Review Article

Narrative review of artificial intelligence in diabetic macular edema: Diagnosis and predicting treatment response using optical coherence tomography

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Diabetic macular edema (DME), being a frequent manifestation of DR, disrupts the retinal symmetry. This event is particularly triggered by vascular endothelial growth factors (VEGF). Intravitreal injections of anti-VEGFs have been the most practiced treatment but an expensive option. A major challenge associated with this treatment is determining an optimal treatment regimen and differentiating patients who do not respond to anti-VEGF. As it has a significant burden for both the patient and the health care providers if the patient is not responding, any clinically acceptable method to predict the treatment outcomes holds huge value in the efficient management of DME. In such situations, artificial intelligence (AI) or machine learning (ML)-based algorithms come useful as they can analyze past clinical details of the patients and help clinicians to predict the patient's response to an anti-VEGF agent. The work presented here attempts to review the literature that is available from the peer research community to discuss solutions provided by AI/ML methodologies to tackle challenges in DME management. Lastly, a possibility for using two different types of data has been proposed, which is believed to be the key differentiators as compared to the similar and recent contributions from the peer research community.

Key words: Anti-VEGF treatment options, CNN, deep learning, diabetic macular edema, diabetic population, DME detection, Lucentis, machine learning, ranibizumab, regression, RF, SVM, visual outcomes

In the last decade, artificial intelligence (AI) and machine learning (ML)-based systems disrupted almost every industry that one can imagine. Although a bit late, the healthcare industry is also getting overwhelmed with the recent advancement of these powerful technologies. AI could be a technique that allows computers to mimic human behavior. AI is being used in an exceedingly myriad of healthcare infrastructure, including hospitals, clinical laboratories, and research facilities. Ophthalmology shares the space with other therapeutic areas within healthcare and utilizes the capabilities of AI and ML for various purposes such as automatic screening,[1] decision support system for primary clinics,[2] automatic disease severity classification,[3] and treatment optimization,[4] and can be integrated into workflows to reduce the burden of repetitive tasks and increase diagnostic precision. AI and ML-based technologies are often used in the field of medicine for repetitive tasks, tasks for which the trained manpower is less, and for identifying new signals that are difficult to predict by the physician. In the field of ophthalmology, imaging provides a way to objectively detect and diagnose the progression of pathologies and response to treatment. AI/ML-based algorithms have made progress in recent times, in diseases such as diabetic retinopathy (DR),[5-8] age-related macular degeneration (AMD),[9,10] glaucoma,[11]

cataract,[12] retinopathy of prematurity (ROP),[13] and retinal vein occlusion (RVO).[14]

India has the second-highest number of people with diabetes in the world (77 million, 2019) following China.[15] Diabetic retinopathy (DR) is the most common microvascular ocular complication of diabetes and occurs in both type 1 and type 2 diabetes.[16] The population-based studies in India over the last two decades reported the prevalence of DR as 18% in urban areas and 10% in rural areas.[17] Bressler *et al.*[18] reported that among those who showed evidence of DR, one-third had macular edema, approximately one-fourth had non-clinically significant macular edema (non-CSME), and 1 in 16 had CSME. Diabetic macular edema (DME) is a common cause of visual impairment among people with diabetes. Though DME can be detected using stereo retinal photographs, the retinal thickness that is affected by the presence of DME can be better measured by optical coherence tomography (OCT).[19] The choice of management of DME is also based on OCT features. Currently, anti-vascular endothelial growth factor (anti-VEGF) agents are the mainstay of DME treatment. However, the clinical and OCT response after intravitreal anti-VEGF is variable, with both responder and non-responder seen in real-life situations.

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However, the ophthalmic research community may also have an interest to understand how AI/ML techniques are performing on various aspects of vision-threatening DR called DME. In recent times, AI/ML techniques have been explored in the management of DME. These techniques have been used for the diagnosis of DME from retinal photographs or OCT. There is evidence of using AI/ML techniques for predicting the treatment response.

In this review, we systematically reviewed AI/ML-based techniques used to analyze various aspects of DME, starting from its detection to treatment optimization. Through this article, a possibility for using two types of data has been proposed, which is believed to be the key differentiators as compared to the similar and recent contributions from the peer research community.

Methods

A comprehensive literature search was conducted on Google Scholar and PubMed by using the MESH term (machine learning) AND (visual outcomes) AND (Lucentis) OR (ranibizumab) OR (treatment options) AND (diabetic macular edema) AND (diabetic population) for the time period of 2009–2020. Only studies with full texts published in English were included. A hierarchical approach was adopted when selecting articles by three reviewers independently: relevant articles were initially selected based on their titles and abstracts. The full texts of these articles were then obtained and reviewed in more detail. Out of 80 hits, 20 relevant hits were obtained. We reviewed articles on AI that involved DME management by anti-VEGF comparing the efficacy, whereas the articles dealing with other ophthalmic conditions and other DME and DR management were excluded.

Need for identifying and predicting algorithm in DME management

Identifying DME

The presence of DME is a feature of sight-threatening DR. A definitive diagnosis of DME needs measurement of central subfield thickness on OCT. DME rarely occurs unless the patient has at least moderate NPDR. OCT is not mandatory if there are no signs of DR or in very mild retinopathy (<5 microaneurysms). However, for all other cases, to initiate the treatment of DME, doing an OCT and classifying DME to non-central involving and central involving DME is often required.

