Detecting Keratoconus From Corneal Imaging Data Using Machine Learning

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ABSTRACT Keratoconus affects approximately one in 2,000 individuals worldwide. It is typically associated with the decrease in visual acuity. Given its wide prevalence, there is an unmet need for the development of new tools that can diagnose the disease at an early stage in order to prevent disease progression and vision loss. The aim of this study is to develop and test a machine learning algorithm that can detect keratoconus at early stages. We applied several machine learning algorithms to detect keratoconus and then tested the algorithms using real world medical data, including corneal topography, elevation, and pachymetry parameters collected from OCT-based topography instruments from several corneal clinics in Japan. We implemented 25 different machine learning models in Matlab and achieved a range of 62% to 94.0% accuracy. The highest accuracy level of 94% was obtained by a support vector machine (SVM) algorithm using a subset of eight corneal parameters with the highest discriminating power. The proposed model may aid physicians in assessing corneal status and detecting keratoconus, which is otherwise challenging through subjective evaluations, particularly at the preclinical and early stages of the disease. The algorithm can be integrated into corneal imaging devices or used as a stand-alone-software for cornea assessment and detecting early stage keratoconus.

INDEX TERMS Keratoconus, machine learning, corneal imaging data, data mining, support vector machine.

I. INTRODUCTION

Keratoconus is a noninflammatory corneal disorder which often affects both eyes. Keratoconus affects approximately 45 per 100,000 individuals in the US [1].

In clinics, more advanced stages of keratoconus cases can usually be detected easily because of the manifestation of obvious signs, however, detecting early stage and suspect keratoconus cases is challenging due to unclear manifestation of disease, requiring a more comprehensive assessment of corneal characteristics [2], [3]. Keratoconus emerges in all races and genders.

Keratoconus involves the deformation of the cornea to a conical shape, followed by the thinning of the stroma. The thinned cornea determines the emergence of an uneven

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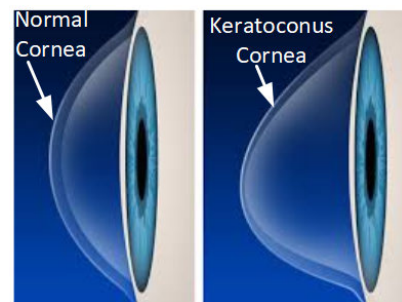

FIGURE 1. Normal cornea versus a cornea affected by keratoconus [6].

astigmatism which is often challenging to be managed and typically leads to the worsening of sight. As can be seen in Figure 1, the keratoconus cornea may have a cone shaped structure with uneven thinning at some regions. Progressive

keratoconus may cause a gradual decline in vision and eventually impacts the quality of the patient's life.

The distortion of the cornea results in irregular astigmatism along with myopia, leading to decreased visual accuracy. Keratoconus usually develops during puberty and becomes stabilized in the fourth decade of life [4].

The possible mechanisms, including the genetic and enzymatic ones, have been studied on a large scale; even so, the etiology of keratoconus currently remains unclear and the major factors that trigger the disease are largely unknown [5].

Keratoconus symptoms may vary partly due to the disease stage. When the symptoms are obvious, keratoconus can be simply diagnosed by an ophthalmologist. However, since the symptoms are not obvious in suspect keratoconus cases or those in the early stages of the disease, the diagnosis becomes challenging.

Given the fact that keratoconus usually affects individuals at puberty, with children mostly affected, developing and designing new tools that can aid identifying the disease at an early stage may help to prevent or slow the progression of the disease, and lead to preserving the sight of young populations.

Thus, the diagnosis of keratoconus at an early stage isn't simple to do, with a great variety of investigations and analyses which pertain to the observation of corneal topography and the careful monitorization of its thickness. Since keratoconus affects young children, it is mandatory to implement new diagnostic techniques and tools that will contribute to the increase in quality of life and ultimately save lives. Oftentimes, due to worsened sight brought upon by a late diagnosis, the children affected by the illness meet hindrances when it comes to finishing studies and integrating within society.

However, developing such models is challenging since there is a significant variability in corneal parameters of normal eyes and eyes with early stage keratoconus. It is even more challenging to detect suspect (forme fruste) keratoconus subjects who are at higher risk of developing keratoconus, with unappreciable disease manifestation. Therefore, several imaging technologies such as corneal topography based on Placido's discs, elevation-based topography, optical coherence tomography (OCT)-based topography, or topography and elevation maps generated by Scheimpflug imaging technology [7] are used for corneal assessment to detect keratoconus. Even with all these technologies, reliable detection of early stage keratoconus remains a difficult task.

