OCTA Image-Based Machine Learning Models for Discriminating Alzheimer's Disease from Neurodegenerative and Ocular Conditions

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that poses a significant challenge, particularly as the global population ages. Timely diagnosis is crucial for managing AD, and this study aims to contribute to early detection by analyzing Optical Coherence Tomography Angiography (OCTA) images using machine learning models. In this work, we leverage the structural and functional connections between the eye and brain to enhance the discrimination of AD from other neurodegenerative and ocular conditions. We also compiled a comprehensive dataset of OCTA images from various imaging devices, representing a range of diseases. Using a pre-trained nnU-Net, we segmented vascular structures and calculated vascular density metrics, while also extracting histogram and Gray-Level Co-occurrence Matrix (GLCM) features for texture analysis. Various machine learning models were trained and evaluated through five-fold cross-validation, with the Random Forest model achieving 78.15% accuracy in classifying multi-disease OCTA images. The model exhibited high recall for stroke, diabetes, and age-related macular degeneration, but lower recall for AD, congenital heart disease, and hypertension, indicating potential misclassification. Our findings emphasize the utility of OCTA imaging and machine learning for early AD diagnosis, paving the way for future research to refine image processing and classification methods.

1 INTRODUCTION

The burgeoning global elderly population has led to a proportional rise in the prevalence of Alzheimer's disease (AD), a progressive neurodegenerative disorder that poses significant healthcare challenges. With current estimates suggesting that over 130 million individuals will be affected by 2050, the urgency to develop effective diagnostic and therapeutic strategies is paramount(Nichols et al., 2022). The economic and social burden of AD is further exacerbated by its increasing incidence among younger demographics, highlighting the necessity for early and accurate detection methods to mitigate disease progression(Hassen et al., 2024). The quest for early diagnostic markers has led researchers to explore the intricate relationship between the eye and the brain(Diogo et al., 2022; Hassen et al., 2024). The retina's structural and functional connections to the central nervous system make it a viable window into brain health, with preliminary abnormalities often manifesting in the retina prior to the onset of neurological symptoms(O'Bryhim et al., 2018). This insight has spurred interest in non-invasive ocular imaging techniques as potential diagnostic tools for early AD detection.

Optical Coherence Tomography Angiography (OCTA) has emerged as a pivotal technology in this domain, offering high-resolution, non-invasive imaging of the retinal and choroidal microvasculature(Naseripour et al., 2020; Liu et al., 2024; Turkan and Tek, 2023). OCTA's ability to track red blood cell movement within the vasculature provides a unique perspective on the microvascular changes that may precede AD-related neurological symptoms.

Despite the promising results of OCTA, existing diagnostic methods still face limitations, particularly in large-scale screenings and among elderly populations where coexisting eye conditions can confound interpretations of OCTA images(Turkan and Tek, 2022). Differentiating early signs of AD from other retinal pathologies requires sophisticated analytical techniques to improve diagnostic accuracy(Katsimpris et al., 2022).

Recent advancements in OCTA have facilitated a deeper understanding of retinal vascular changes associated with AD. Studies have reported reduced retinal vascular density in AD patients, suggesting a cor-

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relation with cerebral vascular alterations(Yoon et al., 2024). Additionally, OCTA has shown potential in distinguishing AD from other neurodegenerative diseases and common eye conditions such as diabetic retinopathy (DR) and age-related macular degeneration (Li et al., 2023).

The academic community has increasingly recognized the importance of retinal biomarkers in dementia diagnosis, with OCTA playing a significant role. Systematic reviews and high-resolution imaging studies have begun to elucidate the morphological characteristics of the retinal microvasculature in relation to various diseases.

This paper aims to build on these foundations by exploring the utility of OCTA in differentiating AD from other eye diseases and neurodegenerative conditions. We focus on quantitatively assessing the distinguishability of OCTA features associated with AD and other diseases to enhance early diagnostic accuracy. Through the application of machine learning algorithms to a comprehensive dataset of OCTA images, we seek to provide new insights and methods for early AD detection, potentially alleviating the societal impact of this pervasive disease.

