**Combining Spectral-Domain OCT and Air-puff Tonometry Analysis to Diagnose Keratoconus ~~Using Artificial Intelligence~~**

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**ABSTRACT**

**Purpose:** To investigate the diagnostic capacity of SD-OCT combined with air-puff tonometry using artificial intelligence (AI) in differentiating between normal and KC eyes.

**Methods:** Patients who had either: undergone uneventful LVC with at least 3 years of stable follow-up, forme fruste keratoconus (FFKC), early keratoconus (EKC), or advanced keratoconus (AKC) were included.SD-OCT and biomechanical information from air-puff tonometry was divided into training and validation sets. AI models based on random forest (RF) or neural networks (NN) were trained to distinguish FFKC from normal eyes. Model accuracy was independently tested in FFKC and normal eyes. Receiver operating characteristic (ROC) curves were generated to determine area under the curve (AUC), sensitivity, and specificity values.

**Results:** 223 normal eyes from 223 patients, 69 FFKC eyes from 69 patients, 72 EKC eyes from 72 patients, and 258 AKC eyes from 258 patients were included.The top AUC ROC values (normal eyes compared with AKC and EKC) were Pentacam Random Forest Index (PRFI) (AUC=0.985 and 0.958), Tomographic and Biomechanical Index (TBI) (AUC=0.983 and 0.925), and Belin-Ambrósio Deviation Index (BAD-D) (AUC=0.981 and 0.922). When SD-OCT and air-puff tonometry data were combined, the RF AI model provided the highest accuracy with 99% AUC for FFKC (75.00% sensitivity; 94.74% specificity).

**Conclusions:** Currently, AI parameters accurately diagnose AKC and EKC, but have a limited ability to diagnose FFKC. AI-assisted diagnostic technology that utilizes both SD-OCT and air-puff tonometry may overcome this limitation, leading to improved management of patients with KC.

**INTRODUCTION**

Keratoconus (KC) is a relatively common bilateral corneal ectasia disease 1, characterized by local biomechanical weakness with possible asymmetric binocular involvement. As the disease develops, the weakening cornea becomes increasingly unable to resist the distension caused by intraocular pressure. This may lead to the development of a cone-shaped protrusion that causes increasing myopia and irregular astigmatism. Early screening for KC is important for laser vision correction (LVC) to prevent triggering the KC pathological process in susceptible patients. In addition, the timely diagnosis with close follow-ups enables the early application of corneal cross-linking (CXL) to halt disease progression and vision loss.

Nowadays, there are three types of non-contact clinical instruments used to diagnose KC. The first type uses the Placido or Scheimpflug techniques to obtain shape parameters that include corneal curvature, thickness, and surface elevations. The second is anterior segment optical coherence tomography (AS-OCT), which provides measures of corneal epithelium thickness alongside corneal curvature and thickness 2. The third is air-puff tonometry, which the pathological impact KC has on corneal biomechanical integrity. To date, most researchers have applied these methods separately to diagnose early-stage KC. Although each instrument is continually optimized through software updates, the diagnostic efficiency of each individual instrument is limited by its technical specifications. Since these methods are complementary, it would be important to consider a clinical approach that combines the contributions of multiple instrument types. To this end, Hwang et al. 3 recently combined AS-OCT with Scheimpflug-based tomography to detect highly asymmetric KC. However, this combination was restricted to structural diagnoses, which may not enable the full spectrum of patients with KC to be diagnosed. Indeed, others have shown using air-puff technology that corneal biomechanical strength deteriorates in patients with KC, before evidence of topographic anomalies can be observed 4,5. In line with this finding, Ambrósio et al. combined Scheimpflug-based tomography with an air-puff device to detect subclinical ectasia 6; but the study did not record any information on the state of the epithelium. Finally, irregular epithelial profiles can influence tomographic measurements 7,8, further highlighting the utility of using complementary techniques.

Inspired by these examples, the present study explores the diagnostic capability of combining AS-OCT with air-puff tonometry to differentiate between normal and KC corneas. If successful, the combination may provide an improved approach to diagnose early-stage and forme fruste KC.

**METHODS**

This diagnostic study was conducted with the approval of the Ethics Committee of the Eye Hospital of Wenzhou Medical University. The study adhered to the tenets of the Declaration of Helsinki and its statement of ethical principles guiding the conduct of medical research involving human subjects. All participants signed informed consent.

**Patients Groups**

This study considered four groups of volunteers: a normal/control group, a group with forme fruste keratoconus (FFKC), a group with early-stage KC (EKC), and a group with advanced KC (AKC), each defined according to the criteria described below. Given the large correlation between the fellow eyes of healthy participants, one randomly selected eye was included per person in the normal group. For the FFKC and EKC groups, only the eye that met the inclusion criteria was analyzed. The exception was in the AKC group where the contralateral eye from the FFKC and EKC patients were included if they meet the AKC group criteria.

