

Review Article

A Review on Machine Learning Methods in Diabetic Retinopathy Detection

Zahra Alaeddini ^{1,*}, MS

1. Department of Computer Science, Alzahra University, Tehran, Iran.

***Corresponding Author:** Zahra Alaeddini

E-mail: alaeddini.zahra@gmail.com

Abstract

Ocular disorders have a broad spectrum. Some of them, such as Diabetic Retinopathy, are more common in low-income or low-resource countries. Diabetic Retinopathy is a cause related to vision loss and ocular impairment in the world. By identifying the symptoms in the early stages, it is possible to prevent the progress of the disease and also reach blindness. Considering the prevalence of different branches of Artificial Intelligence in many fields, including medicine, and the significant progress achieved in the use of big data to investigate ocular impairments, the potential of Artificial Intelligence algorithms to process and analyze Fundus images was used to identify symptoms associated with Diabetic Retinopathy. Under the studies, the proposed models for transformers provide better interpretability for doctors and scientists. Artificial Intelligence algorithms are also helpful in anticipating future health issues after appraising premature cases of the ailment. Especially in ophthalmology, a trustworthy diagnosis of visual outcomes helps physicians in advising disease and clinical decision-making while reducing health management costs.

Keywords: Artificial Intelligence; Diabetic Retinopathy; Deep Learning; Fundus Images; Machine Learning.

Article Notes: Received: Jun. 26, 2020; Received in revised form: Aug. 15, 2020; Accepted: Oct. 19, 2020; Available Online: Jan. 2, 2021.

How to cite this article: Alaeddini Z. A Review on Machine Learning Methods in Diabetic Retinopathy Detection. Journal of Ophthalmic and Optometric Sciences . 2021;5(1): 52-66.

Introduction

Globally, the number of people living with diabetes will be reached 600 million by 2040¹. This statistic demonstrates the growing eye diseases related to diabetes in the coming years. Also, this shows the need to diagnose eye disorders such as Diabetic Retinopathy (DR) in the early stages and even before the clinical symptoms appear.

With Artificial Intelligence (AI) coming and its branches such as Machine Learning (ML) and Deep Learning (DL), the availability of the huge amount of data, high-speed, and also cheap hardware, it has been possible to benefit from it in many industries such as medicine²⁻⁷. Ophthalmology has a remarkable potential in benefiting from AI in disease diagnostic such as diabetic eye complications. With the help of AI algorithms, it is possible to predict Ocular diseases in the early stages and even before the appearance of initial clinical symptoms; this prevents blindness and vision impairment. DR includes five stages, which are: 1- no Diabetic Retinopathy - 2- Mild Diabetic Retinopathy - 3- Mediate Diabetic Retinopathy - 4- Serious Diabetic Retinopathy and - 5- Proliferative Diabetic Retinopathy (PDR)⁸⁻¹⁰. Accurate diagnosis of different stages of DR requires highly skilled doctors. But even conversant doctors make mistakes in the exact classification of DR. Since the correct categorization of cases and early disclosure of signs can hinder vision deficit, the potential of ML and DL algorithms for the correct type of ailment stages has accepted much concentration in recent years¹¹.

The data required for AI algorithms are produced in clinical examinations performed by ophthalmologists. This data can include multifocal ocular images and other measures such as Visual Acuity (VA) and Intraocular Pressure (IoP). According to the type of data

available, the use of ML and DL algorithms to identify or predict eye impairments such as Diabetic Retinopathy, Age-related Macular Degeneration (AMD)¹², Glaucoma, and many eye-related disorders are a concern to many health institutions located all over the world¹³⁻¹⁹.

Therefore, improving AI algorithms for ophthalmology has increased inmates' access to monitoring and clinical interpretation, as well as diminished healthcare costs, particularly in countries with low income and insufficient resources^{20, 21}. In addition, by employing AI algorithms for Optical Coherence Tomography (OCT) and Fundus images^{22, 23}, they are possibly used to identify ailment aspects, disease advancement, and the treatment response of retinal disorders such as DR in the early stages²⁴.

Many screening programs for DR detection using OCT and Fundus images, with the aim of timely referring the patient to ophthalmologists for timely treatment and prevention of decreased vision, are being implemented around the world^{25, 26}. In this article, an attempt has been made to review the most recent articles associated with DR categorization. In the following, first, a definition of Diabetic Retinopathy is provided. Then, an introduction to Artificial Intelligence and its most widely used techniques, Machine Learning and Deep Learning are described. After that, the datasets used in developing proposed AI algorithms in the field of ophthalmology are provided. Finally, a revision of the current claims of ML and DL algorithms in ophthalmology and DR-accompanying disorders has been done.

