Artificial intelligence in cornea and ocular surface diseases

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Abstract:

In modern ophthalmology, the advent of artificial intelligence (AI) is gradually showing promising results. The application of complex algorithms to machine and deep learning has the potential to improve the diagnosis of various corneal and ocular surface diseases, customize the treatment, and enhance patient outcomes. Moreover, the use of AI can ameliorate the efficiency of the health-care system by providing more accurate results, reducing the workload of ophthalmologists, allowing the analysis of a big amount of data, and reducing the time and resources required for manual image acquisition and analysis. In this article, we reviewed the most important and recently published applications of AI in the field of cornea and ocular surface diseases, with a particular focus on keratoconus, infectious keratitis, corneal transplants, and the use of *in vivo* confocal microscopy.

Keywords:

Artificial intelligence, cornea, dry eye disease, keratoconus, ocular surface

Introduction

With the improvement in computational power and the development of learning algorithms, big data, and accessible deep neural networks, the use of artificial intelligence (AI) in health care has become a promising reality.[1-5]

There has been a recent increase in AI research on the imaging of diseases affecting the anterior segment of the eye.[1,6,7] In addition, the integration of AI technology and telemedicine is becoming a potential solution to address health-care resource limitations.[8,9]

In this article, we provide an overview of AI applications in cornea and ocular surface diseases, important clinical considerations for adoption, potential integration with telemedicine, as well as future directions.

Fields of Applications

Big data and image-based analysis have been the main areas of focus for the majority of AI research in ophthalmology to date. Similar trends have been seen in corneal AI research, where the focus has shifted from basic science to clinical applications, including slit-lamp photography, corneal topography/tomography, anterior-segment optical coherence tomography (AS-OCT), specular microscopy, and *in vivo* confocal microscopy (IVCM). Herein, we review AI applications in the field of cornea using these corneal imaging modalities, focusing on keratoconus (KC) detection, infectious keratitis (IK) diagnosis, and corneal graft complication prediction, among others.

Keratoconus

KC is a progressive and bilateral corneal condition that causes myopia, irregular astigmatism, and eventually visual impairment. The prevalence rate is estimated to be between 1 in 500 and 1 in 2000 people.[10] Early detection of KC is important as treatment options, such as corneal cross-linking, can help preserve good vision if the condition is diagnosed promptly.[10] However, it is still challenging for clinicians to early identify patients with mild or subclinical forms of corneal ectasia.[11]

Diagnosis and assessment of KC patients usually rely on different imaging techniques such as corneal topography with Placido disc systems, like Orbscan, three-dimensional tomographic reconstruction with Placido-Scheimpflug systems, like Pentacam, and AS-OCT.

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In a retrospective study on 851 subjects, Issarti *et al*.[12] used a computer-aided diagnosis system to differentiate between patients with normal eyes and suspected and clinically diagnosed KC. Their mathematical algorithm showed an accuracy of 96.56% in subjects with suspect KC and 99.50% in patients with mild-to-moderate KC.

An interesting application of AI in KC is represented by the use of deep learning (DL) with convolutional neural network (CNN) models. Kuo *et al*.[13] found an overall sensitivity and specificity of their DL models over 90% to identify patients with KC, with one model reaching a specificity of 97%. In another prospective study, a neural network called CorneaNet was designed and trained to assess AS-OCT corneal layer in normal and KC patients.[14] The algorithm measured the epithelium, Bowman's layer, and stroma thickness correctly identifying KC subjects with an accuracy ranging between 99.4% and 99.6%. Another example of CNN model application in KC is represented by KeratoDetect.[15] This machine learning (ML) algorithm was trained using 1500 healthy eye topographies and 1500 KC eye topographies. The system showed an accuracy of 99.3% in identifying keratoconus-related ectasia on a test set of 200 eyes. Further, Kamiya *et al*.[16] used DL with six color-coded maps obtained from AS-OCT to discriminate between normal and ectatic corneas in KC patients, as well as to stage the disease, with an accuracy ranging from 97.6% to 99.3%.

