Automated diagnosis of AD using OCT and OCTA: A systematic review

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Abstract

Retinal optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) are promising tools for the early-stage diagnosis of Alzheimer’s disease (AD). These non-invasive imaging techniques are cost-effective and more accessible than alternative neuroimaging tools. However, the current literature lacks an extensive review of AD or cognitive impairment diagnosis using OCT or OCTA. This motivated us to examine recent deep learning studies using the PRISMA approach to systematic review. We used Publish or Perish software to locate relevant research from databases such as Scopus, PubMed, and Web of Science, obtaining an initial pool of 2725 references. We then followed the PRISMA review process to identify twelve relevant studies and two patent applications for detailed analysis. Half of the papers we reviewed described longitudinal mouse studies targeting early AD detection. Whereas earlier research used patient demographics and pre-computed features as inputs to the classical machine learning classifiers, more recent studies tend to employ end-to-end deep learning models with OCT and OCTA image inputs. However, this approach presents issues such as small datasets and an absence of scanning standards, which the reviewed literature addresses in various ways. We discuss the lack of open OCT/OCTA datasets (about Alzheimer’s disease) as the main issue impeding progress in the field.

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INTRODUCTION

Alzheimer’s disease (AD) is an irreversible and progressive brain disorder characterized by a decline in cognitive function, and is the most prevalent type of dementia. It currently has no known cure and is marked by a significant reduction in brain size (neurodegeneration) caused by the accumulation of proteins (amyloid-beta and tau) in neurons.¹ As the retina and brain originate from the same neural tube, the eyes are often regarded as an extension of the brain,² and postmortem studies show that amyloid-beta and tau protein accumulate in the retinas of individuals with AD.³ High-resolution visual imaging technologies, such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) have recently been proposed to examine structural and vascular changes in the retinas of AD patients. In a recent study, Vij et al.⁴ reviewed advances in retinal modalities for diagnosing Alzheimer’s disease. Their review
encompasses a range of structural, functional, and multimodal/paired imaging modalities. Among these, OCT is the most commonly studied tool, used in 57% of diagnoses, primarily due to its non-invasive, cost-efficient, and user-friendly nature. Another relatively new imaging technique that has gained attention in recent years is OCT angiography (OCTA), a visualization of retinal blood flow computed from consecutive OCT scans without the need for contrast agents. Several studies have combined OCT and OCTA to enhance AD diagnosis\textsuperscript{5,6,7} and the two techniques have also shown promising results in diagnosing other cognitive impairments.\textsuperscript{8,9,10,11,12,13,14,15,16} Overall, OCT and OCTA are practical and cost-effective retinal imaging tools that show considerable promise for the diagnosis of AD and cognitive impairment. However, interpreting the high-dimensional and multimodal retinal scans generated by OCT and OCTA is an extensive and time-consuming process. Consequently, automated approaches based on machine learning (ML) or deep learning (DL) have been developed to improve the efficiency of diagnosing retinal abnormalities. Although deep learning methods present several methodological challenges for retinal disease analysis,\textsuperscript{17} they have been used to improve image quality and segment retinal layers, as well as to diagnose and predict disease course.\textsuperscript{18,19,20,21}

Figure 1 illustrates the number of deep learning studies conducted on OCT and OCTA images listed in PubMed over the last six years. Notably, the small number of publications on OCTA compared to OCT reflects the relatively recent development and limited availability of data sets. Bourkhime et al.\textsuperscript{22} recently reviewed 13 studies on machine learning and novel ophthalmologic biomarkers (not specific to OCT or OCTA) for Alzheimer's disease (AD) screening. However, the use of deep learning (DL) for AD diagnosis based on OCT and OCTA scans or biomarkers is yet to be surveyed - a significant gap, given the potential benefits of these techniques for early detection. Accordingly, we conducted a comprehensive literature search using various terms and databases (including theses) and also considered animal studies. We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines\textsuperscript{23} (Section 2).

We examine the twelve relevant studies in detail in Section 3, considering them from the perspectives of deep learning, quality assessment, bias, and study type (human or animal-based). We present our discussion and conclusions in Sections 4 and 5.

**METHODS**

To review ML/DL-based approaches for AD or MCI diagnosis in OCT and/or OCTA scans, we followed the guidelines of the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA).\textsuperscript{23} Figure 2 shows the PRISMA flow chart for our systemic review. 

**Information Sources:** We performed an exhaustive search of Pubmed, Web of Science, Scopus, Google Scholar, Semantic Scholar and CrossRef for relevant studies published between 2015-2022. 

**Search Strategy:** We surveyed the databases above using Publish or Perish software,\textsuperscript{24} which retrieves and analyzes academic citations. Our search strategy was based on the following combinations of terms: ("Alzheimer’s" OR "dementia" OR "cognitive impairment") AND ("optical coherence tomography" OR "optical coherence tomography angiography" OR "retinal imaging") AND ("neural networks" OR "machine learning" OR "deep learning")

**Eligibility criteria:** Articles meeting all the criteria below were selected for analysis:

- The article was available in English.
- An English abstract was available for non-English language articles.
- It was published as a primary research paper in a peer-reviewed journal. Conference papers, duplicates, datasets, book chapters, and articles that only provided statistical analysis were excluded.
- It described an ML model for AD detection, screening, or prediction using only OCT/OCTA scan images or data derived from these. Articles only related to segmentation or image quality improvement were excluded.
- It focused solely on AD and/or MCI (not other diseases such as Age-related macular degeneration, Drusen, etc.).

