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THE VALIDITY OF ARTIFICIAL INTELLIGENCE (AI) FOR DIABETIC RETINOPATHY SCREENING IN ASIA: A SYSTEMATIC REVIEW

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Abstract

Introduction: Diabetic retinopathy (DR) is a significant complication of diabetes mellitus (DM) that can cause visual impairment. Unfortunately, over one-third of diabetic patients in Asia have never received an ophthalmological examination due to a shortage of resources for eye care, i.e., in Bangladesh and Sri Lanka. Screening for DR is crucial for DM management, and artificial intelligence (AI) has become increasingly popular for DR screening due to its ability to automatically process large amounts of data using Deep Learning (DL) technologies. This review aims to assess the validity of AI as a DR screening tool in Asian countries compared to ophthalmologist DR grading as a reference standard.

Methods: A comprehensive search was conducted using relevant search terms from the electronic database (Pubmed, Cochrane, and EMBASE). Studies conducted in humans with DL algorithm in Asian countries and evaluated for its sensitivity, specificity, and AUC are included, whereas non-English articles are excluded.

Result: Twelve studies, most of which were conducted in China and India between 2017 and 2021, reported a good sensitivity of AI for detecting Referable DR (RDR). The lowest sensitivity was 79.2 %, and the highest was 100 %. For specificity, eleven studies reported reasonable specificity, with only one study reporting a low value, with only 68.8% for detecting RDR.

Conclusion: The AI can detect DR by screening large amounts of retina images with acceptable validity without the assistance of a trained retina specialist. In this review of local Asia population settings, AI has a good result for detecting RDR in almost all studies..

Keywords: artificial intelligence, deep learning, diabetic retinopathy

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INTRODUCTION

DM is a systemic disorder that affects 6.5 % of the world's population. The International Diabetic Federation (IDF) estimated that there would be 537 million patients with DM worldwide in 2021, and this number will increase to more than 780 million by 2045.[1] DR is an ocular manifestation in DM that may lead to visual impairment or even blindness.[2] There are disparities in the availability of eye care human resources in Asia, i.e., in Bangladesh and Sri Lanka, and this worsens the problem of limited access to eye care.[3] DR has become the most common cause of blindness in the working-age population. Parallel with DR's rising prevalence, the social and economic burden is also substantially increasing.[4]

Prevention, therefore becomes essential to tackle the increasing burden of DR. Recommendation from The American Academy of Ophthalmology (AAO) for diabetic patients to be screened annually. This recommendation is based on the fact that early treatment of DR could reduce the risk of visual impairment by more than 90 %. The objective is to treat DR before visual impairment becomes severe and irreversible.[5]

Screening for DR is conventionally done through manual fundus examination or reading the fundus images.[6] Low availability of ophthalmologists and lack of eye care services lead to less DR screening coverage. Thus, low DR screening coverage means more patients with DM will lose opportunities to get treated.[7] New screening strategies with better efficiency and accessibility are needed to address the rapid growth of DR, especially in Asian countries.[8]

Studies of Artificial intelligence (AI) in ophthalmology have been increasing recently because Deep Learning (DL), a new generation of AI can process a large amount of data without human intervention. The basis of DL incorporation in the DR screening method consisted of the application of an image-based approach, which can be done due to the large number of images accessible for DL to be trained.[9]

Although developing DL may be expensive, DR screening with DL has been proven to lead to societal cost-savings and improved health outcomes.[10] Also, validating AI algorithms using Asian-specific datasets is crucial before implementing them in the real world. Many initial algorithm developments and validations were based on image databases from America and Europe, which may differ from the Asian population. Therefore, we performed a systematic, up-to-date literature review to assess AI's validity in screening DR in Asian countries.[11]

METHODS

The literature search was conducted from online databases including Pubmed, Cochrane, and EMBASE using various keyword combinations related to relevant articles: “diabetic retinopathy”, “screening”, “artificial intelligence”, or any suitable synonyms. English-written articles were reviewed with no restriction on publication date. The reference list from the included studies was also checked for potentially relevant articles.

The included articles were screened by reviewing abstracts to obtain the articles related to the aim of this systematic review. The eligibility criteria were (1) study on a human subject, (2) use DL algorithm, (3) outcomes in the form of sensitivity, specificity, and Area Under the Curve (AUC), and (4) study was done in Asian countries. Studies were excluded if the articles were not written in English.

