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Recent advances in the application of artificial intelligence in age-related macular degeneration

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ABSTRACT

Recent advancements in ophthalmology have been driven by the incorporation of artificial intelligence (AI), especially in diagnosing, monitoring treatment and predicting outcomes for age-related macular degeneration (AMD). AMD is a leading cause of irreversible vision loss worldwide, and its increasing prevalence among the ageing population presents a significant challenge for managing the disease. AI holds considerable promise in tackling this issue. This paper provides an overview of the latest developments in AI applications for AMD. However, current limitations include insufficient and unbalanced data, lack of interpretability in models, dependence on data quality and limited generality.

INTRODUCTION

Age-related macular degeneration (AMD) primarily affects the macula, the central part of the retina essential for clear vision. AMD can significantly impact daily activities such as reading, driving and facial recognition.[1] Over the past 30 years, the prevalence of AMD has consistently increased.[2 3] As the population ages, this trend is expected to continue, with projections suggesting that the number of AMD cases will reach 288 million by 2040, posing a significant public health challenge.[4] The staging of AMD is complex; early-stage patients often show minimal symptoms, while late-stage AMD can lead to severe vision loss. Treatment efficacy for wet AMD varies, as most patients experience delayed disease progression, while others respond poorly to therapy.[5] Similarly, treatment modalities for atrophic dry AMD are also evolving.[6]

Advancements in retinal imaging technology now allow for accurate identification of biomarkers associated with late-stage macular degeneration and assessment of disease severity. This technology finds widespread application in ophthalmology, particularly among elderly patients with AMD. As AMD prevalence continues to rise, nearly all ophthalmic facilities have accumulated extensive retinal imaging data, including fundus photographs, optical coherence tomography (OCT) images and fluorescein fundus angiography (FFA) images. This presents both challenges and opportunities for ophthalmologists.

The ongoing advancement of artificial intelligence (AI) technology has significantly impacted ophthalmology, providing new possibilities for diagnosing and treating AMD. By leveraging machine learning and deep learning techniques, AI can effectively analyse and interpret large-scale medical data, achieving accuracy comparable to that of human practitioners, particularly in image recognition and natural language processing.[7] Consequently, it has emerged as an important adjunct tool for medical diagnosis and treatment. It is especially valuable in enhancing the accuracy of early diagnosis, individualising treatment efficacy and predicting therapeutic outcomes in AMD. This review offers an overview of AI technology's role in assisting with the diagnosis and treatment of AMD, highlighting its potential to improve diagnostic accuracy and therapeutic efficacy.

METHODS

We conducted a systematic search of the Web of Science database for studies published between August 2005 and March 2024. The search strategy included the following terms: ('artificial intelligence' OR 'AI' OR 'machine learning' OR 'deep learning') AND ('age-related macular degeneration' OR 'AMD') AND ('fundus photograph' OR 'optical coherence tomography' OR 'fluorescein fundus angiography'). Studies that did not involve AI or AMD were excluded from the review. This article is based on previously published research and does not contain any new studies involving human or animal subjects conducted by the authors.

AI FOR FUNDUS DISEASE

AI is a technology that enables computers to simulate human behavior.[8] AI algorithms are typically grounded in mathematical concepts, such as machine learning[9] and deep learning.[10] The models derived from these algorithms are employed for various tasks, including classification, prediction and data generation. Commonly used algorithms encompass decision trees, random forests (RFs), support vector machines (SVM) and artificial neural networks (ANN).

Retinal diseases are complex ocular disorders that pose a significant threat to public health, especially with an ageing population. Thus, enhancing the objectivity and consistency of medical image diagnosis has become an urgent priority in ophthalmic healthcare. Recent advancements in AI technology have made significant strides in addressing this need. AI has shown notable progress in the study of retinal diseases, particularly AMD, diabetic retinopathy,[11] retinal vein occlusion[12] and retinopathy of prematurity.[13] AI systems trained on extensive retinal image datasets can efficiently and accurately analyse images, identify various lesions and offer diagnostic recommendations, thereby significantly enhancing diagnosis and screening processes.[14 15] This technology empowers healthcare professionals to detect diseases at earlier stages, ultimately improving diagnostic accuracy and timeliness.

AI-driven retinal diagnostic systems also provide personalised treatment plans tailored to each patient's characteristics and condition.[16] By analysing retinal images and clinical data, these systems can predict disease progression and recommend appropriate treatments.[17] This personalised approach enhances precision in ophthalmic care, leading to higher patient satisfaction and an improvement in quality of life.

The integration of AI in retinal disease management presents promising solutions to ongoing challenges in AMD. Despite being a common cause of blindness, AMD remains difficult to diagnose early, customise treatment, control costs and monitor over time. AI can address these issues by facilitating faster and more accurate early diagnosis through retinal image and OCT scan analysis. Additionally, AI leverages big data to predict disease progression and develop personalised treatment plans based on individual patient data. Further details will be discussed in subsequent sections.

