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Optical Coherence Tomography Image Analysis for Detection of Alzheimer's Disease: A Comprehensive Structured Review

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ABSTRACT

Optical Coherence Tomography (OCT) has emerged as a promising non-invasive imaging modality for the early detection of Alzheimer's Disease (AD). This systematic literature review aims to consolidate current research on OCT image analysis for AD detection, addressing the growing need for early and accurate diagnostic tools. Despite the advances in neuroimaging, early diagnosis of AD remains challenging due to its asymptomatic nature in initial stages and the invasiveness of traditional methods. To achieve this, we conducted an extensive search of related articles from reputable databases (Scopus and Web of Science), focusing on studies published between 2022-2024. The flow of study was based on PRISMA framework. The database found (n = 29) final primary data. This review was divided into three themes, (1) retinal and ocular biomarkers for AD, (2) optical coherence tomography angiography (OCTA) and imaging techniques, and (3) machine learning and computational approaches for Alzheimer's disease diagnosis. Key findings include the enlargement of the periarteriole capillary-free zone and changes in retinal nerve fibre layer thickness as potential AD biomarkers. Based on the review, the implementation of image analysis for OCT images have shown substantial potential for AD detection. By evaluating the past studies, gaps for the current research were discovered including the need for larger, more diverse cohorts and longitudinal studies to validate these biomarkers. In summary, detection of AD is possible through thorough OCT image analysis, but further research could be suggested to enhance its clinical applicability and reliability.

Keywords:
Optical coherence tomography; Retina; Alzheimer's disease; Detection

1. Introduction

Millions of people across the globe are affected by Alzheimer's disease (AD), a degenerative mental illness and dementia's most common cause [1,2]. This implies that AD is a significant problem for individuals, families, and healthcare providers due to its progressive cognitive decline and

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memory loss. In this light, amyloid-beta plaques as well as neurofibrillary tangles accumulate in the brain causing neuron death and atrophy of the brain, which are all part of Alzheimer's pathology. Early diagnosis is essential in managing and treating AD since it slows the progression of the condition leading to better outcomes. Though available diagnostic techniques such as clinical appraisal, neuropsychological tests, magnetic resonance imaging (MRI) neuroimaging along with positron emission tomography (PET) have some limitations regarding accessibility cost as well as invasiveness [3,4]. Consequently, more affordable, less invasive and accessible tools for diagnosis are needed urgently.

AD diagnostics have seen the rise of optical coherence tomography (OCT) as a promising imaging modality. OCT is an imaging technology that is non-invasive, and it can be used to capture high-resolution, cross-sectional images of living tissues through using low-coherence interferometry. OCT was originally developed for ophthalmology and specially for imaging the retina; however, its potential to detect AD related neurodegenerative changes has attracted much attention [5-7]. The retina being an extension CNS undergoes similar degeneration process just like that in brain. This, therefore, makes retinal imaging a useful parameter for studying and diagnosing neurodegenerative disorders like Alzheimer's disease (AD). There are several studies that have shown specific retinal biomarkers discernible by means of OCT which are associated with AD. These include thinning of RNFL, loss of ganglion cells and changes in overall retinal thickness. It has been proposed that these abnormalities in the retina could mirror the neuropathological modifications in brains characterizing the early stages of AD. Figure 1 shows mechanism of neuronal damage and Alzheimer's disease (AD) progression [3]. In addition to this concept, it has also been hypothesized about "retinal amyloidopathy" where amyloid-beta deposits central to AD pathology may accumulate within the eye's retina as well. These findings have spurred interest in using OCT as a diagnostic tool for AD.

The integration of advanced image analysis techniques, mainly those involving machine learning (ML) and deep learning (DL), has led to a great deal of improvement in the diagnostic potential for OCT. For example, OCT images can be analysed by machine learning algorithms like support vector machines (SVM) and convolutional neural networks (CNN) in order to detect subtle and complex patterns which are indicative of AD. These algorithms can process large datasets and extract features that cannot be easily seen by human observers thereby enhancing diagnostic accuracy and reliability [8-10]. Some studies have shown that ML and DL methods achieve high sensitivity and specificity for distinguishing patients with AD from healthy subjects based on OCT images alone [11-14]. However, there remain some issues that must be solved before OCT is fully embraced as a tool for diagnosing AD. Standardized methods are imperative so as to ensure uniformity across different OCT devices, imaging protocols, as well as patient populations. Furthermore, long-term studies need to be conducted so that the temporal relationship between retinal changes could establish with disease progression. Integrating OCT findings with other biomarkers, such as cerebrospinal fluid (CSF) biomarkers and genetic markers, could provide a more comprehensive understanding of AD pathology and enhance diagnostic precision.