In 2017, Ruiz Hidalgo *et al*.[17] validated a support vector machine (SVM) algorithm called Keratoconus Assistant to detect patients with early forms of KC. The system reached a good agreement with corneal specialists in identifying subjects with suspect of subclinical keratoconus-related ectasias. Finally, many studies have demonstrated the utility of automated decision tree classification in detecting fruste KC.[18-20]

Dry Eye Disease

Dry eye disease is an ocular surface disorder affecting between 6% and 34% of the adult population.[21] The most common form is represented by meibomian gland disease (MGD), a condition in which alterations of meibomian gland anatomy or function lead to ocular surface impairment, eyelid inflammation, and evaporative dry eye. In the attempt to improve the assessment and management of MGD, some authors have used ML to segment the gland atrophy or to evaluate the quantity of the tears by measuring the meniscus tear film thickness.[22,23] Saha *et al*.[24] used a fully automated DL system to assess various quantitative parameters of the meibomian gland morphology. Their method achieved an accuracy higher than MGD experts for the meiboscore classification. Fineide *et al*.[25] tested different AI systems to evaluate the tear breakup time (TBUT) in patients with dry eyes. Their results show that the DL algorithms can not only correctly identify subsets with reduced TBUT but can also assess the risk factors to predict tear film instability. In a prospective study, Pellegrini *et al*.[26] used a new algorithm to analyze slit-lamp photos of the corneal staining of patients with Sjogren syndrome (SS) and ocular graft-versus-host disease (GVHD). The digital image analysis technique showed a good correlation with experts' scores of the staining pattern, as well as good specificity and sensibility to differentiate between SS and GVHD patients.

Refractive Surgery

AI is being utilized to screen individuals who are at a high risk of developing progressive Postlaser *in situ* keratomileusis ectasia (PLE) and visual disability. Detecting high-risk eyes for iatrogenic ectasia remains a challenge during preoperative screening because of the minimal changes in the cornea's surface and thickness. Lopes *et al*. tested an ML technique using preoperative Pentacam data and achieved 94.2% sensitivity and 98.8% specificity with the Pentacam Random Forest Index.[27] This result outperformed the Belin-Ambrosio display which had only 55.3% correct classification of PLE eyes. Further, Saad and Gatinel[28] used a linear discriminant model with the Orbscan to detect PLE with 93% sensitivity and 92% specificity. Yoo *et al*.[29] created an ML model using preoperative data from 10561 eyes to predict the suitability of refractive surgery with 93.4% accuracy and an area under the curve (AUC) of 0.97 in external validation. Cui *et al*.[30] utilized a multilayer perceptron algorithm to enhance the accuracy of nomogram models for SMILE outcomes. The model was equal in safety and predictability but more effective compared to the surgeon group. However, the model was less predictable for eyes with high myopia and astigmatism.

Infectious Keratitis

IK represents the fourth leading cause of corneal blindness with an estimated incidence ranging between 11 and 40 cases/100,000 person-years in developed countries.[31] Untreated corneal infections may result in severe complications such as corneal perforation, endophthalmitis, and vision loss. The gold standard to identify the cause of the infection is corneal scraping, but studies show that its positivity rate can range between 30% and 80%.[32] In this scenario, the AI can help clinicians identify the microorganism, choose the treatment, and assess the improvement at follow-up. Saini *et al*.[33] trained an artificial neural network (ANN) to classify corneal ulcers in fungal and bacterial. The system scored much better than expert clinicians (90% vs. 62.8% of accuracy), with a specificity of 76.5% and 100% for fungal and bacterial infections, respectively. Algorithms have been also used to analyze corneal ulcer photos and perform semi-automated segmentation.[34] The AI can standardize the corneal epithelial defect and infiltrate measurement reducing the variability between examiners. In a retrospective study,[35] a DL algorithm was developed to identify the keratitis pathogen by analyzing slit-lamp photos. The system assessed 4300 images showing an accuracy of more than 90% for *Acanthamoeba*, bacterial, fungi, and herpes infections.

