RESEARCH PAPER

Retinal Imaging as a Non-Invasive Biomarker for Alzheimer's Disease: A Survey of Segmentation and Deep Learning Approaches

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Abstract - Retinal imaging has become an essential non-invasive method of diagnosis of ophthalmic and neurodegenerative diseases, such as Alzheimer disease (AD) and mild cognitive impairment (MCI). The recent developments in the field of deep learning have facilitated the automated segmentation of the retinal vessels and optic disc, which benefits the detection of diseases and clinical decisions made. The paper overviews the current state of art in retinal image analysis, including convolutional neural networks (CNNs), transformer - based models, and state-space models including Mamba. Also, it examines how retinal imaging modalities such as fundus photography, optical coherence tomography (OCT), OCT angiography (OCTA), and hyper spectral imaging can be used in early detection of neurodegenerative diseases. The review indicates newer dynamics in the field of hybrid architectures, multi-scale and multi-view feature fusion, and explainable AI techniques, and points out issues concerning the lack of data, quality of features, computational demands, and clinical interpretability. Through a critical evaluation of current approaches and shortcomings, the paper offers a broad vision to inform future studies in automated retinal image recognition and detection of early AD.

Keywords - Retinal Biomarkers, Alzheimer's Disease, OCTA, Retinal Vessel Segmentation, Deep Learning, Transformer and Mamba Models, Explainable AI, Multimodal Learning.

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1. Introduction

During the last decade, the world has observed an immense rise in medical scenes and healthcare field. This growth has helped in the improvement of health indicators and a high growth in life expectancy which has resulted into a steady increase in the world population which is estimated to be about 11.2 billion by 2100 [1]. Due to this demographic change, the percentage of the ageing population is set to experience a significant growth. It is estimated that close to 60% of the population will be above 60 years old by 2050, and this will make the population about 2 billion of the elderly individuals in the world [2]. As the number of aging people grows at a high rate, age-related disorders have become the issue of higher order, and one of the most serious and problematic disorders is the Alzheimer disease (AD). A research conducted in [3] has estimated that the number of people that will be affected by Alzheimer disease by the year 2050 is about 1 out of every 85 people in the world.

Alzheimer disease is the most prevalent type of disease which is a type of dementia. AD is a progressive and irreversible neurodegenerative disease that is marked by the loss of memory, cognitive decline, behavioral changes, and the inability to carry out everyday tasks [4]. Despite the fact that the etiology of AD is now well known, but genetic disposition, environmental factors, lifestyle related factors are considered as substantial contributors to the development of this disorder. AD is pathologically linked to the hyper phosphorylated tau protein accumulation of amyloid-b plaques and neurofibrillary tangles, in the brain [5]. Figure 1 depicts the progression of Alzheimer's disease. These pathological alterations affect synaptic transmission, neuronal communication and eventually neuronal cell death hence cortical atrophy and enlargement of cerebral ventricles [6]. Besides the classical neuropath logical symptoms, recent research has also emphasized the vascular impairment in the development of Alzheimer disease.

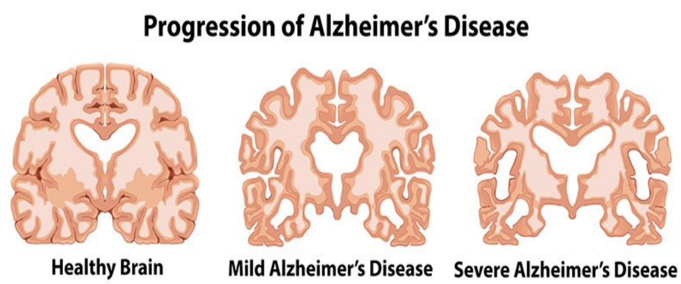

Figure 1. Alzheimer's disease severity

Besides the classical neuropath logical symptoms, recent research has also emphasized the vascular impairment in the development of Alzheimer disease. Both at an early and late stage of AD, reduced cerebral blood flow, degeneration of micro vessels, and failure of neurovascular coupling have been revealed. Such vascular anomalies are considered to be associated with neuronal damage and cognitive impairment which implies that AD is not purely a neurodegenerative disease but has also a robust vascular component. This has led to the development of vascular biomarkers as a significant area of research in early diagnosis and monitoring of the disease. Nowadays the AD diagnosis mainly depends on clinical evaluation, neuropsychological testing, cerebrospinal fluid, and neuroimaging, including magnetic resonance imaging (MRI), and positron emission tomography (PET) [7,8]. Although these procedures offer great diagnostic data, most of them are costly, intrusive, time-consuming, and cannot be used to conduct mass screening or frequent follow-ups. This makes it very urgent to have non-invasive, cost-effective, and readily available diagnostic methods that can be used to detect early pathological changes related to AD.