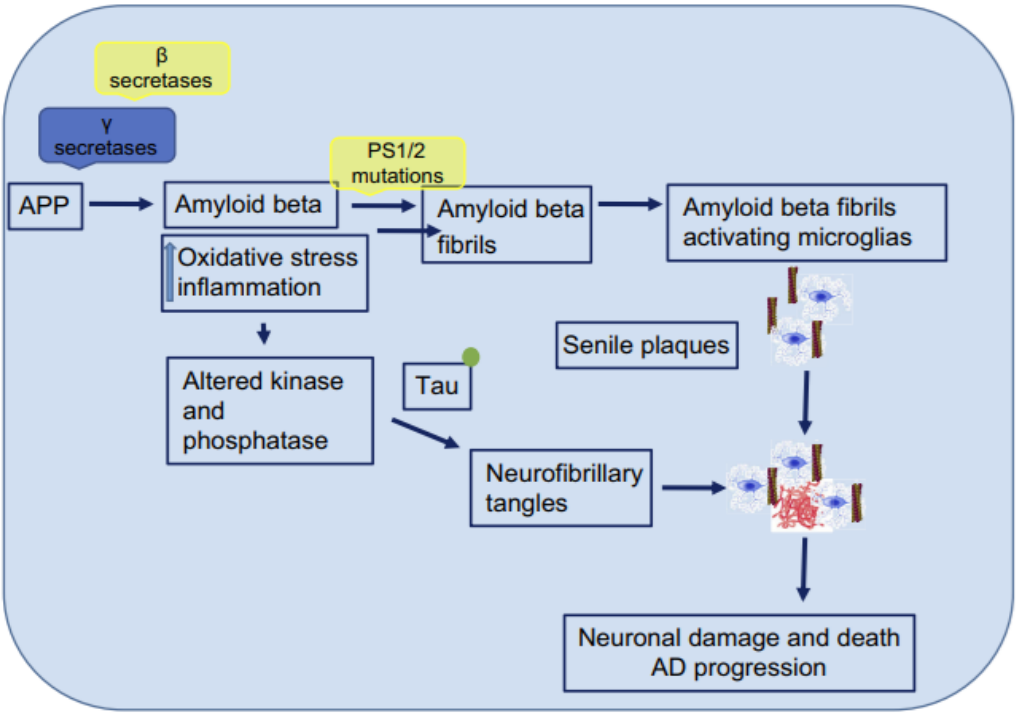

Fig. 1. Mechanism of neuronal damage and Alzheimer's disease (AD) progression [3]

To sum up, optical coherence tomography is a very significant method for early diagnosis and monitoring of Alzheimer's disease. Besides being non-invasive, it can also identify differences in the retina that are related to AD implying a possible future usage as an extra diagnostic tool instead of traditional ones. It is foreseeable that utilization of machine learning and deep learning techniques improved by advancements in imaging technology will even increase the usefulness of OCT in the clinic. With more research ongoing, OCT may become an indispensable tool for diagnosing Alzheimer's, presenting new avenues for early intervention or better patient outcome.

2. Literature Review

Optical coherence tomography (OCT) has become a major instrument for the early detection and monitoring of AD. OCT imaging in the retina allows the in vivo, non-invasive observation of changes to the retinal microvascular and neural structures that may correlate with AD progression. Chen *et al.,* [15], Popovic *et al.,* [16] and Adejumo *et al.,* [17] report that studies demonstrate that the developments in the retina, as shown by measures of microvascular complexity and WLR abnormalities, are the most prominent markers for neurodegenerative processes related to AD. These alterations become measurable even before the first clinical symptoms are manifested, thus placing OCT as a potential early diagnostic tool. Chen *et al.,* [15] performed a meta-analysis associating the positive correlation in retinal thickness associated with hippocampal volume in patients with AD. The authors' systematic review revealed that retinal thinning in patients with AD is correlated with hippocampal atrophy, which is a hallmark of AD. This association might indicate that imaging of the retina could reflect the CNS component of AD changes, opening a window into the health of the brain through the eyes. This study complements the findings by Popovic *et al.*, who pointed out retinal microvascular complexity as a potential marker of biological age and age-related diseases including AD. These data on reduced retinal microvascular complexity are based on quantification methods, in particular Sholl's and box-counting fractal analysis. Further reinforcing

these results, Adejumo *et al.,* [17] showed that OCT could measure the WLR in the retinal blood vessels, showing abnormalities in the mouse models of AD. In their research, they employed adaptive vessel tracing and segmentation methods to achieve this measurement with very high accuracy, hence further defining the potential use of OCT in the detection of early pathological changes within retinal structures. It suggests that microvascular changes at the retina may act as sensitive markers for the early detection of AD and follow-up. Further, Hui *et al.,* [18] used DRL in combination with OCT for automatic AD detection. While reviewing their study, it was realized that DRL would enhance the precision and efficiency of analysis in retinal imaging. It will therefore deploy state-of-the-art AI techniques to enhance diagnostic accuracy of OCT and help the technique find broader applications in the clinic. Empowerment using AI in retinal imaging would make it possible to diagnose the early stages of AD and subsequently monitor patients by identifying those at high risk and monitoring disease progression non-invasively.

