

Artificial intelligence in individualized retinal disease management

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Abstract

• Owing to the rapid development of modern computer technologies, artificial intelligence (AI) has emerged as an essential instrument for intelligent analysis across a range of fields. AI has been proven to be highly effective in ophthalmology, where it is frequently used for identifying, diagnosing, and typing retinal diseases. An increasing number of researchers have begun to comprehensively map patients' retinal diseases using AI, which has made individualized clinical prediction and treatment possible. These include prognostic improvement, risk prediction, progression assessment, and interventional therapies for retinal diseases. Researchers have used a range of input data methods to increase the accuracy and dependability of the results, including the use of tabular, textual, or image-based input data. They also combined the analyses of multiple types of input data. To give ophthalmologists access to precise, individualized, and high-quality treatment strategies that will further optimize treatment outcomes, this review summarizes the latest findings in AI research related to the prediction and guidance of clinical diagnosis and treatment of retinal diseases.

• **KEYWORDS:** artificial intelligence; artificial intelligence in ophthalmology; retinal disease

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INTRODUCTION

Artificial Intelligence Concepts Artificial intelligence (AI) constitutes a pivotal domain within computer science. Tremendous advances in computer technology for data collection, storage, and processing have led to the application of AI in medical diagnosis, bioinformatics, and many other fields. Machine learning (ML), a subfield of AI, focuses on devising algorithms that extract general principles of data to model the relationship between a set of input and output values and make predictions about new data^[1]. Traditional ML includes support vector machines (SVMs), random forests (RFs), and other algorithms. Depending on whether the data samples used are labeled, ML can be classified into supervised or unsupervised learning^[2]. Deep learning (DL), a subset of ML, is a novel ML technique based on artificial neural networks that has brought about a new technological revolution in ML (Figure 1). DL can automatically extract high-order abstract feature representations from raw inputs using multi-layer artificial neural networks. Compared to traditional ML, DL can handle more complex and broader datasets, has decision-making capabilities, and contains more hidden layers with scalability and hierarchical feature learning capabilities, this makes DL capable of exploring more complex non-linear patterns in the data and automatically identifying the correct labels from the new features. DL algorithms such as convolutional neural networks (CNNs), recursive neural networks, deep belief networks, and deep neural networks have been used to achieve remarkable success in image recognition, semantic understanding, and speech recognition (Figure 2)^[3-4].

Advantages of Artificial Intelligence in Ophthalmology Practice AI has shown significant promise in medicine, particularly in ophthalmology, owing to enhanced mathematical models, upgraded graphics processing units (GPUs), and the widespread use of Hadoop^[5]. First imaging tests play a major role in the diagnosis and treatment of ocular diseases. High-resolution images from techniques such as spectral-domain optical coherence tomography (SD-OCT), fundus fluorescence angiography, and ultra-wide-field fundus imaging, which have become more sophisticated in ocular imaging technology, offer rich and comprehensive information on retinal morphology. These high-precision imaging techniques provide invaluable

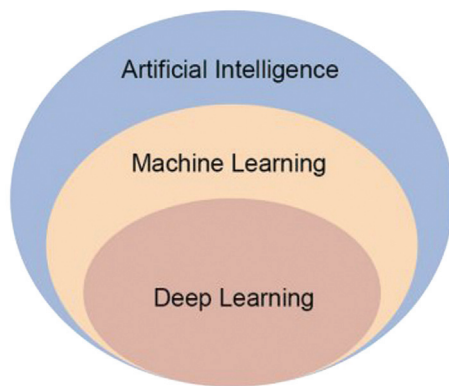


Figure 1 Relationship between artificial intelligence, machine learning, and deep learning.

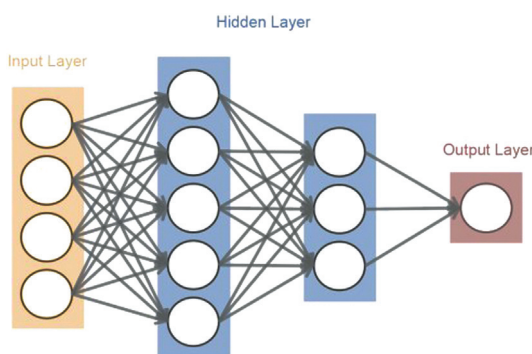


Figure 2 Schematic of deep learning network structure.

clinical data for the development and training of AI models, which are the key drivers for their widespread application in ophthalmology^[6-7]. The availability of equipment for ocular examination is another important factor. Second, the convenience of using ocular examination tools makes it possible to conduct widespread population screening. The volume and consistency of this data-gathering process ensure the availability of a strong database for iterations during AI model optimization. Thus, AI models continually improve and learn to assist clinicians in diagnosing patients with high precision. AI can also learn from and summarize a vast number of previous cases. Feature patterns can be identified in large datasets to automatically diagnose disease activity in ocular image data. This automated and standardized assessment process provides a strong basis for accurate and individualized clinical diagnosis and treatment, enabling the individualized prediction of ocular disease progression, treatment response, ideal retreatment intervals, and prognosis. The following research has been conducted over the last several years and serves as the basis for this investigation^[8-9].

