DOI: 10.5603/oj.100575

Artificial intelligence in age-related macular degeneration — a review

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ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of blindness globally, affecting mainly individuals over 55 years old. Diagnosis typically involves dilated fundus examination and optical coherence tomography (OCT). Artificial intelligence (AI) shows promising results in the field of medicine. Machine learning, especially deep learning, creates models capable of processing complex data, such as images, videos, speech, and audio. The aim of this review was to establish the utility of AI in the screening and management of AMD. Pubmed and Google Scholar databases were searched using the keywords. Original articles in English, published between 2017-2024 were included. Articles that did not meet the selected criteria were excluded. Machine learning technologies have demonstrated encouraging outcomes in detection, staging, progression prediction, differentiation, and treatment efficacy assessment. AI-based screening has the potential to identify asymptomatic patients at an early stage who require further investigation by an ophthalmologist. Diagnostic accuracy and clinical management can be enhanced by selecting patients requiring more frequent evaluation and medical interventions. However, further investigations are necessary to fully establish the utility of AI in future clinical practice.

KEY WORDS: artificial intelligence; AI; machine learning; deep learning; age-related macular degeneration; AMD

Ophthalmol J 2024; Vol. 9, 188–193

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide [1]. It is characterized by damage to the macular region resulting in central vision loss. It affects individuals over the age of 55 years [2]. The global prevalence of AMD is estimated at 8.69% [3]. AMD is classified as early-stage (medium-sized drusen and retinal pigmentary changes) to late-stage (neovascular and atrophic) [4]. "Dry" AMD refers to the presence of drusen and atrophy and is the most common type of AMD (80–85%). "Wet" AMD (exu-

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dative/neovascular) is the type with developed neovascularization leading to hemorrhaging and leakage of fluid in the inner retinal layers. It affects 15–20% of cases. 10–15% of dry AMD progress to wet AMD. Diagnosis is made by dilated fundus examination — evaluation of macula for drusen, pigmentary changes, geographic atrophy, hemorrhage, fluid, exudate, scar formation, and fibrosis. Optical coherence tomography (OCT) is helpful in the differentiation between wet and dry AMD and the characterization of disease activity [5].

Artificial intelligence (AI) is a computer technology for the simulation and extension of human intelligence. Currently, AI plays a significant role in various disciplines where it is applied [6]. In the field of medicine, it has the potential to improve diagnosis, screening, and treatment, among other use cases [7]. Machine learning is the discipline focusing on how computers learn from data [8]. Deep learning, a subset of machine learning, implements a representation learning approach that involves not only learning to assign a certain data representation to output data but also learning the representation itself. It enables computers to learn complex dependencies in data by introducing representations of data that are expressed in terms of other, simpler representations [9]. Deep convolutional networks, a type of deep learning model, have revolutionized the processing of images, videos, speech, and audio [10]. The development of artificial intelligence technologies has significantly influenced ophthalmology due to its dependency on image-based clinical decision-making and investigations [11]. Over the past decade, machine learning technologies have demonstrated the potential to transform the clinical management of AMD. Besides that, they support research for a better understanding of the disease [12]. The aim of this review was to establish the utility of AI in the screening and management of AMD.

MATERIALS AND METHODS

PubMed and Google Scholar databases were searched using the keywords: "Artificial intelligence in age-related macular degeneration", "Machine learning in age-related macular degeneration", "Deep learning in age-related macular degeneration", "Artificial Intelligence", and "Age-related macular degeneration". Original articles in English, published between 2017–2024, were included. Articles that did not meet the selected criteria were excluded.

DETECTION AND CLASSIFICATION OF AMD

Given the prevalence and sight-threatening nature of the disease, developing a diagnostic system for AMD screening is essential, especially for people with limited access to healthcare. Numerous studies have investigated the detection of AMD using AI.

Burlina et al. [13] measured and compared deep learning performance versus human clinicians in classifying fundus images. Deep convolutional neural network results were comparable with human performance levels (accuracy score = 88.7% *vs.* 90.2%). Sensitivity and specificity were 84.6% and 92.0% respectively. The authors suggest using AI to help find patients who should be referred to an ophthalmologist in the management of AMD.

Ting et al. [14] proved AUC 0.931, 93.2% sensitivity, and 88.7% specificity of deep learning systems for identifying AMD using retinal fundus images.

Another study investigating AI performance in the diagnosis of AMD based on ocular fundus photographs reached an accuracy of 97.3%, a sensitivity of 88.1%, and a specificity of 97.6% in the identification of AMD [15].

AI can successfully detect AMD patients based on OCT scans. The trained deep neural network showed an accuracy of 93.45%, a sensitivity of 92.64%, and a specificity of 93.69% in detecting AMD from OCT images [16].

Kadry et al. [17] tested AI in detecting AMD from fundus retinal images (FRI) and OCT images separately. Detection accuracies were 97.08% for FRI and 97.50% for OCT images.