The quest for retinal imaging biomarkers is further enriched by work from Batista *et al.,* [19], where changes in retinal thickness in animal models with AD were investigated. These studies detected changes at the early stages of illness, which showed important retinal changes; as such, these biomarkers would have been detected many years prior to the clinical beginning of the disease—very basic for timely intervention and thus better patient outcomes. This study has also demonstrated the feasibility of optical coherence elastography in association with OCT for in situ measurements of retinal elasticity, hence providing access to additional layers of diagnostic information. On a clinical scale, Cordeiro *et al.,* [20] have designed Detection of Apoptosing Retinal Cells technology using Annexin A5 fluorescently labelled to highlight stressed and apoptotic cells in the retina. This technology, according to them, proved through research that DARC, in association with AI algorithms, is capable of actually making some disease activity predictions related to glaucoma and AMD patients. An extension of this technology to AD will have provided another non-invasive biomarker for early detection and follow-up in the disease. The research body underlines the role of OCT in detecting AD-related changes within the retina. Studies have been very strong to the effect that retinal imaging discloses an AD-associated microvascular and structural alteration. It, therefore, becomes a very useful non-invasive tool in early diagnosis and monitoring. Advanced imaging integrated with AI enlarges the diagnostic possibilities of OCT and holds significant potential for improvement in the management of AD.

This has been the case with optical coherence tomography image analysis in Alzheimer's Disease detection, where it has huge potential as a non-invasive diagnostic tool. Actually, several studies have used the advanced imaging techniques to study changes in the retina associated with AD, delineating a possible role for OCT in the early detection and follow-up of AD. Nahid Sami *et al.,* [21] have pointed out the role of deep learning algorithms combined with OCT and OCT angiography techniques for identifying early-stage AD biomarkers. Their detailed analysis explained how such technologies might provide a better prediction for AD by capturing local and global retinal features, which are very important for therapy and treatment planning. The avenue for early intervention in the process of AD may be a combination of both: non-invasive imaging and sophisticated computer algorithms. Jianyang Xie *et al.,* [22] focus on the application of Optical Coherence Tomography Angiography (OCTA) to investigate changes in the retinal microvasculature in the process of AD and amnestic mild cognitive impairment. Their study showed that vessel area and length densities were significantly reduced, especially at inner vascular complexes of AD patients compared to HC. These vascular changes, reflecting the advancement of AD and MCI, further support OCTA as a very useful diagnostic tool. Their framework, with a deep learning model-based standardized analysis, provides a robust way for further clinical applications and research. T. Prasath and V. Sumathi [23] presented a review of various techniques with a base of imaging in AD detection, placing an emphasis on the shift from

brain imaging to retinal imaging. The scientists said in the review that non-invasive approaches, like OCT and digital retinal photography, easily identify biomarkers associated with neurodegeneration; thus, offering quite a feasible solution for the diagnosis of early AD. In that respect, the thickness of the RNFL layer is related to the seriousness of AD. This goes on to mean that, especially in the case of OCT imaging, this technology might be an effective process of screening within a clinical context.

Carol Y. Cheung *et al.,* [24] have gone a step further to explain the relationship that exists between the change in the retina and cognitive impairment. From their findings, it has been shown that the OCT quantitative measurements were significantly associated with AD, relating to the thinning of various retinal layers and reduced capillary density. Computer algorithms in the analysis of retinal images have been developed, which further enhances the potential of OCT as a quick screening tool and facilitates early detection and monitoring of AD progression. Figure 2 shows imaging of retinal capillary network using optical coherence tomography angiography (OCTA), which is not visualised using conventional retinal camera [24]. Lastly, Susanne Jentsch *et al.,* [25] used fluorescence lifetime imaging ophthalmoscopy for the detection of retinal changes in patients suffering from AD. Their pilot study revealed that FLIO parameters were significantly correlated to non-ocular markers specific to AD, including the MMSE score and cerebrospinal fluid concentrations of amyloid-β and tau proteins. In contrast to conventional OCT, FLIO was able to deliver further details about the retinal changes related to AD, thus supporting the possibility that combinations of different imaging methods might improve diagnostic accuracy.

Fig. 2. Imaging of retinal capillary network using optical coherence tomography angiography (OCTA) [24]

Overall, advances in OCT and related imaging technologies have contributed enormously to the early detection and monitoring of Alzheimer's disease. Researchers could further enhance diagnostic capabilities brought in by these non-invasive techniques with deep learning algorithms, only after developing appropriate innovative analysis frameworks. It is such potential of OCT and OCTA techniques, integrated into clinical practice, which is going to accomplish timely and accurate diagnosis of AD, very necessary for its effective treatment and management.

3. Material and Methods

3.1 Identification

Several key steps in the systematic review process were used to choose a great deal of relevant literature for this study. First, keywords are selected, and then related terms are searched for using

dictionaries, thesaurus, encyclopaedias, and past research. All relevant keywords were selected once the search strings for the WoS and Scopus databases were created (see Table 1). During the first stage of the systematic review process, 448 publications were successfully retrieved for the current study project from both databases.

