The enhanced pachymetry-adjusted/inferior-superior index for keratoconus detection with artificial intelligence: a tribute to Dr. Yaron Rabinowitz

Aprimorando o índice PA/I-S para detecção do ceratocone com inteligência artificial: um tributo ao Dr. Yaron Rabinowitz

Aydano Pamponet Machado[1], Laís Dagnésia Lopes Lessa[1], Edvalcio Nunes dos Santos[2], Andrea Maria Cavalcante Santos[3], Giovanna Quintella Jucá Duarte Oiticica[3], Renato Ambrósio Júnior[4]

[1] Computing Institute, Universidade Federal de Alagoas, Maceió, AL, Brazil.
[2] Department of Ophthalmology, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
[3] University Hospital Prof. Alberto Antunes, Universidade Federal de Alagoas, Maceió, AL, Brazil.
[4] Department of Ophthalmology, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

How to cite:
Machado AP, Lessa LD, Santos EN, Santos AM, Oiticica GQ, Ambrósio Júnior R. The enhanced pachymetry-adjusted/inferior-superior index for keratoconus detection with artificial intelligence: a tribute to Dr. Yaron Rabinowitz. Rev Bras Oftalmol. 2026;85:e0105.

doi:
https://doi.org/10.37039/1982.8551.20260105

Keywords:
Keratoconus; Corneal topography; Artificial intelligence; Machine learning; Corneal pachymetry

Descritores:
Ceratocone; Topografia corneana; Inteligência artificial; Aprendizado de máquina; Paquimetria corneana

ABSTRACT

Objective: To pay a scientific tribute to Dr. Yaron Rabinowitz by enhancing his PA/I-S index through machine learning-based predictive models using the Applied Artificial Intelligence (A²I) methodology.

Methods: A retrospective study with 2,705 eyes (1,680 normal and 1,025 VAE) to develop a predictive model (AI Tribute) following the KDD knowledge discovery framework, whose performance was assessed in two clinical scenarios – Normal *versus* Clinical Ectasia (KC+VAE-E) (N=3,335) and Normal *versus* VAE-NT (N=2,231) – by AUC and the DeLong test.

Results: In the Normal *versus* Clinical Ectasia scenario, AI Tribute achieved an AUC of 0.985, significantly outperforming PA/I-S index (0.978), I-S value (0.968), KISA% (0.953), and pachy min (0.938). In the Normal versus VAE-NT scenario, AI Tribute achieved an AUC of 0.791, remaining superior to all reference indices.

Conclusion: Machine learning modeling of Dr. Rabinowitz's foundational variables significantly improved keratoconus detection across both clinical scenarios, demonstrating that the A²I approach amplifies established clinical knowledge even in the challenging task of detecting topographically normal ectatic eyes.

RESUMO

Objetivo: O objetivo deste estudo foi prestar uma homenagem científica ao Dr. Yaron Rabinowitz, aprimorando seu índice paquimetria ajustada/inferior-superior por meio de modelos preditivos baseados em aprendizado de máquina e na metodologia de Inteligência Artificial Aplicada.

Métodos: Trata-se de estudo retrospectivo com 2.705 olhos para desenvolver um modelo preditivo (AI Tribute) seguindo o *framework* de descoberta de conhecimento KDD, cujo desempenho foi avaliado em dois cenários – normal *versus* ectasia clínica (n = 3.335) e normal *versus* VAE-NT (n = 2.231) – por meio da área sob a curva e do teste de DeLong.

Resultados: No cenário normal *versus* ectasia clínica, o *artificial intelligence tribute* alcançou área sob a curva de 0,985, superando significativamente o índice paquimetria ajustada/inferior-superior (0,978), o valor inferior-superior (0,968), o KISA% (0,953) e o pachy min (0,938). No cenário normal *versus* VAE-NT, o *artificial intelligence tribute* alcançou área sob a curva de 0,791, mantendo-se superior a todos os índices de referência.

Conclusão: A modelagem por aprendizado de máquina das variáveis utilizadas pelo Dr. Rabinowitz melhorou significativamente a detecção de ectasia em ambos os cenários clínicos, ilustrando que a abordagem de Inteligência Artificial Aplicada amplia o conhecimento clínico estabelecido, mesmo na tarefa desafiadora de detectar ectasia em olhos com topografia aparentemente normal.

Received on:
April 22, 2026

Accepted on:
July 5, 2026

Corresponding author:
Aydano Machado
E-mail: aydano.machado@ic.ufal.br

Institution:
Universidade Federal de Alagoas, Maceió, AL, Brazil.

Conflict of interest:
Dr. Ambrósio is a consultant for Oculus. Dr. Ambrósio and Dr. Machado are partners in Brazilian Artificial Intelligence Network in Medicine (BrAIN). The remaining authors declared that they have no conflicts of interest.

