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REVIEW

A Systematic Review of Advances in AI-Assisted Analysis of Fundus Fluorescein Angiography (FFA) Images: From Detection to Report Generation

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ABSTRACT

Fundus fluorescein angiography (FFA) serves as the current gold standard for visualizing retinal vasculature and detecting various fundus diseases, but its interpretation is labor-intensive and requires much expertise from ophthalmologists. The medical application of artificial intelligence (AI), especially deep learning and machine learning, has revolutionized the field of automatic FFA image analysis, leading to the rapid advancements in AI-assisted lesion detection, diagnosis, and report generation. This review examined studies in PubMed, Web of Science, and Google Scholar databases from January 2019 to August 2024, with a total of 23 articles incorporated. By integrating current research findings, this review highlights crucial breakthroughs in AI-assisted FFA analysis and explores their potential implications for ophthalmic clinical practice. These advances in AI-assisted FFA analysis have shown promising results in improving diagnostic accuracy and workflow efficiency. However, further research is needed to enhance model transparency and ensure robust performance across diverse populations. Challenges such as data privacy and technical infrastructure remain for broader clinical applications.

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Keywords: Artificial intelligence; Fundus fluorescein angiography; Ophthalmology; Deep learning

Key Summary Points

Why carry out this study?

Retinal diseases are major causes of vision impairment globally, affecting millions and burdening healthcare systems. Fluorescein fundus angiography (FFA), the gold standard for diagnosing these diseases, is labor-intensive and subject to variability, causing diagnostic delays.

This study investigates whether artificial intelligence (AI) can enhance diagnostic accuracy and workflow efficiency in FFA image analysis, improving clinical workflow in ophthalmology.

What was learned from the study?

AI tools significantly improve diagnostic accuracy and workflow efficiency in FFA analysis, with advancements in automated lesion detection, diagnostic support, and report generation.

AI can reduce ophthalmologists' workloads, support large-scale screening, achieve cost-savings, and expand healthcare access through telemedicine. Despite promising results, challenges remain, including the need for diverse datasets, transparent AI models, and smoother integration into clinical workflows to ensure broader clinical adoption.

INTRODUCTION

Retinal diseases, such as diabetic retinopathy (DR), retinal vein occlusion (RVO), and age-related macular degeneration (AMD), are leading causes of vision impairment globally [19, 32]. For instance, in 2020, it was estimated that 103.12 million people were affected by DR, with numbers projected to rise to 160.50 million by 2045 [36], posing a significant burden on healthcare systems worldwide. Fundus fluorescein angiography (FFA) has long been regarded as the gold standard for detecting retinal vascular abnormalities associated with these diseases [1]. By utilizing FFA imaging, clinicians can detect and analyze retinal lesions, assess microvascular structures and blood flow, and generate comprehensive diagnostic reports, each essential for accurately diagnosing conditions and guiding therapeutic decisions [11].

Nevertheless, the traditional manual interpretation of FFA images is time-consuming and relies on clinicians' expertise, often leading to subjective variability, diagnostic delays, and inconsistent accuracy. Experts have noted that manual grading of conditions such as capillary non-perfusion is subjective and difficult to standardize, emphasizing the need for artificial intelligence (AI) tools to enhance efficiency and consistency [30].

In recent years, advancements in AI, particularly deep learning and machine learning, have transformed medical image analysis. Within ophthalmology, AI-assisted analysis of FFA images has gained considerable momentum, demonstrating robust performance in automated diagnosis, lesion detection, pathology segmentation, and medical report generation [37]. For example, FFA-Lens developed by Veena et al. [20] can automate the identification of lesions, helping to increase diagnostic efficiency and improve clinical disease management strategies. Moreover, Nunez do Rio et al.'s deep learning model automates capillary non-perfusion segmentation and quantification in ultrawide field fluorescein angiography images, improving detection consistency and reducing manual grading variability [30]. These AI-assisted models significantly alleviate the workload of healthcare professionals, achieving promising results in diagnostic accuracy and disease management, indicating the great potential to improve clinical efficiency. From a health economics perspective, the integration of AI into ophthalmic diagnostics has the potential to significantly reduce healthcare costs by improving early detection, minimizing unnecessary treatments, and optimizing resource allocation, particularly in areas with limited access to retinal specialists [17, 40]. In conclusion, AI-assisted analysis of FFA images not only improves diagnostic speed and accuracy, reduces healthcare costs [1, 17], but also undertakes multiple tasks such as pathology segmentation, greatly easing the burden on ophthalmologists.

This systematic review aims to assess recent progress in the application of AI technologies for the analysis of FFA images from 2019 to 2024. Specifically, this review focuses on AI-assisted lesion detection, diagnostic support, and report generation, examining how AI enhances diagnostic accuracy, reduces diagnostic time, and improves clinical workflows. By consolidating current research findings, this review highlights key advancements in AI-assisted FFA analysis and explores their potential implications for clinical practice in ophthalmology.

METHODS

This systematic review was conducted in compliance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The objective was to evaluate the role of AI in ophthalmology, particularly in the analysis of FFA for diagnostic purposes.