In 2019, the World Health Organization published its World Vision Report, which identified several significant causes of moderate-to-severe visual impairment and even blindness, including age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vein occlusion (RVO), and other ocular fundus disorders^[10]. The etiologies of

retinal disorders are multifaceted, and managing them often requires a protracted therapeutic process. Most diagnoses and efficacy assessments of these diseases rely on imaging examinations, such as ocular fundus photography, OCT, and slit lamp microscopy. Consequently, early diagnosis and prompt treatment are essential to preserve visual function and minimize the damage caused by the disease. AI has had a significant impact on the field owing to its unique advantages. AI can identify patterns in retinal diseases and correlate individual features to build disease prediction models by detecting and learning features from a large amount of image data, and many multimodal ocular images provide massive data for the development of AI models. AI's application not only reduces the treatment expenditures of patients but also enhances their quality of life, simultaneously relieving physicians of some of the burdens associated with managing diseases^[11-12]. Therefore, AI is anticipated to advance the field of individualized medicine and has a significant potential to increase the effectiveness of retinal disease management.

Artificial Intelligence and Age-related Macular Degeneration

AMD emerges as the principal factor causing irreversible blindness among elderly people. Patients with early-stage AMD tend to be asymptomatic and often experience a gradual decline in visual acuity (VA). As the condition progresses, early-stage AMD advances to late-stage AMD, which is classified into two primary subtypes: atrophic AMD and neovascular AMD (nAMD), characterized by geographic atrophy (GA) and choroidal neovascularization (CNV), respectively^[13]. Owing to variations among individuals, the progression of AMD is unpredictable, and not all patients progress to the late stages. Early-stage AMD is characterized by focal cellular metabolic deposition (drusen) between the retinal pigment epithelium (RPE) and the Bruch's membrane in the macular area^[14]. Excessive accumulation of drusen can cause RPE damage, trigger inflammatory responses, and provoke degenerative changes, leading to retinal atrophy, vascular endothelial growth factor (VEGF) expression, and neovascularization. In many instances, late-stage AMD develops precisely where drusen degeneration is prominent. There are still no treatments that can effectively halt the progression of mid- to late-stage AMD. Therefore, it is imperative to identify pathomorphological changes associated with early-stage AMD. The use of AI to extract sensitive and specific biomarkers from fundus images is promising for predicting the type and timing of AMD progression in individual patients. This approach offers the potential for the early screening and individualized clinical management of high-risk patients (Table 1)^[15-22].

Hallak *et al*^[15] performed a retrospective analysis of 686 fellow eyes with non-neovascular AMD from the HARBOR randomized clinical trial. They used ML for automatic feature

Table 1 Prediction models for progression and prognosis of age-related macular degeneration

Author	Year	Sample size	Data type	Algorithms	Task
Hallak <i>et al</i> ^[15]	2019	686	Demographic and clinical data/OCT	ML	Determine the features associated with the conversion to nAMD.
Yim <i>et al</i> ^[16]	2020	3111	OCT	DL	Predict the progression of nAMD in the second eye.
Liefers <i>et al</i> ^[17]	2020	238	CFIs	DL	Extract structural markers of GA that forecast its progression velocity.
Schmidt-Erfurth <i>et al</i> ^[18]	2018	495	Genetic and Demographic data/OCT	ML	Analyze imaging biomarkers to predict the risk of AMD progression.
Waldstein <i>et al</i> ^[19]	2020	1097	OCT	ML	Characterizes drusen and hyperreflective foci in AMD patients.
Riedl <i>et al</i> ^[20]	2020	185	OCT	DL	Quantitatively assess photoreceptor morphology and its correlation with disease morphology and function.
Schmidt-Erfurth <i>et al</i> ^[21]	2018	614	OCT	RF	Investigate the prognostic significance of current imaging biomarkers in nAMD.
Yeh <i>et al</i> ^[22]	2022	698	Demographic data/OCT	CNN	Predict visual acuity 12mo after anti-VEGF treatment in nAMD.

OCT: Optical coherence tomography; ML: Machine learning; CFIs: Color fundus images; DL: Deep learning; RF: Random forest; nAMD: Neovascular age-related macular degeneration; GA: Geographic atrophy; CNN: Convolutional neural networks.

extraction from SD-OCT images, refined the feature set *via* least absolute shrinkage and selection operator (LASSO) regression, and investigated the association between imaging features, genetics, demographic factors, and conversion to nAMD using survival analysis and Cox modeling. Eventually, the area and reflectivity of drusen were correlated with AMD progression. The discovery of OCT biomarkers can help predict disease progression in patients with mid-stage AMD and guide the development of individualized interventions. Yim *et al*^[16] introduced an AI system to predict the progression of nAMD in the second eye for patients with a current diagnosis in one eye. It integrates 3D OCT images and corresponding automatic tissue maps to forecast onset within 6mo, achieving high sensitivity and specificity. This demonstrates AI's potential in early diagnosis and intervention in AMD progression, thus facilitating personalized treatment for patients before vision loss.

