



The role of artificial intelligence in the diagnosis of diabetic retinopathy through retinal lesion features: a narrative review

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Background and Objective: In the field of ophthalmology, diabetic retinopathy (DR) is a diabetes-related eye condition that damages the retina. DR is a serious issue for working-age people and it is important to solve it at an early stage to avoid complete vision loss. The review covers together technical and clinical perspectives of using the artificial intelligence (AI)-based systems in clinical institutes to help the ophthalmologists interpret and diagnose DR at the early stages.

Methods: AI plays a significant role in assisting ophthalmologists with timely and effective treatment of patients by early and accurate detection and classification of DR. The study selection method followed specified searching criteria to complete the data collection task in the area of DR screening through AI.

Key Content and Findings: The review covers literature published in the nearest one decade or more for analyzing automated DR diagnostics through the identification of retinal lesions and evaluates the approaches of advanced AI-based models for the development of early and accurate DR diagnostic processes. The DR-related datasets and performance evaluation metrics used for segmentation and classification tasks of DR, are also included in this review. Moreover, the authors performed critical analysis and provided possible solutions against DR-based potential problems.

Conclusions: Hence, the study serves as a helping guide for the researchers to utilize their skills with advanced AI-based approaches in the technical and clinical perspectives of DR diagnostics. In conclusion, a freely available repository is created to facilitate the relevant researchers with up-to-date articles and open-source implementations for DR screening at <https://github.com/muhammadmateen319/progress-of-diabetic-retinopathy-screening>.

Keywords: Artificial intelligence (AI); diabetic retinopathy (DR); meta learning; multimodality; explainable AI (XAI)

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Introduction

According to the World Health Organization (WHO), diabetic retinopathy (DR) is a common complication of diabetes (1) and is the leading cause of blindness in working-age adults. When the blood sugar level increases in the body, the blood vessels are damaged in the retina, located in the backside of the eye. This damage can cause blood vessels to leak fluid or bleed, leading to swelling and distortion of the retina (2). Diabetic patients can have a risk of developing DR, and the risk increases with the duration of diabetes. The risk of developing DR can also be influenced by factors such as, high cholesterol, high blood pressure, poor blood sugar control, and smoking (3).

DR can be classified into two types: non-proliferative DR (NPDR) and proliferative DR (PDR). NPDR is the early stage of the disease and is characterized by the presence of small, dilated blood vessels in the retina, as well as tiny deposits of fluid or blood. PDR, on the other hand, is a more advanced stage and is characterized by the growth of new, abnormal blood vessels in the retina (4). If left untreated, DR can lead to complete vision loss. However, due to accurate and early identification and treatment of DR, the risk of blindness can be greatly reduced. Treatment options include laser surgery to seal leaking blood vessels and injections of medication to stop the growth of abnormal blood vessels. People with diabetes should have regular eye examinations to monitor for the development of DR (5). Automatic retina screening is highly recommended not only to save manual tasks because the cost of manual tasks is very high and time-consuming, but also to scale up the tasks (6). In addition, non-invasive procedure for DR screening is more suitable, because most of the patients are above 45 years of age. According to medical researchers and ophthalmologists, fundus scans are a comfortable and non-invasive technique that optometrists use during DR screening. There are different parameters and retinal abnormalities that indicate DR, namely as neovascularization, hemorrhages, microaneurysms, cotton wool spots, and exudates, are examined for the screening of DR (7). *Figure 1* shows the difference between normal retina and DR (8).

According to the international clinical DR (ICDR), a standardized scaling protocol mostly used for DR grading including proliferative, severe, moderate, mild, and normal, and also for clinical scales. Most artificial intelligence (AI)-based approaches used ICDR for the classification and grading of DR (9). In general, DR is

subdivided into two main categories which are NPDR and PDR. The non-proliferative is also divided into severe, moderate, and mild NPDR (10). The details of benchmark features for DR are provided in *Table 1* (11). The outflow of the blood vessels into the retinal part is considered an abnormal feature of DR represented as NPDR and there is an inflamed and wet condition at the end retina. The abnormal features of the retina include microaneurysms, exudates, and hemorrhage which can be found at the level of NPDR. The retinal hemorrhages are considered as blood dots presented on the retina. Similarly, exudates are also the basic cause of two types of DR, where hard retinal exudates are represented as yellow waxy spots, whereas soft retinal exudates are identified as the small size of white or yellow dots having distracted edges in the back side of the eye (12). Furthermore, microaneurysms are considered early symptoms of DR because of new abnormal retinal neovascularization. *Figure 2* represents the different levels of DR; the images taken from publicly available Indian diabetic retinopathy image dataset (IDRiD) (13).

Recently, the development of medical image processing has modernized the sectors of computer vision and healthcare. The improved level of medical imaging provides clinical experts with the supreme vision of human organs to help them with accurate diagnosis, which leads toward optimal and early treatment plans. The high-resolution images captured on both soft and hard tissue structures provide valuable insights (14). Medical image analysis helps resolve the clinical challenges through applying different kinds of image processing techniques to deliver the detailed analysis of medical scans, supporting applications in diagnosis, treatment, and patient monitoring. The general process of medical image analysis based on different stages includes image preprocessing involving image de-noising, image enhancement and color space transformation, while image segmentation is for detect boundaries and objects, whereas feature extraction stage is to capture or extract the meaningful information from the images and image classification stage is used to classify different levels of disease or to handle the grading tasks of medical imaging based challenges (15).

Artificial intelligence (AI) has the potential to solve the problems of ophthalmology including screening in resource-limiting regions, and rising eye care costs (16) by providing accurate and efficient diagnoses with telemedicine, remote care and reduced cost, personalized treatment plans, and better patient outcomes. Particularly, AI-enabled models integrate various machine learning (ML) and

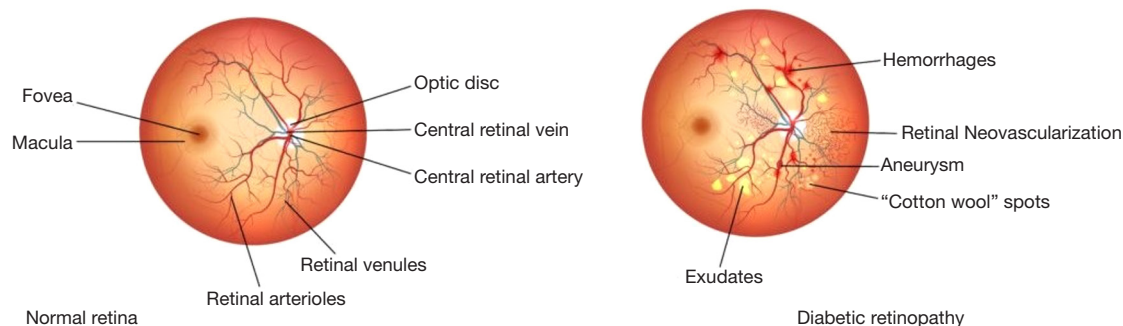


Figure 1 Normal retina and DR. The image was reproduced as-is, and was originally published under the Creative Commons Attribution 4.0 International (CC BY) license [Mateen *et al.* 2018 (8)]. DR, diabetic retinopathy.

Table 1 The standard lesion features of DR for ICDR scaling

Standard features of DR	ICDR scaling
Neovascularization (new vessels); vitreous/pre-retinal hemorrhage	PDR
More than 20 intra-retinal hemorrhages in all four quadrants; definite venous beading in two or more quadrants; prominent intra-retinal micro-vascular abnormality in one or more quadrants; no signs of PDR	Severe NPDR
Number of signs of micro-aneurysms, dot or blot hemorrhages, and HEs or cotton wool spots, no signs of severe NPDR	Moderate NPDR
The basic signs of retinal micro-aneurysms	Mild NPDR
No abnormalities	No DR

DR, diabetic retinopathy; HE, hard exudate; ICDR, international clinical DR; NPDR, non-proliferative DR; PDR, proliferative DR.

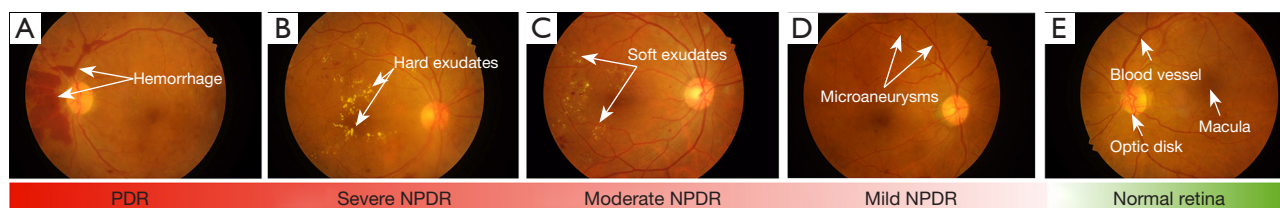


Figure 2 Normal retina and different stages of DR with retinal lesion features; samples are taken from publicly available IDRiD dataset (13). Source: <https://ieee-dataport.org/open-access/indian-diabetic-retinopathy-image-dataset-idrid>. DR, diabetic retinopathy; IDRiD, Indian diabetic retinopathy image dataset; NPDR, non-proliferative DR; PDR, proliferative DR.

deep learning (DL) algorithms to enhance the efficacy of system architectures deployed commercially for detecting DR disease (17). AI-based algorithms can be used for the analysis of retinal images for early and accurate detection of DR to help ophthalmologists for timely treatment of the disease. Furthermore, AI can help to accelerate the discovery of new drugs for ophthalmic diseases by analyzing large datasets and predicting the efficacy of potential drug

candidates (18). In DR management, early detection and timely treatment can reduce the level of DR. Currently, AI performing a significant role along with advanced approaches of ML and DL to empower the systems for DR screening in an accurate manner. The automated DR detection (19) approaches can reduce the cost and effort, as well as providing more effective way of DR diagnosis than traditional schemes (20). Generally, there are three

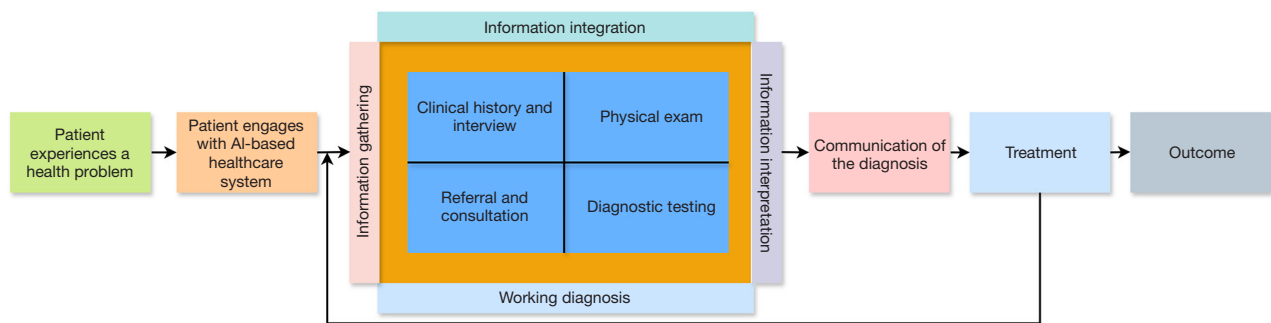


Figure 3 The basic concept of DR diagnostic process. AI, artificial intelligence; DR, diabetic retinopathy.

basic applications of AI applied through supervised learning mechanisms, namely segmentation, classification, and prediction (21). Supervised learning-based segmentation is a machine-learning mechanism that can be used for the automated detection and segmentation of various features in DR images. This approach requires a dataset of labeled images, where each image is annotated with information about the location and boundaries of specific features, such as exudates, hemorrhages, and cotton wool spots. Whereas, supervised learning-based classification supports the automatic categorization of DR scans into different classes based on their severity. This approach requires a dataset of labeled images, where each image is annotated with information about its severity level, such as mild, moderate, or severe DR. Supervised learning-based prediction can be used for the prediction of DR progression in individual patients on the basis of their medical history and clinical data. This approach requires a dataset of labeled patient data, where each patient is classified into different categories based on their DR progression, such as stable, progressing, or advanced stages of the disease (21). The basic concept of the DR diagnostic process is presented in *Figure 3* (22).