Search Strategy

A comprehensive literature search was performed across PubMed, Google Scholar, and Web of Science databases from January 1, 2019 to August 1, 2024. Keywords were selected from three topics of interest: FFA-related terms (fundus fluorescein angiography, FFA, retinal fluorescein angiography, fluorescein angiogram), AI-related terms (artificial intelligence, deep learning, machine learning) and ophthalmology-related terms (ophthalmology, eye diseases, ophthalmic disorders, ophthalmic diagnostics).

The final combined term is as follows: ("Ophthalmology" OR "Eye Diseases" OR "Ophthalmic Disorders" OR "Ophthalmic Diagnostics") AND ("Artificial Intelligence" OR "Deep Learning" OR "Machine Learning") AND ("Fundus Fluorescein Angiography" OR "FFA" OR "Retinal Fluorescein Angiography" OR "Fluorescein Angiogram"). The terms from each category were cross-referenced independently with terms from the other category.

Inclusion and Exclusion Criteria

For this systematic review, we targeted literature published between January 1, 2019 and August 1, 2024 to encompass the latest research. Our initial search yielded 224 potential articles based on titles and abstracts. We included studies that were reviews or original research, all concentrating on the use of AI in ophthalmology, with an emphasis on automatic FFA image analysis for tasks from lesion detection to report generation.

Exclusions were applied for: (1) non-English articles, (2) duplicate publications, (3) content outside the scope of ophthalmology or AI applications, (4) conference abstracts, and (5) non-empirical works like editorials, case reports, and commentaries.

Figure 1 outlines the research process of AI-assisted FFA image analysis, including detailed steps of literature screening and inclusion criteria.

Study Selection and Quality Assessment

Eligibility assessment was conducted by two independent reviewers, with disagreements resolved through consensus or by a third reviewer. The quality of the included studies was assessed based on predefined criteria such as study design, methodology, and validity of AI algorithms used.

Data Extraction and Analysis

A standardized data abstraction form was used to extract the following data from the selected studies: key themes, information on datasets, the purpose, and methods of AI-assisted FFA image analysis, as well as the results and conclusions.

In addition, we gave particular attention to how AI models processed FFA images—whether they analyzed single images or the entire sequence. Given the dynamic nature of FFA, this distinction is crucial for ensuring the completeness and accuracy of the analysis. If

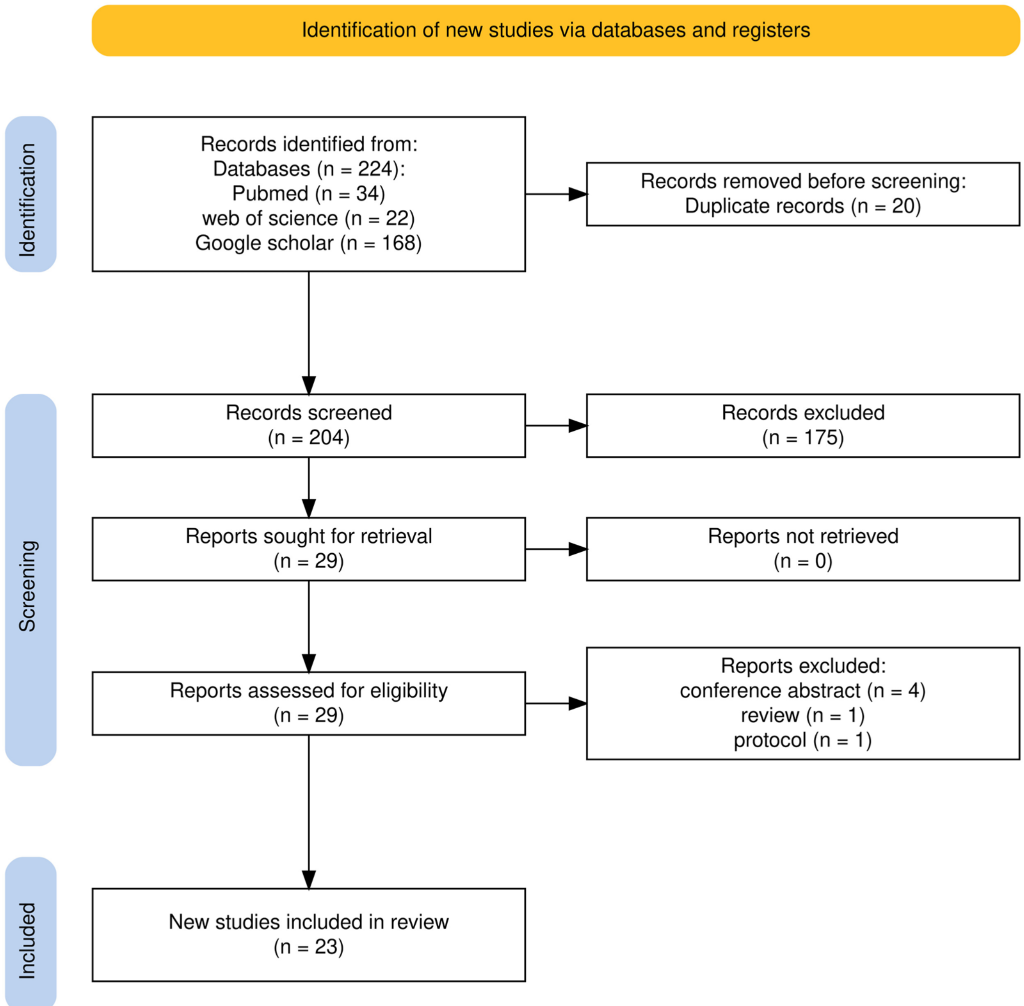

Fig. 1 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 flow diagram for the systematic review of artificial intelligence analysis tools of fundus fluorescein angiography (FFA) images. It should be noted that the excluded records contained non-English papers (e.g., German, French, Chinese, Japanese)

only individual frames are considered, valuable temporal information may be lost, which could affect the overall interpretation. Therefore, studies where AI models accounted for the full image sequence were prioritized in our analysis.

