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MINI REVIEW

Corneal biomechanics in early diagnosis of keratoconus using artificial intelligence

Yan Huo[1] · Xuan Chen[1] · Gauhar Ali Khan[2] · Yan Wang[1,2,3,4]

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Abstract
Keratoconus is a blinding eye disease that affects activities of daily living; therefore, early diagnosis is crucial. Great efforts have been made toward an early diagnosis of keratoconus. Recent studies have shown that corneal biomechanics is associated with the occurrence and progression of keratoconus. Hence, detecting changes in corneal biomechanics may provide a novel strategy for early diagnosis. However, an early keratoconus diagnosis remains challenging due to the subtle and localized nature of its lesions. Artificial intelligence has been used to help address this problem. Herein, we reviewed the literature regarding three aspects of keratoconus (keratoconus, early keratoconus, and keratoconus grading) based on corneal biomechanical properties using artificial intelligence. Furthermore, we summarized the current research progress, limitations, and possible prospects.

Keywords Corneal biomechanics · Artificial intelligence · Machine learning · Keratoconus · Early keratoconus

Abbreviations

AI	Artificial intelligence
AUROC	The area under the receiver-operating characteristic curve
CART	Classification and regression tree
CH	Corneal hysteresis
CRF	Corneal resistance factor
FFKC	Forme fruste keratoconus
ML	Machine learning
RF	Random forest
SKC	Subclinical keratoconus
SVM	Support vector machine
TBI	Tomographic and Biomechanical Index
TKC	Topographical keratoconus classification system

Yan Huo and Xuan Chen contributed equally to this work.

Extended author information available on the last page of the article

Key messages

What was known before:

- Keratoconus is a progressive blinding eye disease that affects activities of daily living; therefore, early diagnosis is crucial. Early keratoconus diagnosis remains challenging due to the subtle and localized nature of its lesions.
- The biomechanical properties of early keratoconus are weaker than those of normal corneas, and artificial intelligence has been used to distinguish early keratoconus from the perspective of biomechanics.

What this review adds:

- This review includes 19 articles regarding three aspects of keratoconus (keratoconus diagnosis, early keratoconus diagnosis, and keratoconus grading) based on corneal biomechanical properties using artificial intelligence.
- This review summarized the current research progress and limitations; prospected the possible future in early keratoconus diagnosis and grading from the perspective of corneal biomechanics.
- The recent advances in AI-based diagnosis, early detection, and grading of keratoconus are significant from the perspective of corneal biomechanics.

Introduction

Corneal biomechanical properties participate in the maintenance of corneal morphology and are closely related to the occurrence and progression of keratoconus [1–3]. Keratoconus is an irreversible ectatic eye disease that predominantly occurs in adolescents and influences their quality of life [4]. The biomechanical properties of keratoconus are weaker than those of normal eyes [5, 6]. An increase in proteolytic enzyme levels and proteolytic enzyme activity enhancement lead to a loss of keratocytes, dissolution of collagen fibrils, and disruption of the orthogonal arrangement of collagen fibrils, which explain the pathological weakening of the biomechanical properties of keratoconus [7–9]. Typical keratoconus demonstrates Munson's sign, Vogt's striae, Fleischer's ring, and other clinical signs, and their morphologies change considerably; therefore, keratoconus could accurately be diagnosed via slit lamp examination of clinical manifestations and corneal topographical findings [10].

However, early keratoconus diagnosis is challenging due to the subtle and localized nature of the lesions, and thus early keratoconus is difficult to detect based only on corneal imaging [11–14]. Recent studies have shown that proteoglycans denaturation around collagen fibrils in keratoconus leads to fragmentation and degeneration of collagen fibrils, which attenuate local corneal biomechanics, thereby leading to morphological changes such as corneal stroma thinning and increased keratometry [15–19]. Therefore, the detection of changes in corneal biomechanical properties will likely solve the challenge of early diagnosis [20], although this has not been clinically confirmed [21, 22].

Artificial intelligence (AI) has been recently applied to solve the problem of early keratoconus diagnosis since an in-depth analysis of several relevant parameters can be achieved with known links when the logical associations between influencing factors and outcomes are unknown or complex. The application of machine learning (ML), a subfield of AI, in keratoconus management has recently become widespread [23–25]. ML can be divided into supervised and unsupervised learning. Supervised learning uses labeled data to train the model to predict the output results of unlabeled data. Unsupervised learning can solve problems in pattern recognition and discover previously unknown disease features or subtypes without using labeled data for training. Presently, the common ML methods used in studies include random forest (RF), neural networks, logistic regression, support vector machine (SVM), and discriminant analysis [26]. Combining corneal biomechanical properties with ML is expected to improve the accuracy of early keratoconus diagnosis. Therefore, we review the progress of keratoconus diagnosis and research based on corneal biomechanical properties using AI.