The world's latest survey by the American Academy of Ophthalmology reported that 103.12 million adults are diagnosed with DR and this number could be increased to 160.50 million by 2045 (23). For early identification and better management of DR, AI-based methods are applied for retinal abnormality detection, but still, there is also a lot of AI potential that needs to be discovered with advanced DL approaches, because, AI with related techniques would take part in the eye care and treatment and a major contribution in healthcare business. As a result, there is a lot of interest in AI, due to lowering costs in healthcare and improvement in eye treatment. The review covers together technical and clinical perspectives of using the AI-based

systems in clinical institutes to help the ophthalmologists by interpreting and diagnosis of DR at the early stages. Furthermore, the key challenges of interpreting AI predictions in clinical settings and the potential for integrating explainable AI (XAI) approaches and clinical implications are covered to improve the acceptance and trust of ophthalmologists on AI applications. The review would also explain the importance of retinal multimodal imaging, datasets, AI-based approaches, and evaluation metrics to analyze the performance of the methodologies in the case of DR segmentation and classification. The main purpose of this review article is to help young research experts in the area of ophthalmology and AI for a better understanding of retinal issues and to continue their work to solve real-world problems. We present this article in accordance with the Narrative Review reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-24-1791/rc>).

The major contributions of the study are as follows:

- ❖ The detailed review covers more than one decade to analyze the automated DR diagnosis through retinal lesion features.
- ❖ The details of private and publicly available datasets used for DR segmentation, classification, and prediction are provided with possible accessibility and limitations concerning dataset size, diversity, and the generalizability of models are presented.
- ❖ A detailed review of traditional and advanced AI-based approaches for DR segmentation, classification, and prediction has been incorporated with comparative analysis to identify the particular gaps in existing studies.
- ❖ AI-based DR segmentation, classification, and prediction approaches have been evaluated and various performance metrics are provided with descriptions

Table 2 The search strategy summary

Items	Specification
Date of search	May 25 th , 2024
Databases and other sources searched	Web of Science, Google Scholar, and PubMed
Search terms used	The keywords used to search the related information were included as DR, microaneurysms, exudates, retinal hemorrhage, neovascularization, ML, and advanced DL approaches
Timeframe	From 2015 to 2024
Inclusion criteria	Restricted to English articles
Selection process	D.X. and B.N. independently participated in the selection process of relevant studies and Tao Peng served as an arbitrator, the inclusion of studies carried out through the agreement of all three authors

DL, deep learning; DR, diabetic retinopathy; ML, machine learning.

- and formulas to guide the readers.
- ❖ Moreover, the authors performed critical analysis to understand the practical deployment challenges in diverse clinical settings and provided possible solutions to address the research problems regarding DR diagnostics.
 - ❖ Finally, a freely available repository is created to facilitate the researchers with relevant up-to-date articles and open-source implementations in the field of DR diagnosis at <https://github.com/muhammadmateen319/progress-of-diabetic-retinopathy-screening>.

Research methodology

This section is composed of the basic components of the DR diagnostic system, in the initial stage; we provided the details of DR-related datasets and the accessibility criteria. After that, AI-based methods related to the diagnosis of DR, collected through Web of Science, Google Scholar, and PubMed are evaluated and critical analysis of the existing studies is performed. In the next phase, performance evaluation metrics used in the diagnosis of DR, are presented with a description. The summary of the search strategy is presented in *Table 2*. The eligible criterion was fixed on the experimental and clinical outcomes of DR, including retinal lesion features. Moreover, ML and DL approaches for DR detection and classification. The keywords used to search the related information were included as DR, microaneurysms, exudates, retinal hemorrhage, neovascularization, ML, and advanced DL approaches. The extracted information taken from each

paper was saved in a separate document, where findings were related to experimental and clinical articles, datasets, methodologies, and outcomes of technical literature with evaluation metrics, while few studies contained insufficient information, so couldn't be accessed the complete version of those studies.

Datasets

The dataset is a basic component of the proposed framework used for the analysis of the specified task. The collection of data is the collection of records that preserve useful information, for example, medical or insurance records used by a specified system to complete the assigned task (24). There are several types of retinal imaging techniques used in ophthalmology to visualize the retina, and diagnose and monitor eye diseases. Multimodal retinal imaging can assist diagnostic approaches for more accurate detection of retinal abnormalities including DR (25). The applications of multimodal imaging are becoming more useful due to advanced AI-based disease diagnostic and retinal multimodal imaging techniques are invaluable tools for ophthalmologists in diagnosing and monitoring a wide range of eye diseases and can help improve patient outcomes and quality of life. An *et al.* (26) applied multimodal imaging to diagnose glaucoma with optical coherence tomography (OCT) and fundus scans retinal modalities. Whereas, Vaghefi *et al.* (27) achieved better accuracy using multimodal imaging with OCT and fundus scans to diagnose dry age-related macular degeneration (AMD). The details of the most common retinal imaging modalities are given and shown in *Figure 4*.

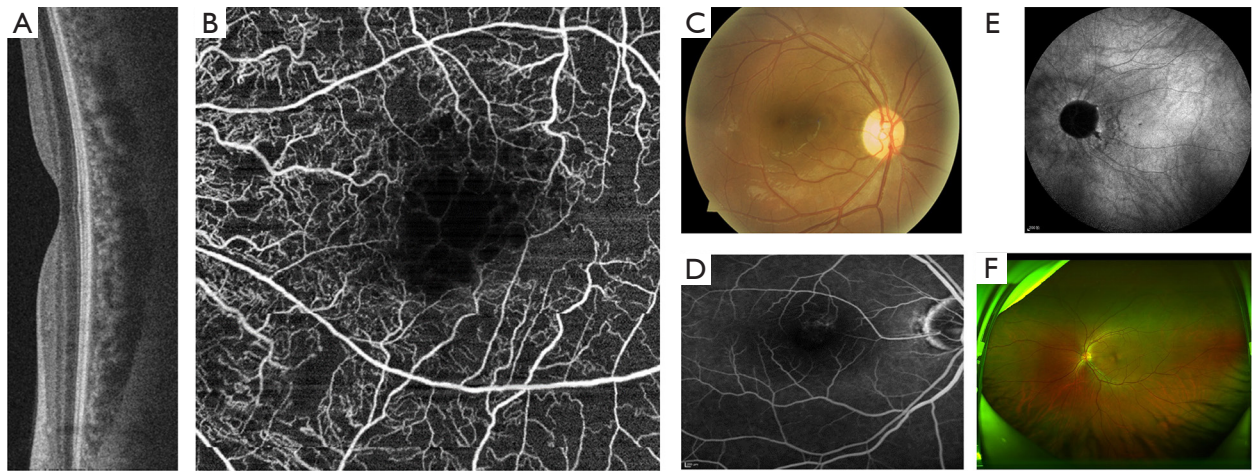


Figure 4 Retinal imaging modalities. (A) OCT scan, taken from our own private dataset, JSIEC of Shantou University and the Chinese University of Hong Kong, China; (B) OCTA scan, taken from our own private dataset, JSIEC of Shantou University and the Chinese University of Hong Kong, China; (C) fundus scan, taken from our own private dataset, He Eye Specialist Hospital, Liaoning province, China; (D) FA scan, taken from public dataset, APTOS Ophthalmology Society Big Data Competition 2023, available at (28). Source: <https://tianchialiyuncom/competition/entrance/532160>; (E) ICGA scan, taken from our own private dataset, Shanghai General Hospital, Shanghai, China; (F) LO scan, taken from the UWF4DR2024 Challenge public dataset, available at (29). Source: <https://codalablisnupsaclayfr/competitions/18605>. APTOS, Asia Pacific Tele-Ophthalmology Society; FA, fluorescein angiography; ICGA, indocyanine green angiography; JSIEC, Joint Shantou International Eye Center; LO, laser ophthalmoscopy; OCT, optical coherence tomography; OCTA, OCT angiography.

OCT is a non-invasive imaging method that creates high-resolution photographs of the retina. It is mostly used for the detection and monitoring the abnormal conditions such as diabetic macular edema (DME), macular degeneration, and glaucoma. OCT angiography (OCTA) is an emerging non-invasive imaging modality technique that has great potential to support the diagnosis of retinal vascular disease (30). Fundus photography (FP) is also a familiar technique that uses a specialized camera to take high-resolution color images of the retina. These images can provide a detailed view of the retina and are useful for diagnosing and monitoring abnormal conditions of retinal detachment, DR, and macular degeneration, while, fluorescein angiography (FA) is a technique that involves injecting a fluorescent dye into a patient's arm and taking a series of photographs of retina. This technique is very useful for DR diagnosis. Indocyanine green angiography (ICGA) uses a tricarboyaninedye that is better suited for imaging deeper blood vessels and evaluating choroidal vasculature. It is particularly useful for diagnosing and monitoring conditions such as choroidal neovascularization (CNV) (31). Whereas, scanning laser ophthalmoscopy (SLO) is a technique that uses a laser beam to create high-resolution images of the retina. It is particularly useful for

macular degeneration and DR diagnosis (32). The datasets of DR contain information on various retinal modalities, including OCT and fundus scans mostly used for the analysis of DR. In the collection of datasets, it has come to know that most research experts used publicly available databases, which are available through specific sources. The datasets are generally split into training, and testing parts for the assessment of the proposed methodologies. In the training and testing of the proposed model, there are more important concerns or limitations need to be considered including size, diversity, and generalizability regarding datasets. Dataset size contains the basic significance while training and testing the model because insufficient data may lead towards overfitting of the model, where the model can perform well on training data, while fails to perform on external dataset. Moreover, small amount of datasets may not be able to cover sufficient variations regarding input features, which may lead to dropout the knowledge of the DL models.

The second concern of dataset is about the lack of diversity (population samples, cultural context) in the data, may lead towards the biased prediction. Furthermore, the trained model with narrow contexts would not be applicable to handle the real-world scenarios. The third important

concern about the selection of the dataset is to train the model with sufficient generalizability in the data. In the case of small amount of dataset use for training the model, resultant into overfitting, limited task transfer, and real-world failures due to non-generalizability in the data and it can be handled through increase the diversity feature in the datasets (33). For example, DRIVE dataset that contains only 40 scans is considered as the small dataset labeled and annotated with high quality, which outweighs the quantity. In the DR diagnosis, DRIVE is a well-known dataset towards the researchers to segment the retinal vessels as provided high quality and richness of annotations for segmentation tasks (34,35). Furthermore, Messidor-2 dataset is also a famous dataset containing 1,748 high-quality fundus images with wide range of DR severity used for DR classification, while having lack of lesion level annotation, limited diversity, and class imbalance problem. IDRiD dataset containing 516 fundus images for diverse tasks with comprehensive notations but having image quality variability (33).