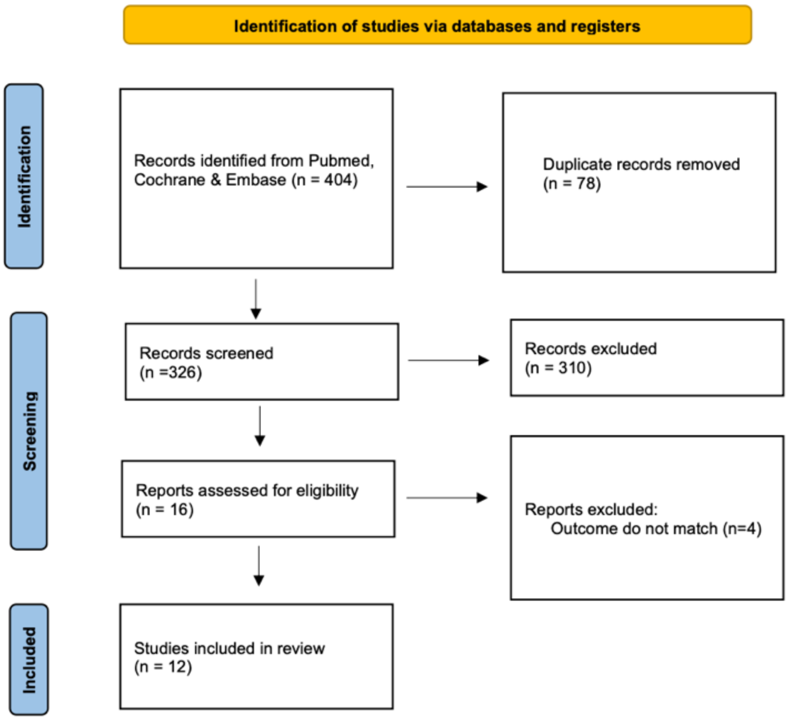

Figure 1 Flow chart for literature search according to PRISMA

RESULT

The initial search yielded 404 articles. After screening the abstracts, articles with relevant studies were reviewed. Twelve eligible studies were published between 2017 and 2021, met the inclusion criteria, and were reviewed (Table 1). The studies were conducted in Asia countries, including China, India, Taiwan, and Singapore. All studies use grading criteria of DR based on the International Clinical Diabetic Retinopathy Severity Scale (ICDRS). All twelve studies compare the performance of AI for DR screening with ophthalmologist grading as a reference standard.

The DL algorithm was trained before the validation study using different training datasets in all studies in this review. The number of images used in the training dataset varies from the lowest of 31386 images in the study by Lu et al. [12] and the highest by He et al.[13], with a total of 1.2 million images.

Various types of fundus photography cameras were used in the studies in this review. Four studies from India used Remidio Fundus on Phone (FOP) as a smartphone retinal-based imaging. Eight out of the twelve studies mentioned the number of retinal images used in their study; four studies by Ming et al.[15], Natarajan et al.[17], and both studies by Sosale et al.[19,21] only mentioned the number of participants who took part in their study.

In this review, we evaluated the sensitivity, specificity, and area under curve (AUC) as the outcomes of the validity of AI screening of DR (Table 2). The DR categories are divided into three gradings: referable DR (RDR), Any DR, and visual-threatening DR (VTDR). For the RDR group, the lowest sensitivity value from a study by Ming et al.[15] was 79.2 %, and the highest sensitivity number from a study by Natarajan et al.[17] was 100 %. For specificity, the lowest was 68.8% by Rajalakshmi et al.[16]. The highest was 99.2 % by Gulshan et al.[18]. The AUC value from this group varied from the lowest by Sosale et al.[21] with 0.88 and the highest 0.98 by Gulshan et al.[18] and Lu et al.[12].

For detecting Any DR, both studies by Ming et al.[15] and Sosale et al.[21] record the lowest sensitivity from these criteria at 83.3 %, while Shah et al.[20] report the highest sensitivity with 99.71 %.

