

A new handheld fundus camera combined with visual artificial intelligence facilitates diabetic retinopathy screening

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Abstract

• **AIM:** To explore the performance in diabetic retinopathy (DR) screening of artificial intelligence (AI) system by evaluating the image quality of a handheld Optomed Aurora fundus camera in comparison to traditional tabletop fundus cameras and the diagnostic accuracy of DR of the two modalities.

• **METHODS:** Overall, 630 eyes were included from three centers and screened by a handheld camera (Aurora, Optomed, Oulu, Finland) and a table-top camera. Image quality was graded by three masked and experienced ophthalmologists. The diagnostic accuracy of the handheld camera and AI system was evaluated in assessing DR lesions and referable DR.

• **RESULTS:** Under nonmydriasis status, the handheld fundus camera had better image quality in centration, clarity, and visible range (1.47, 1.48, and 1.40) than conventional tabletop cameras (1.30, 1.28, and 1.18;

and macular edema were comparable between the two modalities, in principle, with the area under the curve of the handheld fundus camera slightly lower. The sensitivity and specificity for the detection of referable DR with the handheld camera were 82.1% (95%CI: 72.1%-92.2%) and 97.4% (95%CI: 95.4%-99.5%), respectively. The performance of AI detection of DR using the Phoebus Algorithm was satisfactory; however, Phoebus showed a high sensitivity (88.2%, 95%CI: 79.4%-97.1%) and low specificity (40.7%, 95%CI: 34.1%-47.2%) when detecting referable DR.

• **CONCLUSION:** The handheld Aurora fundus camera combined with autonomous AI system is well-suited in DR screening without mydriasis because of its high sensitivity of DR detection as well as its image quality, but its specificity needs to be improved with better modeling of the data. Use of this new system is safe and effective in the detection of referable DR in real world practice.

• **KEYWORDS:** diabetic retinopathy; image quality; handheld camera; artificial intelligence

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INTRODUCTION

Diabetic retinopathy (DR) is the most common retinal vascular complication of diabetes mellitus (DM) and the leading cause of vision impairment and blindness among working-age adults^[1-5]. In Chinese adults, the overall standardized prevalence of diabetes using the WHO criteria is 11.2%, of which prediabetes accounts for 35.2%^[6]. DR is largely asymptomatic in the early stages, but neural retinal damage and clinically invisible microvascular changes progress during these early stages^[7]. It has therefore been widely accepted that periodic eye examinations should be conducted

Table 1 The classification of diabetic retinopathy used in the present study

Classification	Definition	Need for referral
No apparent DR	No abnormalities	Non-referable
Mild nonproliferative DR	Microaneurysms only	Non-referable
Moderate nonproliferative DR	Microaneurysms and other signs (<i>e.g.</i> , dot and blot hemorrhages, hard exudates, cotton wool spots), but less than severe nonproliferative DR	Referable
Severe nonproliferative DR	Moderate nonproliferative DR with any of the following: • intraretinal hemorrhages (≥ 20 in each quadrant); • definite venous beading (in 2 quadrants); • intraretinal microvascular abnormalities (in 1 quadrant); • no signs of proliferative retinopathy	Referable
Proliferative DR	Severe nonproliferative DR and 1 or more of the following: • neovascularization • vitreous/preretinal hemorrhage	Referable

DR: Diabetic retinopathy.

provide prompt interventions when necessary, which is thought to be the most effective method to reduce potential DR-related visual disabilities^[8-9].

Fundus photography has served as a useful tool in detecting and documenting the presence and the progression of retinopathy in diabetic patients in communities. On this basis, the development of digital fundus cameras further facilitates rapid acquisition and interpretation of fundus images and the rapid deployment of retinal imaging for DR screening worldwide^[10]. These cameras produce high quality images that can be assessed for the presence of DR by eye care providers (optometrists or ophthalmologists) or trained readers in a deferred manner on site or remotely. Moreover, many computer-aided algorithms for automated image analysis have been developed, which are expected to be a promising alternative for retinal fundus image analysis for future applications in eye care^[11-13]. Artificial intelligence (AI) systems have been widely demonstrated to lower cost, improve diagnostic accuracy, and increase patient access to DR screening. In April 2018, the United States Food and Drug Administration approved the world's first AI medical device for detecting DR, the IDx-DR^[14].