Materials and methods

We searched PubMed, Embase, and Web of Science databases. The search keywords used included "machine learning," "deep learning," "artificial intelligence," "corneal biomechanics," "corneal biomechanical," "corneal mechanical," "corneal ectasia," "keratoconus," "early keratoconus," "subclinical keratoconus," "forme fruste

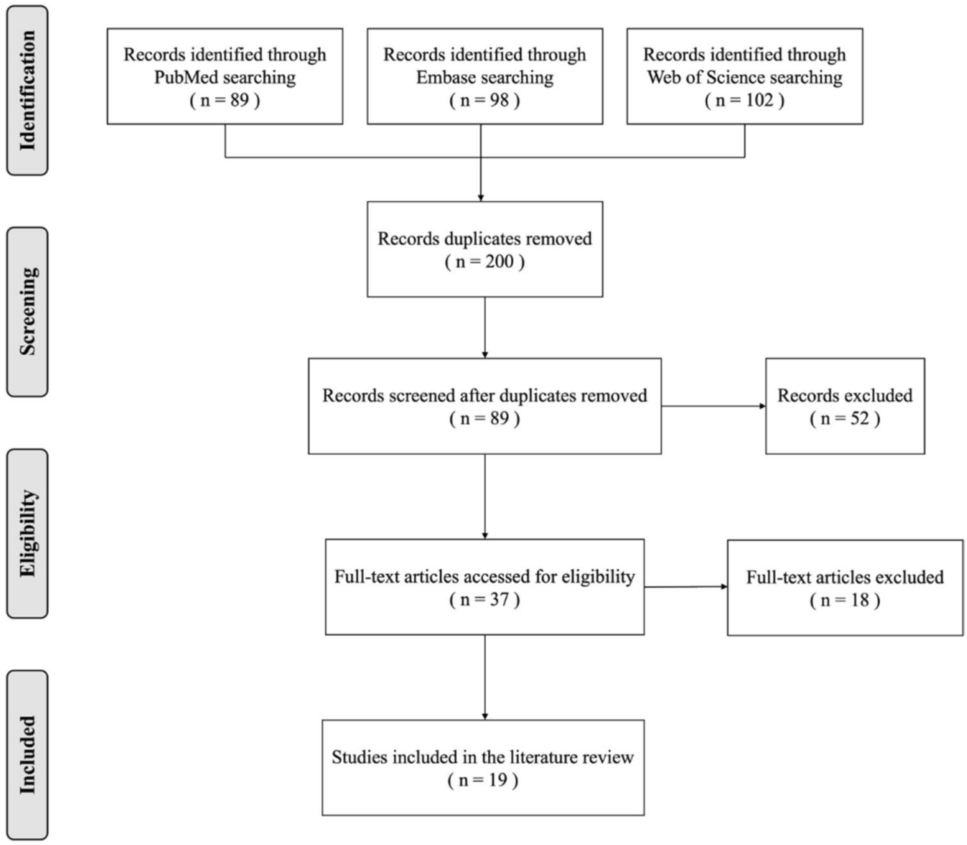

Fig. 1 Filtering steps for study inclusion in this review

keratoconus," "keratoconus suspect," "keratectasia," and "asymmetric ectasia." Before citation, articles were screened for relevance and significance (Fig. 1). A total of 19 articles published from June 2013 to September 2022 were included in this review. Finally, the current application of AI in the field of keratoconus from the perspective of corneal biomechanics was summarized and reviewed from three aspects: diagnosis of keratoconus, diagnostic attempts for early keratoconus, and grading keratoconus; the details regarding each related study are presented in Table 1.

Results

Keratoconus diagnosis with ML

The ocular response analyzer (ORA; Reichert Ophthalmic Instruments Inc. Buffalo, NY, USA) and the corneal visualization Scheimpflug technology (Corvis ST; Oculus, Wetzlar, Germany) are currently used to measure the clinical in vivo corneal biomechanical properties. The application of the ORA and Corvis ST has promoted the current understanding of in vivo corneal biomechanics [27].

Keratoconus diagnosis with ML using ORA

The ORA uses symmetrically reduced airflow to compress the corneal center region by 3–6 mm. When the first applanation is achieved during the corneal applanation process, the air pump of the air pulse closes, and the pressure applied to the cornea decreases inversely and symmetrically. As the pressure reduces, the cornea undergoes the highest depression, and the second applanation returns the cornea to its natural state. The corneal hysteresis (CH), corneal resistance factor (CRF), and 41 waveform parameters are obtained to characterize corneal biomechanics [28, 29].

The CH and CRF are two widely used clinical parameters. The CH indicates the pressure difference between the two corneal applanation processes; it represents the cornea's viscoelastic properties and the corneal tissue's ability to absorb and consume energy. The CRF is calculated using the ORA software and describes the corneal resistance to external forces. The CH and CRF of keratoconus are lower than those of normal eyes [30], but the distribution of CH and CRF values in keratoconus and normal eyes overlap; therefore, the accuracy of a single parameter in diagnosing keratoconus is unsatisfactory [31, 32]. Labiris et al. [33] found that the keratoconus match index calculated using

Table 1 Machine learning in KC diagnosis based on corneal biomechanical properties