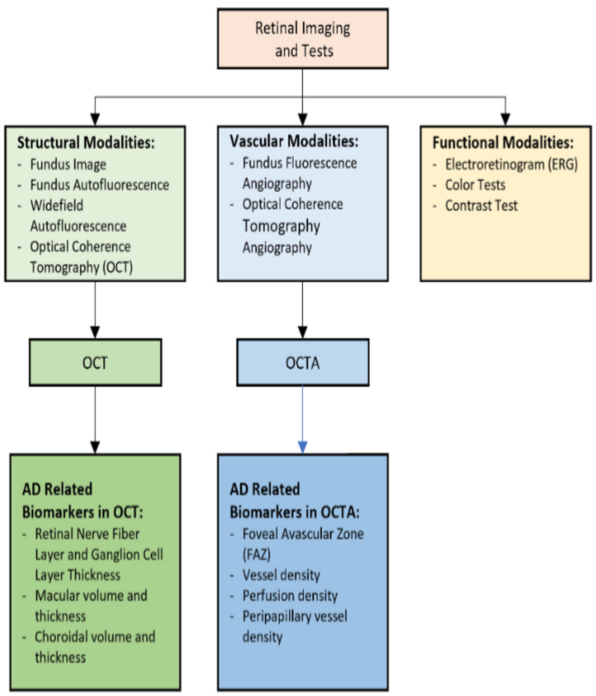

Figure 2. Retinal tests and biomarkers

In this regard, the retina has been considered a good alternative since retinal imaging has been shown to be promising as the retina has embryological and anatomical similarities with the brain [9,10]. Changes in cerebral vascular in the Alzheimer disease might be observed in the retinal microvasculature. High-resolution, non-invasive imaging modalities, including Optical Coherence Tomography Angiography (OCTA) are the ideal candidates to be utilized in the exploration of AD-related biomarkers [11,12]. OCTA is able to identify early onset microvascular changes that are indicative of Alzheimer disease including decreased vessel density, and an increase in the foveal avascular zone and capillary dropout, especially of the superficial and deep vascular plexuses [13,14]. The observed changes are associated with cerebral vascular damage and cognitive impairment, which means that OCTA may be the biomarker of the early diagnosis and monitoring the disease. OCTA is non-invasive, cost-effective, and allows frequent follow-ups, in comparison with other conventional neuroimaging methods, which may provide large-scale screening and longitudinal studies. Retinal structural changes, such as the thinning of the retinal nerve fiber layer and ganglion cell layer, can also be used in addition to vascular processes to detect and track AD-related neurodegeneration. Based on these retinal biomarkers, there has been a growing interest in using artificial intelligence (AI), machine learning (ML), and deep learning (DL) methods in order to automate and improve the identification of Alzheimer disease [15, 16].

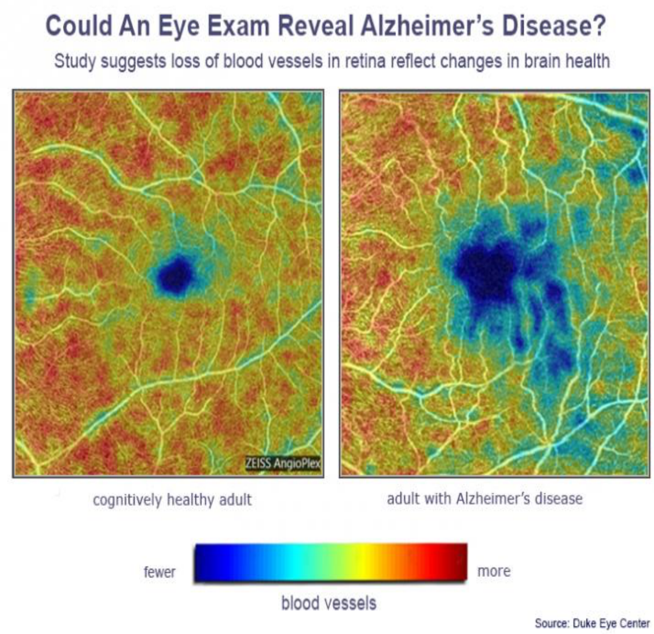

Figure 3. Blood vessel loss impact on Alzheimer's

Such computational methods have the ability to process retinal images, compute quantitative features and detect delicate patterns that cannot be easily discerned by human observers. In ML-based models, retinal imaging-based features (e.g., FAZ area, vessel density, tortuosity, and retinal nerve fiber layer thickness) serve as input to classifiers such as Support Vector Machines (SVM), Random Forests, and XGBoost [17]. These procedures present interpretable models that have the ability to differentiate between healthy subjects and those with AD or mild cognitive impairment (MCI). Classical ML methods are highly sensitive to the quality and relevance of manually engineered features although they perform well with a small dataset. Several methods have been discussed in this domain where supervised ML approaches are widely adopted for AD classification tasks which are described in section II.

Deep learning and in particular convolutional neural networks (CNNs) provide an even more effective option as it allows end-to-end learning on retinal images [18]. CNN based models are capable of learning hierarchical representations of both structural and vascular modifications relating to AD automatically. As an illustration, OCT and

OCTA images have been subjected to CNNs to classify the subject as healthy, MCI or AD with high accuracy without manually extracting features [19]. Other variants, including U-Net and Attention U-Net, have been especially effective in segmenting the Foveal Avascular Zone (FAZ) and retinal vessels, and as a consequence can enable accurate measurement of the microvascular pathologies [20]. Segmentation results may be in turn fed to ML classifiers or worked out as features in longitudinal disease progression tracking. Combination Hybrid methods have also been suggested to combine the effectiveness of both paradigms through deep learning-based segmentation and ML-based classification. As an example, the analyzed FAZ and vessel maps segmented with U-Net may be used to extract quantitative vascular features, which are subsequently used as inputs to the ML classifiers to enhance interpretability and diagnostic quality. These hybrid pipelines hold an exciting potential in the detection and monitoring of AD at an early stage by the retinal imaging.

Although these have been advanced, there are a number of challenges that are faced such as the lack of big annotated databases, inconsistency in image acquisition procedures, and the standardization of retinal biomarkers to have clinical applicability. These issues are critical to the translation of AI-based retinal imaging solutions into useful tools to screen early AD, conduct studies in large populations and provide customized surveillance.

2. Literature review

This section reviews existing research on retinal vessel segmentation, optic disc segmentation, and automated retinal disease detection, with particular emphasis on deep learning–based approaches and recent architectural advancements.

2.1. Filtering and Segmentation of OCT and OCTA images

2.1.1. Filtering

Zhou et al. [21] reported that quality of raw OCT images is affected by speckle noise which complicates the retinal structures and adversely impacts the image analysis tasks. Therefore, authors introduced Conditional Generative Adversarial networks to eliminate the speckle noise. To remedy the problems, authors proposed the Cycle-Consistent GAN (CycleGAN) to transfer the style of dataset and mini cGAN by utilizing patchGAN to alleviate the speckle the noise presented in the OCT images. Tayal et al. [22] proposed DL based automated method to diagnose ocular disease with the help of OCT scans. This paper applies CNN where the different depths are five, seven and nine layers to carry out the classification task. In addition, this model employs image pre-processing techniques to enhance the precision in the detection of diseases. Similarly, Khan et al [23] also focused effects of several types of noise on MRI quality and its eventual impact on diagnosis. To address these issues, authors proposed a genetic programming solution to the Rician noise reduction, combining the feature extraction and optimization methods. Moreover, this article also introduces a deep learning model and that detects the Alzheimer disease in terms of SHAP values. The effectiveness of deep learning in medical image enhancing and classifying was demonstrated by their methodology which used the oversampling strategies in the context of managing imbalances in classes.