Screening of DR utilizes fundus cameras to capture retinal images, which are then graded for presence and severity of DR. For epidemiology studies, stereoscopic retinal photographs were taken to ensure a correct diagnosis of DME. However, in routine screening taking stereoscopic retinal photographs is time-consuming and often needs specialized skills. Evidence is emerging on the development of algorithms for retinal images utilizing the ground truth of the grader or utilizing the OCT data of the same patient to diagnose DME.[20]

Predicting response to Intravitreal anti-VEGF

Intravitreal anti-VEGF therapy is the most commonly used treatment approach in the management of DME because of its efficacy as validated by clinical trial data and has become the first line of treatment for DME. Patients in the RISE and RIDE trials had, on average, an approximately 40% reduction in central retinal thickness on optical coherence tomography (OCT) within the first 3 months of initiating monthly treatment with ranibizumab.[21] Although anti-VEGF therapy is often very effective, a subset of patients (about 30%–40%) appear to be refractory and often require other forms of medical management, including alternative anti-VEGF therapies and/or steroids.[20] Prompt and efficacious treatment of DME is important to maximize visual outcomes, and that delay in effective treatment may adversely affect vision. As most patients diagnosed with DME receive anti-VEGF therapy, early identification of anti-VEGF response status is important. A method to identify responders to anti-VEGF therapy would aid physicians to tailor treatment to likely patient outcomes. At present, the decision of non-responder is often made after initiating the treatment with anti-VEGF and utilizing few clinical (OCT-based) biomarkers (not extensively studied). There is evidence on algorithms trying to predict the response of anti-VEGF in DME.[22,23]

Review of major contributions

There are two types of problems in DME management that have been addressed through different AI/ML approaches: a) identification of DME and b) understanding treatment responses using anti-VEGF agents. Numerous research articles address the detection of DME; however, the treatment response prediction remains a challenge in the management of the disease with anti-VEGF treatment options. The literature review taxonomy is provided through an illustration [Fig. 1]. The identification of DME is done through a traditional ML-based approach, performing the classification whether DME is present. With the advancement of DL techniques, DME identification is also done using various DL models in terms of DME classification or detecting and quantifying the fluids using the segmentation approach. The response prediction of DME treatment is mainly done using DL techniques or combining DL.

Use of traditional ML-based techniques used for identifying DME
Identification of DME has been primarily carried out on OCT data, where AI/ML-based techniques try to classify the DME accurately. Srinivasan *et al*.[25] used the traditional approach to extract the features (histogram of gradient (HOG)) from OCT images and then used support vector machines (SVM) as a classification tool. On a dataset of 45°CT cubes with 15 in each category, 42-fold cross-validations were carried out, showing a 100% classification rate on AMD and DME.

Lemaître *et al*.[26] described a binary classification framework that separates DME from normal patients using spectral-domain OCT data. Local binary pattern (LBP) has been chosen as a feature extraction tool, while the feature transformation (high-level to low-level discriminative features) is done through Bag-of-Word approach. For the classification task, several classifiers were involved: (i) k-nearest neighbor, (ii) logistic regression, (iii) random forest (RF), (iv) gradient boosting, and (v) SVM. RF showed higher sensitivity while SVM outperformed in terms of specificity.

The same research group had published a similar work[27] before this article was published.

In another old research article, Liu *et al*.[28] proposed a four-class classification technique considering macular hole, macular edema (ME), AMD, and normal as classes. A multiscale texture and shape features have been considered as features followed by SVM as a classification technique. 131 ZEISS SD-OCT® cubes from 37 subjects across the classes were considered as test data. The outcomes of one-versus-all based four binary classifications have been reported using the two-class classification paradigm realized through the SVM classifier. A minimum area under curve (AUC) of 0.94 was achieved.

To detect DME, Alsaih K *et al*.[29] classified DME for normal SD-OCT cubes collected from Singapore Eye Research Institute. After preprocessing, the histograms of oriented gradients and LBP were extracted as features. Feature sets were then transformed and compactly represented through principal
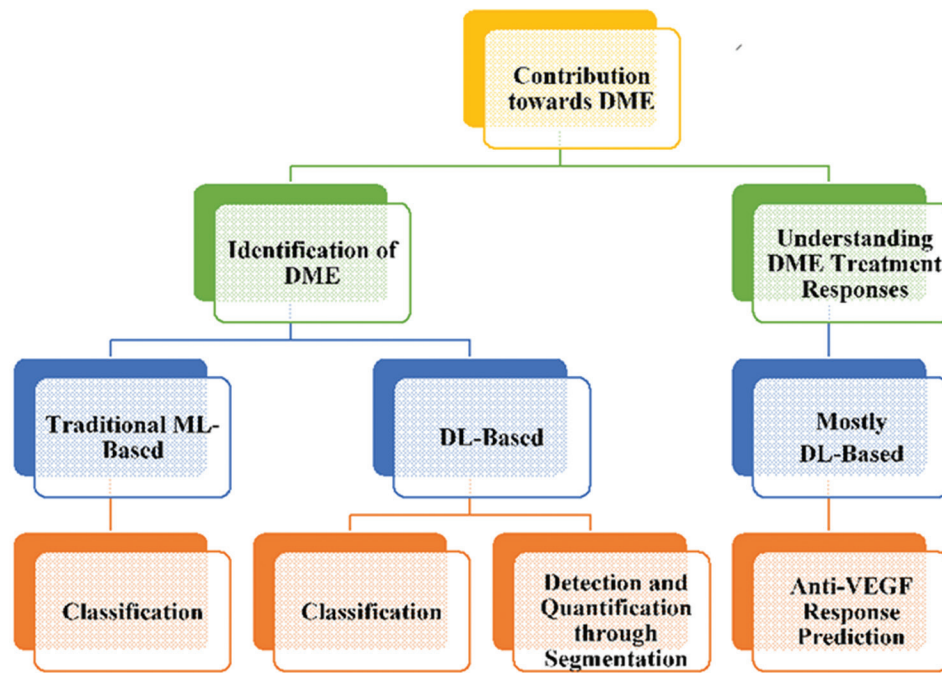
Figure 1: Taxonomy of literature describing contribution toward DME

component analysis. Finally, classification was analyzed by both linear and nonlinear SVMs and using RF. The work showed the highest 87.5% sensitivity and 87.5% specificity from linear SVM.