Table 1. Characteristics of the reviewed study

Author	Year	Country	Retinal Camera	AI	Training dataset	Number of Images / Patients	Grading scale	Pupil
He et al.[13]	2020	China	Topcon TRC-NW400	Inception-V4	1.2 million images from ImageNet	3556 images	ICDRS	Not dilated
Zhang et al.[14]	2020	China	Multiple non-mydriatic retinal camera	VoxelCloud	1. 112849 images from various hospitals 2. 1184 images from public China hospital	94199 images	ICDRS	Not dilated
Lu et al.[12]	2021	China	Multiple retinal camera	VGG-16	31386 images from 18 hospital	7846 images	ICDRS	Unclear
Ming et al.[15]	2021	China	Canon CR-2 Digital camera	EyeWisdom	1. 25297 images from Kaggle 2. 3785 images from Henan Eye Hospital	193 patients	ICDRS	Not dilated
Rajalakshmi et al.[16]	2018	India	Remidio	Eye-Art	78685 images from EyePACS	2408 images	ICDRS	Dilated
Natarajan et al.[17]	2019	India	Remidio	Medios	1. 34278 images EyePACS 2. 14266 images from Diacon Hospital 3. 4350 images from screening camps	231 patients	ICDRS	Dilated
Gulshan et al.[18]	2019	India	Forus 3nethra camera	Inception-V4	103634 images	5652 images	ICDRS	Not dilated
Sosale et al.[19]	2020	India	Remidio	Medios	34278 images EyePACS	304 patients	ICDRS	Dilated
Shah et al.[20]	2020	India	Topcon TRC-50DX & Topcon DRI TRITON	Inception-V3	112849 images from various hospitals	Internal: 1533 images External: 1200 images	ICDRS	Dilated & Not dilated
Sosale et al.[21]	2020	India	Remidio	Medios	1. 34278 images from EyePACS 2. 4350 images from screening camps	900 patients	ICDRS	Not dilated
Ting et al.[22]	2017	Singapore	Multiple retinal camera	SERI-NUS	76730 images from Singapore National Diabetic Retinopathy	71896 images	ICDRS	Unclear
Hsieh et al.[23]	2021	Taiwan	Canon CR-2 Digital camera	VeriSee	1. 35126 images from EyePACS 2. 5649 images from National Taiwan University Hospital	1875 images	ICDRS	Not dilated

Rajalakshmi et al.[16] show the lowest specificity with 80.2%, while Shah et al.[20] report the highest specificity with 98.5%. The AUC value from the lowest was Sosale et al.[21] with 0.9, and the highest was Shah et al.[20] with 0.991.

Table 2. Outcome assessed in each study

Author	RDR			Any DR			STDR		
	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
He et al.[13]	91.18 %	98.79 %	0.95	90.79 %	98.5 %	0.946	-	-	-
Zhang et al.[14]	83.3 %	92.5 %	-	-	-	-	-	-	-
Lu et al.[12]	96 %	90 %	0.98	-	-	-	-	-	-
Ming et al.[15]	79.2 %	98.3 %	0.887	83.3 %	97.9 %	0.906	-	-	-
Rajalakshmi et al.[16]	99.3 %	68.8 %	-	95.8 %	80.2 %	-	99.1 %	80.4 %	-
Natarajan et al.[17]	100 %	88.4 %	-	85.2 %	92 %	-	-	-	-
Sosale et al.[19]	98.84 %	86.73 %	0.92	86.78 %	95.45 %	0.91	-	-	-
Gulshan et al.[18]	88.9% Aravind	99.2 % aravind	0.963	-	-	-	-	-	-
	92.1 % sankara	95.2 % sankara	0.98	-	-	-	-	-	-
Shah et al.[20]	99.98 % internal	94.84 % internal	0.969	99.71 %	98.5 %	0.991	97.55 %	56.31 %	0.769
	94.68 % External	97.40 % external	0.960	90.37 %	91.03 %	0.907	91.67 %	92.92 %	0.923
Sosale et al.[21]	93 %	92.5 %	0.88	83.3 %	95.5 %	0.9	-	-	-
Ting et al.[22]	90 %	91.6%	0.936	-	-	-	100 %	91.1%	0.958
Hsieh et al.[23]	89.2 %	90.1 %	0.950	92.2 %	89.5 %	0.955	90.9 %	99.3 %	0.984

Table 3. Comparison of ungradable images between studies with dilated and non-dilated pupil.