ADVANCEMENTS IN AI APPLICATION FOR AMD

AI application for AMD based on fundus photography

Fundus photography is a non-invasive, low-cost method for screening AMD, used to identify related lesions such as vitreous warts, macular haemorrhage and geographic atrophy (GA). This technique plays a key role in the screening and diagnosis of AMD. A brief process of applying the AI model to diagnose and screen for AMD is shown in online supplemental figure S1.

Researchers like Mark and Andrés have developed machine learning models for retinal image analysis, which accurately detect and quantify abnormal deposits in the macula from fundus images. These models can automatically prediagnose AMD and assess the risk of its progression.[18 19] Findings show that these machine learning systems perform comparably to human observers in automated AMD risk assessment, offering a promising solution for faster and more reliable diagnosis. Furthermore, Feeny *et al* created a fully automatic segmentation model using RFs to effectively segment GA areas in colour fundus images, enabling more precise segmentation.[20] In addition, Abd *et al* designed a machine learning model for classifying AMD stages, including no AMD, intermediate AMD, dry AMD and wet AMD. Their study employed eleven classification models, optimising their performance through comparison.[21] This approach not only achieved high accuracy but also provided detailed assessments of retinal severity, aligning the final diagnosis with clinicians' understanding of AMD. As a result, these models aid clinicians in the ongoing management and follow-up of AMD patients.

Deep learning models, particularly convolutional neural networks (CNNs) and their variants, are increasingly applied in ophthalmology. Unlike traditional machine learning, deep learning processes images directly, minimising errors from feature computation and segmentation. For example, Burlina *et al* used CNN

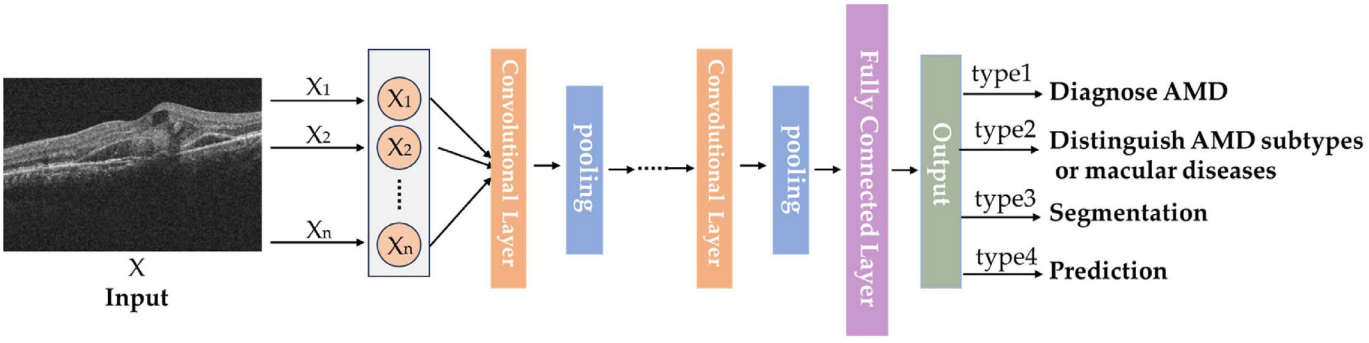

Figure 1 Convolutional neural network (CNN) processing flow. CNN learns image features by performing a series of convolution and pooling, and finally outputs the corresponding results by different modules. AMD, age-related macular degeneration.

to classify fundus images of individuals with no AMD, early-stage AMD and those with intermediate or advanced AMD. The model's performance in grading was comparable to that of clinicians, but it required significantly less time.[22 23] Liu *et al* concentrated on early-stage AMD detection using deep learning within a multiple instance learning framework, allowing the model to capture subtle features for early diagnosis.[24] Grassmann *et al* enhanced this approach by employing six neural networks to stage AMD into 13 categories, including nine based on the age-related eye disease study (AREDS) severity scale, three late-stage categories and one ungradable category. Integrating RF models with these networks further improved the accuracy of AMD staging.[25] Xu *et al* developed DeepDrAMD, a deep learning model that efficiently distinguishes AMD subtypes by leveraging hierarchical visual transformers, data augmentation techniques and SwinTransformer. It achieved classification accuracies of 93.46% for dry AMD and 91.55% for wet AMD, with the wet AMD subtype showing exceptional performance, with an area under curve (AUC) of 99.36%.[26] Chen *et al* and Peng *et al* introduced DeepSeeNet, a deep learning model designed for automatic classification of AMD severity, extracting disease features from colour fundus images of both eyes and categorising patients based on severity ratings.[27 28] These models, while comparable to expert evaluations, offer significant cost savings and improved efficiency. The advancements in deep learning are set to provide vital support in AMD detection and diagnosis, significantly assisting healthcare professionals.