The main contribution of this paper is the implementation and testing of a machine learning algorithm, which can allow for the diagnosis of an early stage keratoconus. The detection algorithm is validated on medical data. This algorithm needs to come into the help of the ophthalmologist by allowing the observation and analysis of certain corneal patterns which cannot otherwise be easily seen by the human user.

The accuracy of the developed algorithm allows for the correct treatment to be applied when the illness is at an early stage, thus greatly contributing to the increase in the quality of life. The obtained results represent the validation and performance evaluation of the developed algorithm that can be integrated easily in an instrument used by the ophthalmologist and can contribute to the early keratoconus detection.

II. RELATED WORK

Machine learning analysis has become of significant interest in different domains of medicine, including ophthalmology over the past few years. For instance, two automated machine learning models based on an independent set demographic, optical, pachymetric, and morpho-geometric were developed to characterize the structure of the cornea from an optic-geometric standpoint in the various stages of the keratoconus disease [8]. The proposed model achieved an accuracy of approximately 70% considering different severity levels of keratoconus.

Hallett *et al.* proposed a deep learning-based unsupervised and semi-supervised classification model to identify keratoconus at an early stage with the aim of providing clinicians ample time to select an appropriate treatment [9]. They achieved an accuracy level of 80.3% using 124 keratoconus eyes. However, their small sample size may limit generalization of their findings.

In [10], a logistic regression statistical model was used to detect early stage keratoconus cases. However, the only corneal parameter used in this study was auto-keratometer. In [11], the authors have proposed a classification technique using cornea shape data obtained from OCT-based instruments and obtained an accuracy level of 92% using 244 eyes. However, there is no information on the severity level of the keratoconus eyes and whether the eyes at the early stages of keratoconus were included. Moreover, this study used a relatively small sample. Machine learning has been also applied in keratoconus management with regard to guiding intra-corneal ring segment implantation [12]. This is promising and shows that AI models can be applied to different aspects of keratoconus management to enhance care delivery.

A short review of several machine learning techniques for detecting keratoconus has recently been published [13]. In addition, the role and importance of the development of artificial intelligence (AI) algorithms in prevention and monitoring keratoconus was recently highlighted [14]. As of now, AI models have generated promising results, but more efforts are required to stimulate and encourage development of more accurate algorithms for detecting keratoconus particularly at early stages of the disease.

Included in our results below, we provide a comprehensive summary of previous work on major machine learning models including multi-layer perceptron, support vector machine (SVM), unsupervised machine learning algorithms, artificial neural networks, radial basis networks, convolutional neural networks and decision tree techniques that have been developed to detect keratoconus (Figure 2). The algorithm was built on these previous findings in order to target the development and validation of machine learning algorithms that identify early stage keratoconus at high accuracy levels using large scale multi-center datasets collected from multiple corneal clinics.
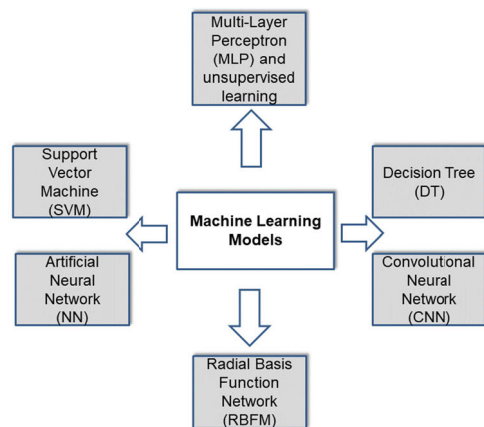
FIGURE 2. Machine learning algorithms that can be used in keratoconus detection.

TABLE 1. Ectasia screening index (ESI).

