



Diabetic Retinopathy Screening Approaches in Developing Countries: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Diabetic retinopathy (DR) is one of the primary causes of vision loss among people living with diabetes and is expected to rise globally in the coming years. Effective screening strategies are essential, particularly in developing countries where resources and access to specialized care are limited. Our objective was to assess how accurately different screening methods detect DR, specifically artificial intelligence (AI)-based tools, portable fundus cameras, and trained non-ophthalmologist personnel, implemented in a developing country.

Materials and Methods: A literature search was conducted in ScienceDirect, PubMed, and the Cochrane Library. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. While all included studies were reviewed qualitatively, only those evaluating AI-based screening tools were included in the meta-analysis. Meta-analysis was performed using MetaDisc 2.0 to calculate pooled sensitivity, specificity, diagnostic odds ratio, and likelihood ratios for any DR, referable DR, and vision-threatening DR.

Results: A total of 25 studies were included, with 21 AI-based studies eligible for the meta-analysis. The pooled sensitivity and specificity respectively were 0.890 (95% confidence interval [CI]: 0.845-0.924) and

0.900 (95% CI: 0.832-0.942) for any DR, 0.933 (95% CI: 0.890-0.960) and 0.903 (95% CI: 0.871-0.928) for referable DR, and 0.891 (95% CI: 0.393-0.990) and 0.936 (95% CI: 0.837-0.977) for vision-threatening DR. Meta-regression identified camera type as a significant factor. Portable fundus cameras and general physicians showed good agreement with the gold standards.

Conclusion: These findings support the potential of AI-assisted DR screening in low-resource settings and highlight the complementary roles of portable imaging and task-shifting to trained non-specialists.

Keywords: Diabetic retinopathy screening, artificial intelligence, portable fundus camera, non-specialist, developing countries

Introduction

Diabetes mellitus (DM) is a long-term metabolic disorder that may result in microvascular and macrovascular complications. As living standards have improved significantly, changes in dietary habits and lifestyles have contributed to a steady rise in the prevalence of DM. The primary microvascular complication associated with DM is diabetic retinopathy (DR). It is the leading cause of vision impairment among adults and older individuals.¹ The global incidence of DR is expected to rise significantly, increasing from approximately 103 million people in 2020 to an estimated 130 million by 2030 and nearly 161 million by 2045.^{2,3} Meanwhile, cases of vision-threatening diabetic retinopathy (VTDR) are projected to grow by 26.3%, reaching 36 million by 2030 and 44.82 million by 2045.³

The ideal method for diagnosing DR is a thorough eye examination with pupil dilation, performed by an ophthalmologist utilizing either an indirect ophthalmoscope or a slit lamp biomicroscope. However, various obstacles limit optimal DR screening, such as limited healthcare access, time

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limitations, substantial personnel costs, insufficient awareness and comprehension, and inadequate care coordination.⁴ In clinical trials, the Early Treatment Diabetic Retinopathy Study (ETDRS) seven-standard field protocol, comprising 7 stereoscopic 30-degree fundus photographs, has long been considered the benchmark for DR assessment. Nevertheless, single-field fundus imaging is a practical and effective alternative, particularly considering the logistical, financial, and time-related limitations that make the ETDRS approach unsuitable for routine screening.⁵

The current recommended guidelines for DR management strategies strongly focus on screening and fundus evaluation. Recent technological advancements, including improved camera technology and artificial intelligence (AI), are becoming more affordable and accessible in low- and middle-income countries. Digitizing health records for individuals with DR would support the creation of a registry, allowing for efficient patient tracking, monitoring disease progression, and assessing referral and treatment outcomes.⁶ Therefore, this study aimed to present an overview of the implementation of DR screening modalities in developing countries, including using AI, fundus camera technology, and other community-based screening, and compare them to opportunistic-based screening approaches.

Materials and Methods

Data Sources and Search Strategy

This review followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^{7,8} The study was registered in the International Prospective Register of Systematic Reviews (CRD420251007510). Seven reviewers independently searched for studies published in PubMed, ScienceDirect, and the Cochrane database for relevant articles. The following search terms were used to identify potentially relevant articles: “diabetic retinopathy” AND “screening” AND “community based” OR “telemedicine” OR “teleophthalmology” OR “artificial intelligence” OR “camera” AND “developing countries” OR “low-income countries” OR “middle income countries.” The terms from each category were independently compared and cross-referenced with those from other categories.

Selection Criteria and Selection

This systematic review and meta-analysis included studies conducted in developing countries (i.e., low- and middle-income countries) that involved participants with type 1 or type 2 DM, and provided data on the sensitivity, specificity, or agreement level of the screening methods used. The screening modalities included AI, telemedicine, camera technology, or other community-based programs. The selected studies must have also compared these interventional screening modalities with standard care screening. The “developing countries” in this research were classified based on World Bank data when the studies were conducted. Any country categorized as a low- or middle-income country was included under the term “developing countries.”

Studies were excluded if they lacked sufficient data, focused solely on the prevalence of DR or on comorbid eye diseases, or were case reports, guidelines, editorials, commentaries, opinions, or reviews. Titles and abstracts of the selected articles were screened by seven reviewers, with full texts of potentially eligible studies examined for final inclusion. Any disagreements were resolved through discussion.

Quality Assessment

The seven reviewers independently assessed the quality of all included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.⁹ The QUADAS-2 scale comprised four bias risk assessment domains: patient selection, index test, reference standard, and flow and timing. Each domain included two or three individual questions. Risk in a domain was considered low if all questions were answered affirmatively. This scale also evaluated applicability of the study based on patient selection, index test, and reference standard.

Data Extraction and Analysis

After article selection, the seven reviewers summarized and extracted data related to the screening methods’ diagnostic accuracy. These data included total participants, the country where the study was conducted, interventional screening methods, technical characteristics (pupil dilation status, AI system, device), indicators measured, and outcomes such as DR type, sensitivity, specificity, and agreement. Since not all studies analyzed each of these indicators, our meta-analysis was further divided into subgroups based on the available uniform indicators. We used the web application MetaDisc 2.0 for the outcome variables of true positives, false positives, false negatives, and true negatives. We also generated a summary receiver operating characteristic (SROC) curve and forest plots to visualize the pooled results. The bivariate I^2 test was used to assess heterogeneity resulting from a potential non-threshold effect in this meta-analysis. If I^2 exceeds 50%, it is deemed considerable heterogeneity. MetaDisc 2.0 supports bivariate meta-analysis and provides global heterogeneity (bivariate I^2), but does not compute subgroup-specific I^2 directly.

Next, subgroup analysis and meta-regression techniques (pupil dilation status, AI algorithm, and camera device) were applied to diagnostic accuracy and heterogeneity to evaluate the possible impact of the covariates. This approach allowed us to maximize its diagnostic meta-analysis strength while acknowledging its limitations. To assess diagnostic accuracy, a bivariate random-effects model was employed to derive pooled sensitivity, specificity, diagnostic odds ratio (DOR), and likelihood ratios (LR+ and LR-). The area under the SROC curve reflected the AI’s performance in diagnosing DR.

Results

Study Selection and Characteristics

[Figure 1](#) summarizes the literature search and selection process. Initially, a total of 3,216 relevant articles were identified from the specified databases using a structured retrieval approach.