GA typically occurs in the late stages of AMD, and it is characterized by progressive atrophy of the RPE, overlying photoreceptors, and underlying choriocapillaris^[23]. GA often develops outside the central sulcus and gradually expands into it, eventually leading to severe vision loss. Given the inter-individual variations, understanding the rate of GA growth is pivotal for devising individual treatment strategies. Liefers *et al*^[17] developed a DL model based on an encoder-re-encoder structure for segmenting the GA from color fundus images. By combining fundus biomarkers at the baseline with GA growth rate in a linear regression analysis, nine automatically segmented structural markers (*e.g.*, area, filled area, convex area) were found to be significantly correlated with GA growth rate, notably highlighting that the GA area grows quadratically before stabilizing or decreasing once it reaches 12 mm². Schmidt-Erfurth *et al*^[18] used an ML prediction model to predict the development of AMD eyes into GA or CNV

within two years. They amalgamated the SD-OCT image features, genetic, and demographic data with predictions using two Cox proportional risk regression models. They observed that GA prediction was more accurate and that GA and CNV progression exhibited distinctive feature patterns, with CNV predictive markers predominantly influenced by drusen and GA markers more strongly associated with age and neurosensory retina. Specifically, the features most strongly linked to GA progression included the outer retinal thickness, hyperreflective foci, and drusen areas. Further studies have focused on identifying whether OCT exhibits distinct morphological patterns in eyes with GA or CNV. Waldstein *et al*^[19] used a previously validated segmentation algorithm to characterize drusen and hyperreflective foci as biomarkers of AMD progression in SD-OCT images, which incorporated 8529 SD-OCT images from the HARBOR dataset of 1097 patients over two years and found that eyes that progressed to CNV had higher drusen with thicker hyperreflective foci overlying it in the macular central concavity, whereas eyes that progressed to GA did not show the same distribution pattern in the central concavity, suggesting that fewer drusen in the central concavity may be the first step in triggering photoreception, RPE, and choroidal atrophy. These findings suggest that it is possible to personalize the prediction of AMD progression using biomarkers on ophthalmic examination images such as OCT and color fundus images. By modeling disease progression in a predictive and interpretable manner, we can improve risk management for patients with early-stage AMD and gain deeper insights into the pathophysiological mechanisms underlying its progression.

Anti-VEGF therapy is the mainstream treatment for nAMD. nAMD patients receiving anti-VEGF therapy can improve their best-corrected visual acuity (BCVA) by one to two lines after one year of treatment compared with baseline

Table 2 Prediction models of diabetic retinopathy

Author	Year	Sample size	Data type	Algorithms	AUC	Sensitivity (%)	Specificity (%)	Task
Tsao <i>et al</i> ^[32]	2018	536	Clinical data	SVM	0.839	93.3	72.4	Predict the risk of DR
Li <i>et al</i> ^[33]	2021	32452	Clinical data	XGBoost	0.9	70	90	
Zhao <i>et al</i> ^[34]	2022	7943	Demographic and clinical data	XGBoost	0.803	74.0	81.1	
Cao <i>et al</i> ^[35]	2020	258	Clinical data	RF	0.84	92.3	75	
Arcadu <i>et al</i> ^[36]	2019	645	CFIs	DCNN	0.79	91	65	Predict the progression of DR
Dai <i>et al</i> ^[37]	2024	179327	CFIs	DL	-	-	-	
Cao <i>et al</i> ^[38]	2021	712	OCT	RF	0.923	90.0	85.1	Predict the therapeutic response in DR
Zhang <i>et al</i> ^[39]	2022	281	Clinical data/OCT	ML	-	-	-	

AUC: Area under the curve; SVM: Support vector machine; XGBoost: Extreme gradient boosting; RF: Random forest; DR: Diabetic retinopathy OCT: Optical coherence tomography; ML: Machine learning; CFIs: Color fundus images; DCNN: Deep convolutional neural networks; DL: Deep learning.

VA^[24]. However, it is clinically difficult to predict the efficacy of anti-VEGF therapy in nAMD patients owing to individual differences in patient responses to therapy. Presently, the identified biomarkers of VA are mainly based on OCT features, such as intraretinal fluid (IRF), degree of photoreceptor loss, and features based on fluorescence angiography fundus images, such as CNV area^[25-26]. Riedl *et al*^[20] quantitatively assessed the morphological integrity of photoreceptors during the anti-VEGF treatment of nAMD, and they analyzed the association between these features, disease morphology, and their functions. They manually quantified the ellipsoid zone (EZ) integrity of SD-OCT images obtained from 185 patients at three follow-up visits spanning 12mo, and they automatically segmented the IRF, subretinal fluid (SRF), and pigment epithelial detachment (PED) using DL models. Using spatiotemporal correlation and bivariate analyses, they found that the enhancement of EZ integrity was predominantly observed in the central concave region. Moreover, they observed a protective effect of SRF on photoreceptor integrity, with photoreceptor integrity correlating with BCVA. Schmidt-Erfurth *et al*^[21] harnessed a DL algorithm based on graph theory and a CNN to execute spatially resolved 3D segmentation of the retinal layers, SRF, IRF, and PED from an impressive dataset of 41 840 SD-OCT scans derived from 1817 patients. Their study utilized an RF algorithm to correlate SD-OCT image parameters extracted within the initial 3mo with BCVA measurements to predict VA status after 12mo of standardized anti-VEGF treatment. They observed that the predictive accuracy of their model increased with the duration of the initial phase, reaching a value of 0.70, and the horizontal extension of the IRF in the central concave region was identified as the foremost predictor of BCVA. Collectively, these studies offer compelling evidence that changes in SD-OCT images coupled with concomitant nAMD features can be used to predict the visual functional outcomes of patients. This can aid the development of individualized anti-VEGF treatment regimens tailored for individual nAMD patients. Yeh *et al*^[22] proposed the

Heterogeneous Data Fusion Net that integrated pre-treatment OCT images and demographic data to predict VA outcomes 12mo after anti-VEGF treatment in nAMD, demonstrating high accuracy, sensitivity, and specificity. This approach underscores the potential of DL in leveraging diverse clinical data for personalized treatment strategies in nAMD.

