International Journal of
INTELLIGENT SYSTEMS AND APPLICATIONS IN ENGINEERING
ISSN:2147-6799 www.ijisae.org Original Research Paper

A Comparative Analysis of Risk Prediction Models for Diabetic Retinopathy using Machine Learning and Deep Learning

[1]Jyoti, [2]Dr.Namit Gupta

Submitted: 16/09/2024 **Revised**: 20/10/2024 **Accepted**: 03/11/2024

Abstract: Diabetic Retinopathy (DR) is one of the leading causes of vision impairment among diabetic patients. With advancements in Machine Learning (ML) and Deep Learning (DL) techniques, predictive models for DR have significantly improved in accuracy and precision. This comparative analysis systematically explores various ML and DL approaches used in DR risk prediction, focusing on key techniques such as Convolutional Neural Networks (CNN), hybrid models, and advanced pre-processing methods. Following a comprehensive literature search from 2019 to 2024, using databases like Web of Science, Scopus, ResearchGate, ScienceDirect, and Springer, this review adheres to PRISMA guidelines to ensure methodological rigor. Studies have demonstrated promising results, with several models achieving high accuracy rates, such as 99.18% for vision-threatening DR detection. The key observation of this study is that deep learning, particularly with the latest technologies, outperforms traditional ML methods in every aspect of the prediction and classification of image datasets. However, challenges persist, particularly in terms of model generalization, data labeling, and computational complexity. This study provides a detailed comparative analysis of these techniques and identifies research gaps, including the integration of unsupervised learning methods and improving computational efficiency for real-world applications.

Keywords: *Deep Learning, Diabetic Retinopathy, Feature Extraction, Machine Learning, Computer Vision.*

1. Introduction

Diabetes is a non-infectious, metabolic disease that occurs when insulin secreted by the pancreas (necessary to control blood sugar) is not released or metabolized by blood sugar [1,2]. Diabetic Retinopathy (DR) does not cause any symptoms at first, but over time it can develop along with other eye diseases, so everyone should have their eyes checked at least once a year to protect their eyes as soon as possible. Gestational diabetes during pregnancy can cause DR. Genetics also play an important role in DR associated with glucose, low lipoprotein, and systolic blood pressure [3-7]. There are three very effective and important treatments for DR, including laser surgery, corticosteroid injections or Anti Vascular Endothelial Growth Factor (VEGF) drugs, and vitrectomy [8- 10]. The key to delaying the onset of DR is to maintain good blood sugar control [11]. High blood sugar (hyperglycemia) is the result of persistent blood sugar and, over time, can cause serious damage to many organs in the body, including veins and arteries. Similarly, dangerous sugar can build up in the retina's blood vessels over time, leading to blindness, so eyes with DR should be worried.

[1]*Research Scholar, Teerthankar Mahaveer University, Moradabad, Uttar Pradesh*
erjyotiagarwal1901@gmail.com
[2]*Associate Professor, Teerthankar Mahaveer University, Moradabad, Uttar Pradesh*
namit.k.gupta@gmail.com

Figure 1 shows the real Optical Coherence Tomography (OCT) diabetic image set that illustrates various stages of diabetic retinal disease, progressing from a normal retina (A) with smooth, intact layers to advanced stages characterized by significant structural damage.

Image (B) shows mild diabetic changes with minor undulations that suggest early fluid accumulation, a precursor to more serious retinal issues. In (C), Diabetic Macular Edema (DME) is evident with substantial swelling and cystoid spaces, indicating fluid build-up that can impair vision. Image (D) represents advanced DR, with pronounced structural abnormalities and potential neovascularization, where fragile, new blood vessels may leak fluid or blood. Finally, (E) shows severe cystoid macular edema or a macular hole with large cystic spaces or retinal thinning, representing significant progression that could lead to serious visual impairment. This sequence emphasizes the importance of early detection and treatment in diabetic eye care.

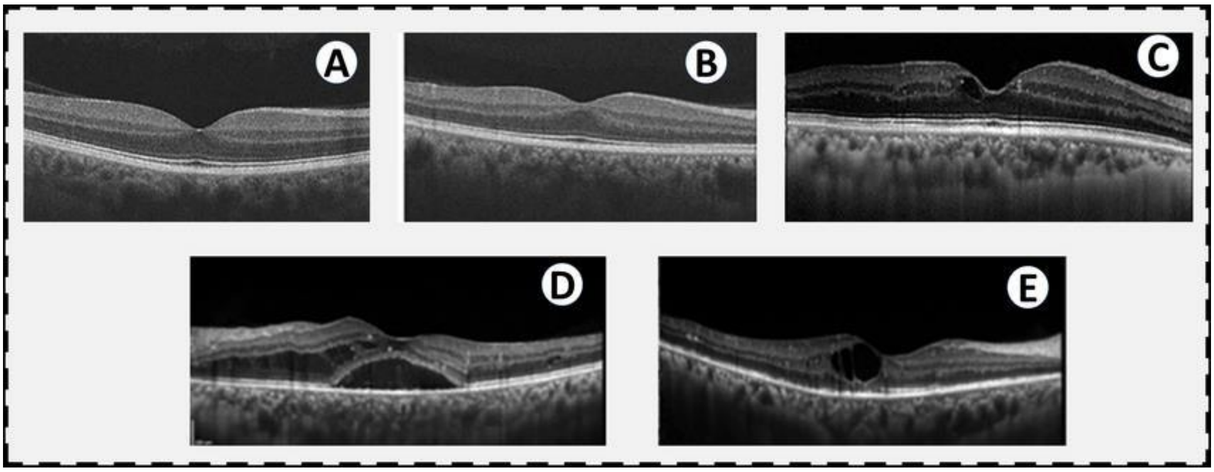

Figure 1: The OCT Diabetic Eye Images from (NDR to DR)

ML plays a critical role in diagnosing and predicting DR among people who have diabetes [12-15]. Through the analysis of extensive data, including retinal images, patient history, and clinical factors, ML algorithms can identify patterns and features related to the early onset and progression of DR [16]. Because of this, most ML techniques are used for classification and predictive purposes. These models are trained on labeled datasets, where the algorithm learns to identify key markers of DR [17,18]. Trained models can provide faster, more accurate and automated prediction and thus improve early detection rates. Early diagnosis through ML helps ophthalmologists in better decision-making and timely treatment, which forbids complications like vision loss [19,20]. The ML models can also include multiple risk factors such as glucose, genetics, and lifestyle data to provide a comprehensive risk profile to the patients and, therefore, have an enhanced treatment plan and improved patient outcomes [21,22].

Deep learning (DL), on the other hand, is also a subset of ML, which has proven promising results in DR detection and prediction. It is especially efficient at analyzing medical images for diagnosing DR [23]. Unlike most of the traditional models based on ML, which require manual extraction of features during a learning process, DL models can automatically learn intricate patterns and features from raw image data without any human interference in the learning process [24-26]. As the DL technique offers better accuracy and can well process complex information, its applications in DR screening have increased rapidly in recent times [27]. These models were trained based on huge sets of labelled images and can now determine quite accurately the earliest possible signs of DR, even better than many traditional learning algorithms as well as expert ophthalmologists [28,29]. Most notably, transfer learning and ensemble models, two of the recent advances in deep learning, have improved the existing effectiveness of DR detection. Transfer learning allows large datasets to be fine-tuned for specific tasks, thus decreasing the requirement for huge datasets that tend to be challenging to obtain in the medical field [30]. This makes deep learning models highly accurate but, at the same time, practical enough for their deployment in real- world clinical environments [31].

1.1 Sign and Symptoms of diabetic retinopathy

The following are some of the signs of diabetic retinopathy and Figure 2 shows these in pictorial form.

- Retinal hemorrhages deep (dot and blot) are common and superficial (flame-shaped) at capillary leakage.
- Hard exudates look like yellow-white waxy patches at a macular area in a circinate/clump pattern.
- Vitreous hemorrhage develops due to the proliferation of nonvascularized vessels in the plane of the retina.
- When blood sugar levels are not under control, the lens produces enzymes that convert glucose to sorbitol, a hazy substance that causes cataracts to form [32,33].

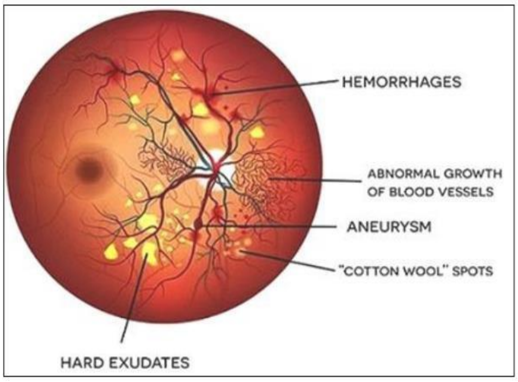

Figure 2: Sign of Diabetic Retinopathy [34].

The following are the symptoms of diabetic retinopathy:

- Floaters/dark strings, due to high blood sugar levels in bloodstream vessels get leaked, and the blood spots in the retina create a shadow of tiny particles called floater/dark strings.
- Leakage from damaged blood vessels in the macula is responsible for central blindness [35,36].
- A distorted vision can lead to an oedematous macula due to leaky capillaries with visual distortion and discomfort in night vision take place.
- Complete blindness occurs due to high blood sugar, further damage to the retina, and even total blindness [37].

1.2 Types of diabetic retinopathies

This section outlines the different types of DR, ranging from no apparent symptoms in the early stages to more severe forms like Proliferative Diabetic Retinopathy (PDR), which can lead to vision impairment and complications such as Diabetic Macular Oedema (DME).

➢ **No apparent diabetic retinopathy**

There are no symptoms in this stage, but the risk of infection and blindness can require regular monitoring and appropriate treatment. It includes all abnormalities and requires periodic evaluation of the retina.

➢ **Mild non-proliferative diabetic retinopathy**

Micro aneurysm is a sign with a latency period of 6 to 12 months and needs to be financially controlled.

➢ **Moderate non-proliferative diabetic retinopathy**

Symptoms include microaneurysms, pinpoint hemorrhages (intraretinal hemorrhages or venous bead hemorrhages), hard exudates, and cottony spots. The presence of Intraretinal Microvascular Abnormality (IRMA) indicates ischemia and is a precursor to neovascularization [38].

➢ **Proliferative Diabetic Retinopathy (PDR)**

The most common type of DR is characterized by neovascularization of the optic disc, retina, iris, and angle alone or tractional retinal detachment with vitreous/preretinal hemorrhages or blurred vision [39]. Figure 3 shows the various stages of diabetic retinopathy.