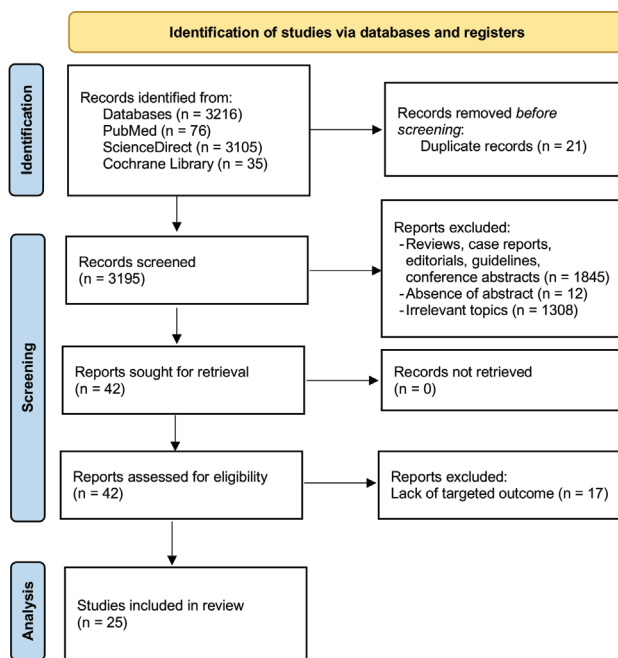


Figure 1. The study identification and selection process

Studies that were duplicates, conference abstracts, or one of the article types specified in the exclusion criteria (case report, guideline, editorial, commentary, opinion, or review, including meta-analysis), those without available full texts, and those with titles or abstracts unrelated to our review were excluded. After this initial screening, 42 original studies remained. Further evaluation led to the exclusion of papers with unclear methodologies or incomplete or irrelevant targeted outcomes.

The characteristics of the remaining 25 studies are summarized in [Table 1](#). These studies used several screening modalities for detecting DR: 21 evaluated the accuracy of AI-based/assisted screening, 2 assessed the accuracy of handheld/smartphone-based fundus cameras, and 2 reported about empowering trained general physicians to enhance the coverage of DR detection. The studies were performed in developing countries in Asia (China, India, Sri Lanka, Philippines, and Thailand), South America (Brazil and Mexico), and Africa (Zambia and Kenya). The primary goal of screening studies involving general physicians using an AI-based portable device was to evaluate and compare their accuracy to standard care for identifying any grade of DR, referable diabetic retinopathy (RDR), and VTDR. Most studies employed the International Clinical Diabetic Retinopathy Severity Scale classification system, where moderate nonproliferative diabetic retinopathy (NPDR) or worse was considered RDR, and severe NPDR or worse was considered VTDR. We included more-than-mild DR in the RDR group.

Quality Assessment

Twenty-five studies were reviewed for methodological quality and potential bias, following the QUADAS-2 guidelines. The evaluation revealed a risk of patient selection bias in

approximately 40% of the studies ([Figure 2](#)). An overview of the quality assessment for each study is provided in [Figure 3](#). For the remaining three domains (index test, reference standard, and flow and timing), the results suggested a generally low risk of bias and few issues with applicability. No studies were excluded following the quality assessment.

The Performance of Screening Modalities for Detecting Diabetic Retinopathy

Twenty-one studies were included in the final meta-analysis stage. These studies evaluated the performance of AI-based/assisted screening for DR in developing countries compared to standard/reference screening methods. They reported the performance of AI in detecting RDR (n=18), VTDR (n=3), and DR of any severity (n=11). We further evaluated AI's performance in detecting any DR and RDR based on pupil dilation status (mydriatic or non-mydriatic), algorithm (convolutional neural network [CNN] or deep learning [DL]), and camera device (smartphone-based/portable retinal camera or retinal fundus camera). Studies where pupil dilation was performed only when necessary were classified under the non-mydriatic group, whereas those employing combined methods were included in the mydriatic group. Most studies excluded ungradable images, while some performed analyses with and without the ungradable images. In this review, we only included the results for gradable images (see [Table 2](#)).

We used MetaDisc 2.0 to analyze the performance of AI-based screening in the included studies. [Table 2](#) presents the pooled sensitivity, specificity, DOR, LR+, LR-, and I^2 for any DR, RDR, and VTDR. The forest plots of sensitivity, specificity, and SROC curve are shown in [Figures 4, 5, and 6](#), respectively. The SROC curves illustrate the overall diagnostic performance of AI models for detecting any DR and RDR. The SROC curve for RDR demonstrates a more concentrated confidence ellipse, indicating greater consistency across studies. In contrast, the wider prediction ellipse in the any-DR SROC suggests higher variability in diagnostic accuracy. This variability may reflect differences in study populations, image quality, or AI model architectures. Overall, the AI models exhibited more stable and reliable performance in detecting RDR, whereas their effectiveness in identifying any DR appears more heterogeneous.

The I^2 values were high overall, with 0.809 for any DR and 0.82 for RDR, indicating substantial heterogeneity. We also performed a meta-regression with MetaDisc 2.0 using the subgroup analysis parameters to explore potential sources of heterogeneity. The outcomes are presented in [Tables 3 and 4](#). For the meta-regression analysis, only studies utilizing CNN or DL algorithms were included for the AI algorithm covariate because one study employed a machine learning approach, which was insufficient to form a meaningful subgroup or allow for reliable meta-regression. In addition, one study was also excluded from the meta-regression evaluating pupil dilation status and camera type because it did not clearly state whether images were obtained using a mydriatic or non-mydriatic method, nor did it specify the type of camera used.

Table 1. Characteristics of the studies assessing the performance of diabetic retinopathy screening methods

Author, year	Country	Study design	Image acquisition	Intervention screening	Reference screening	Device/AI used	Evaluated metric	Participants	Classification
Bellemo et al. ³⁸ , 2019	Zambia	Cross-sectional	The digital retinopathy system fundus camera; NM	Mobile screening, AI-algorithm (CNNs)	Retinal specialist	Adapted VGGNet architecture + ResNet architecture	Sensitivity, specificity, AUC, heatmaps for detecting RDR, and VTDR	1,574	ICDRSS
Natarajan et al. ³⁶ , 2019	India	Prospective cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); NM	AI-algorithm (CNNs)	Vitreoretinal resident and surgeon	Medios AI (Remidio)	Sensitivity, specificity, for detecting DR and RDR	231	ICDRSS
Nunez do Rio et al. ³⁷ , 2022	India	Prospective cross-sectional	Retinal fundus camera (Topcon NW400); NM	AI-algorithm (DL)	Trained optometrist or ophthalmologist	VISUHEALTH-AI DR (software version 1.8)	Sensitivity, specificity for detecting RDR	11,199	ICDRSS
Gulshan et al. ³⁸ , 2019	India	Prospective observational	Retinal fundus camera (NMTRC; Topcon Medical Systems; 3nethra; Forus Health); NM	AI-algorithm (DL)	Trained grader and retinal specialist	NA	Sensitivity, specificity for detecting RDR	3,049	ICDRSS
Ruamviboonsuk et al. ³⁹ , 2022	Thailand	Prospective interventional cohort	Retinal fundus camera (Topcon Maestro 3D OCT-1, Topcon TRC-NW300, Nidek AFC-230, Nidek AFC-210, and Nidek AFC-300), MD when needed	AI-algorithm (DL)	Retinal specialist	NA	Sensitivity, specificity, PPV, NPV for detecting RDR	7,651	ICDRSS
Sosale et al. ⁴⁰ , 2020	India	Cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); NM	AI-algorithm (CNNs)	Retinal specialist	Medios AI	Sensitivity, specificity, PPV, NPV for detecting any DR, RDR, and VTDR	900	ICDRSS
Penha et al. ²² , 2023	Brazil	Retrospective	Smartphone-based fundus camera (Eyer, Phelcom); MD	AI-algorithm (CNNs)	Retinal specialist	EyerMaps, Phelcom Technologies	Sensitivity, specificity, PPNV, NPV for detecting mtmDR	686	ICDRSS
Jain et al. ²¹ , 2021	India	Cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); MD	AI-algorithm (CNNs)	Retinal specialist	Medios AI (Remidio)	Sensitivity, specificity, heatmaps for detecting RDR	1,294	ICDRSS
Pawar et al. ²³ , 2021	India	Cross-sectional	Portable fundus camera (Intucam Prime); Combined (MD > NM)	AI-algorithm (DL)	Ophthalmologist	NA	Sensitivity, specificity for detecting RDR	138	ICDRSS
Noriega et al. ²⁹ , 2021	Mexico	Randomized controlled	NA	AI-algorithm (DL)	Ophthalmologist and retina specialists	ARIA system	Sensitivity, specificity, and heatmaps for detecting RDR	100	ICDRSS