We have identified and synthesized key themes on the supportive role of AI in identifying FFA images. These themes are presented clearly to explain the current state of the field. Table 1 summarizes the studies on AI-assisted FFA image analysis, including model performance and areas of application.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Table 1 Summary of studies in AI-assisted analysis of FFA images

References	Year	Image acquisition method	Application	AI models	Performance measure
Chen et al. [7]	2024	Zeiss FF450 Plus and Heidelberg SPECTRALIS cameras from Heidelberg, Germany, with a resolution of 768 × 768 pixels	Automated report generation and medical question-answering	Llama 2	Accuracy (0.88–0.93), specificity (0.94–0.97), precision (0.63–0.76), sensitivity (0.66–0.89)
Huang et al. [15]	2023	The resolution varies between 768 × 868 and 3608 × 3608 pixels	CF-to-FFA translation and lesion-region segmentation	LA-GAN	SSIM 0.536, LPIPS 0.312; the lesion-region segmentation performance: mean Dice increased from 0.714 to 0.797, the mean accuracy increased from 0.873 to 0.905
Sun et al. [35]	2021	The resolution of 768 × 768 and different view fields of 30°, 35°, or 55°	Vessel segmentation in FFA sequential images	MCU-net	Public Duke dataset: *F*1-score (0.7991), AUC (0.9870); our own dataset: *F*1-score (0.7531), AUC (0.9858)
Shi et al. [34]	2023	CF images: Topcon TRC-50XF and Zeiss FF450 Plus (Carl Zeiss, Inc) cameras, with resolutions ranging from 1110 × 1467 to 2600 × 3200 FFA images: Zeiss FF450 Plus and Heidelberg SPECTRALIS (Heidelberg Engineering) cameras, with a resolution of 768 × 768	CF-to-FFA translation and DR detection	Pix2PixHD	The MAE, PSNR, SSIM, and FID were 111.46, 21.07, 0.61, and 46.28, respectively, for venous-phase FFA and 123.07, 22.11, 0.65, and 32.72, respectively, for late-phase FFA

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Miao et al. [27]	2022	CF photographs: Canon INC, CR-2 AF, Japan FFA: the SPECTRALIS HRA2 (Heidelberg Engineering, Heidelberg, Germany), 1024 pixels × 1024 pixels	Automatically detect the ischemia type and the NPA from CF photographs of patients with BRVO	CNN	The first: the recall, precision, accuracy, and AUC were 0.75 ± 0.08, 0.80 ± 0.07, 0.79 ± 0.02, and 0.82 ± 0.03, respectively; The second: the recall, precision, accuracy, and AUC were 0.74 ± 0.05, 0.87 ± 0.02, 0.89 ± 0.02, and 0.96 ± 0.02, respectively
Gao et al. [11]	2023	–	Prediagnosis assessment and lesion classification	LeNet-5, VGG16, ResNet18	ResNet18 got the best result, accuracy 80.79–93.34% for prediagnosis assessment and accuracy 63.67–88.88% for lesion detection
Zhang et al. [44]	2023	The Heidelberg retina angiograph (Heidelberg Engineering, Germany) device, 768 × 768 pixels	Detect microaneurysms	MA-YOLO	The recall, precision, *F*1 score, and average precision, which were 88.23%, 97.98%, 92.85%, and 94.62% respectively

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Li et al. [25]	2020	–	Effectively exploit multi-modal data for retinal disease diagnosis	ResNet18, CycleGAN	On the Ichallenge-AMD dataset, the method achieved an AUC of 74.58%, close to the supervised learning baseline (77.19%) On the Ichallenge-PM dataset, the method outperformed other methods in all five evaluation metrics, especially with an AUC that exceeded the state-of-the-art method by 1.29%
Nunez et al. [30]	2020	Optos 200Tx (Optos, Plc, Dunfermline, Scotland)	Quantify capillary non-perfusion topographically in UWF-FA images	U-Net	The model for dense segmentation was five-fold cross-validated achieving area under the receiving operating characteristic of 0.82 (0.03) and area under precision-recall curve 0.73 (0.05)