The list of datasets with possible availability status of fundus and OCT modalities is given in *Table 3*, whereas *Figure 5* represents the citation ratio of datasets in the collection of existing studies.

AI-based diagnosis of DR through retinal lesion features

In the diagnosis of DR, AI has also utilized the features of retinal lesions and played an essential role in classifying the stages of DR and allowing timely treatment for the patients. Many AI-based approaches have been reported for the detection of DR based on retinal lesion features using different retinal imaging modalities. This section of the review focuses on the traditional and advanced AI-based approaches from the last decade in the area of DR segmentation and detection with the most relevant retinal lesion features including microaneurysms, exudates, hemorrhages, and neovascularization as shown in *Figure 6*.

Microaneurysms detection

In DR, microaneurysms are the micro spots and basic signs that appear at an early stage in fundus images. The main reason for microaneurysms is the leakage of blood vessels in the retina, in which are later shaped as red rounded spots. The identification of microaneurysms is a critical task because of their small size and difficulty to distinguish from the surface of the retina and is important to diagnosis at the early stage of DR (36). In the domain of ophthalmology, DR

is a main issue to address and various AI-based applications have been developed to diagnose the microaneurysms by identifying the red spots on the surface of retina. A few of them are going to be presented in this section to understand the development of AI for the analysis of DR. There are several classifiers have been applied for the classification of retinal abnormalities, where Lam *et al.* introduced an image patches-based lesion identification model using DL (37), where a dataset of 243 fundus images was used for the testing phase and examined by two eye medical experts. The Kaggle dataset was used as an input in the reported approach, which was further subdivided into retinal patches including retinal secularization, normal-appearing structures, exudates, hemorrhages, and microaneurysms. The convolutional neural network (CNN)-based approach was designed and applied for the identification and classification of lesions in five types. Furthermore, to identify the abnormality from retinal images, Chowdhury *et al.* (38) presented a new approach based on a random forest classifier (RFC) for accurate classification of red lesions and help the ophthalmologists. In the reported approach, ML and K-means clustering methodologies have been used to identify and classify retinal abnormalities. The classification performance of the reported approach was presented as the RFC classifier provided 93.58% of classification accuracy, which is comparatively better than 83.63% provided by Naïve Bayes. Similarly, to identify the red lesions, a new method has been introduced by Orlando *et al.* (39), using domain knowledge and DL approaches. The incorporation of handcrafted features learned from CNN had been performed in the reported approach to identify the red lesions and further for the classification of red lesions a RFC had been used. Moreover, an ML-based method was used to classify the DR through microaneurysm detection by Cao *et al.* (40). The reported approach also included principal component analysis (PCA) for the identification of microaneurysms in an appropriate manner. In this framework, data augmentation is performed and patches of 25×25 pixels were applied as input data for the identification of microaneurysms using fundus photographs. In the experimental phase, the DIARETDB1 dataset was used for the analysis of the presented approach, where PCA was used for dimensionality reduction, while random forest, support vector machine (SVM), and neural network were applied to perform the classification through the useful extracted features.

A few of them are going to be presented in *Table 4* to understand the development of AI for the analysis of DR.

Table 3 List of fundus and OCT imaging datasets

Sr.#	Database	Status		
		Freely available	On-demand	Not available
Fundus datasets				
1	DR1	√		
2	DR2	√		
3	ARIA	√		
4	FAZ	√		
5	CHASE-DB1	√		
6	Messidor	√		
7	Messidor-2		√	
8	DRIVE	√		
9	DIARETDB0	√		
10	STARE	√		
11	DIARETDB1	√		
12	ROC	√		
13	Kaggle	√		
14	E-Ophtha	√		
15	DRiDB		√	
16	AGAR300	√		
17	APTOS 2019 Blindness Detection	√		
18	Diabetic retinopathy detection	√		
19	IDRiD	√		
20	Diabetic retinopathy debrecen	√		
21	Retinal-lesions	√		
22	RFMiD	√		
23	FGADR	√		
24	Kaggle EyePACS	√		
25	DDR-dataset	√		
26	TMUMDH			√
27	Moorfields Eye Hospital			√
28	CLEOPATRA			√
29	JMU			√
30	SNDRSP			√
31	LECHC DR India			√
32	KMCM, India			√
33	Southwest Medical University			√
34	Rawalpindi Medical University, Pakistan			√
35	University of California			√
36	Silchar Medical College and Hospital			√
37	Aravind Eye Hospital, Coimbatore			√
38	2nd Affiliated Hospital, Eye Center at Zhejiang University			√
39	HUPM, Cádiz, Spain			√

Table 3 (continued)

Table 3 (continued)

Sr.#	Database	Status		
		Freely available	On-demand	Not available
OCT datasets				
1	BIOMISA	✓		
2	Dukes	✓		
3	OPTIMA cyst segmentation challenge		✓	
4	NEH	✓		
5	Mendeley (Kermany dataset)	✓		
6	Dukes2	✓		
7	Retinal OCT classification challenge		✓	
8	RETOUCH		✓	
9	OCTID		✓	
10	Zhang dataset	✓		
11	Rabbani	✓		
12	Diabetic retinopathy retinal OCT images	✓		
13	ROAD (OCT-A dataset)	✓		
14	University of Louisville Hospital (OCT data)			✓

AGAR, Agarwal; APTOS, Asia Pacific Tele-Ophthalmology Society; ARIA, automated retinal image analysis; BIOMISA, biomedical image and signal analysis; CHASE-DB1, child health and study England-database 1; CLEOPATRA, CLinical Evaluation Of Pertuzumab And TRAstuzumab; DDR, dataset for diabetic retinopathy; DIARETDB, diabetic retinopathy database; DR, diabetic retinopathy; DRiDB, diabetic retinopathy image database; DRIVE, digital retinal images for vessel extraction; E-Ophtha, ophthalmology; EyePACS, eye picture archive communication system; FAZ, foveal avascular zone; FGADR, fine-grained annotated diabetic retinography; HUPM, Hospital Universitario Puerta del Mar; IDRiD, Indian diabetic retinopathy image dataset; JMU, Jichi Medical University; KMCM, Kasturba Medical College, Manipal; LECHC, Lotus Eye Care Hospital Coimbatore; Messidor, methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology; NEH, Noor Eye Hospital; OCT, optical coherence tomography; OCT-A, OCT-angiography; OCTID, OCT image retinal database; OPTIMA, ophthalmic image analysis; RETOUCH, retinal OCT fluid challenge; RFMiD, retinal fundus multi-disease image dataset; ROC, retinopathy online challenge; ROAD, retinal OCT-A diabetic retinopathy; SDRSP, Singapore National Diabetic Retinopathy Screening Program; STARE, structured analysis of the retina; TMUMDH, Tianjin Medical University Metabolic Diseases Hospital.

It is notable that the highest result of microaneurysms detection in terms of sensitivity was reported 98.74% by Steffi and Sam Emmanuel (43) using ML-based resilient back-propagation approach, whereas specificity was presented 97.5% by Prasad *et al.* using segmentation and morphological operations (56).

Exudates detection

In the DR, exudates are also basic signs and serious retinal abnormality. There are two kinds of exudates, one is known as hard exudate (HE) and the other is called soft exudate (SE). The yellow waxy parts on the surface of the retina are known as HE whereas cotton wool spots can be considered as SE, which are white or light-yellow shape regions. The varieties of methodologies to identify the SE and HE are reported in this portion (57). Timely detection of exudate is very significant for better treatment and

recovery of the affected people of DR. In this way, a study is reported to diagnose retinal exudate using residual networks (ResNet-50) and SVM for better classification outcomes (58). The authors applied various kinds of CNN approaches and then finalized the comparatively better approach for the identification of exudates with an accuracy of 98%. Furthermore, for DR analysis, an exudate segmentation approach has been introduced by Kaur and Mittal (59) to assist the retinal experts for early diagnosis, and better treatment. The discussed approach applied a dynamic decision technique for an accurate and reliable way of exudate segmentation. The reported approach was a robust method with a choice of threshold values in a dynamic way. In the defined model, 1,307 retinal images were used as input with a diversity of shapes, colors, sizes, and locations. Furthermore, a new exudate identification technique based on deep CNNs was introduced by Prentašić and Lončarić (60).

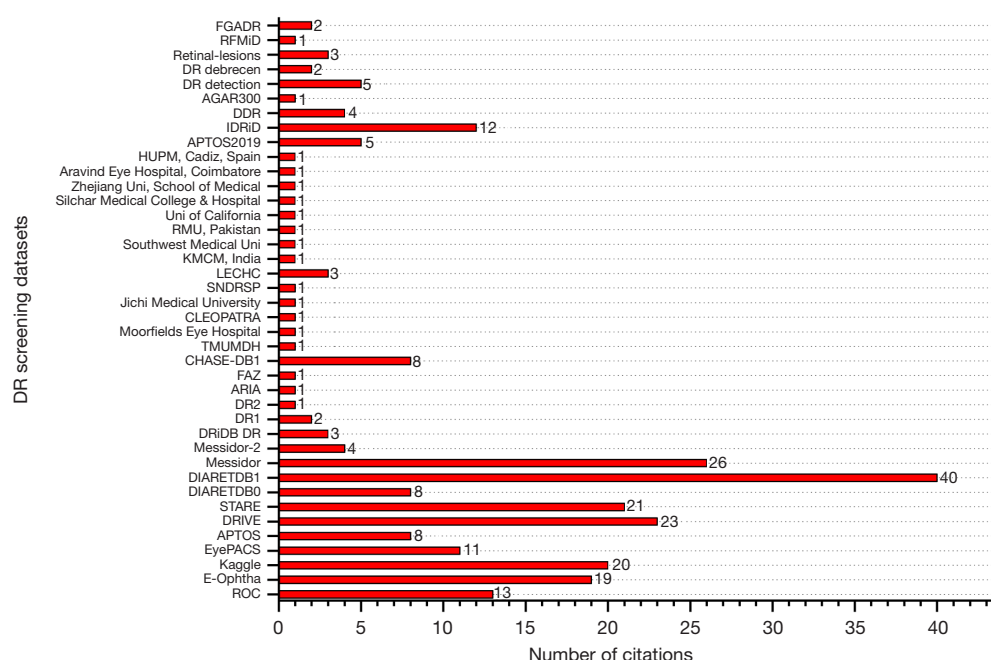


Figure 5 Dataset citations in the review. AGAR, Agarwal; APTOS, Asia Pacific Tele-Ophthalmology Society; ARIA, automated retinal image analysis; CHASE-DB1, child health and study England-database1; CLEOPATRA, CLinical Evaluation Of Pertuzumab And TRAstuzumab; DDR, dataset for diabetic retinopathy; DIARETDB, diabetic retinopathy database; DR, diabetic retinopathy; DRiDB, diabetic retinopathy image database; DRIVE, digital retinal images for vessel extraction; E-Ophtha, ophthalmology; EyePACS, eye picture archive communication system; FAZ, foveal avascular zone; FGADR, fine-grained annotated diabetic retinopathy; HUPM, Hospital Universitario Puerta del Mar; IDRiD, Indian diabetic retinopathy image dataset; KMCM, Kasturba Medical College, Manipal; LECHC, Lotus Eye Care Hospital Coimbatore; Messidor, methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology (in French); RFMID, retinal fundus multi-disease image dataset; RMU, Rawalpindi Medical University; ROC, retinopathy online challenge; SNDRSP, Singapore National Diabetic Retinopathy Screening Program; STARE, structured analysis of the retina; TMUMDH, Tianjin Medical University Metabolic Diseases Hospital; Uni, University.