Diabetic Retinopathy

Diabetic Retinopathy is the leading cause of Ocular impairment in patients with diabetes under 50 years of age²⁷. DR occurs

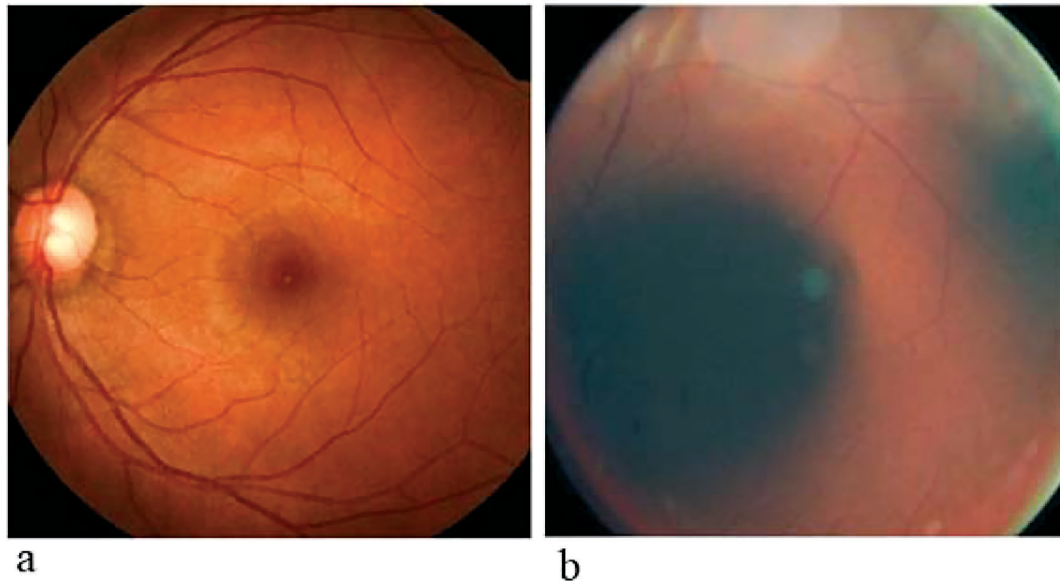


Figure 1: a- Human retinal without Diabetic Retinopathy, b- Human retinal in PDR stage(29)

due to microvascular damage to the retinal capillaries. There is evidence that retinal nerve dysfunction may occur before vascular changes are observed^{10, 27}. DR is one of the central vision problems related to diabetes, which accounts for 2.6 % of sightlessness globally²⁸. In this condition, Glucose that is not digested by the pancreas can block the blood vessels of the eye. This can cause eye damage due to swelling and leakage of blood vessels in the eye.

DR is detached into two typical phases, Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) (Figure 1a, 1b).

The NPDR stage, known as the early stage of DR, is characterized by less than five microaneurysms, retinal hemorrhages, and hard exudates⁸⁻¹⁰. Microaneurysms and retinal hemorrhages usually appear as red lesions. While the stage of PDR, the most common type of sight-threatening lesion in type 1 diabetes, is defined by the detection of retinal neovascularization. Therefore, identifying the early symptoms can help speed up the

treatment process and prevent the disease from becoming acute³⁰.

Artificial Intelligence background

Any system that can perform independently and intelligently has benefited from Artificial Intelligence techniques³¹. Considering the breadth of this field of computer science, Machine Learning is a particular subfield of AI used in many areas (Figure 1a, 1b). ML refers to a set of algorithms that can learn from a large amount of data. The dataset consists of samples with a specific topic, such as eye impairments. These samples are characterized by variables associated with the ailment and involve dispassionate details such as age, gender, or Intraocular Pressure. Samples are categorized into groups noted as classes³².

Also, Deep Learning is a subgroup of ML methods. Their engineering is inspired by biological neural networks. DL algorithms can engineer features automatically. The most common DL algorithm usual in ophthalmology is noted as Neural Network (NN)^{33, 34}. Neural networks (Figure 2) contain various layers of

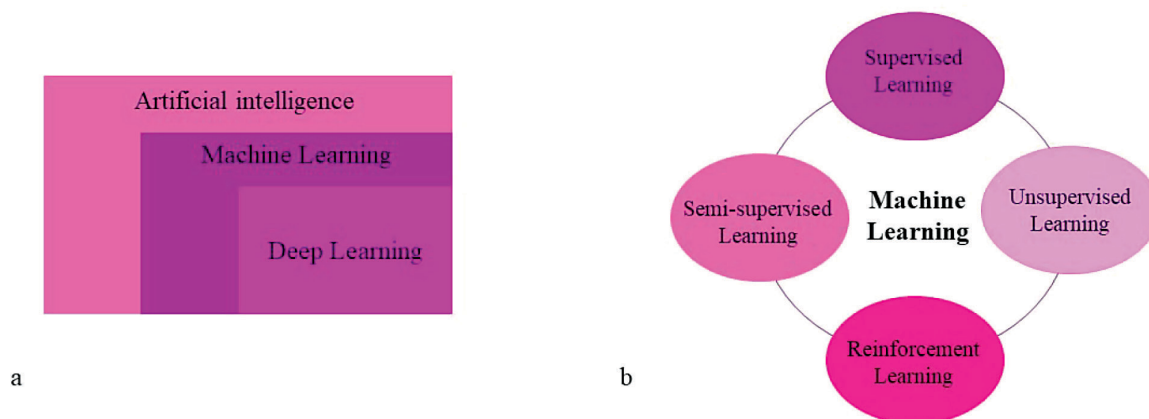


Figure 2: a- AI and its subsets, b- Machine Learning categorization

nodes termed neurons. Neurons of the first layer are displayed by unique variables for a sample. Each neuron in the algorithm is affiliated to the whole set of neurons in the next layer.

These connections have variable weight. So that each neuron of the first layer increases or diminishes the value of each neuron in the second layer. Therefore, the value of each neuron in the second layer is contingent upon the total of the weighted values of all the neurons in the first layer. Finally, the output layer concludes predefined classes in the dataset (such as DR vs. normal). When a dataset is trained with accompanying samples of known classes through NN, the variables of each instance lead to an output that illustrates a particular class.