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Xu et al. [42]	2021	FFA: Heidelberg SPECTRALIS, Heidelberg, Germany ICGA: Heidelberg SPECTRALIS, Heidelberg, Germany OCTA: RTVue XR Avanti with AngioVue; Optovue Inc., Fremont, CA, USA OCT: Heidelberg SPECTRALIS, Heidelberg, Germany	Predict subretinal fluid absorption at 1, 3, and 6 months after laser treatment in patients with CSC	Decision Tree, AdaBoost. R2, Gradient Boosting, XGBoost, random forest, and extra-trees	Original models, random forest had the best performance in the internal validation, and XGBoost performed best at external validation; simplified models, gradient boosting had the best performance for internal validation, and the blending algorithm performed best at external validation
Li et al. [24]	2024	CF photographs: Digital Retinal Camera, CR-2 AF, Canon, Tokyo, Japan FFA: FF450 plus, Carl Zeiss Meditec AG, Jena, Germany	Automated detection of DR, RVO, AMD, and other fundus conditions	ResNet101, EfficientNetV2-M, ConvNeXt-base	The ConvNeXt-base + attention model achieved remarkable metrics, including AUC 0.943, $F1$ score 0.870, and a Cohen's kappa of 0.778 for DR detection. For RVO, AUC of 0.960, $F1$ score 0.854, and a Cohen's kappa of 0.819. In AMD detection, AUC 0.959, $F1$ score 0.727, and a Cohen's kappa of 0.686

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Huang et al. [16]	2024	The tabletop HRA-II system at 30°(Heidelberg, Germany), at 768 × 768	Diagnose and classify RVO using FFA images	ResNet50, VGG19, InceptionV3	The InceptionV3 model outperformed ResNet50 and VGG19 in labeling and interpreting FFA images for RVO diagnosis, achieving 77.63–96.45% accuracy for basic information labels and 81.72–96.45% for RVO-relevant labels
Gao et al. [10]	2022	The Heidelberg retina angiograph (Heidelberg Engineering, Heidelberg, Germany) with a 30° field of view, with a resolution of 768 × 768	DR grading	VGG16, ResNet50, DenseNet	VGG16 performed the best, with a maximum accuracy of 94.17%, and had an AUC of 0.972, 0.922, and 0.994 for levels 1, 2, and 3, respectively
Pan et al. [31]	2020	Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany) with a 30° field of view, 768 × 768	Automatically detect and classify the lesions of DR	DenseNet, ResNet50, VGG16	DenseNet: AUC 0.8703, 0.9435, 0.9647, 0.9653 for NP, microaneurysms, leakages, laser scars; ResNet50: AUC 0.8140, 0.9097,0.9585,0.9115for NP, microaneurysms, leakages, laser scars; VGG16: AUC 0.7125, 0.5569, 0.9177, 0.8537 for NP, microaneurysms, leakages, laser scars

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Zhao et al. [45]	2023	SPECTRALIS HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) with a 55° viewing field	Interpret FFA images	ai-Doctor	Image phase identification (AUC, 0.991–0.999); DR and BRVO diagnosis (AUC, 0.979–0.992); non-perfusion area segmentation (DSC, 89.7–90.1%); IRDs (central RVO and retinal vasculitis), DSCs 89.2%,83.6%
Jin et al. [18]	2020	Tabletop systems HRA-II at 30° (Heidelberg, Germany), at 768 × 768 pixels	Identify lesions and segmentation of NPA	DenseNet, ResNet 50, VGG 16	DenseNet: AUC 0.8855,0.9782,0.9765 for NP regions, microaneurysms, leakage classifier, respectively; ResNet 50: AUC 0.7895, 0.8633, 0.9305 for NP regions, microaneurysms, leakage classifier, respectively; VGG 16: AUC 0.7689, 0.8396, 0.9430 for NP regions, microaneurysms, leakage classifier, respectively

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Xu et al. [41]	2021	–	Predict visual acuity and post-therapeutic OCT images 1, 3, and 6 months after laser treatment in patients with CSC	LASSO, AdaBoost.R2, Gradient Boosting, XGBoost, Random Forest, Extra-Trees	In the visual acuity predictions on the Xiamen Eye Center dataset, the MAEs were between 0.074 and 0.098 logMAR (within four to five letters) for 1-, 3-, and 6-month predictions, respectively, and the root mean square errors were between 0.096 and 0.127 logMAR (within five to seven letters) for the respective predictions. Among the synthetic OCT images, only about 5.15% (5 out of 97) could be accurately identified as synthetic by the specialists. The MAEs of the central macular thickness in the synthetic OCT images were 30.15 ± 13.28 μm and 22.46 ± 9.71 μm for the 1- and 3-month predictions, respectively
Chen et al. [5]	2021	Tabletop systems HRA-II at 30° (Heidelberg Engineering, Heidelberg, Germany) at 768 × 768 pixels	Detect the leakage points of CSC automatically	AGN	The AGN alone: perfectly matched 37 out of 61 cases (60.7%), dice 0.811. Using an elimination procedure: perfectly matched 57 out of 61 (93.4%), dice 0.949