Financial support:
the authors received no financial support for this work.

Data availability statement:
the data that support the findings of this study are not openly available but are available from the corresponding author upon reasonable request.

Associate editor:
Ricardo Augusto Paletta Guedes
Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil
https://orcid.org/0000-0002-9451-738X

Copyright ©2026

INTRODUCTION

Keratoconus is a progressive, non-inflammatory ectatic disorder of the cornea characterized by stromal thinning, anterior protrusion, and irregular astigmatism, collectively resulting in significant visual impairment.[1] Accurate and early identification of keratoconus, including its preclinical forms and susceptibility in refractive surgery candidates, remains a central clinical challenge. Over the past three decades, the field has been profoundly shaped by the pioneering contributions of Dr. Yaron Rabinowitz, whose systematic, quantitative approach to corneal topography analysis established a scientific framework that continues to support contemporary ectasia screening.[2,3]

Among Dr. Rabinowitz's most enduring contributions are the KISA% index [2], which integrates keratometry (K), I-S value, skewed radial axis (SRAX), and astigmatism into a single diagnostic score; the inferior-superior (I-S) value, which quantifies the dioptric asymmetry between inferior and superior corneal zones;[3] and the pachymetry-adjusted I-S (PA/I-S) index, which normalizes the I-S value for corneal thickness, thereby adding a structural dimension to functional asymmetry assessment.[4] These indices exemplify his vision of transforming complex clinical data into actionable, reproducible diagnostic criteria.

The emergence of Artificial Intelligence (AI) offers a complementary path for extending the utility of these established indices.[5] The Applied Artificial Intelligence methodology (AAI or A²I), as defined in this work, is built upon three core pillars: foundation (grounding in domain-specific scientific knowledge), methodology (rigorous application of Knowledge Discovery in Databases, KDD), and competence (mastery of machine learning techniques and their clinical validation).[6,7] Rather than replacing prior knowledge, this paradigm seeks to amplify it.

Building on this foundation, the present study was designed as a tribute to Dr. Rabinowitz by enhancing the PA/I-S index with AI, demonstrating how he could have applied the artificial intelligence (A²I) methodology to improve it. To accomplish this, we developed an AI predictive model called AI Tribute, using the constitutive elements of the PA/I-S index – minimum pachymetry and I-S value – as inputs, trained on normal and VAE (videokeratography-asymmetric ectasia [VAE-E] + videokeratography-asymmetric ectasia with normal topography [VAE-NT]) eyes to capture the full clinical spectrum of ectasia susceptibility. This model was then evaluated in two complementary clinical scenarios – normal versus clinical ectasia and normal versus VAE-NT – and compared to Dr. Rabinowitz's established indices, as detailed below.

METHODS

Study design and ethical considerations

This was a retrospective, cross-sectional study. All data were collected from a pre-existing, de-identified database, and no new patient data were collected for this investigation.[5] The study was conducted in accordance with the principles of the Declaration of Helsinki, and data handling adhered to applicable institutional data governance standards. The institutional review board and human ethics committee of the *Universidade Federal de São Paulo* (Unifesp), São Paulo, Brazil, approved this study.

Database and study population

The dataset included 3,886 unoperated eyes from 3,412 patients, divided into four clinically defined groups: Group 1 (N) consisted of 1,680 eyes from normal (N) patients with no ocular disease or prior surgical history; one eye was randomly selected from each bilateral case to prevent intra-subject correlation within the same group; Group 2 (KC) consisted of 1,181 eyes, with one randomly selected eye from bilateral keratoconus (KC) patients; Group 3 (VAE-E) included 474 unoperated ectatic eyes from patients with videokeratography-asymmetric ectasia (VAE-E); Group 4 (VAE-NT) comprised 551 eyes classified as videokeratography-asymmetric ectasia with normal topography (VAE-NT), that is, the topographically normal fellow eye of patients whose other eye showed ectatic features.

The VAE concept involves diagnosing ectasia in one eye even when the other eye appears clinically normal, showing normal biomicroscopy and relatively normal anterior surface curvature according to Pentacam topometric data.[5,8]

All topographic and tomographic data were acquired using the Pentacam® HR (Oculus Optikgeräte GmbH, Wetzlar, Germany), a validated rotating Scheimpflug imaging system. Only examinations that met the device's internal quality criteria and passed manual review for consistent acquisition and segmentation were included.

The Knowledge Discovery in Database Framework and Applied Artificial Intelligence

The development of the predictive models followed the KDD framework,[7] a structured, step-by-step process for transforming raw clinical data into validated and interpretable computational knowledge. The KDD pipeline comprises five sequential stages: data selection,

preprocessing, transformation, data mining, and model evaluation. Each stage is described in the subsections below.

