Advanced International Journal for Research (AIJFR)
E-ISSN: 3048-7641 ● Website: www.aijfr.com ● Email: editor@aijfr.com

Machine Learning–Based Fundus Image Analysis for Early Diagnosis of Diabetic Retinopathy: A Comprehensive Systematic Review

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Abstract

Diabetic retinopathy (DR) culminates to be the main reason of visual impairments that can be avoided. The early diagnosis by means of regular screenings turns out to be extremely important in the reduction of permanent eyesight loss risk. Color fundus photography is commonly used for the DR screening, but manual assessment is time-consuming and depends on the availability of the trained specialists. To address these limitations, automated analysis of the fundus images has been widely studied. This review presents the structured synthesis of the learning-based methods for DR grading, and lesion analysis using the fundus images. The literature covers traditional feature-based techniques, deep learning models, hybrid, and transfer learning frameworks, and lesion-level segmentation approaches. The common datasets, preprocessing methods, model designs, and evaluation metrics are reviewed to identify the key trends, and methodological differences. Evidence from more than fifty literature studies indicates that the deep convolutional models, and the transfer learning approaches achieve higher accuracy than the conventional methods on benchmark datasets. Detection and segmentation of lesions certainly enhance the clinical interpretability but they do come with the limitation of required annotation efforts and data variability. The major issues that are still to be resolved are the diversity of datasets, unequal distribution of classes, poor external validation, and challenges in incorporating the results into the clinical setting. Progress in standardization, privacy-aware learning, and multimodal analysis is essential for the reliable as well as clinically usable DR screening systems.

Keywords: Deep learning, diabetic retinopathy, fundus imaging, machine learning, medical image analysis, screening etc.

1. Introduction

Diabetic retinopathy (DR) is the most frequent microvascular complication experienced by people with diabetes, and it is still one of the main causes of preventable blindness among the economically active population in the world. The rapid diabetes spread, mainly in developing countries, has been accompanied by an increase in the number of DR cases, which has made the healthcare systems suffer enormously

[1][2]. DR-related vision loss is, however, mostly preventable if the disease is caught and treated in time; this is so because in such a case, the patient can be put on glycemic control, receive laser therapy, or get intravitreal injections which can all drastically slow down or even stop the disease progression. Nevertheless, the early detection of DR, which is mostly asymptomatic, brings about a delay in diagnosis that results in irreversible retinal damage, thus underscoring the need for systematic screening programs [3].

Even though there is a strong clinical agreement on the importance of frequent retinal screening, the actual implementation still faces a number of obstacles. Regular eye screening depends on the manual evaluation of retinal fundus images taken by trained ophthalmologists or graders, which is a long, costly, and variable process between different operators. The existence of a shortage of eye care specialists in many areas, especially rural and disadvantaged ones, has made the situation worse by further limiting screening availability [4]. The mentioned obstacles have consequently resulted in the exploration of automated and semi-automated screening methods which not only would be the support for the clinicians, but also the reduction of their burden and providing more access for the early diagnosis.

The clinical motivation and technical workflow of automated DR screening using fundus imaging are presented in Fig. 1 which shows the disease burden connected to the algorithmic analysis [5][6].

At the same time, color fundus photography has become the most preferred imaging method for DR screening due to its non-invasive nature, low cost, and capability to capture the essential pathological features such as microaneurysms, hemorrhages, exudates, and neovascularization. The developments in the fields of digital imaging and data storage have made it possible to build vast fundus image repositories, thereby promoting the use of machine learning (ML) and deep learning (DL) methods for automated DR analysis [7]. The initial methods were based on manual feature extraction combined with classical classifiers, where domain-specific features describing texture, color, and morphology were engineered manually. On the other hand, deep learning models, especially convolutional neural networks, have been able to outperform the earlier mentioned techniques by directly learning hierarchical representations from raw images, thereby achieving expert-level accuracy in controlled environments very often [8].