ESI Interval	Diagnosis	Classes	Samples
$ESI \in [0-4]$	Normal Eye	Class 1	1970
$ESI \in [5-29]$	Suspect keratoconus	Class 2	791
$ESI \geq 30$	Keratoconus	Class 3	390

III. SUBJECTS AND PARTICIPANTS

We included 3,151 corneal images collected from 3,146 eyes using SS-1000 CASIA OCT Imaging Systems (Tomey, Japan). The data was made publicly available through previous studies [15], [16]. About 43% of the participants were male and the mean age was 69.7 years (standard deviation; SD = 16.2). The Ectasia Screening Index (ESI) provided by Casia instrument [17] to objectively label eyes to normal was used. If ESI was between 0 and 4, suspect (or forme fruste) keratoconus, if ESI was between 5 and 29, and keratoconus, if ESI was equal or greater than 30. Using ESI labeling, our dataset included 1970 normal eyes, 791 eyes with forme fruste keratoconus, and 390 eyes with keratoconus (Table 1).

ESI is basically an instrument-guided screening index, which has been shown to have a good agreement with Pentacam keratoconus screening index. ESI provides an objective way of establishing ground truth and removes the human subjectivity in evaluations and minimizes bias in labeling eyes. Institutional review board (IRB) was obtained by the "Jichi Medical University IRB Office" and the study was conducted in accordance with the ethical standards in the Declaration of Helsinki.

IV. METHODS

A. SELECTED MACHINE LEARNING MODEL

Figure 3 presents the diagram of the pipeline that was used to train and test machine learning algorithms and identifying the model with the highest accuracy.

We first performed data preprocessing to exclude irrelevant features (parameters) from the data. The next step was
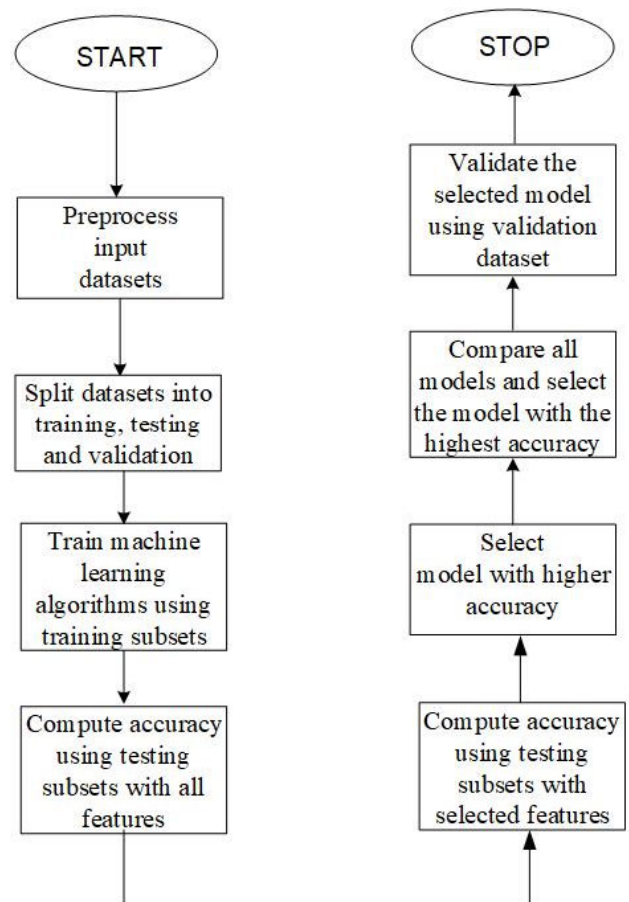
FIGURE 3. Logical diagram of the machine learning setup.

to divide the data into three subsets; training, testing, and validation. We trained several machine learning models using the training subset and subsequently tested the models using testing subsets. The widely used 10-fold cross-validated to evaluate the accuracy of each model was employed. This approach involves randomly dividing the input samples into ten non-overlapping subsets, or folds, of approximately equal size. The models were trained using combined nine folds and tested the model using the remaining non-overlapping fold [18].

We repeated this process ten times each time we tested the mode on a new fold and then averaged the results. To avoid confusing the machine learning classifiers with correlated or non-discriminative corneal parameters (features), we performed feature selection prior to applying machine learning models. Thus, therefore eliminated possible redundant features and generated simpler and more interpretable models, while enhancing the discrimination power of the models. Moreover, using feature selection, we reduced the computational complexity of the algorithms.