The algorithm indicates an error when it makes an incorrect class prediction. Then, it determines which weighted connections to change in the NN to ensure it selects the correct class³⁵. After the algorithm has altered its internal weighted connections, the NN is retrained, accompanying the dataset. This process is accomplished iteratively, and the algorithm persists in regulating its internal programming just before it can dependably categorize samples into the correct classes. Finally, the developing NN is tested on an

entirely new dataset of samples accompanying known classes, noted as the validation dataset. This tests the algorithm's capability to categorize new samples correctly. Using the results of the validation dataset, metrics such as sensitivity and precision are possibly driven. Success in correctly predicting classes in ML and DL relies on classification algorithms. There are different classification algorithms for various purposes in ML. Some commonly used classifiers are Support Vector Machine (SVM), Random Forest (RF), Logistic Regression (LR), Decision Tree (DT), Naïve Bayes (NB), and K-Nearest Neighbor (KNN). It can be said that the main difference between ML and DL is the feature extraction technique that the classification algorithm works on. In DL, features are extracted using multiple nonlinear hidden layers. This issue causes DL classification algorithms to perform better than classification algorithms in ML. Because feature extraction in ML algorithms relies on their non-automatic extraction. There are different types of classifiers in DL, some of which are: Recurrent Neural Network (RNN), Convolutional Neural Network (CNN), Boltzmann Machine (BM), AutoEncoder (AE), and Deep Belief Network (DBN)³⁶.

From the mentioned DL algorithms, CNN^{33,37} is the best regular in image processing topics

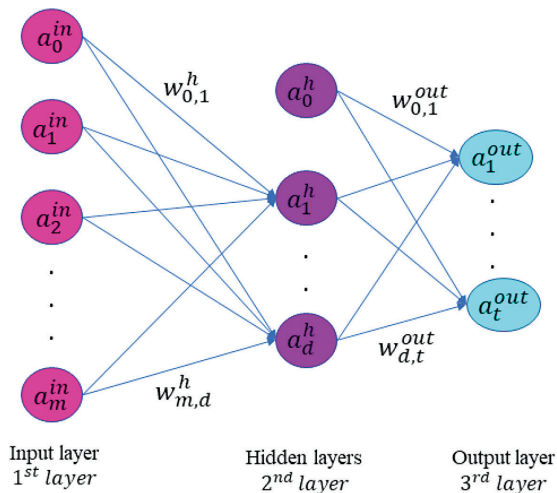


Figure 3: A fully connected Artificial Neural Network. The input layer represents variables. Weights must be between 0 and 1.0. the output layer indicates the predicted class

in the way that image processing for DR disclosure. In CNN, the engineering of the layers is specific that it avoids the dilemma of image processing in the form of part refining that was ordinary in NNs. CNN can recognize patterns in images. Specifically, the layers of CNN assist the network to learn various features of an image. Indiscriminate, the architecture of a CNN subsists of an input layer, an output layer, and various hidden layers. In each hidden layer, the weight of the neurons and the bias values are unchanging. But the network invariably amends the weights of the neurons all the while training. Updating the weights of the neurons in the hidden layers means that the neurons are detecting particular features. Three transcendent coarse layers that lie between the input and output layers are pooling, convolution, and ReLU, which transform data to learn distinguishing features. The convolution layer applies a set of filters on the input images that activate definite features of the images. The ReLU activation function acknowledges tighter training. Because of the

consistency of positive values and mapping negative values to zero, it transfers only the activated features to the next layer. By operating sampling, the pooling layer reduces the dimensions of the features, and thus, the number of parameters that the network must learn and the number of computations aspiring decreased. The last layer, which is a sufficiently connected layer, resides in a vector accompanying k length which is the number of classes into that the CNN commits to categorize the data. On this layer, the SoftMax activation function is enforced to label images. Figure 4 illustrates a simple concept of CNN. The most influential models of CNN that have been used apathetic types of research aims are AlexNet, GoogLeNet, ZFNet, LeNet, and ResNet.

A point that concedes the possibility be acclaimed in AI studies, particularly studies related to image processing, is that it is mainly to illustrate the community at which point the DL method was advanced and tested. Reporting dataset attributes such as principal population representing data substrates in the way that visibility and reference standard are outstanding in ophthalmology. Especially DL methods can anticipate extra features that cannot be discovered by non-automated inspection. In ophthalmology, the reference standards are generally ophthalmologists, graders, or optometrists. In terms of test procedures, they may be executed as clinical examinations or image-based examinations.

Datasets

The set of images used in training ML and DL algorithms available in public form are Messidor³⁸, IDRiD³⁹, DRIVE⁴⁰, DIARETDB^{41, 42}, ODIR⁴³, DDR⁴⁴, STARE⁴⁵, EyePACKS⁴⁶, and APTOS⁴⁷. Table 1 represents the general information of these

Table 1: Some datasets were utilized to train DL and ML models for DR detection. The number of labels is associated with DR stages (N, DR, MDR, SDR, PDR)

Dataset	Number of images	Image size (pixel)	Number of labels	Train+ validation, Test
EyePACS 2015(46)	88,702	433×289 ~ 5184×3456	25810, 2443, 5292, 873, 708	35126, 53576
APTOS 2019(47)	3,660	-	-	-
Messidor(38)	1,200	1440×960 ~ 2304×1536	-	-
Messidor-2(38)	1,748	1440×960 ~ 2304×1536	-	-
IDiRD(39)	516	4288×2848	-	413, 103
DRIVE(40)	40	565×584	33, 7	20, 20
DIARETDB0(42)	130	1500×1152	20, 110	-
DIARETDB1(41)	89	1500×1152	5, 84	28, 61
ODIR(43)	10,000	-	1620, 8380	9000, 1000
DDR(44)	13,673	-	6266, 6256	9568, 4105
STARE(45)	~ 400	-	-	-

datasets.