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Chen et al. [6]	2024	–	Utilize the power of ChatGPT to significantly enhance semantic comprehension in image analysis and address various visual question-answering tasks associated with FFA images	Bootstrapping Language-Image Pre-training framework	For “microaneurysm”, “diabetic retinopathy”, “arteriosclerosis”, accuracy values: 0.94, 0.94, 0.87, respectively; *F*1 scores: 0.87, 0.84, 0.72, respectively
Veena et al. [20]	2024	–	Detect lesions	FFA-lens	The obtained precision and recall scores were approximately 0.856 and 0.834, respectively
Hao et al. [13]	2022	Reticam 3100, Chongqing Beaoxin Vision Medical Equipment Company	Observe the consistency of a preliminary report of AI in the clinical practice of fundus screening for DR using non-mydriatic fundus photography	an automated DR grading software developed by VoxelCloud in China, using Inception-ResNet v2 structure	When considering moderate nonproliferative retinopathy as the cut-off point, the kappa coefficient was 0.75 ($p < 0.001$), the sensitivity was 0.973, and the precision was 0.642, which was shown in the precision–recall curve. Fifty-nine patients referred to receive FFA were compared with non-mydriatic AI diagnoses. The kappa coefficient was 0.53, and the coincidence rate was 66.9%

Table 1 continued

References	Year	Image acquisition method	Application	AI models	Performance measure
Wongchaisuwat et al. [38]	2022	SPECTRALIS (Heidelberg Engineering, Heidelberg, Germany)	Distinguish PCV from wet AMD	ResNet, Optic-Net	AUC:0.8 and 0.81 for the training and external validation data sets, respectively. The sensitivity/specificity:100%/60%, 85%/71% for the training and external validation data sets, respectively
El-Ateif et al. [9]	2024	–	Assess and compare the performance of both mono-modality and late fusion multimodality strategies when using most recent and frequent seven deep learning techniques in eye diseases classification	VGG19, DenseNet121, InceptionV3, InceptionResNetV2, Xception, ResNet50V2, MobileNetV2	DenseNet121 and ResNet50V2 were the top performing and less sensitive techniques on the three datasets using mono-modality with accuracy values of 99.57% and 99.51% respectively. ResNet50V2 late fusion was the best late fusion technique and scored 100% in accuracy across all three datasets

AI artificial intelligence, *CF* color fundus, *FFA* fundus fluorescein angiography, *LA-GAN* lesion-aware generative adversarial networks, *SSIM* structural similarity, *LPIPS* learned perceptual image patch similarity, *MCU-net* multi-path cascaded U-net, *AUC* the area under receiver operating characteristic (ROC) curve, *DR* diabetic retinopathy, *MAE* mean absolute error, *PSNR* peak signal-to-noise ratio, *FID* Fréchet inception distance, *NPA* non-perfusion area, *BRVO* branch retinal vein occlusion, *CNN* convolutional neural network, *AMD* age-related macular degeneration, *PM* pathologic myopia, *UWF-FA* ultrawide field fluorescein angiography, *ICGA* indocyanine green angiography, *OCTA* optical coherence tomography angiography, *OCT* optical coherence tomography, *CSC* central serous chorioretinopathy, *RVO* retinal vein occlusion, *DSC* dice similarity coefficient, *NP* non-perfusion, *AGN* attention gated network

RESULTS

According to our review, in recent years, there has been significant progress in the AI-assisted analysis of FFA images, particularly in three main areas: identifying lesions, aiding in diagnostics, and generating automatic reports. This review highlights the key achievements in each area, emphasizing the specific methods and contributions from various research teams. These studies have utilized advanced deep-learning models and algorithms to improve the accuracy and efficiency of FFA image analysis, with tangible applications in clinical practice. Figure 2 shows the process of analyzing FFA images using an AI model.

Lesion Detection

AI-driven lesion detection in FFA images has made substantial progress, particularly in the identification and segmentation of retinal abnormalities. Several research teams have employed deep learning models to detect and classify lesions, improving both accuracy and speed in clinical workflows.

In addition to lesion detection, fluorescein leakage, and staining are critical in diagnosing retinal diseases using FFA. These features help detect conditions like diabetic macular edema (DME) and AMD, as well as identify microaneurysms, non-perfused areas, and vascular abnormalities [12]. AI can enhance the accuracy of these assessments, supporting more precise disease evaluation and treatment planning.