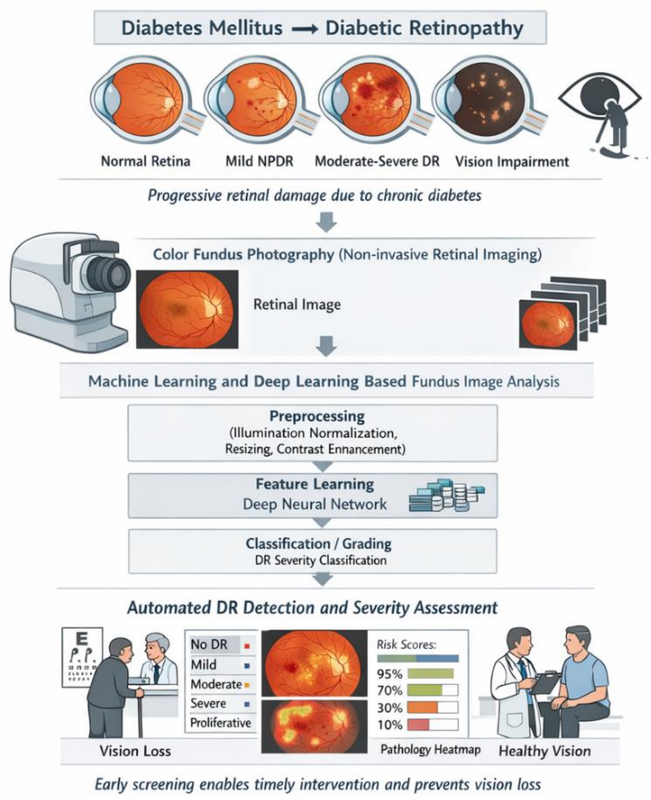

Fig. 1. Overview of diabetic retinopathy screening using fundus photography and machine learning, illustrating disease progression, fundus image acquisition, automated analysis pipelines, and the role of early detection in preventing vision loss.

The combination of algorithmic improvements and the expansion of research areas has led to the generation of an impressive volume of literature that is not only large but also very diverse. Such literature varies greatly with respect to data used, ways of handling data, models employed, evaluation criteria, and finally, performance measurement metrics. Although there are a few review articles, most of them either deal with a small part of the methods or do not have a systematic and reproducible reviewing protocol [9]. The result of this fragmentation is that it is very difficult for both researchers and practitioners to get a clear view regarding the leading techniques, their comparative performance, and the possibility of them being used in real-world settings [10].

The current review is the one that meets this need since it offers a broad and systematic review of the application of machine learning and deep learning methods to fundus image analysis for early diagnosis of diabetic retinopathy. The review's main theme is reproducibility and transparency, which is why it includes a wide range of trials such as publicly available datasets, usual preprocessing and augmentation techniques, typical model architectures, and standardized evaluation metrics. A PRISMA-guided literature selection strategy is used to guarantee that the studies to be included and excluded are chosen according to objective criteria, which in turn allows for the comparison of more than fifty peer-reviewed contributions meaningfully. Apart from summarizing prior work, the review also gives a critical overview of the methodological flaws, the obstacles to generalization, and the discrepancies between the performance in the experiments and that required by the clinics. It then suggests a ranked research agenda with priorities that will help to steer the future investigations.

2.Machine-Learning Methods (Taxonomy)

The various methods of automated analysis of retinal fundus images for diabetic retinopathy (DR) have come a long way; from reliance on handcrafted features to modern self-supervised deep learning frameworks. The following part of the paper offers a systematic classification of the machine-learning (ML) techniques that have been documented in the literature, showcasing their respective algorithms, performance traits, and practical strengths and weaknesses.

A. Taxonomy Overview

Fig. 2 summarizes the evolution and categorization of machine-learning approaches for fundus-based DR analysis, showing the transition from handcrafted feature pipelines to deep and weakly supervised learning paradigms.

B. Traditional Machine-Learning Pipelines

Early DR detection systems relied on handcrafted feature extraction followed by classical classifiers. Retinal texture, color, vessel morphology, and lesion-specific such as microaneurysm size and location were among the characteristics that the features aimed to capture. The classifiers that were commonly used were SVM, RF, k-NN, and logistic regression [21-26].

Such representative studies showed moderate performance on small to medium datasets like Messidor and DIARETDB1 with reported accuracies from 80% to 90% for DR binary detection interpretations [22], [24] Being interpretable and computationally cheaper were among the advantages of these methods for early screening systems. Nevertheless, their performance was highly image quality and feature design dependent, thus limiting their use to a particular dataset and imaging device.

Strengths: interpretability, low computational cost.

Weaknesses: limited scalability, dependence on handcrafted features, poor robustness to dataset shift.

