

## RESEARCH

# Use of Artificial Intelligence (AI) as a Diagnostic Modality for Keratoconus: A Comprehensive Meta-Analysis

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## Abstract

**Introduction:** Keratoconus is a degenerative corneal disorder leading to vision impairment. It is important to detect it early to prevent its progression by corneal cross-linking (CXL). Keratoconus is diagnosed using videokeratography and Scheimpflug tomography, which provide valuable data on the corneal surface. However, distinguishing keratoconus from normal variations remains challenging. Recent advances in artificial intelligence (AI) offer promising improvements in detecting subtle corneal changes, enhancing keratoconus detection and diagnosis. **Purpose:** To analyze AI as a diagnostic modality for keratoconus by calculating the pooled sensitivity and specificity to evaluate its accuracy. **Methods:** Databases involved PubMed, Scopus, Google Scholar, Embase, and Science Direct, from 2018 to March 2024. Also, to include unpublished works, the grey literature was searched, using the OpenGrey repository. Studies were included when they met the inclusion criteria. **Results:** We involved a total of 19 studies in this meta-analysis. The pooled sensitivity for detecting keratoconus was 95% confidence interval (CI) (91% to 98%), with a pooled specificity of 98% CI (96% to 99%). Additionally, the random forest model had a pooled sensitivity of 98.11% (CI, 96.77% to 99.44%), with a pooled specificity of 99% (CI, 98.24% to 99.76%). On the other hand, the convolutional neural network (CNN) model had a pooled sensitivity of 89.73% CI (79.77% to 99.69%), with a pooled specificity of 95.27% CI (91.88% to 98.66%). **Conclusion:** The results confirmed the reliability of different AI models in diagnosing keratoconus, especially the random forest model. This is important, as the early and accurate detection of keratoconus provides opportunities to reduce risk factors and offer treatments, including CXL, which can potentially slow its progression and improve the patient's quality of life.

**Keywords:** keratoconus; diagnosis; early detection; artificial intelligence (AI); machine learning; meta-analysis

## Introduction

Keratoconus is a degenerative disorder characterized by progressive corneal thinning, myopia, irregular astigmatism, and scarring, which can significantly impact a patient's quality of life.<sup>[1]</sup> Early and accurate detection of keratoconus is crucial for mitigating risk factors and providing treatments that slow its progression.<sup>[1]</sup> Also, the detection of early keratoconus has become more important due to the availability of corneal cross-linking (CXL).<sup>[2]</sup> It is challenging to detect it early due to minor initial changes that may be overlooked during routine clinical exams.<sup>[1]</sup> Videokeratography and Scheimpflug tomography are standard methods that provide valuable data on the anterior and posterior corneal surfaces. However, detecting keratoconus from normal eyes is difficult based on this data alone.<sup>[3]</sup> Machine learning (ML) and artificial intelligence (AI) have provided new opportunities for the early detection of keratoconus.

AI models, deep learning (DL) algorithms like convolutional neural networks (CNNs), can process complex corneal tomography and topography data.<sup>[1]</sup> These models have been used to improve the diagnosis and management of keratoconus.<sup>[4]</sup> Due to the challenges in diagnosing keratoconus, scholars have