**Data extraction, quality assessment, and bias analysis:** The data were first extracted and cross-
checked. We then analyzed the eligible studies and obtained information such as the number of participants, year of publication, the algorithms applied and their characteristics, model prediction parameters, and performance metrics, including accuracy, discrimination sensitivity, and specificity rates. We used the Quality Assessment for Diagnostic Accuracy Studies (QUADAS-2) tool to assess the risk of bias and the applicability of the studies included in the review. Our findings and analysis are set out in the following sections.

RESULTS

Our search initially retrieved 2725 references. After applying the elimination steps (see Figure 2), we identified 14 studies that met our inclusion criteria. Two of these had previously been identified by Bourkhime et al. Table 1 displays the main features, algorithms, and reported performances of the reviewed publications. In addition to peer-reviewed studies, our manual search also yielded two patents. The first patent application (U.S. Patent No. 6,988,995 B2, 2006), by Carl Zeiss Meditec, Inc., claimed a method based on artificial neural networks and RNFL images to classify Alzheimer’s disease. The second patent application (U.S. Patent No. 1128801B2, 2022), filed by the National Chin-Yi University of Technology, Chi Medical Center, claimed CNN-based methods for segmenting and classifying OCT images.

Challenges to deep learning approaches

There is growing interest in using ML/DL models to study AD in OCT/OCTA images, as depicted in Figure 3. While only five studies were published between 2015 and 2021, a further seven dated from 2022, highlighting the recent surge of interest in the field. However, several challenges discussed in Yanagihara et al. remain, including limited datasets, lack of image collection standards, non-standardized evaluation metrics, and computational limitations. It is worth noting that although these issues apply to all 2725 DL studies, research into AD or MCI seems particularly challenging, with only 12 of 2725 studies focusing on the former disease. In contrast, other illnesses such as glaucoma have received greater levels of attention, possibly due to the wider availability of datasets. The lack of openly available OCT datasets for AD and MCI therefore presents a particular challenge to advances in these fields. Despite the associated challenges, deep learning models were favored over their machine learning (ML) counterparts in research from 2022, as Figure 4 shows. To better understand how researchers have addressed these challenges, we reviewed the eligible DL studies and summarize their proposed solutions in Table 2.

Small datasets and overfitting

ML and particularly DL models require large amounts of data (examples) to generalize learned tasks. This requirement makes overfitting a significant concern when working with small datasets. Our review revealed that the most widespread solution to this issue was to increase the size of datasets by producing new examples using data augmentation. Additionally, some studies employed regularization, dropout, batch normalization, and early stopping techniques to prevent overfitting of the models. Another widely used method was transfer learning, which entails copying some of the network weight values from the low-level layers of another network previously trained on a large generic image database such as ImageNet. After transferring the weights, the network is fine-tuned on the specific challenge database for a few epochs to complete the training. The OCT AD studies in our sample transferred their weights from a range of pre-trained networks, including Inception-v3, DenseNet, and ResNet18 to warm-start (i.e., fine-tune) their OCT image training for AD diagnosis. However, none of these transfer learning examples could use 3D OCT scans directly as inputs because the source networks were trained on generic two-dimensional (RGB colour) images, which comprise ImageNet-like databases. The limited number of cases in small OCT datasets can make it challenging for DL networks to identify features associated with complex problems like AD or MCI. To tackle this issue, some studies integrated supplementary information - including descriptive patient
data and OCT-derived quantitative data such as Retinal Nerve Fiber Layer (RNFL) thickness - into their models. Wisely et al.'s study compared various input combinations, finding that the best single input was the GC-IPL thickness image obtained from OCT. However, combining multimodal retinal images, OCT and OCTA quantitative data, and patient data produced a marginally improved performance. In their recent study, Wang et al. exclusively utilized OCTA images, indicating a potential shift toward sole reliance on image inputs.

Low image quality and standards

Enhancing image quality using computer vision (CV) techniques before ML or DL is a popular topic in medical imaging research. The physical and clinical nature of OCT scans can impact image quality. Raw OCT slice images are susceptible to speckle noise due to coherent light scattering, while low signal levels in some devices result in other types of noise. In response, researchers have utilized various image improvement techniques, including normalization, histogram equalization, contrast enhancement, as well as Gaussian and median filters to enhance the quality of OCT scans. Because the retina is a non-rigid, moving layer of tissue inside a mobile body, non-standard frames, motion blur, and artifacts may result. To address these issues, studies have implemented resizing, cropping, and recentering of images, alongside artifact removal.

Computational Restrictions

It has become common practice in ML and DL studies to use high-performance workstations with GPUs to overcome computational limitations. In addition, transfer learning techniques have gained popularity due to their ability to use pre-trained networks that require minimal training of the output layers. These techniques were also used to solve the issues with small datasets and overfitting analyzed in section 3.1.1. Such solutions were based on 2D OCT scans, even though OCT scans could be tiled to generate 3D volumes. However, working on 3D volumetric data has its own computational challenges: while some recent research has focused on 3D OCT images, there were no 3D OCT studies on AD or MCI.

Black box models and explainability

Despite the accurate classification provided by deep neural network architectures, they are often viewed as black-box models. Establishing trust in their predictions is essential for medical decision-making. In their seminal work, Ribeiro et al. posed the question, "Why Should I Trust You?" and argued that understanding the rationale behind a model’s predictions would lead to increased trust. Accordingly, several interpretability methods have been tested in OCT/OCTA-based AD diagnosis. Among these, Grad-CAM and CAM have featured most often. Singh et al. evaluated 13 deep learning explainability methods for OCT scans and found that the Deep Taylor (DTaylor) method outperformed others in diagnosing CNV, DME, and drusen using the Inception-v3 model. Guimaraes et al. also applied this technique to analyze their results. Originally introduced as a tool to enhance the performance of recurrent neural networks in machine translation, attention-based models have been applied to a wide variety of tasks from different domains, including language, speech, and vision. The transformer architecture proposed by Google researchers was the first self-attention model capable of computing its input-output representation without using CNNs or RNNs. These transformer-based attention models have not only improved performance and reduced the time needed for pattern and image recognition tasks but also simplified the task of visualizing and interpreting network outputs and classifiers. They achieve this by highlighting which parts of the input are utilized by the neural network to make predictions. Recent studies have demonstrated the use of attention in OCT-based AD diagnosis.
Incomparable tests and metrics