The next step was to compare the accuracy of different machine learning models in terms of the area under the ROC (Receiver Operating Characteristic) curve and obtained accuracy. The ESI label of samples as the ground truth to compare different machine learning models was used. We also

**TABLE 2.** Selected features for machine learning processing.

Corneal parameter	Details
1.Higher order irregular astigmatism	Derived by applying Fourier transform on corneal parameters by CASIA instrument;
2.Maximum keratometric power (in 10 mm region)	Kmax (Keratometric) represents the maximum keratometric Power value in ϕ10 mm region (D) measured by the CASIA equipment;
3. Best Fit Sphere (vertical axis)	BFS (Best Fit Sphere) measured by the CASIA equipment represents the reference spherical surface that is most fitting to the curvature of the cornea with respect to Y offsets;
4. Highest irregularity parameter (in 5 mm region)	The irregularity parameter measured in the 5mm cornea zone;
5.Standard deviation of pachymetry (in 5 mm region)	Standard Deviation of Thickness (SD_T5mm) is defined as a standard deviation of corneal thickness (Pachymetry) within a 5mm region of cornea recorded by CASIA;
6.Higher-order aberrations (in 4 mm region)	Higher-order aberrations of anterior and posterior corneal surface in 4 mm region;
7.Aberration parameters in coma orders 5	Aberration parameters of the corneal surface in one primary coma order 5 measured;
8.Aberration parameters in Sphere orders 5	Aberration parameters of the corneal surface in one primary sphere order 5 measured;

used two schemes to compare models. The first scheme was designed to separate normal eyes from eyes with either suspect keratoconus or keratoconus (a combination of these two groups). This was essentially a 2-class or binary problem. The second scheme was designed to identify normal eyes, suspect keratoconus, and keratoconus eyes. In another word, this scheme was based on a 3-class problem. The confusion matrices of these scenarios were also computed to provide more insight to the accuracy of each model. We then compared the accuracy of all models and selected the machine learning model with the highest accuracy. Finally, to assure the generalizability, the selected model by recomputing the accuracy using the non-overlapping validation subset was validated. Models were developed and tested in Matlab [19]. Feature selections were developed in Weka [20].

B. CORNEAL PARAMETERS WITH THE MOST DISCRIMINATIVE POWER IN IDENTIFYING KERATOCONUS

We used the two major categories of feature selection approaches, namely, subset selection and feature ranking. The subset selection approach typically involves a learning model and searches for the best accuracy of the reduced subset of features. This process involves searching the space of all possible feature combinations using forward selection or backward elimination techniques to find a subset of features leading to the highest accuracy. The greedy hill climbing algorithm was used to explore the space of possible subsets of features. The tested algorithm quantifies the importance of a subset of attributes, taking into account the predictive ability of each characteristic, alongside the degree of redundancy of the data. The search method implemented in the feature ranking algorithm was Best First [21].

Independent feature ranking, however, evaluates the worth of each feature and its impact on the output class considering the degree of redundancy of features. This process provides a list of ranked features based on a particular metric most notably information theoretic metrics such as gain ratio [22]. Table 2 presents the corneal parameters with the most discriminative power in identifying keratoconus.
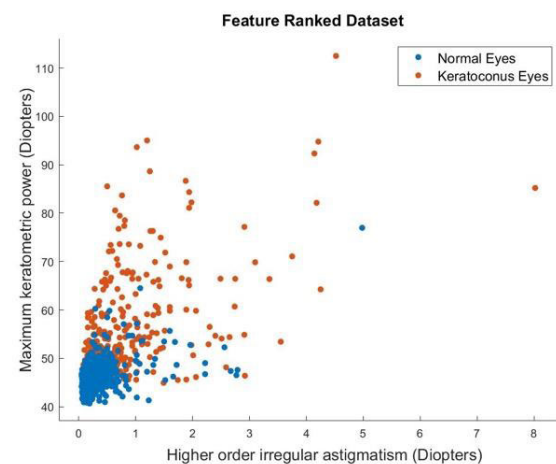
FIGURE 4. Classes cluster for the machine learning algorithm with 2 classes.
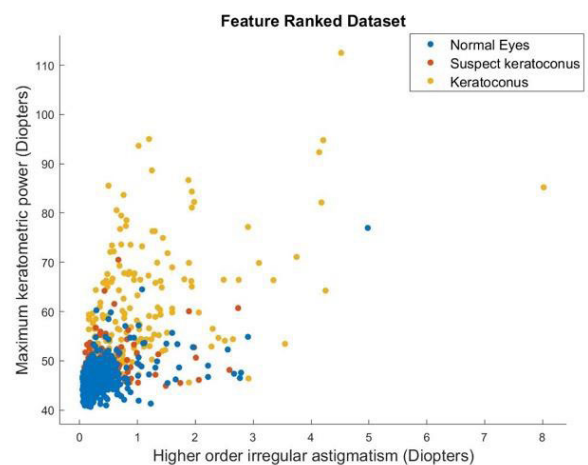
FIGURE 5. Classes cluster for the machine learning algorithm with 3 classes.