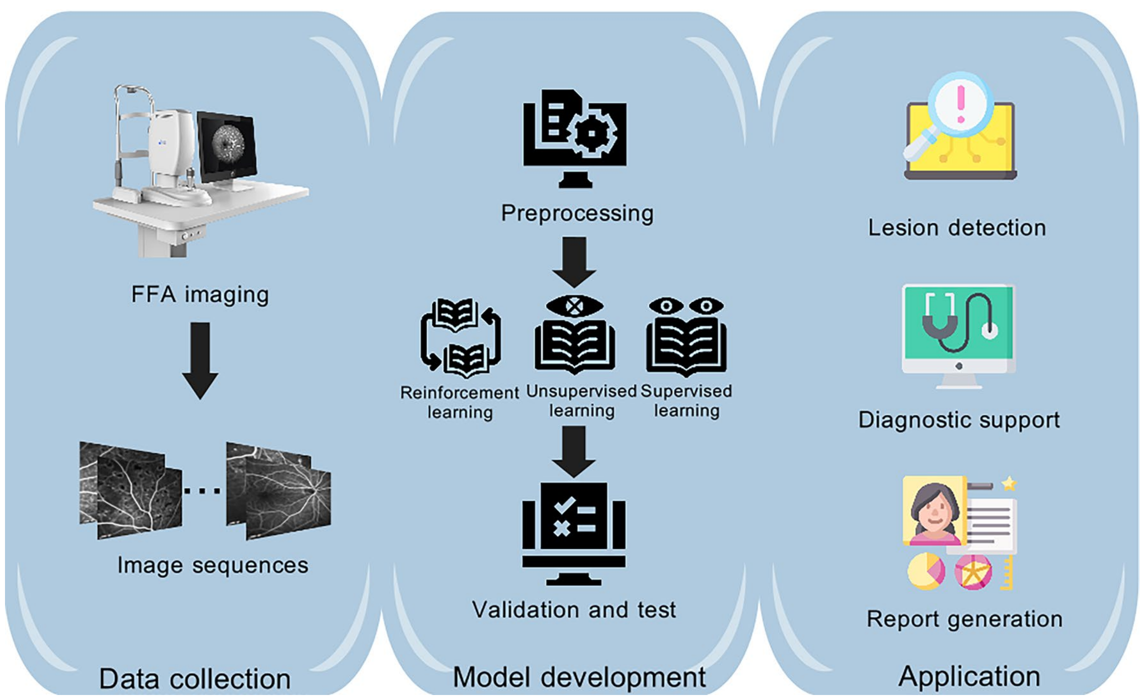

Fig. 2 In this flowchart, fundus fluorescein angiography (FFA) images are first obtained and then the sequence photos are processed developing an artificial intelligence (AI) model to identify lesions, provide diagnostic support, and generate a comprehensive report. The AI-driven approach streamlines the ophthalmic diagnostic workflow, improving accuracy and efficiency. The figure was created with BioGDP.com. The icons of reinforcement learning, unsupervised learning, and supervised learning are created by orvipixel. Other icons are created by Freepik. The machine picture is taken from https://www.microcleartech.com/zh/product?type=all. The FFA images were taken from Eye Center, The Second Affiliated Hospital, School of Medicine, Zhejiang University

For example, the detection and segmentation of non-perfusion areas (NPA) in DME were a key focus of Jin et al. [18], who utilized deep learning models to compare performance with human experts. The study included 3014 FFA sequence images of 221 patients with DME. The top-performing model achieved an average NPA detection precision of 0.643, demonstrating significant potential for automatic detection of retinal lesions, including fluorescein leakage and staining patterns, in FFA images for the diagnosis and monitoring of DME. This research indicates that deep learning models could play a crucial role in improving the accuracy and speed of retinal disease diagnosis, particularly in detecting critical features such as leakage and abnormal vascular patterns.

Similarly, the team of Sun [35] proposed a multi-path cascade U-Net (MCU-net) architecture for vessel segmentation in FFA sequence images. This model integrates vessel features from different image modalities to enhance segmentation accuracy. Trained and tested on both the public external dataset and internal data, MCU-net outperformed current state-of-the-art methods in terms of F1 score, sensitivity, and accuracy. Notably, the model excelled at preserving fine details, such as microvasculature and vascular connectivity. The MCU-net also demonstrated robustness in handling FFA images captured at different perfusion stages, showing potential for the accurate quantification of vessel morphology in FFA sequences. This method provides valuable tools for detailed vascular segmentation and analysis, with promising applications in clinical retinal imaging.

These advancements highlight the growing potential of AI to enhance precision in retinal lesion detection, providing valuable support to clinicians while reducing diagnostic variability and workload.

Diagnostic Support

AI-assisted diagnostic support has shown great potential in automating and improving the accuracy of disease diagnosis from FFA images. Several research teams have focused on using deep learning models to aid clinicians in diagnosing retinal conditions such as RVO, DR, and AMD. Key studies have employed novel AI architectures to enhance diagnostic precision and efficiency.

A detailed study aimed at developing a deep learning system for the automatic diagnosis of RVO in FFA images was carried out by Huang et al. [16], demonstrating improved accuracy. The study included 4028 FFA sequence images of 467 eyes from 463 patients, which were collected and annotated. When compared to ophthalmologists, the accuracy of the best model was able to equal or even exceed that of ophthalmologists for most of the labels. These findings highlight the potential of deep learning models in assisting medical professionals in image analysis tasks.

Addressing the challenges of detecting DR, RVO, and AMD, Li et al. [24] combined convolutional neural networks (CNNs) with an attention mechanism for multi-label classification of FFA and color fundus photography (CFP) images. In this study, they curated a dataset consisting of 15,089 CFPs obtained from 8110 patients who underwent FFA examination. Their model demonstrated high area under curve (AUC) values and reliable *F*1 scores in detecting these conditions. In some instances, its performance matched that of human ophthalmologists, underscoring the potential of AI in automating the detection of major retinal diseases. This approach shows how deep learning can effectively handle complex multi-disease tasks, making it a valuable tool for clinical diagnosis.

Gao et al. [11] focused on the automatic analysis of FFA images from patients with DR. They collected 15,599 sequence images from 1558 eyes of 845 patients and used this dataset to train three CNN models to evaluate image quality, eye localization, and disease staging. The model that performed best achieved diagnostic accuracy ranging from 80.79 to 93.34% in pre-diagnosis evaluations and 63.67 to 88.88% in lesion detection. The performance of the AI models was comparable to that of junior ophthalmologists, demonstrating the potential of CNN models in assisting with automatic diagnosis.