This approach is consistent with the Applied Artificial Intelligence (A^2I) paradigm,[6] which integrates three foundational pillars: domain foundation, grounded in the established scientific contributions of Dr. Rabinowitz and collaborators; rigorous methodology, operationalized through the KDD framework; and technical competence, through the application of validated machine learning algorithms. The A^2I philosophy is not there to displace prior clinical knowledge but to extend and formalize it computationally.

Data and Feature Engineering

Feature selection was guided exclusively by the scientific contributions of Dr. Yaron Rabinowitz, with the explicit aim of computationally enhancing – rather than replacing – his established indices. The following input features were extracted from the database:

- I-S value: defined as the algebraic difference between the mean dioptric power of the inferior corneal hemisphere and that of the superior hemisphere, measured at a defined annular zone around the corneal apex.[3] It quantifies the topographic asymmetry, a hallmark of early keratoconus.
- Minimum pachymetry (pachy min): the minimum corneal thickness as measured by Scheimpflug tomography. This parameter was retained as an independent structural input variable for the AI Tribute model, consistent with its established discriminative value in ectasia screening[9] and with its role in the original PA/I-S formulation.

No data preprocessing, such as normalization or transformation, was required. The PA/I-S index was calculated according to Dr. Rabinowitz's original formulation,[3,4] using the pachy min value as the pachymetric reference.

Machine Learning and Predictive Model Development

Three families of supervised classification algorithms were systematically evaluated to identify the most appropriate model architecture: each one was selected for its distinct representational properties.

- Logistic regression (LR) was applied as a linear baseline model. Its simplicity and interpretability provide a useful lower bound for evaluating the benefits of more complex nonlinear approaches. The hyperparameter C for the L1 penalty was tuned (0.001-1000) to achieve the best fit.
- Support Vector Machines (SVM) were implemented with radial basis function (RBF) kernels, enabling nonlinear classification in high-dimensional feature spaces. Hyperparameters explored included the regularization parameter C (1-1000) and the kernel coefficient gamma (0.1-0.00001).
- Multilayer perceptron (MLP) neural networks constituted the principal model family, selected for their capacity to model complex, nonlinear interactions among clinical features. Architectural hyperparameters were optimized through an exhaustive grid search covering the number of hidden-layer neurons,[3,10] activation functions (logistic sigmoid, hyperbolic tangent, and rectified linear unit – ReLU), and the learning rate alpha (0.001-0.1). The Limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) solver was used for weight optimization, and training was capped at a range of 500-3,000 iterations. The optimal architecture identified for the AI Tribute model consisted of a single hidden layer, consistent with the principle of parsimony and model interpretability.

A predictive model was built based on Dr. Rabinowitz's conceptual PA/I-S index framework. Therefore, AI Tribute was created using pachy min and I-S value as model inputs. This selection directly incorporates the two main concepts behind the PA/I-S index – structural thickness and topographic asymmetry.

For model training, the classification task was defined as normal (Group 1) versus VAE (Groups 3 and 4 combined, VAE-E + VAE-NT; n = 2,705 eyes), representing the clinically relevant boundary between health and susceptibility to ectasia. To evaluate the model's discriminative performance across distinct ectasia phenotypes, two separate Receiver Operating Characteristic (ROC) analyses were conducted: normal versus clinical ectasia, combining KC (Group 2) and VAE-E (Group 3) cases (n = 3,335 eyes); and normal versus VAE-NT (Group 4) cases (n = 2,231 eyes). The KC group was not included in model training to avoid class imbalance, given that the VAE-E group already provided a clinically representative and numerically sufficient sample of ectatic eyes.

The KC group was not included in model training by design. The model was intentionally trained to learn the clinically most relevant decision boundary – the transition between normality and ectasia susceptibility – including its topographically silent form, rather than the distinction between normality and manifest disease. This

approach also serves as an effective test of the model's ability to generalize, since KC cases represent a phenotype unseen during training. Their inclusion in the evaluation provides an independent measure of whether the learned representations cover the entire spectrum of ectasia severity.

All models were implemented in Python 3.8.5 using the scikit-learn library (version 0.23.2).

Cross-validation and model evaluation

All models were evaluated using stratified 10-fold cross-validation. The dataset was partitioned into ten equal-sized, class-proportional subsets. In each iteration, nine folds were used for training and hyperparameter optimization, while the remaining fold served as the held-out test set. This procedure was repeated ten times, ensuring that every observation was used exactly once for testing. Stratification ensured that the proportion of each clinical group (N, VAE-NT, VAE-E) was preserved across all folds. This well-established validation framework[7] guards against overfitting and ensures that performance estimates reflect the model's expected generalization to unseen data, rather than memorization of the training set.