We reviewed the range of input modalities and features, testing methods, and accuracy metrics employed in these studies (Table 1). It is difficult to compare their reported performances for several reasons: (1) They were trained and tested on highly distinct private datasets. (2) They use different methodologies for distributing instances among training/testing partitions. (3) Their final classification decision may be based on results from either one or both eyes. (4) They report performance using various metrics (e.g., accuracy, AUC, F-1 score, and sensitivity). While such discrepancies are typical in the early stages of a problem, the cura- tion and introduction of open benchmark datasets and associated public challenges promote homogenization and comparability over time, supporting joint progress in the field.

Quality assessment and bias analysis

To assess the risk of bias, we evaluated the patient selection, index test, reference standard, and flow and timing across the selected studies. Applying the QUADAS-2 criteria, we found that the overall quality of the research was high (see Table 3). We used the criteria to classify the studies as having unclear, low, or high levels of bias. In the domain of patient selection, we considered ten studies (83%) to be at low risk of bias because participants were enrolled consecutively and inappropriate exclusions were avoided. The risk of bias in two human studies was unclear due to poor reporting on the sampling procedure and exclusion criteria. Comparing human to mouse studies, we observed that patient selection was more effective in the latter type. In most of the studies, the conduct and interpretation of the index test and reference standard were clearly defined, and no concerns about applicability were noted regarding these two domains of biases. In the domain of flow and timing, there was a low risk of bias in all studies (100%) because every patient was accounted for in the analysis or the reasons for missing data were given, and there was an appropriate interval between the index test and the reference standard. None of the studies raised concerns as to whether the applicability of the patients and setting, the conduct and interpretation of the index test, and the target condition (as defined by the reference standard) were suited to the review question. However, it is worth noting that this positive appraisal was based on the inclusion criteria set for the review. Due to the heterogeneity of the index test, this judgment of applicability may have been overstated.

Cognitive impairment vs AD studies

Individuals with MCI are at an increased risk of developing AD or other forms of dementia, making early detection and interven- tion of particular importance. However, despite recent studies deploying fundus images to examine cognitive impairment, we found no research using ML/DL models with OCT/OCTA data to investigate this topic. However, newer OCT/OCTA dataset collection initiatives for MCI and AD patients will stimulate further research.

Animal vs. human studies

Six of the studies were conducted using mice, which conserve 99% of the human genome. Mouse studies are also valuable because they enable longitudinal and age detection research into AD, as nine mice days are roughly equivalent to one human year. The six studies used OCT scans of healthy wild-type (WT) and triple-transgenic mouse models (3xTg-AD or TMM) of AD. TMMs mimic human characteristics of AD, such as amyloid-β and tau protein aggregation. Additionally, we identified two recent OCT-based human age detection studies. Mouse and human studies benefit from each other’s findings and are examined separately in the following two subsections.
Mouse studies

We analyzed the inputs, feature extraction methods, classification techniques, and results of the mouse studies (Figure 5). Bernardes et al.\textsuperscript{51} aimed to detect AD in OCT scans of mouse cohorts comprising 23 triple-transgenic AD mice and 22 wild-type mice aged 4 and 8 months. They segmented the OCT scans into three layers based on retinal features. The first layer contained the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), and outer plexiform layer (OPL), the second included the outer nuclear layer (ONL) and external limiting membrane (ELM), while the third layer comprised the ellipsoid zone and retinal pigment epithelium RPE. From each layer, they derived Mean Value Fundus (MVF) images before calculating a vector of features based on the gray-level co-occurrence matrix (GCLM). The classification was carried out using radial basis kernel support vector machine (SVM). The study demonstrated that AD could be detected in mice using OCT scans, with early detection achievable at over 80% accuracy when they are 4-month-old mice and over 90% when they are 8-month-old mice. The second animal study was conducted by Trindade\textsuperscript{30} on a cohort of 57 3xTg-AD and 58 WT mice. The researchers segmented OCT data to create six distinct images corresponding to specific retinal layers or layer aggregates (MVFs), namely RNFL-GCL, IPL, INL, OPL, ONL, and the total retina (TR), encompassing all anatomical layers. Correspondingly, six, Inception-v3-based, pretrained, convolutional deep learning models (CNNs) were trained and tested to assess the ability of particular layers to distinguish between TMM and WT OCT scans. The authors reported that RNFL-GCL achieved the highest classification accuracy (89.2%) for early AD detection. Combining the output of six CNNs as an input to an additional feed-forward neural network (FFNN) did not improve the classification performance. The authors also used GradCAM explanations to generate heat maps indicating the most effective areas for classification. Moreover, they observed that the right and left eyes might convey different information. The third study conducted by Ferreira et al.\textsuperscript{28} used 57 3xTg-AD and 57 WT mice of varying ages. Mean-value-fundus (MVF) images were generated from the segmented OCT layers RNFL-GCL, IPL, INL, OPL, and ONL. The images were pre-processed to improve performance, and a data augmentation technique was employed to mitigate overfitting. Transfer learning from the inception-v3 model was used to train the network with mice at 3, 4, and 8 months, while classification tests were conducted with mice at 1, 2, and 12 months. The study concluded that the MVF data calculated using the RNFL-GCL layer produced the best classification performance (88.1% accuracy, 87.7% sensitivity, 88.5% specificity, and an F1 score of 88.5%). Error rates were also measured for mice of different ages, showing that the total classification error for 12-month-old mice (15%) was smaller than for 2-month-old mice (16.9%) even though the younger mice were closer in age to the trained group. The fourth study, by Bernardes et al.\textsuperscript{29} differed from the first three in both its segmentation process and research design. Rather than using vendor application software to segment the OCT layers, the researchers employed a DL model to process OCT scans directly. They derived MVF images from these segmentation values and then conducted a statistical analysis of the GCLM measures calculated from the MVF images. They reported that the significance of the difference increased with the age of the mice. Ultimately, the study concluded that the retinas of mice with AD age differently from healthy mice. The fifth study, by Guimaraes et al.\textsuperscript{27} was conducted on 60 3xTg-AD and 57 WT mice. The research used OCT scans to evaluate the impact of aging on the retinas of 3xTg-AD mice. The researchers chose to use only OCT images as inputs to the DL model instead of segmentation and MVF image inputs. Two separate networks were initialized by transfer learning from a pre-trained ImageNet model. One of the networks was then fine-tuned exclusively with WT mice OCT scans, and the other with 3xTg-AD mice OCT scans. Age prediction tests were conducted for both groups. They found that retinal aging differed significantly between WT and TMM mice, suggesting that the presence of mutated genes affected the aging process. Surprisingly, WT mouse retinas were predicted to be older than TMM mice after four months, which contradicts their expectations. While the precise factors contributing to these observations remain unclear, the study demonstrates the potential of OCT as a powerful early screening tool for AD if similar findings are confirmed in human subjects. The final work we examined was that of Sayeed et al.\textsuperscript{32} who used 24 3xTg-AD and 2256 WT mice to compare the classification accuracy of various machine learning (ML) algorithms, including decision trees, neural networks, random forest, and SVM. They generated 22 different features of the ganglion cell and inner plexiform layers (GCLM) from a normalized covariance matrix of fundus and
OCT images. The SVM algorithm demonstrated the best performance (99% accuracy, 98% sensitivity, and 99% specificity). The decision tree algorithm registered the second-best performance (96% accuracy, 94% sensitivity, and 97% specificity) while the worst performer was the neural network algorithm, with 74% accuracy, 98% sensitivity, and 73% specificity.