Table 1. Continued

Author, year	Country	Study design	Image acquisition	Intervention screening	Reference screening	Device/AI used	Evaluated metric	Participants	Classification
Pei et al. ⁴¹ , 2022	China	Cross-sectional	Retinal fundus camera (Zeiss Non-mydiatic Fundus Camera); NM	AI algorithm (DL)	Ophthalmologist	EyeWisdom DSS and EyeWisdom MCS	Sensitivity, specificity, AUC, PPV, NPV, kappa test for detecting Any DR, NPDR, PDR	549	ICDRSS
Dong et al. ⁴² , 2022	China	Cross-sectional	Retinal fundus camera (RetiCam 3100); NM	AI algorithm (CNN)	Ophthalmologist and retinal specialist	CARE system	Sensitivity, specificity, PPV, NPV for detecting any DR, mmdr, VTDR, DME	443	ICDRSS
Ming et al. ⁴³ , 2021	China	Prospective cross-sectional	Retinal fundus camera (Canon CR-2 Digital Retinal Camera); NM	AI algorithm (DL)	Ophthalmologist	EyeWisdom	Sensitivity, specificity, AUC for detecting any DR and RDR	173	ICDRSS
Zhang et al. ⁴⁴ , 2020	China	Prospective cross-sectional	Retinal fundus camera (Topcon TRC-NW400, MiiS DSC-200, Canon CR-2 PLUS AF, Canon CR-2 AF and Zeiss VISUCAM200); NM	AI algorithm (DL)	Ophthalmologist	VoxelCloud Retina	Sensitivity, specificity, PPV, NPV for detecting RDR	40,665	ICDRSS
Li et al. ⁴⁵ , 2021	China	Prospective cross-sectional	Retinal fundus camera (KOWA nonmyd WX); NM	AI algorithm (DL)	Retinal specialist	VoxelCloud Retina	Sensitivity, specificity, AUC for detecting RDR	1,147	ICDRSS
Bawankar et al. ⁴⁶ , 2017	India	Prospective open-label	Portable fundus camera (Bosch non-mydiatic fundus camera); NM and 7-Standard Field stereoscopic Digital Color Fundus (reference); MD	AI algorithm (CNNs)	Ophthalmologist	Bosch DR Algorithm	Sensitivity, specificity, PPV, NPV for detecting any DR	560	ETDRS
Yang et al. ²⁴ , 2022	China	Prospective observational controlled	Retinal fundus camera (Zeiss Visucam FF450, Topcon TRC-50DX, Topcon NW-400); MD	AI algorithm (CNNs)	Ophthalmologist	AIDRScreening system v. 1.0	Sensitivity, specificity, PPV, NPV for detecting RDR	962	COS guidelines
Al Turk et al. ⁴⁷ , 2020	China, Kenya	Retrospective	Retinal fundus camera (Optovue iCam, Centervue DRS, Topcon NW and Canon CR1/DGi/CR2); NM	AI algorithm (CNNs)	Ophthalmologist	DAPHNE	Sensitivity, specificity, kappa agreement test for detecting RDR, PDR	39,700	NSC (China), ICDRSS (Kenya)

Table 1. Continued

Author, year	Country	Study design	Image acquisition	Intervention screening	Reference screening	Device/AI used	Evaluated metric	Participants	Classification
Rajalakshmi et al. ⁴⁸ , 2018	India	Cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); MD	AI algorithm (DL)	Ophthalmologist	EyeArt	Sensitivity, specificity, PPV, NPV, kappa test for detecting any DR, DME, PDR, STDR, RDR	296	ICDRSS
Hansen et al. ⁴⁹ , 2015	Kenya	Retrospective cross-sectional	Retinal fundus camera (Topcon1 NW/6S non-mydiatic retinal camera); MD	AI algorithm (ML)	Ophthalmologist	Iowa Diabetic Retinopathy (IDP)	Sensitivity, specificity, PPV, NPV for detecting any DR	3,126	ICDRSS
Malerbi et al. ⁵⁰ , 2024	Brazil	Cross-sectional	Smartphone-based fundus camera (The Eyer); MD	AI algorithm (CNN)	Ophthalmologist, retinal specialist	Retinal Alteration Score (RAS), Diabetic Retinopathy Alteration Score (DRAS)	Sensitivity, specificity for detecting any DR and mtrmDR	327	ICDRSS
Salongcay et al. ¹¹ , 2022	Philippines	Prospective cross-sectional	Fundus photography with different handheld retinal cameras; Combined NM and MD	NM and MD handheld retinal imaging	ETDRS 7-field fundus camera	iNview, RetinaVue 700, Smartscope (SSNM), Aurora (AUNM)	Sensitivity and Specificity for detecting any DR, RDR, and VTDR	116	ICDRSS
Wintergerst et al. ¹⁰ , 2020	India	Cross-sectional	All participants were divided into groups with different retinal camera; MD	Four SBFi approaches	Conventional 7-field color fundus photography	Direct SBFi: Peek Retina, D-EYE, a do-it-yourself by Sankara Eye Foundation Indirect SBFi: Paxos Scope	Image quality, examination time, and agreement for detecting any DR, severe DR, DME.	193	ICDRSS
Cunha et al. ¹² , 2018	Brazil	Cross-sectional	Retinal fundus camera (Canon CR-2); NM	Grading by non-ophthalmologist (family physicians)	Grading by ophthalmologist (ophthalmologist and retinal specialist)	NA	Sensitivity, specificity, PPV, NPV, kappa agreement for detecting any DR, DME, NPDR/PDR	200	ICDRSS
Piyasena et al. ¹³ , 2019	Sri Lanka	Cross-sectional	Hand-held non-mydiatic (Visucout 100®-Germany) digital retinal camera; NM	Grading by general physicians	Dilated fundus examination by retinologist using slit-lamp bio-microscopy with a 90D lens and indirect ophthalmoscopy using a 20D lens.	Visucout 100®-Germany	Sensitivity, specificity, PPV, NPV, kappa agreement for detecting any DR, RDR, and maculopathy	700	United Kingdom National Screening System