Traditional tabletop-based, mydriatic retinal imaging modality is effective but is less available in underdeveloped rural areas^[15-16]. Handheld cameras are now emerging as a new low cost tool for DR screening, which can be conveniently used for patients who may not have access to ophthalmological care, with the potential of improving DR screening^[17].

In this study, we described a new portable Optomed Aurora fundus camera, and compared the image quality and DR detection with traditional tabletop fundus cameras. We also evaluated the feasibility of using a deep learning system (Phoebe, Shanghai, China) to detect different signs of DR to determine the possibility of combining the handheld fundus camera and AI technology during DR screening.

SUBJECTS AND METHODS

General Hospital Institutional Review Board at Shanghai Jiao Tong University. Informed consent was obtained from all participants. The study was conducted in compliance with the Declaration of Helsinki, in accordance with the ICH-GCP (International Conference on Harmonization-Good Clinical Practice) guidelines (clinicaltrials.gov Registration Number: NCT03903042).

Enrollment This was a multi-centered, double-blinded, observational clinical study enrolling patients from three hospitals (Shanghai General Hospital, Shanghai, China; West Nanjing Road Community Health Center, Shanghai, China; and Zhaoqing Gaoyao People's Hospital, Guangdong, China). Individuals of ages 18y and older who had been diagnosed with DM were enrolled. Patients were excluded if the retina specialist could not visualize the fundus on examination or if they had previously undergone vitreoretinal surgery and/or laser photocoagulation. Classification of the severity stage of DR was determined using the International Clinical Diabetic Retinopathy Disease Severity Scale grading system developed by the American Academy of Ophthalmology (AAO)^[18] (Table 1).

Imaging Four fundus photographs per eye were taken by a well-trained ophthalmic photographer: papilla- and macula-centered images using the tabletop and handheld Optomed Aurora fundus cameras (Optomed, Oulu, Finland), respectively, with or without pupil dilation with 1% tropicamide. The images obtained with the handheld fundus camera had a field of view of 50° and 5 mega-pixel resolution. Images from both kinds of cameras were acquired on the same day, which allowed for direct pathological identification and comparisons between these camera types. The characteristics of five types of fundus cameras are detailed in Table 2. The images were stored as JPEG (Joint Photographic Experts Group) files after removing patient names. Fundus images were transferred to the grading center, Shanghai General Hospital through the INSIGHT real-world patient registry platform www.chinadr.org.cn (Phoebe Medical, Shanghai, China), for remote digital