These datasets are used to compare different classification methods of DR. To check the accuracy of the model trained on these datasets, the clinical datasets collected from the participating laboratories are used. Among the mentioned datasets, Messidor is used to train DL and ML models.

Developed algorithms for the diagnosis of DR Fundus cameras are used to examine the eyes of patients for DR. The resulting images are then graded to identify and assess the severity of DR; several AI-based systems have been developed by different groups using retinal fundus images to diagnose DR. Our review paper investigates DR classification using AI methods. We divided the investigation results into three groups Supervised ⁴⁸, Self-Supervised ⁴⁹, and Transformers ⁵⁰, and two subgroups are binary and multiple classifications.

Supervised

1-Binary classification

Pao et al. ⁵¹ determined a model that uses the deterioration of each Fundus image to recognize the lesion and generate important areas for feature extraction by a binary classification algorithm. This model reached 87.37 % accuracy. In this study, the ROC curve was used as the main accomplishment sign, however the inequality in the Fundus data. Hua et al. ⁵² developed a model based on ResNet-101 for image classification called RFA-BNET. Although this model achieved less accuracy than the ensemble models, it was considered due to the method used. They reported accuracy, specificity, sensitivity, and Area Under the Receiver Operating characteristic Curve (AUROC) to 95.1 %, 97.4 %, 79.32 %, and 0.9732 respectively.

Paisan et al. ²⁰, to evaluate the performance

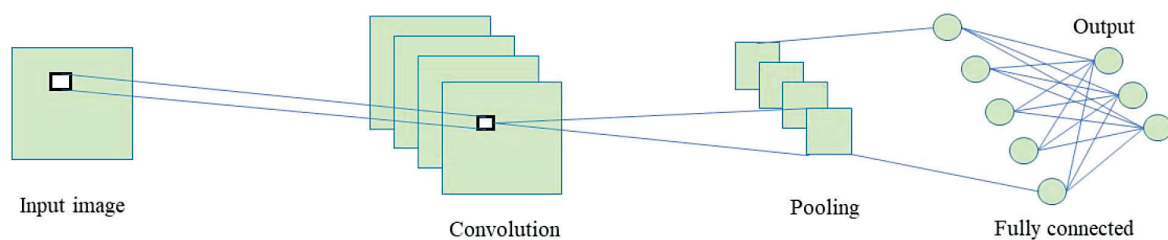


Figure 4: A simple conception of CNN with Convolution, Pooling, and a Fully connected layer

of AI-based systems in the real world, experimented with Thailand's health system. The DL algorithm investigated in this study achieved accuracy over 94 %, specificity equal to 95.4 %, and sensitivity was 91.4 %. Pragati et al.⁵³ developed an integrated ML approach that used SVM, Principal Component Analysis (PCA), and optimization techniques. In this study, DR datasets were applied to DT, SVM, RF, and NB Machine Learning algorithms. The SVM algorithm performed nearly 76 % better than the other algorithms. Also, in this study, found that only the RF algorithm using PCA performed better. For the mentioned combination of RF and PCA, accuracy, specificity, sensitivity, precision, recall, and F1_score had been reported to be 67.09 %, 67.6 %, 66.3 %, 67 %, 67 %, and 67 % respectively. Also, to improve the performance of SVM and PCA, they used the optimization method known as butterfly flame. The result of this approach was an 85.61 % performance improvement. Also, the measured six mentioned evaluation metrics were 86.3 %, 75.2 %, 94.2 %, and specificity, sensitivity, and F1_score were equal to 86 %. Garcia et al.⁵⁴ used the AlexNet and VGGnet16 frameworks to develop a new method to investigate the left and right eyes separately. VGG16 achieved 83.68 % accuracy without a fully bonded layer. Also, AUROC for the proposed method was 0.996. But the different

stages of DR were not classified.

2- Multiple classifications

Zago et al.^{55, 56} conducted a study using VGG16 and CNN. DIARETDB1 dataset was used to train the model. They used images with dimensions of 65 x 65 pixels. These images are obtained using the mentioned frames with five layers of two-dimensional convolution. They used Messidor-2, Kaggle, DDR, Messidor, IDRiD, and DIARETDB0 datasets to test and classify DR. The reported sensitivity and AUROC for the proposed method were 0.94 and 0.916 respectively⁵⁶.

Prabha et al.⁵⁷ developed a classification algorithm based on CNN to diagnose DR in the early stages. They extracted the required data, which were fundus images, to train the algorithm from the STARE and DRIVE datasets. In this method, image thresholding using the repeated selection method was used for image segmentation. The proposed system achieved high accuracy of 95 % and sensitivity of 94.7 %.

Keel et al.^{58, 59} developed two CNN-based DL systems, one of which was for diagnosing DR. In this algorithm, regions of the image that were distinct in terms of time were identified. After this step, a thermal map of the areas necessary for early disease diagnosis was prepared. Among the most critical areas for the early prediction of the disease, which is 96 %

of cases, that cause a true positive referral of DR, were the areas that suffered from retinal bleeding.