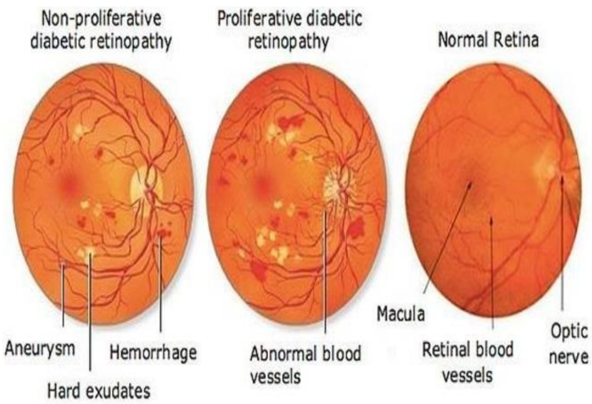

Figure 3: Stages of Diabetic Retinopathy [34].

Among the most difficult challenges that ophthalmologists face daily is predicting the progression of DR [40]. Because early therapy can slow down the progression of DR, a common goal is to detect it early before it causes irreversible visual loss [41–43]. There is an urgent need for more investigation and understanding of the evolution of DR in clinical practice and research.

The development of DR and the rate at which it progresses in various individuals can be explained, in part, by the role that risk factors play in these processes [44,45]. These factors also contribute to the development of DR and its advancement to the sight-threatening stage of PDR. To address the growing risk of vision loss and lower the expenses associated with managing advanced stages of DR, it is crucial to screen for persons at high risk of the disease progressing from the non-proliferative to the proliferative stage and to intervene early [46]. Preventative medicine and individualized treatment can't proceed without a thorough comprehension of DR progression according to these risk variables. Accurately forecasting the progression of DR and using important risk factors as input variables to develop predictive models is important [47,48]. ML algorithms with mathematical formulas make up a risk prediction model, which measures the likelihood of specific negative occurrences happening in the future.

1.3 Machine learning for DR

Machine Learning, and notably deep convolutional neural networks, are certain to find their way into risk prediction models. This is because these networks are so good at mining massive amounts of patient data for complex patterns and at deducing the complex interrelationships between risk factors and people's histories of illness [49,50]. Models utilizing ML approaches have been suggested lately, with three main types of predictors or risk factors: genetics, socio-demographics, and fundus imaging [51–55]. To get better results from models, some research mixes many risk factors. Consequently, there have been a lot of efforts to create reliable prediction models for early detection of DR [56]. Conventional models, built using statistical analysis and feature engineering by hand, lack robustness and discriminative capability when compared to models trained using ML techniques; as a result, they normally display less-than-ideal predictive performance.

1.3.1 Deep Neural Networks for DR

Deep Neural Network (DNN) is an ML technique built on the foundation of Artificial Neural Networks (ANNs) [57,58]. Many areas of computer vision, speech recognition, medication design for Natural language processing (NLP), medical image analysis, and game programming have effectively utilized deep learning architecture [59– 63]. Furthermore, methods such as hyperparameter optimization have been effectively used to further improve the performance of conventional DNN models. These methods show great promise for automating pathological screening and disease prediction through data analysis, thus reducing the need for human interpretation. Therefore, it is crucial to use these advanced DNN models to detect DR to slow the progression of the disease, which causes lifelong blindness.

Deep learning is an approach in ML as well as artificial intelligence that seeks to replicate human learning processes for the acquisition of specific types of information. Through the use of DL, computer models can acquire the ability to learn how to classify images, texts, and sounds [64-66]. It aids in achieving precision levels that are higher than human capability. Neural network topologies with several layers are used to train models from big quantities of labeled data. The activation functions used by each layer aid in the fragmentation of useful information and the elimination of irrelevant information. Data scientists rely heavily on deep learning, a platform for automating predictive analytics through statistical and predictive modeling methods [67]. The below figure 4 shows the deep learning framework for the detection of DR. The general flow for detecting DR using DL begins with collecting retinal images, which are then pre-processed to enhance their quality by improving contrast and removing noise. These enhanced images are fed into a deep learning model, which automatically extracts features from the image, such as hemorrhages, exudates, or abnormal blood vessels. The model learns to identify and classify these features by training on large datasets of labeled images. The extracted features are then used to classify the severity of DR into different stages, such as no DR, mild, moderate, severe non-proliferative DR, or proliferative DR. By continuously optimizing the model's parameters through methods like backpropagation and using performance metrics such as accuracy, sensitivity, and specificity, the deep learning system can make predictions that help in early diagnosis and treatment planning for DR.

Features

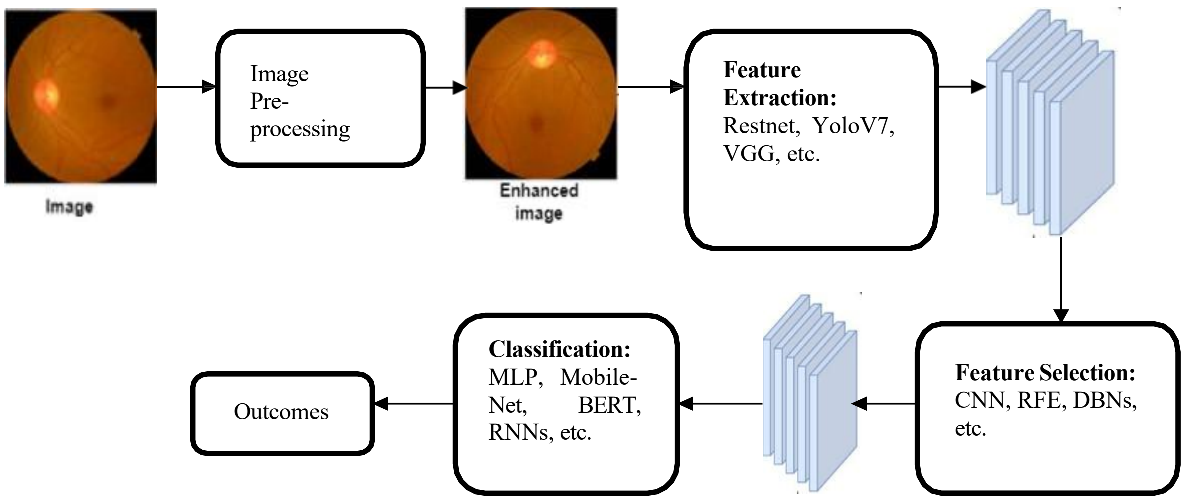

Figure 4: General framework for Detection of DR using Deep Learning [68].

The algorithms used in deep learning are structured hierarchically, with each level of abstraction and complexity building upon the one below. A statistical model is produced as an output by the algorithm in the hierarchy once it has learned to employ non-linear transportation on its input. The process is repeated until the output is accurate enough to be considered acceptable. Rather than relying on human feature extraction, deep learning approaches train their models using large datasets with labels and topologies for neural networks that learn from the data, with a capacity to hold nearly 150 hidden layers [69]. A subset of DNN known as CNNs learns features from input data and processes two-dimensional visual data using convolutional layers [70–72]. It takes pictures as input and automatically extracts features, doing away with the need for human intervention. When it comes to computer vision object classification tasks, deep learning models perform better since the features are learned as the network trains on a set of photos, a process also called autonomous feature extraction. Using the hidden layers, it can detect image features [73–75]. Colored images of the fundus of a patient have been analyzed using deep CNN to identify and differentiate characteristics associated with macular oedema and diabetic retina [76,77]. Equations for certain summations and convolutions are the building blocks of neural networks' mathematical models. The DR's class and grade are determined by receiving input and calculating the output by using the neural network. Due to the iterative nature of deep learning neural networks, optimization functions are utilized by all DNN models to determine the optimal combination of hyperparameters [78]. A data-driven approach is taken to adjust the output calculation parameters to reduce the inaccuracy in class detection and manual annotations [79].

This review paper aims to critically evaluate risk prediction models for DR using ML and DL techniques. The primary objective is to assess the effectiveness of these models in predicting the onset and progression of DR by analyzing various ML and DL approaches, including CNN and hybrid models, along with the datasets and performance metrics used. The study discusses the salient imaging features of the retina useful for prediction and analyzes the way different models use these features. It further discusses the standard datasets used for carrying out research in DR, pointing out potential challenges for ML/DL applications. Finally, it discusses evaluation metrics like sensitivity, specificity, and AUC, providing an appropriate comparative analysis of the accuracy, robustness, and interpretability of the various models in real-time healthcare scenarios. The review thus adds to the present corpus of knowledge by integrating results from many studies to deliver an all-around evaluation of the benefits and drawbacks of ML/DL models regarding the DR risk. It also reminds areas where further efforts are required by pointing out gaps in the current literature.

The scope of this review paper deals with a comprehensive evaluation of ML and DL approaches applied to DR risk prediction, mainly covering diverse algorithms, models, and data types. Key ML techniques covered include Decision Trees (DT), Logistic Regression (LR), Random Forests (RF), and Support Vector Machines (SVM), while DL techniques emphasize CNN, Recurrent Neural Networks (RNN), and hybrid models like CNN-RNN. This paper discusses how such models process retinal images, blood glucose levels, patient history, and even fundus images, all of which are considered valid to predict the risk correctly for DR. It also analyzes the pre- processing techniques that improve the quality of images, image feature extraction, and how the model treats the effects of data augmentation, segmentation, and normalization. This study explores the key aspects of providing a better understanding of the developments and challenges in DR risk prediction, particularly on model selection, optimization, and clinical applicability.\

2. Literature Review

In this section, studies and research focused on Risk prediction for diabetic retinopathy using ML and DL techniques are discussed:

Jabbar et al., (2024) [80] proposed a deep-learning approach to classify DR fundus images at various grades of severity using enhanced variants of ResNet and GoogleNet models with the Adaptive Particle Swarm Optimizer (APSO) to enhance feature extraction. The features retrieved from the hybrid model were used as input to several machine-learning models. Experimental results showed that the proposed hybrid framework outperformed the advanced methodologies with an impressive 94% accuracy on the standard dataset.

Oulhadj et al., (2023) [81] suggested the approach for detecting severity levels of DR. The approach adopted made use of a modified inception block combined with the modified capsule network, where the images were passed through the model following the preprocessing step. In the pre-processing step, the discrete wavelet transformation was used to decompose the retinal image up to 3 levels. APTOS dataset was considered for validation of methodology with 86.54% accuracy.

Hu et al., (2022) [82] proposed a graph-based adversarial transfer learning method for DR detection. To improve the model, the research used adversarial training as well as graph neural networks to find possible features. Researchers attained an accuracy of 94.3% for DR classification on the same dataset and 83.5% accuracy for different DR classifications on APTOS2019 datasets.