After the feature rank classification processing the selected data sets characteristic is more fit for classification algorithms, as can be seen in Figure 4 and Figure 5.

TABLE 3. Machine learning algorithms.

|	Machine Learning Algorithm	Measured Accuracy	
		2 classes (Keratoconus and Healthy Eyes) [%]	3 classes (Keratoconus, Fruste Keratoconus and Healthy Eyes) [%]
1.	Fine Tree	91.5	90.2
2.	Medium Tree	93.1	91.3
3.	Coarse Tree	92.2	91.1
4.	Linear Discriminant	91.4	90.4
5.	Quadric Discriminant	92.2	90.5
6.	Logistic Regression	93.0	NA
7.	Gaussian Naive Bayes	92.3	89.9
8.	Kernel Naive Bayes	90.9	87.1
9.	Linear Support Vector Machine	92.2	91.5
10.	Quadratic Support Vector Machine	93.6	**93**
11.	Cubic Support Vector Machine	**94**	62
12.	Fine Gaussian Support Vector Machine	93.4	91.6
13.	Medium Gaussian Support Vector Machine	93.4	91.7
14.	Coarse Gaussian Support Vector Machine	92.1	90.9
15.	Fine k-Nearest Neighbors (KNN)	91.4	89.9
16.	Medium k-Nearest Neighbors (KNN)	92.8	91.4
17.	Coarse k-Nearest Neighbors (KNN)	91.8	90.4
18.	Cosine k-Nearest Neighbors (KNN)	93.1	90.8
19.	Cubic k-Nearest Neighbors (KNN)	92.5	91.4
20.	Weighted k-Nearest Neighbors (KNN)	92.9	91.5
21.	Ensemble Boosted Trees	93.8	92.1
22.	Ensemble Bagged Trees	92.8	92.2
23.	Ensemble Subspace Discriminant	91	90.3
24.	Ensemble Subspace KNN	92.1	90.8
25.	Ensemble RUSBoosted Trees	91	84.7

Using subset feature selection, we determined that higher order irregular astigmatism, maximum keratometric power (in 10 mm region), best fit sphere (vertical axis), highest irregularity parameter (in 5 mm region), standard deviation of pachymetry (in 5 mm region), higher-order aberrations (in 4 mm region), and aberration parameters (in coma and sphere orders 5) were the most promising in detecting keratoconus.

V. RESULTS

We used 3,151 samples corresponding to 3,146 eyes, each with 443 corneal parameters. A total of 3,003 samples were used for training and testing and 148 samples were set aside for final validation. The best performing model was achieved using eight selected features.

We implemented 25 different machine learning models for binary classification of samples and achieved a range of 62% to 94.0% accuracy. The highest accuracy level of 94.0% was obtained employing a support vector machine (SVM) algorithm with a subset of 8 corneal parameters with most discriminating power.

The obtained results are those stated in Table 3 and represent the obtained accuracy when using different machine learning techniques.
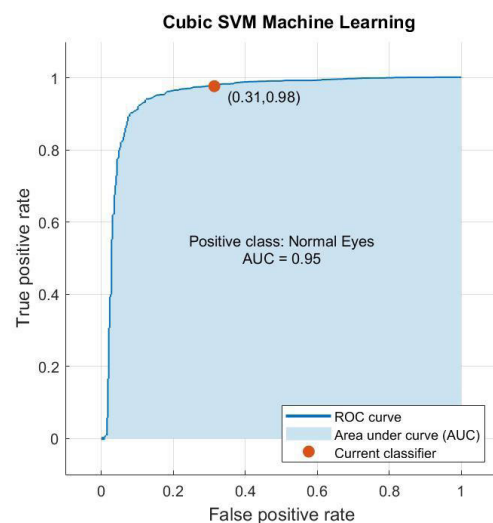

FIGURE 6. Receiver operating characteristic ROC curve of the 2-class problem (normal group versus combined forme fruste or keratoconus).