An interesting idea has been presented by Sidibé *et al.*,[30] where classification between DME and normal OCT cubes was treated as anomaly detection or one-class classification problem. A Gaussian mixture model (GMM) has been developed on the features extracted from the B-scans of normal OCT cubes. During verification, B-scans with DME pathology presence were supposed to be flagged as an anomaly, while the normal B-scans were identified as a member of the same class as the GMM model. On two different datasets, the method showed sensitivities and specificities better than contemporary techniques.

In a very recent study,[31] a unique approach has been adopted to find the retina region from a B-scan by first segmenting it through K-means and then applying Gaussian filtering regularized level set algorithm to identify the region of pathologies that correspond to DME. This two-step based robust algorithm achieved a comparable sensitivity and specificity when compared against manual segmentation. A notable claim of this algorithm is it being 66 times faster than the manual process.

The literature described above uses the conventional feature extraction-transformation-modeling trio, where a feature set has been transformed first and then modeled using traditional classification techniques. Like other application areas, we also found that the performances of such traditional ML-based techniques get saturated as we involve more data. Next, we discuss some identification techniques based on advanced technologies such as DL.

Use of DL-based techniques used for identifying DME
In this subsection, the first two paragraphs describe DME identification and pathology quantification using the segmentation approach, while the rest of the paragraphs contain conventional DL-based approaches adopted by various

research groups to address pure OCT classification, where one of the classes is DME.

A classical DL-based approach to detect and quantify retinal biomarkers was shown by Schlegl *et al.*[32] An autoencoder was used to detect patches of IRC and SRF for each B-scan in a cube and then aggregated over all the B-scans to calculate the total fluid deposition for the cube. The method was found to be robust enough to predict the fluid detection well on various diseases such as AMD and retinal vein occultations (RVO) other than DME. The author also showed the versatility of the algorithm on two different OCT imaging devices.

A very similar approach has been attempted by Lee *et al.*,[6] where the detection of intraretinal fluid (IRF) was evaluated to estimate ME. Segmented maps were generated from OCT B-scan to detect IRF. The authors used the Dice coefficient to determine the match between expert annotations and the algorithm's output. Around 1300 B-scans were involved to cross-validate the developed model that resulted in a Dice coefficient of 0.911.

In another study[33], features were extracted from various layers of a VGG-16 network. These features were then modeled through various classifiers to classify between normal and DME OCT cubes. This approach is not an end-to-end DL-based approach, which is not commonly found among the attempts done by various researchers. This article, however, shows 93.5% and 81% sensitivity and specificity, respectively.

In this context, it is worth mentioning that the first end-to-end DME classification technique was proposed by Perdomo *et al.*[34] through a convolutional neural network (CNN)-based approach called OCT-NET. On a small dataset consisting of 32 cubes with 16 normal and 16 DME, the classification experiment showed 93.5% as equal accuracy, sensitivity, and specificity.

A pure DL-based approach has been reported by Ravi *et al.*,[35] where Inception-Resnet-v2 architecture was used to classify DME from a Normal OCT scan. The work showed

100% accuracy (also 100% sensitivity and specificity) on the same Singapore Eye Research Institute (SERI) dataset used earlier by Awais *et al*.[33] and Perdomo *et al*.[34] This also proves that the proposed method is the best among its predecessors.

A similar approach has been developed by De-Kuang Hwang[36] for DME screening using OCT data. A total of 4932°CT images of 173 diabetic patients with DME who received intravitreal injections (IVIs) of either anti-VEGF or corticosteroid in Taipei Veterans General Hospital during January of 2017 to December of 2017 were collected for the study, out of which 3495 images passed the image quality control and were used in this study. Two CNN architectures, InceptionV3 and VGG16, were applied to establish the AI models and achieved an accuracy of 93.42% and 93.15%, respectively. The external validation of both the models was done using 227 DME and 135 non-DME OCT images, where InceptionV3 achieved an accuracy of 93.09%, a sensitivity of 95.15%, and a specificity of 89.48%, while the VGG16 model achieved 92.82% accuracy, 96.48% sensitivity, and 86.67% specificity.

A slightly different approach based on the multiscale transfer learning algorithm was attempted by Quan Zhang *et al*.[37] The algorithm was developed using 38,057°CT images (Drusen, DME, CNV, and Normal) in two parts: the self-enhancement model and the disease detection model. The two-dimensional CNN-based multiscale edge detection is the core of the self-enhancement module. The disease detection module was developed using Inception V3 architecture. This two-stage classification module achieved 94.5% accuracy, 97.2% precision, 97.7% sensitivity, and 97% specificity in the independent testing dataset.

Varadarajan *et al*.[20] used OCT images for DME grading of fundus images. With this cross-modality grading approach, the DL model trained using only fundus images outperforms the previous models in terms of higher specificity. The model can also detect the presence of intraretinal fluid (AUC: 0.81; 95% CI: 0.81–0.86) and subretinal fluid (AUC 0.88; 95% CI: 0.85–0.91). This approach provides the possibility of using fundus images in DME diagnosis and achieved 81% accuracy, 85% sensitivity, and 80% specificity when evaluated on primary dataset while it achieved 88% accuracy, 57% sensitivity and 91% specificity when evaluated on the secondary validation set (EyePACS-DME dataset).

In a very recent study by Takumasa *et al*.,[38] a novel capsule network has been proposed to address a four-way classification among DME, choroidal neovascular membrane, Drusen, and normal OCT scans. A very large dataset has been used to conduct the experiments, unlike previous approaches where the datasets were very small. This contribution reported 99.6% accuracy claiming 3.2% higher than those of contemporary methods.