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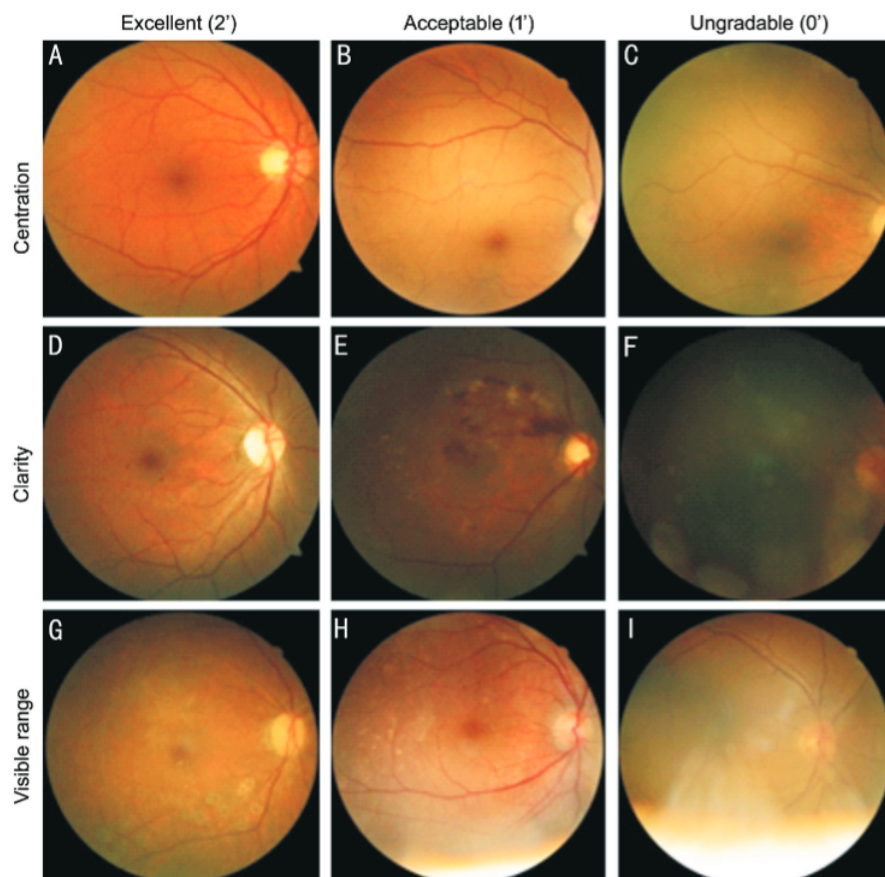


Figure 1 Definition of image quality A: Macula/optic disc within 1 papillary diameter range of the image center; B: Macula/optic disc within 2 papillary diameter range of the image center; C: Macula/optic disc out of 2 papillary diameter range of the image center; D: Image clear focused; E: Image recognizable; F: Image unrecognizable; G: Visible range is the whole image; H: Visible range >80%; I: Visible range <80%.

Table 2 Comparisons of handheld and tabletop fundus cameras

Parameters	Handheld fundus camera optomed aurora	Mydriasis conventional fundus camera		Nonmydriasis conventional fundus camera	
		Zeiss Visucam 200	Topcon TRC-50DX	Canon CR-2	Newvision Reticam 3100
Dimension (mm ³)	122×202×98	410×480×650	340×505×506	305×500×473	380×550×475
Field of view	50°	45°	50°	45°	50°
Resolution (megapixels)	5	5	11	24	24
Pupil size (mm)	≥3.1	≥4.0	≥4.0	≥3.3	≥3.3
Weight (kg)	0.47	30	35	15	26.5

In this study, the images were uploaded to the deep learning system, Phoebus (Phoebus), and the detection of DR features was assessed. Phoebus provides a DR grade per image as well as visual representations of detected microaneurysms, retinal hemorrhages, hard exudations, and macular edemas. The DR output from Phoebus was further used to generate a prediction for the referral requirement.

Quality Control All photographs were randomized and presented to three masked and experienced ophthalmologists. The ophthalmologists separately evaluated their image quality and made diagnoses without information about the patients or

Fundus Photographic Quality Assessment Three parameters were assessed by the graders to investigate various aspects of image quality (Figure 1). For each parameter the quality score ranged from 2 (excellent) to 0 (ungradable). Images were considered to be excellent quality if the macula or optic disc was well-centered, showing clarity of the fundus vessels, with any retinopathy and the whole image being visible. If the macula or optic disc was partially centered and the fundus vessels and any retinopathy were recognizable and more than 80% of the image was visible, the images were defined as acceptable. If images were not centered, blurred without