AI application for AMD based on OCT images

Compared with fundus photography, OCT provides clearer, high-resolution images of retinal structures and subtle changes, including layers such as the retinal pigment epithelium and neurosensory layers. This enhanced imaging allows for the detection of AMD-related abnormalities such as subretinal fluid (SRF), retinal pigment epithelial detachment (PED) and macular cystoid oedema, providing physicians with a better understanding of the disease. To better understand the structure of the model, figure 1 shows the detailed process using CNN as an example.

Classification

Deep learning AI models have proven effective in classifying OCT images to detect AMD, distinguish it from other macular lesions and identify various stages of the disease. This leads to faster, more accurate diagnoses, enabling timely interventions, improving diagnostic efficiency and allowing for more timely treatment.

Initial work on classifying AMD OCT images relied on traditional machine learning techniques such as principal component analysis, SVMs and RFs. However, the advent of deep learning has brought about substantial advancements. Early deep learning efforts focused primarily on distinguishing AMD images from normal ones. For instance, Lee *et al* modified the VGG16 CNN model to identify AMD and used occlusion tests to verify the model's robustness and generalizability, achieving sensitivity and specificity of 92.64% and 93.69%, respectively.[29] Shi *et al* developed a deep learning model called Med-XAI-Net, designed to detect GA in OCT volume scans. Its unique design, incorporating two key attention modules, enhances interpretability by identifying the most relevant B scans for GA detection. The model achieved an accuracy of 91.5%, AUC of 93.5%, sensitivity of 82.8% and specificity of 94.6%.[30] Sun *et al* employed a residual networks-50 (ResNet-50) CNN model to diagnose AMD using the Duke dataset and a proprietary dataset. The model reached 98.17% accuracy, 99.26% sensitivity and 95.65% specificity on the Duke dataset. For the proprietary dataset, which included both diabetic macular oedema (DMO) and AMD images, a fine-tuned ResNet-50 with various classifiers (SVM, CNN, CNN_CBAM) achieved high accuracy through fivefold cross-validation.[31] He *et al* introduced an automated AMD detection method combining deep learning with the local outlier factor (LOF) algorithm. Using ResNet-50 for feature extraction and LOF for classification, their method was trained on the University of California, San Diego (UCSD) dataset and tested on both UCSD and Duke datasets, achieving 99.87% accuracy on UCSD and 97.56% on Duke. Compared with other methods, this study demonstrated high efficiency in AMD detection.[32]

Some studies have focused on differentiating AMD from other macular diseases. For example, Kermany *et al* used deep learning to classify OCT images of wet AMD, normal eyes, DMO and epiretinal membrane, achieving 96.6% sensitivity, 94% specificity and 93.4% accuracy. Their model's performance equalled that of ophthalmic experts and demonstrated robustness in occlusion tests.[33] Li *et al* applied deep transfer learning using the VGG-16 network to classify AMD and DMO in OCT images, involving 109 312 images covering various conditions and normal cases. Their method achieved 98.6% accuracy, 97.8% sensitivity, 99.4% specificity and 100% AUC in OCT image detection.[34] Baharlouei *et al* proposed a CNN-based method using wavelet scattering transform to detect retinal abnormalities from OCT images. Their study, using the Heidelberg and Duke datasets, classified images into DMO, AMD and normal categories, achieving 97.1% and 94.4% accuracy, respectively.[35]

Given the differences in treatment for wet and dry AMD, several studies have aimed to distinguish between the various stages of the disease. Deng *et al* and Serener and Serte developed machine learning and deep CNN models for the rapid classification of dry and wet AMD, with the ResNet model outperforming the AlexNet model in classification accuracy.[36 37] Motazawa *et al* created a deep learning model to differentiate between normal and AMD OCT images and to distinguish AMD with and without exudation. Their study used two models: a basic CNN and a transfer learning model designed to improve stability and efficiency. The basic CNN model achieved a sensitivity of 100%, specificity of 91.8% and accuracy of