Menaouer et al., (2022) [83] designed a hybrid deep learning approach for the detection and classification of DR based on the visual risk related to the severity of retinal ischemia using a deep CNN method with two Visual Geometry Group (VGG) network models, VGG19 and VGG16. The experiments were performed using 5584 images and gave an accuracy of 90.60%, recall of 95%, and F1 score of 94%.

Kumar et al., (2021) [84] introduced a new architecture for classifying DR, known as Diabetic Retinopathy categorization by Analyzing Retinal Images (DRISTI). This architecture employed a hybrid deep learning model comprising VGG16 and a capsule network. The method achieved an accuracy of 82.06% on the five-class classification job and 96.24% in the binary classification. The constraint of their methodology was rooted in the imbalanced class distribution of the utilized dataset.

Fan et al., (2021) [85] classified the diagnosis of retinopathy utilizing multiscale feature fusion through an adaptive weighted operation, wherein features taken from several convolutional layers were subsequently amalgamated via an adaptive weighted mechanism. Researchers attained an accuracy of 85.32%. The proposed method has a significant limitation due to the incomprehensible results obtained from irrelevant features generated by the attention model with division operations.

Bodapati et al., (2021) [86] suggested a DNN-gated-attention hybrid for DR detection task classification. The APTOS dataset was used to validate their methods. As a result, researchers achieved an accuracy of 82.54% and a kappa value of 97% on the APTOS dataset. A stacked convolutional autoencoder with spatial attention was proposed as a means of DR identification. The accuracy achieved by the proposed method was 84.17% on the APTOS dataset and 63.24% on the IDRiD dataset.

Alfian et al., (2020) [87] proposed a DNN integrated with Recursive Feature Elimination (RFE) for the early prediction of DR utilizing individual risk factors. The suggested model employed RFE to eliminate unnecessary features along with DNN for classification. A publicly accessible dataset was employed to forecast DR in its early phases. The suggested model achieved an accuracy of 82.033%, demonstrating a superior performance compared to existing models.

3. Review Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement is utilized as a set of criteria for screening and refining research. A detailed literature assessment on this phenomenon was conducted using the SCOPUS database, which includes records published from 2019 to 2024. This review includes all records categorized as articles, journals, and publications from the Scopus database. Table 1 shows the keywords that are used in the Scopus database to find the papers related to the topic:

Table 1: Searching Keywords
Source: Authors own elaboration

Databases	Keyword used
Scopus	(TITLE-ABS-KEY ("Machine Learning" AND "Deep Learning") AND TITLE-ABS-KEY ("Diabetic Retinopathy") OR TITLE-ABS-KEY ("Risk Prediction")) AND PUBYEAR > 2018 AND PUBYEAR < 2025 AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "cp") OR LIMIT-TO (DOCTYPE, "cr") OR LIMIT-TO (DOCTYPE, "re")) AND (LIMIT-TO (PUBSTAGE, "final")) AND (LIMIT-TO (

	LANGUAGE, "English"))

In literature analysis, only records categorized as articles are subjected to further analysis and assessment, as they are considered for evaluation purposes. The below-presented table 2 exclusively examined records that met the specified inclusion and exclusion criteria:

Table 2: The criteria for determining what is Included and Excluded

Source: Authors own elaboration

Criterion	**Inclusion**	**Exclusion**
Keywords	Records conferring the relationship between risk prediction models for diabetic retinopathy using machine learning and deep learning techniques, including hybrid models.	Records excluded in which variables have no relation.
Type of Literature	Journals, Review Articles	Book, book series, book chapter.
Language	English	Other than English
Timeframe	Concerning 2019-2024	<2019
Category	Open Access	Paid Access

3.1 Prisma Model

The reviews are assisted by the PRISMA statement "preferred reporting items for systematic reviews and meta- analyses". PRISMA demonstrates the review's caliber and enables readers to grasp its advantages and disadvantages as well as replicate review strategies.

Figure 5 depicts the comprehensive PRISMA flow diagram outlining the process of study identification, screening, eligibility assessment, and inclusion. The process begins with identifying relevant studies from both previous studies and new sources such as databases, registers, and other methods. The total studies screened include sources from IEEE, Web of Science, Scopus, ResearchGate, ScienceDirect, and Springer databases. After an initial identification of 17,750 records, automation tools removed duplicates and ineligible studies, leaving 534 studies to be screened. Of these, 438 reports were sought for retrieval, and 277 reports were fully assessed for eligibility based on predefined inclusion criteria. During the eligibility assessment, 86 reports were excluded due to insufficient data, 5 due to irrelevance, and 23 due to improper methodology, leaving 112 reports for inclusion in the systematic review. Following further domain-based screening to ensure alignment with the study's variables, 22 publications met the final criteria. The language screening step resulted in the exclusion of non- English works, ensuring that all retained studies were in English. This final review led to the inclusion of 22 publications after the comprehensive filtering process.

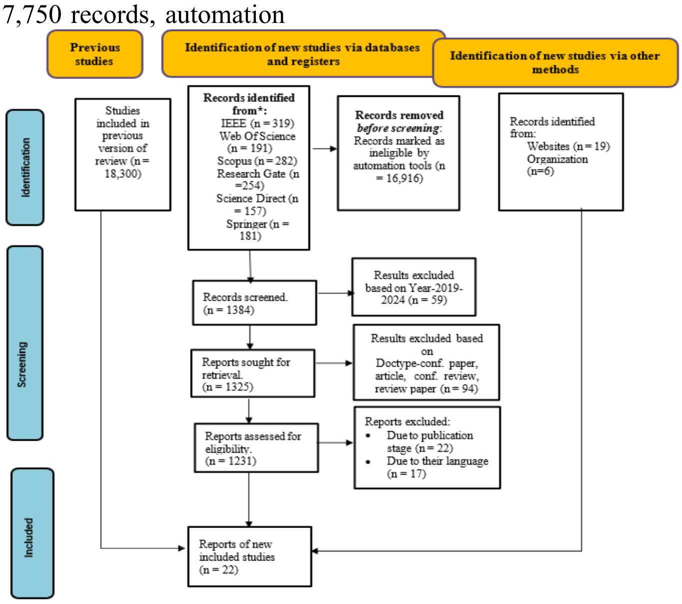

Figure 5: Prisma Model.

Figure 6 depicts the number of selected papers from the top 6 research areas. Computer Science leads with approximately 650 papers, indicating its dominance in research domains such as artificial intelligence, data processing, and computational models. Medicine follows with around 500 papers, underscoring its crucial role in advancing healthcare research, diagnostics, and treatment methodologies.

Engineering comes third with around 450 papers, reflecting contributions across fields like mechanical, civil, and electrical engineering. Mathematics and Decision Sciences each contribute around 200 papers, indicating their roles in theoretical research and decision-making models. Lastly, Biochemistry, Genetics, as well as Molecular Biology show the lowest number of selected papers at around 100, representing focused research on molecular mechanisms and genetic innovations. This distribution highlights the significant interdisciplinary focus of modern research, with a strong emphasis on technological and healthcare advancements.

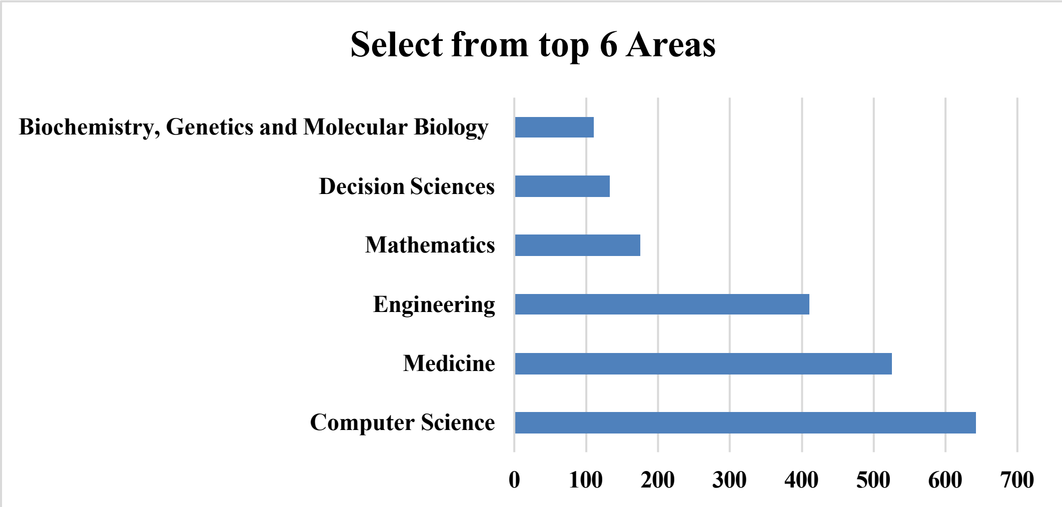

Figure 6: Selected papers from the top 6 Areas.
Source: Authors own elaboration

Figure 7 showcases the distribution of various keywords related to research in DR using ML and deep learning. Deep Learning" leads with 964 documents, showcasing its dominant role in developing sophisticated models for image processing and analysis in healthcare applications. "Machine Learning" follows with 726 documents, indicating its critical importance in predictive modeling and classification tasks. "Diabetic Retinopathy" is featured in 605 documents, emphasizing the research focus on this condition. "Human" is mentioned in 545 documents, highlighting its relevance in studies involving human subjects or manual annotations. Lastly, "Eye Protection" appears in 346 documents, reflecting attention to preventive measures and strategies in vision health. This data underscores the significant intersection of deep learning, ML, and healthcare, particularly in the context of DR.

List of Various Keywords
Eye Protection
Human Diabetic Retinopathy Machine Learning Deep Learning

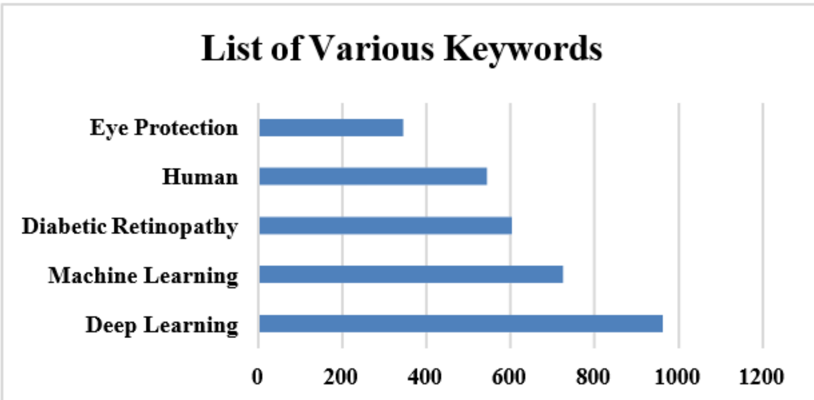

Figure 7: List of various Keywords.