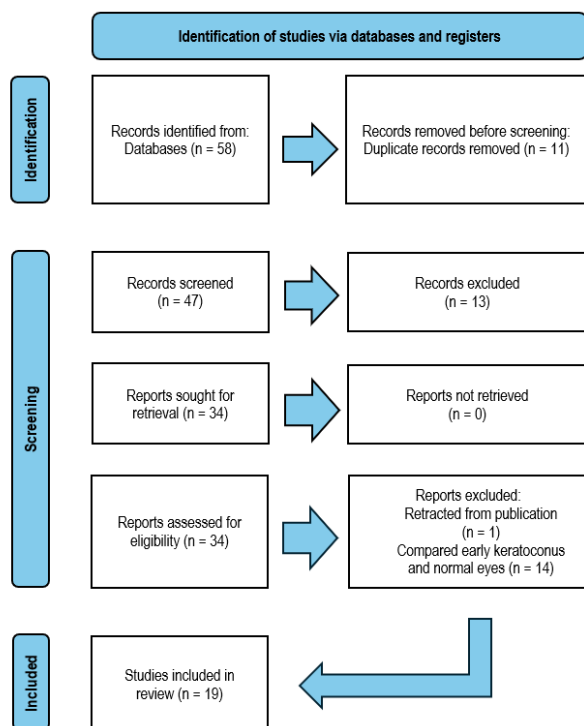


Figure 1. PRISMA 2020 flow diagram.

utilized AI to aid in disease diagnosis. A recent systematic review provided a significant report on keratoconus classification and the accuracy of machine learning algorithms in detecting keratoconus.<sup>[4]</sup> Also, many studies<sup>[1],[5],[6]</sup> have analyzed the accuracy of different AI models in detecting keratoconus in terms of sensitivity and specificity, including the random forest, the CNN, and other models. They found different AI models to have high sensitivity and specificity in diagnosing keratoconus.<sup>[1],[5],[6]</sup> These studies employed various imaging modalities to capture corneal parameters, with the Pentacam HR (Oculus Optikgeräte, Wetzlar, Germany) being the most commonly used imaging modality.<sup>[1],[5],[6]</sup> However, most studies discussed the performance of single AI models, while some conducted a meta-analysis of a small sample. To our knowledge, no study has compared two AI models with the same imaging modality in the diagnosis of keratoconus. Unlike previous studies<sup>[4]</sup>, which focused primarily on neural networks and naive Bayes models, our meta-analysis incorporates a broader range of AI models, directly compares their diagnostic accuracy using the same imaging modality and provides a comprehensive pooled sensitivity and specificity analysis to enhance the reliability of AI-based keratoconus detection. In this study, we aimed to conduct a meta-analysis of a large sample on the performance of different AI models in terms of sensitivity and specificity in diagnosing keratoconus. Additionally, we directly compared the two most common AI models: the Random Forest and the CNN. Other models were included in the combined meta-analysis.

## Methods

### Literature search strategy

A systematic search of databases, including PubMed, Scopus, Web of Science, Google Scholar, Embase, and ScienceDirect, was conducted from inception to 2024. Additionally, to incorporate unpublished works, a search was conducted within the grey literature using the OpenGrey repository. We followed the 2020 Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) guidelines. The search strategy used was a combination of search terms: (“Artificial Intelligence” OR “Machine Learning”) AND “Keratoconus” AND (“Diagnostic Accuracy” OR “Sensitivity” OR “Specificity”).

### Inclusion and exclusion criteria

A total of 58 studies were identified from the databases (Figure 1), eleven of which were duplicate studies and were excluded.<sup>[2],[7],[8],[9],[10],[11],[12],[13],[14]</sup> Two independent researchers screened the titles and abstracts of the 47 studies, 13 of which were excluded, as they did not use AI models.<sup>[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27]</sup> Thirty-four studies were assessed for eligibility. The inclusion criteria were: 1) studies utilizing AI for keratoconus diagnosis across various platforms, including published articles in scholarly journals and significant grey literature, like technical reports and dissertations; 2) studies employing diverse AI models; and 3) studies incorporating novel imaging techniques. Systematic reviews, reply articles, and studies with insufficient data were excluded. Seven studies<sup>[4],[28],[29],[30],[31],[32],[33]</sup> were excluded because they did not meet the inclusion criteria. From the remaining 27 studies, eight studies<sup>[8],[9],[11],[12],[23],[34],[35],[36]</sup> compared normal and early keratoconus eyes, so they were excluded, whereas 19 studies compared normal and keratoconus eyes, and were included in the meta-analysis<sup>[1],[2],[6],[7],[13],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48]</sup>, these involved retrospective experimental studies.