The convolutional neural networks model trained on OCT images presented by Motozawa et al. [18] was able to classify AMD and normal OCT images with 100% sensitivity, 91.8% specificity, and 99% accuracy. The second model could classify AMD as exudative or non-exudative with 98.4% sensitivity, 88.3% specificity, and 93.9% accuracy.

Liefers et al. [19] developed a deep learning model for segmenting 13 features from OCT scans that can be associated with neovascular and atrophic AMD. The model's performance was comparable with that of human experienced graders.

Grassmann et al. [20] proved that AI correctly classified 94.3% of healthy fundus images. The accuracy rate in differentiating AMD's early and late stages was 84.2%. Their deep learning algorithm outperformed human graders.

Currently, the diagnosis of choroidal neovascularization (CNV) primarily relies on OCT

Table 1. Summary of the results of the studies

Authors	Imaging method	Accuracy	Sensitivity	Specificity
Burlina et al. [13]	Fundus images	88.7%	84.6%	92.0%
Ting et al. [14]	Fundus images	–	93.2%	88.7%
Dong et al. [15]	Fundus images	97.3%	88.1%	97.6%
Lee et al. [16]	OCT scan	93.45%	92.64%	93.69%
Kadry et al. [17]	Fundus images	97.08%	–	–
	OCT scan	97.50%	–	–
Motozawa et al. [18]	OCT scan	99%	100%	91.8%

OCT — optical coherence tomography

and OCT angiography (OCTA) imaging modalities. However, the use of fluorescein angiography (FA) is sometimes necessary due to its ability to visualize the dynamics of dye leakage over time. In a study involving patients with neovascular age-related macular degeneration (nAMD), automated predictions were more frequently rated as high-quality compared to manual human annotations. This suggests that the proposed deep learning models achieve at least human-level performance in both the "FA-CNV" and "FA-Leakage" datasets [21].

These studies prove that AI achieves a high accuracy in detecting and classifying AMD. AI can identify AMD patients from fundus images, OCT scans, and fluorescein angiography. Using deep learning models has the potential to improve reporting and decision-making in the clinical approach. It could also reduce subjectivity in clinicians' assessments, increase interpretation speed, and improve personalized care. A summary of the results can be found in Table 1.

PREDICTION OF PROGRESSION TO LATE AMD

AI can be used to predict risk for progression to late AMD. The model based on AMD scores combined with sociodemographic clinical data achieved 86.36% accuracy in the prediction of 2-year incidence of late AMD, 66.88% for dry, and 67.15% for wet AMD [22].

Peng et al. [23] created a survival model to analyze time to late AMD. The model inputs were:

Severity grade predicted by the neural network from fundus images.

Additional deep features are extracted from this network.

Patient-related features — age, smoking status, and genotype.

The model achieved high prognostic accuracy (86.4%) that exceeded the assessment of retinal specialists using two clinical standards (accuracy of 81.3% and 82%) [23].

Banerjee et al. [24] used a deep learning approach to predict the risk of exudation in non-exudative AMD patients. They proved to have high performance in the prediction of exudation within 3 months of testing the model on the clinical dataset (0.82 area under the receiver operating characteristic curve — AUROC). However, prediction within 21 months presented a decrease in performance (0.68 AUROC).

The AI-based algorithm was used to predict progression to retinal atrophy for nonexudative AMD cases in OCT scans. It reached accurate predictions for four years and longer. Additionally, a personalized atrophy progression risk map with a color-coded time scale was developed [25].

Ajana et al. [26] developed an AI model for selecting the best predictors of advanced AMD development. The model retained age, phenotypic predictors (presence of intermediate drusens, hyperpigmentation, and Age-Related Eye Disease Study simplified score), genetic risk score, smoking, diet, education, and pulse pressure. It reached high discrimination abilities with cross-validated area under the curve (AUC) estimation of 0.92 at 5 years, 0.92 at 10 years, and 0.91 at 15 years [26].

Identification of patients with a high risk of progression to late AMD may select those with the need for more frequent detailed screening and medical interventions.

IDENTIFICATION OF PREDICTIVE FACTORS

The potential of machine learning was investigated to predict best corrected visual acuity (BCVA) outcomes in patients receiving anti-vascular endo-

thelial growth factor (anti-VEGF) therapy (ranibizumab). Retinal features extracted from OCT images and BCVA measurements were used as markers to predict BCVA at 12 months. BCVA at month 3 represented the strongest predictive factor (the accuracy was R2 = 0.70). The most relevant marker from the OCT scan was a horizontal extension of intraretinal cystoid fluid in the foveal region, although other retinal features showed limited predictive value [27].