Table 1
The search string

Database	Search String
Scopus	TITLE-ABS-KEY (("Optical Coherence Tomography" OR oct) AND detect* AND alzheimer*) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2024)) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (SRCTYPE , "j") OR LIMIT-TO (SRCTYPE , "p")) AND (LIMIT-TO (DOCTYPE , "cp") OR LIMIT-TO (DOCTYPE , "ar")) Access Date: May 2024
WoS	("Optical Coherence Tomography" OR oct) AND detect* AND alzheimer* (Topic) and Article or Proceeding Paper (Document Types) and English (Languages) and 2021 or 2022 or 2023 or 2024 (Publication Years) and 2024 or 2023 or 2022 (Publication Years) Access Date: May 2024

3.2 Screening

Researchers created inclusion and exclusion criteria, which were used to screen 448 papers during the first phase (see Table 2). The literature in the form of research articles and conference proceedings was the main selection criterion because it offers useful information. As a result, publications such as books, book chapters, meta-analyses, reviews, systematic reviews, and reviews were excluded from the study. Furthermore, only English-language papers were included in the review. It is imperative to emphasize that the study was conducted over a three-year period (2022–2024). A total of 353 publications were disqualified according to a particular criterion. Twenty materials that were duplicates in both databases were also eliminated in the second round.

Table 2
The selection criterion in searching

Criterion	Inclusion	Exclusion
Language	English	Non-English
Timeline	2022 – 2024	< 2022
Literature type	Journal (Article) and proceeding	Book, Review
Publication Stage	Final	In Press

3.3 Eligibility

The third stage was the eligibility assessment, whereby seventy-five articles were aggregated. This involved an in-depth analysis of each article's title and texts to ascertain whether the papers fitted within the set inclusion criteria and were relevant to the study aim being undertaken. 46 datasets, papers and articles were therefore determined as ineligible for inclusion. Excluded in the process were: those that were irrelevant to the reason for the study, their abstracts turning out to be of no relevance to the investigation at hand, those outside this field, and articles with no full-text accessibility supported by empirical data. This has therefore reduced it to 29 papers to be reviewed in the future.

3.4 Data Abstraction and Analysis

This section discusses the results obtained from the surface pressure measurement study. The effects of angle of attack, Reynolds number and leading-edge bluntness are discussed in the next sub section. In this study, an integrative analysis was employed as one of the assessment strategies to examine and synthesize a range of research designs, specifically focusing on quantitative methods. The primary aim of the study was to identify relevant topics and subtopics. The initial step in theme development was the data collection stage. As depicted in Figure 3, the authors meticulously analysed a compilation of 29 publications for assertions or material pertinent to the study's topics. Subsequently, they evaluated significant studies related to optical coherence tomography image analysis for Alzheimer's disease detection. The methodologies and research results of these studies were thoroughly investigated. The author, along with co-authors, collaborated to develop themes based on the evidence within the context of this study. A log was maintained throughout the data analysis process to record any analyses, viewpoints, puzzles, or other thoughts relevant to data interpretation. Finally, the authors compared the results to identify any inconsistencies in the theme design process. In cases of conceptual disagreements, the authors discussed them amongst themselves. The resulting themes were refined to ensure consistency. Three experts conducted the analysis selection to determine the validity of the issues. The expert review phase ensured the clarity, importance, and suitability of each sub-theme by establishing domain validity.

Based on the overall reviews on the literature, the questions are as follow:

i. What are the most promising retinal biomarkers for the early detection of Alzheimer's disease?
ii. How do retinal structural changes correlate with cognitive impairment and neurodegeneration in Alzheimer's disease?
iii. Can retinal biomarkers serve as non-invasive tools for early diagnosis and monitoring of Alzheimer's disease progression?
iv. How effective is OCTA in identifying early biomarkers of Alzheimer's disease compared to other imaging techniques?
v. What specific retinal vascular changes can OCTA detect that correlate with Alzheimer's disease progression?
vi. Can OCTA be integrated into routine clinical practice for the early detection and differentiation of Alzheimer's disease subtypes?
vii. How can machine learning models enhance the accuracy of Alzheimer's disease diagnosis using retinal imaging data?
viii. What are the most effective machine learning algorithms for detecting early signs of Alzheimer's disease from retinal images?
ix. How can computational approaches integrate multimodal retinal imaging data to improve the prediction of Alzheimer's disease progression?