Human studies

Nunes et al. applied classical machine learning techniques to differentiate between healthy (NC), Alzheimer’s (AD) and Parkinson’s disease (PD) patients. First, they segmented OCT volumes to extract the retinal layers and computed the mean value of fundus images for six layers (RNFL, GCL, IPL, INL, OPL and ONL). They also computed the thickness of these layers, and extracted textural features from the layer images, resulting in 86 measurements per layer. They used a support vector classifier to classify the entire feature vector and obtained median sensitivities of 88.7%, 79.5%, and 77.8% for the NC, AD, and PD classes, respectively. Their study suggests that textural features from different retinal layers can provide valuable independent information beyond layer thickness measurements. Sandeep et al. utilized a Fixed-grid WaveNet Network (FGWN) for OCT scan segmentation to identify the RNFL layer. They then extracted morphological features, including area, perimeter, curvature variance, and ellipticity from the RNFL image. When the back-propagation (BP) and radial basis function (RBF) neural networks were compared for classification, the latter registered lower false acceptance and false rejection rates. Since the authors chose to employ manually designed features, the segmentation algorithm was a crucial factor in the classification performance. Lemmens et al. combined hyperspectral images with OCT data to identify AD patients among 10 probable AD, 7 biomarker-proven AD, and 22 NC subjects. They computed the average reflectance of four retinal regions from the hyperspectral images and combined this with RNFL thickness measurements obtained from four different regions of the OCT. They reported an average area under the curve of 74% for AD classification, suggesting that using hyperspectral images in conjunction with OCT data could improve AD detection performance. In Wisely et al.’s recent study, a deep residual convolutional model (ResNet18) was used to detect AD using multimodal retinal images. Image data, numerical data obtained from OCT/OCTA, and patient information were simultaneously inputted into an artificial neural network (ANN) through separate channels. Two-dimensional images were fed into convolutional neural network branches, while OCT-based numerical data and patient information were processed in a fully connected subnet structure. The authors reported that the GC-IPL thickness color map image superimposed on the OCTA image provided the best-performing single input (AUC 0.809). The combination of numerical information obtained from the OCT and GC-IPL images yielded the best classification performance (AUC 0.841), which was not improved by non-OCT modalities such as FFA and UWF. This study’s importance lies in highlighting the effectiveness of GC-IPL and OCTA (AUC 0.828). However, the dataset included only 36 AD patients and was collected cross-sectionally. Wang et al. compared different machine learning models to classify AD using various biomarkers and patient data. The authors first calculated the correlations between patient data, neuropsychological assessments, numerical data extracted from OCT, CSF biomarkers, and APOE genotypes. They discovered that OCT measures of RNFL thickness and macular variables were significantly correlated with neuropsychological, CSF, and APOE genotypes. The authors also compared six common machine learning algorithms and reported that XGBoost had the best classification accuracy (Acc=74%, AUC=69%, F1 score=0.7, recall=74%). These results suggest that OCT measures may serve as useful biomarkers for AD diagnosis and monitoring, especially in combination with other patient data. Another study to investigate the use of OCTA in dementia was conducted by Wang et al. The researchers proposed an end-to-end deep learning network called MUCO-Net, which utilizes attention and fusion techniques to predict dementia from multi-projection OCTA images. Multiple OCTA projections provide information on the fundus vessels at the same location but with varying thicknesses, implying that consistent and complementary data could exist across the different projections. They compared the performance of MUCO-Net with Resnet50, a single-projection OCTA imaging method, as well as with various fusion networks. Their model achieved the best results, with accuracy of 86%, an F1 score of 0.86, and a Kappa of 0.67. The researchers also used Grad-CAM for explainability. They conducted
an extended experiment to evaluate their network using alternative datasets for different diseases, such as Diabetic Retinopathy and AMD. They reported that their model outperformed the other tested networks.