AI: Artificial intelligence, AUC: Area under the curve, CNN: Convolutional neural networks, COS: Chinese Ophthalmic Society, D: Dioptric, DL: Deep learning, DME: Diabetic macular edema, DR: Diabetic retinopathy, ICDRSS: International Clinical Diabetic Retinopathy Severity Scale, MD: Mydiatic, ML: Machine learning, mtrmDR: More-than-mild diabetic retinopathy, NA: Not available, NM: Non-mydiatic, NPDR: Non-proliferative diabetic retinopathy, NPV: Negative predictive value, NSC: National Screening Committee, RDR: Referable diabetic retinopathy, PDR: Proliferative diabetic retinopathy, PPV: Positive predictive value, SBFi: Smartphone-based fundus imaging, VTDR: vision threatening diabetic retinopathy

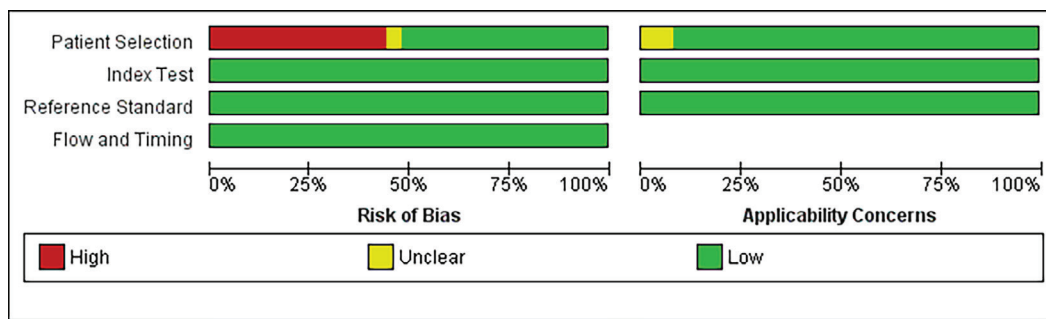


Figure 2. Risk of bias graph chart with QUADAS-2
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2



Figure 3. Risk of bias for individual studies included in the review

These exclusions were made to maintain consistency in covariate classification and preserve the validity of the meta-regression analysis. However, all excluded studies were still included in the overall pooled analysis of diagnostic accuracy. We found that for any DR, none of the covariates significantly explained the heterogeneity. In contrast, for RDR detection, p values indicated statistical significance for camera device ($p < 0.05$), suggesting that variations in the type of camera used for RDR detection could contribute to the heterogeneity across studies.

Two studies evaluated handheld or smartphone-based fundus imaging (SBFI) as a portable device alternative to standard fundus photography. Wintergerst et al.¹⁰ compared four SBFI modalities, three using direct and one using indirect ophthalmoscopy. The images were compared against reference standards of 7-field color fundus photography. Meanwhile, indirect ophthalmoscopy conducted by a specialist was evaluated for image clarity, coverage area, duration of examination, and accuracy in diagnosing DR.

Among 381 eyes of 193 subjects, all SBFI methods produced clear images, but direct SBFI had more artifacts and lower contrast than indirect SBFI. Across different smartphone-based imaging systems, sensitivity for any DR detection ranged from 67% to 79% while specificity remained high, between 98% and 100%. For RDR (moderate NPDR or worse), sensitivity varied between 76% and 87%, with specificity between 96% and 100%. Detection of severe DR (severe NPDR or PDR) achieved 100% sensitivity and specificity with some devices. For diabetic maculopathy, sensitivity ranged from 79% to 83%, while specificity was consistently 100%. The authors concluded that indirect ophthalmoscopy-based SBFI provided the highest diagnostic accuracy, with a strong agreement with the reference standard (Cohen's kappa: 0.868).¹⁰

Salongcay et al.¹¹ evaluated non-mydratic and mydratic handheld retinal imaging versus ETDRS 7-standard field fundus photography in 225 eyes of 116 patients. For detection of any DR, non-mydratic devices demonstrated sensitivities ranging from 80% to 89% and specificities between 88% and 97%. Sensitivity for RDR was 87%-93%, while specificity varied from 76% to 92%. For VTDR (severe NPDR or worse, including PDR and DME), sensitivity ranged from 83% to 88% but specificity was lower, ranging from 69% to 86%. Smartscope NM and Aurora/RetinaVue-700 MD images achieved 80%

Categories	Number of studies	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	DOR (95% CI)	LR+ (95% CI)	LR- (95% CI)	I ²
Categories of DR							
Any DR	11	0.890 (0.845-0.924)	0.900 (0.832-0.942)	72.680 (40.102-131.723)	8.867 (5.256-14.956)	0.122 (0.087-0.172)	0.809
RDR	18	0.933 (0.89-0.96)	0.903 (0.871-0.928)	130.617 (74.629-228.609)	9.665 (7.271-12.849)	0.074 (0.045-0.123)	0.82
VTDR	3	0.891 (0.393-0.990)	0.936 (0.837-0.977)	120.198 (7.706-1874.779)	13.972 (5.027-38.834)	0.116 (0.012-1.117)	NA
Pupil dilation status							
Mydriatic							
Any DR	5	0.904 (0.839-0.944)	0.874 (0.747-0.942)	64.965 (27.304-154.574)	7.153 (3.453-14.817)	0.11 (0.066-0.184)	NA
RDR	6	0.963 (0.907-0.986)	0.863 (0.79-0.914)	163.695 (57.747-464.023)	7.047 (4.521-10.985)	0.043 (0.017-0.109)	NA
Non-mydriatic							
Any DR	6	0.877 (0.808-0.924)	0.918 (0.835-0.961)	79.761 (36.096-176.244)	10.663 (5.267-21.587)	0.134 (0.086-0.209)	NA
RDR	11	0.908 (0.84-0.949)	0.92 (0.887-0.944)	113.552 (57.141-225.654)	11.382 (8.048-16.097)	0.1 (0.057-0.177)	NA
AI Algorithm							
Convolutional neural networks							
Any DR	6	0.879 (0.81-0.925)	0.923 (0.851-0.961)	86.348 (50.429-147.851)	11.349 (5.997-21.478)	0.131 (0.086-0.202)	NA
RDR	9	0.934 (0.869-0.968)	0.898 (0.849-0.932)	124.164 (57.798-266.734)	9.158 (6.19-13.549)	0.074 (0.037-0.147)	NA
Deep learning							
Any DR	4	0.929 (0.862-0.964)	0.892 (0.767-0.954)	107.024 (50.597-226.378)	8.572 (3.909-18.799)	0.08 (0.043-0.15)	NA
RDR	9	0.933 (0.864-0.968)	0.909 (0.862-0.941)	138.245 (62.156-307.479)	10.248 (6.78-15.489)	0.074 (0.036-0.152)	NA
Camera device							
Smartphone-based/portable camera							
Any DR	7	0.916 (0.872-0.946)	0.906 (0.822-0.953)	104.602 (57.669-189.729)	9.733 (5.119-18.509)	0.093 (0.063-0.138)	NA
RDR	6	0.97 (0.929-0.988)	0.856 (0.792-0.903)	194.987 (69.095-550.256)	6.75 (4.602-9.901)	0.035 (0.014-0.085)	NA
Retinal fundus camera							
Any DR	4	0.831 (0.735-0.898)	0.885 (0.744-0.953)	37.875 (17.862-80.309)	7.221 (3.234-16.123)	0.191 (0.126-0.289)	NA
RDR	11	0.894 (0.823-0.938)	0.927 (0.897-0.948)	106.674 (52.418-217.09)	12.239 (8.598-17.421)	0.115 (0.068-0.195)	NA