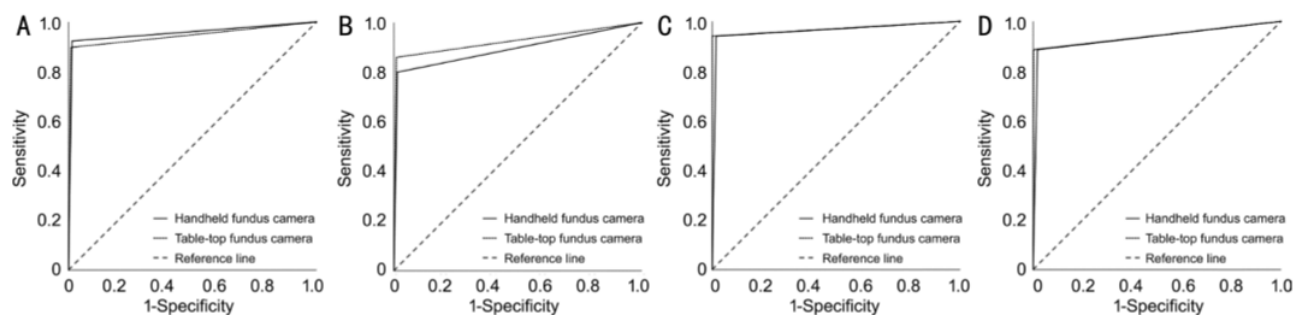


Figure 2 Receiver operating characteristic curves for diabetic retinopathy screening of handheld and tabletop fundus cameras A: Microaneurysm; B: Retinal hemorrhage; C: Hard exudation; D: Macular edema.

less than 80% of the image was visible, they were defined as ungradable.

Statistical Analysis Statistical analysis was performed using SPSS statistical software for Windows, version 20.0 (SPSS, Chicago, IL, USA). The data are presented as the mean±SD or median (IQR) for continuous variables and frequency (%) for categorical variables. Participant age was categorized by intervals of 10y, and age at diagnosis of diabetes was categorized by intervals of 5y. Sensitivity, specificity, and area under the receiver operator curve (AUC) with a 95% confidence interval (95%CI) were calculated to evaluate diagnostic accuracy. We used a receiver operating characteristic (ROC) curve to evaluate the classification ability of our built model.

RESULTS

Demographics Overall, a total of 630 eyes of 315 DM patients were included in this study. The patients were on average 65.5±11.1y of age, and 53.7% were female (n=169). The median duration of diabetes was 10y (3-15y), with more than one-third of the patients diagnosed with diabetes for less than 5y, and only 20 (6.3%) patients were diagnosed with diabetes for over 20y (Table 3).

Image Quality Of the 630 eyes examined, 242 eyes (38.4%) were photographed in the non-dilated state, while the remaining 388 eyes were dilated. The mean scores of the non-mydriasis image quality regarding image centration, sharpness, and visible range for the handheld fundus camera were 1.47, 1.48, and 1.40, separately, resulting in a significant advantage over the conventional tabletop cameras (1.30, 1.28, 1.18, separately, *P*<0.001). However, regarding the image sharpness score under mydriasis, photography with the conventional tabletop cameras performed better than the images acquired by the Aurora handheld fundus camera (*P*<0.05). The assessment of mydriasis images regarding image centration (*P*=0.146) and visible range (*P*=0.945) did not reach a significant difference (Table 4).

Diabetic Retinopathy Detection and Referral We compared the ability to reveal common manifestations of DR between

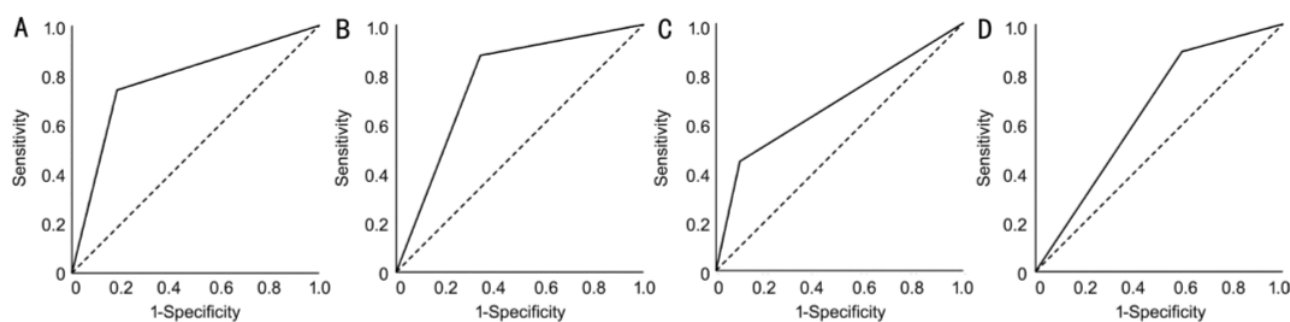
Table 3 Demographic information of participants with diabetes