DISCUSSION

This systematic review used the PRISMA framework\textsuperscript{23} to evaluate the effectiveness of machine learning (ML) and deep learning (DL) approaches in detecting or diagnosing Alzheimer’s disease (AD) using OCT and OCTA scans. Our study focused solely on OCT and OCTA-based biomarkers for AD diagnosis. Our review identified 14 studies, including six that used mice as subjects and two that were US patent applications. Based on the QUADAS-2 criteria \textsuperscript{25}, the overall quality of the reviewed studies was high. We observed no issues with bias in the mouse studies or the application domains. Our analysis revealed a shift from classical ML pipelines to fully automated DL models for detecting AD from OCT images. There was evidence of a move away from hand-crafted features such as layer thickness measurements and textural metrics and toward direct processing of images as inputs. This transition was evident in recent mouse\textsuperscript{29,27,32} and human studies \textsuperscript{5,26} built on end-to-end DL architectures. Bernardes et al.\textsuperscript{29} also segmented retinal layers using a DL-based network architecture (U-Net). Additionally, our review addressed the challenges of applying DL to OCT images, as outlined by Yanagihara et al.\textsuperscript{17} One major issue with the human-based studies we analyzed was their small sample size - typically less than 50 AD subjects. To address this issue, many researchers applied techniques such as data augmentation, regularization, dropout, batch normalization, adding quantitative features, early stopping, and transfer learning. Most studies also used both eyes (left and right) to double the dataset size. Nunes et al.\textsuperscript{52} found that classification accuracy improved from 82\% to 96\% when both eyes received the same classification. At present, there are no networks pre-trained on the OCT domain available for transfer learning. The reviewed studies utilized transfer learning from generic networks pre-trained on ImageNet-like databases. However, OCT scan slice images differ significantly from images in general databases, as the pixel values represent the measured depth of retinal tissue at a resolution of a few micrometers, which may limit the benefits of transfer learning. As pre-trained networks specific to the OCT modality become available, the benefits of transfer learning are likely to increase. Another challenge involved OCT image quality and standardization issues, which were addressed through various image transformation, enhancement, and artifact removal techniques. The black-box DL models also posed challenges in explaining how decisions were made. To overcome this, some studies utilized attention and interpretability tools, such as Grad-CAM, CAM, and D'Taylor. Computational issues arising from complex data were resolved by high-performance desktops and transfer learning, with cloud computing a relatively unpopular option. Finally, inconsistencies between the metrics used in different studies made it difficult to compare results. Early detection of Alzheimer’s disease is crucial because it is a progressive illness. The mouse studies we reviewed focused on the early stages of cognitive impairment and disease progression, as did one human dementia study and two human age detection studies.\textsuperscript{49,50,26} Since one human year is roughly equivalent to nine mice days, mouse studies are crucial for longitudinal and age detection research into early AD progression. Wisely et al.\textsuperscript{5} employed a convolutional neural network-based architecture processing a combination of OCTA images and other data to predict AD. Testing modalities such as ultra-widefield color and fundus autofluorescence, they discovered that color maps of the Ganglion Cell Inner Plexiform Layer thickness overlaid on OCTA (GC-IPL) provided the best inputs for AD vs. non-AD classification. They found that the optimal input combination was to use OCT/OCTA-based numerical data, such as RNFL thickness and the area of the foveal avascular zone, along with patient data, such as demographics and MMSE scores, and GC-IPL images. In further experiments, they found that images alone also performed well without requiring supplementary quantitative data. OCTA is a relatively new imaging technique that emerged as a byproduct of OCT scans. It involves computing the difference between two consecutive OCT scans to reveal blood flow and micro-vascular retinal structures at a resolution of micrometers. Medical research based on OCTA has identified reduced vessel density in different regions and a thicker foveal zone in AD patients. Wang et al.\textsuperscript{26} were the first to use a full-scale deep-learning solution to process raw OCT
scans as input for predicting dementia. This study incorporated advanced deep learning techniques, such as attention and fusion. Research on AD using both OCT and OCTA modalities is gaining momentum, potentially leading to the discovery of new AD-specific biomarkers. Advances in computational power and cloud services have enabled the analysis of 3D volumetric retinal images. Working with raw 3D OCT scans has the potential to unveil fresh viewpoints in this domain and accelerate the search for novel biomarkers. However, the substantial increase in input dimensionality will require a significant amount of data. Publicly available data are an invaluable resource for academic research. Large-scale global datasets, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI)\textsuperscript{56} which includes MRI, PET, and related data from thousands of subjects - are essential for neuroimaging-based AD ophthalmology research. Nevertheless, data availability remains a major obstacle to progress in the OCT/OCTA field, and there is an urgent need to compile more comprehensive datasets. The UK Biobank provides a database containing thousands of OCT scans and is accessible to researchers worldwide who submit a research proposal and pay the required fee. Fortunately, discount schemes are available to support research students. Wagner et al.’s AlzEye initiative\textsuperscript{57} currently represents the most extensive dataset of ophthalmic images but was not publicly available at the time of writing. The American Alzheimer’s Association has initiated the collaborative Atlas of Retinal Imaging in Alzheimer’s Study (ARIAS),\textsuperscript{58} This study defined a "minimum dataset" framework for SD-OCT retinal image acquisition and analysis, and an ongoing data collection initiative that adheres to the framework.\textsuperscript{59} The dataset is intended to be a publicly available longitudinal study of structural, functional, metabolic, and angiographic retinal AD biomarkers in a large cohort (N=330 aged 55-80; 50 NC–low AD risk, 200 NC–high AD risk, 50 MCI, and 30 mild AD). As noted by Sampson et al.,\textsuperscript{60} efforts are underway to standardize retinal OCT imaging. Patients with Alzheimer’s disease, typically older individuals, have a higher risk of developing multiple dementias\textsuperscript{61} as well as retinal disorders such as age-related macular degeneration\textsuperscript{62}. Biomarkers such as RNFL thickness, which are frequently compared or cited in OCT-based AD detection studies, are also highly relevant in commonly observed diseases like glaucoma. Hence, datasets curated for AD often exclude patients with glaucoma, potentially hindering the discovery of AD-specific biomarkers and differential diagnoses of multiple retinal diseases. Although numerous studies have explored deep learning-based simultaneous detection of multiple retinal diseases using OCT/OCTA\textsuperscript{63}, none have specifically focused on AD or MCI. Accordingly, future data collection initiatives should include samples from AD, other dementias, and other retinal diseases to facilitate differential diagnosis.