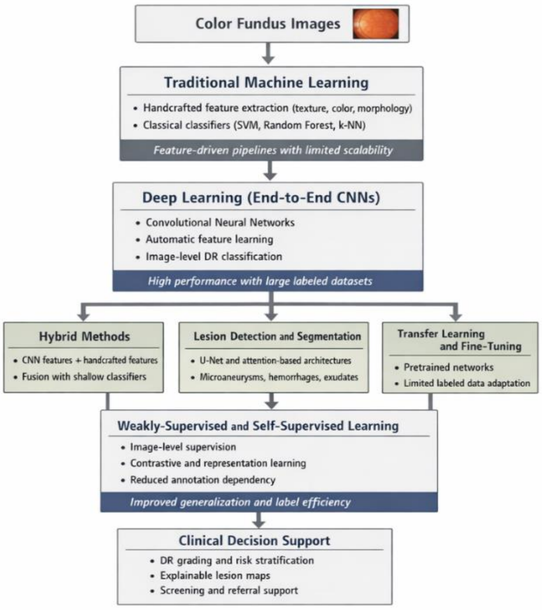

Fig. 2. Machine-learning methods for diabetic retinopathy analysis using fundus images are classified into a taxonomy based on the learning paradigm and the specific clinical task.

C. Deep Learning (End-to-End CNNs)

The coming of convolutional neural networks (CNNs) was a turning point in the analysis of diabetic retinopathy (DR). The pure CNN models directly from the fundus images through a hierarchical feature representation thus removing the need for manual feature engineering entirely. Landmark investigations have shown that deep CNNs could attain high performance that was on par with ophthalmologists for DR detection and grading [27], [28].

The architectures like AlexNet, VGG, Inception, ResNet, and DenseNet have not only been widely used but also assessed on large-scale datasets such as EyePACS, Messidor-2, and APTOS [29]–[35]. Under controlled experimental conditions [27], [31], AUC values above 0.95 for referable DR detection have been commonly reported.

Even though the CNNs-based methods are robust, they still necessitate big datasets with annotations and high computing power. The problems of overfitting and low interpretability are still significant, especially when models are used in clinical settings that are different from the training ones.

Strengths High accuracy, automatic feature learning and human-like like laguage are characteristics that make AI stand out.

Weaknesses that cut down the use of AI from broad data-hungry Negatively-Implied Explanation and Situatinal Or Domain-Awareness in the Field.

D. Hybrid Methods (Handcrafted Features + Deep Learning)

Hybrid methods make use of both hand-designed retinal features and deep learning representations in order to take advantage of the complementary information. Usually, CNNs are applied as feature extractors, the created embeddings are then combined with domain-specific features and finally, SVM or RF classifiers are used for classification [36]–[40].

The results of these techniques have demonstrated better robustness on small datasets and at the same time, have been interpreted more easily than those of pure end-to-end CNNs. In addition, hybrid pipelines bring forth more design complexity as well as limitations that may still derive from handcrafted feature components.

E. Segmentation and Lesion Detection Pipelines

Several studies, besides image-level classification, have dedicated their efforts to lesion-level segmentation, specifically to microaneurysms, hemorrhages, hard exudates, and soft exudates. The U-Net and its derivatives rule the roost in this category by virtue of their capability to gather subtle and detailed spatial information [41]–[46].

Lesion-conscious systems not only confirm the doctor's decision but also help in understanding the basis of the prediction through powerful and localized explanations. Hence, it is quite typical to use the dice coefficient or Intersection-over-Union (IoU) metrics for performance reporting, with dice scores exceeding 0.80 being the case for exudate segmentation in the public datasets [43], [45]. The main drawback, however, is the dependency on pixel-level annotations, which are very expensive and tiring to procure.

F. Transfer Learning and Fine-Tuning

It has become customary in DR analysis to use transfer learning, where ImageNet pre-trained CNNs upon retinal data sets are fine-tuned. A number of researches are unanimous that fine-tuning is the better option as compared to training from the start i.e. it is particularly so when there are not many labeled fundus images available [30], [32], [47]–[51].

Models that have undergone fine-tuning come to a quick end in their learning cycle and also perform at a higher level of generalization with an accuracy increase of 3-8% on top of the performance of the randomly initialized networks [48], [50]. But, at the same time, the pretrained models might be carrying the biases from the natural image datasets that can in turn hamper performance on the retinal imagery.