Artificial Intelligence and Diabetic Retinopathy DR, emerging as the predominant cause of visual loss in the global working-age population, represents the most frequent microvascular complication associated with diabetes. Approximately one-third of individuals diagnosed with diabetes are affected by this condition. The pathogenic transformations in DR are mainly retinal capillary endothelial damage, including selective pericyte loss, basement membrane thickening, capillary occlusion, and leakage of plasma components owing to endothelial barrier dysfunction^[27]. DR is classified into non-proliferative DR (NPDR) and proliferative DR (PDR) based on lesion severity. Regular screening is recommended for NPDR patients, and early diagnosis and treatment with lasers or intravitreal anti-VEGF injections are required to maintain residual vision^[28].

Numerous studies have extensively explored the risk factors of DR^[29-30], but no definitive conclusions have been reached. DR's complexity is attributable to the fact that diabetes mellitus and the development of DR are the result of a multifactorial combination of factors, such as postprandial glucose, the duration of diabetes mellitus, hemoglobin A1c (HbA1c), and hypertension^[31]. Risk assessment of DR should integrate the combination of factors. The application of AI in DR risk prediction has attracted widespread attention (Table 2)^[32-39]. Tsao *et al*^[32] used several ML algorithms, including decision trees, SVMs, logistic regression (LR), and artificial neural networks, to develop a prediction model for DR in type 2 diabetes mellitus patients. The study showed that SVMs performed better than other ML algorithms in terms of prediction performance, and the sensitivity of the algorithm using a percentage split (*i.e.*, the dataset was divided into 80% for training and 20% for testing) reached 79.5%. In particular,

their study identified the use of insulin and the duration of diabetes as new predictive features. This suggests that clinical features combined with appropriate ML algorithms can be effective in predicting DR to identify high-risk populations to provide individualized treatment plans, thereby improving the rationality of medical resource allocation. The sample size of this study was small and included only 10 clinical indicators; however, the complexity of DR risk factors requires larger sample sizes to study and build predictive models. When analyzing larger sample sizes and datasets, the extreme gradient boosting (XGBoost) algorithm performed better than LR. Li *et al*^[33] compared four learning algorithm models, LR, SVM, RF, and XGBoost, based on 32 452 samples and found that the XGBoost model achieved the highest area under the curve (AUC) value in predicting the risk of DR on the internal validation set. In addition, the combined effects of several indicators, including blood glucose, renal function, liver function, and coagulation function, were analyzed using ML algorithms. The results showed that the elevated levels of HbA1c, the presence of nephropathy, serum creatinine concentrations, insulin therapy, and peripheral arterial disease in diabetic patients were positively correlated with the heightened risk of developing DR. In contrast, increasing age was inversely associated with this risk. However, this study was a single-center study relied on internal validation; therefore, future multicenter studies will require extra work. Zhao *et al*^[34] collected the electronic health record data of 7943 inpatients with type 2 diabetes mellitus and developed five risk prediction ML models for the future development of DR. Notably, the XGboost model, known for its high runtime speed and good scalability, showed the best predictive performance, evidenced by an AUC of 0.803, accuracy of 88.9%, sensitivity of 74.0%, and specificity of 81.1%. In addition to diabetes duration, HbA1c, fasting blood glucose, and age, which are classical risk factors for DR, low-density lipoprotein cholesterol, serum uric acid, estimated glomerular filtration rate, total cholesterol, and triglyceride were first considered important factors for DR prediction. Data analysis from multiple time points showed that the XGBoost model could pre-diagnose DR in the absence of fundus images. The application of this model can help clinicians to accurately identify high-risk groups for DR and develop individualized health management strategies for patients, thereby reducing the incidence and progression of DR.

In addition, there is growing evidence that the development of DR is greatly affected by various cytokines found in retinal tissues, including VEGF, matrix metalloproteinases, and tissue inhibitors of metalloproteinases, through angiogenic, inflammatory, and fibrotic reactions^[40-41]. Cao *et al*^[35] investigated the association between plasma cytokines and

NPDR and developed an ML classifier to predict NPDR in type 2 diabetes mellitus patients. Their study demonstrates that angiopoietin-1, platelet-derived growth factor-BB, and VEGF receptor 2 are associated with NPDR. An RF algorithm based on the concentrations of these three cytokines in plasma had the best performance in discriminating NPDR, with a sensitivity of 92.3% and an AUC of 0.84 in the test set.

Early diagnosis and treatment of DR can significantly reduce the risk of blindness, and international organizations recommend regular DR screening for all diabetics^[42]. Given the vast differences in DR progression risk among individuals, developing personalized risk models and accurate prediction of the progression of the disease is crucial. AI demonstrates significant potential in this area, with the hope of providing individualized screening plans and timely medical interventions for high-risk individuals, optimizing resource allocation, and improving personalized treatment and disease management. Arcadu *et al*^[36] developed deep CNNs based on 7-field color fundus images, enabling the prediction of significant DR progression at an individual level over 2y following the baseline visit. One of these algorithms (forecast at monthly twelve) achieved an AUC of 0.79, which indicated that using color fundus images obtained from a patient in a single visit can predict future DR progression. Dai *et al*^[37] employed 717 308 fundus images from 179 327 diabetic individuals to pre-train the DeepDR Plus system to predict personalized risk and time to DR progression. The subsequent real-world study indicated that the mean screening interval might be extended to nearly 3y with less delayed detection of DR progression when this system had been integrated into the clinical workflow of patients, which demonstrated the potential of the system to enhance patient-specific risk assessment and offer further personalized care for DR management.