**CONCLUSION**

This paper has reviewed the use of OCT and OCTA retinal imaging to diagnose Alzheimer’s disease and mild cognitive impairment. We examined recent deep learning approaches and OCT/OCTA datasets targeting the diagnosis of these disorders. Our search identified twelve ML-/DL-based studies and two patents that aimed to detect AD from OCT/OCTA scans. The small number of results indicates that the research field remains at an early stage. Deep learning with OCT/OCTA scans presents several challenges, including small dataset size, low image quality and standards, black box algorithms, and computational restrictions. Although many studies have attempted to address these issues, the lack of common benchmark datasets for testing and inconsistent metrics remains a persistent challenge. Our review indicates a trend in recent studies toward using end-to-end deep learning models as opposed to traditional machine learning ones. While these studies also utilized scanned images directly as input, none used raw 3D-OCT scans directly, despite their availability. Alzheimer’s disease is a prolonged progressive illness, and early-stage detection may improve patient outcomes. However, relevant studies are based on mouse models. Machine or deep learning-based early AD detection studies on human retinal scans have not yet commenced because, for humans, "early" means at least a few years of time compared to months of mice. Thus, the collection of such datasets would require substantially more effort due to the necessity of tracking and screening many subjects for at least five or ten years. OCTA is a relatively new technique developed as a byproduct of OCT scans. It computes the difference between two consecutive OCT scans to reveal blood flow and micro-vascular retinal structure.
at micrometer-level resolution. To date, medical research has identified reduced vessel density in different regions and a thicker foveal zone in AD patients. Wang et al. was the first full-scale deep-learning solution to process raw OCT scans as input. The study used multi-projection OCTA images to predict dementia, incorporating enhanced deep-learning techniques such as attention and fusion. As AD-related research in both OCT and OCTA modalities gains further momentum via rapid technical advances, we anticipate the discovery of additional biomarkers. For instance, increased computational power and expanded cloud services facilitate the analysis of 3D volumetric retinal images. By working with unprocessed 3D OCT scans, it may be possible to uncover fresh insights in this field and expedite the exploration of new biomarkers. However, such a dramatic increase in input dimensionality will require substantially more data. Alzheimer’s disease patients are typically older adults with more potential for multiple dementias and retinal diseases such as age-related macular degeneration or glaucoma. A range of studies has been conducted on deep learning-based multiple retinal disease detection using OCT/OCTA. Current AD research exclude data from patients with other eye diseases or abnormalities commonly seen in the elderly population, making it challenging to develop a practical diagnostic tool to differentiate MCI, AD, and other diseases in OCT scans. We believe that creating larger and more comprehensive open-access datasets will resolve this issue and further advance the field.

CONSENT STATEMENT

The purpose of this paper is to provide a survey of existing literature, and no data is being collected from human subjects. Therefore, no consent is needed for this study.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

Yasemin Turkan: Concept, methodology, invest, data curation, data extraction, quality assessment, bias analysis, writing org. draft. Faik Boray Tek: concept, method, writing review editing, supervision

FUNDING

This work was supported by TUBITAK ARDEB 1001 program (No. 122E509)
References

3. London Anat, Benhar Inbal, Schwartz Michal. The retina as a window to the brain - From eye research to CNS disorders.


5. ClinicalTrials. ClinicalTrials: a website and online database of clinical research studies and information about their results.

[Online; accessed 2022-08-13]; 2022.


FIGURE 1 Deep Learning papers on OCT, and OCTA applications listed on PubMed since 2015. Numbers obtained from Harzing’s Publish or Perish application with the following keywords: ((Deep Learning) OR (Neural Networks)) AND (Optical Coherence Tomography)

FIGURE 2 The review process: ML/DL-based studies targeting AD or MCI diagnosis using OCT and/or OCTA.
ML/DL-based studies targeting AD or MCI diagnosis using OCT and/or OCTA. **FIGURE 5** ML/DL-based studies targeting AD or MCI diagnosis using OCT and/or OCTA. **TABLE 1** Development details of ML/DL models using OCT and OCTA data: GC-IPL (ganglion cell-inner plexiform layer), RNFL (retinal nerve fiber layer), IPL (inner plexiform layer), INL (inner nuclear layer), OPL (outer plexiform layer), Sens (sensitivity), Spec (specificity), Acc (accuracy), 3xTg-AD (triple transgenic AD), and WD (wild-type).

