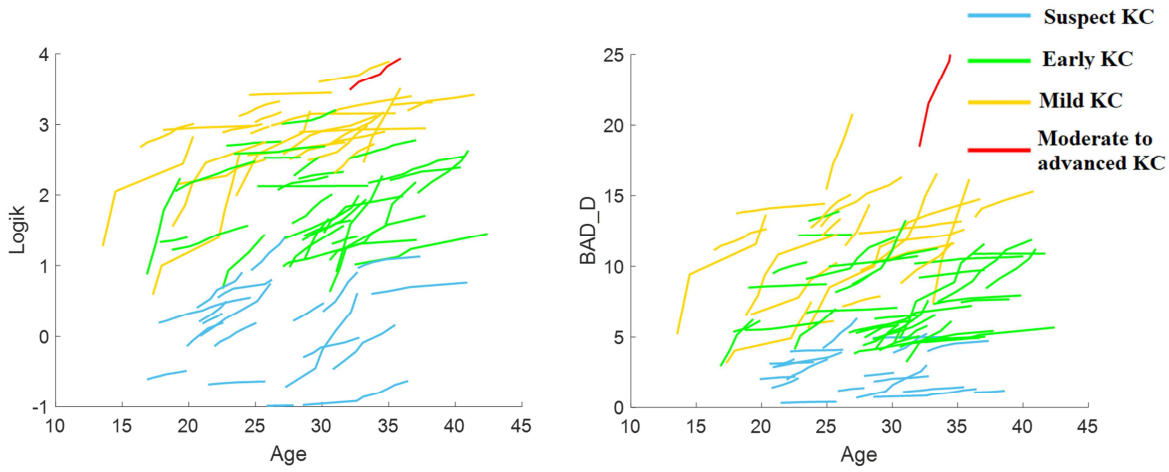

Figure 7: Longitudinal evolution of Logik (left) and BAD_D (right) for the common increasing 100 KC subjects with at least 4 measurements. The graphs of Logik and BAD_D are adjusted according to MAF.

Table 5: Confusion matrix of the agreement level of Logik and BAD_D (n=308)

		BAD_D		
		Increase	*Decrease*	*Total*
Logik	***Increase***	*177*	*43*	*220*
	Decrease	*38*	*50*	*88*

Total	*215*	*93*

4. Discussion

Reliable identification and severity scoring system of keratoconus is of great importance in ophthalmology, since it allows adequate diagnosis and assessment of disease progression. For this purpose, we developed an objective, consistent, time-continuous system for keratoconus identification and severity scoring, named Logistic Index for Keratoconus (Logik). Currently, there is no consistent or clear definition of progression [1] and many researchers assessed the longitudinal variations of quantitative parameters for this purpose [15–20]. Mostly, these parameters have been acknowledged as unreliable and poorly associated with disease severity [18]. Logik is an automated time continuous system for severity scoring, as well as for the detection of suspect keratoconus.

Even though Amsler-Krumeich [32] is the most widely used classification system for keratoconus, many researchers and clinicians consider it insufficient or even outdated [1]. Longitudinal observations such as corneal thinning and corneal steepening as sign of progression as well as a decline in visual acuity are traditionally considered [33]. These indications, however, are subjective and rely on longitudinal observation of corneal changes, which requires time to assess whether a given patient would progress or not. Later studies have suggested computer assisted diagnostic scores for disease staging [10,11,15,34,35], these systems, however, were based on an old screening method (videokeratoscopy), and provide discrete time scoring values,

with no progress between dissimilar cases within the same stage. Recent systems have demonstrated the same inconsistency limitations for scoring the disease continuously [36–40]. Moreover, the longitudinal follow-up of keratoconus patients, often show inherent variabilities. Therefore, Logik overcomes the previous limitations by providing an objective, consistent time continuous severity scoring system for keratoconus. Logik classifies keratoconus severity into five main stages (suspect, early, mild, moderate, advanced) in addition to the normal healthy stage. The system showed a continuous logistic trend with the disease severity (Figure 6) and was consistent with the previously defined keratoconus stages (Table 2). As BAD_D is also considered as an accurate parameter for keratoconus, it was used here as a reference to assess the consistency of Logik for measuring the severity, even though it was not originally intended for this purpose. The comparison demonstrated that Logik was able to score the disease impact and showed an increase even within the same category. In following up KCs patients (Figure 7), Logik showed less variability than BAD_D (Table 5). A comparation of Logik or BAD_D with the keratoconus ABCD grading system [8] was not possible as ABCD relies on four metrics where each consider a different aspect of keratoconus progression.