Of course, the study of Abramoff et al.^{60,61} was the first time that an advanced DL algorithm based on CNN was used for the automatic diagnosis of DR. Messidor-2 dataset was used to train this algorithm. The sensitivity and specificity of this algorithm were reported 87.2 % and 90.7 % respectively.

Wang et al.⁶² used a classical BP Neural Network algorithm to diagnose retinopathy. They used the Levenberg-Marquardt method as the training function. Ophthalmologists used 80 datasets to evaluate it. The accuracy result was satisfactory. Dota et al.⁶³ to solve the problem related to the Garcia et al. study, used the Kaggle DR dataset to apply to three DL models: Deep Neural Network (DNN), Fully connected Neural Network (FNN), and CNN. After the preprocessing steps, the DNN achieved an accuracy of nearly 90 %.

Xu et al.⁶⁴ Developed a DL architecture in which they categorized the Fundus images using CNN and a Stochastic Gradient Descent optimizer. The proposed model trained on the Kaggle and EyePACS datasets, which were images of Fundus retinopathy. The model's architecture was such that out of 8 two-dimensional convolutional layers, included four max-pooling layers, followed by two convolutional layers. Finally, it was related to two layers utterly related to a softmax activation function. The model saw the identified features such as hard transpiration, microaneurysms, blood vessels, and red lesions. They compared the method of feeding the trees with the extracted features to CNN. Gradient Boosting Machine (GBM) hyper-parameters are then used for the number of classes. The proposed model achieved an accuracy of over 94 %.

Self-Supervised

1-Binary classification

In the model developed by Lu et al.⁶⁵ appointed SFCN, trained on 25 images from the DRIVE dataset, an accuracy of 87.6 % and Area Under Curve (AUC) equal to 0.85 had been recorded. In comparison, Hua et al.⁵² RFA-BNET utilized 20 images accompanying thorough augmentations and reached an accuracy of 95.1 %. Also, other metrics such as sensitivity, specificity, and AUROC have been reported to be 79.32 %, 97.41 %, and 97.32 % respectively. Kanagasinget et al.⁶⁶ developed a DL algorithm using data from DiaRetDB1, EyePACS, and the Australian Eye DR Database. The desired algorithm achieved a specificity of 92 % on 193 patients in an Australian clinic.

2-Multiple-classification

He et al.⁶⁷ trained CABNet on the EyePACS dataset. This block makes it easier for the model and parts of the Fundus images to be embedded. This makes the model superior and acceptable. CABNet also reached 85.69 % accuracy and 0.8542 was reported for kappa. In a study conducted in 2018 by Hemanth et al.⁶⁸, they developed Hopfield's Neural Networks (HNN) to classify retinal images. This network can adjust the weight and output together. The weights are dynamic in the proposed method. The proposed algorithm called MHNN achieved 99 % accuracy, sensitivity, and specificity of nearly 99 %. This algorithm was evaluated better than many neural networks and HNN methods for DR diagnosing.

Transformers

1-Binary classification

Panwar et al.⁶⁹ attended a study utilizing

a CNN trained to accompany a transfer model. The model was trained by extracting a feature vector from the test set of images. This vector forges the capability to categorize new images accompanying extreme accuracy in other classifiers. This study showed that a DL architecture using transfer learning can precisely classify spots in fundus images. Sun et al.⁷⁰ proposed a transformer model, which was based on a pixel relational encoder and a decoder. The developed model uses only image labels. This model compensated for the gap between the grading of DR and the diagnosis of the lesion.

In another study by Papadopoulos et al.⁷¹, a transformer model was developed that uses the attention mechanism to devise heat maps. This procedure extracts the required information by combining various four-sided sections accompanying an attention form concentrated on the domains of the eye that have spots. The model was evaluated on Messidor-2 and Kaggle datasets. Also, AUC, sensitivity, and specificity for evaluation on the Kaggle dataset were 0.957, 95.1 %, and 75.3 % for high sensitivity points respectively. But, for the high specificity points, the reported specificity was 84.3 % and sensitivity was equal to 95.1 %. On the other hand, AUC, sensitivity, and specificity for the evaluation by Messidor-2 were 0.976, 95.4 %, and 84.5 % on the high sensitivity points respectively. While the reported sensitivity on the high specificity points was equal to 85.6 % and specificity was 95.1 %.

2- Multiple-classification

MIL-VT is a similar model to MIL that uses the same approach as Vanilla ViT^{72, 73}. Using the APTOS dataset, 85.5 % accuracy was reached in the DR image classifying. The elite of this proposed model achieved higher accuracy

compared to GREEN-SE-ResNext50.

Recent advances and the use of AI algorithms in ophthalmology have provided more accessible access to screening systems that lead to more accessible and more accurate diagnosis, and classification of DR. Of course, inexpensive smartphone-based fundus cameras such as DIYretcam, T3retcam, MIIretcam, JaizRetcam, and Hopescope provide rapid image analysis⁷⁴. Thus, in a study conducted by Sosale et al., Medios AI evaluated the Remidio Fundus phone. The sensitivity and specificity for it were higher than 92 %⁷⁴.

Conclusion

In this article, 23 papers have been investigated to review the proposed methods for diagnosing Diabetic Retinopathy in the early stages. 13 articles related to supervised methods, six articles for self-supervised methods, and four selected papers suggested methods with transformers reviewed. This article lets researchers be aware of the advances in Artificial Intelligence algorithms for Diabetic Retinopathy detection.