n=315	
Characteristics	Statistics
Age, y, n (%)	
18-30	5 (1.6)
31-40	6 (1.9)
41-50	16 (5.1)
51-60	55 (17.4)
61-70	124 (39.4)
>70	109 (34.6)
Mean±SD	65.5±11.1
Female	169 (53.7)
Duration of diabetes, y, n (%)	
1-5	108 (34.3)
6-10	79 (25.1)
10-15	62 (19.6)
16-20	46 (14.7)
>20	20 (6.3)
Median (IQR)	10 (3-15)

IQR: Interquartile range.

sensitivity and specificity to detect microaneurysms reached 94.4% (95%CI: 87.0%-100.0%) and 98.4% (95%CI: 97.3%-99.5%), respectively, using the Aurora camera, compared to 89.7% (95%CI: 80.2%-99.3%) and 98.6% (95%CI: 97.6%-99.6%) using the conventional tabletop camera (Table 6). Detection of retinal hemorrhage, hard exudation, and macular edema were comparable, with that of the AUC of the handheld fundus camera being slightly lower. When detecting referable DR, the Aurora camera obtained an AUC of 88.2% (95%CI: 83.5%-92.8%), corresponding to a sensitivity of 82.1% (95%CI: 72.1%-92.2%) and a specificity of 97.4% (95%CI: 95.4%-99.5%), when compared to 92.7% (95%CI: 85.9%-99.6%) and 95.9% (95%CI: 93.2%-98.5%) using the conventional tabletop camera. The corresponding ROC curves are shown in Figure 2.

Accuracy of the Phoebe Algorithm in DR Detection

Diagnostic value of aurora camera in DR screening**Figure 3 Receiver operating characteristic curves for the Phoebe Algorithm diagnosis of diabetic retinopathy lesions and the need for referrals** A: Retinal hemorrhage; B: Hard exudation; C: Macular edema; D: Referral requirement.**Table 4 Comparison of image quality based on the dilation status**

Parameters	Non-mydratic			Mydratic		
	Aurora	Table-top	P	Aurora	Table-top	P
Centration	1.47±0.46	1.30±0.58	0.000 ^c	1.76±0.29	1.73±0.29	0.146
Sharpness	1.48±0.40	1.28±0.19	0.000 ^c	1.73±0.28	1.77±0.30	0.047 ^a
Visible range	1.40±0.47	1.18±0.61	0.000 ^c	1.73±0.33	1.73±0.35	0.945

^aP<0.05; ^cP<0.001.**Table 5 Diagnostic accuracy of Aurora and tabletop cameras in DR screening**

%(95%CI)

Parameters	Aurora			Table-top		
	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Microaneurysms	94.4 (87.0-100.0)	98.4 (97.3-99.5)	95.5 (90.6-100.0)	89.7 (80.2-99.3)	98.6 (97.6-99.6)	94.4 (88.8-100.0)
Retinal hemorrhage	80.4 (69.0-91.9)	98.2 (97.0-99.4)	89.3 (82.7-95.9)	86.0 (76.4-95.6)	98.6 (97.6-99.6)	92.5 (86.8-98.2)
Hard exudation	91.7 (83.8-99.5)	97.5 (96.2-98.9)	96.2 (92.3-100.0)	94.0 (87.4-100.0)	99.6 (99.0-100.0)	97.0 (93.2-100.0)
Macular edema	88.2 (77.4-99.1)	98.4 (97.3-99.5)	93.4 (87.2-99.6)	88.6 (78.0-99.1)	99.8 (99.4-100.0)	94.2 (88.0-100.0)
Referral requirement	82.1 (72.1-92.2)	97.4 (95.4-99.5)	88.2 (83.5-92.8)	92.7 (85.9-99.6)	95.9 (93.2-98.5)	94.5 (91.5-97.5)

AUC: Area under the curve; CI: Confidence interval.