Existing AI/ML-based techniques determine the effectiveness of anti-VEGF in DME patients

Lately, researchers are reporting more on the efficacies of anti-VEGF treatment on DME rather than publishing their researchers on detection. It is well understood from the retina specialist that the anti-VEGF injections are the first line of treatment to manage the DME, and they know that there would be a definite reduction of central subfield thickness (CST) after the application of the anti-VEGF agent. However, they are unsure to what extent such a reduction would take place given the pre-medical condition of the patient.

An AI-based algorithm can play a very vital role here to provide clinicians with a near accurate estimate of such

reduction for better treatment outcomes. We present here two such recent studies that attempted to represent this newer concept within the regime of treatment optimization.

Shao *et al*.[39] used an artificial neural network (ANN) to predict VA after ranibizumab treatment in DME. Ranibizumab, a well-known anti-VEGF agent, is safe and effective for DME treatment as it stops fluid leakage, reverses macular thickening, and improves vision. To train the ANN, the authors used patient demographic information, a little clinical information, diabetes type or condition, systemic diseases, eye status, and treatment timetables. On a publicly available dataset from the National Institutes of Health, the algorithm finds a good correlation between predicted VA against the ground truth on various time periods such as 52, 78, and 104 weeks. The method however neither used any OCT images nor predicted CST values directly.

On a complementary method as shown by [24], only OCT images have been used to predict CST of post-treatment of 127 subjects. Here, pre-treatment OCT images have been considered as input to a CNN, while the differential thickness has been chosen as output/target. The authors proposed a novel prediction algorithm called CADNet, a modification of the VGG network. For fine-tuning the model, 5-fold cross-validation has been chosen to generalize the performance of the algorithm that shows an average AUC of 0.866 in discriminating responsive from non-responsive patients.

A similar task was attempted by Cao *et al*.[40] with a different approach. As feature extractions, features like retinal layer segmentation and disruption ratio, intraretinal and subretinal fluid segmentation and area quantization, number of hyperreflective dots, and optical density ratio of intraretinal and subretinal fluid measurements are extracted using DL techniques. The classification of anti-VEGF response was performed using RF and SVMs with different kernel functions. Among all experimented classifiers, RF achieved the best performance of 90.7% specificity, 87.7% sensitivity, and 95.1% AUC.

Instead of classifying the response of the anti-VEGF treatment, Liu *et al*.[41] predicted the post-injection CST value using the combined both DL and traditional ML techniques. The deep fusion features were extracted from the OCT images using an ensemble of three convolutional neural networks, AlexNet, Vgg16, and ResNet18. These features were then combined with the clinical parameters, such as the measurement data, CFT, age, gender, baseline BCVA, and serum glucose, followed by the ensemble such as RF, SVM, decision tree, and Lasso continuous ML (CML) models to predict the CFT and BCVA values. This multilevel ensemble technique achieved mean absolute error (MAE), root mean square error (RMSE), and R^2 values of the best-performing model in the training set as 66.59, 93.73, and 0.71, respectively, for CFT prediction. While for BCVA prediction, the MAE, RMSE, and R^2 of the best-performing model in the training set was 0.19, 0.29, and 0.60, respectively. On the external validation set, the system achieved MAE, RMSR, and R^2 of 68.08, 97.63, and 0.74, respectively, for CFT prediction and 0.13, 0.20, and 0.68, respectively, for BCVA prediction.

The effect of anti-VEGF treatment in terms of volumetric change of intraretinal fluid (IRF) and subretinal fluid (SRF) was examined by Roberts *et al*.[42] The IRF and SRF were quantified using a DL-based approach and the performance of such an algorithm was also described in a study.[24] This post-hoc analysis of a randomized clinical trial of 570 patients concludes that the Aflibercept was associated with greater reduction of IRF volume compared with bevacizumab after the first injection.

Table 1: Summary of research articles on applicability of AI in DME management

Year of publication	Author	Objective	Dataset	Methodology	Performance Metrics
Sep 2014	Pratul P. Srinivasan *et al.*[25]	Automatic detection of DME and dry AMD from OCT images	45°CT cubes with 15 in each of three categories, Normal, AMD, and DME	A traditional approach to extract HOG feature vector from denoised SD-OCT images followed by SVM classifier.	Achieved 100% accuracy for AMD and DME classification while 86.67% accuracy for Normal OCT cube classification
Jul 2016	Guillaume Lemaître *et al.* [26]	DME classification of SD-OCT volumes using local binary patterns	The dataset, 32°CT volumes (16 DME and 16 normal cases) was acquired by the Singapore Eye Research Institute (SERI), using CIRRUS (Carl Zeiss Meditec, Inc., Dublin, CA) SD-OCT device	As a feature extraction tool, LBP was used followed by feature transformation using Bag-of-Word. Several classifiers, k-NN, LR, RF, GB, and SVM, were involved.	The highest sensitivity (81.2%) was achieved using RF while the highest specificity (93.7%) was achieved by SVM.
Oct 2011	Yu-Ying Liu *et al.*[28]	Classification of Macular Hole (MH), Macular Edema (ME), and Age-related Macular Degeneration (AMD) from normal using SD-OCT cubes	131 ZEISS SD-OCT cubes from 37 subjects across the four classes were considered as test data while 326 scans from 136 subjects were used for the development	A multiscale texture and shape features have been considered as features followed by SVM as a classification technique.	Two-class SVM classifiers achieved AUC of 0.978, 0.969, 0.941, and 0.975 for identifying normal macula, MH, ME, and AMD, respectively.
Jun 2017	Alsaih K *et al.*[29]	Machine learning techniques for diabetic macular edema (DME) classification on SD-OCT images	Singapore Eye Research Institute (SERI) dataset - 32°CT cubes with 16 normal and 16 DME cubes	BM3D, flattering, and cropping were used as preprocessing followed by HOG and LBP feature extractions. Features were then transformed and represented through PCA. Linear and nonlinear SVM and RF were used for the classification.	Linear SVM achieved a sensitivity and specificity of 87.5% and 87.5%, respectively.
Feb 2017	Désiré Sidibé *et al.*[30]	An anomaly detection approach for the identification of DME patients using SD-OCT images	Two different datasets: 1). SERI dataset - 32°CT cubes with 16 normal and 16 DME cubes 2). Duke dataset consists of 45 SD-OCT volumes from 15 DME patients, 15 AMD patients and 15 normal subjects, respectively.	The normal OCT mages were modeled using GMM and abnormal OCT images were detected as outliers.	This anomaly detection method achieves a sensitivity of 80% and a specificity of 93% on the first dataset, and 100% and 80% on the second dataset.
Apr 2020	Zhenhua Wang *et al.*[31]	Detection of DME in OCT image using an improved level set algorithm	The OCT dataset contains 100°CT images (10 normal images and 80 DR images with DME and 10 DR images with no signs of DME), acquired using Heidelberg SD-OCT device	A novel algorithm for the detection and segmentation of DME region in OCT image based on the K-means clustering algorithm and improved Selective Binary and Gaussian Filtering Regularized Level Set.	Algorithm achieved 97.7% precision (97.7%), sensitivity (91.8%), and specificity (99.2%)