Since Machine Learning and Deep Learning methods have entered the mainstream of medicine, Diabetic Retinopathy can be diagnosed in the early stages using these techniques. This way, the statistics of blindness and vision loss caused by Diabetic Retinopathy going to reduce. According to the studies, the proposed models for transformers provide better interpretability for doctors and researchers. In addition, more rigorous scientific evidence on safety, validity, usability, patient, and physician satisfaction is necessary before using AI-based systems. On the other hand, AI algorithms are valuable in anticipating future health consequences after evaluating former cases of the ailment. In ophthalmology, the reliable prophecy of visual

issues assists physicians in ailment counseling and clinical administration while reducing healthcare costs. But there are still questions regarding using these systems in medicine and ophthalmology. For instance, if a patient is misdiagnosed using AI-based technologies,

who will be responsible? Therefore, future research should try to address such questions.

Authors ORCIDs

Zahra Alaeddini:

 <https://orcid.org/0000-0001-6436-9286>

References

1. Kharroubi AT. Diabetes mellitus: The epidemic of the century. *World J Diabetes*. 2015;6(6):850.
2. Thrall JH, Li X, Li Q, Cruz C, Do S, Dreyer K, et al. Artificial Intelligence and Machine Learning in Radiology: Opportunities, Challenges, Pitfalls, and Criteria for Success. *J Am Coll Radiol*. 2018;15(3 Pt B):504–8.
3. Li C, Hou L, Sharma BY, Li H, Chen CS, Li Y, et al. Developing a new intelligent system for the diagnosis of tuberculous pleural effusion. *Comput Methods Programs Biomed*. 2018;153:211–25.
4. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 2017 542:7639. 2017;542(7639):115–8.
5. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart*. 2018;104(14):1156–64.
6. Nemati S, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU. *Crit Care Med*. 2018;46(4):547–53.
7. Havaei M, Davy A, Warde-Farley D, Biard A, Courville A, Bengio Y, et al. Brain tumor segmentation with Deep Neural Networks. *Med Image Anal*. 2017;35:18–31.
8. Murugesan N, Üstunkaya T, Feener EP. Thrombosis and Hemorrhage in Diabetic Retinopathy: A Perspective from an Inflammatory Standpoint. Vol. 41, *Seminars in Thrombosis and Hemostasis*. Thieme Medical Publishers, Inc.; 2015. p. 659–64.
9. Vora P, Shrestha S. Detecting Diabetic Retinopathy Using Embedded Computer Vision. *Applied Sciences*. 2020;10(20):7274.
10. Mamtora S, Wong Y, Bell D, Sandinha T. Bilateral Birdshot Retinochoroiditis and Retinal Astrocytoma. *Case Rep Ophthalmol Med*. 2017;2017:1–4.
11. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. Vol. 125, *Ophthalmology*. Elsevier Inc.; 2018. p. 1608–22.
12. 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(9):1410–20.
13. Kermany DS, Goldbaum M, Cai W, Valentim CCS, Liang H, Baxter SL, et al.

- Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. *Cell*. 2018;172(5):1122–31.
14. de Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med*. 2018;24(9):1342–50.
 15. 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(11):1170–6.
 16. Zhang Y, Jin JL, Yan P, Tang J, Fang SX, Lin WL, et al. Long-term variations of major atmospheric compositions observed at the background stations in three key areas of China. *Advances in Climate Change Research*. 2020;11(4):370–80.
 17. Ting DSW, Cheung CYL, 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(22):2211–23.
 18. Gargeya R, Leng T. Automated Identification of Diabetic Retinopathy Using Deep Learning. *Ophthalmology*. 2017;124(7):962–9.
 19. 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(22):2402–10.
 20. Ruamviboonsuk P, Tiwari R, Sayres R, Nganthavee V, Hemarat K, Kongprayoon A, et al. Real-time diabetic retinopathy screening by deep learning in a multisite national screening programme: a prospective interventional cohort study. *Lancet Digit Health*. 2022;4(4):e235–44.
 21. Yuan A, Lee AY. Artificial intelligence deployment in diabetic retinopathy: the last step of the translation continuum. *Lancet Digit Health*. 2022;4(4):e208–9.
 22. Ramasamy R, Vannucci SJ, Yan SS du, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. *Glycobiology*. 2005;15(7).
 23. Miyamoto K, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. *Proc Natl Acad Sci U S A*. 1999;96(19):10836–41.
 24. al Hazaimeh OM, Nahar KMO, al Naami B, Gharaibeh N. An effective image processing method for detection of diabetic retinopathy diseases from retinal fundus images. *International Journal of Signal and Imaging Systems Engineering*. 2018;11(4):206.
 25. Fujita H, Uchiyama Y, Nakagawa T, Fukuoka D, Hatanaka Y, Hara T, et al. Computer-aided diagnosis: The emerging of three CAD systems induced by Japanese health care needs. *Comput Methods Programs Biomed*. 2008;92(3):238–48.
 26. Silva C, Bouwmans T, Frélicot C. An extended center-symmetric local binary pattern for background modeling and subtraction in videos. In: *VISAPP 2015 - 10th International Conference on Computer Vision Theory and Applications; VISIGRAPP, Proceedings*. SciTePress; 2015. p. 395–402.
 27. Sikorski BL, Malukiewicz G, Stafiej J, Lesiewska-Junk H, Raczynska D. The diagnostic function of OCT in diabetic maculopathy. *Mediators Inflamm*. 2013;2013.
 28. World Health Organization. World report on vision. Vol. 214, World health Organisation.