Author	Non-dilated Pupil	Author	Dilated Pupil
Zhang et al.[27]	23.6 %	Natarajan et al.[20]	7.8 %
Ming et al.[25]	16.8 %	Sosale et al.[22]	2.3 %
Sosale et al.[21]	0.86 %	Rajalakshmi et al.[24]	2.1 %

Table 4. Comparison of ungradable images between studies using conventional retinal cameras and smartphone-based retinal camera

Author	Conventional Retinal Camera	Author	Smartphone-based retinal camera
Zhang et al.[27]	23.6 %	Natarajan et al.[20]	7.8 %
Ming et al.[25]	16.8 %	Sosale et al.[22]	2.3 %
Lu et al.[23]	6.3 %	Rajalakshmi et al.[24]	2.1 %
		Sosale et al.[21]	0.86 %

In detecting VTDR, only studies by Rajalakshmi et al.[16], Shah et al.[20], Ting et al.[22], and Hsieh et al.[23] made the comparison in this group. In this group, the lowest sensitivity by Shah et al.[20] was 91.67% , while the highest sensitivity by Ting et al.[22] was 100%. For specificity, Shah et al.[20] found the lowest in this group by 56.31% for internal validation, while the highest by Hsieh et al.[23] with 92.3 %. The most inferior AUC was a study by Shah et al.[20] with 0.769, and the highest was by Ting et al.[22] with 0.958.

We evaluated the percentage of ungradable images between dilated and non-dilated pupil groups (Table 3). Only six studies mentioned pupillary conditions during DR screening and reported the rate of ungradable images. The results showed that the group with a non-dilated pupil has the largest ungradable images in a study by Zhang et al.[14] up to 23.6 %. Meanwhile, in the dilated pupil group, the largest ungradable images by Natarajan et al.[17] was 7.8 %.

In this review, we also compare the ungradable images between studies conducted with a conventional and smartphone-based retinal camera. We found that seven out of twelve studies in this review mentioned the type of retinal camera they used and reported a percentage of ungradable images. The study by Zhang et al.[14] shows the highest percentage of ungradable images with 23.6 % in the conventional retinal camera group. The study by Sosale et al.[21] has the lowest ungradable images with only 0.86 %. Table 4 shows the percentage of ungradable images in each study.

DISCUSSION

This review aimed to determine the validity of using an AI-assisted algorithm for DR screening in Asia. Six of the ten countries with the highest diabetic population worldwide (China, India, Pakistan, Indonesia, Bangladesh and Japan) are in Asia.[1] In countries with limited resources, particularly in Asia, the availability of ophthalmologists and retinal consultants has become a serious obstacle to adequate DR screening. [24]

The advancement of computing technologies has resulted in deep learning (DL) development. DL is a branch of AI focusing on algorithms that learn to do tasks without explicit instructions. Specifically, the AI can be trained to differentiate diagnostic outputs based on inputs such as a retinal image. Each image is examined and compared to extensive data in the storage database. AI can detect pathognomonic features on the retina for DR, such as exudates, microaneurysms, and hemorrhages. The AI then classified the detected feature as normal or abnormal, generating the final output.[25,26]

Validation of such technologies is essential for proving the reliability and applicability of DL among clinicians and scientists. Large amounts of testing data and comprehensive image interpretations as reference gold standards are required for the development. Sensitivity, specificity, and AUC are standard statistical analyses that evaluate the algorithm's output validity. [27]

Real-world settings validation is an essential step for implementing AI for DR screening. Van der Heijden et al.[28] were the first to incorporate IDX-DR AI in real-world settings, with a sensitivity for detecting RDR of only 68 %. Abràmoff et al.[39] were the first to acquire Food and Drug Administration (FDA) approval in a large pivotal study for the use of a DL in the screening of DR from retinal images that achieved an AUC of 0.98 and a sensitivity and specificity of 96.8% and 87.0%, respectively for detecting RDR on a publicly available color fundus dataset (Messidor-2). The FDA requires the AI algorithm to cross the minimum threshold with a sensitivity of 85 % and a specificity of 82.5 %. [30]

There has been continuous interest in applying DL systems for DR screening in Asia. The research direction was arguably towards evaluating the applicability of AI to the local population in Asia. China, India, Singapore, and Taiwan are countries in Asia where the studies in this review were conducted, and also countries with rapid technological development. Most research on the use of AI in DR screening in Asia is carried out in these countries, especially in China and India, with many studies coming from these two countries.[31 32]

A study by Ming et al.[15] used The EyeWisdom (Visionary Intelligence Ltd, Beijing, China), a locally made AI algorithm. The AI was incorporated into a picture archiving and communication system (PACS) to enable the upload of retina photographs, automatic grading, and generated single-page grading reports. According to a pre-validation assessment of The EyeWisdom AI algorithm by Gao et al.[33], EyeWisdom achieved a 90.4% sensitivity and 95.4% specificity for detecting RDR.