Source: Authors own elaboration

Figure 8 offers valuable information regarding the years in which the papers were published. For this systematic literature review, the search terms were selected specifically to explore risk prediction models for DR using ML and deep learning techniques.

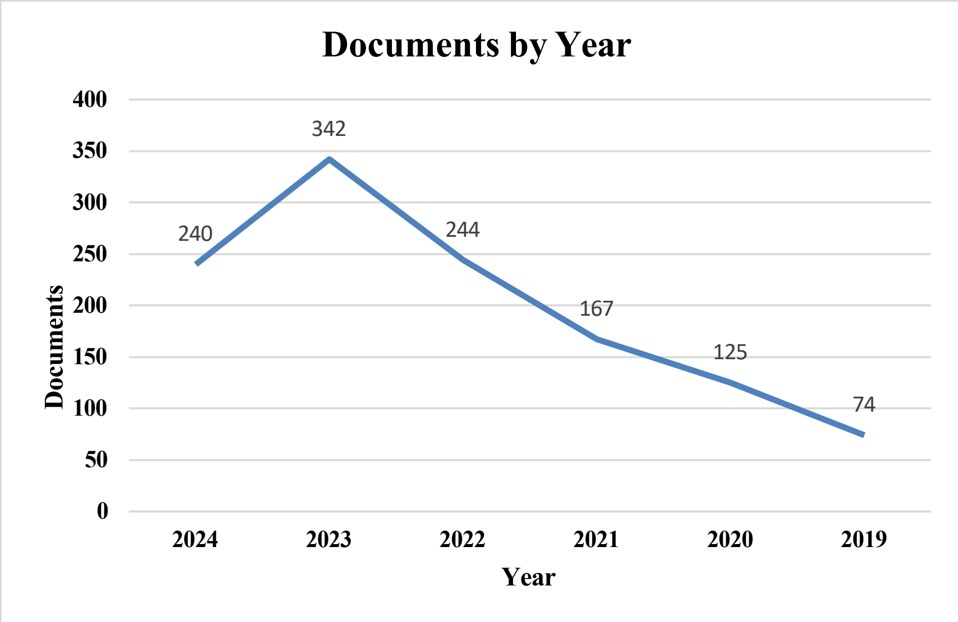

Figure 8: Trend in published papers.
Source: Authors own elaboration

3.2 Research questions

The following are the research questions (Q1 - Q3) derived from the objectives of this SLR:

Q1: What machine learning techniques are used for predicting DR progression, and what are the strengths and limitations of these models?

Q2: What are the deep learning techniques and hybrid models available for predicting diabetic retinopathy (DR)?

Q3: What are the key research challenges and gaps in the diagnosis of diabetic retinopathy (DR)?

4. Machine learning techniques for risk predicting of DR

Machine learning techniques for DR risk prediction utilize advanced algorithms to analyze retinal images and identify early signs of the disease. By training models on large datasets, these techniques, including DT, SVM, and RF, can predict the likelihood of DR development, aiding in early diagnosis and personalized treatment. **Sumathy et al., (2022) [88]** concentrated on early identification of DR utilizing patient data. The dataset was utilized to predict DR employing bagged tree, LR, SVM, and K-nearest neighbors (KNN), along with boosted tree classifiers. Two cross-validation methods were employed to identify optimal features and mitigate overfitting. The dataset comprised 900 people with diabetes. With a 10% hold-out validation, the boosted tree attained the maximum classification accuracy of 90.1%. The KNN model attained an accuracy of 88.9%. The research indicated that bagged trees, as well as KNN, were effective classifiers for DR. Additionally, **Odeh et al., (2021) [89]** presented a novel approach to detecting DR through the use of Ensemble ML.

Furthermore, researchers utilized a multitude of feature engineering techniques and a considerable stack of classification algorithms, culminating in a Meta-Classifier, to address the underperformance of earlier models and achieve optimal accuracy. For the Messidor dataset, the suggested framework attained accuracies of 70.7% and 75.1%, respectively, which were the best rates among all other popular classification algorithms. Moreover, **Sharma et al., (2021) [90]** proposed a system that used ML and image processing to identify DR. Standard databases supply the retinal pictures that were input to the proposed system. To automate the detection process, the system used a mix of fundamental image processing stages, with an emphasis on pre-processing to acquire clear images for feature extraction and additional ML algorithms for classification. After the pre-processing stage, the blood vessels and their exudate were used to extract statistical parameters, including area and perimeter. The results were analyzed using three ML algorithms: Weighted KNN (85.8% accuracy), Cubic SVM (87.2% accuracy), and Simple Tree (88.6% accuracy).

Further, **Huda et al., (2019) [91]** developed a model for an automated system that detects the early signs of proliferative DR in diabetic individuals. The suggested method's classification algorithms used an existing DR dataset on various features. Following feature extraction, the presence of DR was predicted. For the prediction, the suggested system utilized DT, LR, and SVM. By replacing the pointless feature-building of current methods with a tree-based feature selection strategy, the suggested solution achieved 88% accuracy. Lastly, **Tsao et al., (2018) [92]** utilized data mining techniques such as SVM, DT, ANN, and LR to construct a model that predicted the DR in type 2 diabetic mellitus. With an accuracy rate of 79.5 percent, supporting vector machines outperformed the other ML methods in the experiments. Table 3 presents a summary of various ML techniques applied by different authors to predict DR.

Table 3: Performance analysis of various ML technologies used for risk prediction of diabetic retinopathy

Author	Technique Used	Dataset	Accuracy	Drawbacks	Research Gaps
Sumathy et al., (2022) [88]	LR, KNN, SVM, Bagged Tree, Boosted Tree	DR	Boosted Tree: 90.1%,	Limited dataset size (900 patients), possible overfitting mitigation needed	Need for validation on larger datasets and across diverse populations.
Odeh et al., (2021) [89]	Ensemble ML with Meta-Classifier	Messidor	70.7% and 75.1%	Underperformance of earlier models, accuracy improvement needed	Further improvement in ensemble techniques for better accuracy
Sharma et al., (2021) [90]	Weighted KNN, Cubic SVM, Simple Tree	DIARETDB0 and DIARETDB1	Weighted KNN: 85.8%, Cubic SVM: 87.2%, Simple Tree: 88.6%	Pre-processing stage-dependent, complexity in feature extraction	Optimization of pre-processing steps for larger- scale application
Tsao et al., (2018) [91]	SVM, DT, ANN, LR	DIARET-DB	SVM: 79.5%	Lower accuracy compared to other advanced techniques	Need for exploration of more advanced models for higher accuracy
Huda et al., (2019) [92]	DT, LR, and SVM with Tree-Based Feature Selection	DM shared care	88%	Focuses on feature selection, but potential overfitting concerns	Refinement of feature selection strategies to enhance performance

Figure 9 provides a visual comparison of the accuracy achieved by various ML techniques for predicting DR. The Boosted Tree method shows the highest accuracy at 90.1%, followed by Weighted KNN, Cubic SVM, and Simple Tree, with accuracies ranging from 85.8% to 88.6%. In comparison, the two models that showed relatively low accuracy rates were Ensemble ML, with an accuracy of 75.10%. It appears that practitioners such as Boosted Tree and Simple Tree generally appear to have more hope of early DR, whereas methods such as Ensemble Learning can have further fine-tuning to reach a perfect level of accuracy.

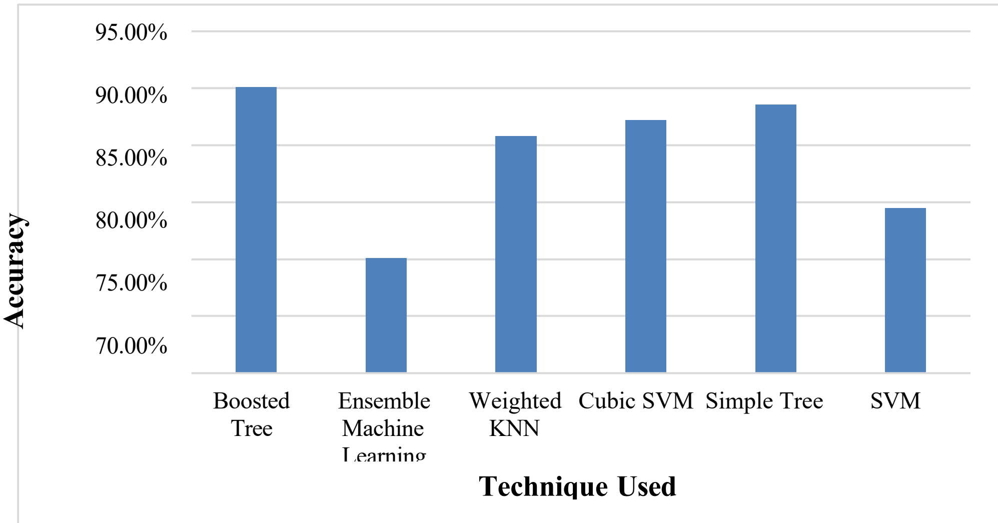

Figure 9: Comparative Analysis of various ML techniques

5. Deep learning techniques and hybrid model for diabetic retinopathy risk prediction

Deep learning techniques and hybrid models for predicting DR have used the latest computational methods for the detection and quantification of diabetic damage to the retina. Such systems, combining deep learning algorithms like CNNs with hybrid models, improve their diagnostic accuracy and, thereby, present possible early detection and early intervention before loss of vision among patients who have diabetes. **Taifa et al., (2024) [93]** suggested a combined model that included predictions from multiple classifiers, including DT, RF, SVMs, and others. Researchers used three deep learning models named MobileNetV2, DenseNet121, and InceptionResNetV2 to extract features from retina imaging. For each classifier, hyperparameter adjustment was done to provide the best possible performance. With an impressive accuracy of 95.30% in multi-class and 98.16% in binary classification, the hybrid model showed great potential. Similarly, **Bilal et al., (2024) [94]** presented a new approach that improved the detection process's accuracy and robustness. Data pre-processing, feature extraction using a Convolutional Neural Network-Singular Value Decomposition (CNN-SVD) hybrid model, and classification using a combination of DT, KNN, and Improved Support Vector Machine-Radial Basis Function (ISVM-RBF) were the steps in the suggested multi-stage approach. The hybrid model outperformed previous approaches in detecting Vision-Threatening Diabetic Retinopathy (VTDR) with an accuracy of 99.18%, sensitivity of 98.15%, and specificity of 100% when tested on the IDRiD dataset.