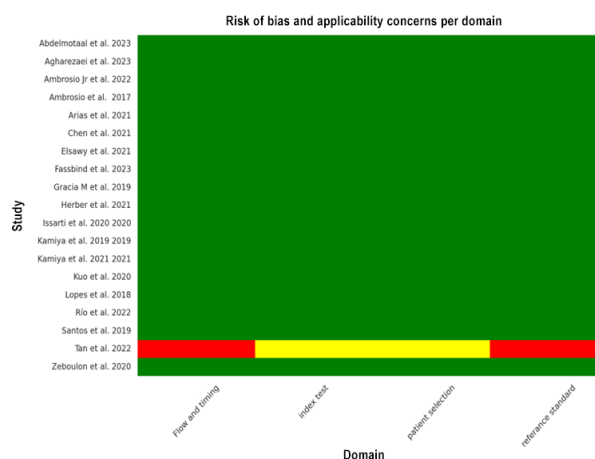


Figure 2. Risk of bias and applicability concerns per domain plot (Green = Low risk; Yellow = Unclear risk, and Red = High risk).

**Table 1.** Studies utilizing machine learning models to detect keratoconus (number of centers, AI model, and imaging modality used).

Authors	Number of eyes	Number of centers involved (country)	AI model used	Imaging modality or parameters
Chen et al. <sup>[1]</sup>	279	3 (UK, Iran, New Zealand)	Convolutional neural network	Pentacam HR
Kamiya et al. (2019) <sup>[36]</sup>	543	1 (Japan)	Convolutional neural network	Pentacam HR
Kamiya et al. (2021) <sup>[37]</sup>	220	1 (Japan)	Deep learning	Placido disk corneal topographer
Ambrósio et al. (2017) <sup>[2]</sup>	2861	25 (Brazil)	Random Forest	Pentacam HR and Corvis ST
Zéboulon et al. <sup>[42]</sup>	2000	1 (France)	Convolutional neural network	Pentacam HR
Lopes et al. <sup>[41]</sup>	3460	15 (UK, Brazil, Italy, USA)	Random Forest	Pentacam HR
Elsawy et al. <sup>[43]</sup>	236	1 (USA)	Deep learning	AS-OCT
del Río et al. <sup>[44]</sup>	475	1 (Mexico)	Random Forest	Pentacam HR
Bustamante-Arias et al. <sup>[48]</sup>	93	1 (Switzerland)	Support Vector Machine	SD- OCT
Tan et al. <sup>[12]</sup>	354	1 (China)	Feed Forward Neural Network	Pentacam HR and Corvis ST
Ambrósio et al. (2023) <sup>[7]</sup>	684	2 (Brazil, Italy)	Random Forest	Pentacam HR and Corvis ST
Santos et al. <sup>[5]</sup>	142	1 (Austria)	CorneaNet	AS-OCT
Kuo et al. <sup>[6]</sup>	326	1 (Taiwan)	Convolutional neural network	Pentacam HR
Abdelmotaal et al. <sup>[13]</sup>	734	2 (Brazil, Iran)	Convolutional neural network	Pentacam HR and Corvis ST
Agharezaei et al. <sup>[39]</sup>	1758	1 (Iran)	Convolutional neural network	Pentacam HR
Fassbind et al. <sup>[38]</sup>	1009	1 (Germany)	Convolutional neural network	AS-OCT
Issarti et al. (2020) <sup>[45]</sup>	503	2 (Belgium)	Feed Forward Neural Network	Pentacam HR
Castro-Luna et al. <sup>[47]</sup>	60	1 (Spain)	naïve Bayes	CSO topography system
Herber et al. <sup>[46]</sup>	220	1 (Germany)	Linear Discriminant Analysis	Pentacam HR and Corvis ST