Study objectives	First author	Year	Groups	Method	Sample size (eyes)		Corneal biomechanical modality	Result (%)		
					training set	Validation set		Accuracy	Sensitivity	Specificity
Detect KC eyes from controls	Labiris et al. [33]	2013	KC, NL	ANN	223	-	ORA	97.7%	91.18%	94.34%
	Vinciguerra et al. [21]	2016	KC, NL	LoR	329	329	Corvis ST	98.8%	100%	98.4%
	Ambrósio et al. [36]	2017	KC, VAE, NL	RF	850	-	Corvis ST	97.5%	96.2%	98.8%
	Tan et al. [37]	2022	KC, NL	ANN	276	78	Corvis ST	98.7%	97.4%	100%
Detect EKC eyes from controls	Ventura et al. [42]	2013	MKC (AK grade 1), NL	ANN	204	-	ORA	AUROC=0.964		
	Luz et al. [44]	2016	FFKC, NL	LoR	97	-	ORA	-	85.71%	98.68%
	Pena–Garcia et al. [47]	2016	SKC, NL	DA	212	-	Corvis ST	-	85.7%	82.07%
	Francis et al. [48, 49]	2017	KC, FFKC, NL	LoR	458	264	Corvis ST	99.6%	99.5%	100%
	Karimi et al. [56]	2018	KC, KCS, NL	ANN	80	155	Corvis ST	83.33%	-	-
	Atalay et al. [46]	2020	SKC, NL	DA	248	-	ORA	-	87.1%	91.4%
	Shiga et al. 54]	2021	FFKC, NL	LoR	75	-	Corvis ST	-	91.3%	90.38%
	Zhang et al. [45]	2021	KC, FFKC, NL	LoR	110	-	ORA, Corvis ST	-	100%	84%
	Perez–Rueda et al. [53]	2021	SKC, NL	LoR	81	-	Corvis ST	94.9%	89.5%	96.7%
	Tian et al. [50]	2021	FFKC, MKC (TKC 1,1-2,2), TNC	ANN	153	-	Corvis ST	91%	-	-
	Song et al. [52]	2022	SKC, NL	DT	194	66	Corvis ST	92.4%	90.3%	94.3%
	Lu et al. [55]	2022	KC, FFKC, MKC (AK grade 1)	RF	622	-	Corvis ST	88.89%	75%	94.74%
KC grading	Herber et al. [58]	2021	KC (TKC), NL	RF	434	-	Corvis ST	78%	-	-
	Langenbucher et al. [59]	2021	KC (TKC), NL	SVM	439	-	Corvis ST	65.1%	-	-
	Flockerzi et al. [60, 61]	2022	KC (Belin's ABCD classification), NL	LoR	560	-	Corvis ST	-	-	-

KC, keratoconus; *EKC*, early keratoconus; *NL*, normal eyes; *MKC*, mild keratoconus; *FFKC*, forme fruste keratoconus; *SKC*, subclinical keratoconus; *KCS*, keratoconus suspect; *AK*, Amsler–Krumeich; *TKC*, topographical keratoconus classification system; *AUROC*, area under the receiver-operating characteristic curve; *TNC*, thin normal cornea; *RF*, random forest; *ANN*, artificial neural network; *LoR*, logistic regression; *SVM*, support vector machine; *DT*, decision tree; *DA*, discriminant analysis; *Corvis ST*, Corneal Visualization Scheimpflug Technology; *ORA*, Ocular Response Analyzer

KC grading accuracy is the overall accuracy

Method list optimal model data

-, unspecified

seven ORA waveform parameters via the neural network had a high keratoconus diagnostic accuracy in 223 eyes (accuracy = 97.7%, sensitivity = 91.18%, and specificity = 94.34%), indicating that ML can effectively improve the detection of keratoconus.

Keratoconus diagnosis with ML using Corvis ST

Corvis ST utilizes an ultra-high-speed Scheimpflug camera to record corneal deformation along the horizontal meridian at 8 mm. After the air-puff, the camera device automatically identifies the corneal deformation and captures 140 images within 31 ms [34]. The cornea undergoes three states (first applanation, highest concavity, and second applanation) during deformation to produce a corneal waveform, a dynamic deformation video, and dynamic response parameters to characterize corneal biomechanics [35].

Vinciguerra et al. [21] used stepwise logistic regression to combine dynamic response parameters with Ambrósio Relational Thickness to the horizontal profile of 329 eyes to introduce the Corvis Biomechanical Index, which accurately distinguished between normal eyes and keratoconus in the external validation set (329 eyes); the accuracy, sensitivity, and specificity were 98.8%, 100%, and 98.4%, respectively. Stepwise logistic regression is suitable in cases with many independent variables that do not greatly affect the dependent variable and in interactions between the independent variables. In the regression process, independent variables are screened, and a multiple regression model with a better prediction effect is established.

Ambrósio et al. [36] analyzed corneal morphological parameters from Pentacam (Oculus, Wetzlar, Germany) and biomechanical parameters from Corvis ST in 850 eyes using three ML methods, including logistic regression, RF, and SVM. Moreover, they combined the Corvis Biomechanical Index with the Belin/Ambrósio Deviation Index. They used the RF method to train the model, which discriminated keratoconus from normal eyes with the highest accuracy. Validation was performed using the leave-one-out cross-validation method, and the Tomographic and Biomechanical Index (TBI) was subsequently obtained. When the TBI cut-off value was 0.45, the area under the receiver-operating characteristic curve (AUROC) reached 0.996, resulting in an excellent diagnostic accuracy for keratoconus (accuracy = 97.5%, sensitivity = 96.2%, and specificity = 98.8%).

Tan et al. [37] segmented 276 corneal dynamic deformation videos and calculated four new biomechanical parameters, namely the time of the first applanation, deformation amplitude at the highest concavity, central corneal thickness, and radius at the highest concavity. Further, they used a neural network to train the model, which achieved an accuracy, sensitivity, and specificity of 98.7%, 97.4%, and 100%, respectively, in discriminating keratoconus from normal eyes in the external validation set (78 eyes).