- 2013.
29. Vora P, Shrestha S. Detecting Diabetic Retinopathy Using Embedded Computer Vision. *Applied Sciences*. 2020;10(20):7274.
 30. 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. *Nature Communications* 2020 11:1. 2020;11(1):1–8.
 31. Patel VL, Shortliffe EH, Stefanelli M, Szolovits P, Berthold MR, Bellazzi R, et al. The coming of age of artificial intelligence in medicine. *Artif Intell Med*. 2009;46(1):5–17.
 32. Poplin R, Varadarajan A v., Blumer K, Liu Y, McConnell M v., Corrado GS, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng*. 2018;2(3):158–64.
 33. Lecun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015 521:7553. 2015;521(7553):436–44.
 34. Lee CS, Tying 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(7):3440.
 35. Ahmed E, Jones M, Marks TK. An improved deep learning architecture for person re-identification. *Proceedings of the IEEE Computer Society Conference on Computer Vision and Pattern Recognition*. 2015;07-12-June-2015:3908–16.
 36. Khan P, Kader MF, Islam SMR, Rahman AB, Kamal MS, Toha MU, et al. Machine Learning and Deep Learning Approaches for Brain Disease Diagnosis: Principles and Recent Advances. *IEEE Access*. 2021;9:37622–55.
 37. Mahmud M, Kaiser MS, Hussain A, Vassanelli S. Applications of Deep Learning and Reinforcement Learning to Biological Data. *IEEE Trans Neural Netw Learn Syst*. 2018 Jun 1;29(6):2063–79.
 38. Decencière E, Zhang X, Cazuguel G, Laÿ B, Cochener B, Trone C, et al. FEEDBACK ON A PUBLICLY DISTRIBUTED IMAGE DATABASE: THE MESSIDOR DATABASE. *Image Analysis & Stereology*. 2014;33(3):231–4.
 39. Porwal P, Pachade S, Kamble R, Kokare M, Deshmukh G, Sahasrabuddhe V, et al. Indian diabetic retinopathy image dataset (IDRiD): a database for diabetic retinopathy screening research. *Data*. 2018;3(3):25.
 40. Taher Azar A, El-Bendary N, Ella Hassaanien A, Ella Hassanien A. Ant Colony based Feature Selection Heuristics for Retinal Vessel Segmentation. 2014;1–10.
 41. Kauppi T, Kalesnykiene V, Kamarainen JK, Lensu L, Sorri I, Raninen A, et al. The DIARETDB1 diabetic retinopathy database and evaluation protocol. *BMVC 2007 - Proceedings of the British Machine Vision Conference 2007*.
 42. Kauppi T, Kalesnykiene V, Kamarainen J-K, Lensu L, Sorri I, Uusitalo H, et al. DIARETDB0: Evaluation database and methodology for diabetic retinopathy algorithms. *Machine Vision and Pattern Recognition Research Group, Lappeenranta University of Technology, Finland*. 2006;73:1–17.
 43. Introduction-竞赛简介 - Grand Challenge. Available from: <https://odir2019.grand-challenge.org/>
 44. Li T, Gao Y, Wang K, Guo S, Liu H, Kang H. Diagnostic assessment of deep learning algorithms for diabetic retinopathy screening. *Inf Sci (N Y)*. 2019;501:511–22.
 45. The STARE Project. Available from: <https://cecas.clemson.edu/~ahoover/stare/>
 46. Diabetic Retinopathy Detection | Kaggle. Available from: <https://www.kaggle.com/c/>



- diabetic-retinopathy-detection
47. APTOS 2019 Blindness Detection | Kaggle. Available from: <https://www.kaggle.com/c/aptos2019-blindness-detection>
 48. Schmidhuber J. Deep Learning in neural networks: An overview. Vol. 61, Neural Networks. Elsevier Ltd; 2015. p. 85–117.
 49. Nadif M, Role F. Unsupervised and self-supervised deep learning approaches for biomedical text mining. *Brief Bioinform.* 2021;22(2):1592–603.
 50. Tay Y, Dehghani M, Bahri D, Metzler D. Efficient transformers: A survey. *ACM Computing Surveys (CSUR).* 2020.
 51. Pao SI, Lin HZ, Chien KH, Tai MC, Chen JT, Lin GM. Detection of Diabetic Retinopathy Using Bichannel Convolutional Neural Network. *J Ophthalmol.* 2020.
 52. Hua C-H, Huynh-The T, Lee S, editors. Retinal vessel segmentation using round-wise features aggregation on bracket-shaped convolutional neural networks. 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2019: IEEE.
 53. Pragathi P, Nagaraja Rao A. An effective integrated machine learning approach for detecting diabetic retinopathy. *Open Computer Science.* 2022;12(1):83–91
 54. Garcia Nespolo R, Yi D, Cole E, Valikodath N, Luciano C, Leiderman YI. Evaluation of Artificial Intelligence–Based Intraoperative Guidance Tools for Phacoemulsification Cataract Surgery. *JAMA Ophthalmol.* 2022;140(2):170–7.
 55. Zago GT, Andreão RV, Dorizzi B, Teatini Salles EO. Diabetic retinopathy detection using red lesion localization and convolutional neural networks. *Comput Biol Med.* 2020;116.
 56. Simonyan K, Zisserman A. Very Deep Convolutional Networks for Large-Scale Image Recognition. 3rd International Conference on Learning Representations, ICLR 2015 - Conference Track Proceedings. 2014.
 57. Prabha S, Reddy MA, Sreehari M, Sankaran KS. Machine Learning Technique for Analysing the Diabetic Retinopathy. In: International Conference on Sustainable Computing and Data Communication Systems, ICSCDS 2022 - Proceedings. Institute of Electrical and Electronics Engineers Inc.; 2022. p. 54–8.
 58. Keel S, Wu J, Lee PY, Scheetz J, He M. Visualizing Deep Learning Models for the Detection of Referable Diabetic Retinopathy and Glaucoma. *JAMA Ophthalmol.* 2019;137(3):288–92.
 59. Li Z, Keel S, Liu C, He Y, Meng W, Scheetz J, et al. An Automated Grading System for Detection of Vision-Threatening Referable Diabetic Retinopathy on the Basis of Color Fundus Photographs. *Diabetes Care.* 2018;41(12):2509–16.
 60. Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *npj Digital Medicine* 2018 1:1. 2018;1(1):1–8.
 61. Abramoff 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(13):5200–6.
 62. Li W, Yang Y, Zhang K, Long E, He L, Zhang L, et al. Dense anatomical annotation of slit-lamp images improves the performance of deep learning for the diagnosis of ophthalmic disorders. *Nat Biomed Eng.* 2020;4(8):767–77.
 63. Dota A, Sakamoto A, Nagano T, Murakami T, Matsugi T. Effect of diquafosol ophthalmic solution on airflow-induced ocular surface disorder in diabetic rats. *Clinical*