Additionally, **Oulhadj et al., (2024) [95]** introduced a novel automatic technique for identifying the degree of severity of diabetic retinopathy based on a new hybrid deep learning approach (DenseNet121, Xception, and EfficientNetB3) with a pre-processing step. After that, the retinal image quality was enhanced using the pre- processing step. Researchers fed the generated image to the hybrid deep learning model that starts with the three- transfer learning models to generate the feature maps, and then they served these feature maps to a classification sub-model to make decisions and detect images that were surfing from DR. To validate the proposed approach and show its performance, researchers tested it on the APTOS dataset and obtained an impressive accuracy score of 86%. Along with this, **Rodríguez et al., (2024) [96]** utilized CNN-RNN, a combination of convolutional and recurrent neural networks, to assess consecutive full OCT cubes and forecast the presence of DME within a practical software for screening for diabetic retinopathy. To determine the best threshold for binary classification of DME, researchers tuned each trained CNN-RNN model. Lastly, the most effective models were chosen based on sensitivity and specificity, along with their 95% confidence interval (95%CI). Furthermore, **Prabha et al., (2024) [97]** presented a retinal illness OCT Net that is both lightweight and hybrid, allowing for automatic disease categorization while reducing the number of trainable parameters. For multiclass classification, a Hybrid Learning Retinal Disease OCT Net (RD-OCT) was employed to identify normal retinal conditions, DME, Neovascular Age-Related Macular Degeneration (nAMD), and Retinal Vein Occlusion (RVO). The Normal group achieved 97% accuracy, while the Hybrid Learning RD-OCT Net achieved 97.6% for nAMD, 98.08% for DME, and 98% for RVO. Similarly, **Khan et al., (2024) [98]** suggested an improved hybrid learning model for the classification of four separate types of retinal disorders in OCT images. The hybrid model was built using the robust and well- known ResNet50 and EfficientNetB0 architectures. Researchers take advantage of the best features of both architectures by pre-training the hybrid model on large datasets like ImageNet and then refining it on publicly available OCT image datasets. The overall classification accuracy reached an impressive 97.50%, and the results showed better performance than previous techniques.

Further, **Gürcan et al., (2023) [99]** suggested a model that combines deep learning with metaheuristics. For feature extraction, a deep learning model called InceptionV3 was utilized with a transfer learning strategy. The next step was to use Simulated Annealing for feature selection, which reduced the number of features in the produced feature vectors. Finally, the XGBoost model made use of the top characteristics for representation. A binary classification test was completed with an accurate rate of 92.55% by the XGBoost algorithm. Likewise, **Ali et al., (2023) [100]** suggested a new method for detecting diabetic retinopathy using a CNN model. The suggested model combined the feature extraction results from two DL models, Inceptionv3 and Resnet50. A publicly accessible dataset comprising fundus images was used to evaluate the suggested model. According to the testing results, a greater accuracy of 96.85% was attained by the suggested CNN model.

Moreover, **Butt et al., (2022) [101]** developed a hybrid approach to identify and categorize DR in fundus images of the eye. To create a hybrid feature vector, features were extracted using Transfer Learning (TL) on pre-trained CNN models. Researchers compared the system's performance with new methods for DR detection and used several measures to determine its overall health. In terms of DR detection for fundus images, the suggested strategy significantly improved performance. The suggested improved technique reached a peak accuracy of 97.8% for binary classification.

Similarly, **Ayala et al., (2021) [102]** employed a model of a convolutional neural network to identify diabetic retinopathy by analyzing the structure of the eye. The parameters of the model were fine-tuned by applying the transfer-learning technique for label-to-image mapping. Medical fundus oculi photographs served as the training and testing dataset, with labels derived from a severity scale of eye diseases. From normal eye function to the presence of proliferative diabetic retinopathy, images were classified into five categories based on the severity scale. With the suggested method's 97.78% accuracy, diabetic retinopathy in fundus oculi images was confidently predicted. Later, **Narayanan et al., (2020) [103]** showcased a hybrid architecture for ML for the detection of diabetic retinopathy severity. Researchers proposed a method for the grading phase that involved integrating a support vector machine classifier, principal component analysis to reduce dimensionality, and several convolutional neural networks. Researchers proved that the suggested design was capable of handling class imbalance and sparse training data better. In terms of DR detection, they were 98.4 percent accurate. Lastly, **Ayon et al., (2019) [104]** proposed an approach for diagnosing diabetes via a deep neural network, employing five-fold as well as ten-fold cross-validation for training its features. The findings from the Pima Indian Diabetes (PID) dataset indicated that the deep learning methodology developed an effective system for diabetes prediction and achieved a prediction accuracy of 98.35% through five-fold cross-validation. Table 4 presents a summary of various deep-learning and hybrid techniques applied by different authors for risk prediction of diabetic retinopathy.

Table 4: Performance analysis of various deep learning and hybrid technologies used for risk prediction of Diabetic Retinopathy

Author	Technique Used	Dataset	Accuracy	Drawbacks	Research Gaps
Taifa et al., (2024) [93]	Hybrid of MobileNetV2, DenseNet121, and InceptionResNetV2	APTOS 2019	95.50% (multi-class), 98.36% (binary)	High computational requirements due to multiple models	Further validation on diverse and larger datasets, reducing
					computational costs
Bilal et al., (2024) [94]	CNN-SVD, ISVM-RBF.	IDRiD	99.18% accuracy, 98.15% sensitivity, 100% specificity	Complex hybrid model requires high computational power	More real-world testing, improvement in robustness across various datasets
Oulhadj et al., (2024) [95]	DenseNet121, Xception, EfficientNetB3	APTOS	86%	Moderate accuracy needs improvement in severity classification	Enhancement for multi-class classification and higher-resolution images
Rodríguez et al., (2024) [96]	CNN-RNN	Topcon 3D OCT-Maestro 1	95%	Limited real- world use and missing non- foveal DME.	Need for validated, interpretable AI to analyze full OCT cubes.
Prabha et al., (2024) [97]	RD-OCT Net	OCT retinal images	97.6% for nAMD, 98.08% for DME, 98% for RVO	Limited model complexity may miss subtle retinal disease features	Need for lightweight design with robust feature extraction for diverse retinal diseases.
Khan et al., (2024) [98]	ResNet50 and EfficientNetB0	OCT image	97.50%	High model complexity may hinder real-time clinical deployment	Need for efficient, interpretable hybrid models for accurate real-time OCT analysis in clinics
Gürcan et al., (2023) [99]	InceptionV3 and XGBoost	Messidor- 2	92.55%	Feature selection might miss important features,	Improvement of feature selection methods and validation on larger datasets
				moderate accuracy	
Ali et al., (2023) [100]	ResNet50 and Inceptionv3	OCT fundus images	96.85%	Requires more data diversity for generalization	Improving robustness across varied datasets andrefining hyperparameters

Butt et al., (2022) [101]	Hybrid CNN	APTOS	97.8%	Transfer learning limitations in handling unseen data	Optimization in transfer learning for unseen data
Ayala et al., (2021) [102]	CNN	APTOS	97.78%	Potential overfitting and limited robustness	Further validation with larger and more diverse datasets
Narayanan et al., (2020) [103]	Hybrid CNN with PCA and SVM	APTOS 2019	98.4%	Sensitive to class imbalance and small datasets	Addressing class imbalance and exploring other dimensionality reduction techniques
Ayon et al., (2019) [104]	Deep neural network with five-fold and ten- fold cross-validation	PID	98.35%	Limited validation on external datasets	Validation of different populations and external data sources

Figure 10 illustrates the accuracy of various deep learning and hybrid models for diabetic retinopathy risk prediction. The highest accuracy was reported at 99.18% of the CNN-SVD model. A combination of ResNet50 and Inceptionv3 resulted in 96.85%. The model, InceptionV3 with XGBoost, attained 92.55%, while the hybrid model, using a combination of DenseNet121, Xception, and EfficientNetB3, presented an accuracy of 86%. Hence, the hybrid models are quite effective in DR detection, and the best-performing model is CNN-SVD.

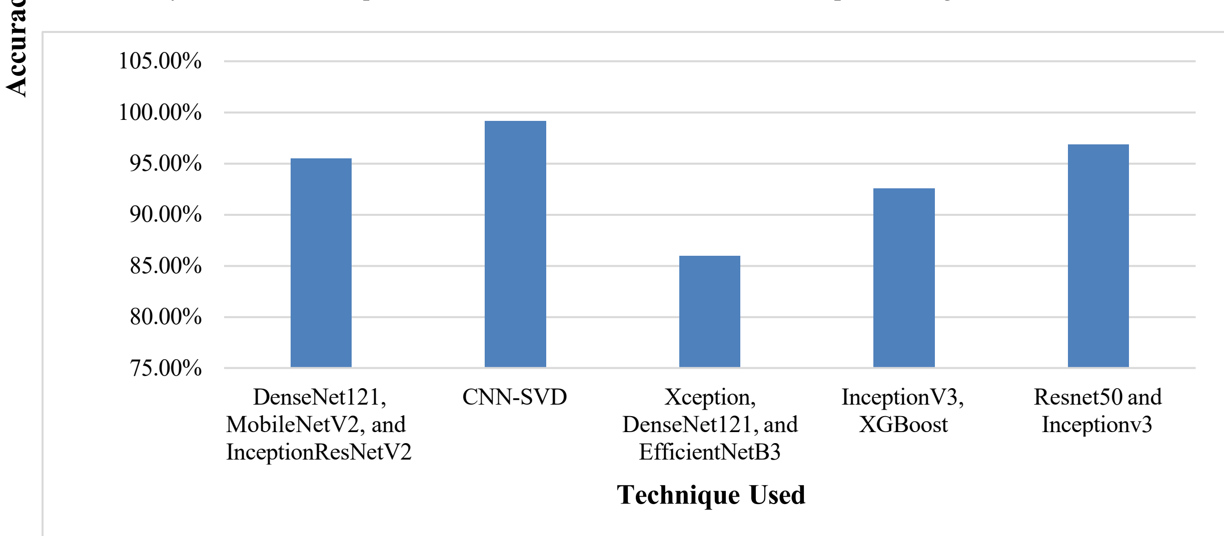

Figure 10: Comparative Analysis of various deep learning techniques

6. Discussion and Comparisons

This section performs a statistical analysis of the ML and DL methods discussed in previous sections. It compares techniques and accuracies of models for predicting diabetic retinopathy, highlighting methods like CNNs and hybrid models. Furthermore, the proposed AQs proposed in Section 3 is called to present some analytical reports as follows:

Q1: What machine learning techniques are used for predicting DR progression, and what are the strengths and limitations of these models?