The feature extraction also plays important role to analyse the images for appropriate diagnosis. Authors in [24] emphasized on significant of automated feature extraction in retinal images. Moreover, this research outlined the comparison of several CNN designs, such as a basic five-layer model, AlexNet, and ResNet, to categorize retinal images into several pathological states, such as a choroidal neovascularization (CNV), a drusen, and diabetic macular edema (DME). The optimizers such as adaptive moment estimation (ADM) and stochastic gradient descent (SGD) were used to evaluate the performance of these models with ADM proving to be more accurate.

According to Liu et al. [25], the retinal blood vessels segmentation is significant in the diagnosis of the retinal diseases. This paper proposed an encoder-decoder hybrid deep learning model. This structure used over-parameterized depth-wise convolution layers to obtain the robust features. To avoid the information loss during the pooling operation, a pooling fusion block and attention fusion block was developed to improve the multi-scale feature expression. The robust feature extraction is useful in enhancing the classification performance. Continuing the discussion about CNNs in the medical imaging field, Slootweg et al. [26] studied the role of multimodal retinal imaging to predict the Amylu-PET status. This study used denoising diffusion probabilistic models (DDPMs) to create synthetic training data, pretraining CNN classifiers and then fine-tuning them on actual patient data, the result of the present study showed that synthetic data is capable to enhance the performance of models and also reduce the need of the volume of labeled data. Nevertheless, this is not the case with the OCTA imaging as it has other challenges especially because of bulk motion artifacts (BMA) that occur as a result of patient micromovements. Ren et al. [27] introduced a self-supervised content-aware algorithm in order to deal with BMA removal. This approach identified structural and appearance characteristics in the affected areas and used a training scheme that excluded defects areas enabling the model to learn the efficient artifact removal and at the same time retain crucial retinal information. Cao et al. [28] also discussed image degradation in OCTA by formulating a two-step model of noise removal and contrast enhancement. This article presents a Stripe Removal Net (SR-Net) model to remove stripe artifacts and Perceptual Structure Generative Adversarial Network (PS-GAN) to enhance vessels. With the function of perceptual loss and structural loss combined together, the model obtained better visualization of retinal microvasculature, which allowed clinical interpretation to be more accurate.

The other significant problem in OCTA imaging is shadow artifacts that occur due to obstructions like vitreous floaters and pupil boundaries. Li et al. [29] proposed an adversarial neural network to eliminate these artifacts by modelling shadow formation as a linear illumination transformation. The proposed approach enhanced volumetric data significantly, which is important to trace the progression of retinal diseases. In spite of these developments, the majority of deep learning-based methods are largely dependent on high-quality labeled data, which might not be easily available because of imaging hardware constraints and differences in data acquisition conditions. To counteract this problem, Jiang et al. [30] have made a weakly supervised deep learning OCTA reconstruction framework that can work even without the high-quality labels. This new solution brings in fresh opportunities to improve retinal imaging in clinical practice, not to rely on the large quantities of manual annotations.

Table 1. Summary of state-of-the-art deep learning frameworks for retinal image enhancement and analysis across OCT and OCTA modalities

Ref	Imaging Modality	Method / Model	Key Contributions	Outcome / Performance
Zhou et al. [21]	OCT	CycleGAN + mini cGAN	Speckle noise reduction using style transfer and patchGAN	Enhanced image quality for subsequent analysis
Tayal et al. [22]	OCT	CNN (5,7,9 layers)	AI-based classification with preprocessing	Improved ocular disease detection accuracy
Khan et al. [23]	MRI / OCT	Genetic programming + SHAP	Rician noise reduction, interpretable AD detection	Effective noise mitigation and interpretable results
Liu et al. [25]	OCT	Encoder-decoder with depth-wise convolution + pooling fusion + attention	Multi-scale feature extraction	Improved retinal vessel segmentation and disease classification
Slootweg et al. [26]	Fundus / OCT	DDPM + CNN	Synthetic data generation for pretraining	Enhanced CNN performance with fewer labeled samples
Ren et al. [27]	OCTA	Self-supervised content-aware model	Bulk motion artifact removal	Preserved retinal structural details
Cao et al. [28]	OCTA	SR-Net + PS-GAN	Stripe artifact removal and vessel enhancement	Improved visualization and microvasculature detection
Li et al. [29]	OCTA	Adversarial neural network	Shadow artifact detection and removal	Improved volumetric data integrity
Jiang et al. [30]	OCTA	Weakly supervised DL	OCTA reconstruction without high-quality labels	Enables scalable image enhancement in real-world scenarios

2.1.2. Segmentation

The image segmentation task also plays crucial role in medical image analysis tasks. Recently, the deep learning based methods have gained huge attention in automated segmentation tasks. Wang et al. [31] introduced an adaptation of Segment Anything Model (SAM) named as SAM-OCTA Low-Rank Adaptation (LoRA) and attained a high degree of segmentation accuracy of anatomically important area such as FAZ, artery-vein-region. intervention. The focus in this approach on the FAZ morphology in the diagnosis of the vascular diseases and is the first that low-rank Tensors estimation is used in the diagnosis in this one. Additionally, to improve the vascular segmentation, Zou et al. [33] designed OCTAMamba, a new U-shaped neural architecture that is founded on Mamba. The model incorporates a mixture of multi-scale dilated convolution, quad-stream feature extraction and feature furthermore, the study proposed a prompt-point methodology to improve the segmentation performance of the anatomically significant landmark such as FAZ, artery-vein-region. Therefore, the article points out the significance of domain specific segmentation with the help of foundation models adaption in the domain of biomedical imaging. Besides this, Sedighin et al. [32], adopted a low-rank-based model on FAZ segmentation that employed both the use of the tensor ring decomposition and morphological operations during localization, followed by denoising and refinement recalibration modules to model both the local and global vessel information with minimal computational cost.