Moreover, it is helpful to detect anatomical landmarks through DL approaches. The reported framework helps ophthalmologists for early detection of exudates using fundus images. A novel approach (61) has been designed to obtain information on hyper-reflective dots and HEs in OCT images for DME subjects. Bland Altman and dice coefficient were used for the evaluation of the developed approach designed for clinical practices. OCT and fundus photographs were used to detect and classify the DR and DME through two kinds of existing AI-based models, and model evaluation was performed via specificity and sensitivity (62). The relevant approaches of exudate detection are further discussed in *Table 5*. In the case of exudate detection, it is noteworthy that Thulker *et al.* (77) achieved the highest score of specificity as 97.1% using tree-based forward search approach, while achieved 100% score of sensitivity. Furthermore, the highest results of precision

with 84.03% and F1-score with 77% are achieved by Tang *et al.* (68) and Prentašić and Lončarić (78), respectively.

Hemorrhages detection

Retinal hemorrhage is considered a basic and severe cause of DR, which exists in retinal imaging. In this scenario, accurate and early diagnosis of retinal hemorrhage is extremely helpful and important in the process of timely recovery of affected persons. The retinal hemorrhages are basically present in the deep and shallow retina. In fundus photographs, bright red lesions are presented in the backside of the eye known as the shallow retina, whereas dark red lesions exist in the deep retinal part. The identification of retinal hemorrhages is performed through different kinds of approaches which are going to be discussed in this portion (79). Hemorrhage detection for DR was performed by Wu *et al.* (80), where a new method has been introduced

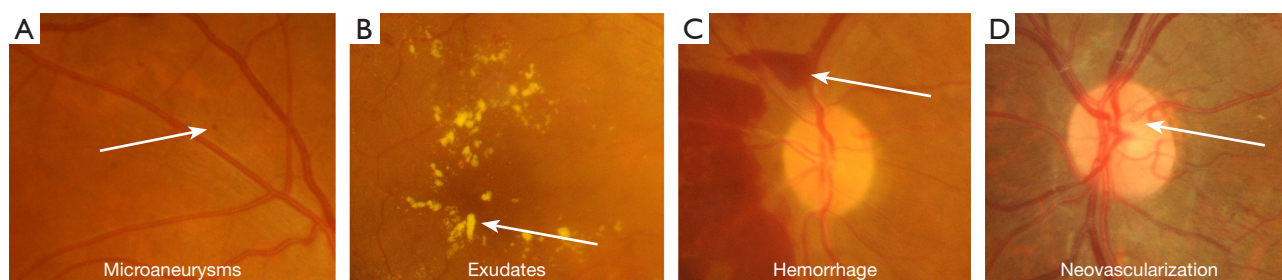


Figure 6 DR-based retinal lesions; samples are taken from publicly available IDRiD dataset (13). Source: <https://ieee-dataport.org/open-access/indian-diabetic-retinopathy-image-dataset-idrid>. (A) Microaneurysms (arrow); (B) exudates (arrow); (C) hemorrhage (arrow); and (D) neovascularization (arrow). DR, diabetic retinopathy; IDRiD, Indian diabetic retinopathy image dataset.

Table 4 Microaneurysms detection approaches

Year	Reference	Methodologies	Database	Results with evaluation metrics
2024	Jayachandran and Ratheesh Kumar (41)	Auto weight dilated with CNN used to learnable set of parameters	RIM-ONE-R1, ORIGA, Messidor	Accuracy: 98.76%, 98.95%, 99.28%
2024	Alotaibi (42)	CNN, Inception-V3, transfer learning, (MA-RTCNN-Inception-V3-EOA), equilibrium optimization algorithm	E-Ophtha	Sensitivity: 75.45%; specificity: 67.63%; accuracy: 82.61%; F-measure: 77.61%
2024	Steffi and Sam Emmanuel (43)	ML-based resilient back-propagation to detect shape and texture features	ROC, DIARETDB1, E-Ophtha-MA, Messidor	Specificity: 97.12%; sensitivity: 98.74%; accuracy: 98.01%; AUC: 91.72%
2023	Alam <i>et al.</i> (44)	Fully CNN enhances approach, a modified GoogLeNet architecture	Kaggle, EyePACS	Mean accuracy: 87.71%
2023	Nunez do Rio <i>et al.</i> (45)	DLS, ResNet34 architectures, image preprocessing through subtraction of local average color, normalizing	SM1, SM2	Sensitivity: 93.86%; specificity: 96.00%
2022	Du <i>et al.</i> (46)	Multi-context ensemble learning and TS	ROC, DIARETDB1, E-Ophtha-MA	FROC: 0.306, 0.429, 0.518
2022	Hervella <i>et al.</i> (47)	Generative adversarial networks, adversarial multimodal reconstruction	DDR, ROC, E-Ophtha	Average precision: 33.55%, 31.36%, 64.90%
2022	Deng <i>et al.</i> (48)	LSAMFC, ring gradient descriptor, gradient boosting decision tree	E-Ophtha-MA, ROC	AUC: 0.9751, 0.9409
2021	Ayala <i>et al.</i> (49)	CNN model, DenseNet121 model having three dense-blocks	Kaggle, APTOS, Messidor	Accuracy: 97.78%
2021	Zhang <i>et al.</i> (50)	Feature-distance-based algorithm, feature-transfer network	ROC, DB1, E-Ophtha-MA, RetinaCheck	Sensitivity: 98.3%, 100%, 99.3%, 100%, 96.5%
2021	Dai <i>et al.</i> (51)	DeepDR system, ResNet, mask RCNN, sub networks for assessment of image quality, lesion awareness, and DR grading	SIM cohort	AUC: 90.1%
2020	Deepa and Narayanan (52)	Feed forward neural networks	DIARETDB1	Accuracy: 98.89%

Table 4 (continued)

Table 4 (continued)

Year	Reference	Methodologies	Database	Results with evaluation metrics
2020	Du <i>et al.</i> (53)	LCT, under sampling boosting based classifier	ROC, DIARETDB1, E-Ophtha-MA	FROC: 0.293, 0.402, 0.516
2019	Mateen <i>et al.</i> (8)	VGG-19, SVD, and PCA	Kaggle	Accuracy: 98.34%
2018	Lam <i>et al.</i> (37)	Standard five CNN models include Inception-V3, ResNet, GoogLeNet, AlexNet	E-Ophtha	AUC: 95%
2017	Gondal <i>et al.</i> (54)	CNNs for generate the class activation mappings	DIARETDB1	AUC: 95.4%
2016	Paing <i>et al.</i> (55)	Artificial neural networks and ROI localization	DIARETDB1	Accuracy: 96%
2015	Prasad <i>et al.</i> (56)	Segmentation approaches, morphological operations, one rule and BPNN classifier algorithms	DIARETDB1	Specificity: 97.5%; AUC: 97%; accuracy: 97.75%; sensitivity: 97.8%

AUC, area under the curve; APTOS, Asia Pacific Tele-Ophthalmology Society; BPNN, back-propagation neural network; CNN, convolutional neural network; DB, database; DDR, dataset for diabetic retinopathy; DIARETDB, diabetic retinopathy database; DLS, deep learning system; DR, diabetic retinopathy; E-Ophtha, ophthalmology; EOA, equilibrium optimization algorithm; EyePACS, eye picture archive communication system; FROC, free response operating characteristic; LCT, local cross-section transformation; LSAMFC, local structure awareness-based multi-feature combination; MA, microaneurysms; MA-RTCNN, micro aneurysm detection using residual-based temporal attention convolutional neural network; Messidor, methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology; ML, machine learning; ORIGA, online retinal fundus image database for glaucoma analysis and research; PCA, principal component analysis; RCNN, residual-based convolutional neural network; RIM-ONE-R1, retinal image database for optic nerve evaluation-release 1; ROC, retinopathy online challenge; ROI, region of interest; SIM, Shanghai Integrated Model; SM, SMART-India; SVD, singular value decomposition; TS, transformation splicing; VGG, visual geometry group.

with the combination of dual approaches. The hemorrhage classification was performed using background estimation and watershed segmentation approaches. Initially, the preprocessing approach was performed through an adaptive histogram of the retinal digital fundus photographs. In the next phase of the proposed methodology, feature extraction was initiated for the purpose of segmentation. Dual approaches were performed to visualize the feature extraction of retinal hemorrhages. At the last stage, visual features were used to obtain the accuracy of hemorrhage detection, which was observed as 95.42%. The traditional data augmentation approaches namely geometric and color transformations were used by Ayhan and Berens (81) for fundus image segmentation. The author used the DNN approach for the prediction of abnormalities Kaggle database to achieve comparatively better uncertain estimation. The retinal fundus image segmentation for hemorrhage detection was performed (82) with the help of the R-sGAN technique. The presented approach followed supervised learning for synthetic fundus photographs and

achieved comparatively better segmentation outcomes after the training process of the synthetic dataset. The authors (83) presented CNN's performance enhancement approach to overcome the experimental time of the whole part to analyze the fundus images. The identification, as well as classification process of hemorrhage in retinal images, was based on heuristical samples. Furthermore, a classification approach was introduced for the detection of hemorrhages (84). The authors used a supervised approach for the overlapping segmentation for partitions of retinal color images. The feature extraction process was done through each splat, which defines features towards its neighbors and used a filter-based wrapper technique for the interaction of neighbor splats. Maqsood *et al.* (85) proposed a novel approach to identify the retinal hemorrhage using fundus images. Initially, contrast enhancement approach performed to get the details of edges in fundus images. The remaining stages of the reported work were based on three-dimensional (3D) CNNs for feature extraction, feature fusion approach used to fuse the extracted features and then