The study explores various machine learning techniques used for predicting diabetic retinopathy progression, highlighting their strengths and limitations. Techniques like Boosted Tree and Simple Tree achieved high accuracy levels, with the Boosted Tree reaching 90.1% and Simple Tree at 88.6%, making them reliable for early DR detection. However, ensemble methods such as Ensemble ML showed lower accuracy at 75.1%, indicating room for improvement in such models. Additionally, SVM achieved moderate accuracy (79.5%), suggesting the need for advanced techniques to enhance prediction performance. Limitations across the models include overfitting, dependency on pre-processing and challenges with small or imbalanced datasets. Each model's applicability and accuracy depend on factors like dataset size, diversity, and computational resources, highlighting the importance of refining these models for better real-world applications.

Q2: What are the deep learning techniques and hybrid models available for predicting Diabetic

Retinopathy (DR)?

Various deep-learning techniques and hybrid models have been utilized for predicting diabetic retinopathy, demonstrating notable accuracy levels. The hybrid model using DenseNet121, MobileNetV2, and InceptionResNetV2 achieved 95.50% accuracy for multi-class and 98.36% for binary classification, showcasing strong performance but with high computational demands. The CNN-SVD hybrid model combined with ISVM- RBF, DT, and KNN attained the highest accuracy of 99.18%, with 98.15% sensitivity and 100% specificity in detecting vision-threatening DR. Another hybrid approach integrating DenseNet121, Xception, and EfficientNetB3 reached an accuracy of 86%, indicating room for improvement in severity classification. The InceptionV3 and XGBoost hybrid models achieved 92.55% accuracy, while the combination of ResNet50 and InceptionV3 yielded 96.85% accuracy. Lastly, the Hybrid CNN model utilizing transfer learning demonstrated 97.8% accuracy for binary classification. These techniques highlight the efficacy of hybrid models in DR prediction, although challenges remain in terms of computational complexity and scalability.

Q3: What are the key research challenges and gaps in the diagnosis of Diabetic Retinopathy (DR)?

The study identifies several challenges and gaps in the diagnosis of diabetic retinopathy using ML, deep learning, and hybrid models. The scalability and ability of the ML techniques of DT and SVMs to handle huge and diverse data sets are still limited. These models also suffer from class imbalance, where a DR severity level is not well represented in training data and leads to poor predictions in the categories. Further, there is an issue of overfitting, which is often found in models in which advanced regularization or feature selection techniques are not implemented. Deep learning techniques, like DenseNet121, MobileNetV2, and InceptionResNetV2, also extremely require resources when training. This is a major limitation of their application within the smaller clinics and resource-constrained environments.

Further, such models require large and diverse datasets for better generalization because they seem to do very well in controlled environments but face difficulties with unseen data in real-world scenarios. This also leads to an increased reliance on pre-processing operations, such as data augmentation, which is complex and time-consuming. There are hybrid schemes that couple models like CNN-SVD with ISVM-RBF, DT, CNN-RNN, and KNN and suffer from the complexity of the hybrid architecture itself which is highly resource-intensive from a computational standpoint. This also gives rise to the problem of hyperparameter tuning; it is hard to find optimum values of the hyperparameters of these models, especially for any given dataset. In some models, such as InceptionV3 with XGBoost, most of the critical information in the feature selection scheme gets missed, and thus the model performance could be suboptimal. Practical deployment of hybrid models also lags, with limited validation in diverse healthcare settings, impacting their robustness and reliability for real-world applications. This lack of adaptability is particularly apparent in models such as the RD-OCT, which, while achieving high classification accuracy in normal and disease classes like DME, nAMD, and RVO, still require further testing to ensure consistent performance in clinical settings. Another limitation for hybrid models that include deep learning is that they face limitations when adapting to unseen data, requiring further refinement of robustness and reliability in clinical applications. Current gaps and challenges thus require continuous upgrades in feature selection, model efficiency, generalizability and efforts toward validating the technique in real-world scenarios across different clinical settings.

7. Conclusion and Future Scope

This systematic comparative study assessed machine learning and deep learning approaches for diabetic retinopathy risk prediction from 2019 to 2024, focusing on 22 rigorously selected papers based on PRISMA guidelines. The initial identification phase involved screening papers based on document type, language, and publication year. After the removal of duplicates and irrelevant studies, 22 papers remained, each contributing to the understanding of ML and DL's role in diabetic retinopathy risk prediction. In addressing Q1, the review highlights that while traditional ML models like DT and SVM play a role, they often face challenges with scalability, overfitting, and dataset diversity, as seen with Ensemble ML's lower accuracy of 75.1%. Q2 reveals that combining DL, such as InceptionV3, XGBoost, DenseNet121, Xception, and EfficientNetB3, significantly improves detection rates, underscoring the effectiveness of hybrid approaches such as CNN-SVD achieving detection rates up to 99.18%. These DL models excel at automatically extracting features from raw data, reducing manual intervention, and offering higher accuracy, especially for complex datasets as compared to ML models but these models increase the complexity. Q3 identified research gaps, including the need for larger datasets, better handling of class imbalances, and computational inefficiencies in DL models. Future research should focus on these challenges by developing scalable, real-time models, exploring unsupervised learning techniques, and improving data labeling processes. Ultimately, while current DL Hybrid models provide superior accuracy, future advancements should refine these models further to ensure more efficient, scalable, and clinically applicable solutions, particularly for real-world deployment in diverse clinical environments.

References

[1] Varsha, Mehra, Mishra Smita, Gupta Nomita, and Khatri Manisha. "Diabetes: The next epidemic." *International Journal of Life Sciences International Peer Reviewed Open Access Refereed Journal Int. J. of Life Sciences* 6 (2018): 665-680.

[2] Rongioletti, Franco. "Pancreas disease and diabetes mellitus." *Clinical and pathological aspects of skin diseases in endocrine, metabolic, nutritional and deposition disease* (2010): 11-25.

[3] National Eye Institute, National Institutes of Health. Facts about Diabetic Eye Disease. Available at: https://www.nei.nih.gov/learn-about-eye-health/out reach-resources/diabetic-eye-disease resources#:~:text=Diabetic%20eye%20disease%20at%20a%20glance&text=Having%20diabetes%20incre ases%20the%20risk,)%2C%20cataract%2C%20and%20glauc oma. Accessed on 24 November 2023.

[4] Forrest, Iain S., Kumardeep Chaudhary, Ishan Paranjpe, Ha My T. Vy, Carla Marquez-Luna, Ghislain Rocheleau, Aparna Saha et al. "Genome-wide polygenic risk score for retinopathy of type 2 diabetes." *Human Molecular Genetics* 30, no. 10 (2021): 952-960.

[5] NHS Choices. Diabetic eye screening. 2016. Available at: https://www.nhs.uk/conditions/ diabetic-eye- screening/. Accessed on 24 November 2023.

[6] Solomon, Sharon D., Emily Chew, Elia J. Duh, Lucia Sobrin, Jennifer K. Sun, Brian L. VanderBeek, Charles C. Wykoff, and Thomas W. Gardner. "Diabetic retinopathy: a position statement by the American Diabetes Association." *Diabetes Care* 40, no. 3 (2017): 412.

[7] Liu, Yao, and Rebecca Swearingen. "Diabetic eye screening: knowledge and perspectives from providers and patients." *Current diabetes reports* 17 (2017): 1-8.

[8] Nsiah-Kumi, Phyllis, Stacie R. Ortmeier, and Amy E. Brown. "Disparities in diabetic retinopathy screening and disease for racial and ethnic minority populations—a literature review." *Journal of the National Medical Association* 101, no. 5 (2009): 430-438.

[9] Lawrenson JG, Graham-Rowe E, Lorencatto F, Burr J, Bunce C, Francis JJ, et al. Interventions to increase attendance for diabetic retinopathy screening. Cochrane Database Syst Rev. 2018;1(1):CD012054.

[10] Masharani U. Diabetes Ocular complications. Chronic Complications of Diabetes. Armenian Medical Network. 2006

[11] News-Medical Life Sciences. Diabetes and Vision. Available at: https://www.news-medical.net/health/ Diabetes-and-Vision.aspx. Accessed on 24 November 2023.

[12] Selvachandran, Ganeshsree, Shio Gai Quek, Raveendran Paramesran, Weiping Ding, and Le Hoang Son. "Developments in the detection of diabetic retinopathy: a state-of-the-art review of computer-aided diagnosis and machine learning methods." Artificial intelligence review 56, no. 2 (2023): 915-964.

[13] Arcadu, Filippo, Fethallah Benmansour, Andreas Maunz, Jeff Willis, Zdenka Haskova, and Marco Prunotto. "Deep learning algorithm predicts diabetic retinopathy progression in individual patients." NPJ digital medicine 2, no. 1 (2019): 92.

[14] Emon, Minhaz Uddin, Raihana Zannat, Tania Khatun, Mahfujur Rahman, and Maria Sultana Keya. "Performance analysis of diabetic retinopathy prediction using machine learning models." In 2021 6th International Conference on Inventive Computation Technologies (ICICT), pp. 1048-1052. IEEE, 2021.

[15] Reddy, G. Thippa, Sweta Bhattacharya, S. Siva Ramakrishnan, Chiranji Lal Chowdhary, Saqib Hakak, Rajesh Kaluri, and M. Praveen Kumar Reddy. "An ensemble-based machine learning model for diabetic retinopathy classification." In 2020 international conference on emerging trends in information technology and engineering (ic-ETITE), pp. 1-6. IEEE, 2020.

[16] Xiao, Di, Alauddin Bhuiyan, Shaun Frost, Janardhan Vignarajan, Mei-Ling Tay-Kearney, and Yogesan Kanagasingam. "Major automatic diabetic retinopathy screening systems and related core algorithms: a review." Machine Vision and Applications 30 (2019): 423-446.

[17] SK, Somasundaram, and Alli P. "A machine learning ensemble classifier for early prediction of diabetic retinopathy." Journal of Medical Systems 41 (2017): 1-12.

[18] Li, Wanyue, Yanan Song, Kang Chen, Jun Ying, Zhong Zheng, Shen Qiao, Ming Yang, Maonian Zhang, and Ying Zhang. "Predictive model and risk analysis for diabetic retinopathy using machine learning: a retrospective cohort study in China." *Bmj Open* 11, no. 11 (2021): e050989.

[19] Aldahiri, Amani, Bashair Alrashed, and Walayat Hussain. "Trends in using IoT with machine learning in health prediction system." Forecasting 3, no. 1 (2021): 181-206.