The volunteers in the normal group were recruited from patients presenting for LVC in the Eye Hospital of Wenzhou Medical University, using the inclusion criteria of no ocular or systemic abnormalities, no ocular surgery history, a stable corrected distance visual acuity (CDVA) ≥ 20/20 for 2 years before surgery and a 3-year follow-up after LVC to exclude those with no clinical or tomographic signs of iatrogenic ectasia 9.

The diagnosis of KC required at least 1 slit-lamp finding (Fleischer ring, Vogt striae or central thinning) and 2 signs of KC on Scheimpflug topography (Pentacam HR, Oculus Optikgeräte, Wetzlar, Germany), such as decreased thinnest pachymetry, skewed asymmetric bowtie/inferior steep [SAB/IS] or increased inferior steepness.

For the FFKC group, the inclusion criteria were: 1) the contralateral eye was diagnosed with KC according to the criteria above, 2) best CDVA ≥20/20, 3) no KC signs in the slit-lamp, 4) Kmax <47.4 D, 5) thinnest pachymetry ≥ 480 μm obtained in 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) <1.4 D, no AB/IS, and keratoconus percentage index (KISA%) <60.

The inclusion criteria for the EKC group were based on severity 1 in the Amsler-Krumeich classification of KC: 1) Kmax <48.5 D and smallest thickness >480 μm, 2) best CDVA ≥16/20, and 3) no central scars and fewer than two slit-lamp findings.

Finally, the AKC group included all those keratoconic eyes with parameters exceeding the criteria of the FFKC and EKC groups (i.e., Kmax ≥48.5 D, smallest thickness <480 μm, best CDVA <16/20, with at least one slit-lamp finding).

**Data Acquisition and Evaluated Parameters**

Participants were asked to discontinue wearing soft contact lenses for at least 2 weeks before the examination, or at least 4 weeks of rigid gas-permeable contact lenses wear.

***Pentacam HR Scheimpflug Topography Data***

In order to classify the patients, tomography measurements were obtained with a Pentacam HR (Oculus Optikgeräte, Wetzlar, Germany, software version 1.21r59). Only eyes with a good quality score were considered, using the following parameters to assign the eyes to a severity group: K1, K2, Kmax, thinnest pachymetry, the difference between average inferior and superior corneal powers within 3 mm from the corneal center (IS-Value), and two artificial intelligence (AI) parameters - the Belin-Ambrósio deviation index (BADD) and the Pentacam Random Forest Index (PRFI). The Pentacam data were only used for the initial classification and were not included in the feature selection or AI training.

***RTVue-XR Spectral-Domain OCT Data***

First, a measurement was performed with the RTVue-XR Spectral-Domain OCT (Optovue, Inc., Fremont, CA, USA), which is known to provide repeatable thickness maps of anomalous corneas 10. This provided thickness maps for the whole cornea (CT), the corneal epithelium (ET), and stroma (ST) in the central (2 mm diameter), paracentral (2 to 5 mm), midperipheral (5 to 7 mm), and peripheral regions (7 to 9 mm). In the latter three regions, the thickness was monitored in 8 equally spaced points along the median circumference of the region, including the temporal (T), superior-temporal (ST), superior (S), superior-nasal (SN), nasal (N), inferior-nasal (IN), inferior (I) and inferior-temporal (IT) positions.

***Corvis ST biomechanical Data***

Finally, Corvis ST (software version 1.21r59, Oculus Optikgeräte) measurements were performed, which recorded 41 parameters in two categories: (1) independent parameters, such as intraocular pressure (IOP), biomechanically-corrected IOP (bIOP), pachymetry, and 35 dynamic corneal response (DCR) parameters. The latter group included the ratio between the central deformation and the average of peripheral deformation at either 1.0 mm or 2.0 mm from center (DA ratio 1 mm/2 mm), peripheral corneal thickness increase (Pachy Slope), the Ambrósio’s relational thickness to the horizontal profile (ARTh), the reciprocal of the radius during the concave state of the cornea (integrated radius), and the stiffness parameter at first applanation (SPA1) 11. (2) Three other parameters were also recorded: the Stress-Strain Index (SSI); two AI parameters - the Corvis Biomechanical Index (CBI) developed from DCR parameters, and the Tomographic and Biomechanical Index (TBI) developed from DCR and topography parameters. Only measurements with a good quality score were considered for analysis.

**Artificial Intelligence**

We used R (version 4.0.4, R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>) to develop two AI models based on Random Forests (RF) and Neural Networks (NN).

In the current study, before the AI models were trained based on SD-OCT and/or Corvis ST, feature selection was required among the parameters exported from SD-OCT and Corvis ST using the Boruta package (Version 7.0.0) 12 for two reasons: (1) surgeons often prefer the use of minimal-optimal parameters for KC diagnosis; (2) large features slow down AI models' algorithms, particularly in NN, and will simultaneously decrease the models’ best possible performance 13.