Statistical analysis

Model performance was quantified using the area under the ROC curve (AUC), which provides a threshold-independent measure of discriminative ability across the full range of sensitivity-specificity trade-offs. AUC values were compared pairwise using DeLong's nonparametric test,[10] the appropriate method for comparing correlated AUC estimates derived from the same dataset. The binomial exact method was used to compute 95% confidence intervals (CIs) for individual AUC estimates. A p-value below 0.05 was considered statistically significant.

The AI Tribute model was compared against established reference indices – I-S value, PA/I-S index, KISA%, and pachy min – in two evaluation scenarios (normal *versus* clinical ectasia and normal *versus* VAE-NT). All statistical analyses were performed using MedCalc Statistical Software (version 23.4.8; MedCalc Software Ltd., Ostend, Belgium).

RESULTS

Study population

The AI Tribute model was trained on 2,705 eyes: 1,680 (62.11%) normal (negative class) and 1,025 (37.89%) from the ectatic spectrum (positive class), combining VAE-E (474 eyes) and VAE-NT (551 eyes). The model was subsequently evaluated in two distinct clinical scenarios: normal *versus* clinical ectasia, comprising 3,335 eyes (1,655 ectatic (KC + VAE-E) and 1,680 normal); and normal *versus* VAE-NT, comprising 2,231 eyes (551 VAE-NT and 1,680 normal). The demographic and topographic characteristics of the study population have been previously described in (5,8,9) and are not repeated here.

Model architecture

Among all machine learning algorithms evaluated, the MLP neural network yielded the best-performing model for AI Tribute. Logistic regression and SVM classifiers showed lower cross-validated AUCs, indicating that the nonlinear representational capacity of the MLP was essential to fully utilize the discriminative information in the two input features. The final optimal architecture for AI Tribute consisted of a single hidden layer with three neurons, a ReLU activation function, a learning rate (alpha) of 0.001, and a maximum of 500 training iterations, reflecting the principle of parsimony in model design.

Performance of AI Tribute – normal *versus* clinical ectasia

In the normal *versus* clinical ectasia scenario (n = 3,335; 1,655 ectatic and 1,680 normal), AI Tribute achieved an AUC of 0.985 (95%CI 0.980-0.989), with a sensitivity of 94.32% and a specificity of 97.74% at the optimal cutoff (>0.655, Youden index = 0.9206). This represented statistically significant superiority over all reference indices (Table 1, Figure 1). Compared with the PA/I-S index (AUC = 0.978), the difference was 0.00712 (p = 0.0061). Against the I-S value (AUC = 0.968), the difference was 0.0174 (p < 0.0001). Against KISA% (AUC = 0.953), the difference was 0.0318 (p < 0.0001). The largest gain was over pachy min (AUC = 0.938), with a difference of 0.0469 (p < 0.0001). All pairwise comparisons were statistically significant (Table 2).

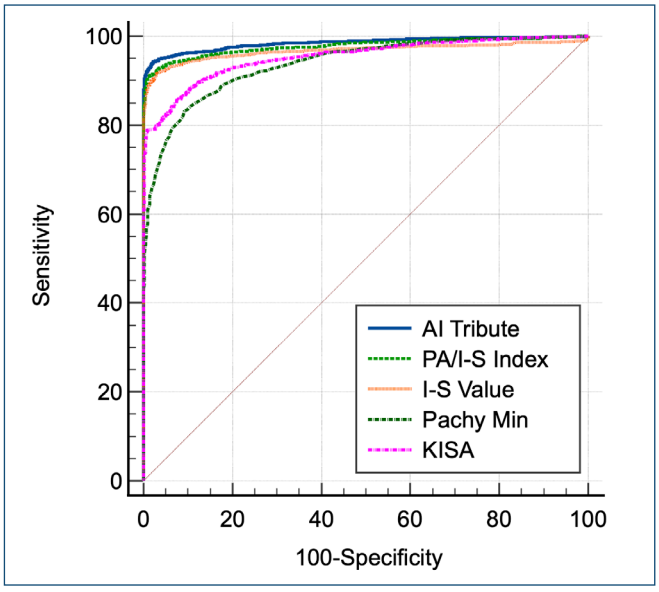
Performance of AI Tribute – normal versus VAE-NT

In the Normal *versus* VAE-NT scenario (n = 2,231; 551 VAE-NT and 1,680 normal), AI Tribute achieved an AUC of 0.791 (95%CI 0.774-0.808), with a sensitivity of 72.41% and a specificity of 70.83% at the optimal cutoff (> 0.249, Youden index = 0.4325). Despite the greater difficulty of this task – as VAE-NT eyes are topographically normal by definition – AI Tribute remained significantly superior to