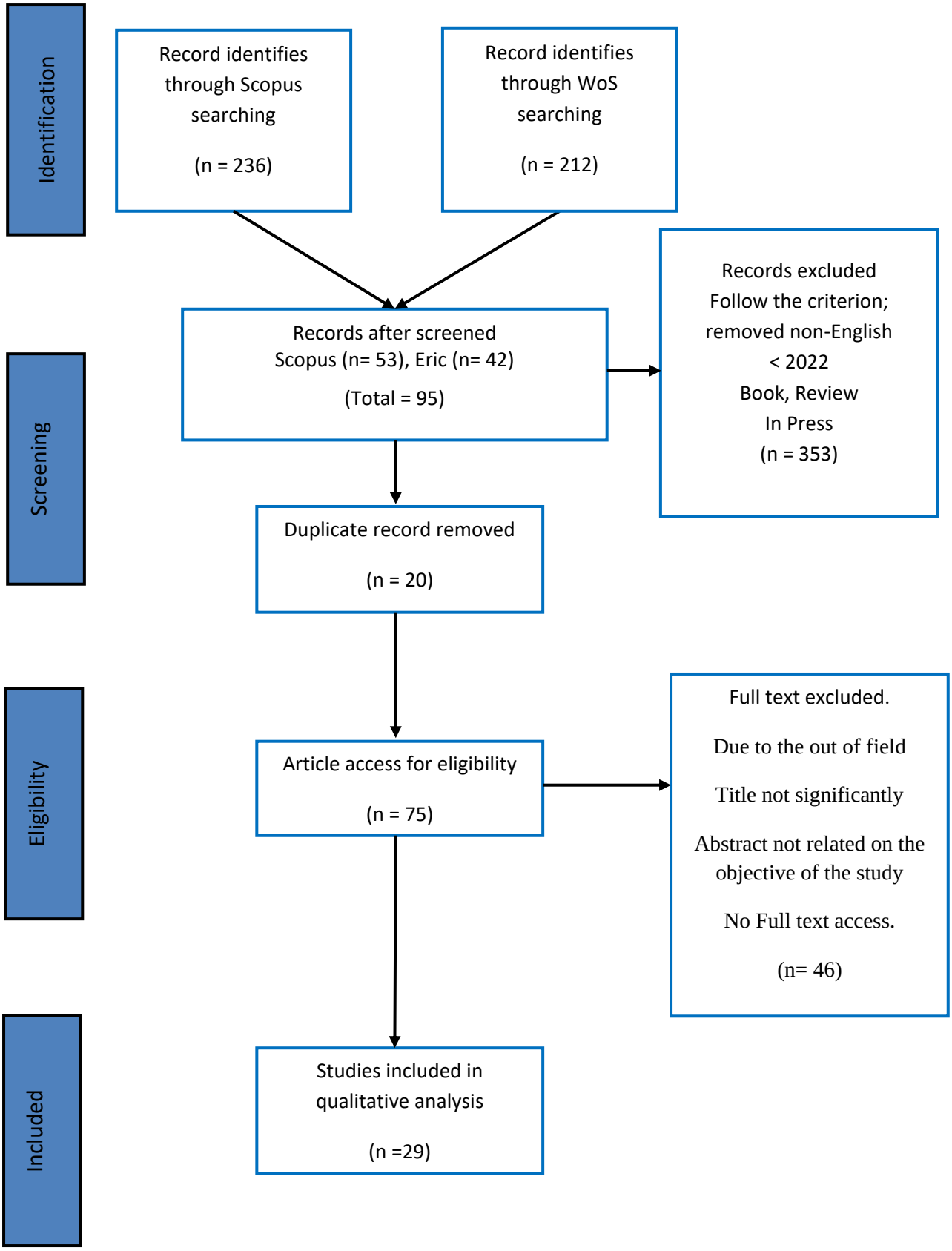

Fig. 3. Flow diagram of the proposed searching study [26,27]

4. Results and Findings

This review was divided into three main themes which could be beneficial for future research. Details on each theme was discussed based on the 29 final data determined in the previous section.

4.1 Retinal and Ocular Biomarkers for Alzheimer's Disease

Recently, interest has shifted to the retinal and ocular biomarkers for the diagnosis of AD due to embryological similarity shared between the retina and the brain. Advanced imaging techniques, of which the most important ones are either OCT or OCTA, have further illuminated the way toward the identification of neurodegenerative changes associated with AD in the early stages of its development. Some studies did not find any correlation with macular vessel density in the superficial plexus regarding CSF biomarkers, while others found there to be significant reductions in macular microvascular density in AD patients that could be potential diagnostic biomarkers. The discrepancies here are such that the issue obviously requires further research. It has also been shown that there are prominent thinning of the retinal ganglion cell layer (GCL) and retinal nerve fibre layer (RNFL), correlating with reduced brain volumes, underscoring the potential utility of OCT for the early detection of neurodegenerative changes. A reduction in the levels of amyloid-beta in tears correlated with the retinal changes and brain changes related to AD, thus acting as a non-invasive biomarker for its early detection. Moreover, strong correlations in severe reductions of retinal thickness and vessel density with cognitive decline support the sensitivity of these measures for detecting AD. Comparative studies on retinal thinning patterns in AD and multiple sclerosis demonstrate a clear specificity. This is further confirmed by meta-analyses. The findings in this study of significant correlations between retinal microvasculature changes and grey matter volume in people at risk for AD during midlife prove that these changes are an early retinal indication of AD. Quantified capillary-free zones show large zones as a major feature in high-risk individuals, which could work as novel biomarkers for the early detection of AD risks. These works together support the potential use of retinal imaging as a resourceful tool for unravelling AD neurodegeneration. Actually, these Avivements indicate that measurements of retinal biomarkers of AD, like macular VD, GCL, and RNFL thickness, provide optimum potential for non-invasive, presymptomatic diagnosis of AD, in addition to amyloid-β levels in tears. Such methods will only be successful if techniques further develop and requiring large, prospective cohort studies to create trustworthy diagnostic tools for AD.