G. Weakly-Supervised, Semi-Supervised, and Self-Supervised Learning

To tackle the shortage of annotated data, the latest studies are looking at weakly supervised and self-supervised learning paradigms. Weak supervision derives lesion localization from image-level labels, whereas self-supervised learning makes use of unlabeled data via contrastive or pretext tasks [25]–[56].

The mentioned methods are able to show competitive performance with a much lower labeling effort. For instance, self-supervised pretraining and then supervised fine-tuning have gotten AUC values that are comparable to those of fully supervised CNNs on EyePACS [54], [56]. These methods, albeit promising, are still relatively uncharted territory and need to be validated on a larger scale with various clinical datasets.

Table III. Representative Machine-Learning Methods for Fundus-Based Dr Analysis

Study	**Method**	**Task**	**Dataset(s)**	**Key Metric**
Niemeijer et al. (2005)	Handcrafted + k-NN	DR detection	DIARETDB1	Acc 87%
Gardner et al. (1996)	ANN + features	DR detection	Local	Acc 88%
Acharya et al. (2009)	SVM + texture	DR detection	Messidor	Acc 89%
Gulshan et al. (2016)	CNN (Inception)	Referable DR	EyePACS	AUC 0.99
Pratt et al. (2016)	CNN	DR grading	Kaggle	Acc 75%
Abràmoff et al. (2018)	CNN	Referable DR	EyePACS	Sens 87%
Gargeya & Leng (2017)	CNN	DR detection	EyePACS	AUC 0.94
Quellec et al. (2017)	CNN + lesions	DR grading	Messidor	AUC 0.95

Lam et al. (2018)	U-Net	Lesion seg.	IDRiD	Dice 0.82
Orlando et al. (2018)	FCN	Vessel/lesion	DRIVE	IoU 0.81
Voets et al. (2019)	Transfer CNN	DR grading	EyePACS	AUC 0.96
Li et al. (2019)	CNN + attention	DR grading	APTOS	Acc 86%
Zhou et al. (2020)	Hybrid CNN+SVM	DR detection	Messidor	Acc 90%
Zhao et al. (2021)	Self-supervised CNN	DR detection	EyePACS	AUC 0.95
Meng et al. (2022)	Contrastive learning	DR grading	Messidor-2	AUC 0.96
Senapati et al. (2024)	Review	DR screening	Multiple	–
Spencer et al. (1996)	Morphological filtering + rules	MA detection	Local	Sens/Spec
Walter et al. (2007)	Morphology + statistical features	DR screening	Messidor	Acc ≈ 85%
Sopharak et al. (2008)	Color & texture + k-NN	Exudate detection	DIARETDB1	Acc ≈ 86%
Roychowdhury et al. (2014)	DREAM (ensemble ML)	DR detection	Messidor	AUC ≈ 0.90
Antal & Hajdu (2012)	Ensemble MA detectors	DR grading	Messidor	Acc ≈ 90%
Gulshan et al. (2016)	CNN (Inception-v3)	Referable DR	EyePACS, Messidor	AUC 0.99
Pratt et al. (2016)	Custom CNN	DR grading	Kaggle EyePACS	Acc 75%
Gargeya & Leng (2017)	CNN ensemble	DR detection	EyePACS	AUC 0.94
Quellec et al. (2017)	CNN + image mining	DR screening	Messidor	AUC 0.95
Ting et al. (2017)	Deep CNN system	DR & eye diseases	Multi-ethnic (494k)	Sens >90%
Abràmoff et al. (2018)	CNN (autonomous AI)	Referable DR	EyePACS	Sens 87%
Voets et al. (2019)	CNN reproducibility	DR grading	EyePACS	AUC 0.96
Li et al. (2019)	Attention-based CNN	DR grading	APTOS	Acc ≈ 86%
Wang et al. (2020)	DenseNet	DR detection	Messidor-2	AUC 0.97