Table 1. Comparison summary of Receiver Operating Characteristic curves: normal *versus* clinical ectasia (n = 3,335)

Variable	AUC	SE*	95%CI†	Cutoff	Sens. (%)	95%CI	Spec. (%)	95%CI
AI Tribute	0.985	0.00204	0.980-0.989	>0.655	94.32	93.1-95.4	97.74	96.9-98.4
PA/I-S index	0.978	0.00259	0.972-0.983	≤95.53	91.06	89.6-92.4	98.93	98.3-99.4
I-S value	0.968	0.00359	0.961-0.973	>1.06	91.66	90.2-92.9	96.85	95.9-97.6
KISA%	0.953	0.00357	0.945-0.960	>32.07	85.38	83.6-87.0	92.86	91.5-94.0
Pachy min	0.938	0.00398	0.929-0.946	≤509	83.08	81.2-84.9	90.71	89.2-92.1

Sample size: 3,335 eyes (positive group 1,655 (49.63%); negative group 1,680 (50.37%)). Area under the curve values from cross-validated model evaluation.
Cutoff at maximum Youden index.
Sensitivity and specificity reported at the Receiver Operating Characteristic cutoff point.
*DeLong et al.;[10] † binomial exact.
AUC: area under the curve; SE: standard error; 95%CI 95% of confidence interval; Sens.: sensitivity; Spec: specificity; AI: artificial intelligence; PA: pachymetry-adjusted; I-S: inferior-superior.



AI: artificial intelligence; PA: pachymetry-adjusted; I-S: inferior-superior.

Figure 1. Normal *versus* clinical ectasia

Table 2. Normal *versus* clinical ectasia. Pairwise comparison of Receiver Operating Characteristic curves. Artificial intelligence tribute analysis

Comparison	AUC difference	SE*	95%CI	z	p-value
AI Tribute ~ PA/I-S index	0.00712	0.00259	0.0020-0.0122	2.744	0.0061
AI Tribute ~ I-S value	0.01740	0.00274	0.0121-0.0228	6.372	< 0.0001
AI Tribute ~ pachy min	0.04690	0.00365	0.0397-0.0540	12.840	< 0.0001
AI Tribute ~ KISA%	0.03180	0.00365	0.0247-0.0390	8.732	< 0.0001
PA/I-S index ~ I-S value	0.01030	0.00296	0.0045-0.0161	3.483	0.0005
PA/I-S index ~ pachy min	0.03980	0.00446	0.0310-0.0485	8.914	< 0.0001
PA/I-S index ~ KISA%	0.02470	0.00369	0.0175-0.0320	6.694	< 0.0001
I-S value ~ pachy min	0.02940	0.00516	0.0193-0.0396	5.701	< 0.0001
I-S value ~ KISA%	0.01440	0.00442	0.0057-0.0231	3.261	0.0011
Pachy min ~ KISA%	0.01500	0.00489	0.0055-0.0246	3.075	0.0021

All pairwise comparisons were statistically significant (p < 0.05, DeLong's test). Area under the curve difference = difference between areas.
*DeLong et al., 1988.[10]
AUC: area under the curve; SE: standard error; 95%CI 95% of confidence interval; AI: artificial intelligence; PA: pachymetry-adjusted; I-S: inferior-superior.

all reference indices (Table 3, Figure 2). Compared with pachy min (AUC = 0.762), the difference was 0.0293 (p = 0.0002). Against the I-S value (AUC = 0.730), the difference was 0.0607 (p < 0.0001). Against the PA/I-S index (AUC = 0.688), the difference was 0.1040 (p < 0.0001). The largest gain was observed against KISA% (AUC = 0.633), with a difference of 0.1580 (p < 0.0001). The only non-significant pairwise comparison among reference indices was I-S value versus pachy min (p = 0.0609). All pairwise comparisons are detailed in table 4.