Studies by Marquié *et al.,* [28,29] and García-Sánchez *et al.,* [30] evaluated the relationship of macular VD within the superficial plexus to CSF biomarkers of AD in subjects with aMCI and non-demented controls. These studies independently reached the same conclusion: no evidence was noted for a significant relationship between macular VD and CSF biomarkers, including Aβ1-42, p181-tau, and t-tau, and further, that brain vascular pathology and atrophy were found to be unrelated. These findings suggest that macular VD in the superficial plexus might not reflect early cerebrovascular impairment in the context of AD. Oppositely, Wang *et al.,* [31] recently present evidence for a significant decrease in macular microvascular density in a group of AD patients compared with matched controls. This decrease in macular microvascular density correlated with the cognitive impairment and APOE ε4 genotypes, which suggested that the macular VD could be used as one diagnostic index for AD. These discrepancies may be because of varying designs, populations and stages of diseases associated with studies, thereby indicating further research into the topic is required to rectify these findings.

The study by López-de-Eguileta *et al.,* [32] and Mathew *et al.,* [33] focused on the retinal ganglion cell layer and retinal nerve fibre layer. López-de-Eguileta *et al.,* [32] found that in subjects free of

cognitive deficits but positive for CSF biomarkers of AD, such as tau proteins, there was significant thinning of the GCL and RNFL. The authors mentioned that this thinning went with a reduced hippocampal volume, and therefore, OCT may become useful in the description of early neurodegenerative changes before the appearance of cognitive symptoms. Similarly, Mathew *et al.,* evaluated the positive associations between RNFL thickness with brain volumes of areas such as the hippocampus and temporal lobe. These findings back clearly the potential utilities for RNFL measurements in monitoring brain neurodegeneration, which aids diagnosis of AD. Therefore, the correlational consistency of retinal layer thinning with a reduction in brain volume underpins these retinal biomarkers within the context of AD.

Gharbiya *et al.,* [34] investigated the potential diagnosis of AD using the levels of Aβ1–42 in tears. According to the results, there is a strong correlation between the decrease in tear Aβ1–42 and MCI and AD. At the same time, this decrease was strongly correlated with CT thinning and thus reflects that tear biomarkers could be helpful in supplying non-minimally invasive early detection of AD. These results are in agreement with a previous investigation by Hu *et al.,* [35], which observed remarkable correlations between retinal changes and anatomic brain alterations in patients with the AD spectrum, thus providing further support for the application of non-invasive biomarkers in the early diagnosis of AD. AD patients, as opposed to Chaitanuwong *et al.,* [36], exhibited substantial reductions in the thickness of the macula and vessel density at the level of the parafovea and perifovea compared with age-matched normal controls. These reductions correlated positively with cognitive decline, measured by Thai Mental State Examination scores. In this respect, it underlines the sensitivity of retinal thickness and VD in neurodegenerative changes associated with AD. Similarly, Hu *et al.,* [35] observed correlations between the density of retinal vessels and hippocampal subfield volumes, as well as white matter tract integrity—retinal microvascular measures that may be early markers for structural brain changes related to AD. Garcia-Martin *et al.,* [37] examined the differences in retinal thickness between AD and MS patients, showing different patterns of retinal thinning in these two conditions. This allows a priori differentiation from other neurodegenerative diseases finally resulting in dementia and underlines the specificity of the retinal changes associated with AD, which might be assessed by means of OCT. This specificity was further supported by Sheriff *et al.,* [38], in a meta-analysis done to confirm the association of retinal thickness and vascular parameters with AD, to differentiate it from other neurological conditions.

The collective evidence underlines the potential of retinal imaging, particularly OCT and OCTA, to provide key insights into AD-related neurodegeneration. Some studies positioning the measurement of retinal changes as pertinent surrogates for AD biomarkers have established prominent associations, but others indicate a necessity for further replication across different populations and disease stages—which does not seem entirely improbable. The retinal biomarkers that currently show great promise for the non-invasive early diagnosis of AD are retinal vessel density, ganglion cell layer and RNFL thickness, and more sophisticated parameters such as the levels of amyloid-beta in tears. Further advances in imaging and larger prospective studies will be required to confirm the usefulness of these retinal parameters as diagnostic markers of AD.

Specifically, Rashid *et al.,* [39] investigated changes in retinal microvasculature within OCTA data for individuals from mid-life who are at risk of developing AD. According to the results, it was found that there were highly significant correlations between retinal vessel metrics and grey matter volume regions. These findings underline further the potential of changes to retinal microvasculature as early markers for AD and its asymptomatic stages. In a recent study, Arthur *et al.,* [40] have quantified the capillary-free zone at the periarteriole and perivenule in cognitively unimpaired older adults at high risk for AD. High-risk individuals had larger CFZs compared with low-risk controls, hence representing another potential novel retinal vascular biomarker for early risk detection of AD. Chimthanawala *et*

al., [41] performed a review regarding non-invasive biomarkers for the early detection of AD and underlined the role of techniques of retinal imaging. These biomarkers are detectable in various biological samples and show a positive correlation with brain pathology of AD, thus allowing an early diagnosis and management.