AI: Artificial intelligence, DOR: Diagnostic odds ratio, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, DR: Diabetic retinopathy, RDR: Referable diabetic retinopathy, VTDR: Vision threatening diabetic retinopathy, NA: Not available

sensitivity and 95% specificity for detecting DR, meeting thresholds for RDR and DME. However, no device met the 95% specificity requirement for VTDR. Non-mydriatic imaging also had higher ungradable rates (15.1%-38.3% for DR) than mydriatic imaging (0%-33.8%).¹¹

Next, two studies evaluated the agreement and diagnostic accuracy of non-ophthalmologists in DR screening. Cunha et al.¹² assessed the efficacy of non-mydriatic fundus photography in DR screening by analyzing the diagnostic agreement across qualified family physicians (FP), general ophthalmologists (GO), and a retinal specialist. A total of 397 eyes of 200 individuals with diabetes were examined. The retinal specialist diagnosed DR in 41.8% of eyes, whereas GO1 and GO2 diagnosed DR in 28.7% and 45.8% of cases, respectively. Diagnostic agreement between the FPs and the retinal specialist for DR diagnosis varied from modest to considerable, with kappa values as follows: FP1 = 0.56, FP2 = 0.69, FP3 = 0.73, FP4 = 0.71. Similarly, agreement in DR severity grading was moderate to substantial

(FP1 = 0.51, FP2 = 0.66, FP3 = 0.69, FP4 = 0.64). However, the agreement for DME diagnosis was lower, varying from fair (FP1 = 0.33, FP2 = 0.39, FP3 = 0.37) to moderate (FP4 = 0.51).¹²

Furthermore, Piyasena et al.¹³ evaluated the diagnostic accuracy of a handheld non-mydriatic fundus camera in Sri Lanka, where nine general physicians were trained by ophthalmologists to perform DR screening. Two physicians with the highest agreement with the retinal specialist ($k = 0.8-0.9$) were selected as final graders. For any DR, sensitivity in non-mydriatic imaging ranged from 78.3% to 82.7%, while specificity ranged from 70.4% to 76.2%. With pupil dilation, sensitivity ranged from 78.0% to 79.3%, and specificity improved to 89.2%-91.5%. The kappa agreement value with a retinal specialist for any DR improved from 0.42-0.47 in non-mydriatic imaging to 0.66-0.68 after pupil dilation. For RDR, sensitivity in non-mydriatic imaging ranged from 84.9% to 86.8%, while specificity ranged from 71.7% to 77.3%. With pupil dilation, sensitivity

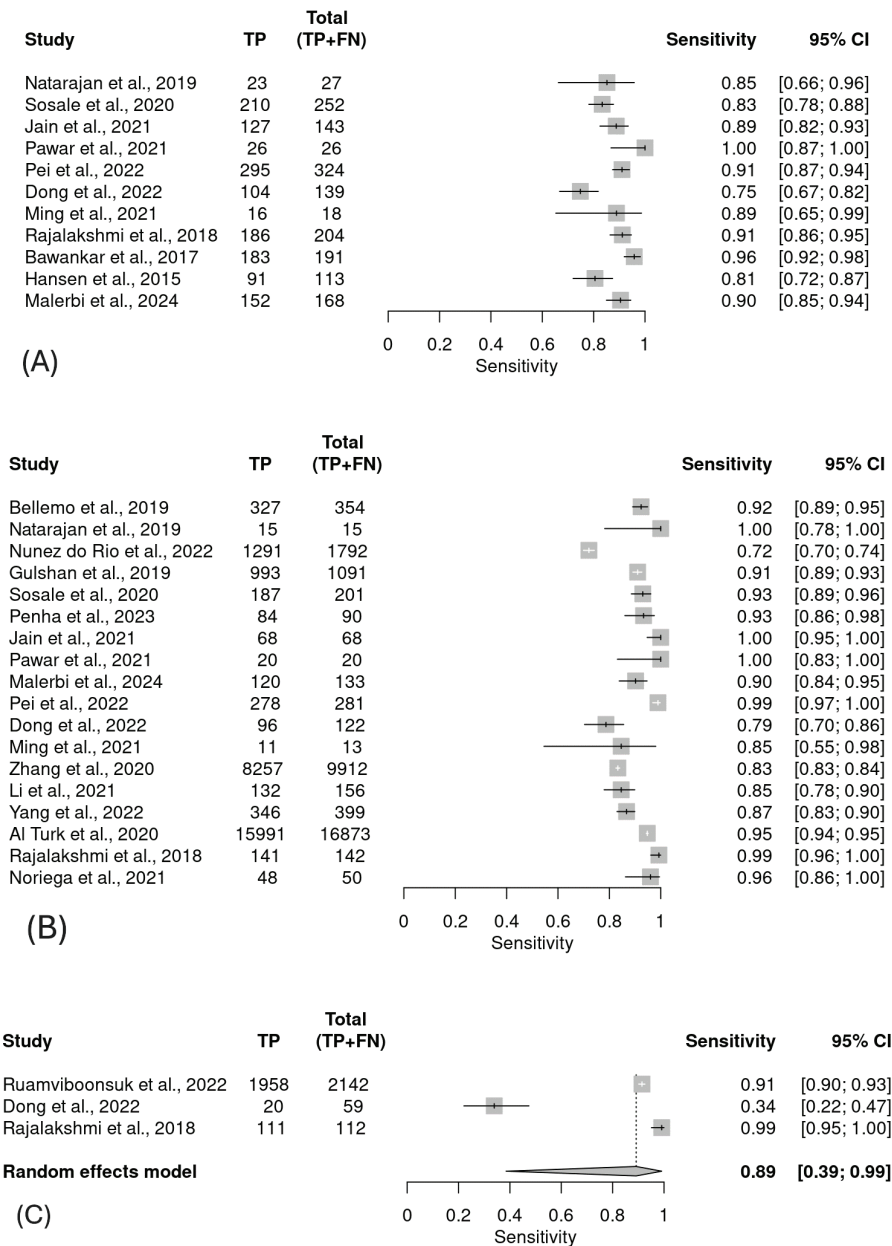


Figure 4. Forest plots of pooled sensitivity in all the studies included in the meta-analysis. A) Forest plot of any diabetic retinopathy (DR). B) Forest plot of referable DR. C) Forest plot of vision-threatening DR
 TP: True positives, FN: False negatives, CI: Confidence interval

improved to 88.7%-92.5% and specificity increased to 94.9%-96.4%. The kappa agreement values for RDR detection were 0.23-0.29 in non-mydratic imaging and increased to 0.68-0.76 in mydratic imaging. For maculopathy detection, sensitivity in non-mydratic imaging was 89.2%, specificity was 70.1%, and the kappa agreement with the reference standard was 0.29. The percentage of ungradable images was 43.4% in non-mydratic imaging and decreased to 12.8% after pupil dilation.¹³

Discussion

This study assessed the diagnostic effectiveness of different DR detection methods to increase screening availability in developing countries. Recent technological advancements hold significant potential to enhance healthcare services, especially in developing countries. This research analyzed 25 studies, of which 21 were included in the meta-analysis and 4 were included in the qualitative review.