Table 1 A summary of the research on classification in the article

Reference	Purpose	Neural network backbone	Optimisation strategy	Performance
Lee *et al*[29]	Detecting AMD from AMD and normal	VGG-16	Stochastic gradient descent	Accuracy 87.63% AUC 92.77% Sensitivity 84.63% Specificity 91.54%
Shi *et al*[30]	Detecting AMD from AMD and normal	Med-XAI-Net	Region-attention module, image-attention module and loss function	Accuracy 91.5% AUC 93.5% Sensitivity 82.8% Specificity 94.6%
Sun *et al*[31]	Detecting AMD from AMD, DMO and normal	ResNet-50	Convolutional block attention module	Mean accuracy 98.17% Sensitivity 99.26% Specificity 95.65%
He *et al*[32]	Detecting AMD from AMD and normal	ResNet-50 and LOF algorithm	Residual network	Internal validation: average accuracy 99.78%, AUC 100% External validation: average accuracy 97.56%, AUC 99.54%
Kermany *et al*[33]	Distinguish CNV, DMO, drusen, normal	Transfer learning	NA	Accuracy 93.4% Sensitivity 96.6% Specificity 94%
Li *et al*[34]	Detecting dry AMD and DMO from normal, drusen, wet AMD and DMO	VGG-16	Convolution filters and backpropagation	Accuracy 98.6% Sensitivity 97.8% Specificity 99.4%
Baharlouei *et al*[35]	Distinguishing AMD, DMO, normal	CNN	Wavelet scattering transform	Heidelberg dataset: accuracy 97.1% Duke dataset: accuracy 94.4%
Deng *et al*[36]	Detecting dry AMD and wet AMD from normal, dry AMD and wet AMD	RF, SVM, neural network	Gabor filtering Supervised	Accuracy 94.7%, 97.1%, 84.7%
Serener and Serte[37]	Detecting dry AMD and wet AMD from normal, dry AMD, wet AMD and DMO	ResNet AlexNet	NA	Dry AMD: ResNet model accuracy 99.5%, AUC 94%, sensitivity 98.0%, specificity 100% AlexNet model: accuracy 81.0%, AUC 81.0%, sensitivity 93.8%, specificity 99.73% Wet AMD: ResNet model accuracy 98.8%, AUC 63%, sensitivity 95.6%, specificity 99.9% AlexNet model: accuracy 96.5%, AUC 61.0%, sensitivity 88%, specificity 99.3%
Motozawa *et al*[38]	CNN models for distinguishing normal and AMD Migration learning models for distinguishing AMD with and without exudative changes	CNN Transfer learning	Data augmentation and dropout technique	CNN: accuracy 99%, sensitivity 100%, specificity 91.8% Transfer learning: accuracy 93.9%, sensitivity 98.4%, specificity 88.3%

Continued

Table 1 Continued

Reference	Purpose	Neural network backbone	Optimisation strategy	Performance
Hwang *et al*[39]	Identify normal macula and three types of AMD: dry AMD (drusen), inactive wet AMD and active wet AMD	VGG16 InceptionV3 ResNet-50	Data augmentation	VGG16: accuracy 91.40%, AUC 98.3% InceptionV3: accuracy 92.67%, AUC 97.8% ResNet-50: accuracy 90.73%, AUC 98.7%
Hwang *et al*[40]	Detecting PCV and RAP from AMD and normal	VGG-19	Data augmentation and transfer learning	Accuracy 89.1% AUC 95.3% Sensitivity 89.4% Specificity 88.8%
Wongchaisuwat *et al*[41]	Distinguish PCV, wet AMD	ResNet-50	Transfer learning technique and attention blocks	AUC 81% Sensitivity 85% Specificity 71%

AMD, age-related macular degeneration; AUC, area under the curve; CNN, convolutional neural network; CNV, choroidal neovascularization; DMO, diabetic macular oedema; LOF, local outlier factor; PCV, polypoidal choroidal vasculopathy; RAP, retinal angiomatous proliferation; ResNet, residual network; RF, random forest; SVM, support vector machines.

99.0% in distinguishing AMD from normal images. The transfer learning model achieved a sensitivity of 98.4%, specificity of 88.3% and accuracy of 93.9% in identifying AMD with or without exudation.[38] Hwang *et al* proposed three CNN architectures—VGG16, InceptionV3,and ResNet-50—to classify normal retinas and three types of AMD: dry AMD (drusen), inactive wet AMD and active wet AMD. The models demonstrated accuracies of 91.40%, 92.67% and 90.73%, respectively, with AUC values of 98.3%, 97.8% and 98.7%. All three models showed high sensitivity (>99%) in detecting normal retinals.[39] Hwang *et al* further developed a deep learning model to differentiate retinal angiomatous proliferation from polypoidal choroidal vasculopathy (PCV), adjusting the VGG-19-based CNN for this purpose. The model's performance was evaluated through sensitivity, specificity, accuracy and AUC, while Cohen's kappa coefficient measured agreement between two retinal specialists and between the model and each specialist.[40] Wongchaisuwat *et al* employed multiple CNN models to differentiate between PCV and wet AMD. Their study used 2334 OCT images for training and 1171 images for external validation. The best-performing model, incorporating an attention mechanism within the ResNet architecture, achieved an AUC of 81%, sensitivity of 85% and specificity of 71% on the external validation set.[41]

Table 1 provides detailed information on the outcomes of these studies.

Segmentation

Segmentation enables the identification of AMD features, such as drusen and subretinal hyperreflective material (SHRM), in retinal images, allowing for precise localization and quantification of lesions in OCT scans. This process supports the monitoring of disease progression, evaluation of treatment efficacy and improved understanding of AMD pathology, thereby enhancing diagnosis and patient management.