Diabetic macular edema (DME) represents the primary etiology of vision loss in association with DR, attributable to the accumulation of fluid in the central retina and macular thickening owing to blood-retinal barrier dysfunction. Laser photocoagulation was once recommended as the standard treatment option for DME; however, its effectiveness in improving the VA has been limited. Therapeutic interventions targeting VEGF can alleviate macular edema and prevent further retinal damage^[43-44]. Nevertheless, a proportion of patients exhibit either partial or no response to anti-VEGF treatments, which suggests the need for a prompt transition to other viable treatment options at an early stage. Therefore, the early prediction of responsiveness to anti-VEGF therapy in DME patients is essential to determine the optimal therapeutic regimen. Cao *et al*^[38] classified 712 DME patients into poor and good responders according to the decrease in central macular thickness after three months of anti-VEGF therapy, and then

Table 3 Prediction models for prognosis of RVO

Author	Year	Sample size	Data type	Algorithms	Task
Gallardo <i>et al</i> ^[47]	2021	333	Demographic data/OCT	RF	Predict low and high treatment demand in RVO
Waldstein <i>et al</i> ^[48]	2017	391	OCT	ML	Evaluate the impact of VMA on anti-VEGF therapy for RVO
Etheridge <i>et al</i> ^[49]	2021	362	OCT	ML	Evaluate the association between EZ and VALS in RVO
Michl <i>et al</i> ^[50]	2022	66	Clinical data/OCT	SVM	Determine the prognosis of the BCVA during the continuous anti-VEGF treatment in RVO
Arepalli <i>et al</i> ^[51]	2023	26	OCT	ML	Evaluate the association between cytokine expression, specific OCT features, and treatment response in RVO
Muste <i>et al</i> ^[52]	2022	92	OCT	DL	Evaluate the impact of persistent IRF or SRF on BCVA in RVO

RF: Random forest; OCT: Optical coherence tomography; ML: Machine learning; DL: Deep learning; RVO: Retinal vein occlusion; VMA: Vitreomacular adhesion; EZ: Ellipsoid zone; VALS: Visual acuity letter score; SVM: Support vector machine; BCVA: Best-corrected visual acuity; IRF: Intraretinal fluid; SRF: Subretinal fluid; VEGF: Vascular endothelial growth factor.

developed ML models based on relevant features automatically extracted from OCT images using DL algorithms to predict the anti-VEGF therapy response. The RF model outperformed other predictive models, with a sensitivity of 0.900, a specificity of 0.851, and an impressive AUC of 0.923. This study helps predict treatment needs in advance and provides DME patients with the best individualized management. Similarly, Zhang *et al*^[39] carried out a retrospective analysis on a cohort consisting of 281 eyes affected by DME, which had been treated with intravitreal injections of anti-VEGF therapies. The prediction of VA outcomes following treatment was conducted using six different ML algorithms, which analyzed 18 features derived from electronic health records and OCT. The integrated algorithm combining linear regression with an RF regressor demonstrated efficacy in accurately predicting VA and VA variance at a one-month follow-up. This has significant clinical value for customizing patient-specific treatments and establishing realistic expectations for outcomes. Nevertheless, the study's limited sample size indicates a need for a larger dataset to enhance the predictive accuracy of the algorithm.

ARTIFICIAL INTELLIGENCE AND RETINAL VEIN OCCLUSION

The second leading cause of blindness after DR is RVO, which is a degenerative retinal disease. The primary cause of its pathogenesis is the obstruction of retinal circulation, which can be caused by several factors, including changes in blood rheology and hemodynamics, endothelial damage to the vessel wall, intraocular pressure, and local ocular compression, which can result in hemorrhage, exudation, and edema in large areas of the ocular fundus^[45]. Depending on the location of the venous obstruction, RVO can be classified as either branch retinal vein occlusion (BRVO) or central RVO. Currently, anti-VEGF therapy is effective in improving the visual outcomes in individuals with RVO^[46]. Nonetheless, there is considerable variation in the treatment requirements and modalities among patients; thus, it is critical to establish individualized treatment plans for each patient (Table 3)^[47-52].

The two most popular treatment approaches are *pro re nata* and the treat-and-extend regime (TER)^[53], both of which rely on OCT of the central retinal region to track the course of the disease and the effectiveness of the therapy. It will be possible to create treatment plans based on various prognostic predictions and optimize treatment regimens for specific patients by predicting the responsiveness of patients to treatment regimens at the beginning of the treatment process. Gallardo *et al*^[47] employed 333 eyes diagnosed with DME or RVO that underwent anti-VEGF therapy adhering to a predefined TER and classified them into low, moderate, and high therapeutic demands. They subsequently trained two RF models to predict the demand for treatment and analyzed both the performance of the models and the consistency of the features they used with those utilized by clinicians. This ML classifier can predict the long-term need for anti-VEGF therapy in RVO patients and may help improve individualized therapeutic regimens for patients. However, the study cohort consisted primarily of elderly patients; therefore, the applicability of the algorithm to younger patients is questionable.