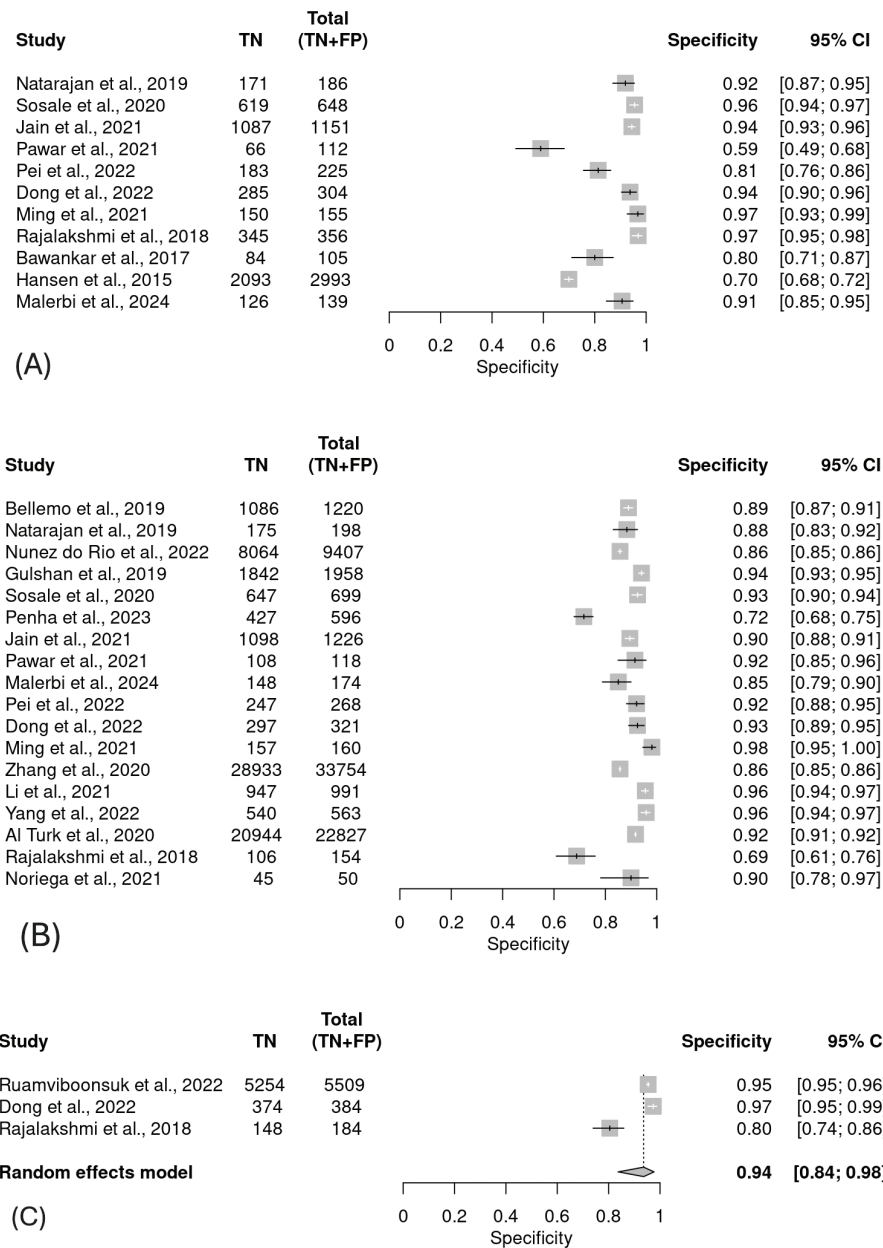


Figure 5. Forest plots of pooled specificity in all the studies included in the meta-analysis. A) Forest plot of any diabetic retinopathy (DR). B) Forest plot of referable DR. C) Forest plot of vision-threatening DR
TN: True negatives, FP: False positives, CI: Confidence interval

Among the 21 meta-analyzed studies, the diagnostic performance of AI-based/assisted screening demonstrated strong diagnostic ability with a pooled sensitivity of 0.890, specificity of 0.900, and DOR of 72.680 for detecting DR. Similarly, the diagnostic performance of AI-based/assisted screening for detecting RDR had a pooled sensitivity of 0.933, specificity of 0.903, and an even higher DOR of 130.617, demonstrating high accuracy for identifying more severe cases requiring referral.

Meanwhile, although only three studies evaluated VTDR, the pooled results still suggest encouraging performance, with pooled sensitivity at 0.891 and specificity at 0.936, though the limited data warrant careful interpretation. These results exceeded the Food and Drug Administration established 85% sensitivity and 82.5% specificity endpoints.¹⁴ They are also consistent with those found in earlier systematic reviews and meta-analyses that evaluated the diagnostic accuracy of AI algorithms in DR