2 RELATED WORKS

2.1 Vascular Density and Vessel Segmentation

Optical Coherence Tomography Angiography (OCTA) often uses Blood Vessel Density (BVD) as a key metric because it is simple to calculate and useful for assessing the severity of eye diseases like Diabetic Retinopathy (DR) and Glaucoma. The process of deriving BVD from OCTA images is considered a segmentation task, making deep learning techniques such as U-Net particularly suitable. For instance, Convolutional Neural Network (CNN) models have been successfully applied to segment choroidal blood vessels, which is more challenging than retinal segmentation due to the higher density of larger vessels in the choroid and greater signal loss in deeper tissues. Liu et al. has shown that BVD measurements obtained through this method are comparable to those from manual segmentation(Liu et al., 2019).

Furthermore, various U-Net models have helped standardize BVD measurements across different devices and improve resistance to projection artifacts. Vessel segmentation can also be improved with image enhancement techniques, as better image quality increases the contrast between blood flow and background pixels. Like most OCTA measurement techniques, these methods can be applied to en-face images, which are essential for accurate anatomical slice segmentation. Another approach, the Image Projection Network (IPN), utilizes CNNs to extract features and perform projections simultaneously. It has been tested on two key areas of retinal image segmentation—retinal vessel segmentation and Foveal Avascular Zone (FAZ) segmentation. Results indicate that the IPN is an effective implementation of 3D to 2D segmentation networks, outperforming standard methods(Li et al., 2020).

2.2 Biomarkers and Features for Developing Computer-Aided Diagnostic Systems

The combination of biomarkers and unique features is crucial for creating CAD systems. Traditional methods like logistic regression have proven effective, and machine learning models are also viable options. CAD systems that utilize OCTA data have been designed to DR at various severity levels (Krittanawong et al., 2020). Research has shown that using a Random Forest model with inputs such as structural OCT reflectivity, curvature and thickness, OCTA vascular density, the number of vascular bifurcations and crossings, and the size of the Foveal Avascular Zone (FAZ) has resulted in an area under the receiver operating characteristic curve exceeding 95%. This performance was key in differentiating eyes with DR from those without and in classifying the conditions of patients with non-proliferative DR.

Additionally, studies that combined clinical indicators with OCTA features, using a hybrid approach of a balanced optimizer and Support Vector Machine for feature selection and classification, have produced promising results for Vogt-Koyanagi-Harada syndrome (Dhodapkar et al., 2022). Concurrently, research has explored deep learning systems that integrate macular Blood Vessel Density (BVD) with the thickness of the ganglion cell layer/inner plexiform layer. The combination of these metrics, learned through AI, has outperformed individual measurements.

Deep learning has also been applied to the diagnosis of Age-Related Macular Degeneration (AMD), with studies indicating that CNN can accurately predict the progression of AMD from intermediate to advanced stages (Peng et al., 2020). Moreover, as previously mentioned, CNNs' ability to detect Choroidal Neovascularization (CNV) makes deep learning a viable option for classifying neovascular patterns in AMD. The effectiveness of these CAD systems relies on the quality of input feature measurements;

therefore, continuous improvements in feature quantification will support the development of CAD systems. However, their overall performance remains constrained by predefined functionalities.

2.3 AI-Enhanced Analysis of OCTA Images and Disease Diagnosis

AI-based diagnostic systems utilizing OCTA imaging are widely employed for assessing retinal diseases and identifying various eye conditions. However, these AI diagnostic tools, despite being validated, encounter numerous challenges. Firstly, the resolution and details of retinal blood vessels captured by fundus images are limited, which hampers the ability to accurately measure the curvature of microvessels near the fovea and across different retinal layers (Dhodapkar et al., 2022).

Additionally, the quality of OCTA images can vary due to factors like eye movement, eyelid obstruction, and artifacts from optical coherence tomography, which significantly affects manual annotations and leads to inconsistencies in subjective assessments (Lauermann et al., 2019). Consequently, diagnostic systems that rely on supervised machine learning algorithms struggle with poor performance in quantitative feature analysis and lack of diagnostic accuracy.

Furthermore, understanding the reasoning behind AI model decisions is crucial for clinical disease diagnosis, and providing clear interpretability of algorithms will be essential for the clinical integration of AI-assisted OCTA disease diagnosis. Moreover, deep learning systems require large and verifiable databases, ranging from 100,000 to several million images, for effective training and optimization (Le et al., 2024). Even after successfully training AI systems, differences among databases from various imaging centers make it extremely difficult to provide reliable accuracy metrics (Yang et al., 2023). At the same time, creating large multicenter databases for the effective use of AI diagnostic tools presents a significant challenge, especially for new retinal imaging techniques like OCTA. Nevertheless, AI is expected to help realize the full potential of OCTA imaging.