Table 6 Performance of the Phoebe algorithm in DR screening

%(95%CI)

Screening result	Sensitivity	Specificity	AUC
Retinal hemorrhage	73.9 (61.2-86.6)	81.5 (78.0-84.9)	77.8 (70.2-85.4)
Hard exudation	87.5 (78.1-96.9)	65.4 (61.2-69.7)	76.7 (70.5-83.0)
Macular edema	44.1 (27.4-60.8)	90.1 (87.4-92.7)	67.2 (56.4-78.1)
Referral requirement	88.2 (79.4-97.1)	40.7 (34.1-47.2)	64.8 (59.6-70.1)

AUC: Area under the curve; CI: Confidence interval.

Algorithm is shown in Table 6. On images taken from the handheld camera, the Phoebe Algorithm achieved an AUC of 77.8% (95%CI 70.2%-85.4%) when detecting retinal hemorrhage, corresponding to a sensitivity of 73.9% (95%CI 61.2%-86.6%) and a specificity of 81.5% (95%CI 78.0%-84.9%). When detecting hard exudation, the Phoebe Algorithm obtained an AUC of 76.7% (95%CI 70.5%-83.0%), corresponding to a sensitivity of 87.5% (95%CI 78.1%-96.9%) and a specificity of 65.4% (95%CI 61.2%-69.7%). For the referral requirements, the Phoebe Algorithm achieved an AUC of 64.8% (95%CI 59.6%-70.1%), corresponding to a sensitivity of 88.2% (95%CI 79.4%-97.1%) and a specificity of 40.7% (95%CI 34.1%-47.2%). The corresponding ROC

DISCUSSION

In this study, we introduced a new handheld Optomed Aurora fundus camera, and found it significantly better than traditional tabletop fundus cameras regarding image quality during the non-mydrasis state. The detections of different signs of DR were comparable with the tabletop cameras. The Aurora fundus camera combined with an autonomous AI system had high sensitivity and specificity for DR detection. Furthermore, it was safe and effective in the detection of referable DR in real practice.

Early detection and prompt treatment of DR is the key to reducing preventable vision loss worldwide, which requires regular fundus screening. However, because of the paucity

practitioners per million people, which reduces the accessibility of DR screenings^[19]. Even in the United States and the United Kingdom, the absolute number of ophthalmologists (49 and 59 ophthalmologists per million people, respectively) still cannot meet the need of a growing number of DR patients, especially in rural areas^[20-21]. Fundus photography has been widely proven to be an effective method to monitor the extent of DR and to identify patients who could benefit from early treatment^[22-25]. However, the large size, weight, and high cost of the conventional tabletop fundus cameras limit its use for large-scale screening in communities lacking a sufficient screening process. In rural and remote communities with few ophthalmologists or table-top fundus cameras, tele-ophthalmology based on portable fundus cameras used by well-trained physicians is a viable solution to increase DR screening. Therefore, non-mydriatic portable ocular fundus photography is a promising solution when combined with telemedicine^[15-26]. The dimension of our new handheld Aurora fundus camera is approximately 122×202×98 mm³, which is much smaller than all tabletop cameras (Table 2), making it possible to be carried and used for training for those without experience.