Table 5 Exudates detection approaches

Year	Reference	Methods	Database	Results with evaluation metrics
2024	Van Do <i>et al.</i> (63)	Two-stage approach with CNN, VGGUnet, and RITM model	DDR, IDRiD	Mean Dice: 60.8%, 76.6%; mean IoU scores: 45.5%, 62.4%
2024	Guo <i>et al.</i> (64)	Deep multi-scale model, FCN for lesion segmentation	E-Ophtha, DDR, DIARETDB1, IDRiD	DSC: 69.31%; AUPR: 68.84%
2024	Maiti <i>et al.</i> (65)	Enriched encoder-decoder model with CLSTM and RES unit	DIARETDB0, Messidor, DIARETDB1, IDRiD	Overall accuracy: 97.7%; while accuracies of individual dataset respectively: 97.81%, 98.01%, 98.23%, 96.76%
2023	Farahat <i>et al.</i> (66)	U-Net and YOLOv5, Leaky ReLU	Cheikh Zaid Foundation's Ophthalmic Center	Specificity: 85%; sensitivity: 85%; accuracy: 99%
2024	Naik <i>et al.</i> (67)	DenseNet121	APTOS-2019	Accuracy: 96.64%
2023	Tang <i>et al.</i> (68)	Patch-wise density loss, global segmentation loss, discriminative edge inspection	IDRiD	Precision: 84.03%; recall: 65.14%; F1-score: 68.54
2022	Reddy and Gurralla (69)	Hybrid DLCNN-MGWO-VW, DSAM, and DDAM	IDRiD	Accuracy: 96.0%
2022	Hussain <i>et al.</i> (70)	YOLOv5M, classification-extraction-superimposition mechanism	EyePACS	Accuracy: 100%
2023	Sangeethaa and Jothamani (71)	Median filtering, CLAHE	Local dataset: Aravind Eye Hospital, Coimbatore	Accuracy: 95%
2021	Sudha and Ganeshbabu (72)	Deep neural network, VGG-19, gradient descent, structure tensor	Kaggle	Sensitivity: 82%; accuracy: 96%
2021	Cincan <i>et al.</i> (73)	GoogLeNet, SqueezeNet, and ResNet50 models	SUSTech_SYSU	Accuracy: 0.928%
2021	Kurilová <i>et al.</i> (74)	Faster R-CNN, ResNet-50, region proposed network	DIARETDB1, Messidor, E-Ophtha-EX	AUC: 97.27%, 88.5%, 100%
2020	Pan <i>et al.</i> (75)	ResNet50, VGG-16, DenseNet, multi-label classification	2nd Affiliated Hospital, Eye Center at Zhejiang University Hospital	AUC: 96.53%
2020	Theera-Umporn <i>et al.</i> (76)	Adaptive histogram equalization, hierarchical ANFIS, multilayer perceptron	DIARETDB1	AUC: 99.8%
2020	Thulkar <i>et al.</i> (77)	Tree-based forward search approach, SVM	DIARETDB1, IDRiD, IDEDD	Specificity: 97.1%; sensitivity: 100%
2019	Khojasteh <i>et al.</i> (58)	DRBM, ResNet-50, CNNs	E-Ophtha, DIARETDB1	Sensitivity: 99%; accuracy: 98%
2019	Chowdhury <i>et al.</i> (38)	Random forest and Naïve Bayes classifier approach	DIARETDB1, DIARETDB0	Accuracy: 93.58%
2018	Lamet <i>et al.</i> (37)	CNNs, AlexNet, GoogLeNet, VGG16, Inception-V3, ResNet	E-Ophtha	AUC: 95%
2017	Gondal <i>et al.</i> (54)	CNNs, for generate the class activation mappings	DIARETDB1	AUC: 95.4%
2016	Paing <i>et al.</i> (55)	Artificial neural networks, and ROI iocalization	DIARETDB1	Accuracy: 96%
2015	Prentašić and Lončarić (78)	Deep CNNs	DIARETDB1	PPV: 77%; sensitivity: 77%; F1-score: 77%

ANFIS, adaptive network-based fuzzy inference system; APTOS, Asia Pacific Tele-Ophthalmology Society; AUC, area under the curve; AUPR, area under the precision-recall curve; CLAHE, contrast-limited adaptive histogram equalization; CLSTM, contextual long-short term memory; CNN, convolutional neural network; DDAM, disease-dependent attention module; DLCNN, deep learning convolutional neural network; DRBM, discriminative restricted Boltzmann machine; DSC, dice similarity coefficient; DSAM, disease-specific attention module; DDR, dataset for diabetic retinopathy; DIARETDB, diabetic retinopathy database; E-Ophtha, ophthalmology; EX, exudates; EyePACS, eye picture archive communication system; FCN, fully convolutional network; IDEDD, Indian diabetic eye diseases dataset; IDRiD, Indian diabetic retinopathy image dataset; IoU, intersection over union; Messidor, methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology; MGWO, modified grey-wolf optimizer; PPV, positive predictive value; R-CNN, region-based convolutional neural network; ReLU, rectified linear unit; RES, residual extended skip; RITM, reviving iterative training with mask guidance; ROI, region of interest; SUS, Southern University of Science and Technology; SVM, support vector machine; SYSU, Sun Yat-sen university; VGG, visual geometry group; VW, variable weight; YOLOv5, you only look once version 5; YOLOv5M, you only look once version 5 medium.

Table 6 Hemorrhages detection approaches

Year	Reference	Methods	Database	Results with evaluation metrics
2024	Sathiyaseelan <i>et al.</i> (86)	Fast-CNN, modified U-Net, enhanced machine-based diagnostic	IDRiD, DIARETDB1	Specificity: 99.6%; sensitivity: 80%; accuracy: 98.6%
2024	Biju and Shanthi (87)	Enhanced visual geometry group model, data augmentation, Gabor transform, hemorrhages segmentation, and classification module	HRF, DIARETDB1	Specificity: 98.71%, 98.44%; sensitivity: 98.59%, 98.37%; accuracy: 98.66%, 98.74%
2024	Atlas <i>et al.</i> (88)	Maximally stable extremal regions approach, CNN, ELSTM, DPFE	DIARETDB2	Specificity: 98.91%; sensitivity: 98.67%
2023	Li <i>et al.</i> (89)	CNN, ResNet-50, customized computer vision algorithm	Local dataset: University of California	Specificity: 74.5%; sensitivity: 100%; F1-score: 0.932; accuracy: 90.7%
2023	Alwakid <i>et al.</i> (90)	CLAHE filtering approach and ESRGAN network, Inception-V3 model	APTOS datasets	Case1: accuracy: 98.7%; case 2: accuracy: 80.87%
2023	Saranya <i>et al.</i> (91)	CNN, U-Net, morphological operations	Messidor, STARE DIARETDB1, IDRiD	Specificity: 99%; sensitivity: 89%; accuracy: 95.65%
2023	Kiliçarslan (92)	ResNet-50, YOLOv5, and VGG-19	EyePACS	Accuracy: 93.38%, 94.75%, 91.72%
2022	Mondal <i>et al.</i> (93)	ResNeXt, DenseNet101, CLAHE	DIARETDB1, APTOS19	Accuracy: 96.98%; precision: 0.97; recall: 0.97
2023	Xia <i>et al.</i> (94)	MGNet, U-Net	IDRiD, DIARETDB1	Accuracy: 99.12%; sensitivity: 53.53%; specificity: 99.66%
2021	Goel <i>et al.</i> (95)	DL, transfer learning, VGG16	IDRiD	Accuracy: 91.8%; F1-score: 81.5%; precision: 81.5%
2022	Zhang <i>et al.</i> (96)	Inception-V3 model, class activation mapping	Kaggle	Sensitivity: 0.925; specificity: 0.907; harmonic mean: 0.916; AUC: 0.968
2020	Hacisoftaoglu <i>et al.</i> (97)	ResNet50, GoogLeNet, AlexNet models	Messidor-2, EyePACS, Messidor, IDRiD	Specificity: 99.1%; sensitivity: 98.2%; accuracy: 98.6%
2020	Li <i>et al.</i> (98)	DL system, inception ResNet-2	Local dataset: ZOC	Sensitivity: 97.6%; specificity: 99.4%; AUC: 99.9%
2019	Chowdhury <i>et al.</i> (38)	Classifier: random forest and Naïve Bayes classifier approach	Messidor, Tele-Ophtha, DIARETDB1, DIARETDB0	Accuracy: 93.58%
2018	Suriyal <i>et al.</i> (99)	DeepCNNs, MobileNets	Kaggle	Accuracy: 73.3%
2017	Gondal <i>et al.</i> (54)	CNNs, for generate the class activation	DIARETDB1	AUC: 95.4%
2016	Paing <i>et al.</i> (55)	Artificial neural networks, and ROI localization	DIARETDB1	Accuracy: 96%
2015	Guo <i>et al.</i> (100)	Multi-class discriminant analysis, wavelet transformation, and discrete cosine transformation	Real-world dataset	Accuracy: 90.9%

APTOS, Asia Pacific Tele-Ophthalmology Society; AUC, area under the curve; CLAHE, contrast limited adaptive histogram equalization; CNN, convolutional neural network; DIARETDB, diabetic retinopathy database; DL, deep learning; DPFE, double-pierced feature extraction; ELSTM, enhanced long short-term memory; ESRGAN, enhanced super-resolution generative adversarial network; EyePACS, eye picture archive communication system; HRF, high-resolution fundus; IDRiD, Indian diabetic retinopathy image dataset; Messidor, methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology; MGNet, multi-scale gated network; ROI, region of interest; STARE, structured analysis of the retina; VGG, visual geometry group; YOLOv5, you only look once version 5; ZOC, Zhongshan Ophthalmic Center.

best selective features through multi-logistic regression were used to detect the retinal hemorrhage. The reported work also focused on limitations found in the literature work including poor contrast, false hazard, disparate sizes of hemorrhage, and microaneurysms, and addressed the related issues with superior results and less computation time. The hemorrhage identification methods are discussed in *Table 6*. The traditional and advanced-based hemorrhage detection approaches are reported to compare the performances of the techniques by highlighting the obtained results of both trends. Guo *et al.* (100) used multi-class discriminant analysis and obtained 90.9% accuracy, while Sathiyaseelan *et al.* (86) achieved 98.6% accuracy using fast-CNN and modified U-Net architecture. Furthermore, the recent approach of Xia *et al.* (94) used multi-scale gated network (MGNet) with modified U-Net also achieved better results in terms of accuracy of 99.12%.

Neovascularization detection

The neovascularization detection and segmentation are the critical steps for the identification and diagnosis of DR to discriminate the blood vessels from neovascularization. Moreover, identification and segmentation of retinal blood vessels are also considered windows to diagnose brain and heart stroke, which abnormalities found through the vascular system of the retina. The segmentation of retinal blood vessels is more significant and helpful in the non-invasive fundus photograph modality (101). In the case of DR, noise removal and contrast improvement approaches were used by Sahu *et al.* (102) through digital color fundus images. The presented approach focused on resolving the de-noising and enhancement problems using different performance parameters namely correlation coefficient, structural similarity index, peak signal-to-noise ratio (PSNR), and edge preservation index. Moreover, Leopold *et al.* (103) performed better retinal segmentation based on various kinds of performance indicators. The Pixel BNN model was introduced by authors to perfume better segmentation of fundus images and the model evaluation is performed through CHASE_DB1, STARE, and DRIVE databases. The evaluation metrics namely F1-score were used to calculate the performance and computational speed of the defined model. In medical image analysis, a novel framework as a multi-stage structure has been designed by Mahapatra *et al.* (104) based on triplet loss function (TLF) to gradually improve image quality. Furthermore, TLF helps to achieve the quality output of the preceding photograph, which can be the input of the next photograph.

The implementation of TLF obtains a higher level of image resolution, to assist in the diagnosis of eye disease through the fundus photographs. A new approach for the segmentation of retinal vessels was introduced by Wang to identify blood vessels through a complex database (105). The three different kinds of datasets have been used by authors and obtained an accuracy of 95% to 96% of vessel segmentation, which is considered as better performance than the existing relevant approaches. The authors also mentioned that the presented approach would be applicable to relevant tasks of image analysis with pattern recognition. An image matting approach was applied by a fast approach to segment the blood vessels (106). Initially, the authors used an automated tri-map for the utilization of regional features of retinal vessels. Furthermore, a hierarchical approach was applied through image matting to obtain informative data relevant to vessel pixels using region of interest (ROI). The defined approach utilized minimum computational time and achieved better performance to segment the retinal vessels. Hossain and Reza (107) presented a novel approach for DR to segment the retinal images based on Markov random field (MRF). In the reported method, MRF is adopted for experiments to get high performance of segmentation as compared to the complex other relevant segmentation approaches, and in the reported work, fundus photographs are used in blood vessel segmentation using MRF. Feng *et al.* (108) designed a fusion network based on pyramidal modules in U-shape architecture to achieve the challenging tasks namely retinal edema and linear lesion segmentation. Moreover, Xi *et al.* (109) focused on two kinds of challenges faced in CNV in the context of difficulty in small objects for effective model training and better segmentation. The reported CNN model was designed based on an attention mechanism for ROI localization and discrimination. The neovascularization detection approaches are presented in *Table 7*. Neovascularization detection approaches played a vital role to discriminate the blood vessels including recent advance level approach introduced by Vij and Arora (110) used hybrid deep transfer learning to perform the segmentation task to help the accurate DR diagnosis and achieved accuracy of 98.16%, while highest accuracy of 99.71% is obtained by Singh *et al.* (121) using enhanced R2-ATT U-Net model.