2.4 Retinal Neurodegeneration and Vascular Alterations in AD

Studies using OCT have shown considerable retinal neurodegeneration in individuals with AD. A systematic review conducted in 2018 found that patients with AD exhibited thinning in several retinal layers, including the peripapillary retinal nerve fiber layer (pRNFL), macular ganglion cell inner plexiform layer (mGCIPL), ganglion cell complex, and choroidal layers, as well as a decrease in overall macular volume and thinning in both inner and outer macular regions (Chan et al., 2019).

The thinning of the mGCIPL has been linked to the severity of the disease (Ferrari et al., 2017). Various fluorescence-based fundus imaging techniques have been used to visualize and measure retinal pathology associated with AD. For instance, administering curcumin, a *beta*-amyloid binding fluorophore, intravenously resulted in a twofold increase in retinal β-amyloid levels in AD patients. These retinal β-amyloid levels have been associated with cortical β-amyloid levels and reductions in hippocampal volume (Koronyo et al., 2017). Moreover, blue autofluorescence has been employed to measure the surface area of retinal inclusions related to preclinical cortical β-amyloid burden (Snyder et al., 2016). Lastly, fluorescence lifetime imaging ophthalmoscopy has shown differences between AD patients and matched controls.

Retinal vascular alterations have also been observed in fundus images of AD patients. The fractal dimension (FD), which quantitatively represents the complexity of vascular branching, can be assessed using commercial software or expert evaluation. A systematic review from 2019 reported a decrease in vascular FD among AD patients across four case-control studies involving fundus imaging (Lemmens et al., 2020). Additionally, one study noted increased vascular tortuosity and narrowed venous diameters in AD patients, although another study presented conflicting results (Cheung et al., 2014). It can be seen that individuals with AD have an enlarged central arteriolar avascular zone and reduced overall superficial and deep retinal vascular density.

3 FRAMEWORK FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

3.1 Overview

The overarching goal of this study is to harness the potential of OCTA for early diagnosis of AD by differentiating it from other eye diseases and neurodegenerative conditions. Our methodology encompasses the following key steps: First, we assembled a diverse dataset of OCTA images to ensure representation of various imaging devices, disease states, and image resolutions. Second, we employ a pretrained neural network, nnU-Net, we segmented vas-

cular structures from OCTA images to facilitate the extraction of vascular density metrics. Next, we extracted both vascular and image features from the segmented OCTA images, including overall vascular density and regional vascular density based on the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Finally, A suite of machine learning algorithms was trained on the extracted features to classify images into AD and control groups, employing a five-fold cross-validation approach to ensure robustness of the models. The workflow of our methodology, encapsulating dataset compilation, image segmentation, feature extraction, and machine learning model training and validation, is schematically represented in Figure 1.

3.2 Dataset

Our dataset is a curated collection of 2000 OCTA images sourced from multiple open datasets: OCTA-500 (Li et al., 2024), OCTAGON (Díaz et al., 2019), Foveal Avascular Zone Image Database (FAZID) (Agarwal et al., 2020), Soul (Xue et al., 2024) and DRAC2022 (Qian et al., 2024), providing a wide spectrum of disease representations. The dataset includes images from patients with varying conditions, such as stroke, diabetes, age-related macular degeneration (AMD), and AD, as well as a control group. The image resolutions vary, including 3x3 mm², 6x6 mm², 8x8 mm², and 12x12 mm², to simulate real-world clinical scenarios.

3.3 Image Segmentation

nnU-Net is an adaptive neural network architecture that automatically adjusts its structure based on the specific task. In this research, a version of the U-Net architecture tailored for OCTA image segmentation was chosen. Utilizing nnU-Net to segment OCTA images from various devices, sizes, and disease types allows for further feature extraction and pathological analysis. The segmentation network discussed in this chapter uses the OCTA-500 dataset, which consists of 500 OCTA images. Loss Function: A combination of cross-entropy and Dice loss functions was used to address class imbalance and improve segmentation accuracy.

The cross-entropy loss function focuses on pixel-level classification, while the Dice loss function emphasizes overall shape matching. Optimizer and Learning Rate: The Adam optimizer was utilized for model training, starting with a learning rate of 0.001, along with a learning rate decay strategy to adjust the learning rate dynamically during training. This method helps the model converge towards the global optimum. Training Strategy: The model was trained using a five-fold cross-validation approach to evaluate its stability and generalizability. In each fold, 80% of the data was used for training, and 20% was set aside for validation.