The ROC curve of two-class approaches are depicted in Figures 6 and 7.

Two-class (normal group versus combined forme fruste or keratoconus) and 2-class problems (normal versus forme
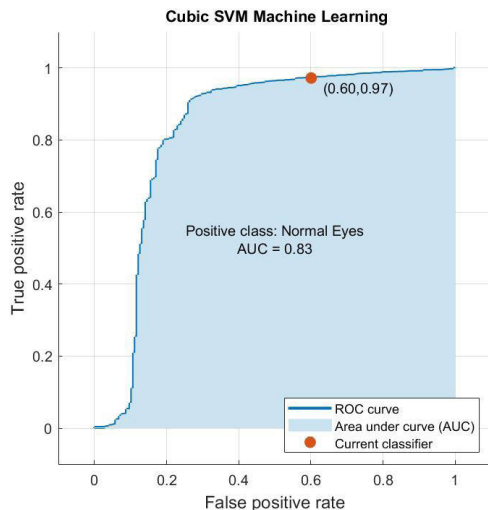
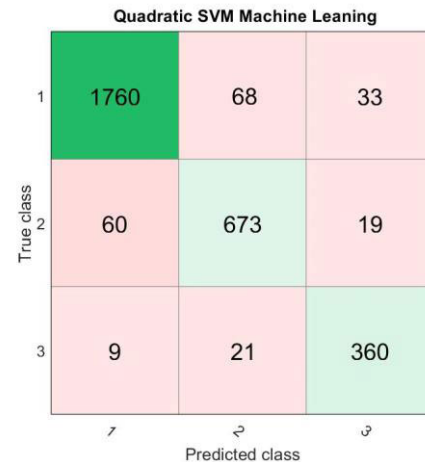**FIGURE 7. Receiver operating characteristic ROC curve of the 2-class problem (normal versus forme fruste keratoconus).**
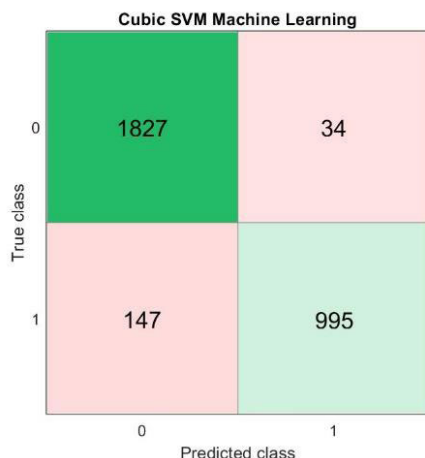
FIGURE 8. Confusion matrix of the selected machine learning for the 2-class problem.

fruste keratoconus), both achieved a relatively high area under the ROC curves of 0.95 and 0.83, respectively. Considering the 2-class problem includes both suspect and early stage keratoconus eyes, the proposed model has identified suspect and early stage keratoconus eyes with a high accuracy.

We have presented the confusion matrix of the winning machine learning classifier with highest accuracy, an SVM machine learning algorithm with cubic kernel function in Figure 8. The green color shows the correct classification and highlights the levels of true positive and true negatives while orange color represents the levels of false positive and false negative.

The highest accuracy level of 94% was obtained by a support vector machine (SVM) algorithm for the 2-class classification problem.

We optimized the parameters of the proposed SVM model to achieve the highest accuracy. This process was integrated with feature selection as well. To highlight other aspects of

FIGURE 9. Confusion matrix of the selected machine learning for the 3-class problem.

the accuracy, we also computed the model's specificity and sensitivity. The model for the 2-class problem achieved a specificity of 0.98 and a sensitivity of 0.87.

Figure 9 presents the confusion Matrix of the selected machine learning for the 3-class problem (normal group versus forme fruste keratoconus versus keratoconus). We obtained an accuracy of 93% for the 3-class classification problem.

Figure 10 shows the parallel coordinates reflecting the influence of each of the eight selected corneal parameters in detecting keratoconus. Parameter "Y axis of the Best Fit Sphere" had the most influence on detecting keratoconus with the lowest number of incorrect model predictions. The corneal parameters are those stated in Table 2 and represent the selected feature for machine learning processing.