In the ASEAN region, Singapore has made its own AI called SERI-NUS, which has already been used in a study by Ting et al.[22] They evaluated the performance of their DL system using color fundus images collected from a Singaporean national DR screening program, achieving an AUC of 0.94 with an achievable sensitivity and specificity of more than 90%. They further validated the algorithm on ten additional multi-ethnic settings datasets and achieved an AUC ranging from 0.89 to 0.98. This study translated this clinically by showing the high performance of a DL-based system throughout multi-ethnic populations, even though the system was not initially trained with the eye with distinct phenotypical characteristics while subjecting to suboptimal real-world image capture configuration.[22]

Although the AI algorithm used varies between studies in this review, the validation results are relatively satisfying for all DR screening criteria. This is because these AI have previously undergone pre-validation using training image datasets. The training image datasets are the initial data AI uses to train its ability to get satisfactory results during validation tests.

Standard fundus photography provides a 30 to 50-degree image of the macula and optic nerve. It is often used in clinical and research settings due to providing fairly solid documentation of DR. A montage image can be created by manually overlapping many retinal images. For example, seven standard 30-degree fundus images can be combined to create a 75-degree horizontal field of view.[34] In this review, eight studies use a conventional retinal camera for DR screening. They all have good sensitivity and specificity for detecting RDR, any DR, and VTDR group.

While conventional fundus camera are widely used in developed regions for DR screening, their deployment in most Asian countries, where most of the people reside in rural areas, remains limited due to the high equipment costs and a lack of mobility. Smartphone-based retinal imaging is emerging as an alternative way of screening for DR in the community. Several technologies have been created to incorporate additional lens elements into smartphone cameras. Smartphones can also be used for indirect ophthalmoscopy by applying the 20D Volk lens and a plastic adapter to hold the lens in one piece with the phone.[35]

In real-time screening conditions, image collection using smartphone-based retinal imaging is usually difficult compared to the conventional retinal camera because we often find many patients with small pupils and media haziness due to cataracts or uncooperative patients. Although smartphone-based retinal imaging is portable, using a portable table and chin rest is preferable to assist stabilization during image acquisition to make the screening process easier. [36]

There was 4 study in this review that use smartphone-based retinal imaging. All of these studies were conducted in India and used Remidio Fundus on Phone (FOP,) a smartphone-based imaging device (Remidio Innovative Solutions Pvt, Ltd, Bangalore, India). The FOP is a portable fundus camera with an excellent quality capable of capturing retinal photographs. After data collection, the DL algorithm is used to grade retinal images. FOP proves the concept of smartphone-based design and demonstrates the technological and economic potential of the smartphone-based retinal imaging system. Screening results in all four FOP studies were quite good, with sensitivity and specificity over 80%. Even a study by Natarajan et al. [17] has a sensitivity of 100 % for detecting RDR. There was no significant difference in accuracy between the conventional retinal camera and smartphone-based retinal imaging.

Currently, most existing AI algorithms require a processor with a high computational capacity, which results in uploading images to the cloud server to speed up the process. In this review, Google Inc AI, VoxelCloud, VGG-16, EyeWisdom, Eye-Art, and VeriSee operate on a cloud-based platform. The performance of cloud-based AI in this review shows promising results in DR screening. The VeriSee, AI algorithm made in Taiwan can be used in two modes, cloud-based or offline, although a study by Hsieh et al.[23] used cloud computing modes.