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Source Data</th>
<th>Study Design</th>
<th>Main Variables</th>
<th>ML Algorithms</th>
<th>Validation method, feature detection (DP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2022⁷⁶</td>
<td>China</td>
<td>West China Hospital</td>
<td>286 HC, 114 subjects with dementia</td>
<td>OCTA Images</td>
<td>U-Net</td>
<td>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, DP</td>
</tr>
<tr>
<td>Bernardes, 2022²⁹</td>
<td>Portugal</td>
<td>University of Coimbra</td>
<td>57 3xTg-AD and 57 WT mice</td>
<td>OCTA Images</td>
<td>A proposed DL model MUCO-Net</td>
<td>Leave-one-out cross-validation, FS, DP</td>
</tr>
</tbody>
</table>
Wang, 2022

China West Hospital

286 HC, 114 subjects with dementia

OCTA Images

U-Net

Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, DP Acc=0.86, F1 score=0.86, Kappa=0.67.

Wang, 2022

China Xiangya Hospital

299 HC, 159 subjects with AD

Patient data, neuropsychological assessments, derived quantitative OCT data, CSF biomarkers

XGBoost, Light GBM, KNN, Random Forest, Gradient Boost, AdaBoost, Logistic Regression

Randomly split into training and testing according to 7:3 ratio

XGBoost has got the highest performance in testing (Acc=0.74, AUC=0.69, F1 score=0.7, recall=0.74).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Institution</th>
<th>Number of Subjects</th>
<th>OCTA Imaging</th>
<th>U-Net</th>
<th>U-Net</th>
<th>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, no FS, DP</th>
<th>Acc, F1, Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guimaraes, 2022</td>
<td>Portugal Coimbra</td>
<td>60 3xTg-AD and 57 WT mice</td>
<td>Mean Image Value of Fundus Dense&gt;Net pre-trained on ImageNet</td>
<td></td>
<td></td>
<td></td>
<td>0.86, 0.86, 0.67</td>
<td></td>
</tr>
<tr>
<td>Ferreira, 2022</td>
<td>Portugal Coimbra</td>
<td>57 3xTg-AD and 57 WT mice</td>
<td>Mean Image Value of Fundus Convolutional Neural Networks (Inception-v3), Convolutional Neural Networks (Inception-v3) pre-trained on ImageNet and ImageNet and ImageNet</td>
<td></td>
<td></td>
<td></td>
<td>4 months = 76%, 8 months = 92%</td>
<td></td>
</tr>
</tbody>
</table>
Wang, 2022

China West Hospital

114 HC, 286 subjects with dementia

OCTA Images

U-Net

Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, DP

Acc=0.86, F1 score=0.86, Kappa=0.67.

Sayeed, 2022

India ACE College of Engineering, Trivandrum 695027, Kerala,

24 3xTg-AD, 2256 WT mice

Derived features from Fundus and OCT images

Derived features from Fundus and OCT images

Derived features from Fundus and OCT images

Derived features from Fundus and OCT images

Decision Tree, Neural network, Random Forest, SVM

Validation method not specified, FS, DP

Decision Tree (96% Acc., 94% Sens, 97% Spec)

Neural Network (74% Acc., 98% Sens, 73% Spec)

Random Forest (98% Acc., 65% Sens, 98% Spec)

SVM (99% Acc., 98% Sens, 99% Spec)
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Subjects</th>
<th>Image Data</th>
<th>OCTA Images</th>
<th>Convolutional Neural Networks (ResNet18)</th>
<th>U-Net</th>
<th>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>West China Hospital, NCT03233646</td>
<td>HC, 123</td>
<td>123 HC, 36 AD</td>
<td>Data, patient data, derived quantitative OCT data</td>
<td>AUC = 0.836</td>
<td>AUC = 0.829</td>
<td>GC-IPL maps, quantitative data and patient data AUC = 0.841</td>
<td></td>
</tr>
<tr>
<td>Wisely, US Duke University</td>
<td>HC, 186</td>
<td>186 eyes for training and validating, 68 eyes for testing, FS, DP</td>
<td>Data, patient data, derived quantitative OCT data</td>
<td>AUC = 0.809</td>
<td>GC-IPL maps, quantitative data and patient data AUC = 0.841</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DP: Deep Learning, GC-IPL: Gangliocytoma Imaging of the Posterior Lobe, OCT: Optical Coherence Tomography, OCTA: Optical Coherence Tomography Angiography.
<table>
<thead>
<tr>
<th>Wang, 2022&lt;sup&gt;26&lt;/sup&gt;</th>
<th>West China Hospital</th>
<th>286 subjects with dementia</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>U-Net</th>
<th>U-Net</th>
<th>DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trindade, Portugal 2021&lt;sup&gt;30&lt;/sup&gt;</td>
<td>University of Coimbra</td>
<td>57 3xTg-AD, 58 WT mice</td>
<td>Fundus images</td>
<td>Fundus images</td>
<td>Fundus images</td>
<td>Fundus images</td>
<td>Convolutional Neural Networks</td>
<td>Convolutional Neural Networks</td>
<td>6 CNNs trained separately resulted with Acc between 79.0% and 89.2%</td>
</tr>
</tbody>
</table>

Randomly split into training and testing according to 8:2 ratio, five-fold cross validation.