3.4 Feature Extraction

The objective of this study is to harness the diagnostic potential of OCTA images for early detection of AD by differentiating it from other eye diseases. A critical step in achieving this objective is the extraction of meaningful features from OCTA images that can serve as inputs for machine learning algorithms. This section outlines our approach to feature extraction, focusing on vascular density measurements and texture analysis.

3.4.1 Vascular Density Calculation

Following the segmentation of OCTA images, vascular density is calculated to quantify the vascular patterns associated with different disease states. This process involves two main steps, which are Overall Image Vascular Density and ETDRS Regional Vascular Density. Overall Image Vascular Density is determined by calculating the ratio of vascular pixels to the total number of pixels in the OCTA image, providing a global measure of vascularization. Meanwhile, The ETDRS grid is used to divide the retina into nine distinct areas. Vascular density is calculated separately for each of these regions, enabling a detailed analysis of local vascular patterns. This regional analysis is crucial for early disease detection and accurate diagnosis, as it allows for the identification of localized vascular changes that may not be apparent in overall density measurements.

3.4.2 Image Feature Extraction

In addition to vascular density, texture analysis plays a vital role in characterizing OCTA images. We focus on two types of image features: histogram features and Gray-Level Co-occurrence Matrix (GLCM) features. For histogram feature extraction, Image histograms provide a statistical representation of gray level distribution, offering insights into brightness and contrast. In this study, 16 histogram features are derived by quantizing image gray levels into 16 bins and counting the pixel occurrences within each bin. These features are indicative of the brightness distribution and contrast information in OCTA images, which are essential for disease analysis.

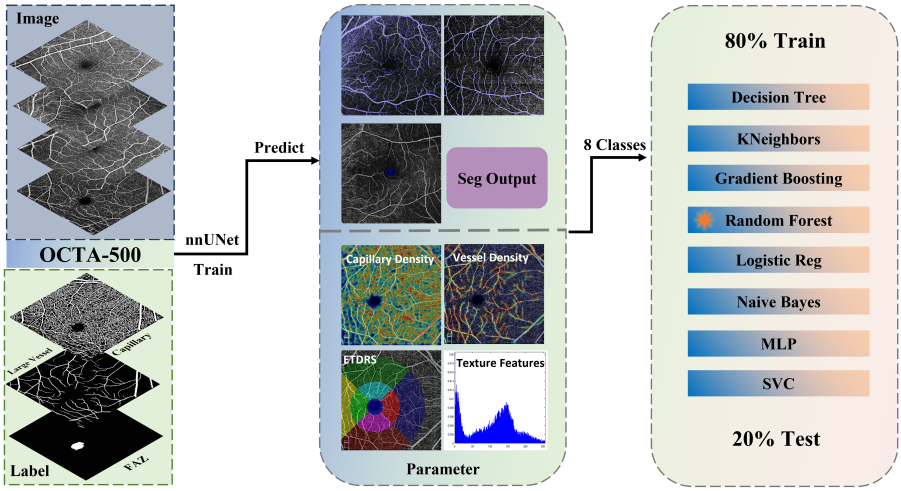

Figure 1: Schematic representation of the methodology for early diagnosis of Alzheimer's disease using OCTA images. The process includes dataset compilation, image preprocessing, segmentation using nnU-Net, feature extraction, model training, validation, and performance evaluation.

On the other hand, The GLCM is a texture analysis technique that captures spatial relationships between gray levels in an image. We extract five GLCM features—contrast, similarity, homogeneity, energy, and correlation—to characterize the texture structure of OCTA images. These features provide a quantitative description of vascular structures, which is vital for subsequent machine learning classification tasks.

3.4.3 Machine Learning Model

The extracted vascular and image features provide a rich set of information for machine learning models, aiding in achieving better performance in classification tasks. This study involved training and evaluating various machine learning models for multi-disease classification. To ensure optimal model performance, a range of common machine learning models were selected, and hyperparameter tuning was performed for each. The models included Random Forest, Support Vector Machine (SVM), K-Nearest Neighbors (KNeighbors), Naive Bayes, Logistic Regression, Decision Tree, Gradient Boosting, and Multilayer Perceptron (MLP). Hyperparameter tuning for each model was conducted using GridSearchCV.

4 EVALUATION

Each model was trained, and a five-fold cross-validation strategy was employed to evaluate model performance. Metrics such as accuracy, macro precision, macro recall, macro F1 score, weighted precision, weighted recall, and weighted F1 score were used for assessment.