Machine learning was used to predict visual function in patients with geographic atrophy. It was based on quantitative imaging biomarkers from OCT. The most significant predictive importance for visual acuity had features within the foveal region (46.5%) and retinal pigment epithelium (RPE) loss (31.1%) [28].

A machine learning model based on quantitative OCT imaging biomarkers was used to predict visual acuity (VA) and treatment needs in a treat-and-extend regimen in neovascular AMD patients. The extendable treatment interval group was predicted with an AUROC of 0.71, whereas VA was predicted with an AUROC of up to 0.87. The most important predictive markers for treatment intervals and visual outcomes were the volume of subretinal fluid and the volume of intraretinal fluid. This study proves the important role of quantitative fluid parameters on OCT [29].

The deep learning-based algorithm was evaluated to determine the correlation of baseline OCT morphological features and fluid measurements to changes in BCVA from baseline to week 52. Total retinal fluid volume at baseline represented the strongest correlation to improvement in BCVA at month 12 [30].

Identification of predictive factors leads to a better understanding of the pathophysiology of the disease. It can also enhance disease monitoring by providing a personalized approach to management and treatment.

DIFFERENTIAL DIAGNOSIS

Polypoidal choroidal vasculopathy (PCV) and wet AMD share similar clinical features — exudation and hemorrhages from abnormal choroidal vasculopathy. Wet AMD demonstrates a better response to anti-VEGF treatment than PCV, while PCV responds more positively to thermal laser photocoagulation and photodynamic therapy [31]. Ma et al. [31] presented a model for automatic differential diagnosis between PCV and wet AMD from OCT images. The authors used neural networks to classify OCT images as normal, AMD, or PCV. They evaluated different classification strategies, and all presented similar and promising results. They also used the gradient-weighted class activation map (Grad-CAM) algorithm, which showed that the AI model has learned to focus on pathological regions of OCT images [31].

TREATMENT

Assessment of visual function and morphological parameters are used for monitoring disease activity during anti-VEGF therapy. Reduction in fluid volume is one of the features considered [32]. A deep learning algorithm was used to quantify the fluid volumes in OCT images. Comparison with human expert readings confirmed that AI precisely measured fluid volumes with an AUC of > 0.9 [33]. Accurate measurement of intraretinal volumes could be useful in evaluating response to treatment.

A deep learning method for localization and quantifying fluid in all retinal compartments was used during the phase III, randomized, multicenter study to evaluate the efficacy and safety of intravitreal ranibizumab injections at 2 dosages and two regimens. The authors proved that AI-based quantification of fluid volume offers a precise measurement of disease activity. This approach allows the identification of response patterns and a correlation of fluid volume activity with functional change. Automated quantification of fluid response may improve the therapeutic management of neovascular AMD [34].

Maunz et al. [35] used machine learning to predict response to ranibizumab therapy in neovascular AMD. Seven models based on:

- quantitative OCT features;
- quantitative OCT features and clinical variables at baseline;
- baseline OCT images only
- were tested.

The models based on AI-segmented OCT features and clinical variables at baseline represented the best prognostic ability. However, further investigations need to be done to realize the clinical utility of these models [35].

Previously developed deep learning models were used to segment geographic atrophy (GA) lesions, photoreceptor integrity, and hyperreflective foci in spectral domain OCT (SD-OCT) at baseline

and 1-year follow-up using the data from clinical trial phase II of intravitreal pegcetacoplan injection versus sham injection. This approach enabled precise localization and quantification of GA progression to obtain an accurate evaluation of therapeutic efficacy. AI has the potential to introduce automatization in clinical trials [36, 37].

Moon et al. [38] developed an AI model to predict anti-VEGF agent-specific anatomic treatment outcomes in neovascular AMD patients receiving three loading injections of ranibizumab or aflibercept. AI model achieved higher sensitivity and specificity than human examiners [38].

CONCLUSIONS

The use of AI in medicine has grown in popularity. Machine learning technologies have shown potential for improving the diagnosis and management of AMD. AI proved to have promising results in detecting, staging, predicting progression, differentiation, and establishing treatment efficacy. AI screening could indicate asymptomatic patients at an early stage of AMD who require further investigation by an ophthalmologist. It could be essential in cases with limited access to healthcare. AI has the potential to improve diagnostic accuracy and clinical management. Indication of patients with a higher risk of late AMD development may select those with the need for more frequent detailed screening and medical interventions. Despite the promising results, further investigations need to be done to establish the utility of AI in future clinical practice.

Author contributions

Conceptualization: K.U., M.W., J.K., and W.R.-K.; methodology: K.U.; resources: K.U., P.W., W.K.; writing — rough preparation: K.U., P.W., M.W., W.K., Z.B., A.B., J.K., W.R.-K., K.P, and A.L.; writing — review and editing: K.U., P.W., and M.W. All authors have read and agreed with the published version of the manuscript.

Funding

No funding.

Conflict of interest

The authors declare no conflict of interests.

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