Evaluation metrics

For accurate detection of DR using retinal images captured by a fundus camera, needs few steps of preprocessing

Table 7 Neovascularization detection approaches

Year	Reference	Methods	Database	Results with evaluation metrics
2024	Vij and Arora (110)	Hybrid deep transfer learning approaches, ResNet34 + U-Net	HRF, DRIVE	Accuracy: 98.16%, 98.53%; recall: 98.28%, 98.53%; precision: 98.33%, 98.81%
2024	Singh <i>et al.</i> (111)	DL, DenseU-Net, U-Net, ATTU-Net, R2U-Net, LadderNet, R2-ATT U-Net	STARE	Accuracy: 97.1%
2024	Ma and Li (112)	U-Net, DFM, SFM, context squeeze, and excitation module	CHASE-DB1, STARE, DRIVE	Accuracy: 96.67%, 96.60%, 95.65%
2023	Kumar and Singh (113)	Ensemble based DL, ResNet-152, VGG-16, efficient Net B0, PCA	STARE	F-measure: 99.22%; recall: 98.25%; precision: 98.63%; accuracy: 99.71%
2022	Bhardwaj <i>et al.</i> (114)	Nature-inspired swarm approach, TDCN models	APTOS 2019	Cohen's kappa: 96.7%; accuracy: 90.3%; AUC: 95.6%
2022	Sethuraman and Palakuzhiyil Gopi (115)	Supervised CNN, Staircase-Net with series of transformations	DRIVE	Drive: accuracy: 97.76%; sensitivity: 94.83%; specificity: 98.71%
2024	Sanjeevani <i>et al.</i> (116)	U-Net, GAN, RNN, SVM	DRIVE	Specificity: 98.38%; sensitivity: 74.36%; accuracy: 95.77%; F1-score: 79.31%
2021	Li <i>et al.</i> (117)	U-Net, Dense-Net, Dice loss function	DRIVE	Specificity: 98.96%; accuracy: 96.98%; sensitivity: 79.31%
2020	Gao <i>et al.</i> (118)	Multiscale vascular enhancement, filtering approach	STARE	Accuracy: 94.01%; sensitivity: 75.81%; specificity: 95.50%
2020	Chen <i>et al.</i> (119)	Semi-supervised learning, U-Net	DRIVE	Accuracy: 0.9631; AUC: 0.976
2019	Xia <i>et al.</i> (105)	One-pass feed forward process, cascade classification framework	DRIVE, STARE, and CHASE-DB1	Accuracy: 96.03%, 96.40%, 95.41%
2018	Fan <i>et al.</i> (106)	Hierarchical image matting model	CHASE-DB1, DRIVE, STARE	Accuracy: 95.7%, 96.0%, 95.1%
2018	Adal <i>et al.</i> (120)	Blobness technique (multi-scale measured), SVM	Rotterdam Eye Hospital	Sensitivity: 98%
2016	Paing <i>et al.</i> (55)	Artificial neural networks, and ROI iocalization	DIARETDB1	Accuracy: 96%
2015	Guo <i>et al.</i> (100)	Wavelet transformation and discrete cosine transformation, multiclass discriminant analysis	Real-world dataset	Accuracy: 90.9%

APTOS, Asia Pacific Tele-Ophthalmology Society; AUC, area under the curve; CHASE-DB1, child health and study England-database 1; CNN, convolutional neural network; DFM, decoder fusion module; DIARETDB, diabetic retinopathy database; DL, deep learning; DRIVE, digital retinal images for vessel extraction; GAN, generative adversarial network; HRF, high-resolution fundus; PCA, principal component analysis; R2-ATT, recurrent residual attention; RNN, recurrent neural network; ROI, region of interest; SFM, supervised fusion module; STARE, structured analysis of the retina; SVM, support vector machine; TDCN, tailored deep convnets; VGG, visual geometry group.

approaches before proceeding with image analysis techniques. There are several preprocessing techniques namely adaptive histogram equalization, contrast adjustment; average filtering, homomorphism, and

median filtering are applied for fundus photographs in the benchmark datasets. After performing an algorithmic approach on retinal photographs, PSNR and mean square error (MSE) are applied to analyze the performance of the

technique (122). In the area of healthcare and medicine, there are two classes of data used for experiment purposes and medical treatment; one is about data without disease, and the other about with disease. The authenticity level of the experiments regarding the treatment of patients is evaluated through sensitivity and specificity measures (123). In retinal image analysis, DR detection and classification are mostly done through digital fundus images, which are determined through the sensitivity and specificity of every image. The improvement of treatment is directly proportional to the values of specificity and sensitivity, if the values are higher, then it is considered as a better treatment approach. The true positive determines the lesion pixels and the true negative shows the non-lesion pixels in the digital fundus photographs. Similarly, false positives show non-lesion pixels that are captured in the wrong way by the designed technique and false negatives represent lesion pixels not captured through the technique. *Table 8* represents the variety of performance evaluation metrics used in the literature and can also help the research experts regarding availability of formulas, terms of choice, and the importance of the various types of evaluation metrics. *Figure 7* mentions the evaluation metrics and demonstrates the citations of the evaluation metrics in the entire study.

DR with XAI

In the recent development of artificial intelligence-based systems, XAI has also become an evolving technology (134). XAI is an advanced feature, which refers to the development and implementation of AI-based systems that helps to provide transparent and understandable explanations for their decisions and actions. While traditional AI models, such as DL neural networks, can be highly accurate in their predictions, they often function as black boxes, making it challenging to understand the underlying factors that contribute to their outputs. XAI aims to address this “black box” problem by incorporating transparency and interpretability into understandable AI models (134).

XAI enables the trust of users, regulators, and developers by providing transparency in the decision-making procedure of AI systems. The researchers have introduced different kinds of XAI tools, which are supportive and applicable in various kinds of domains to make the AI system understandable and transparent (134). Some methods involve designing models that are inherently interpretable, such as decision trees or rule-based systems. Other approaches focus on creating post-hoc explanations by

analyzing and visualizing the internal workings of complex AI models. This could involve techniques like feature importance analysis, attention mechanisms, or generating textual or visual explanations. XAI has gained importance due to ethical, legal, and regulatory considerations. It helps ensure accountability, fairness, and trustworthiness in AI systems. Additionally, XAI has practical applications in various domains, including healthcare, finance, autonomous vehicles, and criminal justice, where clear and interpretable explanations are crucial for decision-making and risk assessment. However, it's important to note that achieving full transparency and interpretability in AI models can be challenging, especially in complex DL architectures and XAI-based systems should be equipped with the advanced level of resources to compete with the challenges of black-box AI to make it more trustable and transparent towards decisions and conclusions (135).

Recently, ML-based predictions faced different kinds of scepticism, particularly in the area of healthcare for early prediction of serious disease and generated lot of discussion about explainable ML-based predictions (135,136). XAI can also play a significant role in the diagnosis and treatment of DR, a common complication of diabetes that affects the eyes (134). The graphical representation of XAI for DR diagnosis is presented in *Figure 8*.

There are a several approaches of XAI (137) which can be applied in the context of DR, such as “decision support” which supports the clinicians and patients to get answer their questions like why a certain diagnosis was made? Moreover, “feature support” is also another way, which can help the researchers to know which retinal lesion is mostly involved in the current stage of DR and this transparency and information may improve the medical treatment and give clear directions for future research efforts. The “visual explanations” is an effective approach of XAI to generate visual details by offering highly intuitive understanding of DR diagnosis through implementation of heat maps instead of complex mathematical models on retinal images to make it easier for clinical inspection and validation. XAI also provides informative approach related with “error analysis” in the case of failure or incorrect predictions of AI based models for DR diagnosis. The information can be applied to refine the AI models to reduce the potential risks. The XAI approach namely “regulatory compliance” is also becoming more important for regulatory bodies and ethics committees in healthcare related applications, which may need AI-based systems having transparency and explanations in their decisions before clinical use.

Table 8 Evaluation metrics used in DR screening

Evaluation metrics of performance	Calculating formula
Accuracy (124)	$Accuracy = \frac{TN + TP}{FP + FN + TP + TN}$
Sensitivity (94)	$Sensitivity = TP / (TP + FN)$
Specificity (125)	$Specificity = TN / (TN + FP)$
Precision (126)	$Precision = \frac{TP}{FP + TP}$
PSNR (127)	$PSNR = 10 \log_{10} \frac{(Peakvalue)^2}{MSE}$
TPR (128)	$TPR = TP / (TP + FN)$
FPR (120)	$FPR = FP / (FP + TN)$
AUC (129)	$AUC = \frac{\sum_{ins_i \in positiveclass} rank_{ins_i} - \frac{M \times (M+1)}{2}}{M \times N}$
SSI (102)	$SSI(x, y) = \left[1(x, y)^{\alpha} \cdot c(x, y)^{\beta} \cdot s(x, y)^{\gamma} \right]$
F1-score (130)	$F1.Score = \frac{2 \times Precision \times Recall}{Precision + Recall}$
PPV (80)	$PPV = TP / (TP + FP)$
E (131)	$E = 1 - \frac{Area(S \cap G)}{Area(S \cup G)}$
A (131)	$A = \frac{1}{2}(Sen + Spe)$
MCC (103)	$N = TP + FP + TN + FN$ $P = TP + FP \times N$ $S = TP + FN \times N$ $MCC = \frac{(TP/N) - S \times P}{\sqrt{P \times S \times (1-S) \times (1-P)}}$
G-means (103)	$G_means = \sqrt{SN * SP}$
Overlap score (132)	$OverlapScore = \frac{area(ODsegmented \cap groundtruth)}{area(ODsegmented \cup groundtruth)}$
EPI (102)	$EPI = \frac{\left(\sum_{m=1}^M \sum_{n=1}^{N-1} X'(m, n+1) + X'(m, n) \right)}{\left(\sum_{p=1}^M \sum_{q=1}^{N-1} X'(m, n+1) + X'(m, n) \right)}$
KC (133)	$KScore = \frac{Acc - Acc_{prob}}{1 - Acc_{prob}}$
CoC (102)	$CoC_{x,x'} = \frac{(E[(x - \rho_x) \cdot (x' - \rho_{x'})])}{\sigma_x \sigma_{x'}}$

A, balanced accuracy; AUC, area under the curve; CoC, correlation coefficient; DR, diabetic retinopathy; E, overlapping error; EPI, edge preservation index; FN, false negative; FP, false positive; FPR, false positive rate; KC, kappa score; MCC, Mathews correlation coefficient; MSE, mean square error; PPV, positive predictive value; PSNR, peak signal-to-noise ratio; SSI, structural similarity index; TN, true negative; TP, true positive; TPR, true positive rate.

XAI can enhance the understanding, trust, and adoption of AI systems in diagnosing and managing DR (138). By providing explanations for AI predictions and highlighting relevant features, XAI empowers clinicians, researchers, and patients to make informed decisions and contribute to improved patient outcomes in the field of ophthalmology.