Vitreomacular adhesion (VMA) has been identified as a prognostic biomarker in cases of RVO subject to anti-VEGF therapy, with research indicating a beneficial effect of VMA presence on VA outcomes following anti-VEGF treatment^[54]. Waldstein *et al*^[48] designed and evaluated a fully automated segmentation algorithm that combined ML and graph cutting for the posterior vitreous boundary. The algorithm analyzed the SD-OCT graphs of 391 patients suffering from RVO. All patients were treated with standardized ranibizumab over periods of either six or twelve months. This algorithm used the developed method combined with unsupervised clustering to distinguish between VMA and non-VMA. Finally, the researchers concluded that eyes with VMA had larger BCVA gains than those of eyes without. BRVO paired with macular edema is a substantial contributor to a decline in prognostic BCVA, and EZ integrity may be related to VA and visual prognosis outcomes in RVO patients with macular edema.

Etheridge *et al*^[49] evaluated the correlation between the VA letter score (VALS) and EZ on SD-OCT in eyes with macular edema secondary to RVO using ML. The results showed that the mean VALS was better in eyes without EZ defects than in eyes with EZ defects and that the EZ defects at month one were related to poorer VALS at the subsequent follow-up. Therefore, the integrity of the EZ obtained from SD-OCT is a biomarker for estimating the prognosis of VA and it can play a significant role in determining the efficacy of therapeutic interventions, enhance disease monitoring, and aid the establishment of individual therapeutic regimens for RVO patients. When treating BRVO patients and macular edema, clinicians need to consider the extent and recurrence of macular edema as well as changes in BCVA throughout the first year of treatment. Michl *et al*^[50] developed an SVM classifier that achieved an accuracy of 0.806 and predicted the prognosis of individual patients over time during the continued anti-VEGF monotherapy phase. This provides a convincing reference index for establishing patient-specific treatment plans. The expression of cytokines in the aqueous humor may also influence the efficacy of anti-VEGF therapy against RVO^[55]. Arepalli *et al*^[51] used an advanced retinal segmentation and feature extraction platform to correlate cytokine expression profiles with OCT image features. It was observed that the levels of VEGF were directly correlated with the volume of IRF, whereas the levels of angiogenin were inversely related to fluid indices. Additionally, individuals who showed positive responses to treatment had higher baseline VEGF levels than those who did not respond, suggesting that cytokine expression is associated with specific OCT features and treatment responses in RVO. In addition, Muste *et al*^[52] used a DL model to quantify the volume of IRF and SRF, and a linear mixed-effect regression model to assess the impact of IRF and SRF on BCVA in RVO patients. These results suggest the prognostic significance of IRF for BCVA in RVO patients.

In addition to directly recognizing image information, AI can be used in conjunction with bioinformatics to analyze the potential applications of biomarkers in clinical decision-making. Pur *et al*^[56] carried out a systematic review of the application of bioinformatics and AI for the analysis of biofluid biomarkers in RVO. Their study highlights the possibility of integrating bioinformatics and AI to develop precision medicine for RVO. For instance, it was discovered that the levels of interleukin (IL)-6, intercellular adhesion molecule-1, VEGF, and IL-8 in the vitreous humor were linked to the pathogenesis of BRVO with macular edema. Additionally, IL-6 and VEGF may be used to predict VA after intravitreal injections or vitrectomy, respectively. Bioinformatics analyses using metabolomics and proteomics in conjunction with AI analyses have the potential to advance the discovery of

biomarkers for RVO, provide predictions for the complications and prognosis of RVO, and guide individualized therapeutic strategies by mapping treatment responses. While the application of AI and bioinformatics in RVO is on the rise, the field remains nascent. Related studies still have certain limitations, such as the lack of healthy control groups and the reliance on small sample sizes, which require further validation and integration of data obtained from multiple sources.

The abovementioned studies offer ophthalmologists new insights into the prognostic treatment of RVO patients and help improve precision medicine and individualized treatment decisions. Although the methods used in these studies have a high predictive value for RVO prognosis, most studies included limited sample sizes and required a longer time to collect the required samples to complete the training and parameter tuning of the models.

ARTIFICIAL INTELLIGENCE AND CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy (CSC) is an idiopathic macular disease characterized by the retinal detachment (RD) of the neurosensory layer caused by SRF accumulation. Prolonged SRF accumulation poses a significant threat to the retinal photoreceptors, potentially leading to irreparable vision loss^[57]. Recent studies have shown that photodynamic therapy (PDT) outperforms other treatment modalities in managing CSC, including micropulse laser therapy, oral saline corticosteroid antagonist therapy, and anti-VEGF therapy^[58]. However, PDT is an invasive treatment method that requires the injection of expensive photosensitizers with unpredictable outcomes. ML or DL models are currently being applied in several studies to identify color fundus images, OCT, or OCT angiography to accurately diagnose or assess CSC^[59-61]. However, research into the development of predictive models to assess the efficacy of PDT in CSC management remains limited.