Table 1: Contd...

Year of publication	Author	Objective	Dataset	Methodology	Performance Metrics
Apr 2018	Thomas Schlegl *et al.*[32]	Automatic detection and quantification of macular fluid in OCT using deep learning	1200°CT volumes of patients (400 AMD, 400 DME and 400 RVO) acquired with CIRRUS™ (Carl Zeiss Meditec, Dublin, CA) (600 cubes) or Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) (600 cubes) OCT devices.	Deep learning-based algorithm to automatically detect and quantify intraretinal cystoid fluid (IRC) and subretinal fluid (SRF) was developed.	Algorithm achieved mean AUC of 0.94, a mean precision of 0.91, and a mean recall of 0.84 for the detection and quantification of IRC for all 3 macular pathologies. While for the detection and measurement of SRF, the algorithm achieved an AUC of 0.92, a mean precision of 0.61, and a mean recall of 0.81.
Jun 2017	Cecilia S. Lee *et al.*[6]	Deep learning-based automated intraretinal fluid (IRF) segmentation to estimate macular edema in OCT	Around 1300°CT macular B-scan images were used for training and cross-validation.	A CNN architecture with 18 convolutional layers was developed to detect the IRF in the OCT images.	The segmentation algorithm achieved a cross-validated Dice coefficient of 0.911 compared with segmentations by experts.
Sep 2017	M. Awais *et al.*[33]	Classification of abnormal and normal OCT image volumes using a pre-trained CNN.	Singapore Eye Research Institute (SERI) dataset - 32°CT cubes with 16 normal and 16 DME cubes acquired with CIRRUS™ (Carl Zeiss Meditec, Dublin, CA).	Classification was performed using different classifiers taking features from different layers of the VGG-16 network.	The algorithm achieved the best accuracy of 87.5% while sensitivity and specificity being 93.5% and 81%, respectively.
May 2018	Oscar Perdomo *et al.*[34]	Automatic classification of normal and diabetic macular edema using SD-OCT volumes	Singapore Eye Research Institute (SERI) dataset - 32°CT cubes with 16 normal and 16 DME cubes acquired with CIRRUS™ (Carl Zeiss Meditec, Dublin, CA).	12 layers OCT-NET, a CNN-based end-to-end classification technique was developed to classify the OCT volumes.	The classification experiment with OCT-NET achieved equal accuracy, sensitivity, and specificity of 93.5%.
Dec 2018	Ravi M. Kamble *et al.*[35]	Classification of DME from normal OCT scan using DL-based approach.	Singapore Eye Research Institute (SERI) dataset - 32°CT cubes with 16 normal and 16 DME cubes acquired with CIRRUS™ (Carl Zeiss Meditec, Dublin, CA).	Inception-Resnet-v2 architecture was used for the classification of DME.	The technique achieved 100% sensitivity and specificity on the SERI dataset.
April 2020	De-Kuang Hwang *et al.*[36]	OCT-based diabetic macula edema screening with artificial intelligence	3495°CT images were collected from 173 diabetic patients with DME who received intravitreal injections (IVIs) of either anti-vascular endothelial growth factor (VEGF) or corticosteroid in Taipei Veterans General Hospital during January of 2017 to December of 2017 were enrolled in the study.	Two CNN architectures (InceptionV3 and VGG16) have been applied to establish the AI models.	The performance of each AI model (InceptionV3 and VGG16) has been verified by For the validation data set, consist of 227 DME and 135 non-DME OCT images, the accuracy of the AI model based on VGG16 and InceptionV3 architectures was 92.82% and 93.09%, respectively while the achieved sensitivity was 96.48% and 95.15% and the specificity was corresponding to 86.67% and 89.63%, respectively.

Table 1: Contd...