These studies showed significant outcomes regarding the application of ML incorporated with corneal biomechanics to improve the accuracy of keratoconus diagnosis.

Early keratoconus diagnosis with ML

Keratoconus diagnosis is clinically feasible, and the development of corneal tomography and topography has improved the screening ability for keratoconus [38]. However, keratoconus is a progressive disease. Most cases are clinically diagnosed at moderate or advanced stages, leading to irreversible vision loss; therefore, it is crucial to diagnose keratoconus as early as possible to allow for early intervention and enhance patient quality of life.

There are no uniform criteria for the definition of early keratoconus, which is generally termed as subclinical keratoconus (SKC), forme fruste keratoconus (FFKC), preclinical keratoconus, and keratoconus suspect [10, 39]. Thus, in this review, the abovementioned terms are collectively referred to as early keratoconus to ensure terminology consistency. Table 2 presents the grouping criteria of early keratoconus used in previous studies. So far, research has focused on the contralateral eye with unilateral keratoconus as an early keratoconus model. The contralateral eye has a higher risk for occult keratoconus, as the global consensus states that keratoconus is a bilateral asymmetric disease [40]. Hence, closely following changes in the contralateral eye may have significant implications for the diagnosis of early keratoconus. Corneal biomechanical properties may change in keratoconus when morphological changes are not evident [41]. Therefore, an ML-assisted evaluation of corneal biomechanical properties can potentially address the challenges of early keratoconus diagnosis.

Early keratoconus diagnosis with ML using ORA

Ventura et al. [42] used a radial basis function neural network to analyze 41 waveform parameters that were measured using the ORA in 204 eyes, which greatly improved the predictive value of mild keratoconus (Amsler–Krumeich grade I [43] and AUROC = 0.964). A radial basis function neural network is a feedforward neural network with excellent performance, strong nonlinear fitting ability, and convenient-to-implement learning rules. These are applicable in situations where many parameters with inter-parameter interactions need to be analyzed.

Luz et al. [44] used a stepwise logistic regression that combined the waveform parameters of the ORA and the tomographic parameters of Pentacam in 97 eyes; the model diagnosed FFKC with a high diagnostic performance

Table 2 Definition of early keratoconus in each study

First author	Year	Group label	Definition of early keratoconus
Ventura et al. [42]	2013	MKC	Krumeich severity classification I
Luz et al. [44]	2016	FFKC	Normal Placido-disk corneal topographies (KISA<60%) with keratoconus in the contralateral eye.
Pena–Garcia et al. [47]	2016	SKC	No clinical signs of keratoconus (Vogt's striae, Fleischer rings, or corneal scarring). Topography was normal with no asymmetric bowtie and no focal or inferior steepening pattern; however, they were contralateral eyes of clinically evident keratoconus in the fellow eye.
Francis et al. [48, 49]	2017	KCS	One eye was affected with keratoconus, and the contralateral eye was tomographically normal on slit lamp evaluation and Scheimpflug tomography.
Karimi et al. [56]	2018	KCS	Following a thorough eye examination using different devices by ophthalmologists, it was not determined whether the eye was normal or had keratoconus.
Atalay et al. [46]	2020	SKC	1) Normal topography, Pentacam topometric indices, and slit lamp examination findings; 2) normal or borderline Belin/Ambrósio Deviation index (< 3.0 SD), back (≤16 mm), and front (≤7 mm) elevation difference; and 3) keratoconus in the contralateral eye.
Shiga et al. [54]	2021	FFKC	FFKC was determined when no corneal abnormalities were observed in the slit-lamp microscopy examination, corneal topography, and corneal tomography in the fellow eye of a patient with keratoconus.
Zhang et al. [45]	2021	FFKC	The contralateral eye of a patient with keratoconus showed the following features: (1) a normal-appearing cornea on slit lamp examination, retinoscopy, and ophthalmoscopy, (2) normal topography with no asymmetric bowtie and no focal or inferior steepening pattern, (3) the level of TKC provided by Pentacam was normal, that is, it was '-', and (4) the patient had no history of contact lens use, ocular surgery, or trauma.
Perez-Rueda et al. [53]	2021	SKC	(1) Minor topographic keratoconus signs and suspicious topographic findings (mild asymmetric bowtie with or without a skewed axis); (2) mean K (mean curvature of keratometry) < 46.5 D; (3) MCT > 490 µm; (4) no slit lamp findings (no central thinning with Fleischer's ring or Vogt's striae); and (5) clinical keratoconus in the contralateral eye.
Tian et al. [50]	2021	FFKC	An eye was diagnosed with FFKC if it was the contralateral eye of a patient with KC and showed the following features (1) a normal-appearing cornea on slit lamp examination, retinoscopy, and ophthalmoscopy; (2) normal topography with no asymmetric bowtie and no focal or inferior steepening pattern; (3) patient had no history of contact lens use, ocular surgery, or trauma.
Song et al. [52]	2022	SKC	Clinical keratoconus in one eye and the contralateral eye: (1) normal slit lamp findings; (2) CDVA of 20/20 or better; (3) normal topographic aspect, a TKC index of 0, the central mean keratometry value < 47.2 D and I-S value < 1.40 D; and (4) BED < 12 µm.
Lu et al. [55]	2022	FFKC	(1) the contralateral eye was diagnosed as having keratoconus (2) CDVA of 20/20 or better, (3) no keratoconus signs on slit lamp examination, (4) maximum keratometry (Kmax) less than 47.40 D, (5) thinnest pachymetry of ≥480 µm obtained by Pentacam HR, and (6) "normal" topography with the difference between the Kmax values in the inferior and superior areas at 3 mm (I-S value) < 1.40 D, no skewed asymmetric bowtie/inferior steep, and KISA% < 60.