Jee *et al*^[62] conducted a multicenter retrospective cohort study to evaluate the performance of a DL model in predicting CSC prognosis. They used multiple sets of OCT images from 832 CSC patients, including detailed data from different retinal and choroidal layers, and used the ResNet50 architecture for model training and validation to optimize prediction performance. They observed that the strategic integration of image sets considerably enhanced the predictive capabilities of DL models. More specifically, predictive models based on OCT B-scans, retinal thickness, and EZ en-face images exhibited remarkable predictive prowess. Pfau *et al*^[63] used a CNN to execute precise segmentation of SD-OCT image data from 57 eyes of 57 CSC patients and matched them with fundus visual field data. This meticulous segmentation was then juxtaposed with the fundus visual field data and integrated using an ML regression model. This innovative approach allowed for the

Table 4 Prediction models for prognosis of retinal detachment and macular hole

Author	Year	Sample size	Data type	Algorithms	AUC	Sensitivity (%)	Specificity (%)
Fung <i>et al</i> ^[68]	2023	6661	Digital images	DL	0.94	73.3	96
Li <i>et al</i> ^[69]	2020	11087	Ultra-widefield fundus images	DL	0.975	90.9	93.8
Zgolli <i>et al</i> ^[70]	2022	120	OCT	ML	0.967	-	-
Xiao <i>et al</i> ^[71]	2023	330	Clinical data/OCT	DL	0.947	97.9	81.5
Obata <i>et al</i> ^[72]	2022	259	OCT	DL	-	-	-
Lachance <i>et al</i> ^[73]	2022	121	Clinical data/OCT	CNN	0.819	67.8	91.3

AUC: Area under the curve; OCT: Optical coherence tomography; ML: Machine learning; CNN: Convolutional neural network.

extrapolation of retinal function from the retinal structure, subsequently predicting retinal sensitivity seven to eight months post-treatment based on baseline patient data. The model had a reasonable prediction accuracy, with an average absolute error of merely 3.38 dB. Yoo *et al*^[64] innovatively combined ResNet50 and the XGBoost framework to develop a novel two-stage DL model for predicting the uptake of SRF in CSCs after PDT. The intricate process of developing the model involved pre-training a ResNet50-based CNN using normal fundus photographs for CSC detection. Subsequently, we used transfer learning to predict the treatability of CSCs with complete SRF uptake. Finally, it seamlessly integrated clinical variables with the deep features of fundus photographs using XGBoost, thereby bolstering prediction accuracy. The exceptional performance of the model, with an AUC of 0.917, underscores the immense value of transfer learning and multimodal linkage strategies in overcoming the clinical prediction challenges often posed by limited data.

Future research should concentrate on developing additional DL models to detect other clinically pertinent prognostic indicators of CSC. These may encompass the final VA, the duration required for complete SRF resorption, and the risk of SRF recurrence. By doing so, we can pave the way for more individualized diagnostic and treatment strategies for CSC, thereby heralding a new era in precision ophthalmology.

ARTIFICIAL INTELLIGENCE AND RETINAL DETACHMENT

RD is one of the most substantial etiologies that leads to vision loss, and surgical intervention is widely acknowledged as the most effective therapeutic method for addressing this vision-impairing condition^[65]. To ensure positive surgical outcomes and patient prognosis, it is critical to accurately predict the anatomical outcomes of RD procedures, which form the basis for providing optimal surgical care. Currently, clinicians predominantly rely on preoperative clinical data to ascertain and forecast surgical anatomic outcomes^[66-67]. As AI technology evolves, applied modeling has emerged as a pioneering approach for predicting surgical outcomes with greater accuracy (Table 4)^[68-73].

Fung *et al*^[68] applied a DL approach based on the Inception-v3 CNN architecture to predict anatomical outcomes after RD

surgery. They used 6661 vitrectomy RD fundus images from the BEAVRS dataset and categorized the images into surgical success and failure cohorts based on surgical outcomes. To solve the data imbalance problem, the research team used the Synthetic Minority Over-sampling Technique for data augmentation and divided the dataset into training, validation, and testing subsets. Through a transfer learning process, the study bolstered classification proficiency by substituting and training the topmost layer of the Inception-v3 framework with a class layer tailored to the BEAVRS dataset. Testing revealed excellent performance, with an AUC of 0.94, sensitivity of 73.3%, and specificity of 96.0%. Li *et al*^[69] further developed a cascade DL system based on fundus images, encompassing two models tasked with identifying and discriminating RD above and below the macula. The system not only accurately recognizes RD, but also extends preoperative postural guidance to patients by assessing macular status, informing them of the optimal timing of surgery and possible postoperative visual prognosis. This innovative system is expected to reduce the progression of RD and significantly reduce the degree of visual impairment caused by RD. Integrating these DL models portends to enhance the capabilities of clinicians in rendering individualized consultation and surgical decision-making for RD patients, further advancing the precision and personalization of ophthalmic care.

ARTIFICIAL INTELLIGENCE AND MACULAR HOLE

Macular hole (MH), a complete tissue deficit affecting the neuroepithelial layer of the retina, specifically in the macular region, is a significant etiology of central vision loss among young individuals^[74]. Despite advancements in surgical methodologies over the past decade that have positively impacted the prognosis of MH, a degree of ambiguity remains in terms of both the prognostic evaluation and outcomes achieved through surgical intervention.

Zgolli *et al*^[70] developed an ML-based medical decision support system model for predicting MH closure status after surgery for idiopathic MH. The study trained the model by measuring quantitative parameters, such as different macular diameters, heights, and angles, in SD-OCT images within a 9-month follow-up period after idiopathic MH and obtained excellent predictive performance with an AUC of 0.967.