Year of publication	Author	Objective	Dataset	Methodology	Performance Metrics
Dec 2020	Quan Zhang *et al*.[37]	Identifying Diabetic Macular Edema and Other Retinal Diseases by Optical Coherence Tomography Image and Multiscale Deep Learning	A total of 38,057°CT images (Drusen, DME, CNV and Normal) to establish and evaluate the model. All data are OCT images of fundus retina. There were 37,457 samples in the training dataset and 600 samples in the validation dataset	The classification system consists of two parts: first the multiscale edge detection and second is Inception V3 CNN architecture-based disease detection model.	The model reached 94.5% accuracy, 97.2% precision, 97.7% sensitivity and 97% specificity in the independent testing dataset
Jan 2020	Varadarajan *et al*.[20]	Predicting OCT-derived diabetic macular edema grades from fundus photographs using deep learning	Thailand dataset consists of 6039 fundus images from 4035 patients were used for the development of the algorithm, During labeling Heidelberg Spectralis OCT data were used for quality labels.	The classification model was developed using Inception-v3 CNN-based architecture.	The model achieved accuracy, sensitivity, and specificity of 81%, 85%, and 80%, respectively for the primary validation set while 88% accuracy, 57% sensitivity, and 91% specificity when evaluated on the secondary validation set.
Mar 2020	Takumasa Tsuji *et al*.[38]	Classification of OCT images using a capsule network	OCT dataset, consist of a training dataset of 83,484 images and a test dataset of 1000 images - 250 images of each category, CNV, DME, drusen, and normal	Instead of CNN-based architecture, the capsule network has been applied for the OCT classification.	This contribution reported 99.6% accuracy claiming 3.2% higher than those of contemporary methods.
Nov 2018	Shao-Chun Chen *et al*.[39]	Predict the visual outcomes in Intravitreal Ranibizumab-treated patients with DME	Publicly available dataset from the National Institutes of Health (DRCR.net) consist of 674 patients while only 454 patients were followed up for more than 52 weeks.	Artificial neural network was used for the regression calculation with the target as the final visual acuity at 52, 78, or 104 weeks.	For the training group, testing group, and validation group, the respective correlation coefficients were 0.75, 0.77, and 0.70 (52 weeks); 0.79, 0.80, and 0.55 (78 weeks); and 0.83, 0.47, and 0.81 (104 weeks), while the mean standard errors of final visual acuity were 6.50, 6.11, and 6.40 (52 weeks); 5.91, 5.83, and 7.59; (78 weeks); and 5.39, 8.70, and 6.81 (104 weeks), respectively
Feb 2020	Reza Rasti *et al*.[24]	Automatically predict the efficacy of anti-VEGF treatment of DME in individual patients based on OCT images	Spectralis SD-OCT data of 127 patients, who underwent three intravitreous anti-VEGF injections. The OCT images are acquired OCT before and after three consecutive anti-VEGF injections spaced 4 to 6 weeks apart.	CADNet predictive framework was developed with the modification of VGG-16 network. Differential retinal thickness was used to partition patients into responsive and non-responsive classes. only patients with showing significantly (more than 10%) reduced retinal thickness were counted as responsive, while patients showing minimally improved or increased retinal thickness were counted as non-responsive	The algorithm achieved an average AUC of 0.866 in discriminating responsive from non-responsive patients, with an average precision, sensitivity, and specificity of 85.5%, 80.1%, and 85.0%, respectively

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Table 1: Contd...

Year of publication	Author	Objective	Dataset	Methodology	Performance Metrics
Jun 2020	Cao et al.[40]	Predict the anti- VEGF therapeutic response of DME patients from OCT at the initiation stage of treatment using a machine learning-based self-explainable system	Spectralis SD-OCT data with scanning protocol used a 20° x 15° volume scan, consisting of 19 sections of 712 DME patients were collected at both baselines and after 3 anti-VEGF injections. The reduction in Central Macular Thickness is considered for the response classification.	Using Deep Leaning techniques, various features like Retinal layer segmentation and disruption ratio, Intraretinal and subretinal fluid segmentation and area quantization, number of Hyperreflective dots, and Optical density ratio of intraretinal and subretinal fluid measurements are extracted followed by RF or SVM-based classification.	The RF classifier achieved the best performance of 90.7% specificity, 87.7% sensitivity, and 95.1% AUC.
Jan 2021	Baoyi Liu et al.[41]	Predict the post-injection CFT and BCVA values using ensembled techniques for the combi image and clinical parameters data of anti-VEGF treatment for DME patients	A total of 363°CT images and 7,587 clinical data records from 363 eyes were included in the training set (304 eyes) and external validation set (59 eyes).	Deep fusion features are extracted from the OCT images using the ensembled DL models. The features are combined with clinical parameters followed by the ensembled CML model to predict the CFT and BCVA values.	Ensembled system achieved MAE, RMSE, and R2 of 66.59, 93.73, and 0.71, respectively, for CFT prediction and 0.19, 0.29, and 0.60 for BCVA prediction. While on the external validation set, the system achieved MAE, RMSE, and R2 of 68.08, 97.63, and 0.74, respectively, for CFT prediction and 0.13, 0.20, and 0.68, respectively, for BCVA prediction.
Jul 2020	Roberts et al.[42]	Examine the volumetric change of IRF and SRF in DME during anti-vascular endothelial growth factor treatment using deep learning algorithms.	SD-OCT data of 570 patients, who underwent anti-VEGF treatment for DME, collected from August 21, 2012, to October 18, 2018.	Preprocessing for automatic alignment and registration of the SD-OCT scans for the intra-patient registration. A deep learning convolutional neural network approach was applied, which classifies voxels as background, IRF, or SRF. IRF and SRF volumes were computed for the central fovea (circle with a 1-mm diameter) and for the parafovea (ring between 1 and 3 mm surrounding the fovea)	The presence of SRF at baseline was associated with a worse baseline BCVA ETDRS score of 63.2 (approximate Snellen equivalent of 20/63) in eyes with SRF vs 66.9 (approximate Snellen equivalent, 20/50) without SRF and a greater gain in ETDRS score every 4 weeks during follow-up in eyes with SRF at baseline vs 0.4 in eyes without SRF at baseline. Aflibercept was associated with greater reduction of IRF volume compared with bevacizumab after the first injection and every 4 weeks thereafter. Ranibizumab was associated with a greater reduction of IRF after the first injection compared with bevacizumab.