### Study selection and data extraction

The systematic review followed the PRISMA guidelines. Two independent reviewers (Bulbanat and Buabbas), screened the titles and abstracts of all identified studies from the literature search. Studies were selected based on the following inclusion criteria: 1) use of AI for keratoconus diagnosis; 2) published between 2018 and 2024; and 3) including metrics like sensitivity and specificity for diagnostic accuracy. Exclusion criteria included review articles, studies with insufficient data, and those that did not employ AI models. Full-text articles were then assessed for eligibility, and any disagreements between reviewers were resolved through discussion with a third reviewer (Aljassar). Data extraction was performed by Alqabandi and Alzalalah, who independently extracted the sensitivity, specificity, confidence intervals (CIs), the AI model used, the imaging parameter used, the number of centers involved, and the number of eyes. The extracted data were cross-verified for accuracy by Buabbas to ensure consistency across the dataset.

### Data and reference management

All data and references from the systematic review were maintained and organized using EndNote (version X9, Clarivate Analytics). EndNote was used to manage citations, remove duplicate records, and track the references throughout the study selection process. The initial search results from databases such as PubMed, Scopus, and Google Scholar were imported into EndNote,

where duplicate entries were identified and excluded before screening. For study selection, Covidence was used to screen abstracts and full texts, maintaining a clear audit trail of the decisions made. After the inclusion and exclusion criteria were applied, Covidence was used to track which studies were included or excluded at each stage of the process. Data from the selected studies were maintained using Microsoft Excel for ease of access and organization.

### Quality assessment

The quality of the evidence in the articles that met the inclusion criteria was then assessed using Cochrane's recommendations for risk of bias and level of evidence (Figure 2). The quality of the included studies was assessed using the Quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool, a standardized method for evaluating the risk of bias and applicability concerns in diagnostic accuracy studies. Each study was independently reviewed across four key domains: patient selection, index test, reference standard, and flow and timing. For each domain, the risk of bias was classified as low, high, or unclear based on predefined criteria. Applicability concerns were also assessed for patient selection, index test, and reference standard to ensure the findings were relevant to real-world clinical practice. Discrepancies in assessments were resolved through discussion among reviewers, ensuring a robust and objective evaluation of study quality.

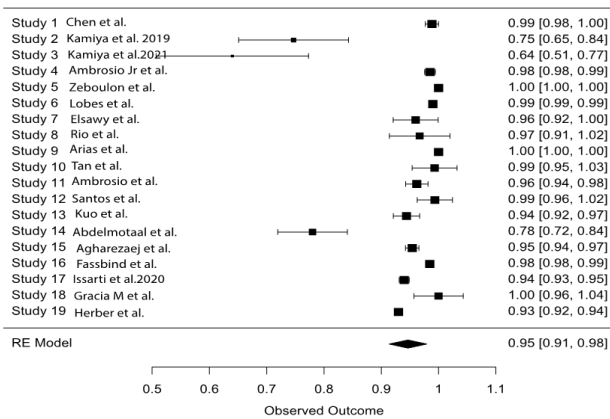


Figure 3. Forest plot sensitivity for all 19 studies 95% (91% to 98%).

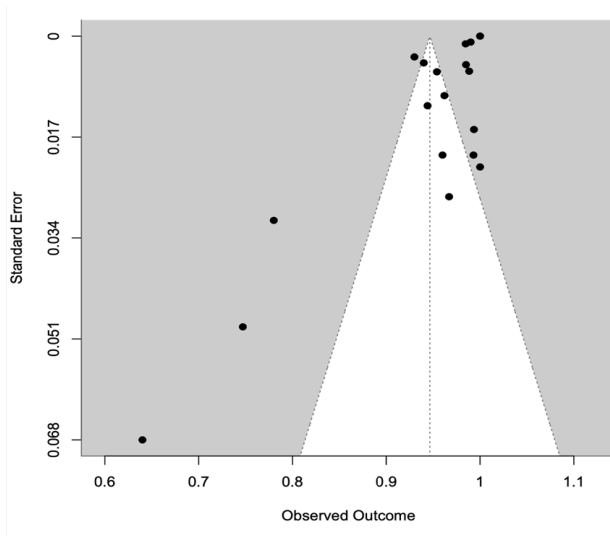


Figure 4. Funnel plot sensitivity for all 19 studies.