Xiao *et al*^[71] constructed a multimodal deep fusion network (MDFN) that integrates preoperative OCT images with other clinical data to predict the postoperative MH status. Compared with the unimodal DL model, the MDFN model has a significant advantage in terms of prediction performance, highlighting the importance of a multimodal approach in enhancing predictive accuracy. Obata *et al*^[72] investigated 259 eyes with MH that were treated with vitrectomy and trained a DL model using OCT images to visualize the VA status of the MH after vitrectomy. They used preoperative OCT images and postoperative VA to train a DL model and performed regression analysis based on the model output. They observed that combining preoperative VA and MH size can improve the prediction of postoperative MH and VA with a high degree of accuracy, emphasizing the potential utility of AI in enhancing surgical outcomes. Furthermore, Lachance *et al*^[73] used a model, combining DL and clinical features, to forecast VA improvement six months after MH surgery. They used 242 HD-OCT B-scan images of 121 MH cases to train a CNN model and combined it with an LR model of preoperative clinical features for prediction. The results showed that both the clinical features and the high-definition OCT (HD-OCT) model exhibited strong predictive capabilities, effectively forecasting vision improvement outcomes after MH surgery. Collectively, these studies offer compelling evidence of the immense potential of AI in fundus image analysis and surgical treatment outcome prediction. By extracting RD preoperative metrics, AI models are capable of accurately predicting the postoperative treatment outcomes and prognosis, which are expected to provide ophthalmologists with more accurate and individualized surgical decision support.

CONCLUSION

Since its inception, ophthalmology, as a branch of clinical medicine, has evolved from empirical medicine to evidence-based medicine, and translational medicine to precision medicine. The process of continuous digital representation and intelligent analysis of life is fundamental to its evolution. In recent years, the research and application of AI in ophthalmology has grown exponentially, and ophthalmology treatment is gradually moving towards an intelligent medical model. AI may be used to identify unique biomarker traits of various ocular fundus disorders and predict the course of ocular diseases based on biomarker characteristics, allowing for individualized treatment. The “ocular image data+AI” model has shown great clinical potential in the diagnosis and treatment of blinding retinal diseases, including AMD, DR, and RVO. In these cases, the efficacy approached or surpassed that of experts in the field. By examining ocular fundus images, AI can not only identify and diagnose fundus disorders, but it can also identify and diagnose associated non-ophthalmic systemic

diseases. Consequently, investigating the connection between systemic diseases and ocular fundus imaging features, as well as developing AI-based diagnostic systems, has emerged as an increasingly popular area of research. AI can act as an “intelligent assistant” to physicians, assisting them in making faster decisions, identifying anomalies, and offering diagnosis and treatment services by analyzing vast amounts of clinical data. With the continuous improvement of AI algorithms and the expansion of databases, AI may evolve into a medical element with independent thinking and command capabilities, thus providing better healthcare services.

However, if certain obstacles are not overcome, the clinical use of AI in ophthalmological diagnosis and treatment will be severely restricted. These obstacles include the following: 1) Owing to the significant differences between actual and research environments, many AI models that have shown superior performance in externally validated datasets may have several issues in actual clinical applications. In the absence of a rigorous prospective evaluation, the safety and effectiveness of AI in actual clinical scenarios cannot be verified. The availability of high-quality evaluation guidelines is essential to guarantee the validity and reliability of clinical ophthalmic AI research as it progresses in actual clinical settings^[75]. 2) The sample size of data and image quality are not at the same level, and the accuracy of the AI model is correlated with both; the more data and image quality, the higher the accuracy of the AI model. However, the accuracy of the AI model varies across different medical institutions and regions owing to variations in ophthalmic examination equipment, image quality, and patient volume, which limits the accuracy and universality of AI. 3) Patient heterogeneity: While the majority of research on AI models to date has used population-based data from a certain region, AI models may be affected by varying patient populations and variations in the previous groupings of patients, such as ethnicity and geographic location. 4) Professional hurdles to AI: As a subfield of computer science, AI is not well understood by most physicians, and this limits the application and updating of AI in clinical work. 5) Lack of patient trust: Despite the potential of AI in outstanding performance, many patients may not be confident in the outcomes of AI-assisted diagnosis and may prefer to visit the hospital for face-to-face consultation with an ophthalmologist. 6) Ophthalmologists are unduly reliant on AI for diagnosis and treatment, which can result in the loss of their diagnostic abilities. These possible drawbacks emphasize the necessity of ongoing AI development in the future^[76-78].

In recent years, significant academic progress has been made in the application of AI in ophthalmology. The in-depth development and widespread application of AI technology are poised to profoundly transform ophthalmic diagnosis and

treatment processes, primary health care services for the blind, telemedicine practice models, and integrated management systems for chronic and common blinding eye diseases. By accurately analyzing ocular images and multimodal medical data, AI can predict disease trajectories, tailor treatment strategies, and optimize outcomes and patient satisfaction. Additionally, AI can track and evaluate patients' treatment responses in real time, ensuring timely adjustments and optimizations to treatment plans for optimal clinical results and patient satisfaction. Notably, the organic integration of AI with telemedicine technology has demonstrated tremendous application potential and societal value. This innovative model can overcome geographical limitations, enable remote and precise diagnosis and treatment of eye diseases, effectively reduce patients' medical burdens, and provide new solutions to the global challenge of uneven distribution of medical resources. Looking ahead, the application of AI in ophthalmology is expected to become even more widespread and profound. Its integration with cutting-edge technologies such as genetic sequencing and biomarker detection may unlock new frontiers in precision medicine, driving the development of personalized therapeutic approaches. Expanding and enhancing the role of AI in ophthalmic prevention, healthcare, and rehabilitation services will provide more comprehensive, efficient, and intelligent support for improving people's ocular health and quality of life. The application and development of this transformative technology will bring unprecedented opportunities and challenges to the global ophthalmic field, potentially ushering in a new era of ophthalmic development.

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