Future AI algorithms could aid in identifying the causative organisms of IK using AS-OCT imaging. Studies have shown that corneal tissue swelling of >950 μm or infiltrate thickness of >400 μm on AS-OCT is indicative of Gram-negative bacterial keratitis.[36] *Acanthamoeba* keratitis can also be imaged on AS-OCT as highly reflective bands in the corneal stroma.[37]

Corneal Transplantation

AI is used to diagnose and predict corneal shape abnormalities including irregular astigmatism. It analyzes corneal data accurately, including astigmatism after keratoplasty.[38] AI's pattern recognition in large datasets precisely detects changes in corneal astigmatism over time, allowing for timely intervention and treatment adjustments. Modern software in corneal analysis aids in understanding post-keratoplasty vision quality, addressing both higher-order and lower-order aberrations for better correction.[39]

Treder *et al*. utilized a DL-based classifier and found that the automated detection of Descemet's membrane endothelial keratoplasty (DMEK) graft dislocation was reliable.[40] The classifier was trained on 1172 AS-OCT images and had a sensitivity of 98%, specificity of 94%, and accuracy of 96% when tested on 100 AS-OCT scans. Although most DMEK graft detachments resolve on their own, early detection of detachment can be challenging to determine. Automated algorithms that can aid in decision-making for these situations are valuable. Hayashi *et al*. created a VGG19 model that evaluates the need for rebubbling of detached grafts after DMEK.[41] The model was the best performing out of eight other models, with an AUC of 0.96, a sensitivity of 96.7%, and a specificity of 91.5%.

Conjunctivitis

Masumoto *et al*.[42] used a neural network, trained with the Japan Ocular Allergy Society classification system, to accurately grade the severity of conjunctival hyperemia. For 71.8% of all images, their software successfully determined the area covered by blood vessels. There was a significant correlation of 0.737 (P < 0.01) between the responses from multiple models and the occupied vessel area. In the case of trachoma, a blinding disease caused by *Chlamydia trachomatis*, ML was utilized to classify changes in the disease using eyelid images from two clinical trials, the Niger arm of the Partnership for Rapid Elimination of Trachoma trial and the Trachoma Amelioration in Northern Amhara trial.[43]

Lacrimal Apparatus

Lacrimal apparatus refers to the tear drainage system, which can be studied through lacrimal scintigraphy (LS). Researchers have used LS images and ML and DL algorithms to classify tear duct issues in patients with excessive tearing.[44] The system has been found to have accuracy similar to a trained specialist in this field.

Pterygium

Pterygium is a frequent eye disorder where the conjunctiva grows abnormally onto the cornea. Automatic detection methods using ANN, SVMs, and CNN have been developed based on anterior segment photographs to distinguish pterygium from normal cases.[45,46] These methods can serve as a useful screening tool for healthy communities. Kim *et al*.[47] used an automated software to analyze 400 histopathological images of pterygium. The method showed good reliability to grade the lesions with a positive predictive value of more than 75%.

Imaging and Segmentation of Corneal Layers

The corneal endothelium's health status is evaluated using three parameters: endothelial cell density, polymegathism, and pleomorphism. Accurate cell segmentation is crucial to estimate these parameters. Standard techniques such as specular microscopy are used to image the endothelium, but these often suffer from noise, distortions, and artifacts that affect image quality.[48]

AI in specular microscopy holds promise for automated cell segmentation and improved diagnostics. In particular, Kolluru *et al*. investigated two DL methods, U-Net and SegNet, for cell segmentation in images and showed promising results for endothelial cell segmentations and to evaluate cornea health with morphological measurements.[49] Furthermore, Vigueras-Guillén *et al*. utilized DL methods to estimate corneal endothelium parameters from 500 specular microscopy images with corneal guttae. Compared to commercial software, the DL approaches produced lessened mean absolute errors.[50]