MKC, mild keratoconus; *FFKC*, forme fruste keratoconus; *SKC*, subclinical keratoconus; *KCS*, keratoconus suspect; *EKC*, early keratoconus; *CDVA*, corrected distance visual acuity; *KISA%*, keratoconus percentage index; *KC*, keratoconus; *MCT*, minimum corneal thickness; *TKC*, topographic keratoconus classification; *BED*, back elevation difference

(AUROC = 0.953, sensitivity = 85.71%, and specificity = 98.68%).

Zhang et al. [45] used stepwise logistic regression to train a model using parameters measured by ORA, Corvis ST, and Pentacam in 110 eyes, achieving 100% sensitivity and 84% specificity for FFKC diagnosis. Logistic regression models are suitable for binary classification as they are highly efficient, do not require great computational efforts, are easily understood, and do not require scaling input features.

Atalay et al. [46] used discriminant function analysis to learn the waveform parameters from ORA and tomographic parameters from Pentacam in 248 eyes; the model demonstrated a considerable SKC diagnostic performance (AUROC = 0.948, sensitivity = 87.1%, and specificity = 91.4%).

Early keratoconus diagnosis with ML using Corvis ST

Pena–Garcia et al. [47] analyzed the Corvis ST parameters of 212 eyes with the aid of discriminant analysis to generate ML model, which has a sensitivity and specificity of 85.7% and 82.07% for detecting SKC.

Francis et al. [48, 49] established a composite viscoelastic model by analyzing the waveform deformation and deflection amplitude in 155 eyes of Corvis ST. They fitted the model's parameters of 458 eyes with multiple logistic regression analysis. The accuracy, sensitivity, and specificity of distinguishing keratoconus (including FFKC) from normal eyes in the validation set (264 eyes) reached approximately 100%.

Tian et al. [50] included 153 eyes of patients with FFKC, mild keratoconus (patients with topographical keratoconus classification system [TKC; Pentacam, Oculus] grades 1, 1-2, and 2) [51], and normal thin corneas (thinnest corneal thickness < 500 μm) in their study. Corneal biomechanical parameters from Corvis ST and topographical parameters from Pentacam were used to build a model via a back propagation neural network, and the overall accuracy of the ML model reached 91%. The back propagation neural network has the advantages of simplicity, rapidity, ease of programming, and flexibility. Only the input parameters need adjustment, and clinicians do not require skills in AI application; thus, it is suitable for clinical workers.

Song et al. [52] analyzed the tomographic parameters (Pentacam) and corneal biomechanical parameters (Corvis ST) of 194 eyes with SKC and normal eyes using Chi-square automatic interaction detection and classification and regression tree (CART) algorithms to generate models. These were internally validated using the ten-fold cross-validation method and externally validated in 66 eyes. In the validation set, the CART model discriminated SKC with 92.4%, 90.3%, and 94.3% accuracy, sensitivity, and specificity, respectively. The CART analysis is a form of decision tree analysis that is commonly used in supervised learning and has the advantage of being easy to implement and comprehend. The CART algorithm is suitable for data classification in the clinic, and the applicable model has high accuracy.

Perez–Rueda et al. [53] trained the Pentacam and Corvis ST parameters of 81 eyes using logistic regression. Their model calculated an SKC index with a sensitivity, specificity, and accuracy of 89.5%, 96.7%, and 94.9% for SKC diagnosis, respectively.

Shiga et al. [54] used logistic regression to train anterior segment optical coherence tomography and Corvis ST parameters of 75 eyes. The sensitivity and specificity of the ML model to diagnose FFKC reached 91.3% and 90.38%, respectively.

Lu et al. [55] used RF and neural networks to train the spectral domain optical coherence tomography and Corvis ST parameters of 622 eyes. The accuracy, sensitivity, and specificity of RF models for FFKC diagnosis reached 88.89%, 75%, and 94.74%, respectively.

Karimi et al. [56] used corneal biomechanical parameters from the Corvis ST of 80 eyes to build a finite element model to calculate the stress value. They trained the neural network model with stress values and corneal biomechanical parameters and achieved an accuracy of 91.20%, 83.33%, and 80.35% in the validation set (155 eyes) for predicting keratoconus, keratoconus suspect, and normal eyes, respectively.

Although studies of early keratoconus from the perspective of corneal biomechanics using ML are rare, they improve the sensitivity, specificity, and accuracy of early keratoconus. Research has proven that ML has a certain degree of accuracy and development potential in early keratoconus diagnosis, although further research is required to strengthen these findings.

Grading keratoconus using ML

There are many staging criteria for keratoconus; nevertheless, none is uniform. Most of these criteria are based on corneal morphology, such as corneal thickness, anterior and posterior corneal surface curvatures, and cone location [10]. However, the management of keratoconus depends on disease severity and progression. Typically, patients with mild, moderate, and severe keratoconus are treated using frame glasses, contact lenses, and surgery (corneal collagen cross-linking, keratoplasty, etc.), respectively [10, 57]. Patients can greatly benefit from an accurate diagnosis of keratoconus severity and a timely, corresponding intervention. From the perspective of corneal biomechanics, ML might be able to carry out keratoconus grading or auxiliary grading.