DISCUSSION

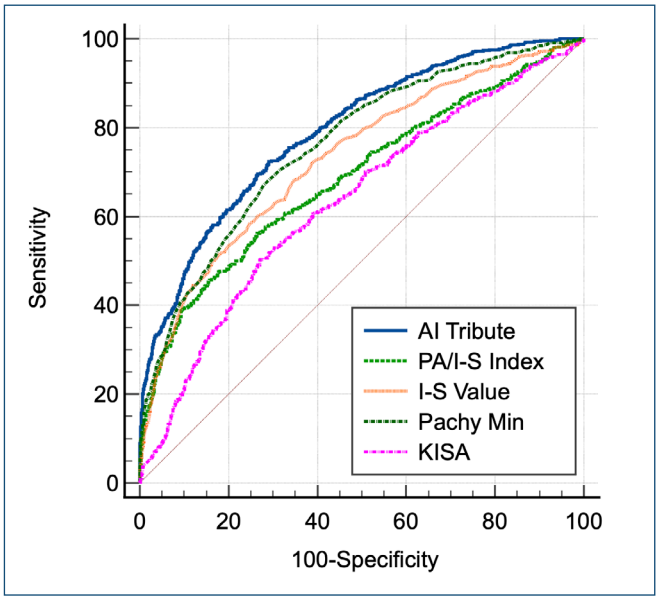
The present study was designed as a scientific tribute to Dr. Yaron Rabinowitz, one of the most influential scientists in the history of keratoconus research. Instead of merely citing his work, we aimed to honor it by demonstrating, through rigorous application of the A²I methodology, how his foundational ideas can be expanded and improved with machine learning while maintaining the scientific logic that originally motivated them.[2-4] The findings support this idea: AI Tribute, trained solely on Dr. Rabinowitz's core variables, achieved statistically significant improvements over all reference indices in both clinical evaluation scenarios – Normal vs. Clinical Ectasia and Normal vs. VAE-NT – showing the A²I approach's ability to extract latent discriminative information from established clinical knowledge.[5,9]

Feature selection was intentionally limited to Dr. Rabinowitz's conceptual domain – topographic asymmetry and minimum pachymetry – without adding biomechanical, elevation, or other tomographic data. This restriction was not a methodological flaw but a design

Table 3. Comparison summary of Receiver Operating Characteristic curves. Normal versus VAE-NT (n = 2,231)

Variable	AUC	SE*	95%CI†	Cutoff	Sens. (%)	95%CI	Spec. (%)	95%CI
AI Tribute	0.791	0.0111	0.774-0.808	>0.249	72.41	68.5-76.1	70.83	68.6-73.0
Pachy min	0.762	0.0118	0.744-0.779	≤529	66.97	62.9-70.9	72.20	70.0-74.3
I-S value	0.730	0.0128	0.712-0.749	>0.46	58.62	54.4-62.8	75.12	73.0-77.2
PA/I-S index	0.688	0.0139	0.668-0.707	≤157	45.74	41.5-50.0	84.23	82.4-85.9
KISA%	0.633	0.0139	0.613-0.653	>8.10	50.45	46.2-54.7	72.68	70.5-74.8

Sample size: 2,231 eyes (positive group 551 (24.70%); negative group 1,680 (75.30%)). Area under the curve values from cross-validated model evaluation.
Sensitivity and reported at the Receiver Operating Characteristic cutoff point. *DeLong et al.[10] † binomial exact.
AUC: area under the curve; SE: standard error; 95%CI 95% of confidence interval; Sens.: sensitivity; Spec.: specificity; AI: artificial intelligence; I-S: inferior-superior; PA: pachymetry-adjusted.



AI: artificial intelligence; PA: pachymetry-adjusted; I-S: inferior-superior.

Figure 2. Normal *versus* VAE-NT.

Table 4. Normal versus VAE-NT. Pairwise comparison of Receiver Operating Characteristic curves – artificial intelligence tribute analysis

Comparison	AUC difference	SE*	95%CI	z	p-value
AI Tribute ~ PA/I-S index	0.1040	0.0131	0.0779-0.1290	7.929	< 0.0001
AI Tribute ~ I-S value	0.0607	0.0105	0.0400-0.0813	5.754	< 0.0001
AI Tribute ~ pachy min	0.0293	0.0078	0.0139-0.0447	3.738	0.0002
AI Tribute ~ KISA%	0.1580	0.0170	0.1250-0.1910	9.316	< 0.0001
PA/I-S index ~ I-S value	0.0429	0.0110	0.0213-0.0645	3.893	0.0001
PA/I-S index ~ pachy min	0.0742	0.0166	0.0418-0.1070	4.481	< 0.0001
PA/I-S index ~ KISA%	0.0544	0.0181	0.0188-0.0899	2.997	0.0027
I-S value ~ pachy min	0.0313	0.0167	−0.0014-0.0641	1.874	0.0609
I-S value ~ KISA%	0.0973	0.0175	0.0630-0.1310	5.570	< 0.0001
Pachy min ~ KISA%	0.1290	0.0180	0.0933-0.1640	7.149	< 0.0001

All pairwise comparisons were statistically significant (p < 0.05, DeLong's test), except I-S value ~ pachy min (p = 0.0609). Area under the curve difference = difference between areas; SE = standard error; CI = confidence interval; z = z statistic; p = Significance level. *DeLong et al.[10]
AUC: area under the curve; AI: artificial intelligence; PA: pachymetry-adjusted; I-S: inferior-superior.

choice, aligned with the A²I paradigm, where domain principles direct computational exploration,[6] and was driven by a specific question: how much discriminative power can be obtained from Dr. Rabinowitz's own variables when modeled nonlinearly by machine learning algorithms?