### Multiple imputation

Nine studies<sup>[7],[13],[36],[37],[38],[42],[43],[44],[45]</sup> featuring the normal and keratoconus comparison had all the data needed to calculate the CI for the sensitivity and specificity of the AI models to detect keratoconus and their standard errors. However, ten studies<sup>[1],[2],[5],[6],[39],[40],[41],[46],[47],[48]</sup> had only the sensitivity and specificity without their CIs and standard errors, so a multiple imputation technique was used to estimate these missing values based on the available data from the nine studies. This multiple imputation was performed using R statistical software, and the standard errors of both sensitivity and specificity, along with their 95% CIs, were calculated for the ten studies.

### Statistical analyses

All analyses were configured using the 'metafor' package from the R statistical software for Mac. To measure the overall machine learning performance for keratoconus detection, the sensitivity and specificity values for all AI models were pooled. A subgroup analysis was conducted for the Random Forest and CNN models by pooling the sensitivity and specificity values of the studies that utilized each model separately.

## Results

### Study characteristics

The studies were conducted in various countries using different imaging modalities and AI models (Table 1). A meta-analysis of all 19 studies<sup>[1],[2],[5],[6],[7],[12],[13],[36],[37],[38],[39],[41],[42],[43],[44],[45],[46],[47],[48]</sup> was conducted with heterogeneity, forest plots, and funnel plots to assess publication bias. A sensitivity analysis was then conducted by performing the meta-analysis on only the nine studies that had all the data without the imputation technique.<sup>[1],[2],[5],[6],[39],[40],[41],[46],[47],[48]</sup> The two meta-analyses were then compared to complete the sensitivity analysis.

### Meta-analysis for 19 studies

After conducting the meta-analysis for the 19 studies, the pooled sensitivity estimate was 94.65% with a 95% CI (91.35% to 97.95%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0050$  and  $\tau = 0.0705$  (Figure 3). The pooled specificity for all 19 studies is presented in Figure 4.

After conducting the meta-analysis for the 19 studies, the pooled specificity estimate was 97.55% with a 95% CI (96.23% to 98.78%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0006$  and  $\tau = 0.0250$  (Figure 5).

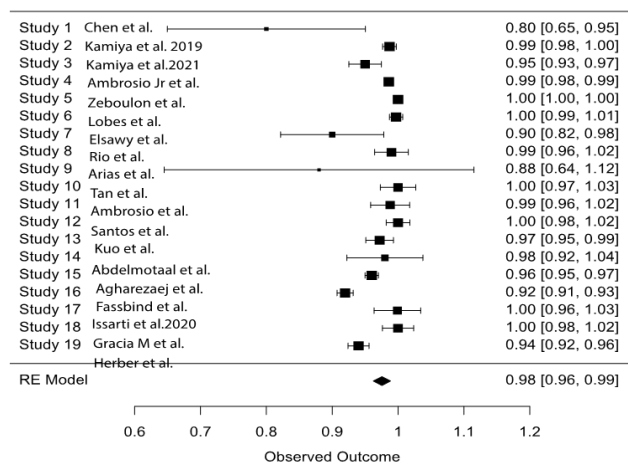


Figure 5. Forest plot specificity for all 19 studies 98% (96% to 99%).