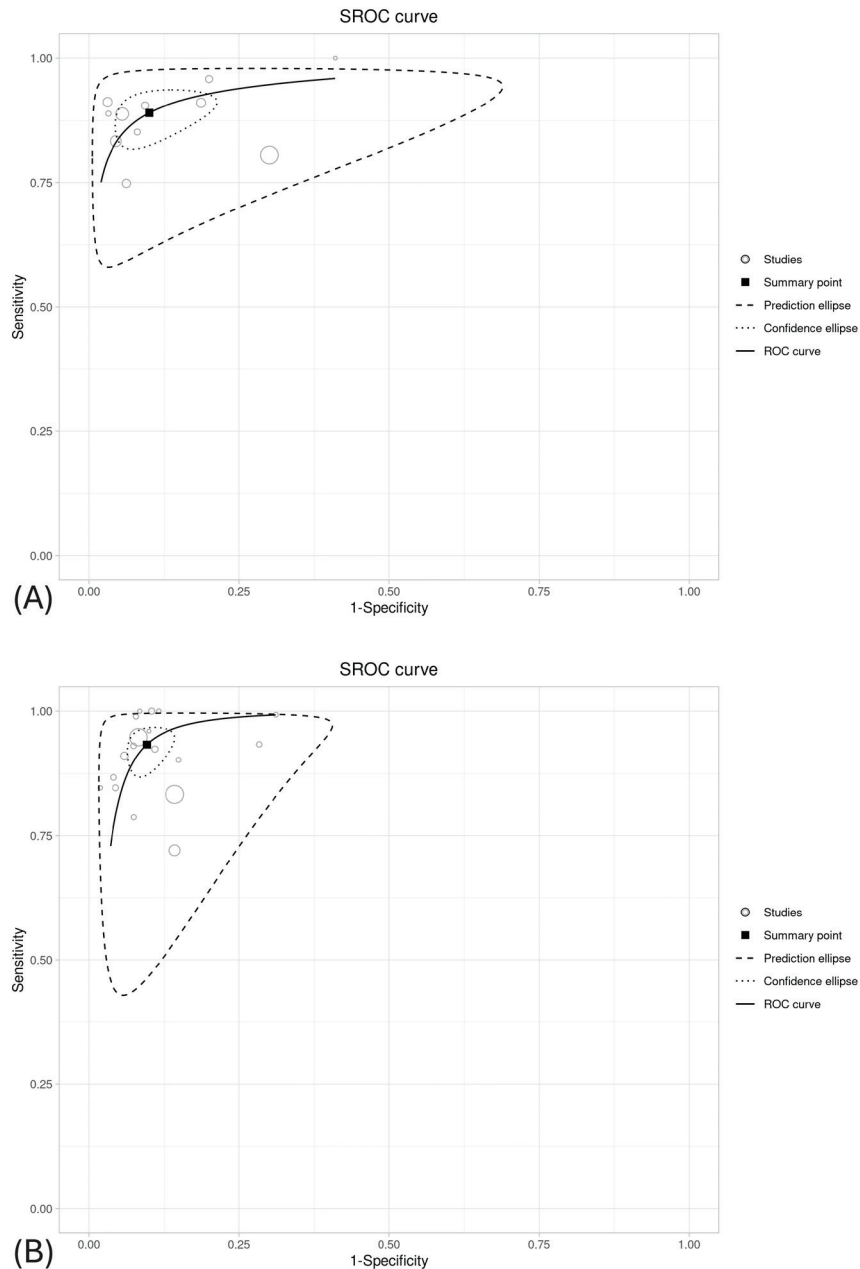


Figure 6. Summary receiver operating characteristic (SROC) curve of included studies in data analysis. A) SROC curve of any diabetic retinopathy (DR). B) SROC curve of referable DR

screening.^{15,16,17} Our results are also comparable to those of meta-analyses on AI-based detection for other eye disease such as glaucoma, pathologic myopia, and dry eye disease.^{18,19,20}

Furthermore, we conducted a subgroup analysis to investigate the factors influencing AI performance in detecting any DR and RDR. AI exhibited similar accuracy in detecting DR from both non-mydriatic and mydriatic images. Mydriatic photographs have slightly better sensitivity but slightly lower specificity than non-mydriatic photographs. This result may be because mydriasis produces more detailed images. False positives occur due to subtle lesions or certain non-DR retinal abnormalities

including drusen, atrophy or hypertrophy of the retinal pigment epithelium, telangiectatic vessels near the macula, tessellated fundus, and retinal vein occlusion.^{21,22,23} However, retinal lesions unrelated to DR still indicate that the patient must consult an ophthalmologist or retina specialist. Therefore, they cannot be considered false positives and of no concern in terms of clinical implications. Meanwhile, in non-mydriatic photographs, the retinal images tend to be darker, may not capture all subtle DR lesions, and could result in a higher percentage of ungradable images.²⁴

Table 3. Meta-regression of included studies for detecting any diabetic retinopathy

Subgroup	Parameter	Estimate	LCL	UCL	p value
Pupil dilation status^a	Relative sensitivity	1.03	0.945	1.123	0.497
	Relative specificity	0.952	0.84	1.079	0.427
	Global test comparison				0.661
Algorithm^b	Relative sensitivity	0.946	0.872	1.027	0.209
	Relative specificity	1.035	0.923	1.16	0.545
	Global test comparison				0.433
Device^c	Relative sensitivity	1.102	0.991	1.224	0.047
	Relative specificity	1.024	0.898	1.168	0.719
	Global test comparison				0.051

^aWhether pupil dilation is done: non-mydratric or mydratric
^bAlgorithm of the artificial intelligence model used: deep learning and convolutional neural networks
^cDevice used to take retinal photographs: smartphone-based or portable camera and retinal fundus camera
LCL: Lower confidence limit, UCL: Upper confidence limit

Table 4. Meta-regression of included studies for detecting referable diabetic retinopathy

Subgroup	Parameter	Estimate	LCL	UCL	p value
Pupil dilation status^a	Relative sensitivity	1.061	0.992	1.135	0.097
	Relative specificity	0.938	0.869	1.013	0.079
	Global test comparison				0.09
Algorithm^b	Relative sensitivity	1.001	0.932	1.075	0.975
	Relative specificity	0.988	0.928	1.051	0.703
	Global test comparison				0.927
Device^c	Relative sensitivity	1.086	1.015	1.162	0.013
	Relative specificity	0.924	0.862	0.99	0.018
	Global test comparison				0.005

^aWhether pupil dilation is done: non-mydratric or mydratric
^bAlgorithm of the artificial intelligence model used: deep learning and convolutional neural networks
^cDevice used to take retinal photographs: smartphone-based or portable camera and retinal fundus camera
LCL: Lower confidence limit, UCL: Upper confidence limit

For the AI algorithm architecture, there was minimal difference in pooled performance between CNN-based models and broader DL algorithms. The pooled sensitivity for DL models was slightly higher than for CNN models, but CNN models achieved better specificity. However, these differences were not statistically significant. Our results suggested that choosing between DL and a CNN architecture did not contribute substantially to diagnostic performance. DL is an advanced branch of machine learning that utilizes multi-layered neural networks to analyze extensive datasets, allowing systems to identify complex visual patterns autonomously. CNN, a specific DL variant, is optimized for image analysis, especially in medical diagnostics.²⁵ CNN-based models utilize convolutional layers to accurately recognize and categorize retinal abnormalities, including microaneurysms, hemorrhages, and exudates, essential for DR detection.²⁶ Since DL-based models demonstrate greater sensitivity, they may be more appropriate for initial screening to minimize missed cases. On the other hand, CNN models could be utilized as reliable confirmation tools, helping to reduce unnecessary referrals due to false positives. Joseph et al.²⁷ also

reported in their meta-analysis that the DL algorithm, which included CNN, demonstrated high accuracy compared to machine learning. Only one study in our review used machine learning. When this study was excluded, the pooled sensitivity and specificity increased to 90% and 91%, respectively, for detecting any DR. The improved efficiency and diagnostic accuracy of DL over traditional machine learning has revolutionized the ability to detect DR using fundus images.^{25,26,27}

Three studies incorporated AI-generated heatmaps to enhance interpretability in DR screening. Bellemo et al.²⁸ used heatmaps to highlight specific areas in the retinal fundus images that most significantly influence CNN determination. These visualizations illustrate the AI system's decision-making process and explain features that may encourage trust in AI models.²⁸ The heatmaps of the lesions provided by the AI can also be utilized for patient education.²¹ Noriega et al.²⁹ also showed that incorporating attention heatmaps highlighted DR lesions and improved grader sensitivity when used in an assistive screening approach. Sayres et al.³⁰ further investigated the heatmaps' impact on ophthalmologists' grading accuracy and confidence.

They found that while heatmaps improved sensitivity for RDR, they also led to overdiagnosis in cases with no DR, increasing false positives for mild NPDR. This result might be because heatmaps can highlight pathological features but cannot effectively indicate the absence of disease. Despite this initial increase in overdiagnosis, grader accuracy improved over time, suggesting that clinicians adapted to interpreting heatmaps with experience.³⁰

Moreover, although 7-field ETDRS group stereoscopic color fundus photography remains the gold standard for DR, its high cost and time demands have led to the use of handheld and smartphone-based cameras, especially in community-based screening initiatives. Regarding camera type, smartphone-based or portable fundus cameras demonstrated higher sensitivity than desktop fundus cameras. However, they exhibited a slight decrease in specificity, particularly for RDR detection. In our meta-analysis, camera type emerged as a significant source of heterogeneity, which suggested that hardware differences, including image quality and field of view, directly influence AI performance, especially in detecting more severe disease stages. These results align with those reported by Tan et al.³¹, who found a pooled sensitivity and specificity of 87% and 94% for any DR and 91% and 89% for RDR, respectively. However, while they observed a progressive increase in sensitivity and specificity as DR severity advanced (pooled sensitivity and specificity were 39% and 95% for mild NPDR, 71% and 95% for moderate NPDR, and 80% and 97% for PDR), our meta-analysis did not specifically assess the accuracy for each DR stage. Such an analysis was not possible due to differences in study methods, reference standards, and DR classification approaches.