Furthermore, the OCTA image dataset lacks a rich labelled dataset in that it impacts the segmentation tasks. This scarcity is relatively high in dataset of 3D that has influence of segmentation models. To solve this challenge, simulation-based framework of segmentation is presented by Wittmann et al. [34] in which synthetic cerebral 3D

OCTA data is generated taking into consideration realistic artifacts including projection effects and signal loss and subsequently a supervised training method without manual annotation is introduced to segmentation. The simulation strategy allows proper and scaled segmentation of the vessels in 3D space. On the same note, Shen et al. [35] aimed at minimizing the reliability of large annotations, thus proposed HAIC-Net a semi-supervised method of combining the self-supervised classification task with dual consistency training. The network uses homologous augmented images and constraints of topological connectivity to obtain vascular features without compromising anatomical integrity. The method greatly minimizes the cost of annotation as well as enhancing the accuracy of segmentation of complicated capillary networks. Zhang et al. [36] introduced LA-Net a 3D-to-2D conversion segmentation of model applying multiple scale layer attention and reverse boundary attention. The network is more effective at segmenting the retinal vessels compared to the conventional approaches of the volumetric OCTA, by prioritizing the information based on the case of the retinal vessel boundaries to information about the layer boundaries, the network is more effective at segmenting the retinal vessels.

The author Jiang et al. [37] proposed DAS-Net as the enhanced form of SegNet-based the model, that is with the help of deformable convolution and Convolutional Block Attention Module (CBAM). The issues that are targeted in this model are continuity issues in the segmenting of the vessel, such as closing the broken capillaries, and making the thick vessel edges smooth by optimizing the loss functions. Li et al. [38] presented the direction guided network such that the physiology provides the direction strength to the vessels. It has directional convolutional layers and direction guidance module to ensure the topology consistency, and preserve thin and possibly fragile connections between the vessels, which is vital to vascular analysis in the retina.

Table 2. Overview of advanced deep learning architectures for OCTA-based vessel and FAZ segmentation, highlighting model innovations, attention mechanisms, and performance improvements in micro vascular analysis

Ref	Imaging Modality	Architecture / Model	Key Contributions	Outcome / Performance
Wang et al. [31]	OCTA	SAM-OCTA + LoRA	Foundation model adaptation with prompt-point	High accuracy FAZ and artery-vein region segmentation
Sedighin et al. [32]	OCTA	Low-rank tensor decomposition	FAZ segmentation using tensor ring decomposition	Effective morphological analysis
Zou et al. [33]	OCTA	OCTAMamba (U-Net + Mamba)	Multi-scale, quad-stream feature extraction	Accurate local/global vessel modeling
Wittmann et al. [34]	OCTA (3D)	Simulation + supervised training	Synthetic 3D data with artifacts	Scalable vessel segmentation
Shen et al. [35]	OCTA	HAIC-Net	Semi-supervised dual consistency + self-supervised	Reduced annotation cost, improved capillary segmentation
Zhang et al. [36]	OCTA	LA-Net	3D-to-2D conversion + layer & boundary attention	Efficient boundary-aware segmentation
Jiang et al. [37]	OCTA	DAS-Net (SegNet + Deformable Conv + CBAM)	Continuity optimization	Preserved thin vessels, smooth borders
Li et al. [38]	OCTA	Direction-guided network	Directional convolution + orientation guidance	Topology-consistent vessel segmentation

2.2. Retinal disease studies

Retinal vessel segmentation is beneficial in the diagnosis of ophthalmic and neurological diseases at their early stages since a vascular change is frequently a sign of pathology. The conventional methods of image processing are image processing-based methods that are sensitive to noise, changes in illumination and low-contrast areas because they are highly reliant on handcrafted features and expert knowledge. As a result, deep learning-based approaches have become the paradigm of choice because these methods exhibit a better ability to represent features. Currently, CNN based approaches, especially the UNet based segmentation methods have reported the promising performance in terms of local spatial and fine vessel-scale structures. Nonetheless, CNNs are naturally unable to capture long-range dependencies because of the small receptive fields. Transformer-based architectures have been proposed to overcome this weakness, where self-attention mechanisms are used to access global contextual information. Despite of their effectiveness, the Transformer based methods suffer from computational complexity which does not allow generalisation to high-resolution retinal images. As an example, state-space models have been growing in popularity recently, including Mamba, capable of modelling long-range dependencies with linearly-computable complexity. Hu et al. [39] presented VM-UNet that combines the VMamba model with the U-Net framework to allow modelling strong global contexts as well as accurate spatial localization. VM-UNet demonstrates higher segmentation performance and efficiency than conventional CNN- and Transformer-based encoder-decoder frameworks through embedding state-space modelling into that framework. Based on this, the authors additionally highlighted that the quality of input feature map could be further improved to achieve a large improvement in the overall performance of Mamba-based architectures, which fuels the creation of Multi-Scale Vision Mamba UNet (MVM-UNet). The proposed MVSS and DMFII modules can eliminate the shortcomings of segmentation robustness and accuracy, as these model can increase the quality of multi-scale fusion of features and input representation. Similarly, Li et al. [40] suggested CRMA-UNet, a hybrid CNN-Mamba design that takes advantage of the complementary capabilities of both designs. The network is able to combine local and global features by design with parallel encoders and by adding modules like PAFF and Mul-CA without increasing the complexity of computations. The paper has demonstrated the possible potential of CNN-Mamba combination in segmenting retinal vessels at high-performance levels. Other works other than the Mamba-based models have involved improving CNN architectures. Duan et al. [41] suggested DAF-UNet that used deformable convolutions to adaptively learn irregular vessel morphologies and a superior ASPP block to obtain multi-scale contextual information. Hybrid loss function was proposed to solve imbalance of vessel thickness. Huy et al. [42] resolved information loss in pooling and skip connections by proposing a Convolution Block Dual Attention Module (CBDAM) to achieve a better contextual feature conservation. Punn et al. [43] also used CNNs jointly with Swin Transformers in CTAUNet and used collaborative feature fusion to promote vessel segmentation at various scales. To diagnose the diseases like glaucoma and diabetic retinopathy, accurate segmentation of the optic disc (OD) is very crucial. Initial strategies were based on the classical image processing methodologies but the technique proved unsuccessful in dealing with noise, occlusion of vessels and fluctuating illumination.

Gowthaman et al. [45] suggested an adaptive model of Fast Circlet Transformation (FCT) and entropy-based vessel characteristics to identify localization of ODs robustly. The algorithm uses the Minkowski weighted K-means clustering and the PDE based inpainting of the vessels and then uses Chan-Vese active contour segmentation. Such techniques are effective, but they involve several manual steps and cannot learn on an end-to-end basis.