Earlier studies on OCT image segmentation relied heavily on machine learning algorithms such as edge detection,[42] SVM[43] and graph cut algorithms.[44] However, the rise of deep learning has led to the development of advanced algorithms such as CNN,[45] U-Net,[46] SegNet,[47] ResNet[48] and fully convolutional network,[49] which have shown significant promise in tackling segmentation tasks related to AMD.

In dry AMD research, Mishra *et al* employed the U-Net model to segment early-stage AMD OCT images. Their algorithm automatically segmented reticular pseudodrusen (RPD), drusen and 11 retinal layers, facilitating early non-exudative AMD analysis and potentially aiding in the development of early treatment options.[50] Similarly, Lu *et al* developed an automated algorithm for segmenting and quantifying calcified drusen in three-dimensional (3D) OCT images, showing strong consistency with human graders and achieving a dice similarity coefficient of 68.27%±11.09%, which holds clinical significance for assessing AMD progression.[51] Ji *et al* proposed an automated segmentation method for GA based on deep learning. The model architecture consists of a deep network with five layers, including an input layer, three hidden layers using sparse autoencoders and an output layer. The study incorporated two datasets comprising a total of 105 OCT images. The first dataset achieved an average mean overlap ratio (OR) of 86.94%, absolute area difference (AAD) of 11.49% and correlation coefficient (CC) of 98.57%. The algorithm applied to the second dataset obtained average OR, AAD and CC values of 81.66%, 83% and 99.52%, respectively.[52] Elsawy *et al* developed the Deep-GA-Net model, which is a 3D deep learning network with a 3D attention layer. This model is designed for detecting GA on spectral-domain OCT scans. The accuracy of the model is reported to be 93%.[53]

Table 2 A summary of the research on segmentation in the article

Reference	Method	Optimisation strategy	Images (n)	Disease	Segmentation type	Performance
Mishra *et al*[50]	U-Net	Shortest path algorithm	1343	AMD	Dursen RPD 11 layers of retina	Drusen: average difference between automatic and manual segmentation 0.75±1.99 pixels RPD: average difference between automatic and manual segmentation 0.41±1.97 pixels
Lu *et al*[51]	Deep learning	Binary map	29	Non-exudative AMD	Calcified drusen	DSC 68.27±11.09%
Ji *et al*[52]	Deep learning	Stochastic gradient descent	105	Non-exudative AMD	GA	Dataset 1: mean OR 86.94%, AAD 11.49%, CC 0.9857 Dataset 2: mean OR 81.66%, AAD 8.30%, CC 0.9952
Elsawy *et al*[53]	Deep-GA-Net	3D loss-based attention layer	1284	AMD	GA	Accuracy 93%
Fernández[54]	GVF Snake algorithm	Multiscale edge detection scheme	7	Wet AMD	SRF IRF PED	Similar to clinical experts
Rashno *et al*[55]	GC KGC	Transform OCT scans to neutrosophic domain and cost functions	796	AMD	SRF IRF PED	GC: dice coefficient 76.10%, sensitivity 80.54%, precision 90.34% KGC: dice coefficient 70.97%, sensitivity 86.40%, precision 77.17%
Moraes *et al*[56]	Deep learning	NA	2966	Wet AMD	Neurosensory Retina RPE IRF SRF SHRM Hyper-reflective foci Drusen Fibrovascular PED Serous PED	SRF: accuracy 90.3% IRF: accuracy 72.7%
Xie *et al*[57]	U-Net DDP	Smoothness constraints and loss functions	384	AMD Normal	Inner limiting membrane Inner retinal pigment epithelium-drusen complex The outer aspect of the Bruch membrane	Mean absolute surface distance±standard deviation (μm): 1.88±1.96
Pawloff *et al*[58]	Deep learning	End to end	41 147	Wet AMD	IRF SRF	HAWK: AUC of 85% for IRF and 87% for SRF in the central millimetre HARRIER: AUC of 93% for IRF and 87% for SRF in the central millimetre

Continued

Table 2 Continued

Reference	Method	Optimisation strategy	Images (n)	Disease	Segmentation type	Performance
Prabha *et al*[59]	AR U-Net++	Attention blocks and residual blocks	2272	Wet AMD	ILM IPL RPE BM IRF SRF PED	Accuracy 99.67% Mean IoU 84% Dice coefficient 94%
Feng *et al*[60]	U-Net	ResNeSt block and pyramid pooling module	116	Wet AMD	CNV	AUC 94.76% Specificity 99.5% Sensitivity 72.71%

AAD, absolute area difference; AMD, age-related macular degeneration; AR, attention residual; AUC, area under curve; BM, Bruch's membrane; CC, correlation coefficient; CNV, choroidal neovascularization; 3D, three-dimensional; DDP, distribute data parallel; DSC, dice similarity coefficient; GA, geographic atrophy; GC, graph cut ; GVF, gradient vector flow; ILM, internal limiting membrane; IoU, intersection over union; IPL, inner plexiform layer; IRF, intraretinal fluid; KGC, kernel graph cut; OCT, optical coherence tomography; OR, overlap ratio; PED, pigment epithelial detachment; RPD, reticular pseudodrusen; RPE, retinal pigment epithelium; SHRM, Subretinal hyperreflective material; SRF, subretinal fluid.