Furthermore, we examined studies that specifically evaluated smartphone-based and handheld fundus imaging for DR detection to understand the impact of device type on diagnostic performance. Wintergerst et al.¹⁰ found that SBFI, especially when using indirect ophthalmoscopy, offered the highest-quality images, the widest field of view, and demonstrated excellent sensitivity and specificity (0.79-0.99 for any DR and 1.0-1.0 for severe DR), and excellent agreement with the reference standard (Cohen's kappa 0.868). Salongcay et al.¹¹ also reported that non-mydriatic and mydriatic handheld retinal imaging obtained good to excellent kappa agreement values with the ETDRS 7-standard field photography. However, the non-mydriatic method was linked to higher rates of ungradable images and lower levels of agreement.¹¹ Similarly, Prathiba et al.³² found that the non-mydriatic retinal camera demonstrated good agreement with standard tabletop fundus photography. Nevertheless, as with other non-mydriatic approaches, a higher proportion of ungradable images was observed, reinforcing the need for selective pupil dilation to improve image quality and reduce screening errors.³² These findings suggest that for community-based DR screening programs, device selection should consider the trade-off between portability, image quality, and the need for pupil dilation to optimize diagnostic accuracy and reduce false positives.

Although this review focuses on diagnostic accuracy, real-world factors like patient adherence are crucial for successful DR screening programs. The RAIDERS trial in Rwanda evaluated how AI-assisted screening influenced follow-up adherence. Mathenge et al.³³ found that immediate AI feedback increased referral adherence by 30.1% (51.5% vs. 39.6%, $p=0.048$) and a faster median time to follow-up (4 vs. 8 days) compared to human grading. Similarly, Liu et al.³⁴ reported a threefold improvement in adherence (55.4% vs. 18.7%) after implementing AI-based screening in a low-income primary care setting. These findings highlight the potential benefits of AI-assisted screening beyond its diagnostic performance. It also aligns with findings from public perception studies where patients demonstrated high confidence in AI-generated medical diagnoses, suggesting that trust in AI may positively influence screening adherence.³⁵ AI-based/assisted screening may also improve real-world patient engagement by reducing delays and enhancing adherence to follow-up care.

Expanding DR screening by task-shifting to non-ophthalmologists is an important strategy, especially in resource-limited settings where access to specialists is scarce. Two studies evaluated the diagnostic agreement between non-ophthalmologists (FPs/general physicians) and retinal specialists in DR screening. Cunha et al.¹² evaluated FP performance in DR screening, comparing it with retinal specialists. They found that FPs achieved moderate to substantial agreement with a retinal specialist ($k=0.56-0.73$), though agreement on macular edema was fair to moderate ($k=0.33-0.51$). However, similar agreement was also demonstrated between GOs and the retinal specialist, which suggests that FPs and GOs had similar diagnostic skills.¹²

Similarly, Piyasena et al.¹³ reported that general physicians achieved high agreement for any DR detection ($k=0.42-0.47$ in non-mydriatic imaging, improving to 0.66-0.68 in mydriatic imaging) and for RDR ($k=0.23-0.29$ non-mydriatic, improving to 0.68-0.76 mydriatic). However, the kappa agreement value for maculopathy detection was lower ($k=0.29$ non-mydriatic). The study also highlighted that ungradable images were high (43.4%) in non-mydriatic imaging but decreased to 12.8% after pupil dilation, reinforcing the importance of image quality for accurate DR screening.¹³ Both studies suggest that trained non-ophthalmologists can effectively detect RDR, but challenges remain in maculopathy detection and handling ungradable images. These findings underscore the need for further training and calibration of primary care providers if task-shifting strategies are to be effectively deployed in low-resource settings.

Our review has several strengths. One of the key strengths is its focus on DR screening in developing countries, where access to ophthalmologists is often limited. By including various screening modalities, such as AI-based/assisted identification, smartphone-based or portable fundus imaging, and trained non-ophthalmologist-assisted screening, this review incorporates a wider range of diagnostic methods, allowing for a broader comparison of different screening approaches and providing valuable insights into practical alternatives for resource-

limited settings. We also performed a meta-regression analysis incorporating multiple relevant factors, offering important insights. Additionally, most of the included studies reflect real-world screening conditions, enhancing the applicability of these findings to national DR screening programs and public health initiatives.

Nevertheless, this review has several limitations. First, the included studies cover a range of study designs, including retrospective, prospective, cross-sectional, and randomized controlled experiments. The heterogeneity in study design may introduce variability in the reported diagnostic performance of the AI models. Second, the meta-regression analysis identified camera type as a significant source of heterogeneity, suggesting that differences in imaging hardware, such as resolution and field of view, impact diagnostic accuracy. However, mydriatic status and AI algorithm type did not significantly contribute to heterogeneity, indicating that other unaccounted factors may still influence screening accuracy. Another limitation is the unequal distribution of studies across subgroups. Moreover, this meta-analysis focused primarily on diagnostic accuracy, without assessing whether earlier detection through AI-assisted or non-ophthalmologist screening improves patient outcomes such as treatment adherence and vision preservation.

Conclusion

This review highlights the growing feasibility of integrating AI-based and portable imaging technologies into DR screening programs in developing countries. Portable fundus cameras integrated with AI-based software can potentially lower the workload of ophthalmologists while reducing missed or incorrect diagnoses, ultimately helping to prevent vision loss caused by DR. Our findings suggest that both non-mydriatic and mydriatic imaging perform well, making them promising options for large-scale screening. However, pupil dilation should be considered for patients with ungradable retinal images to improve sensitivity without compromising specificity, as it can enhance image quality and reduce missed diagnoses. Ideally, this approach should be conducted under the supervision of trained physicians to maintain screening accuracy, reduce unnecessary referrals, and provide timely and appropriate care. These findings also emphasize the importance of quality assurance measures, including regular training, structured feedback loops, and possibly integrating AI decision support to assist non-specialist graders. Standardizing grading criteria, improving image quality, and refining AI models will be essential to developing reliable and scalable DR screening solutions, particularly in resource-limited settings. Our study demonstrated diagnostic accuracy across modalities, which can guide the development of more inclusive, scalable, and economical national screening programs. This insight might help policymakers choose the appropriate technologies based on workforce availability and local infrastructure. Future research to improve diagnostic performance should assess how these screening techniques could affect clinical outcomes including early intervention, treatment

adherence, and long-term vision preservation. These outcome-based studies are essential to fully demonstrate the public health benefits of integrating AI-assisted screening into routine diabetes care.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Declarations

Authorship Contributions

Surgical and Medical Practices: K.A.H., A.A., N.M.A.S., T.E., Concept: Y.Y., K.A.H., Design: Y.Y., K.A.H., Data Collection or Processing: Y.Y., A.C.V.G., N.P.K.M.D., Analysis or Interpretation: Y.Y., K.A.H., A.A., N.M.A.S., T.E., A.C.V.G., N.P.K.M.D., Literature Search: Y.Y., K.A.H., A.A., N.M.A.S., T.E., A.C.V.G., N.P.K.M.D., Writing: Y.Y., K.A.H.

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