However, it is difficult for physicians to perform routine dilated examinations on screened patients to detect non-symptomatic conditions owing to a presumption of patient unwillingness, lack of time, and unwarranted fears of harming patients with known glaucoma^[27]. Therefore, the quality of photography under non-mydriatic conditions is a critical evaluation index in DR screening. Compared to conventional cameras, the Aurora has a smaller minimum pupil size requirement (Table 2). For images taken during a non-mydriasis state, the Aurora handheld fundus camera had significantly better quality in centration, clarity, and visible range (1.47±0.46, 1.48±0.40, and 1.40±0.47, respectively) than conventional tabletop cameras (1.30±0.58, 1.28±0.19, and 1.18±0.61, respectively; $P<0.001$). During the mydriasis state, the Optomed Aurora color images had imaging and grading characteristics similar to those of conventional tabletop cameras. Importantly, the advantage of not requiring pupillary dilation could provide the impetus for DR screening in underdeveloped regions.

During the last two decades, automated image diagnosis based on AI has been used for detection and classification of DR with the advantages of increased efficiency, reproducibility, and coverage of screening programs^[11-28]. However, application in real world situations remains a challenge due to inconsistent image quality and other aspects such as comorbidity^[29-31]. The accuracy of screening by fundus photography is highly dependent on the performance in detecting different manifestations of DR, using either manual grading or AI-assisted grading. The

cameras were comparable in principle. It is worth noting that the Aurora was better than the tabletop cameras in screening sensitivity for detecting microaneurysms (94.4% vs 89.7%), possibly because of the better image quality of the Aurora during the non-mydriasis state. The sensitivity and specificity of the Aurora in the detection of referral-warranted DR were 82.1% and 97.4%, respectively, which met the criteria of The British Diabetic Association, when considering 80% sensitivity and 95% specificity for a viable DR screening program^[32]. Overall, these results indicated a satisfactory quality of Aurora for AI-assisted grading.

We used our self-designed Phoebus algorithm system to examine the performance in detecting DR. The system had independent, validated detectors for lesions characteristic of DR, including retinal hemorrhages, hard exudates, and macular edemas, the outputs of which were then fused into a DR referral requirement output, using a separately trained and validated machine learning algorithm. Several studies have reported the diagnostic performance of AI-based software in the detection of referable DR. The published results appeared promising, showing a sensitivity ranging from 74% to 92.5%, and a specificity between 73.3% and 98.5%^[33]. In the present study, the sensitivity and specificity of the Phoebus Algorithm system in identifying referable DR was 88.2% and 40.7%, respectively, which met the FDA superiority sensitivity cut-offs of 85%, but did not reach a specificity of 82.5%^[34]. However, in contrast, its sensitivity and specificity of macular edema were 44.1% and 90.1%, respectively. One of the possible reasons was that macular edema is not easily captured using 2-dimensional fundus photographs^[35]. In contrast, optical coherence tomography, as a standard diagnostic tool for the assessment of intra- and subretinal fluids, is more sensitive in detecting macular edemas^[36]. Sensitivity is a patient safety criterion, because the AI system's primary goal is to identify as many potential patients with DR that require further evaluation by eye care providers^[34]. Tan *et al*^[37] reported an algorithm that achieved a sensitivity and specificity of 62.57% and 98.93%, respectively, for retinal hemorrhages. Our detection sensitivity and specificity of retinal hemorrhages were 73.9% and 81.5%, respectively, with the corresponding AUC of 77.8%. The AI-assisted grading system of both mydriatic and non-mydriatic images could therefore be valuable in DR screening.

This study had some limitations. First, the inclusion of multiples images was from multiple devices with different fields of view and resolutions. However, it could also be a strength for the resulting algorithms, which could be more reliable in the real world with different camera brands or types. Second, the AI-based specificity of referable DR was relatively low, which could affect the number of people who received a

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DR or mild DR. This could have been due to the small sample size of the study. Real-world data of more DR patients will be needed to improve the analysis.

In conclusion, our study showed that the handheld Aurora fundus camera was well-suited for DR screening with or without mydriasis. This camera had high sensitivity of DR detection as well as satisfactory image quality, but its specificity needs to be improved with better modeling of the data. Our Phoebus AI system helped to improve DR screening. Use of a handheld fundus camera with an AI system was safe and effective in the detection of referable DR in the real world practice.

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