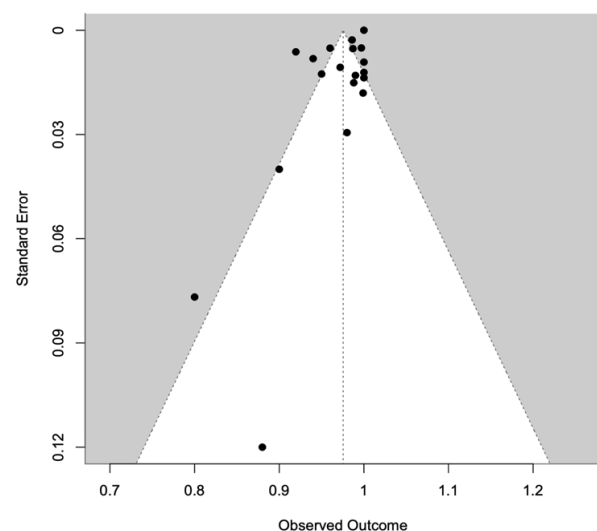
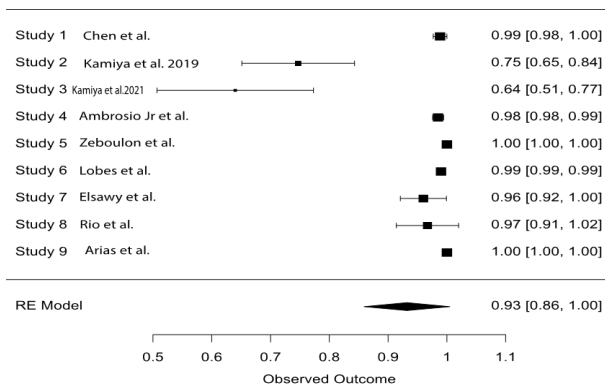
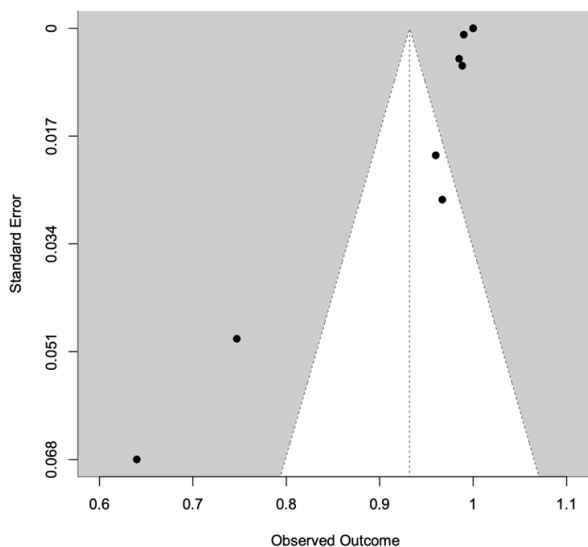


Figure 6. Funnel plot specificity for all 19 studies.





**Figure 7.** Forest plot sensitivity for nine studies without imputed data 93% (86% to 100%).



**Figure 8.** Funnel plot sensitivity for nine studies without imputed data.

#### Meta-analysis for nine studies

After conducting the meta-analysis for the pooled sensitivity of the nine studies without the imputed data, the pooled sensitivity estimate was 93.20% with a 95% CI (85.90% to 100%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0117$  and  $\tau = 0.1083$  (Figure 7). The pooled specificity for the nine studies without imputed data is shown in Figure 8.

After conducting the meta-analysis for the pooled specificity of the nine studies without the imputed data, the pooled specificity estimate was 98.28% with a 95% CI (96.91% to 99.66%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0003$  and  $\tau = 0.0160$  (Figure 9).

