Performance of an automated, offline artificial intelligence tool on a smartphone-based fundus camera in screening various stages of Glaucoma severity

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Abstract

Purpose: To report the performance of an artificial intelligence (AI) system deployed on a smartphone-based fundus camera to detect referable glaucoma of different severity grades when compared with the diagnosis made by glaucoma specialist.

Methods: A prospective study was conducted in a glaucoma clinic of a tertiary eye hospital. One disc-centered image per eye was captured using the study device (validated, portable non-mydriatic fundus camera). The diagnostic ability of the AI tool to detect referable glaucoma against a final diagnosis made by a specialist following thorough glaucoma workup (clinical assessment, SD-OCT, visual field test) was evaluated. The severity of glaucoma was classified based on the visual field mean deviation using Hoddap –Parrish –Anderson criteria.

Results: We included 213 participants with a mean age of 59±15 years (18, 88). The glaucoma specialist diagnosed 129 subjects as confirmed Glaucoma, 33-disc suspects and 51 as no-glaucoma. At a patient level (worse eye diagnosis), the automated AI system with fundus images alone achieved an accuracy of 92.02%, sensitivity of 91.36% (95%CI 85.93% to 95.19%), specificity of 94.12% (83.76% to 98.77%), positive predictive value of 98.01% (94.30% to 99.59%) and negative predictive value of 77.42% (65.03% to 87.07%) for referable glaucoma. The 14 false negatives included 5-disc suspects and 9 confirmed glaucoma (3-Mild, 3-Moderate and 3-Advanced glaucoma). The Sensitivity of AI for detecting mild (out of 23 milds, 13 as glaucoma, 7 as disc suspects), moderate (out of 31-moderates, 22 as glaucoma, 6 as disc suspects), and

advanced glaucoma (out of 75 advanced cases, 71 as glaucoma and 1 as disc suspect) on fundus images alone when compared to a specialist who conducted a full glaucoma work-up was 86.9% (95%CI 66.4-97.2), 90.3% (95%CI 74.3-97.96), and 96% (88.75% to 99.17%) respectively.

Conclusions: The AI-based offline tool integrated on a smartphone fundus camera showed a promising performance in detecting referable glaucoma compared to a glaucoma specialist's diagnosis following a comprehensive glaucoma workup. The AI showed better accuracy in detecting advanced glaucoma followed by moderate and early glaucoma.

Introduction

Glaucoma, a progressive optic neuropathy, is the leading cause of irreversible blindness on a global scale and is usually asymptomatic till its advanced stages.[1] This highlights the critical significance of promptly detecting and effectively managing glaucoma to avert its potential repercussions on an individual's quality of life. In 2013, the worldwide prevalence of Glaucoma was noted at 64.3 million people.[2] This number experienced a marked increase, reaching 76.0 million by 2020, and projections anticipate a further surge to around 111.8 million by 2040.[2]

Glaucoma is characterised by a range of structural alterations, primarily affecting the optic nerve head (ONH) and the retinal nerve fibre layer (RNFL).[1] In developing countries, 90% of them are unaware of the presence of glaucoma.[3] This is critical since the patient is generally asymptomatic at the early stages of glaucoma till the central vision gets affected which is in the advanced stages. The vision-related quality of life (VRQOL) in glaucoma can be influenced by various factors such as level of visual functions, education, income, number of glaucoma medications, follow-up duration and additional variables.[4] It has been observed that as the severity of glaucoma increases, VRQOL tends to deteriorate, with advanced stages exhibiting poorer outcomes when compared to mild and moderate glaucoma.[4,5] The detection of glaucoma is also a complex, subjective, time-consuming process hinging on various examinations and needs clinical expertise. Imaging techniques play a pivotal role in assessing structural irregularities. Monoscopic fundus photography has demonstrated similar diagnostic accuracy for glaucoma detection compared to stereoscopic photography.[6,7] Hence, the utilization of fundus image-based screening for detecting glaucomatous changes proves to be practically beneficial.