Compared to BAD_D and TKC, Logik proved to be an accurate identification system for suspect keratoconus and achieved an accuracy of 74.0% (AUC = 0.87, sensitivity = 85.2%, specificity = 70.0%) versus BAD_D 74.6% (AUC = 0.82, sensitivity = 75.0%, specificity = 74.4%) and TKC 73.9% (AUC = 0.53, sensitivity = 9.3%, specificity = 97.0%). The low sensitivity of TKC could be due to the strictness of our KC group definition. A study [41] that followed the same definition demonstrated that TKC shows no significant difference between healthy cornea and suspect KC. Similarly, the three systems achieved comparable results for other corneas with

varying keratoconus severity with accuracies of 99.9%, 98.2%, 94.8% for Logik, BAD_D, and TKC respectively (Tables 3-4, Figure 5). An external validation of the systems also confirmed the efficiency and the repeatability of Logik (Tables 3-4).

Earlier computer-aided diagnosis systems were based on *videokeratoscopy and topography* profiles. However, subsequent studies based on pachymetry indices and tomography were much better at differentiating healthy from keratoconus eyes [10,22,36]. Of note is the work by Arbelaez et al. [42], who applied support vector machine (SVM) to corneal tomography and allowed detecting subclinical keratoconus with an accuracy of 97.7% (sensitivity = 92.0%, specificity = 97.7%) and clinical keratoconus with an accuracy of 98.2% (sensitivity = 95.0%, specificity = 99.3%). The subclinical keratoconus group of Arbelaez's study included patients with topographical signs of ectasia, this does not match our definition of suspect keratoconus, however, higher sensitivity (99.9%) and specificity (99.9%) were achieved with Logik for clinical keratoconus (Table 2). Due to the lack of a universal definition of 'suspect' and 'early' keratoconus, a direct comparison of accuracies is difficult to establish. One study that adopted similar definition as this paper was by Smadja and associates [6], applying decision trees to tomographic data and resulted in sensitivity (93.6%) and specificity (97.2%) for early keratoconus detection. However, the generalizability performance of this study needed further independent validation using unseen data, which was cited as one of study's limitations. In this work, the accuracies were computed with independent data, both from internal and external centers. Independent validation data tends to reduce the sensitivity and specificity to more reliable and realistic values, which may explain the difference between the respective findings.

Saad and Gatinel [37] described a linear discriminant based model using another corneal Tomographer (Orbscan II; Technolas, Munich, Germany) and founded higher sensitivity (93.0%) and specificity (92.0%) for suspect keratoconus, which was further validated based on independent data [37]. Gatinel's study used predictors that are device-dependent, which has a great potential to enhance the accuracies, but making it difficult to directly compare their results to the current analysis. A previous study by our team [7], however, used Pentacam HR device dependent metrics analysed by a SVM, leading to an accuracy of 93.0% (sensitivity = 79.1%, specificity = 97.9%) for detecting suspect keratoconus. In our opinion, including platform dependent parameters increases the result accuracies. Logik was based only on anterior and posterior corneal surfaces and the value of minimum pachymetry, which we think is one of its major strengths, since it enhances the chance of the platform independency and the reproducibility. Yet this requires a further validation. The restriction manifested in using only elevation data and minimum pachymetry, while implementing Logik causes a decrease of the sensitivity and the specificity. Our group also developed a novel hybrid computer aided diagnosis system (CAD) [31] based on tomographic profile and a hybrid machine learning algorithm achieved higher sensitivity (97.8%) and specificity (99.6%) for suspect keratoconus detection. Although, CAD showed an important and competitive detection ability for suspect keratoconus compared with the last AI/automated systems for KC detection, it was not adequate for disease severity scoring, and incorporate hybrid complex ML. Whereas, Logik is based on a simple algorithm with greater potential for clinical implementation. Since Logik is mainly developed to provide a severity scoring system, a further extension to combine a simplified CAD and Logik will be considered. Other advantages of Logik are its time continuity and the combining of abilities to detect suspect keratoconus and to score the disease to varying levels of

severity. Kovács et al, [43] reached a best accuracy in terms of AUC of 0.88 and AUC of 0.96 for discriminating healthy corneas from suspect keratoconus, defined as the "normal" fellow cornea of an eye diagnosed as KC, and healthy corneas from keratoconus. Logik obtained a similar result for suspect keratoconus detection (AUC = 0.87), and an AUC of 1 for clinical keratoconus detection.