Herber et al. [58] classified 434 eyes into four groups (normal eyes as well as eyes with mild [TKC grade 1], moderate [TKC grade 2], and severe keratoconus [TKC grade 3]) according to the TKC classification and developed a classification model based on corneal biomechanical parameters (Corvis ST) using linear discriminant analysis and RF algorithms. The RF model was used to predict normal eyes as well as eyes with mild, moderate, and severe keratoconus with sensitivities and specificities of 91% and 94%, 80% and 90%, 63% and 87%, and 72% and 95%, respectively, with an overall accuracy of 78%. RF, a classifier composed of multiple decision trees, has the advantages of fast training speed and strong randomness; moreover, it is not easy to overfit and is, therefore, suitable for analyzing large datasets.

Langenbucher et al. [59] classified 439 eyes into grades 1–4 based on the TKC classification and incorporated corneal biomechanical parameters (Corvis ST) into 24 supervised machine models for training; the SVM model exhibited the best performance with 65.1% overall correct classification. SVM, a kind of classifier with good robustness and advantages such as a good classification effect, can reject many redundant samples and perform classification.

Recently, Flockerzi et al. [60, 61] combined the Corvis Biomechanical Index (Corvis ST) with the anterior radius of curvature, the posterior radius of curvature, and the thinnest corneal thickness in ABCD grading. Then, they used linear regression to derive CBiF, which corresponds to the ABCD

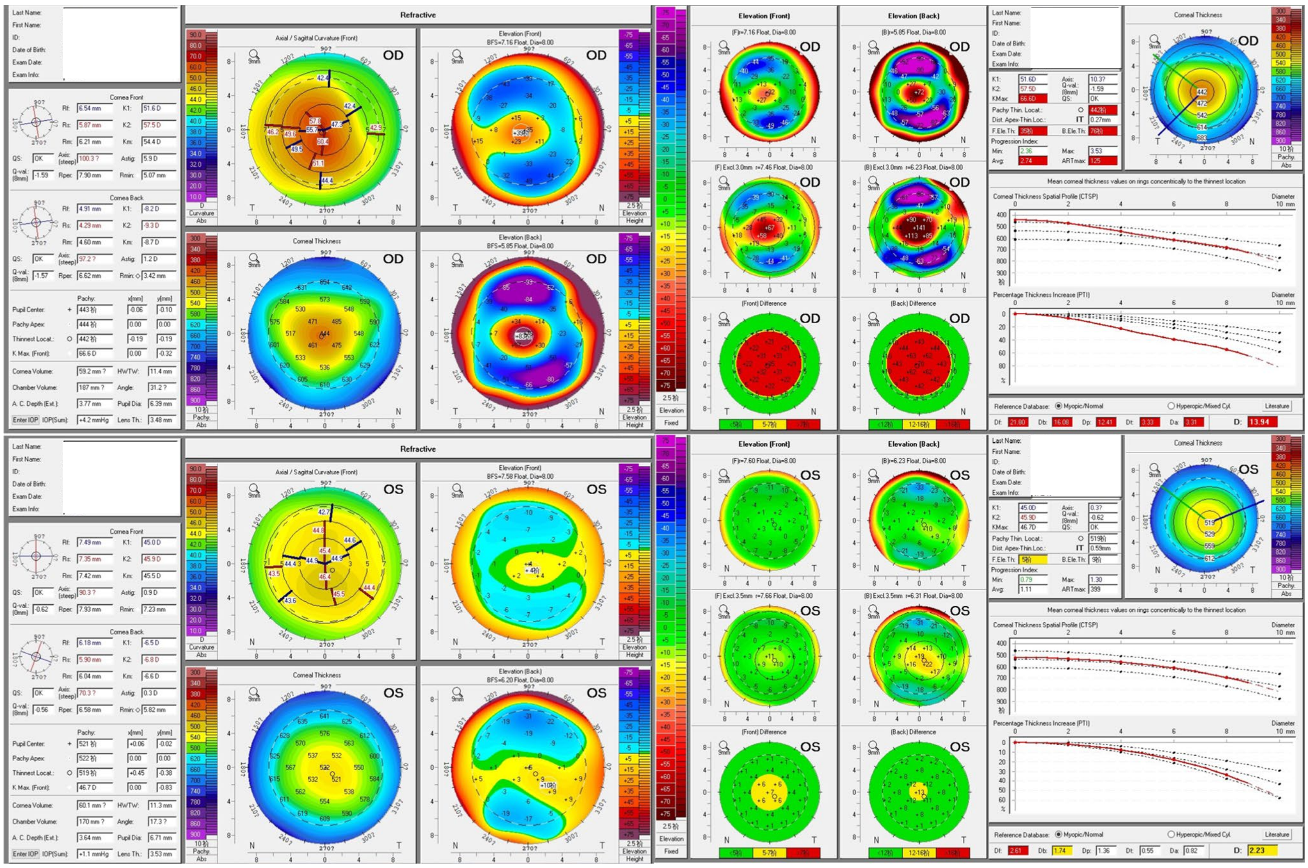

Fig. 2 Oculus Pentacam topography of a patient with subclinical keratoconus, which is defined as early keratoconus in some literatures

grading divided into five grades of severity ranging from E0 to E4 [62], to perform auxiliary keratoconus grading from a biomechanical perspective.