In the Normal versus Clinical Ectasia scenario, all reference indices achieved high discriminative performance, reflecting the pronounced topographic and pachymetric differences that characterize manifest ectasia. Among them, PA/I-S index (AUC = 0.978) outperformed the I-S value (AUC = 0.968), KISA% (AUC = 0.953), and pachy min (AUC = 0.938), with all pairwise differences reaching statistical significance (p < 0.05). This ordering is clinically logical: the PA/I-S formulation, by normalizing topographic asymmetry for corneal thickness, provides a more comprehensive structural representation than the I-S value alone. Its advantage over KISA% suggests that adding SRAX and astigmatism offers limited additional discriminative value in a population where ectasia is already clinically evident.

AI Tribute achieved an AUC of 0.985 in the normal vs. clinical ectasia scenario, demonstrating statistically significant improvements over all reference indices, including a gain over the already high-performing PA/I-S index. Importantly, this improvement was not achieved by adding new clinical variables: the model was trained exclusively on pachy min and I-S value – the two core elements of the PA/I-S index – and its superiority over the PA/I-S index stems entirely from the ability of the MLP architecture to model nonlinear interactions between them. While the PA/I-S formula applies a fixed linear correction for corneal thickness, the neural network learns a flexible, data-driven mapping that adjusts the importance of each input based on the local data structure, extracting discriminative information that the original formula could not capture. This aligns with broader evidence that machine learning models consistently outperform hand-crafted linear indices for ectasia detection, even when limited to the same input features.[5,6,9] The final architecture – a single hidden layer with only three neurons – achieved near-ceiling discrimination with a simple structure, showing that complex design is not necessary for clinical usefulness, and that careful feature selection has a bigger impact than complex models.

The normal versus VAE-NT scenario shows a fundamentally different clinical challenge. VAE-NT eyes are, by definition, topographically normal or apparently normal – they do not show obvious anterior curvature changes – and their classification as ectatic depends on the bilateral asymmetry of their fellow eye, rather than on direct topographic findings of their own. In this context, all reference indices showed substantially reduced discriminative performance compared with the clinical ectasia scenario, and their relative ordering shifted in a clinically instructive way.

Pachy min (AUC = 0.762) emerged as the top-performing reference index, surpassing the I-S value (AUC = 0.730). Meanwhile, the PA/I-S index (AUC = 0.688) scored below both, and KISA% (AUC = 0.633) showed the worst performance. The reversal of the relationship between PA/I-S and I-S is particularly revealing: although the pachymetric correction in the PA/I-S formula enhances sensitivity for manifest ectasia by penalizing abnormally thin

corneas, it paradoxically decreases sensitivity in VAE-NT eyes, where corneal thickness may still be normal. In such cases, the correction reduces rather than accentuates the topographic signal. Conversely, the advantage of pachy min over the I-S value in the VAE-NT group – although not statistically significant (p = 0.0609) – reflects established evidence that subclinical structural compromise, even at the earliest stages, tends to involve pachymetric redistribution before overt curvature changes appear.[5,8,9] KISA%, which combines multiple topographic parameters including SRAX and astigmatism, performed the worst, suggesting that in the absence of clear anterior surface abnormalities, these composite scores increase noise rather than signal.

In the normal versus VAE-NT scenario, AI Tribute achieved an AUC of 0.791, maintaining statistically significant superiority over all reference indices, with gains over pachy min, I-S value, PA/I-S index, and KISA%. The performance difference between the two scenarios – AUC 0.985 versus 0.791 – is not due to a flaw in the model but reflects the inherent biological and epidemiological challenge of the task: detecting ectasia susceptibility in eyes that show no obvious topographic signs of disease is naturally more difficult than distinguishing normal corneas from those with clinically evident ectasia. Any index based solely on topographic and pachymetric parameters will face this limit. Notably, AI Tribute retained its relative advantage over the reference indices even in this more challenging context. This is due to the training approach: by exposing the model to the full VAE spectrum – including VAE-NT eyes in the positive class – the KDD framework ensured that the learned decision boundary was optimized for the subtle patterns associated with early ectasia susceptibility, rather than only for the pronounced deformations typical of active disease. Therefore, the model captured the clinical insight that ectasia exists on a spectrum and that the boundary between health and susceptibility provides more meaningful training targets than the boundary between health and established disease.