AI-driven systems have shown great promise in supporting the diagnosis of retinal diseases through automatic analysis of FFA images. Advanced deep learning architectures have improved the detection and classification of conditions such as RVO, DR, and AMD. By enhancing diagnostic accuracy and efficiency, AI is emerging as a powerful tool that can complement human expertise, offering reliable, faster diagnostic support and contributing to improved clinical decision-making in ophthalmology.

Report Generation

AI-driven automatic report generation from FFA images has significantly advanced, reducing the reliance on retinal specialists and improving efficiency. Several research teams have developed systems that not only generate detailed reports but also offer interactive question-answering capabilities.

An AI system for automating the interpretation of FFA images, including report generation and medical question-answering, was developed by Chen et al. [6, 7]. The model, trained on 654,343 FFA images and 9392 reports, consists of Bootstrapping Language-Image Pre-training framework for report generation and Llama 2 for interactive Q&A. It generates coherent, free-text reports that provide detailed descriptions of the examination site, angiographic process, and clinical indications, closely matching the standardized reports written by ophthalmologists. Its impression section can accurately diagnose specific retinal conditions, rather than offering generic diagnostic patterns. Additionally, the system can address open-ended diagnostic questions, providing further context or clarification for clinicians.

Similarly, the multi-task AI system Ai-Doctor, introduced by Zhao et al. [45], was designed to automatically interpret FFA images and assist in the diagnosis and treatment of ischemic retinal diseases (IRDs). Trained on 24,316 FFA images, Ai-Doctor demonstrated high accuracy in image stage identification, IRD diagnosis, and segmentation of NPA and branch RVO regions. In the reports generated by Ai-Doctor, the image phase, disease diagnosis, ischemic area segmentation, and calculation of the ischemic index are clearly displayed, providing a comprehensive summary of the disease's progression. These reports are essential for guiding clinical decisions, such as laser treatment, and help clinicians assess ischemic severity in a timely manner. Ai-Doctor is expected to reduce reliance on retinal specialists, particularly in resource-limited settings, while providing an efficient tool for clinicians and researchers. Its utility is poised for further validation in broader clinical environments, making it a promising solution for enhancing diagnostic workflows and treatment planning.

Overall, automatic report generation from FFA images has seen notable advancements with AI, streamlining the interpretation process and reducing the dependence on retinal specialists. AI systems are now capable of generating comprehensive, clinically relevant reports, offering interactive question-answering capabilities, and providing key diagnostic information like disease identification, image phase analysis, and ischemic area segmentation. These developments significantly enhance the efficiency of diagnostic workflows, particularly in managing IRDs [45], where AI systems provide accurate and timely insights for clinical decision-making.

DISCUSSION

In recent years, AI-assisted analysis of FFA images has emerged as a transformative approach in ophthalmology, significantly enhancing the efficiency and accuracy of disease diagnosis. AI technologies, particularly those algorithms, are revolutionizing how conditions such as DR and AMD are detected and monitored on deep learning. These advancements are paving the way for more precise and timely interventions, improving patient outcomes [21, 32].

One notable benefit of AI in this field is the capability to facilitate large-scale screening initiatives. AI systems, like the EyeArt platform [33], have been successfully implemented in community health settings to screen for DR. These systems allow for the rapid assessment of thousands of patients, demonstrating high sensitivity and specificity in detecting the disease. This capability is particularly crucial in regions with a high prevalence of diabetes, as early detection through these automatic systems can significantly reduce the risk of vision loss [32].

Moreover, incorporating AI into FFA image analysis leads to considerable cost savings. A cost-offset analysis of AI-assisted glaucoma screening in rural China revealed that integrating AI technology can decrease unnecessary referrals and treatments, thereby lowering overall healthcare expenses [39]. By optimizing resource allocation and reducing misdiagnosis rates, AI contributes to the economic sustainability of healthcare systems [8].

The integration of AI with telemedicine helps bridge healthcare gaps, particularly in underserved or remote areas. AI systems can automate initial screenings and provide diagnostic insights, allowing healthcare providers to prioritize patients who require in-person care. In teleophthalmology, this synergy is particularly effective, as AI-driven analysis can efficiently triage cases, identifying those needing urgent follow-ups. For instance, outreach programs in Western Australia have successfully combined AI and teleophthalmology to extend specialist care to remote communities, maximizing limited resources and improving access to timely diagnosis [8].

Additionally, AI systems significantly reduce the clinical burden on ophthalmologists by automating routine diagnostic tasks, allowing clinicians to focus on more complex cases and enhances their interactions with patients. For example, under the guidance of AI, clinicians can spend less time on preliminary evaluations and more time on treatment strategies and patient education [21]. Compared to traditional manual methods, AI also offers superior diagnostic accuracy and improves time efficiency, especially for large or complex datasets [8].

Overall, the integration of AI in FFA analysis presents numerous advantages, including facilitating large-scale screenings, achieving cost savings, ensuring equitable healthcare distribution through telemedicine, and alleviating clinical burdens. These advancements underscore the transformative potential of AI in improving patient outcomes and optimizing healthcare delivery. Future efforts should focus on addressing associated challenges to maximize these benefits, ensuring that AI serves as a valuable ally to healthcare professionals rather than a replacement [8, 32].