The segmentation concerning wet AMD are as follows. Fernández and Rashno *et al*, among others, have developed segmentation models for fluid in OCT images of wet AMD.[54 55] Moraes *et al* automated the segmentation and quantification of various features of wet AMD in OCT images, including neurosensory retina, retinal pigment epithelium (RPE), intraretinal fluid (IRF), SRF, SHRM, hyper-reflective foci, drusen, fibrovascular PED and serous PED. They also analysed the correlation of these features with visual acuity.[56] Xie *et al* proposed a deep learning model for segmenting individual retinal layers, conducting experiments on two datasets. The results demonstrated subpixel-level accuracy, with average absolute surface distance errors of 1.88±1.96 µm and 2.75±0.94 µm for all segmented surfaces in the two datasets.[57] Pawloff *et al* built on this work, employing deep learning to automatically detect macular fluid and validating the model's reliability through comparisons with manual segmentation results.[58] Prabha *et al* introduced a novel deep learning model called AR U-Net++, specifically for segmenting retinal layers and fluid. The segmentation targets included the inner limiting membrane, inner plexiform layer, RPE, Bruch's membrane and IRF, SRF and PED. Compared with existing U-Net, AR U-Net and AR W-Net models, AR U-Net++ achieved superior accuracy (99.67%), mean intersection over union (84%) and dice coefficient (94%). One notable feature of this model is its ability to identify the exact location and depth of retinal fluid between retinal layers.[59] Feng *et al* developed a model that automatically segmented choroidal neovascularization (CNV) in OCT angiography (OCTA) images. By using the ResNeSt module as the backbone, the CNV segmentation model achieved an AUC of 94.76%, with high specificity (99.5%) and moderate sensitivity (72.71%). The results indicated satisfactory performance of the model in extracting CNV regions from OCTA images of patients with wet AMD.[60]

Detailed information on each of the above studies is shown in table 2.

Predicting

AI's role in predicting AMD progression and treatment efficacy using OCT images is crucial. By quantitatively analysing retinal thickness and pathological features, AI supports doctors more accurately and quickly assess the severity of AMD and understand how the disease is progressing. For wet AMD, while anti-vascular endothelial growth factor (anti-VEGF) medications benefit most patients, some respond poorly, making AI's predictive and evaluative capabilities vital.

Initial efforts to predict the progression from early-stage to late-stage exudative AMD used traditional machine learning techniques, achieving AUC performances of 74% and 68%, respectively.[61 62] Subsequently, Banerjee *et al* built on these studies by introducing a predictive model for sequential learning of longitudinal OCT data captured during multiple visits, enhancing predictive performance while identifying trends in both short-term and long-term progression of AMD.[63] Following this, Waldstein *et al* employed segmentation algorithms to extract drusen and hyper-reflective foci from OCT images, analysing changes over time at the same retinal location to predict the likelihood of early macular degeneration progressing to macular neovascularization and macular atrophy.[64] In 2023, Rudas *et al* proposed a deep learning model (SLIVER-net) that further improved prediction of AMD progression by integrating a large volume of retrospective OCT images with corresponding electronic health records.[65]

The following are related studies on the evaluation of therapeutic efficacy in wet AMD. Bogunovic *et al* proposed a machine learning model to predict the treatment needs of wet AMD patients by analysing clinical data and classifying them into low and high treatment

Table 3 A summary of the research on prediction in the article

Reference	Method	Optimisation strategy	Images (n)	Disease	Forecast content	Performance
de Sisternes *et al*[61]	L1-penalised Poisson model predictors	Piecewise-linear functions and L1-penalised Poisson model	244	Dry AMD	Predicting the transition from early and intermediate age-related macular degeneration to advanced exudative macular degeneration	AUC 0.92
Schmidt-Erfurth *et al*[62]	Cox proportional hazards	Supervised setting, the least absolute shrinkage and selection operator	1095	Dry AMD	Predicting the risk of conversion to advanced AMD in patients with early age-related macular degeneration	CNV: AUC 0.68 GA: AUC 0.80
Banerjee *et al*[63]	RNN	Many-to-many data augmentation and long short-term memory	671	Dry AMD	Predicting the transition from early and intermediate age-related macular degeneration to advanced exudative macular degeneration	Internal validation: 3 months AUC 0.96, 21 months AUC 0.97 External validation: 3 months AUC 0.82, 21 months AUC 0.68
Waldstein *et al*[64]	Deep learning	NA	1097	Dry AMD	Predicting the risk of conversion to advanced AMD in patients with early age-related macular degeneration	MNV: AUC 0.66 MA: AUC 0.73
Rudas *et al*[65]	SLIVER-net	NA	4200	Dry AMD	Predicting progress in wet AMD	AUC 0.82
Bogunovic *et al*[16]	Random forest	NA	1095	Wet AMD	Predicting patient demand for anti-VEGF therapy	Low demand AUC of 0.7 High demand AUC of 0.77
Romo-Bucheli *et al*[66]	DenseNet and RNN	Hyperbolic tangent	350	Wet AMD	Predicting patient demand for anti-VEGF therapy	Low demand AUC of 0.85 High demand AUC of 0.81
Bogunović *et al*[67]	CNN	NA	228	Wet AMD	Predicting treatment needs and visual outcomes	The AUC for the predicted treat-and-extend group was 0.71 The AUC for the visual outcome was 0.87
Liu *et al*[68]	GAN and pix2pixHD	'Coach-to-fine' training strategy	476	Wet AMD	Predicting short-term responses in patients treated with a single anti-vascular endothelial growth factor injection	92% of the synthesised OCT images were considered to be of sufficient quality for clinical interpretation predicting post-treatment macular status (wet or dry) accuracy 85%
Zhao *et al*[69]	SSG-Net	Squeeze and excitation network and class activation	206	Wet AMD	Predicting whether patients will have a positive treatment response after short-term anti-VEGF therapy	Accuracy 84.6%, AUC 0.83, sensitivity 69.2%, specificity 100%