Therefore, ML-assisted grading of keratoconus severity based on corneal biomechanics is still in the initial exploratory stage, whereas it is important and urgent to standardize the classification of keratoconus; hence, in-depth studies are required to enhance ML-assisted keratoconus classification.

Discussion: current limitations and future prospects

This article, which is the first to comprehensively review AI-based diagnosis and research progress for keratoconus in terms of corneal biomechanical properties, demonstrates the high accuracy of AI in keratoconus diagnosis and provides directions for early diagnosis and timely intervention. Overall, there is no optimal ML method, and ML should be used in suitable scenarios, such as logistic regression models are suitable for binary classification. Meanwhile, due to vast differences among datasets, ML methods, and early definitions of keratoconus in each study, individual studies are usually incomparable in nature, making the comparison of performances between individuals difficult and imprecise. Nevertheless, our review outlines that AI's research potential using biomechanical properties in keratoconus is remarkable; hence, we summarized the current limitations and possible future research prospects.

Multi-perspective combination

Current research in in vivo corneal biomechanics combined with ML is without a dynamic observation of keratoconus-related changes from a histological perspective of keratocytes or corneal collagen fibers. The corneal stroma and collagen fibers are the primary carriers of corneal biomechanics [63]. Therefore, the correlation between keratocyte density, keratocyte morphology, and collagen fiber-related corneal biomechanical properties should be investigated. For example, measuring keratocyte density and collagen fibers in the contralateral eye of unilateral KC with in vivo confocal microscopy [64] and making a longitudinal comparison with the in vivo biomechanical parameters. When corneal biomechanical parameters were found to change with alterations in keratocyte density or collagen fibers,

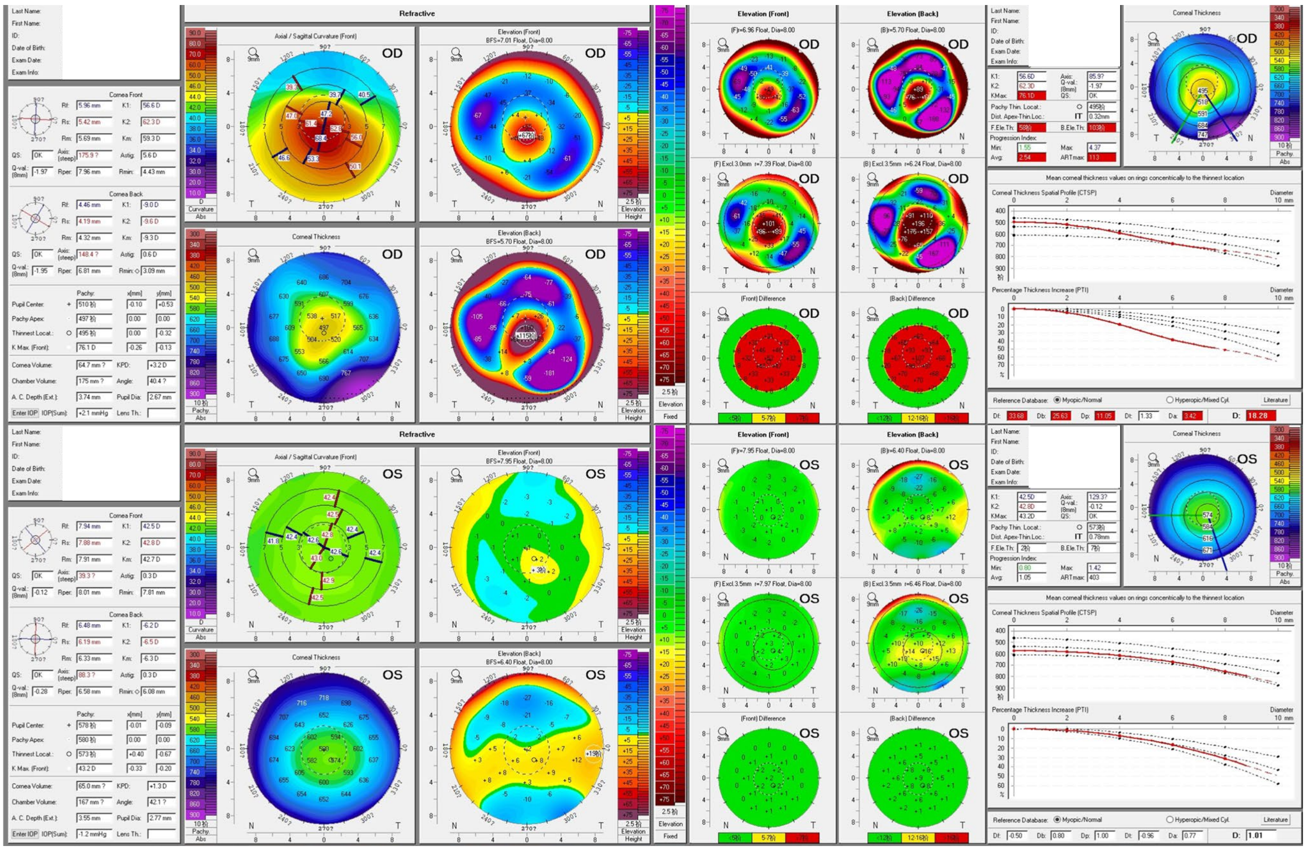

Fig. 3 Oculus Pentacam topography of a patient with forme fruste keratoconus, which is defined as early keratoconus in some literatures

the biomechanical parameters may reflect actual corneal biomechanics. Meanwhile, demonstrating that corneal biomechanics in keratoconus precede morphological changes, providing strong support for early screening for keratoconus and early bilateral diagnosis. We believe that a combination of multiple perspectives with the aid of ML could produce more remarkable results.