RNFL-GCL, IPL, INL, OPL, and Total Retina (TR)
<table>
<thead>
<tr>
<th>Wang, 2022(^{26})</th>
<th>China</th>
<th>West China Hospital</th>
<th>West China Hospital</th>
<th>286</th>
<th>HC, 114 subjects with dementia</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>U-Net</th>
<th>U-Net</th>
<th>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, DP, Acc=0.86, F1 score=0.86, Kappa=0.67.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemmens, Belgium 2020(^{31})</td>
<td>Not available</td>
<td>Not available</td>
<td>10 AD, 7 amyloid proven AD and 22 HC</td>
<td>Amyloid accumulation and RNFL (retinal imaging and hyperspectral snapshot shot)</td>
<td>Amyloid accumulation and RNFL (retinal imaging and hyperspectral snapshot shot)</td>
<td>Amyloid accumulation and RNFL (retinal imaging and hyperspectral snapshot shot)</td>
<td>Amyloid accumulation and RNFL (retinal imaging and hyperspectral snapshot shot)</td>
<td>ML model not identified</td>
<td>ML model not identified</td>
<td>Leave-one-out cross validation, FS, DP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Year</td>
<td>Institution/Department</td>
<td>Subjects</td>
<td>Disease Groups</td>
<td>Imaging Technique</td>
<td>Features</td>
<td>Network</td>
<td>Validation</td>
<td>Accuracy</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>------------------</td>
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<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Wang, 2022</td>
<td>China</td>
<td></td>
<td>West China Hospital</td>
<td>286 HC</td>
<td>26 AD, 114</td>
<td>OCTA Images</td>
<td>Morphological</td>
<td>U-Net</td>
<td>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation</td>
<td>0.86</td>
<td>0.86</td>
<td>0.67</td>
</tr>
<tr>
<td>Sandeep, 2019</td>
<td>India</td>
<td></td>
<td>Department of ECE, College of Engineering, Trivandrum, Kerala</td>
<td>25 AD, 25 HC</td>
<td>28 AD, 28 PD, and 27 age-matched HC</td>
<td>Retinal texture and thickness (fundus images by OCT)</td>
<td>Demographic data</td>
<td>SVM</td>
<td>SVM k-fold cross validation, FS, DP</td>
<td>88.7%</td>
<td>84.9%</td>
<td>-</td>
</tr>
<tr>
<td>Nunes, 2019</td>
<td>Portugal</td>
<td></td>
<td>University of Coimbra</td>
<td>52 AD, 28 PD, and 27 age-matched HC</td>
<td>25 AD, 25 HC</td>
<td>Retinal texture and thickness (fundus images by OCT)</td>
<td>Demographic data</td>
<td>Fixed-Grid Wavenet Network, Radial Basis Function of Neuronal Networks</td>
<td>N/A, FS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### TABLE 2  Deep learning-related challenges in OCT-based AD detection and strategies employed to address them

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Sample Size</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>OCTA Images</th>
<th>U-Net</th>
<th>U-Net</th>
<th>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, F1 score, and Kappa Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2022</td>
<td>China</td>
<td>286 HC, 114 subjects with dementia</td>
<td>OCTA Images</td>
<td>OCTA Images</td>
<td>OCTA Images</td>
<td>OCTA Images</td>
<td>U-Net</td>
<td>U-Net</td>
<td>Randomly split into training and testing according to 8:2 ratio, five-fold cross validation, F1 score, and Kappa Coefficient</td>
<td></td>
</tr>
<tr>
<td>Bernardes, 2017</td>
<td>Portugal</td>
<td>University of Coimbra</td>
<td>22 3xTg-AD and 23 WT mice</td>
<td>Histogram of OCT scans, Mean Value of Fundus Image and Energy and Contrast values of OCT layers</td>
<td>Histogram of OCT scans, Mean Value of Fundus Image and Energy and Contrast values of OCT layers</td>
<td>Histogram of OCT scans, Mean Value of Fundus Image and Energy and Contrast values of OCT layers</td>
<td>SVM</td>
<td>SVM</td>
<td>SVM k-fold cross-validation, F1 score, and Kappa Coefficient</td>
<td></td>
</tr>
<tr>
<td>Et, 2006</td>
<td>US</td>
<td>Patent No:6,988,995</td>
<td>N/A RNFL</td>
<td>RNFL</td>
<td>RNFL</td>
<td>RNFL</td>
<td>Artificial Neural Networks</td>
<td>Artificial Neural Networks</td>
<td>Not available available available</td>
<td></td>
</tr>
</tbody>
</table>
Challenges to studying OCT images proposed solutions

<table>
<thead>
<tr>
<th>Small dataset size</th>
<th>Transfer learning from pre-trained networks: Inception-v3&lt;sup&gt;30,28&lt;/sup&gt;, ResNet18&lt;sup&gt;5&lt;/sup&gt;, ImageNet&lt;sup&gt;27&lt;/sup&gt;,26,28,29,30,31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low image quality &amp; standards</td>
<td>Resizing&lt;sup&gt;27,26&lt;/sup&gt;, Cropping&lt;sup&gt;27,5&lt;/sup&gt; and Recentering&lt;sup&gt;27&lt;/sup&gt; Normalization&lt;sup&gt;27,28,32,30&lt;/sup&gt;, Histogram equalization</td>
</tr>
<tr>
<td>Black box models and explainability</td>
<td>Interoperability Tools: Grad-CAM&lt;sup&gt;30,26&lt;/sup&gt;, CAM&lt;sup&gt;5&lt;/sup&gt;, DTaylor&lt;sup&gt;27&lt;/sup&gt; Attention&lt;sup&gt;26,5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Computational restrictions</td>
<td>High-performance desktops with GPU (all of the studies) Transfer learning from pre-trained networks</td>
</tr>
</tbody>
</table>

**TABLE 3** Results of the Quality Assessment for Diagnostic Accuracy (QUADAS-2) evaluation of studies included in the review

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients selection</th>
<th>Index test</th>
<th>Reference Standard</th>
<th>Flows and Timing</th>
<th>Patients selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandeep, 2017</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Bernardes, 2017</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Nunes, 2019</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lemmens, 2020</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Trindade, 2021</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sayeed, 2022</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wisely, 2022</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wang, 2022</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Guimaraes, 2022</td>
<td>Low</td>
<td>Low</td>
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<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wang, 2022</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Bernardes, 2022</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ferreira, 2022</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>