Although AI-assisted analysis of FFA images offers great potential, several limitations need to be addressed for its successful integration into clinical practice [19, 23].

One of the primary challenges for AI in ophthalmology is ensuring generalizability. Many AI models are trained on datasets lacking diversity, often underrepresenting certain populations, which leads to reduced accuracy when applied to different ethnic or geographic groups. This is particularly significant in ophthalmology, where retinal diseases manifest differently across populations [33]. For instance, models trained on specific groups may struggle to generalize, affecting the reliability of diagnoses in diverse settings. Additionally, AI systems that perform well in controlled environments often see a decline in accuracy when applied to real-world clinical scenarios, where factors such as image quality and equipment variability can differ [33]. To address these challenges, expanding datasets to include a broader range of patient groups, and validating models across various clinical environments and imaging devices, is essential. Collaborative data-sharing efforts, the use of synthetic data generation methods (such as generative adversarial networks), and federated learning approaches can help improve the diversity and robustness of AI models [3, 11]. Federated learning, in particular, allows multiple institutions to collaboratively train models without sharing sensitive patient data, thus addressing privacy concerns and improving generalizability across diverse populations [22].

Technical and logistical challenges also present barriers to the widespread adoption of AI in FFA analysis. AI systems often require advanced infrastructure, including high-quality imaging devices and stable internet connectivity for cloud-based processing. These requirements can be challenging to meet in resource-limited settings, restricting the accessibility of AI technologies. Solutions include developing AI systems that are compatible with a broader range of imaging devices and can function with minimal technical infrastructure. Additionally, ensuring that healthcare providers receive proper training on how to use AI systems effectively is critical for successful integration [43]. Building AI literacy among clinicians and healthcare professionals will be essential to ensure they can trust and utilize AI tools appropriately, for example by incorporating AI training into medical education, which will make AI technologies more accessible and effective in clinical settings [14]. Moreover, addressing cost factors, including the initial investment in technology and training, is crucial to ensure AI systems remain both affordable and sustainable in clinical practice [28].

In addition to these specific challenges, there are more general concerns around transparency and explainability, data privacy, and regulatory oversight. Many AI models, especially deep learning systems, function as "black boxes", making it difficult for clinicians to understand how the AI arrives at its conclusions. This lack of transparency can create mistrust and slow adoption [33]. The development of explainable AI systems, which provide insights into the decision-making process, will be key to building clinician confidence in these tools. Moreover, data privacy must be safeguarded by adhering to regulations like General Data Protection Regulation, and robust ethical frameworks must be implemented to ensure responsible AI use.

By addressing these challenges—improving data diversity, conducting broader clinical validation, reducing technical barriers, and ensuring ethical compliance—AI can fully realize its potential in enhancing FFA image analysis and improving patient care in ophthalmology.

However, FFA examination also has some limitations, especially its invasive nature, as it requires dye injection, which can cause discomfort and allergic reactions in some patients. This makes it less ideal for frequent monitoring or for patients with contraindications. As an alternative, optical coherence tomography angiography (OCTA) offers a non-invasive solution. OCTA provides high-resolution images of retinal blood vessels without the need for dye, making it safer and more comfortable for patients [2]. When combined with AI, OCTA can further improve diagnostic accuracy and accessibility, especially in settings where invasive procedures are not feasible.

The systematic review provides a broad perspective on AI advancements in FFA image analysis from 2019 to 2024, backed by a rigorous search across multiple databases and a stringent selection process, ensuring a high-quality synthesis of current research. Despite its strengths, several limitations need to be considered. One key challenge is publication bias, particularly the underreporting of negative findings, which can skew the overall understanding of the field. To mitigate this, future research should emphasize publishing null or negative results, and journals could adopt policies encouraging such submissions [4]. Additionally, the exclusion of non-English studies in our review may limit the scope and omit valuable global insights; future reviews should aim to include studies from a broader range of languages for a more comprehensive perspective. Finally, the rapid pace of AI advancements makes it difficult to stay up-to-date. However, continuous tracking of recent publications, including preprints and early-stage research, will help ensure the inclusion of the latest studies. Despite these limitations, the review offers valuable insights into AI's potential to enhance diagnostic accuracy and efficiency in ophthalmology.

CONCLUSIONS

The application of AI in FFA image analysis has brought significant benefits to ophthalmic diagnostics, including improved precision, faster workflow efficiency, and reduced clinician workload through automation of tasks such as lesion detection and report generation. AI systems also enhance diagnostic consistency by minimizing human error and variability, offering more reliable insights for clinical decision-making.

However, challenges remain in fully integrating AI into clinical practice. Ensuring data diversity is essential for improving AI's performance across different populations, while enhancing model transparency is crucial to building trust in AI's decision-making processes. Addressing these issues will be key to further integrating AI into clinical practice [29].

Although there are challenges, the role of AI in advancing ophthalmic diagnostics is increasingly evident. By overcoming these hurdles, AI has the potential to significantly enhance patient outcomes and revolutionize ophthalmic care delivery, providing more accessible, efficient, and equitable healthcare solutions [23, 26].

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Declarations

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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