The Pentacam Random Forest Index (PRFI), developed by Lopez et al.[38], is an enhanced tomographic index for detecting corneal ectasia, with a reported comparable sensitivity of 85.2% to Logik but higher specificity of 96.6% versus 70.9%. The PRFI, however, was trained based on a much larger group of controls ($n = 2980$) versus ($n = 304$) in our study, which justifies the lower specificity. When PRFI was compared with BAD_D, the latter showed nearly similar results to PRFI in term of specificity (95.5%), while in, the current study, BAD_D gave a specificity of (74.4%), nearly similar to that of Logik, suggesting that increasing the data of the control group would likely lead to comparable specificity values for Logik and PRFI. Increasing the sample of controls might also lead to an improved accuracy. Since the current implementation of PRFI in the Pentacam software requires both a Corvis and a Pentacam measurement, even though PRFI does not use any biomechanical data, no direct comparison with PRFI could be made as no Corvis data was available for the patients included in this work.

In a recent platform-independent study by Castro-Luna et al.[44] the detection of KC was assessed based on Placido disk indices using a Bayesian network classifier, achieving a sensitivity and specificity of 100% for the classification of early to moderate KC. The data samples were small (control=30, KC=30), and their keratoconus group included cases with subclinical signs of the disease. Similarly, another platform independent study [45] reported

100% sensitivity and specificity from analysing anterior wave front aberrations derived from Placido disk tomography based on the same inclusion criteria of KC. In the current study, Logik demonstrated a sensitivity of 99.1% and specificity of 99.9% for the groups that include subclinical signs of KC. While it is a challenge to obtain high accuracies from platform independent data, the sensitivity and the specificity in our study were similar to the reported results. Finally, there is one more KC grading system proposed based on anterior corneal elevation [46]. This system was not considered in the analysis, however, because it does not include the contributions of the posterior surface, and its discrete steps do not correlate continuously with the disease's severity, thus hampering its ability to accurately track progression. Moreover, their study group was based on a small sample (40 normal eyes and 40 KC eyes), the KC eyes had at least 1 clinical sign (KISA% index≥100) confirmed by the videokeratoscopy. Logik achieved 99% accuracy for the same category.

There are some limitations to this study that need to be acknowledged, most notably the modest overlap between the healthy cases and suspect keratoconus. This may be caused by the larger tomographic similarities between both groups, and the limited sample size of the suspect keratoconus group compared to the normal group. Moreover, the unclear definition of suspect keratoconus, which is still not well established in the literature, makes it difficult to make a direct comparison with previous publications. This study considered suspect keratoconus as the symptomatic fellow eye of a keratoconus cornea, as previously proposed [36], the strictest possible definition. However, a recent study [47] suggests the possibility to develop a promising staging system based on biomechanical data combined with tomographic data, which can be considered as a perspective to improve the current study. Finally, although Logik is a system that

allows keratoconus identification and severity scoring continually tracks progression, it is still unable to predict future progression.

In conclusion, Logik presents two major improvements in comparison with the existing systems for keratoconus detection and classification: it identifies suspect keratoconus with a higher performance than the existing alternatives, and it provides an objective, consistent severity scoring system. The proposed framework can be used to assist ophthalmologists in the process of decision-making alongside other diagnostic criteria. The principles of the followed strategy can also be used to improve other scaling systems previously suggested in the literature.

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Highlights

- A logistic index for keratoconus identification and severity scoring is presented.
- The system is based on a new data design strategy.
- The data design strategy improves the performance of a feedforward neural network to score keratoconus severity.
- The developed approach is platform independent and reproducible.

Conflict of Interest Statement

Manuscript title: Logistic index for keratoconus identification and severity scoring.

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