The results indicate that the Random Forest model outperformed all other models, achieving an accuracy rate of 78.37%. To understand these results, it is essential to analyze the performance of each model in conjunction with the OCTA modality and the selected features. The Random Forest algorithm, which integrates multiple decision trees, effectively handles high-dimensional data and mitigates the risk of overfitting. The rich vascular and image features from OCTA images allow the Random Forest to capture complex relationships between features, thus excelling in classification tasks.

The Gradient Boosting model, which optimizes incrementally, also performs admirably by capturing intricate feature relationships. This model excels in processing nonlinear features, and when combined with the diverse features from OCTA images, it achieves commendable classification results. In contrast, Logistic Regression, which is adept at handling linear features, exhibits limitations when dealing with complex nonlinear characteristics. Although the Multilayer Perceptron possesses strong nonlinear modeling capabilities, its performance in this study may be suboptimal due to the influence of feature selection and model complexity on the given feature data.

In this study, we aimed to explore the distinguishability between AD and other common ophthalmic and chronic diseases. Based on the assessment using the Random Forest model, we provided a detailed analysis of metrics and a confusion matrix. Analysis of the results, as shown in Table II, revealed that AD, congenital heart disease, and hypertension are more likely to be confused with other

Table 1: Classification results of various machine learning models for OCTA image classification.

Model	Accuracy (%)	Macro Precision (%)	Macro Recall (%)	Macro F1 (%)	Weighted Precision (%)	Weighted Recall (%)	Weighted F1 (%)
Decision Tree	65.89	58.32	51.34	52.19	61.16	65.89	61.42
KNeighbors	72.57	59.11	55.55	55.29	71.05	72.57	70.97
Gradient Boosting	76.02	69.52	62.13	63.54	74.50	76.02	74.38
Random Forest	78.37	73.97	70.07	69.08	80.17	76.07	76.81
Logistic Reg	67.82	61.14	52.15	49.87	65.74	67.82	63.16
Naive Bayes	59.20	37.04	53.29	40.31	51.23	59.20	53.06
MLP	63.54	43.58	42.95	40.67	55.40	63.54	55.92
SVC	64.51	43.51	39.72	37.53	55.24	64.51	55.53

Table 2: Performance metrics of the Random Forest model in classifying various diseases from OCTA images.

Disease	Precision (%)	Recall (%)	F1-score (%)
AD	72.73	47.06	57.14
AMD	91.07	94.44	92.73
CHD	100.00	40.00	57.14
Control	93.92	74.73	83.23
DM	68.57	78.69	73.28
DR	63.93	79.59	70.91
HP	62.00	72.09	66.67
Stroke	39.53	73.91	51.52

diseases during classification, attributed to their lower recall rates, suggesting a higher likelihood of these class samples being misclassified. Meanwhile, stroke, diabetes, and AMD demonstrated higher recall rates, indicating that these diseases are more readily and accurately identified by the model, with less confusion with other categories. Notably, the high recall rate for stroke highlights the model's superior performance in identifying this disease, with minimal confusion with other diseases.

Figure 2 presents the confusion matrix, visually revealing the relationships between the model's predicted categories and the actual categories. An in-depth analysis of the confusion matrix not only uncovers the model's performance variances in identifying various diseases but also exposes potential shortcomings, providing a basis for further model optimization. The confusion matrix also aids in understanding the similarities and differences in features between different diseases, thereby assisting in the precision of clinical diagnoses. Additionally, we paid particular attention to the classification of the control group, finding its recall rate to be relatively low, with samples from the control group tending to be misclassified into categories such as diabetes, diabetic retinopathy, hypertension, and stroke.

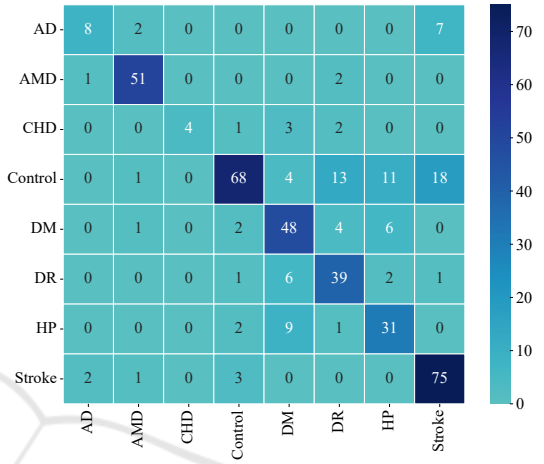

Figure 2: The confusion matrix displays the performance of the Random Forest model in distinguishing between Alzheimer's disease (AD), age-related macular degeneration (AMD), congenital heart disease (CHD), control group, diabetes mellitus (DM), diabetic retinopathy (DR), hypertension (HP), and stroke.