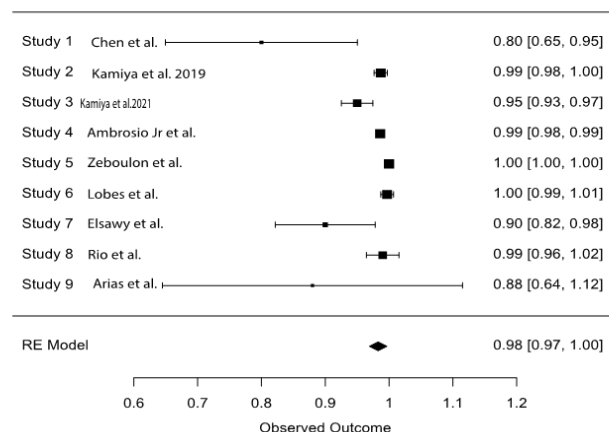
#### Subgroup analysis

Subgroup analysis was conducted, and a meta-analysis was performed for sensitivity and specificity using five studies that utilized the CNN AI model. [1],[36],[38],[39],[40] The pooled sensitivity estimate was 89.73% with a 95% CI (79.77% to 99.69%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0123$  and  $\tau = 0.1109$ . The pooled specificity estimate was 95.27% with the 95% CI (91.88% to 98.66%), with  $p < 0.0001$ . The

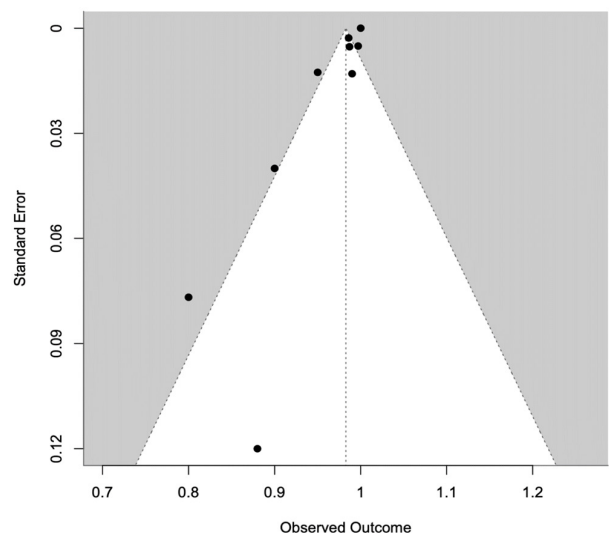
measure of heterogeneity was  $\tau^2 = 0.0011$  and  $\tau = 0.0329$ . A meta-analysis was conducted for the sensitivity and specificity of four studies [2],[6],[41],[44] that utilized the random forest AI model. The pooled sensitivity estimate was 98.11% with a 95% CI (96.77% to 99.44%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0001$  and  $\tau = 0.0107$ . The pooled specificity estimate was 99% with a 95% CI (98.24% to 99.76%), with  $p < 0.0001$ . The measure of heterogeneity was  $\tau^2 = 0.0000$  and  $\tau = 0.0045$ . The subgroup analysis comparing CNN and Random Forest models is summarized in Figure 10.

## Discussion

This study confirmed the reliability of various AI models in the early diagnosis of keratoconus, with high sensitivity and specificity across the 19 studies. In terms of the sensitivity analysis, the pooled sensitivity and specificity were slightly higher when all 19 studies were included, compared to the meta-analysis that included only the nine studies. However, the CIs overlapped, suggesting that the imputed data did not significantly change the overall estimates. Heterogeneity slightly increased for sensitivity when all 19 studies were