Clinical implications for AI-based diagnosis of DR

In the field of DR screening, clinical implications are significant for early diagnosis, cost-effective, and better management of DR to prevent the vision loss. In the development of AI-based models, overall stakeholders must know the requirements of the clinical practice to address the challenges of healthcare delivery. Secondly, there is also important to have a proper validation process for AI-based models through a board of clinical and AI experts to check the biasness of datasets, whether it is complex, sufficient, and heterogeneous according to the specification of the institute (139). The AI-based systems should be monitored to carry out the reliability and safety by clinical decision-making, the trade-offs between sensitivity (reducing false negatives) and specificity (reducing false positives), and the ethical considerations of relying on automated systems in healthcare. Thirdly, the AI-based models must be carefully tested before deployment at the treatment point for safety and competency, similar to the medical devices, medications, and other relevant procedures. In the case of adopting, deciding on, and evaluating of the AI-based systems, the hospitals and healthcare delivery boards will need to brief the post-development technical issues, organizational governance, and clinical concerns for effective implementation (140). Furthermore, the administrative and clinical leadership of healthcare models along with participation of all the concerned stakeholders, including general public and patients must explain the future essentials to improve the clinical outcomes. In this way, AI-based systems can influence a positive change in the domain of healthcare through clearly define these objective states.

Discussion

The detailed research studies demonstrate the application of various computational approaches namely ML, DL, and image analysis for the diagnosis of DR using multimodal imaging, mostly including fundus and OCT images.

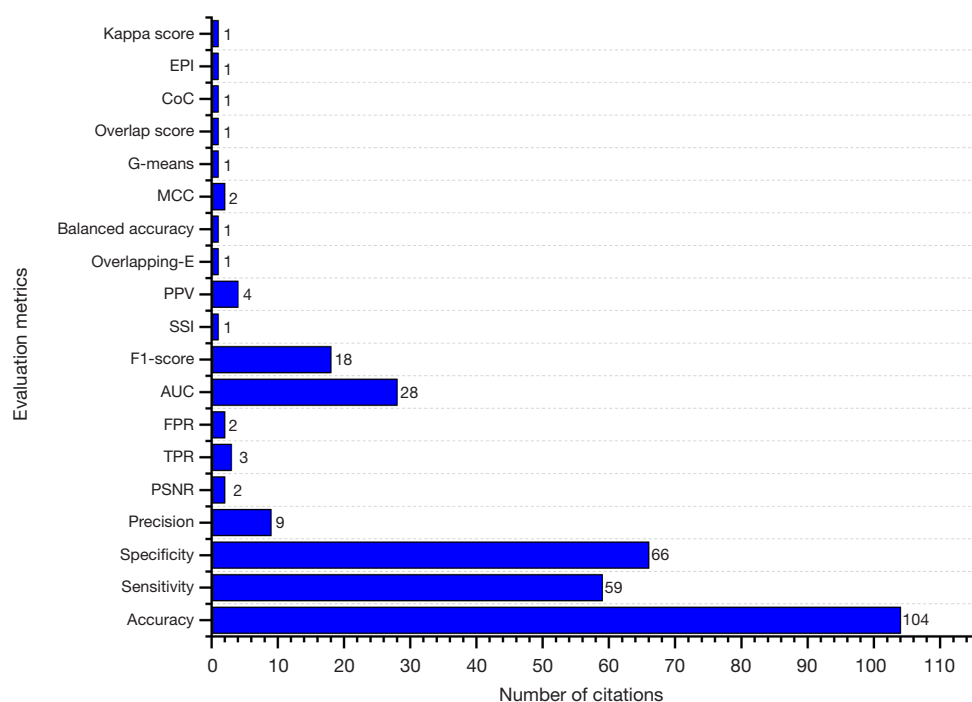


Figure 7 DR diagnosis literature-based evaluation metrics. AUC, area under the curve; CoC, correlation coefficient; DR, diabetic retinopathy; E, error; EPI, edge preservation index; FPR, false positive rate; MCC, Mathews correlation coefficient; PPV, positive predictive value; PSNR, peak signal-to-noise ratio; SSI, structural similarity index; TPR, true positive rate.

The proper way of DR lesion segmentation including microaneurysms, hemorrhages, and exudates was carried out through automatic diagnosis systems. The efficiency of AI-based systems for DR detection depends on feature segmentation from retinal images related to DR, but the process is prone to error and also computationally expensive and the consistency of the whole system moves down by implementing this step. Furthermore, in most cases of literature work, without quantitative measurements, traditional image processing and ML techniques have been applied based on large-scale datasets. In the case of DR diagnosis, several detection techniques have been presented to discriminate the normal and DR real-time grading levels are rare for DR classification with five types of different classes. In recent work, many research experts made contributions to the assessment of DR classification into five categories but some of them worked to analyze and observe the retinal abnormalities based on existing domain expert knowledge. In the context of DR grading, many ML-based approaches have been reported instead of focusing on the whole features of DR. Moreover, it is noted that the outdated hardware was also an obstacle to the development of a diagnostic system of DR with DL

approaches. However, nowadays the capacity of hardware has been increased and can now able to achieve outstanding outcomes through the combination of advanced DL techniques including meta-learning, multitask learning, incremental learning and domain adaptation to detect the retinal abnormalities including DR.

In the future, the overall development of DR detection and classification can be improved through advanced DR diagnostic approaches with the following suggestions:

- ❖ The input data for computer-aided diagnosis systems should contain high-resolution images and also be gathered from different kinds of regions and societies on a large scale.
- ❖ The dynamic features fusion could be applied through hand-crafted and automated features to obtain better classification performance, specifically in the case of severe DR levels.
- ❖ Implement several novel color space and appearance techniques for better performance of classification in the situation of complex patterns.
- ❖ The database of four levels of DR could be replaced with five levels.
- ❖ The examination of DME is also very essential to

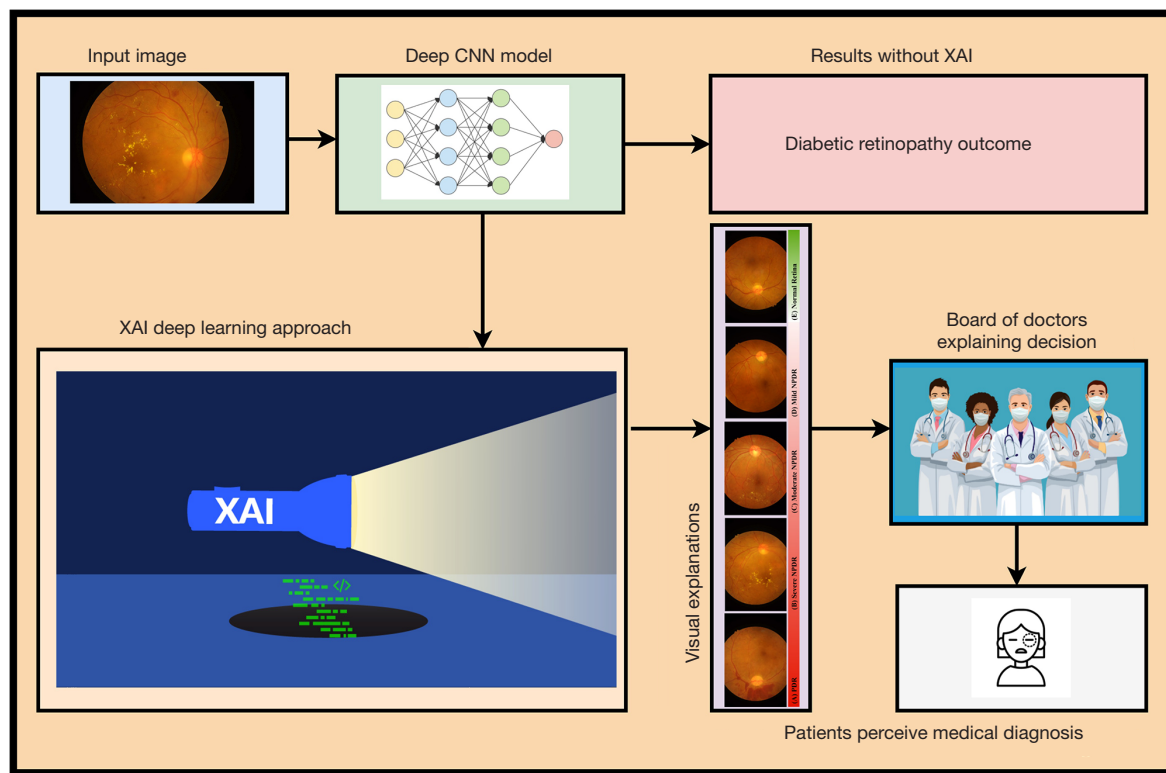


Figure 8 XAI for DR. CNN, convolutional neural network; DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR; XAI, explainable artificial intelligence.

care about eye vision because DME is also a common reason of complete vision loss in diabetic patients.

- ❖ It is recommended that DME diagnosis should be performed using retinal imaging multimodalities including OCT and fundus scans instead of a single modality.
- ❖ It is suggested to design a meta-learning-based framework to facilitate ophthalmologist having less amount of dataset, which would also present more generalization and accuracy.
- ❖ It is suggested to combine the strength of ophthalmologists and AI for DR diagnosis.
- ❖ It is suggested to incorporate XAI-based approaches to overcome the potential challenges of DR misdiagnosis and also recommended to have human-in-the-loop (HITL) in AI-based decisions.

Recently, researchers introduced medical features-based extraction parameters for retinal abnormalities detection namely Diabetes Retinopathy Risk Index (DRRI) and Standards for Reporting Diagnostic accuracy studies (STARD). These parameters are based on the numerical

value of different levels of thresholds to identify the stages of retinal disease. Moreover, these are also useful for the classification of DR through quantitative measurements (141). The review article provides a detailed review of the relevant studies in the area of DR, which completed more than a past decade. *Figure 9* presents the major contributions of the researchers performed in the last decade using AI models for the progress of DR diagnosis with multimodal imaging (142-151).

AI with DL techniques, presented a significant role to achieve the excellent performance in medical image analysis, especially in DR screening using digital retinal images (152). However, still there is a need to discuss more about the important issues and basic development of DL. In the area of computer vision, advanced AI-based applications have been developed to solve the complex problems with new directions using DL. Nevertheless, it is necessary to know about the background knowledge of DL before going to implement it, such as amount of pooling and Convolutional levels, and amount of nodes on each level to get required outcome, and about the selection of model. The DL-based