4.2 Optical Coherence Tomography Angiography (OCTA) and Imaging Techniques

The analysis was made related to OCTA and imaging techniques for several studies and summary on the findings are as tabulated in Table 3.

Table 3
Summary of optical coherence tomography angiography and imaging techniques

Author Name and Year	Objectives	Findings	Conclusion & Future Research
Chua J. *et al.*, [42]	Improve diagnostic ability of OCT retinal biomarkers to differentiate MCI/AD.	Participants with MCI/AD showed significantly thinner measured and compensated cpRNFL, mGCC, and altered retinal vessel density. Compensated RNFL outperformed measured RNFL for discrimination of MCI/AD.	Using interindividual variations in ocular anatomical features in cpRNFL measurements and incorporating macular information may improve detection of person with early cognitive impairment. Future research should explore further on these combinations.
Sun Y. *et al.*, [43]	Investigate fundus markers in PCA patients 4and compare them with typical AD patients to identify patterns.	PCA patients had thinner retinal nerve fibre layer and ganglion cell layer + inner plexiform layer compared to HC.	OCTA may aid in non-invasive detection of AD and PCA. Future research should substantiate these findings and improve diagnostic accuracy.
López-Cuenca I. *et al.,* [44]	Analyse changes in retinal vascular network in subjects with high genetic risk of developing AD.	Increased vascular density in specific retinal sectors in genetically at-risk subjects. Significant changes observed in participants with HCL and HBP.	OCTA shows promise as a biomarker for monitoring early vascular changes in AD. Future research should validate these biomarkers in larger cohorts and explore longitudinal changes.
Wang L. *et al.*, [45]	Explore association between cortical visual system and retinal vascular structures in AD patients.	Cognitive impairment group showed decreased functional connectivity in the cortical visual system and deteriorated retinal vascular structure characteristics.	Retinal vascular structure characteristics could be used for diagnosing and monitoring AD progression. Future research should refine these biomarkers and explore their clinical applicability.
Xie J. *et al.*, [21]	Develop OCTA analysis framework for early detection of retinal microvascular changes in AD and MCI.	Significant decrease in vessel area, length densities, and number of bifurcations in AD and MCI groups.	OCTA provides useful biomarkers for clinical decision-making and diagnosis of AD and MCI. Future research should standardize these tools and validate their use in clinical settings.
Zhao B. *et al.*, [46]	Explore relationships of retinal differences with imaging in AD patients.	Decreased macular thickness associated with cognitive function in mild AD patients.	Future studies should investigate OCTA in evaluating AD. More rigorous and larger studies are needed.
Rashid D. *et al.*, [47]	Investigate retinal phenotypes in mid-life individuals at risk of getting AD using OCTA.	Retinal vascular changes observed between control and at-risk groups.	Future research should focus on relating findings into clinical practice for early AD detection. Longitudinal study can be used to check changes over time.
Liu S.Y. *et al.*, [48]	Develop a clinical-friendly DL model for AD detection in OCTA images.	Polar-Net outperformed existing methods, providing valuable pathological evidence for retinal vascular changes related with AD.	Polar-Net framework shows promise in AD detection. Future research should further validate this model and explore its integration into clinical workflows.

4.3 Machine Learning and Computational Approaches for Alzheimer's Disease Diagnosis

Implementation of machine learning and other computational approaches for diagnosis of AD were summarized in Table 4 in terms of objectives, methodologies implemented in the study, results as well as future research of the study.

Table 4
Summary of machine learning and computational approaches for diagnosis of AD