**Figure 9.** Forest plot specificity for 9 studies without imputed data 98% (97% to 100%).



**Figure 10.** Funnel plot sensitivity for nine studies without imputed data.

included, as indicated by a higher  $\tau^2$  value. For specificity, the heterogeneity slightly decreased. This suggests that the imputed data may have introduced some variability into the sensitivity estimates but not into the specificity estimates. The funnel plots do not provide a clear indication of publication bias, but the presence of asymmetry suggests it cannot be ruled out. It is essential to note that while the inclusion of imputed data did not significantly alter the pooled estimates, it did affect the heterogeneity for sensitivity, suggesting that the imputed data may have contributed to some differences in the variability of the studies' outcomes. Therefore, the sensitivity analysis suggests that the results of the meta-analysis with all 19 studies are consistent with those of the meta-analysis with only the nine original studies, within the bounds of statistical variability and potential publication bias. In addition, it was found the random forest model with the Pentacam HR imaging parameter had a higher sensitivity and specificity from a meta-analysis of four studies<sup>[2],[7],[42],[45]</sup> than the CNN model with the Pentacam HR imaging parameter, according to a meta-analysis of five studies<sup>[1],[37],[39],[40],[41]</sup>. This study expands the existing literature on AI's diagnostic capabilities for keratoconus by conducting a comprehensive analysis of various AI models across a significantly larger sample than prior studies, incorporating 19 high-quality studies assessed using the QUADAS-2 tool. Many previous studies<sup>[4],[9],[33]</sup> used different imaging techniques, which could affect the results. By standardizing the imaging modality (Pentacam HR) in our subgroup analyses, we were able to reduce variability and ensure that differences in performance were due to the AI models rather than the imaging method. Through a meticulous methodology, including multiple imputations and subgroup analyses for five CNN studies and four random forest studies, we managed to provide a direct comparison of the sensitivity and specificity of the two most common AI models in our study. However, caution should still be exercised when attempting to generalize the results to patients of different populations. This could be addressed by conducting a further subgroup analysis for each country or population, which could be an area of future research. This was challenging in our case due to the limited number of studies meeting our inclusion criteria.

#### Contextualization within existing literature

This study showcases a detailed comparison between Random Forest and CNN models in diagnosing keratoconus, highlighting the superior performance of the Random Forest model. This finding is particularly noteworthy when juxtaposed with the findings of Chen et al.<sup>[1]</sup> and Ambrósio et al.<sup>[2]</sup>, which also explored the utility of CNN model and the Random Forest model in keratoconus detection respectively but did not provide a direct comparison between these two models. This

study utilized the Pentacam HR as a common imaging modality for subgroup analysis. The consistency in imaging modalities, as observed by Kamiya et al.<sup>[38]</sup>, facilitates a more reliable comparison across studies and highlights the potential for standardizing diagnostic practices in keratoconus. This study benefits from a large sample size of 19 studies for different AI models, which enhances the reliability of the findings when compared to another meta-analysis in the literature.<sup>[4]</sup> The other meta-analysis conducted found that neural networks and naive Bayes showed the highest accuracy among AI models in diagnosing keratoconus, with a sensitivity of 100%, while random forests had a sensitivity of over 90%. However, their sample consisted of three studies for neural networks, two studies for random forests, and one study for naive Bayes, which was smaller than the sample size of five studies for CNNs and four studies for random forests in this study, and they included studies utilizing different imaging parameters for the different AI models, which would have affected the performance.<sup>[4]</sup>

#### Limitations

Some limitations were reported in this study, which are: 1) Some data were imputed in the meta-analysis on the 19 studies, but this was partly adjusted for by conducting a meta-analysis for the nine studies without imputed data is shown in Figure 6, the pooled sensitivity and specificity of these meta-analyses were compared, and no significant differences were found; 2) Some publication bias was noted, which is related to the sensitivity and specificity of the two meta-analyses; and 3) the different imaging techniques conducted by some of the studies and the different populations and countries involved, which could have contributed to the heterogeneity. This was adjusted for in the subgroup analyses of the CNN and random forest models by including studies utilizing the Pentacam HR imaging parameter. Despite some heterogeneity and publication bias, the findings support the effectiveness of AI, underscoring its potential to revolutionize keratoconus diagnosis and treatment.

#### Approach for future studies

Future research is suggested to focus on refining AI models and imaging techniques within more uniform populations to mitigate heterogeneity and improve the generalizability of findings, thereby enhancing diagnostic accuracy.

#### Conclusions

This study confirmed the reliability of various AI models in terms of sensitivity and specificity in diagnosing keratoconus, particularly the random forest model. This is important, as the early and accurate detection of keratoconus provides opportunities to reduce risk factors

and offer treatments, including CXL, to potentially slow its progression, thereby improving the patient's quality of life.

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