Since then methods based on deep learning have predominated. Zedan et al. [46] proposed RMHA-Net which is based on the residual multiscale feature extractor that involves channel-wise and spatial attention. The residual connections and dilated convolutions boost low-level feature extraction, allowing correct OD and optic cup segmentation to be made under anatomically complicated variations. Xiao et al. [47] introduced a FADNet, an end-to-end architecture that jointly predicts OD segmentation and disease classification by a dynamic weighted feature fusion and showed that the integration of segmentation outputs into classification pipelines is advantageous.

The use of multimodal anatomical structures (vessels and the optic disc at minimum in addition to the original fundus image) is commonly useful in automated retinal disease detection systems. Khurshid et al. [44] suggested an abnormality-aware multiview scheme, which integrates fundus images with vascular and OD segmentation masks via a cross-segmentation framework called VOxSeg. A weighted feature selection method was used to concentrate on the discriminative features which enhanced the classification strength in the different ethnic data.

In a similar manner Yi et al. [48] proposed MSGC-CNN, a multi-step model which combines vessel-removed optic disc imaging with original fundus images in glaucoma diagnosis. The framework enhances the accuracy of a diagnosis, especially on small and high-resolution data, by combining pathological expertise in the domain and training a customized RA-ResNet to this end. To improve the efficiency of feature selection and classification, Vadduri et al. [49] studied a hybrid model that incorporates dynamic segmentation, Elephant Herding Optimisation, and Q-LGAN-based autoencoders.

Based on the literature reviewed, it is clear that CNNs are effective in the extraction of local features, and Transformer and Mamba models are efficient in the extraction of long-range dependencies, but the optimization of the feature quality, multi-scale fusion, and computational efficiency remains a challenge. Recent works focus on hybrid architecture, attention mechanisms and multi-view learning to improve segmentation and diagnostic performance.

Table 3. Recent multi-task and hybrid deep learning models for retinal vessel extraction, optic disc/cup segmentation, and automated disease detection

Ref	Target	Architecture / Model	Key Contributions	Dataset / Notes	Outcome

Hu et al. [39]	Vessel	VM-UNet (U-Net + VMamba)	State-space modeling, input feature improvement	Retinal vessel images	Superior segmentation vs CNN/Transformer
Li et al. [40]	Vessel	CRMA-UNet (CNN + ResMamba)	Parallel encoder fusion, multi-scale attention	Retinal images	Effective local/global feature extraction
Duan et al. [41]	Vessel	DAF-UNet	Deformable conv + ASPP + hybrid loss	Retinal images	Captured irregular vessel morphology
Huy et al. [42]	Vessel	CBDAMUNet / D2CBDAMAttUnet	Dual attention block for feature preservation	Retinal images	Reduced info loss during pooling
Punn et al. [43]	Vessel	CTAUNet (CNN + Swin Transformer)	Collaborative multi-scale feature fusion	Retinal images	Improved segmentation across scales
Gowthaman et al. [45]	OD	FCT + entropy-based features + PDE inpainting	Adaptive OD localization	Retinal images	Robust OD segmentation (classical method)
Zedan et al. [46]	OD / OC	RMHA-Net	Residual multiscale feature + dual attention	Retinal images	Accurate OD/OC segmentation
Xiao et al. [47]	OD + Disease	FADNet	Dynamic weighted feature fusion	Fundus images	Joint segmentation-classification framework
Khurshid et al. [44]	Retinal disease	VOxSeg (multi-view + weighted features)	Integrates vessels, OD, fundus	Diverse ethnic datasets	Enhanced classification robustness
Yi et al. [48]	Glaucoma	MSGC-CNN	Vessel-removed OD + original fundus fusion	Fundus images	Improved diagnostic accuracy
Vadduri et al. [49]	Retinal disease	Dynamic segmentation + EHO + Q-LGAN	Feature selection + classification	Fundus images	Efficient disease identification

2.3. Alzheimer's disease analysis

There is growing evidence that the retina as a result of its common embryological origin and physiological likeness to the brain is a promising non-invasive window by which neurodegenerative disease, including Alzheimer disease (AD) and mild cognitive impairment (MCI), can be detected. Traditional methods of diagnosis such as cerebrospinal fluid (CSF) analysis, and positron emission tomography (PET) are accurate but invasive, expensive and not applicable in large scale screening. As a result, retinal imaging and artificial intelligence have become a possible alternative to early diagnosis in a big scale.

Recent studies have examined various modalities of retinal imaging in order to identify AD-related biomarkers. Dallora et al. [50] explored the application of retinal hyperspectral imaging in detecting amyloid-beta (Ab) deposits, a pathological mechanism of AD. Based on CatBoost machine learning models trained on hyperspectral data measured on different retinal areas, the study showed that it was possible to differentiate between ab-positive and ab-negative patients in a clinical group. This literature identifies hyperspectral imaging as a possible cost-effective and non-invasive substitute of the CSF and PET-based diagnostics.

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) have also received much interest because of their capability of imaging microstructural and microvascular retinal variations. Kesu et al. [51] utilized deep learning to classify AD using retinal OCT, and the transformer-based architecture (TransNetOCT) showed high diagnostic accuracy. The findings proved that raw and segmented OCT images stored in themselves have discriminative features that can be used to detect AD. Similarly, Yoon et al. [54] worked with the foveal avascular zone (FAZ) of OCTA images and isolated various radiomic biomarkers and a light-gradient boosting machine, which enhanced the diagnostic of ADS. In addition to classification accuracy, model interpretability has gained significance in order to be clinically adopted. Yousefzadeh et al. [52] have introduced a model-agnostic explainable AI framework, LAVA, that queries neuron-level activations in CNNs to predict the continuum of AD progression directly based on the retinal images. This method enhances the level of transparency, as well as give information on the stage of the disease without the need of longitudinal clinical records.

Multiple researches have underlined the importance of retinal vascular characteristics in the identification of cognitive impairment. Zhang et al. [53] also constructed machine learning models using vascular features of fundus images to distinguish normal cognition, MCI, and dementia. They found that fundus images that are not explicitly segmented with vessels can be more effective than segmented images, so the global context of the retina may have some extra diagnostic data. Xing et al. [60] also examined the risk of cognitive impairment in diabetic patients through fundus images and suggested the FB_Net, with multi-scale attention mechanisms and Grad-CAM visualization to extract the appropriate biomarkers.