Detection of local biomechanical properties

Corneal biomechanical properties are relatively complex, including viscoelasticity, nonlinear elasticity, and anisotropy [3, 18, 65–67]. The in vivo biomechanical parameters provided by the current measurement devices are calculated from horizontal cross-sections of the cornea. Therefore, it remains controversial whether the device-measured parameters can accurately reflect corneal biomechanical properties [31, 68, 69]. Biomechanical parameters are measured at the center of the cornea, while the thinnest point of a keratoconus is often paracentral. These parameters may not reflect the biomechanical properties of the thinnest point of the keratoconus [70]. Future research should focus on an ML-assisted evaluation of detailed changes in biomechanical properties, which can capture local lesions [71]. Recently our team investigated the corneal deformation contours from a pixel-level data point of view and calculated the biomechanical parameters of corneal deformation according to the pixel points of corneal contours. The model trained by a feedforward neural network can effectively distinguish between normal eyes and keratoconus [37]. We consider that conducting multiple views on keratoconus from a detailed and subtle perspective could obtain more remarkable results.

Multi-information sharing

The current studies on ML models lacked external validation or reported parameters with low accuracies after external validation. For instance, the TBI showed an approximately 28% decrease in sensitivity after external validation [72], which may be related to overfitting of the model and differences in participant baseline data (age, gender, corneal thickness, intraocular pressure, and ethnicity) [73–75]. Due to the difference in basic information between studies, the ML models in each study are not comparable. Future studies should improve the performance of the ML model and reduce the error caused by the abovementioned limitations. It is appealed to upload data to public databases for external validation while giving a comprehensive interpretation of the construction of the ML model in the study, verifying each other to improve the efficiency of ML. Recently, the new parameter TBIv2, trained using data from 25 international centers via the ML method, has a higher diagnostic ability for ectasia than TBI [76]. Furthermore, high-risk factors of keratoconus, such as rubbing the eyes, a history of allergy, and genetic predisposition [77], should be fully considered when training the model to improve its accuracy. Meanwhile, corneal morphology, biomechanics, and histopathology should be combined with ML, and a multi-platform universal model should be created to enhance diagnostic efficacy for early keratoconus.

Unified or standardized definition

The current clinical definitions of early keratoconus are quite confusing (Table 2) [78]. In some literature, SKC is defined as the presence of keratoconus in one eye and a certain degree of corneal topographical alterations or a high suspicion of keratoconus in the contralateral eye (Fig. 2). In contrast, FFKC is defined as the presence of keratoconus in one eye with normal corneal topography and slit lamp manifestations in the contralateral eye (Fig. 3). There is a discrepancy between the corneal biomechanical properties of FFKC and SKC [79]. If both definitions are classified as early keratoconus, then each ML model would produce different results with biases. Future studies should harmonize the classification of early keratoconus and standardize keratoconus grading criteria to improve the ML model performance.

Long-term follow-up and longitudinal analysis

Most current studies are cross-sectional studies, and none of the ML models has a long-term follow-up of patients to demonstrate the accuracy of the unilateral KC contralateral eye as a model to research early keratoconus (Table 1). Although the current consensus considers that keratoconus is a bilateral asymmetric ectatic disease [40, 80, 81], no clinical evidence demonstrates that the contralateral eye of patients with unilateral keratoconus will eventually develop keratoconus [82]. Long-term regular follow-up with longitudinal analysis should be performed to validate the ability of ML models to predict disease progression.

Multi-algorithm evaluation

ML is a "black box" that makes good predictions without providing the logic; therefore, multiple ML algorithms should be evaluated on the same dataset. The optimal algorithm was selected to minimize the algorithmic bias of ML. An effective and reasonable application of ML in clinical practice will eventually guide clinicians in the diagnosis, severity assessment, and observation of treatment effects to create a complete diagnostic and management system for keratoconus.

Conclusion

We conduct a comprehensive review of intelligent diagnosis and grading based on corneal biomechanical properties in the field of keratoconus. The recent advances in AI-based diagnosis, early detection, and grading of keratoconus are significant from the perspective of corneal biomechanics. Despite the challenges, the future is bright regarding keratoconus-related research, owing to in-depth studies of corneal biomechanics, increased integration of AI in clinical practice, the availability of improved experimental equipment, and the global exchange and harmonization of databases.

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Declarations

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Authors and Affiliations

Yan Huo[1] · Xuan Chen[1] · Gauhar Ali Khan[2] · Yan Wang[1,2,3,4]

✉ Yan Wang
wangyan7143@vip.sina.com

[1] School of Medicine, Nankai University, Tianjin, China

[2] Clinical College of Ophthalmology, Tianjin Medical University, Tianjin, China

[3] Tianjin Eye Hospital, Tianjin Key Lab of Ophthalmology and Visual Science, Tianjin Eye Institute, Nankai University Affiliated Eye Hospital, 4 Gansu Road, He-ping District, Tianjin 300020, China

[4] Nankai Eye Institute, Nankai University, Tianjin, China