5 DISCUSSION

AD is a long-term neurodegenerative disorder that often results in dementia among older adults. However, diagnosing AD early is difficult due to the lack of definitive diagnostic tools. The retina, sharing developmental and structural similarities with the brain, offers a unique perspective on brain pathology, as changes in the retina may occur before clinical symptoms of AD appear. Thus, creating a model that links ocular and brain structural characteristics to the disease could help identify early retinal changes, paving the way for improved early screening and diagnosis of AD.

OCTA is vital for examining retinal microvasculature, but the variability of existing image analysis tools hinders its wider use in research and clinical settings. To address this issue, this study utilized machine learning algorithms for multi-disease classification of OCTA images. The results showed that the Random Forest model achieved the highest performance, with an accuracy of 78.37%. This highlights the effectiveness of ensemble learning in managing high-dimensional medical imaging data and minimizing overfitting risks.

Despite these advancements, differentiating between diseases remains a challenge. Specifically, AD,

congenital heart disease, and hypertension showed lower recall rates, indicating a tendency for misclassification, possibly due to less distinct features in OCTA images or similarities with other diseases. Conversely, stroke, diabetes, and AMD had higher recall rates, suggesting that these conditions exhibit more distinct features in OCTA images, resulting in better model accuracy for their identification.

The results of this study not only aid clinicians in gaining a clearer understanding of disease characteristics in OCTA images but also open new avenues for future research. This includes investigating innovative image processing methods to extract more representative features and exploring different algorithmic combinations to further improve classification accuracy and reliability. These initiatives will establish a stronger basis for early diagnosis and treatment, ultimately enhancing patient outcomes.

6 THREATS TO VALIDITY

This study faced several challenges while using OCTA for diagnosing ocular diseases, neurodegenerative disorders, and systemic conditions. One major limitation is the intricate relationship between the superficial and deep retinal blood vessels, which hampers the thorough detection of vascular changes associated with various diseases. Additionally, the quality of OCTA images can vary due to factors like differences in equipment, patient cooperation, eye movements, and eyelid interference, making accurate image analysis difficult. The presence of similar vascular changes in OCTA images across different diseases complicates the ability to distinguish between them.

The effects of neurodegenerative and systemic diseases extend beyond what OCTA can reveal about vascular structure. The varying stages of disease progression may also mean that OCTA does not capture early or subtle vascular changes. The absence of longitudinal data restricts the monitoring of disease progression. The technology for automated quantitative analysis of vascular changes is still being refined, with improvements needed in accuracy and reproducibility. Machine learning models also struggle with generalizability across different populations or devices. There is an urgent need for more validation studies and standardized diagnostic criteria for the clinical use of OCTA. The high cost of the equipment limits its accessibility in resource-constrained environments.

When creating multicenter databases, challenges related to data sharing and patient privacy must be addressed. Finally, the interpretability of AI-assisted diagnostic results and the reliability of clinical decision-making require further validation by healthcare professionals. These limitations indicate that while OCTA technology is a valuable asset for disease research and diagnosis, additional research and technological advancements are necessary to address the current challenges in its practical application.

7 CONCLUSION

In this pilot study, we have explored the early diagnostic potential of Optical Coherence Tomography Angiography (OCTA) imaging enhanced by machine learning for Alzheimer's Disease (AD) and its differentiation from other neurodegenerative and ocular disorders. Our analysis of a diverse OCTA dataset using a pre-trained nnU-Net for segmentation and feature extraction revealed that the Random Forest model achieved a commendable classification accuracy of 78.15%. While acknowledging the possibility of misclassification among AD, congenital heart disease, and hypertension, our results highlight the promising role of OCTA and machine learning in early AD diagnosis.

As future works, we plan to focus on refining image processing techniques to extract more discriminative features and exploring advanced machine learning algorithms to enhance classification accuracy. Additionally, addressing the challenges of varying image resolutions and database inconsistencies across different imaging centers will be crucial for fully harnessing the diagnostic potential of OCTA imaging.

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