[20] Prakash, Chandra, Rajesh Kumar, and Namita

Mittal. "Recent developments in human gait research: parameters, approaches, applications, machine learning techniques, datasets and challenges." Artificial Intelligence Review 49 (2018): 1-40.
[21] Tuppad, Ashwini, and Shantala Devi Patil. "Machine learning for diabetes clinical decision support: a review." Advances in Computational Intelligence 2, no. 2 (2022): 22.
[22] Jagan Mohan, N., R. Murugan, and Tripti Goel. "Deep learning for diabetic retinopathy detection: Challenges and opportunities." Next Generation Healthcare Informatics (2022): 213-232.
[23] Li, Tao, Yingqi Gao, Kai Wang, Song Guo, Hanruo Liu, and Hong Kang. "Diagnostic assessment of deep learning algorithms for diabetic retinopathy screening." Information Sciences 501 (2019): 511-522.
[24] Pal, Ridam, Jayanta Poray, and Mainak Sen. "Application of machine learning algorithms on diabetic retinopathy." In *2017 2nd IEEE International Conference on Recent Trends in Electronics, Information & Communication Technology (RTEICT)*, pp. 2046-2051. IEEE, 2017.
[25] Khamparia, Aditya, and Karan Mehtab Singh. "A systematic review on deep learning architectures and applications." Expert Systems 36, no. 3 (2019): e12400.
[26] Endo, Toshihiro. "Analysis of Conventional Feature Learning Algorithms and Advanced Deep Learning Models." Journal of Robotics Spectrum 1 (2023): 001-012.
[27] Kumar, Upendra. "Applications of machine learning in disease pre-screening." In Research Anthology on Artificial Intelligence Applications in Security, pp. 1052-1084. IGI Global, 2021.
[28] Ting, Daniel SW, Lily Peng, Avinash V. Varadarajan, Pearse A. Keane, Philippe M. Burlina, Michael F. Chiang, Leopold Schmetterer et al. "Deep learning in ophthalmology: the technical and clinical considerations." Progress in retinal and eye research 72 (2019): 100759.
[29] Date, Rishabh C., Sirus J. Jesudasen, and Christina Y. Weng. "Applications of deep learning and artificial intelligence in retina." International Ophthalmology Clinics 59, no. 1 (2019): 39-57.
[30] Gargeya, Rishab, and Theodore Leng. "Automated identification of diabetic retinopathy using deep learning." Ophthalmology 124, no. 7 (2017): 962-969.
[31] Zhang, Angela, Lei Xing, James Zou, and Joseph C. Wu. "Shifting machine learning for healthcare from development to deployment and from models to data." Nature Biomedical Engineering 6, no. 12 (2022): 1330-1345.
[32] Hudson, Chris. "The clinical features and classification of diabetic retinopathy." *Ophthalmic and Physiological Optics* 16 (1996): S43-S48.
[33] Centers for Disease Control and Prevention. Vision Loss. Available at: https://www.cdc.gov/vision health/basic_information/vision_loss.htm. Accessed on 24 November 2023
[34] Srivastava, Namrata, M. Chandra, and Nitesh. "Diabetes and the retinal changes in the eye: a threat to the sight." *International Journal of Community Medicine and Public Health* 11, no. 2 (2024): 1030.
[35] Macular Edema. National Eye Institute. Available at: https://www.nei.nih.gov/learn-about-eye- health/eyeconditions-and-diseases/macular-edema. Accessed on 24 November 2023.
[36] Kulkarni, Amol D., and Michael S. Ip. "Diabetic macular edema: therapeutic options." *Diabetes Therapy* 3 (2012): 1-14.
[37] Priya, P. Vishnu, A. Srinivasarao, and J. V. C. Sharma. "Diabetic retinopathy can lead to complete blindness." *Int. J. Sci. Invent. Today* 2, no. 4 (2013): 254-265.
[38] Hammes, H-P., and Massimo Porta, eds. *Experimental approaches to diabetic retinopathy*. Vol. 20. Karger Medical and Scientific Publishers, 2010.
[39] Lee, Tien Y. Wong, and Charumathi Sabanayagam. "Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss." *Eye and Vision* 2 (2015): 1-25.
[40] Jacoba, Cris Martin P., Leo Anthony Celi, and Paolo S. Silva. "Biomarkers for progression in diabetic retinopathy: expanding personalized medicine through integration of AI with electronic health records." In *Seminars in ophthalmology*, vol. 36, no. 4, pp. 250-257. Taylor & Francis, 2021.
[41] Alyoubi, Wejdan L., Wafaa M. Shalash, and Maysoon F. Abulkhair. "Diabetic retinopathy detection through deep learning techniques: A review." *Informatics in Medicine Unlocked* 20 (2020): 100377.
[42] Ting, Daniel Shu Wei, Gemmy Chui Ming Cheung, and Tien Yin Wong. "Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review." *Clinical & Experimental Ophthalmology* 44, no. 4 (2016): 260-277.
[43] Lin, I-Chan, Yuan–Hung Wang, Cheng-Li Lin, Yen-Jung Chang, Shwu-Huey Lee, and I-Jong Wang. "Diabetic polyneuropathy and the risk of developing diabetic retinopathy: a nationwide, population-based study." *Acta*

Ophthalmologica 93, no. 8 (2015): 713-718.
[44] Lee, Ryan, Tien Y. Wong, and Charumathi Sabanayagam. "Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss." *Eye and Vision* 2 (2015): 1-25.
[45] Kropp, Martina, Olga Golubnitschaja, Alena Mazurakova, Lenka Koklesova, Nafiseh Sargheini, Trong-Tin Kevin Steve Vo, Eline de Clerck et al. "Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications—risks and mitigation." *Epma Journal* 14, no. 1 (2023): 21-42.
[46] Elsharkawy, Mohamed, Mostafa Elrazzaz, Ahmed Sharafeldeen, Marah Alhalabi, Fahmi Khalifa, Ahmed Soliman, Ahmed Elnakib et al. "The role of different retinal imaging modalities in predicting progression of diabetic retinopathy: A survey." *Sensors* 22, no. 9 (2022): 3490.
[47] Burgess, Philip Ian. *Determinants of severity and progression of diabetic retinopathy in Southern Malawi*. The University of Liverpool (United Kingdom), 2015.
[48] Nawaz, Mohd Imtiaz. "Perspective Chapter: Translational Implications of Proliferative Diabetic Retinopathy (PDR) Vitreous Fluid." (2024).
[49] Govindaiah, Arun, Abdul Baten, R. Theodore Smith, Siva Balasubramanian, and Alauddin Bhuiyan. "Optimized prediction models from Fundus Imaging and Genetics for late age-related Macular Degeneration." *Journal of Personalized Medicine* 11, no. 11 (2021): 1127.
[50] Jeong, Yeonwoo, Yu-Jin Hong, and Jae-Ho Han. "Review of machine learning applications using retinal fundus images." *Diagnostics* 12, no. 1 (2022): 134.
[51] Fregoso-Aparicio, Luis, Julieta Noguez, Luis Montesinos, and José A. García-García. "Machine learning and deep learning predictive models for type 2 diabetes: a systematic review." *Diabetology & metabolic syndrome* 13, no. 1 (2021): 148.
[52] Mehta, Tanvi, and Ruby Pant. "Lightweight Machine Learning Algorithm for Automatic Detection of Diabetic Retinopathy in IoT." In *2022 IEEE 2nd Mysore Sub Section International Conference (MysuruCon)*,pp. 1-7. IEEE, 2022.
[53] Libbrecht, Maxwell W., and William Stafford Noble. "Machine learning applications in genetics and genomics." *Nature Reviews Genetics* 16, no. 6 (2015): 321-332.
[54] Réda, Clémence, Emilie Kaufmann, and Andrée Delahaye-Duriez. "Machine learning applications in drug development." *Computational and structural biotechnology journal* 18 (2020): 241-252.
[55] Naushad, Shaik Mohammad, Tajamul Hussain, Bobbala Indumathi, Khatoon Samreen, Salman A. Alrokayan, and Vijay Kumar Kuala. "Machine learning algorithm-based risk prediction model of coronary artery disease." *Molecular Biology Reports* 45, no. 5 (2018): 901-910.
[56] Piersanti, Agnese, Benedetta Salvatori, Piera D'Avino, Laura Burattini, Christian Göbl, Andrea Tura, and Micaela Morettini. "Diabetic Retinopathy Detection: A Machine-Learning Approach Based on Continuous Glucose Monitoring Metrics." In *International Conference on e-Health and Bioengineering*, pp. 763-773. Cham: Springer Nature Switzerland, 2023.
[57] Kufel, Jakub, Katarzyna Bargieł-Łączek, Szymon Kocot, Maciej Koźlik, Wiktoria Bartnikowska, Michał Janik, Łukasz Czogalik et al. "What is machine learning, artificial neural networks and deep learning?—Examples of practical applications in medicine." *Diagnostics* 13, no. 15 (2023): 2582.
[58] Kim, Jin, Nara Shin, Seung Yeon Jo, and Sang Hyun Kim. "Method of intrusion detection using deep neural network." In *2017 IEEE International Conference on big data and smart computing (BigComp)*, pp. 313-316. IEEE, 2017.
[59] Voulodimos, Athanasios, Nikolaos Doulamis, Anastasios Doulamis, and Eftychios Protopapadakis. "Deep learning for computer vision: A brief review." *Computational intelligence and neuroscience* 2018, no. 1 (2018): 7068349.
[60] Osipyan, Hasmik, Bosede Iyiade Edwards, and Adrian David Cheok. *Deep neural network applications*. CRC Press, 2022.
[61] Deng, Li, and John Platt. "Ensemble deep learning for speech recognition." In *Proc. interspeech*. 2014.
[62] Bouhedjar, Khalid, Abdelbasset Boukelia, Abdelmalek Khorief Nacereddine, Anouar Boucheham, Amine Belaidi, and Abdelhafid Djerourou. "A natural language processing approach based on embedding deep learning from heterogeneous compounds for quantitative structure-activity relationship modeling." *Chemical Biology & Drug Design* 96, no. 3 (2020): 961-972.
[63] Chan, Heang-Ping, Ravi K. Samala, Lubomir M. Hadjiiski, and Chuan Zhou. "Deep learning in medical image analysis." *Deep learning in medical image analysis: challenges and applications* (2020): 3-21.
[64] Campesato, Oswald. *Artificial intelligence, machine learning, and deep learning*. Mercury Learning and Information, 2020.

[65] Gupta, Rohan, Devesh Srivastava, Mehar Sahu, Swati Tiwari, Rashmi K. Ambasta, and Pravir Kumar. "Artificial intelligence to deep learning: machine intelligence approach for drug discovery." *Molecular Diversity* 25 (2021): 1315-1360.

[66] Taye, Mohammad Mustafa. "Understanding of machine learning with deep learning: architectures, workflow, applications and future directions." *Computers* 12, no. 5 (2023): 91.

[67] Sarker, Iqbal H. "Deep learning: a comprehensive overview on techniques, taxonomy, applications and research directions." *SN computer science* 2, no. 6 (2021): 420.