This study has certain limitations. Both the training and evaluation were conducted using the same institutional dataset; targeted external validation in independent, multicenter cohorts is essential to verify the model's generalizability across populations with different demographic profiles and disease prevalence. Additionally, the VAE-NT classification is a clinical construct based on bilateral topographic asymmetry of the fellow eye rather than on direct longitudinal confirmation of ectasia progression; prospective studies documenting the natural history of VAE-NT eyes would strengthen the validity of this label as a training and evaluation target. The training strategy – normal versus VAE (VAE-E + VAE-NT) – was intentionally designed to maximize sensitivity at the clinically relevant decision boundary between health and susceptibility to ectasia, including its topographically silent form; the two evaluation scenarios offer complementary insights into the model's performance across the ectasia severity spectrum. Future research should focus on incorporating these models with biomechanical indices and the biomechanical impact of laser vision correction surgery on the cornea,[11] which provides a complementary perspective on ectasia susceptibility not captured by topographic or pachymetric variables alone, and integrating them into clinical decision-support tools to promote practical application.

CONCLUSION

The integration of the A²I methodology with Dr. Yaron Rabinowitz's scientific contributions showed that his fundamental indices for keratoconus detection can be improved through machine learning modeling. AI Tribute, trained exclusively on the constitutive elements of the pachymetry-adjusted/inferior-superior index – minimum pachymetry and inferior-superior value – and evaluated in two clinically distinct scenarios, achieved statistically superior discriminative performance over all reference indices in both comparisons. In the Normal versus Clinical Ectasia scenario, it reached an AUC of 0.985 with high sensitivity (94.32%) and specificity (97.74%) at the optimal cutoff. In the more challenging Normal versus videokeratography-asymmetric ectasia with normal topography scenario – where the model was applied to topographically normal fellow eyes of patients with ectatic disease – it achieved an AUC of 0.791, maintaining statistically significant superiority over the inferior-superior value, the pachymetry-adjusted/inferior-superior index, KISA%, and pachy min. These results highlight the potential of Applied Artificial Intelligence to enhance rather than replace established clinical knowledge and to respect the importance of Dr. Rabinowitz's contributions to the field of corneal ectasia screening.

AUTHORS' CONTRIBUTION

Aydano Machado contributed to the conception, design, and development of the study, as well as to the analysis, interpretation of data, and results. Renato Ambrósio Jr contributed to the study's conception, design, and dataset, as

well as to the analysis, interpretation of data, and results. All authors contributed to the writing and critical review of the manuscript's content. All authors approved the final version of the manuscript and are responsible for all aspects of the manuscript, including ensuring its accuracy and integrity.

ACKNOWLEDGMENT

The authors express profound gratitude to Dr. Yaron Rabinowitz for his extraordinary scientific contributions to the field of keratoconus research and refractive surgery screening.

REFERENCES

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42(4):4:297-319.
2. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. J Cataract Refract Surg. 1999 t;25(10):1327–35.
3. Rabinowitz YS, Garbus J, McDonnell PJ. Computer-assisted corneal topography in family members of patients with keratoconus. Arch Ophthalmol. 1990 r;108(3):365–71.
4. Rabinowitz YS, Li X, Canedo AL, Ambrósio R Jr, Bykhovskaya Y. Optical coherence tomography combined with videokeratography to differentiate mild keratoconus subtypes. J Refract Surg. 2014;30(2):80–7.
5. Ambrósio R Jr, Machado AP, Leão E, Lyra JM, Salomão MQ, Esporcatte LG, et al. Optimized artificial intelligence for enhanced ectasia detection using scheimpflug-based corneal tomography and biomechanical data. Am J Ophthalmol. 2023;251:126–42.
6. Esporcatte LP, Salomão MQ, Machado AP, Ambrósio R Jr. The power of predictive artificial intelligence for the detection of ectasia. Expert Rev Ophthalmol. 2025;20(6):387–400.
7. Fayyad U, Piatetsky-Shapiro G, Smyth P. From Data Mining to Knowledge Discovery in Databases. AI Mag. 1996;17(3):3.
8. Ambrósio R Jr, Lopes BT, Faria-Correia F, Salomão MQ, Bühren J, Roberts CJ, et al. Integration of Scheimpflug-Based corneal tomography and biomechanical assessments for enhancing ectasia detection. J Refract Surg. 2017;33(7):434–43.
9. Lopes BT, Ramos IC, Salomão MQ, Guerra FP, Schallhorn SC, Schallhorn JM, et al. Enhanced Tomographic Assessment to Detect Corneal Ectasia Based on Artificial Intelligence. Am J Ophthalmol. 2018;195:223–32.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45.
11. Machado AP, Esporcatte LP, Salomão MQ, Lopes BT, Lyra JM, Ambrósio R Jr. Development and Validation of the Relational Tissue Altered (RTA) Index: applied artificial intelligence for the assessment of structural impact from laser vision correction. Ophthalmol Ther. 2025 ;14(9):2215–29.