VI. DISCUSSION

Most of the methods for identifying eyes with keratoconus rely on subjective assessment of topographical maps, which can lead to bias by the human observer [7]. To address this shortcoming, several machine learning approaches for detecting keratoconus from noninvasive corneal imaging data objectively were applied. We compared the accuracy of the machine learning models and selected a subset of corneal parameters to achieve the best performing model for keratoconus detection. These machine learning models can augment clinical practice and aid ophthalmologist to better identify keratoconus particularly those at higher risk of developing the disease or those currently at the early stages of the disease. Such models could impact treatment planning and contribute to the long-term management of the disorder, thus improving the patient's quality of life.

Feature selection is an important step in machine learning since it may significantly impact the accuracy of learning models. This is an important task in clinical medicine as well. Identifying which parameters impose a higher risk of developing a particular disease has been of high interest in medicine. To that end, the irrelevant features and those
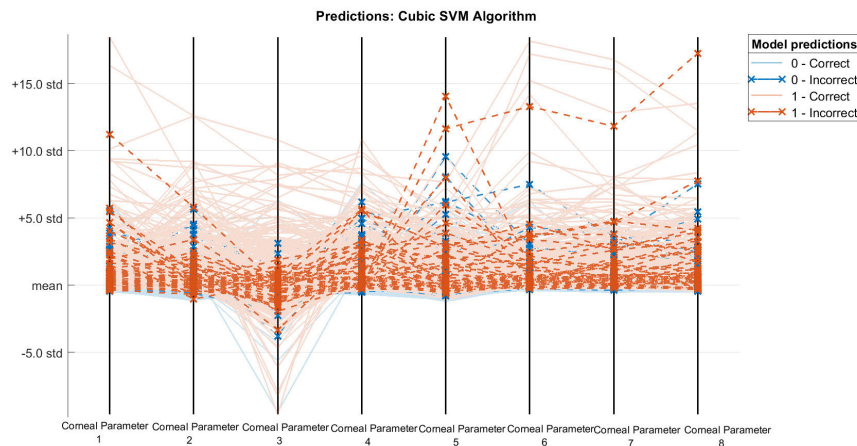
FIGURE 10. Machine-learning parallel coordinate plot of the developed machine learning algorithm.

features with a high degree of correlation that may negatively impact the learning model were excluded and identified those promising ones. Since learning models may become confused with such features, we assessed the performance trained machine learning models with and without feature selection. Consistently, models with feature selection performed better than models without feature selection. Reducing the number of features by feature selection also made our final model simpler, faster, and more explainable.

Some researchers have used only corneal topography parameters for detecting keratoconus [8]–[10]. However, a comprehensive profile of corneal shape, thickness, and elevation parameters to investigate their discriminative power in detecting keratoconus were used. Most promising corneal parameters in detecting keratoconus were higher order irregular astigmatism, maximum keratometric power (in 10 mm region), best fit sphere (vertical axis), highest irregularity parameter (in 5 mm region), standard deviation of pachymetry (in 5 mm region), higher-order aberrations (in 4 mm region), and aberration parameters (in coma and sphere orders 5). We observed that selected parameters were from all three corneal profiles, including shape, thickness, and elevation. Therefore, corneal parameters from all three profiles impact the accuracy of models in detecting keratoconus. This is in agreement with previous research showing that corneal volume, thickness, and shape (anterior and posterior) influenced detecting subclinical and clinical keratoconus [15].

Various machine learning classifiers have been proposed for detecting keratoconus in the literature. However, unlike some of these approaches that studied a limited number of classifiers [9]–[11], [23], [24], we investigated multiple classifiers from different machine learning families. We investigated tree-based learning, artificial neural-network-based learning models such as MLP and CNN, function-based learning models such as SVM, and radial-basis kernel models such as RBFM. We implemented all these models

and ultimately selected an SVM model, as the best performing learning scheme for detecting keratoconus from OCT-based corneal parameters. The selected SVM model achieved a high accuracy with an area under the ROC curve of 0.95 for detecting keratoconus versus normal eyes.