AMD, age-related macular degeneration; AUC, area under the curve; CNN, convolutional neural network; CNV, choroidal neovascularization; GA, geographic atrophy; GAN, generative adversarial network; MA, macular atrophy; MNV, macular neovascularization; OCT, optical coherence tomography; RNN, recursive neural network.

frequency categories, with AUC values of 70% and 77%, respectively.[16] However, simply classifying patients' future treatment needs does not accurately predict treatment outcomes. Romo-Bucheli *et al* improved Bogunovic's model by combining DenseNet and recursive neural network to predict the need for anti-VEGF treatment in wet AMD patients, categorising predictions into high, medium and low demand, with the best performance in predicting low demand.[66] Subsequently, Bogunović *et al* used CNNs to extract OCT image features and then constructed a model using machine learning methods to predict visual outcomes and treatment needs in wet

Table 4 A summary of datasets

Dataset	Author
CFP	
AREDS dataset	Feeny *et al*,[20] Burlina *et al*,[22 23] Grassmann *et al*,[25] Chen *et al*,[27] Peng *et al*[28]
Original dataset	Abd *et al*,[21] Huiyin *et al*,[24] Xu *et al*[26]
AREDS2 dataset	Chen *et al*[27]
STARE dataset	Garcia-Floriano *et al*[19]
Ocular Disease Intelligent Recognition dataset	Xu *et al*[26]
OCT	
HARBOR clinical trial dataset	Schmidt-Erfurth *et al*,[62] Banerjee *et al*,[63] Waldstein *et al*,[64] Bogunovic *et al*[16]
Duke dataset	Sun *et al*,[31] Baharlouei *et al*,[35] Xie *et al*[57]
AREDS2	Elsawy *et al*[53]
Heidelberg Spectralis Imaging Database	Lee *et al*[29]
UCSD dataset	He *et al*[32]
OCTID dataset	Baharlouei *et al*[35]
Topcon dataset	Baharlouei *et al*[35]
Optima dataset	Rashno *et al*[55]
Annotated Retinal OCT Images Database	Prabha *et al*[59]
Original dataset	Sun *et al*,[31] Kermany *et al*,[33] Li *et al*,[34] Baharlouei *et al*,[35] Deng *et al*,[36] Motozawa *et al*,[38] Hwang *et al*,[39 40] Wongchaisuwat *et al*,[41] Mishra *et al*,[50] Lu *et al*,[51] Ji *et al*,[52] Rashno *et al*,[55] Moraes *et al*,[56] Pawloff *et al*,[58] Feng *et al*,[60] de Sisternes *et al*,[61] Rudas *et al*,[65] Romo-Bucheli *et al*,[66] Liu *et al*,[68] Zhao *et al*[69]

AREDS, The age-related eye disease study; CFP, colour fundus photography; OCT, optical coherence tomography; OCTID, optical coherence tomography image database; STARE, structured analysis of the retina; UCSD, University of California, San Diego.

AMD patients under the treat-and-extend regimen.[67] The study found that accurate prediction of treatment intervals and visual outcomes through analysis of OCT images and clinical data supports the implementation of personalised treatment strategies and management of wet AMD patients. Liu *et al* proposed a generative adversarial network model, which, based on learning from 476 pairs of pretreatment and post-treatment OCT images, synthesised post-treatment OCT images from 50 pretreatment OCT images to demonstrate treatment efficacy.[68] The advantage of this method is its use of only images as input and generation of other images as output, eliminating the need for labels, segmentation or clinical information; however, it also increases the difficulty of model interpretability. Building on previous research, Zhao *et al* developed a deep learning model that associates OCT images with best-corrected visual acuity (BCVA), divided patients into responders and non-responders based on changes in BCVA after anti-VEGF injections and predicted changes in visual acuity after treatment.[69]

Detailed information on each of the above studies is shown in table 3.