The study by Rajalakshmi et al. [16] combined smartphone with the EyeArt, a cloud-based AI. From the results for detecting RDR, the sensitivity was 99.3%, while the specificity was only 68.8 %. Many parts of Asia lacked a stable internet connection if not none at all. Three studies in this review by Natarajan et al.[17] and both S et al.[19,21] use the AI algorithm by Medios AI, an offline automated analysis application based on CNN that can be integrated into smartphones. This review showed that Medios AI has a high sensitivity in detecting RDR. The specificity in studies that use Medios AI may be slightly lower, as the Medios AI has classified many mild NPDR cases as RDR. The Medios AI was not trained on mild NPDR images to ensure high specificity in diagnosing no DR and RDR. The AI also often overdiagnoses non-DR retinal lesions such as retinitis pigmentosa, drusen, and retinal pigment epithelium (RPE) changes as DR lesions and lower the specificity results. [17]

An additional Medios AI sensitivity analysis was also conducted by Natarajan et al.[17] using all images, including images that did not reach the minimum quality standard of AI. The results for the sensitivity analysis were still 100%, while specificity only reduced from 88.4 % to 81.9%. The primary advantage of offline AI is that it can be used without internet access on a smartphone, allowing immediate results. In addition, most retinal cameras integrated with cloud-based AI are usually more expensive. In most Asian countries, where mass screening is required, access to steady electricity and internet is problematic. The smartphone with offline AI can solve these operational difficulties in rural or resource-constrained areas. [37]

Despite many publications demonstrating the reliability and accuracy of these DL systems in detecting DR, and support from government authorities such as the FDA, transitioning these systems into clinical settings has not been without difficulties. Implementation has been hindered mainly due to the inscrutability of these algorithms. This is because of the ‘black box’ concept in AI, which refers to the ambiguity surrounding how these networks reach their conclusion. Although this concept is frequently used when studying the applications of DL systems, it carries enormous weight in medicine, where accountability for incorrect decisions is essential and where the patients’ and physicians’ trust is required to accept a novel method.

The medicolegal aspect has also become an important issue that requires our attention. [38,39]

Another difficulty in implementing AI for DR screening is because the participants are mostly older age with characteristics such as small pupils and cataracts, combined with poor patient compliance when doing image capturing will result in poor quality / ungradable images, which will affect the assessment process by AI. Although the AI algorithm can replicate manual grading by an ophthalmologist, it cannot overcome physical limitations, as previously explained. Hence, DR screening in elderly patients with cataracts or in those with small pupils (<3mm) can be a challenge. [19]

In this review, although the sensitivity, specificity and AUC value did not differ significantly between studies with dilated and non-dilated pupil groups, the percentage of ungradable images did differ significantly. The ungradable images were highest in the dilated pupil group with 23.6 %. The difference is significant compared to the study with the highest ungradable images in the non-dilated pupil group, which is only 7.8%. Pupil dilatation with a drop of 1 % tropicamide solution may be needed for DR screening although using a dilating agent may increase the risk of angle-closure glaucoma attack. In addition, it also increases the screening time and the risk of screening rejection due to the fear of transient blurring vision caused by a dilating agent. None of the studies in this review explained the occurrence of angle-closure glaucoma after using a dilating agent.

The dilated pupil increases the quality of a retinal image and highlights the DR characteristic, resulting in higher sensitivity. [21] In the study by Natarajan et al. [17,] the technician who takes retinal pictures is trained to use the device for less than two weeks. This causes not all the images taken were of good quality and explains the higher percentage of ungradable images in the dilated pupil group which is representative of what would typically be expected in large-scale, opportunistic community screening. In DR manual screening settings, the rate of ungradable images or poor-quality images has been reported to be up to 20 %. [40]

The difference is also significant if we compare the percentage of ungradable images taken using a conventional and smartphone-based retinal camera. In the conventional retinal camera groups, the percentage of ungradable images is quite large, varying from 6.3% - 23.6 %, compared to a smartphone-based retinal camera with the highest value of only 7.8%. However, it should be noted that three of four studies in smartphone-based retinal camera had dilated pupil conditions. In comparison, two of three studies in the conventional retinal camera had non-dilated pupil conditions, so the comparison in these two groups may not be accurate.

CONCLUSION

The advantage of AI is that it can detect DR without the assistance of a trained retina specialist and the ability to screen large amounts of images quickly. This would benefit areas with limited healthcare resources like most of Asia. This review of local population settings shows the AI accuracy for detecting any DR with good sensitivity and specificity. AI also has a good result for detecting RDR in almost all studies. Easier accessibility of AI and their integration with conventional or portable retina camera devices will significantly improve DR screening. Even though medicolegal and interpretability issues still exist, AI-augmented DR screening programs have a high potential to improve the efficiency and accessibility of DR screening programs and prevent visual loss and blindness in the DR population in Asia.

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