Multi-view and multimodal frameworks of learning have also demonstrated additional potential to a higher level of diagnostic robustness. A trilateral model of OCT-derived retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL) and anatomical parameters has been proposed by Chua et al. [55]. Combining the results of CNNs, transformers, and probabilistic classifiers with the help of the XGBoost, the model demonstrated a higher level of discrimination between AD, MCI, and healthy controls. Liu et al. [56] have suggested PolarNet + which makes use of OCTA images transformed into polar coordinates and uses graph-based learning to examine regional relationships within the retina.

The model was proven to be very effective in the detection of early-onset AD and MCI, which validates the applicability of retinal microvasculature as a biomarker, and has been supported by large multi-center datasets.

Segmentation and classification Hybrid deep learning architectures have also been investigated. A hierarchical CNN was proposed by Udayararaju et al. [57] in which U-Net would segment OCT and OCTA images, and then special CNNs would be used to classify choroidal neovascularization and predict AD. Transformer-based methods have gone further to enhance these. Jamshidiha et al. [59] proposed Retformer, a transformer-based model, which can effectively process small retinal images with the addition of explainability using Grad-CAM. The model outperformed standard CNN-based models and offered clinically understandable visual explanations.

Comprehensively, the available literature shows that retinal imaging modalities such as fundus photography, OCT, OCTA, and hyperspectral imaging have abundant structural, vascular, and biochemical data applicable in the detection of AD and MCI. Deep learning and transformer-based models have demonstrated promising results, but there are still challenges in enhancing the quality of features, combining multi-scale and multi-view information, and making models interpretable to be used in the clinical. Further, most of the studies are based on classification and not focused on accurate segmentation of the retinal structure and the subsequent effects on neurodegenerative disorders. These shortcomings encourage the creation of current segmentation-based models that can better represent features and increase retinal biomarker reliability in screening early cases of the Alzheimer disease.

Table 4. AI-driven retinal biomarker analysis for neurodegenerative disease detection, highlighting multimodal architectures, explainable frameworks, and reported clinical performance.

Ref	Modality	Model / Architecture	Key Contributions	Dataset / Performance
Dallora et al. [50]	Hyperspectral fundus	CatBoost	Aβ detection from hyperspectral data	57 patients (35 Aβ+, 22 Aβ−)
Kesu et al. [51]	OCT	TransNetOCT	Deep learning classification	98.18–98.91% accuracy (raw & segmented)
Yousefzadeh et al. [52]	Fundus	LAVA (XAI framework)	Model-agnostic explainable AI for disease progression	CNN intermediate layers
Zhang et al. [53]	Fundus	SVM / ELM	Vascular features for MCI & dementia	86 subjects, ROC/AUC metrics
Yoon et al. [54]	OCTA (FAZ)	Light-GBM	AI-based segmentation + multiple radiomic features	37 AD, 48 controls
Chua et al. [55]	OCT	Trilateral model (VGG11, Swin, NB) + XGBoost	Multi-modal OCT integration	AD, MCI vs controls
Liu et al. [56]	OCTA	PolarNet+	Polar mapping + graph-based regional analysis	1,671 participants, AUC: 88.69% (AD), 88.02% (MCI)
Udayaraju et al. [57]	OCT / OCTA	Hierarchical CNN + U-Net	Segmentation + CNV & AD prediction	Multi-class classification
Le et al. [58]	OCTA	VGG16 + transfer learning	DR detection integrated into GUI	32 healthy, 75 DR, 24 NoDR
Jamshidiha et al. [59]	Fundus / OCT	Retformer (Transformer) + Grad-CAM	Explainable AD detection, small dataset	Improved over CNN baselines
Xing et al. [60]	Fundus	FB_Net + AA_Block +	Multi-scale attention +	Diabetic patients, cognitive

		MS_CBAM	Grad-CAM	impairment detection

3. Discussion and critical analysis

3.1. Trends in Retinal Vessel and Optic Disc Segmentation

The segmentation of retinal vessels and optic discs has become one of the essential tasks of ophthalmic image analysis because these parameters are relevant in the diagnosis of different diseases of the eye and the body. Segmentation procedures in the last ten years have vividly changed perspectives of traditional image processing techniques to modern deep learning techniques.

CNNs especially U-Net models, have prevailed in the initial studies as they are able to capture local spatial features and fine vessel morphology. DAF-UNet [3] and CBDAM-UNet [4], incorporated models used deformable convolutions to deal with irregular vessel shapes and atrous spatial pyramid pooling (ASPP) to multi-scale contexts and dual attention respectively to maintain contextual features and reduce information loss during pooling processes. These architectures were more accurate than the conventional rule-based and filter-based segmentation techniques especially when fine vessels and irregular capillaries were identified.

Although successful, CNNs are by nature confined to the receptive fields which limits their capability to model long-range dependencies which are essential in the description of the global vascular architecture. Transformer-based methods and state-space models have been introduced to overcome it. CTAUNet [5] used CNNs with Swin Transformers to jointly compute local and global features, and Mamba-based models such as VM-UNet [1] used linear state-space models to compute long-range dependence without squaring the computational cost of Transformers. These innovations emphasize the trend of the hybrid model that incorporates the locality of CNNs with the global context modeling of Transformers or state-space networks to enhance the performance and robustness of segmentation.

The other trend is the emphasis on the improvement of the quality of input features and the multi-scale fusion of information. The MVM-UNet (a variant of VM-UNet) and modules like MVSS and DMFII were specifically created in order to enable the input feature representations to be optimized, so that the representation of fine-grained vessel features and global retinal context can be better represented. On the same note, CRMA-UNet [2] combined parallel CNN and Mamba encoders with feature fusion modules (PAFF and Mul-CA) to improve local-global feature complementarity, which is indicative of an increased focus on attention-guided multi-scale feature integration.

In the case of optic disc (OD) segmentation, similar trends are observed in vessel segmentation. The classical techniques, including Fast Circlet Transformation (FCT) using entropy-based vessel features [7], were based on several handcrafted steps and did not perform well with changing illumination and noise. Multiscale feature extraction and hybrid attention mechanisms were used together with end-to-end learning frameworks via deep ways of learning, including RMHA-Net [8] and FADNet [9], which enhanced the resistance to anatomical variations and complicated retinal backgrounds. It is also interesting to note that the direct inclusion of segmentation results in downstream applications (e.g., disease classification) has been a major development, such as FADNet, which combines OD segmentation with ocular disease classification. The literature review indicates several key trends in retinal vessel and optic disc segmentation which are as follows:

1. The current researches have replaced the traditional handcrafted methods with advanced deep learning based architectures emphasizing automation and scalability.