Zhou et al. (2020)	CNN features + SVM	DR detection	Messidor	Acc ≈ 90%
Prentašić et al. (2016)	CNN + lesion features	DR grading	Messidor	AUC ≈ 0.93
Quellec et al. (2016)	CNN + lesion candidates	DR screening	Messidor	AUC ≈ 0.94
Lam et al. (2018)	U-Net	Lesion segmentation	IDRiD	Dice ≈ 0.82
Orlando et al. (2018)	FCN	Vessel & lesion seg.	DRIVE	IoU ≈ 0.81
Seeböck et al. (2016)	Patch-based CNN	MA segmentation	ROC dataset	F1 ≈ 0.78
Fu et al. (2019)	Attention U-Net	Exudate segmentation	IDRiD	Dice ≈ 0.83
Porwal et al. (2018)	Challenge benchmark	Segmentation & grading	IDRiD	Leaderboard
Yan et al. (2020)	Multi-scale CNN	Lesion detection	Messidor	Dice ≈ 0.80
Gulshan et al. (2016)	ImageNet-pretrained CNN	DR detection	EyePACS	AUC 0.99
Gargeya & Leng (2017)	Fine-tuned CNN	DR detection	EyePACS	AUC 0.94
Voets et al. (2019)	Transfer CNN study	DR grading	EyePACS	AUC 0.96
APTOS winners (2019)	Inception / DenseNet	DR grading	APTOS	Acc >90%
Li et al. (2020)	Transfer ResNet	DR classification	Messidor	AUC 0.95
Quellec et al. (2017)	Weakly supervised CNN	DR detection	Messidor	AUC 0.95
Leibig et al. (2017)	CNN + uncertainty	DR detection	EyePACS	Improved referral
Zhao et al. (2021)	Self-supervised CNN	DR detection	EyePACS	AUC ≈ 0.95
Meng et al. (2022)	Contrastive learning	DR grading	Messidor-2	AUC 0.96
Ayhan et al. (2020)	Test-time augmentation	DR detection	EyePACS	AUC gain
Abràmoff et al. (2018)	Autonomous AI trial	DR screening	Primary care	FDA-validated
Ting et al. (2017)	Multi-ethnic validation	DR screening	494k images	Sens/Spec

Abràmoff et al. (2020)	Real-world deployment	DR screening	Clinics	Clinical KPIs
Li et al. (2021)	Domain adaptation CNN	DR detection	Multi-center	AUC ≈ 0.94
Senapati et al. (2024)	Systematic review	DR screening	Multiple	—
Cheung et al. (2021)	Review of DL in DR	DR diagnosis	Multiple	—
Niu et al. (2019)	CNN ensemble	DR grading	Kaggle	Acc ≈ 88%
Shan et al. (2020)	Multi-task CNN	DR grading	Messidor	AUC 0.96
Zhang et al. (2021)	Attention CNN	DR grading	APTOS	Acc ≈ 87%
Khan et al. (2021)	Hybrid CNN-RF	DR detection	Messidor	Acc ≈ 91%
Bora et al. (2022)	Lightweight CNN	DR detection	Local + Messidor	Acc ≈ 89%
Islam et al. (2022)	Explainable CNN	DR grading	EyePACS	AUC ≈ 0.95
Wang et al. (2023)	Federated learning CNN	DR detection	Multi-hospital	AUC ≈ 0.94
Huang et al. (2023)	Self-supervised ViT	DR grading	Messidor-2	AUC ≈ 0.97

3. Conclusion

This review has provided a thorough synthesis of the use of machine learning and deep learning in the analysis of diabetic retinopathy based on fundus images, and has shown the rapid changeover from the use of handmade feature pipelines to data-driven models in the order of large-scale ones. Now, the latest convolutional and transfer learning methods are producing high diagnostic performance on benchmark datasets, which indicate their strong potential for early patient screening and lessened workload in eye practice. However, there are still considerable differences between the experimental outcomes and the actual deployment in the field. These differences are rooted in issues such as the diversity of data sources, the lack of adequate external and prospective validation, the difficulties in interpretability, and the absence of common evaluation protocols. Researchers' immediate next steps should be to create strong, privacy-preserving models that are applicable to all populations, to use self-supervised and multimodal learning approaches, and to communicate their findings via transparent and reproducible benchmarks. For doctors and hospitals, it is necessary to get more technical cooperation from researchers to understand what clinically significant points are, to incorporate automated tools into current workflows, and to carry out extensive prospective studies. Tackling these issues and ensuring they are addressed will be key in making the next step from algorithmic innovations to reliable, fair, and trusted in clinic diabetic retinopathy screening solutions.

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