[68] Wahab Sait, Abdul Rahaman. "A lightweight diabetic retinopathy detection model using a deep-learning technique." *Diagnostics* 13, no. 19 (2023): 3120.

[69] Sengupta, Saptarshi, Sanchita Basak, Pallabi Saikia, Sayak Paul, Vasilios Tsalavoutis, Frederick Atiah, Vadlamani Ravi, and Alan Peters. "A review of deep learning with special emphasis on architectures, applications and recent trends." *Knowledge-Based Systems* 194 (2020): 105596.

[70] Pinaya, Walter Hugo Lopez, Sandra Vieira, Rafael Garcia-Dias, and Andrea Mechelli. "Convolutional neural networks." In *Machine learning*, pp. 173-191. Academic Press, 2020.

[71] Dara, Suresh, and Priyanka Tumma. "Feature extraction by using deep learning: A survey." In *2018 Second International Conference on Electronics, communication and Aerospace Technology (ICECA)*, pp. 1795- 1801. IEEE, 2018.

[72] Ketkar, Nikhil, Jojo Moolayil, Nikhil Ketkar, and Jojo Moolayil. "Convolutional neural networks." *Deep learning with Python: learn best practices of deep learning models with PyTorch* (2021): 197-242.

[73] Vij, Richa, and Sakshi Arora. "A systematic review on diabetic retinopathy detection using deep learning techniques." *Archives of Computational Methods in Engineering* 30, no. 3 (2023): 2211-2256.

[74] Jogin, Manjunath, M. S. Madhulika, G. D. Divya, R. K. Meghana, and S. Apoorva. "Feature extraction using convolution neural networks (CNN) and deep learning." In *2018, 3rd IEEE International Conference on recent trends in electronics, information & communication technology (RTEICT)*, pp. 2319-2323. IEEE, 2018.

[75] Ghaderizadeh, Saeed, Dariush Abbasi-Moghadam, Alireza Sharifi, Na Zhao, and Aqil Tariq. "Hyperspectral image classification using a hybrid 3D-2D convolutional neural networks." *IEEE Journal of Selected Topics in Applied Earth Observations and Remote Sensing* 14 (2021): 7570-7588.

[76] Akil, Mohamed, Yaroub Elloumi, and Rostom Kachouri. "Detection of retinal abnormalities in fundus image using CNN deep learning networks." In *State of the Art in Neural Networks and their Applications*, pp. 19-61. Academic Press, 2021.

[77] Chalakkal, Renoh Johnson, Waleed Habib Abdulla, and Sheng Chiong Hong. "Fundus retinal image analyses for screening and diagnosing diabetic retinopathy, macular edema, and glaucoma disorders." In *Diabetes and fundus OCT*, pp. 59-111. Elsevier, 2020.

[78] Balaprakash, Prasanna, Michael Salim, Thomas D. Uram, Venkat Vishwanath, and Stefan M. Wild. "Deephyper: Asynchronous hyperparameter search for deep neural networks." In *2018 IEEE 25th International Conference on high-performance Computing (HiPC)*, pp. 42-51. IEEE, 2018.

[79] Marcus, Gary. "Deep Learning: A Critical Appraisal." *arXiv preprint arXiv:1801.00631* (2018).

[80] Jabbar, Ayesha, Hannan Bin Liaqat, Aftab Akram, Muhammad Usman Sana, Irma Domínguez Azpíroz, Isabel De La Torre Diez, and Imran Ashraf. "A Lesion-Based Diabetic Retinopathy Detection Through Hybrid Deep Learning Model." *IEEE Access* (2024).

[81] Oulhadj, Mohammed, Jamal Riffi, Chaimae Khodriss, Adnane Mohamed Mahraz, Ahmed Bennis, Ali Yahyaouy, Fouad Chraibi, Meriem Abdellaoui, Idriss Benatiya Andaloussi, and Hamid Tairi. "Diabetic retinopathy prediction based on wavelet decomposition and modified capsule network." *Journal of Digital Imaging* 36, no. 4 (2023): 1739-1751.

[82] Hu, Jingbo, Huan Wang, Le Wang, and Ye Lu. "Graph adversarial transfer learning for diabetic retinopathy classification." *IEEE Access* 10 (2022): 119071-119083.

[83] Menaouer, Brahami, Zoulikha Dermane, Nour El Houda Kebir, and Nada Matta. "Diabetic retinopathy classification using hybrid deep learning approach." *SN Computer Science* 3, no. 5 (2022): 357.

[84] Kumar, Gaurav, Shraban Chatterjee, and Chiranjoy Chattopadhyay. "DRISTI: a hybrid deep neural network for diabetic retinopathy diagnosis." *Signal, Image and Video Processing* 15, no. 8 (2021): 1679-1686.

[85] Fan, Runze, Yuhong Liu, and Rongfen Zhang. "Multi-scale feature fusion with adaptive weighting for diabetic retinopathy severity classification." *Electronics* 10, no. 12 (2021): 1369.

[86] Bodapati, Jyostna Devi, Nagur Shareef Shaik, and Veeranjaneyulu Naralasetti. "Composite

deep neural network with gated-attention mechanism for diabetic retinopathy severity classification." *Journal of Ambient Intelligence and Humanized Computing* 12, no. 10 (2021): 9825-9839.
[87] Alfian, Ganjar, Muhammad Syafrudin, Norma Latif Fitriyani, Muhammad Anshari, Pavel Stasa, Jiri Svub, and Jongtae Rhee. "Deep neural network for predicting diabetic retinopathy from risk factors." *Mathematics* 8, no. 9 (2020): 1620.
[88] Sumathy, B., Arindam Chakrabarty, Sandeep Gupta, Sanil S. Hishan, Bhavana Raj, Kamal Gulati, and Gaurav Dhiman. "Prediction of diabetic retinopathy using health records with machine learning classifiers and data science." International Journal of Reliable and Quality E-Healthcare (IJRQEH) 11, no. 2 (2022): 1-16.
[89] Odeh, Israa, Mouhammd Alkasassbeh, and Mohammad Alauthman. "Diabetic retinopathy detection using ensemble machine learning." In 2021 International Conference on Information Technology (ICIT), pp. 173-178. IEEE, 2021.
[90] Sharma, Ayushi, Swapnil Shinde, Imran Ismail Shaikh, Madhav Vyas, and Soumya Rani. "Machine learning approach for detection of diabetic retinopathy with improved pre-processing." In 2021 International Conference on Computing, communication, and intelligent systems (ICCCIS), pp. 517-522. IEEE, 2021.
[91] Huda, SM Asiful, Ishrat Jahan Ila, Shahrier Sarder, Md Shamsujjoha, and Md Nawab Yousuf Ali. "An improved approach for detection of diabetic retinopathy using feature importance and machine learning algorithms." In 2019 7th International Conference on Smart Computing & Communications (ICSCC), pp. 1-5. IEEE, 2019.
[92] Tsao, Hsin-Yi, Pei-Ying Chan, and Emily Chia-Yu Su. "Predicting diabetic retinopathy and identifying interpretable biomedical features using machine learning algorithms." BMC Bioinformatics 19 (2018): 111- 121.
[93] Taifa, Intifa Aman, Deblina Mazumder Setu, Tania Islam, Samrat Kumar Dey, and Tazizur Rahman. "A hybrid approach with customized machine learning classifiers and multiple feature extractors for enhancing diabetic retinopathy detection." Healthcare Analytics (2024): 100346.
[94] Bilal, Anas, Azhar Imran, Talha Imtiaz Baig, Xiaowen Liu, Haixia Long, Abdulkareem Alzahrani, and Muhammad Shafiq. "Improved Support Vector Machine based on CNN-SVD for vision-threatening diabetic retinopathy detection and classification." Plos one 19, no. 1 (2024): e0295951.
[95] Oulhadj, Mohammed, Jamal Riffi, Chaimae Khodriss, Adnane Mohamed Mahraz, Ali Yahyaouy, Meriem Abdellaoui, Idriss Benatiya Andaloussi, and Hamid Tairi. "Diabetic Retinopathy Prediction Based on a Hybrid Deep Learning Approach." In 2024 International Conference on Intelligent Systems and Computer Vision (ISCV), pp. 1-5. IEEE, 2024.
[96] Rodríguez-Miguel, Antonio, Carolina Arruabarrena, Germán Allendes, Maximiliano Olivera, Javier Zarranz-Ventura, and Miguel A. Teus. "Hybrid deep learning models for the screening of Diabetic Macular Edema in optical coherence tomography volumes," *Scientific Reports* 14, no. 1 (2024): 17633.
[97] Prabha, A. Jeya, C. Venkatesan, M. Sameera Fathimal, K. K. Nithiyanantham, and SP Angeline Kirubha. "RD-OCT net: a hybrid learning system for automated diagnosis of macular diseases from OCT retinal images." Biomedical Physics & Engineering Express 10, no. 2 (2024): 025033.
[98] Khan, Umer Sadiq, and Saif Ur Rehman Khan. "Boost diagnostic performance in retinal disease classification utilizing deep ensemble classifiers based on OCT." *Multimedia Tools and Applications* (2024): 1-21.
[99] Gürcan, Ömer Faruk, Uğur Atıcı, and Ömer Faruk Beyca. "A hybrid deep learning-metaheuristic model for diagnosis of diabetic retinopathy." Gazi University Journal of Science 36, no. 2 (2023): 693-703.
[100] Ali, Ghulam, Aqsa Dastgir, Muhammad Waseem Iqbal, Muhammad Anwar, and Muhammad Faheem. "A hybrid convolutional neural network model for automatic diabetic retinopathy classification from fundus images." IEEE Journal of Translational Engineering in Health and Medicine 11 (2023): 341-350.
[101] Butt, Muhammad Mohsin, DNF Awang Iskandar, Sherif E. Abdelhamid, Ghazanfar Latif, and Runna Alghazo. "Diabetic retinopathy detection from fundus images of the eye using hybrid deep learning features." Diagnostics 12, no. 7 (2022): 1607.
[102] Ayala, Angel, Tomas Ortiz Figueroa, Bruno Fernandes, and Francisco Cruz. "Diabetic retinopathy improved detection using deep learning." Applied Sciences 11, no. 24 (2021): 11970.
[103] Narayanan, Barath Narayanan, Russell C. Hardie, Manawaduge Supun De Silva, and Nathaniel K. Kueterman. "Hybrid machine learning architecture for automated detection and grading of retinal images for diabetic retinopathy." Journal of Medical Imaging 7, no. 3 (2020): 034501-034501.
[104] Ayon, Safial Islam, and Md Milon

Islam. "Diabetes prediction: a deep learning approach." International Journal of Information Engineering and Electronic