2. The current techniques have focused on integration of local and global feature modeling through CNN-Transformer hybrids or state-space Mamba networks.

3. Combined with attention mechanisms, multi-scale and multi-layer feature fusion to enhance the accuracy and robustness of segmentation.

4. More emphasis on end-to-end models that bridge between segmentation and downstream diagnostic activities.

5. Limited labeled datasets, 3D OCTA segmentation, and retention of fine vessel topology in thin capillaries are still problems, which are driving semi-supervised and synthetic data approaches.

All these trends are indicative of the shift of the field into high-quality, efficient, and clinically interpretable segmentation frameworks, which is the basis of proper retinal disease diagnosis and neurodegenerative disease analysis.

3.2. Trends in Alzheimer's Disease Detection Using Retinal Imaging

The retina has become a good non-invasive window to the brain that has the potential to detect neurodegenerative diseases including Alzheimer disease (AD) and mild cognitive impairment (MCI). Embryological and vascular similarities at the retina and the brain make retinal imaging to be able to mirror early pathological processes such as the presence of amyloid-beta (Ab) and microvascular changes. The initial research, including the works by Dallora et al. [12], used retinal hyperspectral imaging with the CatBoost machine learning models to differentiate between Ab-positive and Ab-negative patients. This study demonstrated the usefulness of applying the retinal hyperspectral signatures to be an alternative low-cost study applied to invasive cerebrospinal fluid analysis and PET scan. Since then, OCT and OCTA have become the gold standard imaging modalities of AD detection with their capacity to visualize both the microstructural and microvascular architecture. As an example, Kesu et al. [13] used deep learning architectures, specifically the TransNetOCT, with high classification accuracy of raw and segmented OCTs. In a similar manner, Yoon et al. [16] concentrated on FAZ measurements based on the OCTA, and combined several radiomic biomarkers with demographic factors with the help of gradient boosting machine to ensure a better performance in the diagnosis. These researches point to the fact that structural and vascular characteristics of a retina can predict AD and MCI. The recent studies have focused on multi-view and multimodal learning. Chua et al. [17] introduced a trilateral model, which consisted of an outlook of OCT-derived RNFL and GCIPL thickness maps and anatomy parameters. The framework, based on using the outputs of CNNs, Swin Transformers, and probabilistic classifiers with XGBoost, performed better in terms of differentiating between AD, MCI, and healthy controls. Equally, Liu et al. classify choroidal neovascularization. Jamshidiha et al. [21] showed that the transformer-based architectures would be able to work with smaller data sets and be able to view the results as interpretable when compared to the traditional CNNs. In these studies, some definite tendencies can be identified:

- Move towards non-invasive retinal imaging as a non-invasive scale to alternatives of CSF and PET in AD and MCI detection.
- Co-ordination of structural, vascular, and biochemical biomarkers in various modalities of retinal imaging.
- The implementation of the multi-view and multi-modal learning models to enhance the efficiency and predictability.
- The focus on explainable AI and visualization methods to enhance clinical interpretability.
- Hybrid segmentation-classification models using rich retinal features to predict downstream diseases.

These studies reflect an emerging state of sophistication when it comes to the application of retinal imaging in detecting neurodegenerative diseases, in which sophisticated deep learning-based models, integration of multi-modes of features, and interpretability are employed to enable early diagnosis and massive screening.

3.3 Challenges and Gaps

Although there has been immense progress in segmenting retinal images and the detection of the Alzheimer diseases, [18] proposed PolarNet+, which uses polar-coordinate transformation of OCTA images and graph-based learning to learn about the relationship between regions in the retina andwhere the multi-centers datasets confirmed these relationships. Such methods indicate the tendency toward the combination of spatial, vascular and anatomical features to increase predictive performance. Explainability and interpretability are also becoming important issues of clinical adoption. To investigate neuron-level activations in CNNs, Yosefzadeh et al. [14] suggested the LAVA framework, providing information about the disease progression, directly based on retinal images. Transformer-based approaches, including Retformer [21], use Grad-CAM visualizations to give interpretable attention maps, enhancing transparency and clinician trust. In the same vein, Xing et al. [22] and FB_Net employed the use of multi-scale attention and visualization to predetermine the presence of relevant biomarkers of cognitive impairment. Segmentation and classification hybrid architectures have been looked into. In the case of Udayararaju et al. [19], U-Net was employed to perform retinal OCT and OCTA segmentation and then apply special CNNs to predict Alzheimer and

there are still numerous challenges that restrict the applicability and practicality of the current methods. Limited access to high quality annotated datasets, especially of OCTA, hyperspectral, and 3D retinal images, is one of the main problems. The limited amount of labelled data available that can be used to train supervised deep learning models, which frequently leads to semi-supervised, weakly supervised, and synthetic data augmentation methods.

The other vital issue is the input features quality and representation. Mamba and transformer based models rely on precise and context rich input feature maps. The existence of poor feature representations may increase mistakes throughout the iterations and thus, affect the segmentation results negatively thus affecting the downstream outcome of classifying retinal or neurodegenerative diseases. It is also especially difficult to preserve fine structural details, including thin capillaries, microvascular anomalies, and boundaries of foveal avascular zones, which even the latest network cannot do. Topographical convolutions, reverse boundary attention, and topological consistency modules, to some extent, address these problems, although they are not fully in use.

The complexity of computation and scalability is also a constraint, particularly to transformer-based models. Although transformers are effective in modelling long-range dependencies, they suffer from a quadratic computational complexity with high-resolution retinal images, which limits their ability to be applied in large-scale or resource-constrained clinical environments. Hybrid CNNs and Mamba or transformer module architectures have potential but need extra fine-tuning of their efficiency without impacting the accuracy.