***Models***

Following feature selection, RF and NN models were developed based on the selected features from SD-OCT and/or Corvis ST to distinguish the FFKC group from the normal group using the randomForest (RF, Version 4.6-14) and neuralnet (Version 1.44.2) packages. Parameters exported from Pentacam, PRFI, TBI, and BADD were not included in the training. In brief, for the RF model, 500 decision trees were grown and combined to converge the out-of-bag error and improve the prediction performance 14. For the NN model, an artificial neural network was built on multi-layers of interconnected nodes, including two hidden layers and four hidden neurons, using a supervised learning algorithm 15.

***Validation***

The total dataset was randomly divided into a training and a validation set to determine the clinical validity of the two models and their ability to correctly analyze new data: the training data constituted 70% of the total data set and was used to train the models, whilst the remaining data formed the validation set used to evaluate the models’ accuracy. The average value of the classification accuracy obtained after executing a 10-fold cross-validation was recorded.

**STATISTICAL ANALYSIS**

The statistical analysis was performed in SPSS (version 24; IBM Corporation, Armonk, New York, USA) and R (version 4.0.4). The normality of the data was verified using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation. For continuous variables, analysis of variance (ANOVA) and Kruskal-Wallis H test were conducted to analyze the differences between the four groups, and post-hoc tests were performed with a Bonferroni correction. The 95% confidence intervals (CI) were calculated by the Binomial exact. A value of *P* < .05 was considered statistically significant for all tests. To determine the optimal cut-off values, sensitivity, and specificity, we used receiver operating characteristic (ROC) curves and area under the curve (AUC) as accuracy measures. Whereas an AUC value of 1.0 indicates perfect discrimination, values of 0.5 or less show that the assessed parameter has no diagnostic ability. Values between 0.5 and 1.0 refer to a significant difference between the distributions of the considered variables in the compared groups. The top 10 AUC values and existing AI parameters’ ROC result of all compared groups were taken and sorted from high to low.

**RESULTS**

***Demographics***

This retrospective study included 622 eyes of 481 patients for whom the demographic information is shown in **Table 1**; and the parameter distributions and comparisons between groups are shown in **Figure 1**. There were significant age differences between groups (*P* = .017), especially between the FFKC and normal groups, and the FFKC and AKC groups (*P* = .004 and .005, respectively). There were no significant differences in sex distribution and OD:OS ratios (both *P* > .05) between the groups.

***ROC Analysis***

The 10 highest-ranked parameters according to their AUC among those obtained from the SD-OCT (marked with ※), Corvis ST, and Pentacam (only PRFI, BADD, and TBI related with Pentacam) are shown in **Table 2** for the comparisons of the normal group with the three KC groups.In comparing the normal group with the AKC and EKC groups, the top three AUC ROC ranked parameters were the same in sequence: PRFI (AUC = 0.985 and 0.958, respectively), TBI (AUC = 0.983 and 0.925), and BADD (AUC = 0.981 and 0.922). When comparing the normal group with the FFKC group, the best AUC ROC greatly declined, and the top three AUC ROC ranked parameters switched from PRFI, TBI, and BADD to the following independent DCR parameters: A2\_Deflection\_Amp (AUC = 0.761), A2\_Deflection\_Area (AUC = 0.755), and A2\_Deflection\_Length (AUC = 0.701).

***Feature Selection and Artificial Intelligence Models***

The results of feature selection from SD-OCT and Corvis ST are provided in **Table 3**. For AI models performance, based on the selected features from SD-OCT and Corvis ST, the RF and NN performed well, which was far outperformed the existing clinical parameters PRFI, BADD, CBI, and TBI(**Figure 2**).

In detail, the best trained model was based on the RF by combining features from SD-OCT and Corvis ST (AUC = 0.99; 88.89% accuracy; 75.00% sensitivity; 94.74% specificity), following the RF-based model by only using Corvis ST features (AUC = 0.92; 90.00% accuracy; 72.22% sensitivity; 94.44% specificity). The performance of NN-based AI models was worse than that of RF-based AI models. However, the NN-based model that combined features from SD-OCT and Corvis ST (AUC = 0.88; 90.12% accuracy; 73.68% sensitivity; 87.10% specificity) was still better than the NN model that used the features from Corvis ST alone (AUC = 0.89; 90.12% accuracy; 63.16% sensitivity; 96.77% specificity).

**DISCUSSION**

This diagnostic study represents the first attempt to innovative combine diagnostic information from SD-OCT and air-puff devices by AI to enhance clinicians’ ability to detect KC and in particular, FFKC, the results were superior to using either of the devices individually.