Advancements in multimodal models combining various imaging data in AMD

Although OCT is the most common and essential diagnostic tool for AMD, integrating FFA, fundus photography and other clinical data into models is also important. Jointly learning the correlations between different modalities can enhance diagnostic and predictive accuracy.

Yoo *et al* proposed a deep learning model based on OCT, fundus images and their combination to diagnose AMD, comparing the performance of different models. Five models were proposed: (1) RF transfer learning using OCT imaging only; (2) RF transfer learning using fundus images only; (3) RF transfer learning using the combination of OCT and fundus imaging; (4) transfer learning using multimodal restricted Boltzmann machines; and (5) transfer learning using multimodal deep belief networks. The results showed that the multimodal approach combining OCT and other fundus data performed better.[70] Subsequently, Vaghefi *et al* added OCTA to fundus images and OCT, exploring the use of deep learning methods combined with OCT, OCTA and colour fundus images to improve the accuracy of diagnosing intermediate dry AMD. The study found that a CNN using multiple imaging modalities outperformed those using a single modality. In particular, the multimodal CNN combining OCT, OCTA and colour fundus photographs achieved an accuracy of 96% in the AMD group.[71] Chen *et al* proposed a multimodal, multitask, multiattention (M3) deep learning algorithm for

detecting RPD in AMD. The model could analyse either single colour fundus photography (CFP), single fundus autofluorescence (FAF) or their combination. The M3 model performed exceptionally well in RPD detection, achieving AUC values of 83.2%, 93.1% and 93.3% for CFP, FAF and combined images, respectively. Compared with human retinal experts, the performance of the M3 model on CFP was significantly improved.[72] Thakoor *et al* developed a deep learning model to distinguish non-AMD from non-neovascular AMD or neovascular AMD. Nine model variants were trained using different imaging modalities and configurations, including OCTA, OCT structure, 2D B-scan flow images and high-definition 5-line B-scan cubes. The results showed that models trained using multimodal images consistently outperformed those trained using OCT or OCTA alone. In the test dataset, the best-performing model trained using multimodal imaging (MMI) achieved an accuracy of 70.8%±1.12%.[73] Goh *et al* compared the clinical likelihood of predicting the progression of early to late AMD using CFP only versus using MMI, which includes OCT, FAF, near-infrared reflectance and CFP. Their predictions were based on a neural network model with a multimodal model combining age, pigment abnormalities and OCT-based vitreous membrane wart volume. The results showed that the use of MMI had a better clinical performance in predicting the progression of late AMD compared with CFP.[74] Sutton *et al* used machine learning to identify pathological features of OCT, integrating novel characteristics such as OCT-A, FAF imaging, BCVA, microperimetry and genetic profiling. This approach facilitated more personalised predictions regarding the progression of AMD to the intermediate and late stages.[75]

Datasets summary

Datasets are crucial for the effective application of AI models. High-quality datasets determine the learning outcomes and performance of these models, particularly in the medical field, where accurate annotations are essential for reliable diagnosis. Therefore, this paper categorises the datasets of the literature cited in the previous sections. The most common CFP dataset is AREDS dataset; OCT datasets are mainly HARBOR clinical trial dataset and Duke dataset.

Detailed dataset usage is summarised in table 4.

DISCUSSION

AI has made notable progress in diagnosing and managing AMD. This review explores the application of AI across different imaging modalities used for AMD, demonstrating how advanced algorithms enhance disease feature identification, detection, classification, segmentation and prognostication. Despite these advancements, several limitations remain. Current datasets are often biased, with an over-representation of advanced cases and limited inclusion of specific subtypes, leading to data imbalance and insufficiency. Additionally, the quality and consistency of data significantly impact model performance, as AI systems are highly sensitive to variations in image quality, resolution and equipment, resulting in discrepancies in model accuracy. Moreover, the generalisability of AI models is restricted by their reliance on specific datasets, which may not perform consistently across different clinical environments or imaging devices, posing challenges for practical implementation.

Future research should prioritise collecting and annotating more OCT images, integrating additional imaging data to enhance model performance and improving model interpretability through visualisation and attention mechanisms. Efforts should also focus on designing deep learning architectures specifically for OCT analysis, optimising algorithms and incorporating clinical, genetic and lifestyle data for personalised AMD treatment and prediction. Moreover, the development of more effective multimodal fusion techniques is essential to capture intermodal relationships while preserving the unique characteristics of each modality, thereby enhancing diagnostic and therapeutic accuracy. The ultimate objective is to develop a high-performance AI model that supports AMD diagnosis, segmentation, progression prediction and prognosis, thereby assisting physicians in clinical practice, improving treatment efficacy, optimising management and reducing their workload.

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