In addition, explainability and clinical interpretability are under-researched. Even though techniques like Grad-CAM, LAVA, and multi-scale attention visualization offer partial explanations of model predictions, the vast majority of AI models remain a black box and restrict the level of trust and adoption in clinicians. It also does not have extensive multi-modal integration where few studies successfully integrate fundus images, OCT, OCTA, and hyperspectral modalities and segmentation-based feature extraction to detect Alzheimer. Lastly, the lack of consistency in datasets, preprocessing procedures, and performance measures makes it challenging to compare two different models, which underscores the importance of a unified benchmark to evaluate the performance of segmentation and classification procedures in a robust way.

4. Dataset details

This research mainly focus on two dataset which are OCTA-500 and ROSE-I dataset. OCTA-500 data was utilized in the retinal vessel feature extraction and model pretraining. It has OCT and OCTA scans of 500 patients with vascular annotations. Also, ROSE-1 dataset, which contains OCTA images of not only Alzheimer patients but also healthy controls in order to classify Alzheimer. The ROSE-1 data is comprised of 117 OCTA images of 39 subjects, 26 of which are Alzheimer patients. The datasets allow investigating the retinal microvascular alterations related to the Alzheimer disease.

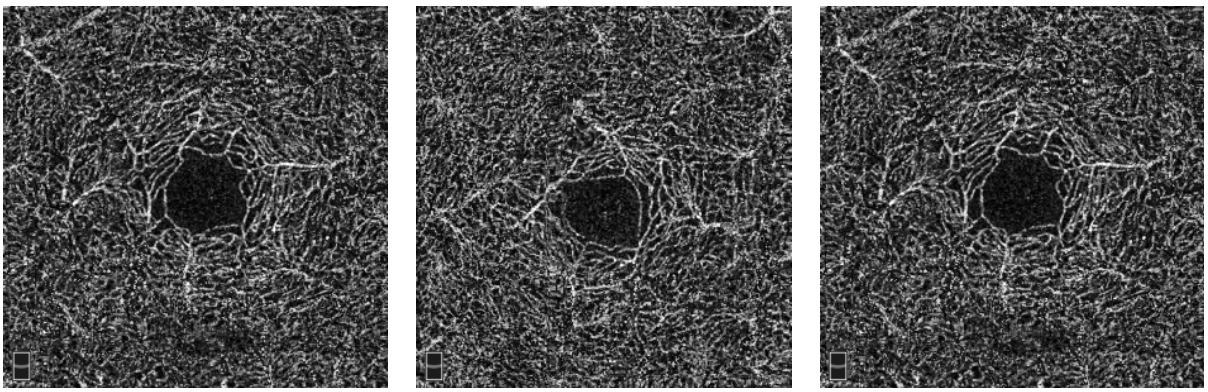

Figure 4. Sample images from OCTA-500 and ROSE-1 dataset

OCTA-500 Dataset

It is one of the largest openly accessible datasets of optical coherence tomography angiography that is used to study the vascularity of the retinal area. It includes imaging information of 500 subjects who were obtained with the spectral-domain OCT systems, both OCT and OCTA volumetric scans as well as various projection maps and rich annotations. The data set gives both imaging modalities OCT and OCTA volumes and two fields of view i.e. 3 mm x 3 mm scan and 6 mm x 6 mm scan. Overall, it is composed microvasculature, which is found to be related to neurodegenerative diseases, including Alzheimer disease.

ROSE-1 Dataset

This dataset is an openly accessible OCTA retinal vessel segmentation dataset, which involves in both Alzheimer disease patients and healthy controls. It has 117 images in total of OCTA gathered on 39 subjects of which, 26 images are on patients diagnosed with the Alzheimer disease and 13 of the images are healthy. The RTVue XR Avanti spectral-domain OCT system was used to obtain the images, and its scan area was 3 mm x 3 mm located at the fovea. The of over 360,000 images, and it takes about 80 GB of storage. Besides the imaging data, OCTA-500 also has text-based labels that are age, gender, eye side and disease category. It also provides pixel level annotations such as retinal vessel segmentation, artery vein classification, foveal avascular zone (FAZ) segmentation and retinal layer boundary. Due to such rich annotations, the dataset has found a large number of applications to tasks including vessel segmentation, microvascular analysis, and pretraining deep learning models to study neurological diseases. The OCTA imaging allows visualizing micron-scale retinal resolution of every image is 304 x 304 pixels and is aimed at the retinal microvascular structure. The dataset has application in retinal vessel segmentation, microvascular feature retrieval, and Alzheimer classification studies. The observed retinal vascular abnormalities with the help of OCTA are regarded as possible biomarkers of the early detection of Alzheimer disease, and therefore ROSE-1 dataset will be especially useful in the investigation of the correlation between retinal microvasculature and neurodegeneration.

Table 5. Comparison of OCTA-500 and ROSE-1 datasets

Feature	OCTA-500	ROSE-1

Dataset Size	500 subjects (~360,000 images, ~80 GB)	117 OCTA images (39 subjects)
Imaging Modality	OCT + OCTA volumetric scans	OCTA (en-face images)
Scan Area	3×3 mm and 6×6 mm	3x3 mm (foveal region)
Resolution	Volumetric scans	304 x 304 pixels
Annotations	Vessel segmentation, artery-vein classification, FAZ segmentation, retinal layer boundaries	Pixel-level vessel segmentation
Clinical Labels	Age, gender, eye side, disease category	AD patients vs healthy controls
Disease Focus	Multiple retinal diseases	Alzheimer's disease
Main Applications	Vessel segmentation, FAZ analysis, microvascular quantification, pretraining models	Vessel segmentation, microvascular analysis, AD biomarker research

5. Conclusion and future work

In this literature review, it is shown that retinal imaging, in combination with superior deep learning architectures, can be an important tool in automated disease diagnosis and the early detection of Alzheimer disease. CNN-based models are still leading in the representation of local spatial features, but transformer-based and Mamba architectures effectively represent long-range dependencies, enhancing segmentation and classification accuracy. Multi-scale feature fusion, hybrid CNN-Mamba networks, multi-view learning has become the key strategies to improve robustness and accuracy. Nevertheless, the limitations are still the lack of annotated datasets, poor input feature representation, computational inefficiency, and clinical interpretability loss. Multi-modal retinal imaging combined with segmentation-based characteristics promises to be effective, especially in identifying minute structural and vascular alterations related to ophthalmic and neurodegenerative diseases.

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