As expected, the parameters already provided by the Pentacam, the Corvis ST, and the SD-OCT had an excellent ability to distinguish between normal and AKC corneas, reflecting normal clinical practice where they are already used to diagnose AKC using topography or tomography maps. The four most successful parameters in identifying AKC corneas were all AI parameters based on either RF (PRFI and TBI) or logistic regression (CBI and BADD), emphasizing the importance of AI-assisted KC diagnosis. The rest of the 10 best performing parameters included the overall standard deviation in epithelial and overall corneal pachymetry thickness (obtained with SD-OCT imaging), which is compatible with the expectation that AKC corneas had undergone a major change in corneal thickness. It is worth noting that SSI, associated with the corneal material’s biomechanical properties, did not appear in the list of best classifiers, which may be a confirmation of the idea that KC originates from a localized (rather than a global) decrease in corneal biomechanics 16.

In comparing the normal and the EKC groups, the three best performing parameters based on AUC were also AI parameters (PRFI, TBI, and BADD). Although the AUC values were lower than for the comparison with the AKC group, they still showed an outstanding diagnostic ability (**Table 2**). For the other parameters, the AUC was considerably lower compared to PRFI, TBI, and BADD, again confirming the importance of AI parameters. Further, the SD-OCT data showed a regional epithelial remodeling (**Table 2**), reported earlier by Silverman et al. 17, confirming epithelial thickness (ET) redistribution as one of the most critical AS-OCT parameters for detecting early-stage KC.

Finally, for discriminating between the normal and FFKC groups, a dramatic decrease in AUC was observed in all parameters measured, compared with the AKC and EKC analyses. Among the 10 top-scoring AUC parameters, independent DCR parameters replaced AI parameters and occupied dominant positions. These parameters, and particularly the first 3 parameters (A2\_Deflection\_Amp, A2\_Deflection\_Area, and A2\_Deflection\_Length), were more focused on the second applanation event, and were not independent variables that formed parts of the CBI and TBI. When compared with the DCR parameters, the tomographic parameters derived from OCT were less important, suggesting that the biomechanical change that takes place in KC occurs earlier than its morphological change in line with earlier literature 5. The BADD and PRFI, based on corneal tomography, are also relevant morphological parameters with some degree of ability to diagnose FFKC.

A literature review conducted by the authors of the present study identified six recent studies that focused on the detection of early-stage KC (including subclinical KC, EKC, and FFKC) by various AI models (**Table 4**). Analysis of these studies identified several limitations. First, the number of early-stage KC eyes included was limited, especially for FFKC eyes; indeed, in three studies 18-20 no FFKC eyes were included. In another study by Xie et al. 21, although a large number of EKC eyes were included, the EKC inclusion criteria were ambiguous. In addition, the inclusion criteria across studies were inconsistent, making it difficult to compare the performance of the AI ​​models used. Finally, no biomechanical information was included, which may have impacted the models’ performance. To address these points, the current study included both FFKC and EKC eyes, and had the same inclusion criteria as the existing comprehensive parameters (PRFI, TBI, and CBI). In addition, both corneal structural and biomechanical information obtained from SD-OCT and Corvis ST were considered in the analyses.

Multinomial logistics regression (MLR) was not applied in the current study as MLR would delete features to get the minimal-optimal features. However, since MLR cannot optimally handle the relationship between the deleted and the reserved features, this process can result in a decrease in the model’s performance. One limitation of this study was the relatively small size of the FFKC group due to the strict inclusion criteria. Since a larger FFKC patient’s population may improve the performance of the AI models, we continue to search for more FFKC patients for future analyses.

In conclusion, this study confirms that existing AI parameters can accurately diagnose AKC and EKC patients, but their ability to diagnose FFKC patients is limited. In contrast, the combined AI-assisted diagnostic technology based on both SD-OCT and Corvis ST, as proposed in this study, can greatly improve healthcare professionals’ ability to diagnose FFKC, leading to an overall improvement in the management of KC patients.

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**Figure Legends**

**Figure 1:** The distributions and comparisons of patients’ demographic characteristics among all groups. IS-Value, the difference between average inferior and superior corneal powers 3 mm from the center of the cornea; bIOP, Biomechanically Corrected Intraocular Pressure; SPA1, stiffness parameter at first applanation; PRFI, Pentacam Random Forest Index; BADD, Belin-Ambrósio Deviation Index; CBI, Corvis Biomechanical Index; SSI, Stress-Strain Index; TBI, Tomographic and Biomechanical Index.

**Figure 2:** Comparison of four artificial intelligence models and existing comprehensive parameters with receiver operating characteristic (ROC) curve analysis. RF, random forests; NN, neural networks; SD-OCT, spectral-domain optical coherence tomography; PRFI, Pentacam Random Forest Index; BADD, Belin-Ambrósio Deviation Index; CBI, Corvis Biomechanical Index; TBI, Tomographic and Biomechanical Index.