Discussion on relative success and failure of methods under comparison

The two types of problems—identification of DME and understanding treatment responses using anti-VEGF agents—tackled by various researchers are summarized in Table 1. No two research works could be compared unless they used the same dataset with equal granularity and performance metrics and the objectives of both methods were the same. It is generally hard to find publicly available datasets in healthcare due to data and patient privacy reasons. In this context, other than the SERI dataset, which comprises 32 OCT cubes with equal composition between normal and DME OCT cubes, to the best of our knowledge, no other existing publicly available datasets consist of DME. However, the traditional ML-based techniques lack generalization as features are handcrafted and may not describe the typical pathology cues, which could be common across a class. Hence, the classifiers could be impacted by these lesser generalized features. From the classification task viewpoint, the conventional classifiers get saturated as the number of data grows; contrary to this, a DL-based classification technique does not suffer from this problem but demands larger data points for training. The above contributions lack considering both OCT and clinical parameters to train an AI model thereby predicting CST. The clinical parameters can play a significant role in the efficacy of prediction models and can impact the treatment response. In the case of diseases like DME, interacting clinical factors such as duration of diabetes, glucose levels, HbA1C levels, previous treatments taken, number of anti-VEGF injections taken, and underlying ophthalmic conditions can influence the response toward the treatment. Images and clinical values are complementary, and we strongly believe a model that accommodates both data types would outperform those of single data stream-based modeling.

Conclusion

DME is one of the common complications that can occur at any stage of DR. The therapeutic aim of anti-VEGF injections in patients with DME is to improve and stabilize the quality of vision and, ultimately, to improve the quality of life which is severely threatened by visual loss. However, due to the complexity of the treatment regimen given to a DME patient and a large number of non-responders to anti-VEGF therapy, it has become essential to deploy a technology-based decision support method that can be useful for eye care providers to make informed decisions about recommending anti-VEGF treatment for the DME patients. The developed and validated AI tool holds huge potential in improving the efficiency of DME disease management by providing the best line of treatment to patients resulting in the reduction of clinical burden for disease management to the retina specialist and huge cost savings to the patient by taking the optimal treatment. Such an AI-based tool can allow precise customizations in the therapeutic schedule for the patients, hence shifting the treatment goal from sight preservation to sight improvement. This will not only improve the quality of life for a patient (with reduced hospital visits and injection burden) but also give confidence to the patient in the treatment. Such AI-based prediction models can become an integral feature of a digital health management platform and allow instant prediction of probability to respond toward anti-VEGF treatment thereby efficiently distributing the medical resources and reducing the disease burden.

Conflicts of interest

There are no conflicts of interest.

References

1. Fiszman M, Chapman WW, Aronsky D, Evans RS, Haug PJ. Automatic detection of acute bacterial pneumonia from chest X-ray reports. J Am Med Inform Assoc 2000;7:593-604.

2. Dekker A, Vinod S, Holloway L, Oberije C, George A, Goozee G, *et al*. Rapid learning in practice: A lung cancer survival decision support system in routine patient care data. Radiother Oncol 2014;113:47-53.

3. Ting DSW, Pasquale LR, Peng L, Campbell JP, Lee AY, Raman R, *et al*. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol 2019;103:167-75.

4. Ting DSW, Cheung CY, Lim G, Tan GSW, Quang ND, Gan A, *et al*. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA 2017;318:2211-23.

5. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, *et al*. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA 2016;316:2402-10.

6. Lee CS, Tyring AJ, Deruyter NP, Wu Y, Rokem A, Lee AY. Deep-learning based automated segmentation of macular edema in optical coherence tomography. Biomed Opt Express 2017;8:3440-8.

7. Abràmoff MD, Lou Y, Erginay A, Clarida W, Amelon R, Folk JC, *et al*. Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learning. Invest Ophthalmol Vis Sci 2016;57:5200-6.

8. Gargeya R, Leng T. Automated identification of diabetic retinopathy using deep learning. Ophthalmology 2017;124:962-9.

9. Burlina PM, Joshi N, Pekala M, Pacheco KD, Freund DE, Bressler NM. Automated grading of age-related macular degeneration from color fundus images using deep convolutional neural networks. JAMA Ophthalmol 2017;135:1170-6.

10. Grassmann F, Mengelkamp J, Brandl C, Harsch S, Zimmermann ME, Linkohr B, *et al*. A deep learning algorithm for prediction of age-related eye disease study severity scale for age-related macular degeneration from color fundus photography. Ophthalmology 2018;125:1410-20.

11. Li Z, He Y, Keel S, Meng W, Chang RT, He M. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. Ophthalmology 2018;125:1199-206.

12. Gao X, Lin S, Wong TY. Automatic feature learning to grade nuclear cataracts based on deep learning. IEEE Trans Biomed Eng 2015;62:2693-701.

13. Brown JM, Campbell JP, Beers A, Chang K, Ostmo S, Chan RVP, *et al*. Automated diagnosis of plus disease in retinopathy of prematurity using deep convolutional neural networks. JAMA Ophthalmol 2018;136:803-10.

14. Nagasato D, Tabuchi H, Masumoto H, Enno H, Ishitobi N, Kameoka M, *et al*. Automated detection of a nonperfusion area caused by retinal vein occlusion in optical coherence tomography angiography images using deep learning. PLoS One 2019;14:e0223965.

15. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, *et al*. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843.

16. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab 2016;20:546-51.

17. Raman R, Gella L, Srinivasan S, Sharma T. Diabetic retinopathy: An epidemic at home and around the world. Indian J Ophthalmol 2016;64:69-75.

18. Diabetic Retinopathy Clinical Research Network, Bressler NM, Miller KM, Beck RW, Bressler SB, Glassman AR, et al. Observational study of subclinical diabetic macular edema. Eye (Lond) 2012;26:833-40.