- Ophthalmology. 2020;14:1019–24.
64. Xu K, Feng D, Mi H. Deep Convolutional Neural Network-Based Early Automated Detection of Diabetic Retinopathy Using Fundus Image. *Molecules*.;22(12).
 65. Luo Y, Pan J, Fan S, Du Z, Zhang G. Retinal Image Classification by Self-Supervised Fuzzy Clustering Network. *IEEE Access*. 2020;8:92352–62.
 66. Kanagasingam Y, Xiao D, Vignarajan J, Preetham A, Tay-Kearney ML, Mehrotra A. Evaluation of Artificial Intelligence-Based Grading of Diabetic Retinopathy in Primary Care. *JAMA Netw Open*. 2018;1(5):e182665–e182665.
 67. He A, Li T, Li N, Wang K, Fu H. CABNet: Category Attention Block for Imbalanced Diabetic Retinopathy Grading. *IEEE Trans Med Imaging*. 2021;40(1):143–53.
 68. Hemanth DJ, Anitha J, Son LH, Mittal M. Diabetic Retinopathy Diagnosis from Retinal Images Using Modified Hopfield Neural Network. *Journal of Medical Systems* 2018 42:12. 2018;42(12):1–6.
 69. Panwar A, Semwal G, Goel S, Gupta S. Stratification of the Lesions in Color Fundus Images of Diabetic Retinopathy Patients Using Deep Learning Models and Machine Learning Classifiers. In: *Lecture Notes in Electrical Engineering*. Springer Science and Business Media Deutschland GmbH; 2022. p. 653–66.
 70. CVPR 2021 Open Access Repository. Available from: https://openaccess.thecvf.com/content/CVPR2021/html/Sun_Lesion-Aware_Transformers_for_Diabetic_Retinopathy_Grading_CVPR_2021_paper.html
 71. Papadopoulos A, Topouzis F, Delopoulos A. An Interpretable Multiple-Instance Approach for the Detection of referable Diabetic Retinopathy from Fundus Images. *Sci Rep*. 2021;11(1).
 72. Dosovitskiy A, Beyer L, Kolesnikov A, Weissenborn D, Zhai X, Unterthiner T, et al. An image is worth 16x16 words: Transformers for image recognition at scale. *arXiv preprint arXiv:2010.11929*. 2020. Available from: <http://arxiv.org/abs/2010.11929>
 73. Yu S, Ma K, Bi Q, Bian C, Ning M, He N, et al., editors. *Mil-vt: Multiple instance learning enhanced vision transformer for fundus image classification*. *International Conference on Medical Image Computing and Computer-Assisted Intervention*; 2021: Springer.
 74. Li D, Zhang L, Sun C, Yin T, Liu C, Yang J. Robust Retinal Image Enhancement via Dual-Tree Complex Wavelet Transform and Morphology-Based Method. *IEEE Access*. 2019;7:47303–16.

Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.

Abbreviations

DR: Diabetic Retinopathy
 AI: Artificial intelligence
 ML: Machine Learning
 DL: Deep Learning
 VA: Visual Acuity
 IoP: Intraocular Pressure
 AMD: Age-related Macular Degeneration
 OCT: Optical Coherence Tomography
 NPDR: Non-Proliferative Diabetic Retinopathy
 PDR: Proliferative Diabetic Retinopathy
 NN: Neural Network
 SVM: Support Vector Machine
 RF: Random Forest
 LR: Logistic Regression
 DT: Decision Tree
 NB: Naïve Bayes



KNN: K-Nearest Neighbor

RNN: Recurrent Neural Network

CNN: Convolutional Neural Network

BM: Boltzmann Machine

AE: AutoEncoder

DBN: Deep Belief Network

PCA: Principal Component Analysis

AUROC: Area Under the Receiver Operating
characteristic Curve

AUC: Area Under Curve