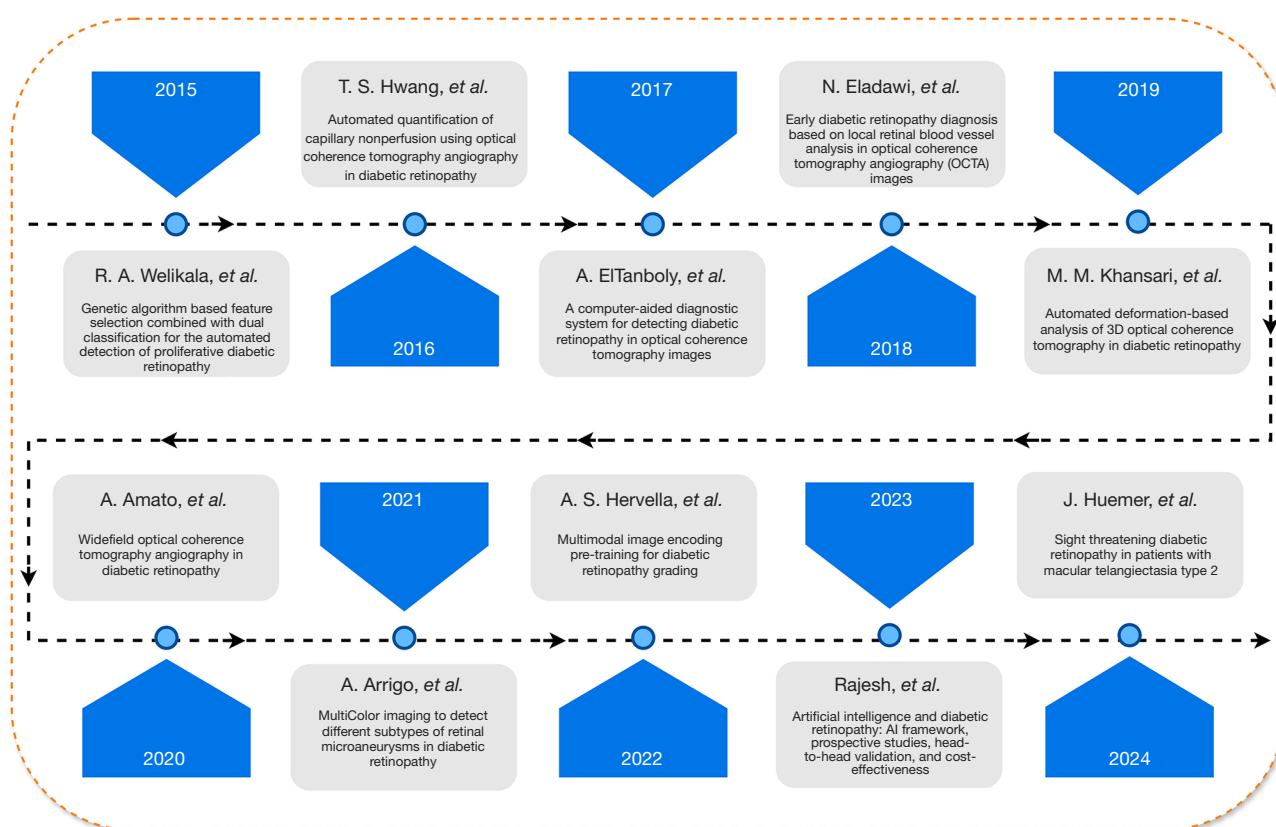


Figure 9 The timeline of the AI based DR diagnosis related major contributions in the last decade with multi-modal imaging. Welikala *et al.* (142), Hwang *et al.* (143), ElTanboly *et al.* (144), Eladawi *et al.* (145), Khansari *et al.* (146), Amato *et al.* (147), Arrigo *et al.* (148), Hervella *et al.* (149), Rajesh *et al.* (150), Huemer *et al.* (151). AI, artificial intelligence; DR, diabetic retinopathy.

approaches perform the wonderful task for the training of a large scale of datasets. Generally, noted about the low quantity of images may confine and affect training task and learning procedure DL. In the recent studies, the two kinds of suggestions were presented to increase the scale of training data, where one to focus on data augmentation approaches to make the dataset more generic and the other is about to data gathering on the basis of weakly supervised learning approaches. In the area of medical image analysis, it is a significant task to overcome the demand of well annotated and large-scale of training data. To address this problem, research experts have introduced different kinds of modern DL techniques namely, meta-learning (153,154), incremental learning (155), multitask learning (156), and domain adaptation (157). In the same way, numerous research experts focused and divert their attention towards the utilization of such advanced techniques for the screening and grading of the retinal pathologies (158). Particularly, He *et al.* (159) worked in the context of unsupervised

domain adaptation using adversarial network which is an appreciable task to segment the structure of retinal image using OCT scans, which are basically attained by Spectralis and Cirrus machines.

Comparative performance analysis

Numerous experts used traditional DL models with one fundus or OCT imaging modality at a time, which needs a large amount of data and also requires high computational power for training the dataset, furthermore, feature extraction through a single retinal modality could be less helpful to achieve better prediction results. To overcome this gap of research work and deficiencies, there could be a research direction using meta-learning based on clinically significant DR diagnosis from fused retinal imaging multimodalities including fundus and OCT imagery; would have tremendous performance, because, in the field of medical imaging, meta-learning is very useful and

Table 9 Traditional and advanced AI-based techniques

Methods	Literature	Abnormalities	Performance (accuracy) (%)
Meta-learning			
Traditional	Morphological operations (56)	Retinal micro-aneurysms	97.75
Advanced	DRNet (162)		98.18
Domain adaptation			
Traditional	RFC (38)	Retinal hemorrhages	93.58
Advanced	Multi-instance learning (163)		95.8
Multi-tasking			
Traditional	Fuzzy techniques (164)	Retinal exudates	93
Advanced	Modified U-Net multi-tasking (165)		99.42

AI, artificial intelligence; RFC, random forest classifier.

beneficial, containing unique features including few-shot learning (160) which can learn to generalize to new tasks using only a few annotated examples. The basic reason for the selection of meta-learning (161) in DR diagnosis is to improve the performance and efficiency of retinal imaging multimodality analysis, especially when faced with limited annotated data and computational power, but high levels of variability and uncertainty. The comparative analysis of the traditional and advanced AI-based techniques is explained in the following:

- ❖ The applications of DL require common weights for DNNs to handle their choices, which were not available in the existing models.
- ❖ The more generalized models are achieved through the integration of non-hand-crafted and handcrafted features.
- ❖ Implementation of the feature learning through layers technique as every level of layered neuron can be trained from previous layered attributes.
- ❖ In the case of DL architectures, the generalization feature can be enhanced by increasing the size with the addition of levels and units in each layer. For example, a DL model such as GoogLeNet has 22 layers.

The DR diagnosis with a comparison of several traditional and advanced AI with DL methods has been presented in *Table 9*, which shows the performance results for the identification of DR lesions as microaneurysms, hemorrhage, and exudates, where advanced AI-based techniques performed better than the traditional handcrafted techniques.

In the case of retinal abnormality detection and

treatment, retinal image registration process performs a vital role. In this context, there are few advanced methodologies are introduced including novel 3D (design, detection, deformation) registration approach for OCT images to deal with serious pathological subjects (166). Furthermore, transformation and feature based image registration approaches have been reported (167). Moreover, multimodal imaging registration approaches (168) contains multi-color scanning laser (MCSL) and ICGA have been introduced with coarse and fine registration stages. Model agnostic meta-learning technique (169) has been utilized by Hasan *et al.* (153) for the registration of multivendor retinal photographs through refinement a transformation matrix in an adversarial manner using spatial transformer. An automatic fast-focusing approach through fringes magnitudes of retinal layers introduced by Liu *et al.* (170) to identify the appropriate position of optical lens without any assistance of OCT and fundus imaging. Recently, you only look once (Yolo)also performed well and provided outstanding results in the case of DR detection using fundus images (171). Wang *et al.* (172) introduced a novel approach for speckle noise de-noising using OCT scans to enhance the performance of model to capture sparse and complex features. Furthermore, Wang *et al.* (173) highlighted the challenges of drusen segmentation for the identification of AMD in OCT images. The authors designed a novel U-shaped architecture-based framework contains multi-scale transformer module to capture non-local features. Moreover, Ju *et al.* (174) used adversarial domain adaptation for the achievement of cross-domain shifts between ultra-wide-field and normal fundus images for

the analysis of glaucoma, AMD and DR. Meng *et al.* (158) proposed ADINet model known as attribute-driven incremental network for learning retinal abnormalities detection tasks using fundus images. An advanced DL-based model is introduced by Peng *et al.* (175) for the detection of Retinopathy of Prematurity (RoP). The presented work is based on five levels of RoP staging handled through EfficientNetB2, DenseNet121, and ResNet18 frameworks for feature extraction.

Future directions and challenges

Currently, AI and image processing have performed an imperative role in DR diagnostic systems to diagnose retinal abnormalities in DR. Several optimal solutions can help for the smart utilization of DL techniques with a small amount of annotated data. The recent studies presented CNN-based models for the development of deep multi-layer frameworks designed for DR detection through retinal fundus images. In contrast, retinal experts and ophthalmologists need to perform retinal image analysis and annotation which is quite expensive as well as a time-consuming task. For that reason, there is a need for effective and advanced deep-learning techniques that can perform well with a limited amount of annotated data. Furthermore, the traditional DL models can be performed well by applying a fusion of dynamic-sized DL-based models sequentially. For this reason, it can overcome the large training requirement and decrease the computational cost in the case of individual DL-based models to better complete the task independently. Moreover, advanced DL approaches including, meta-learning, multitask learning, incremental learning, and domain adaptation can perform better in the case of model generalization with less amount of annotated data. In real-world clinical settings, AI serves as a tool of assistance that reduces the manual workload but cannot fully ignore and eliminate it. Data preprocessing is significant to make sure that the inputs are accurate, whereas, the post-processing validation is useful to confirm that the AI-based outcomes are clinically applicable. In this way, the combination of human expertise and automation, commonly known as HITL in AI, is important for high-standard clinical workflows and for maintaining healthcare. There are still two important challenges regarding poor generalization and lack of reproducibility, which are affecting publications in the domain of AI. To address these serious problems, Barberis *et al.* (176) designed a framework for generalized analysis of software implementation through resampling of

training and testing data, to ensure the reproducibility and robustness of AI models. Gundersen and Kjensmo (177) focused on the importance of reproducibility in AI models and discussed three degrees of reproducibility proposed by Goodman *et al.* (178) are methods, results, and inferential reproducibility. The methods reproducibility is referred to the implementation ability towards the computational and experimental tasks through the same tools and set of data to achieve the same results. The second degree of reproducibility is focused on the results reproducibility to verify the results on the new study by using the same computational and experimental approaches. The third degree of reproducibility is about inferential highlight the similar conclusions on the reanalysis of the novel work or through the independent study with replication. It is suggested that to enhance the transparency in the AI models, it is desirable from the regulator authority using publicly available datasets. Moreover, it is essential to test the medical devices through as much populations and cultural contexts as possible (179).

Conclusions

In the early diagnosis of DR, AI-based approaches play a vital role in the use of retinal imaging. This comprehensive review reported the relevant studies obtained from prestigious and popular repositories of Web of Science, Google Scholar, and PubMed to provide rich information for researchers. The review covered the related private and publicly available datasets with accessibility details, challenges, and suggestions to overcome the biases in the datasets and presented the AI-based DR lesions identification approaches for evaluating retinal abnormality in diabetic patients. Moreover, evaluation metrics are presented with descriptions and formulas for particular tasks of DR detection, classification, and segmentation. In ML-based approaches, statistical-based features including structure and shape provide better performance and in the case of DL models, CNNs are considered as a primary component for automatically better performing the extraction and categorization of DR images. In the context of performance evaluation metrics, area under the curve, specificity, sensitivity, and accuracy are mostly used in DR diagnosis. The critical analysis presents a deep summary of the DR-related topics, which would be helpful and assisting the research experts and clinical professionals working in this domain. Advanced AI-based concepts including, yolo, vision transformers, XAI, meta-learning, incremental

learning, multitask learning, and domain adaptation could be used for the early and accurate detection of DR and also useful to overcome the limitations on areas such as integrating domain knowledge, using multimodal data, or employing transfer learning for resource-constrained settings. AI-based health caring techniques with specified clinical implications can minimize the time to identify the DR and can reduce the cost of DR diagnosis to facilitate the patients and ophthalmologists. The authors are confident that a rich informative review can facilitate medical practitioners and scientists towards the automated DR diagnosis. The readers of this review study would get the required information and achieve future research directions; to further improve research work and progress of DR diagnosis and treatment.

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