19. Sikorski BL, Malukiewicz G, Stafiej J, Lesiewska-Junk H, Raczynska D. The diagnostic function of OCT in diabetic maculopathy. Mediators Inflamm 2013;2013:434560.

20. Varadarajan AV, Bavishi P, Ruamviboonsuk P, Chotcomwongse P, Venugopalan S, Narayanaswamy A, et al. Predicting optical coherence tomography-derived diabetic macular edema grades from fundus photographs using deep learning. Nat Commun 2020;11:130.

21. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: Results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789-801.

22. Lazic R, Lukic M, Boras I, Draca N, Vlasic M, Gabric N, et al. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. Retina 2014;34:719-24.

23. Shah AR, Yonekawa Y, Todorich B, Van Laere L, Hussain R, Woodward MA, et al. Prediction of anti-VEGF response in diabetic macular edema after 1 injection. J Vitreoretin Dis 2017;1:169-74.

24. Rasti R, Allingham MJ, Mettu PS, Kavusi S, Govind K, Cousins SW, et al. Deep learning-based single-shot prediction of differential effects of anti-VEGF treatment in patients with diabetic macular edema. Biomed Opt Express. 2020;11:1139-52.

25. Srinivasan PP, Kim LA, Mettu PS, Cousins SW, Comer GM, Izatt JA, et al. Fully automated detection of diabetic macular edema and dry age-related macular degeneration from optical coherence tomography images. Biomed Opt Express 2014;5:3568-77.

26. Lemaître G, Rastgoo M, Massich J, Cheung CY, Wong TY, Lamoureux E, et al. Classification of SD-OCT volumes using local binary patterns: Experimental validation for DME detection. J Ophthalmol 2016;2016:3298606.

27. Alsaih K, Lemaitre G, Vall JM, Rastgoo M, Sidibe D, Wong TY, et al. Classification of SD-OCT volumes with multi pyramids, LBP and HOG descriptors: Application to DME detections. Annu Int Conf IEEE Eng Med Biol Soc 2016;2016:1344-7.

28. Liu YY, Ishikawa H, Chen M, Wollstein G, Duker JS, Fujimoto JG, et al. Computerized macular pathology diagnosis in spectral-domain optical coherence tomography scans based on multiscale texture and shape features. Invest Ophthalmol Vis Sci 2011;52:8316-22.

29. Alsaih K, Lemaitre G, Rastgoo M, Massich J, Sidibé D, Meriaudeau F. Machine learning techniques for diabetic macular edema (DME) classification on SD-OCT images. Biomed Eng Online 2017;16:68.

30. Sidibé D, Sankar S, Lemaître G, Rastgoo M, Massich J, Cheung CY, et al. An anomaly detection approach for the identification of DME patients using spectral domain optical coherence tomography images. Comput Methods Programs Biomed 2017;139:109-17.

31. Wang Z, Zhang W, Sun Y, Yao M, Yan B. Detection of diabetic macular edema in optical coherence tomography image using an improved level set algorithm. Biomed Res Int 2020;2020:6974215.

32. Schlegl T, Waldstein SM, Bogunovic H, Endstraßer F, Sadeghipour A, Philip AM, et al. Fully automated detection and quantification of macular fluid in OCT using deep learning. Ophthalmology 2018;125:549-58.

33. Awais M, Müller H, Tang TB, Meriaudeau F. Classification of SD-OCT images using a deep learning approach. IEEE International Conference on Signal and Image Processing Applications (ICSIPA), September 2017. P 489-92.

34. Perdomo O, Otálora S, González FA, Meriaudeau F, Müller H. Oct-net: A convolutional network for automatic classification of normal and diabetic macular edema using SD-OCT volumes. IEEE 15th international symposium on biomedical imaging (ISBI 2018). April 2018. p. 1423-6.

35. Kamble RM, Chan GC, Perdomo O, Kokare M, Gonzalez FA, Müller H, et al. Automated diabetic macular edema (DME) analysis using fine tuning with inception-resnet-v2 on OCT images. IEEE-EMBS Conference on Biomedical Engineering and Sciences (IECBES). December 2018. p. 442-6.

36. Hwang DK, Chou YB, Lin TC, Yang HY, Kao ZK, Kao CL, et al. Optical coherence tomography-based diabetic macula edema screening with artificial intelligence. J Chin Med Assoc 2020;83:1034-8.

37. Zhang Q, Liu Z, Li J, Liu G. Identifying diabetic macular edema and other retinal diseases by optical coherence tomography image and multiscale deep learning. Diabetes Metab Syndr Obes 2020;13:4787-800.

38. Tsuji T, Hirose Y, Fujimori K, Hirose T, Oyama A, Saikawa Y, et al. Classification of optical coherence tomography images using a capsule network. BMC Ophthalmol 2020;20:114.

39. Chen SC, Chiu HW, Chen CC, Woung LC, Lo CM. A novel machine learning algorithm to automatically predict visual outcomes in intravitreal ranibizumab-treated patients with diabetic macular edema. J Clin Med 2018;7:475.

40. Cao J, You K, Jin K, Lou L, Wang Y, Chen M, et al. Prediction of response to anti-vascular endothelial growth factor treatment in diabetic macular oedema using an optical coherence tomography-based machine learning method. Acta Ophthalmol 2021;99:e19-27.

41. Liu B, Zhang B, Hu Y, Cao D, Yang D, Wu Q, et al. Automatic prediction of treatment outcomes in patients with diabetic macular edema using ensemble machine learning. Ann Transl Med 2021;9:43.

42. Roberts PK, Vogl WD, Gerendas BS, Glassman AR, Bogunovic H, Jampol LM, et al. Quantification of fluid resolution and visual acuity gain in patients with diabetic macular edema using deep learning: A post hoc analysis of a randomized clinical trial. JAMA Ophthalmol 2020;138:945-53.