Detecting subclinical keratoconus in clinical practice is currently challenging, but the rewards, particularly for early-stage detection, can be substantial. It is challenging because initial, early-stage changes in the cornea due to keratoconus may be subtle, thus requiring a more comprehensive assessment of cornea by an experienced specialist [5], [7]. It could be rewarding because development of automated models that can accurately identify preclinical keratoconus represents a significant, but currently unmet, need. Such models have the potential to augment clinical practice and aid physicians in managing individuals at higher risk of developing keratoconus or those at the early stages, thus preventing vision loss prior to disease progression and significant vision loss. Our proposed machine learning model can detect those who are in the early stages of the disease with a high accuracy (i.e., an area under the ROC curve equivalent to 0.83). Since we combined both preclinical and clinical keratoconus eyes, achieving 0.95 area under the ROC curve reflects the ability of the model to detect suspect eyes and eyes with early stage keratoconus. The proposed model using only normal and suspect keratoconus eyes and only normal and keratoconus eyes and achieved an accuracy of 93% and 98.5%, respectively was investigated. This reflects that the model is highly accurate in detecting keratoconus eyes as well as highly proficient in detecting suspect keratoconus eyes.

Our study has several limitations that can be addressed in follow-up studies. The proposed machine learning models were trained on corneal data from Casia instrument and are thus limited to this instrument. Further testing was beyond the scope of the current study. Most of currently available commercial instruments generate data that are not necessarily

consistent. For instance, while Casia generates around 400 parameters, Pentacam generates over 1,000 corneal parameters. However, the corneal topography the proposed model can be easily trained using other corneal data generated by other instruments such as Pentacam. The Casia ESI index as the ground truth rather than the clinical diagnosis labels was used. While this may not be equivalent to clinical diagnoses, ESI index provides an objective measure of cornea avoiding bias due to human assessment. Moreover, we showed that ESI index has a good agreement with ectasia severity using unsupervised machine learning models [13], [14]. Additionally, accessing clinical diagnosis labels for large number of eyes in such big datasets is a challenging and time-consuming task. Nevertheless, using ESI has several advantages despite considered limitation.

In summary, we developed several machine learning models and performed feature selection to identify both best performing model and a subset of most promising corneal parameters in detecting both preclinical and clinical keratoconus. We used a large dataset with over 3 thousand eyes, utilized objective ground truth, and performed objective and non-biased model evaluation. The selected machine learning model had a high accuracy in identifying both suspect and early stage keratoconus eyes.

VII. CONCLUSION
The main contribution of this paper is represented by the: implementation and testing of an algorithm that facilitates the diagnosis of advanced as well as early keratoconus. This instrument has to come in the help of the ophthalmologist and to facilitate the detection of keratoconus by recognizing specific corneal patterns which cannot be seen by the untrained eye. Thus, adequate treatment can be applied at the correct time, contributing to the long-term management of the illness by slowing down or even stopping the progression of keratoconus, thus greatly improving the patient's quality of life.

Oftentimes, keratoconus sets in during the years prior to puberty, thus affecting children the most. Thus, it is crucial to develop and implement new methods which can lead to easier detection and diagnosis processes, offering the patients the chance of a normal life.

Another contribution of this work includes the analysis of the keratoconus illness and the evaluation of the different methods and algorithms used in the diagnostic process. The aspect of analyzing different parameters that can be integrated in an automated diagnosis system is an open one because what is needed is the continuous improvement of relevant data that can come in handy when it comes to the detection of keratoconus at an early stage.

Also, an analysis of the current methods used in the diagnosis of keratoconus having the identification of the parameters that need to be inputted at the entry level of the diagnostic algorithm was performed. From the obtained results the implemented algorithm ensures an excellent level of performance when the distinction between healthy eyes and

keratoconus eyes is performed. The accuracy in classifying keratoconus versus healthy eyes (e.g. two label classification) is approximately 94 % when using an SVM machine learning algorithm.

In comparison with other machine learning algorithms that exist in specialized literature, the novelty factor of the tested algorithm is constituted by the possibility of differentiating of a fruste keratoconus type (keratoconus at an early stage) from the healthy eye. Due to the fact that the main difficulty is the detection of the illness at an early stage.

Preclinical and clinical keratoconus can be accurately identified using our proposed automated supervised machine learning based on shape, thickness, and elevation profiles of cornea. The automated keratoconus model we developed can augment clinical practice aid corneal specialists in identifying those at higher risk of developing keratoconus or at the early stage of the disease. Results may enhance our understanding of corneal manifestation of keratoconus.

The potential of the algorithm is huge, due to its possible contribution in streamlining the keratoconus diagnosis process and the detection of this illness at an early phase, thus saving lives.

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