In vivo Confocal Microscopy

IVCM is a special microscope that uses a 670-nm wavelength diode laser source to assess the corneal structures.[51] The machine allows an ×800 of the cornea in the clinic without the need for expensive histological tests. The high-resolution images provided by the IVCM can help identify pathological alterations in the corneal layers, as well as in the subbasal nerve plexus, in the stromal nerve, and in the dendritic and nondendritic immune cells.[52,53] In a retrospective cross-sectional study, Aggarwal *et al*. demonstrated a correlation between the dendritic cell (DC) density and morphology and the severity of the disease in patients with dry eyes.[54] The machine has also been used to assess subjects with different microbial keratitis. Müller *et al*. studied corneal nerve degeneration and regeneration in patients with different IK (bacterial, fungal, and *Acanthamoeba*).[55] The authors demonstrated that the corneal nerve loss caused by the acute phase of the infection never recovers completely despite partial nerve regeneration. In a prospective study,[56] Posarelli *et al*. showed that patients with unilateral microbial keratitis have reduced corneal nerve density and sensation, and an increase in DC density. In a recent prospective study,[57] an automated nerve tracing system was used to assess the corneal nerve density in patients with unilateral herpes simplex virus keratitis. The authors demonstrated that patients with central scar have a more severe loss of corneal nerves, a more severe reduction in corneal sensation, and a limited capability to restore corneal innervation. Manual cell and nerve delineation is a time-consuming task that requires an experienced technician. AI-based methods have been shown to provide increased accuracy and speed in evaluating confocal micrographs, with up to 100% accuracy.[58-60]

Future Potential and Consideration

The applications of AI in ophthalmology, in particular in cornea and ocular surface diseases, are continually evolving, and there is a great deal of potential for further development. Some potential future applications of AI include:

Early diagnosis of eye diseases

AI has the potential to improve the early diagnosis of eye diseases, including corneal diseases. Early diagnosis is essential for preventing vision loss and preserving vision quality. AI algorithms can be trained on large datasets of images to identify early signs of corneal diseases, even before symptoms appear.

Personalized treatment planning

AI has the potential to support personalized treatment planning for patients with corneal diseases. AI algorithms can analyze individual patient data, including medical history, imaging results, and patient-specific factors, to develop customized treatment plans that optimize patient outcomes.

Real-time monitoring

AI has the potential to support real-time monitoring of corneal diseases and their progression. AI algorithms can analyze cornea images in real time to identify changes in corneal structure and thickness and to provide immediate feedback to ophthalmologists. Further, they can also standardize the measurement of corneal parameters in various diseases reducing the variability among human examiners.

It is important to note that even if AI algorithms previously mentioned have shown promising results, many of them were trained with limited sample sizes and few have been tested in actual real-world scenarios where the patient population is more varied. This diversity could potentially lead to a decrease in accuracy when the AI algorithms are applied in real-world settings.

In addition, certain factors must be taken into account during implementation. These include the type and severity of the condition, the reversibility of the disease if misdiagnosed, the prevalence of the disease, and the accessibility of the imaging used for diagnosis. For example, a missed diagnosis of IK, which is an acute and potentially vision-threatening condition, has more serious consequences than a missed diagnosis of pterygium, which is usually a chronic and slow-progressing condition.

Conclusion

AI has the potential to significantly improve the diagnosis and treatment of corneal diseases and to enhance patient outcomes in ophthalmology. The applications of AI in cornea and ophthalmology are already showing promising results, and there is great potential for further developments. As AI technology continues to evolve, the use of AI will likely become increasingly widespread. The implementation of AI in clinical practice can lead to faster and more accurate diagnoses, better and more personalized treatment plans, and improved patient outcomes.

Moreover, the use of AI can also lead to improved health-care system efficiency by reducing ophthalmologists' workload and allowing them to focus on more complex cases. AI can assist in reducing the time and resources required for manual image acquisition and analysis and can provide more accurate results in a shorter period.

However, it is important to note that the use of AI is still in its early stages and further research is needed to fully realize its potential. This includes addressing ethical concerns, such as data privacy and bias in AI algorithms, to ensure that the technology is used in a responsible and equitable manner.

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Conflicts of interest

There are no conflicts of interest.

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