Author Name and Year	Objectives	Methodologies	Results	Future research
Yang H. *et al.*, [49]	Develop a distance-based novelty detection model to identify individuals at risk of developing AD.	1. Novelty Detection (ND) 2. Mixture of Gaussian-based ND algorithm 3. Distance to Boundary (DtB) strategy 4. Web-based GUI	AUCs : 0.8757 and 0.9443, sensitivities : 96.79% and 89.09%, specificities : 89.63% and 90.92% for the AIBL and FMUUH datasets respectively.	Future research could enhance model interpretability and integrate additional data sources.
Wisely C.E. *et al.*, [50]	Develop a convolutional neural network (CNN) to detect symptomatic AD using multimodal retinal imaging.	1. Convolutional Neural Network (CNN) 2. Multimodal retinal images 3. OCT and OCTA quantitative data 4. Patient data.	UWF colour 0.450, OCTA SCP 0.582, UWF FAF 0.618, GC-IPL maps 0.809. Combined model AUC 0.836, images only model AUC 0.829, GC-IPL maps and data model AUC 0.841.	Future research may explore incorporating additional biomarkers and enhancing multimodal data integration.
Gao H. *et al.*, [51]	Develop a dual-stream attention neural network to classify individuals with MCI based on multimodal retinal images.	1. Dual-stream attention neural network 2. Cross-modality fusion 3. Variable scale dense residual model 4. Multi-classifier 5. Gradient-based Class Activation Mapping	High precision rates of 84.96% and 80.90% in classifying MCI and positive test scores for cognitive impairment, respectively.	Future research could refine the model and investigate additional retinal biomarkers.
Irfanuddin C.M. *et al.*, [52]	Develop a deep learning approach to detect diseases using retinal images.	1. Deep learning 2. Retinal cross-sectional images 3. Dataset of 21 MS patients & 14 healthy	Accuracy : 98.85% in classifying healthy and diseased individuals.	Future research should explore its application to other diseases and larger datasets.
Lustig-Barzelay Y. *et al.*, [53]	Assess the pupil light reflex (PLR) for early detection of AD in subjects with/without AD.	1. Chromatic Pupilloperimetry 2. Machine Learning (ML) 3. Transient PLR for red and blue light stimuli	AUC-ROC of 0.90 (left-eye) and 0.87 (right-eye). Shorter PRL for dim blue light in high-risk group.	Future research could explore longitudinal studies and PLR parameters.
Mozdbar S. *et al.*, [54]	Examine the predictive ability of structural retinal biomarkers for detecting CI in a primary care.	1. OCT 2. Visual acuity 3. Ocular history questionnaire 4. Eye pressure 5. Fundus imaging	Top biomarkers included various quadrants of the retinal nerve fibre layer.	Future research should validate these findings in larger, diverse populations.

Vinoth Kumar M. *et al.*, [55]	Develop an enhanced LSTM model for early AD prediction using ocular biomarkers.	1. Enhanced Long Short-Term Memory (E-LSTM) 2. Particle Swarm Optimization (PSO)	Improved prediction accuracy by 10% compared to existing systems.	Future research should use larger sample sizes and integrating additional ocular biomarkers.

5. Discussions and Conclusions

Research into the potential of retinal and ocular biomarkers for the diagnosis of Alzheimer's disease has been very promising, especially with the development of advanced imaging techniques such as optical coherence tomography and optical coherence tomography angiography. Some studies have shown associations between changes at the retina and AD biomarkers, which could be indicative of non-invasive early detection for AD. For these retinal measures to be considered as reliable diagnostic tools for AD, much more research and validation in different populations and at different stages of the disease are needed.

Several research studies have pointed out that OCT and OCTA could help not only in early diagnosis but also in differential diagnosis between AD and mild cognitive impairment. These studies assessed that there were significant differences in the retinal biomarkers—cpRNFL and mGCC thickness—between subjects with MCI and AD and those who are cognitively normal. These measurements are improved in terms of diagnostic accuracy by compensation for demographic and anatomical variations. Combining parameters for cpRNFL and mGCC achieves an improved AUC for the detection of MCI and AD, underscoring once more the additional value of multiple retinal layer parameters in assessments. Moreover, it enabled OCTA to detect distinct retinal changes in a subgroup of patients with dementia, namely PCA patients, showing its utility in differential diagnosis between the various forms of dementia. This is also reflected in the retinal vascular changes by genetic predispositions, like ApoE ε4 status, positioning OCTA to monitor those at high risk for AD. Deep-learning-based models analysing OCTA images, such as Polar-Net, further facilitate the detection of retinal changes associated with AD in an Thu fashion, thus consistent with clinical observation, offering great promise for early diagnosis and monitoring of neurodegenerative diseases.

Specifically, owing to the use of advanced imaging and machine learning models, the detection of AD has become one of the prime areas of research aimed at providing an early and accurate diagnosis. Yang *et al.,* present a distance-based novelty detection model on the AIBL and FMUUH cohorts that realizes high sensitivity and specificity, with a user-friendly GUI facilitating the detection of MCI and AD. Wisely *et al.,* demonstrated that a CNN could actively identify AD with integrated multimodal retinal images and patient data; in that, GC-IPL maps were very useful. Gao *et al.,* proposed a dual-stream attention neural network that applied multi-modal retinal images for positioning MCI with high precision, giving more importance to retinal biomarkers. Irfanuddin *et al.,* propose an efficient deep learning approach that yields an accuracy of 98.85% for detecting neurodegenerative diseases from retinal scans and is cost-effective, hence accessible. Lustig-Barzelay *et al.,* describe chromatic pupilloperimetry using machine learning for estimating AD-risk by minute changes in the light reflex of the pupils, hence offering a non-invasive early detection method. For instance, Mozdbar *et al.,* studied the structural retinal biomarkers of cognitive impairment in a primary care setting and identified the main retinal layers that were relevant for prediction. Kumar *et al.,* proposed E-LSTM with an optimization component of Particle Swarm Optimization to improve the accuracy of retinal image segmentation for AD prediction. These studies, when put together, prove the potential role for imaging the retina and machine learning in transforming the diagnosis of

AD. However, additional research work should be done with more integration to get the best out of these approaches for their clinical applications.

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