Artificial intelligence has been successfully applied in image-based diagnosis of acute and chronic ocular conditions such as Diabetic Retinopathy, AMD, cataract, ROP, refractive error and glaucoma.[8,9] The eye also provides a non-invasive observation window for neurovascular pathophysiological changes revealing a new route in disease screening such as type 2 diabetes mellitus, cardiovascular disease hepatobiliary diseases or chronic kidney disease.[10] AI-based screening would be a relatively affordable and convenient model, especially in large-scale screening programs covering different populations and have proven public health impact. A smartphone-based fundus camera (fundus on phone, FOP NM10) with an integrated offline artificial intelligence system to screen referable diabetic retinopathy has been widely used and demonstrated robust performance.[11,12] Recently, an offline glaucoma screening algorithm has been included in the FOP device and the AI development is described in a previous study .[13,14] The vertical cup-to-disc (vCDR) measurements outputted by the glaucoma AI system has been reported to be in good agreement with Spectral-domain Optical Coherence Tomography (SD-OCT) vCDR measurements.[13] The aim of this study is to assess the diagnostic ability of the offline, AI-driven glaucoma screening tool integrated on a smartphone-based fundus camera (FOP) to detect referable glaucoma of different severity against the diagnosis made by a glaucoma specialist following a complete glaucoma evaluation. This presents a portable, user-friendly solution that can be deployed in resource-constrained remote areas, potentially reaching a larger population enabling the early identification of glaucoma and in clinics for photo documentation, monitoring glaucoma progression and building prediction models. By harnessing the power of AI, our goal is to enhance the accuracy, efficiency, and accessibility of glaucoma screening, ultimately contributing to the preservation of visual health and the reduction of avoidable blindness.

Methodology:

This prospective, observational study was conducted in a glaucoma clinic of a tertiary care hospital, in South Asia between September and December 2022. The study was approved by the Ethical Committee (LEC-BHR-P-08-22-919) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the participants. This study was registered under the Clinical Trials Registry of India (CTRI) – details REF/2022/10/058951, allowed to register from Nov 1st 2022.

The primary focus of this study was to evaluate the performance of an offline Glaucoma AI tool integrated on a smartphone-based fundus camera against the expert's diagnosis in a clinical set-up based on different severity levels of glaucoma. Every consecutive patient >= 18 years who consented to participate in the study was recruited. These included patients diagnosed with Glaucoma and control (no glaucoma). The details of exclusion criteria are described in Supplementary Methodology Section 1 A. All the participants underwent a comprehensive eye examination or glaucoma workup and imaging using the study device along with glaucoma AI output.

Clinical Examination: The participants underwent comprehensive eye examination which included refraction, Best-corrected visual acuity (distance and near), intraocular pressure (Goldman applanation tonometry), Gonioscopy (Sussman 4-mirror), anterior (slit lamp) and posterior segment (78D or indirect ophthalmoscopy) examination. The additional investigation for those diagnosed or suspected to have Glaucoma included visual field examination (24-2 or 10-2), SD-OCT (ONH and macular cube), along with fundus photography. Any unreliable visual field reports (>20% rate of fixation loss or >15% false-positive/false-negative), poor OCT signal strength (<6), significant media opacity and other ocular pathology that affected the clear imaging of the fundus were excluded. Following dilation, the severity of cataract was graded based on the Lens opacification classification system (LOCS III). [15] All the respective clinical investigations were conducted by experienced optometrists and the final diagnosis/management of the patient was by a glaucoma specialist (experience >5/10 years). The glaucoma specialist (ground truth) provided a final diagnosis as "definite glaucoma", disc suspect" or "no glaucoma" based on predefined criteria. For those diagnosed with definite glaucoma, the severity of glaucoma was categorized as "early", "moderate" or "advanced" based on Hoddap –Parrish – Anderson criteria.[16]

Fundus Imaging: We used a smartphone-based non-mydriatic portable fundus camera (Remidio Fundus on phone, FOP NM 10) with an integrated offline Glaucoma Artificial Intelligence tool. The imaging protocol included capturing a one-disc centered image (40-degree FOV) for each eye before pupillary dilation. The inbuilt automated quality check outputs the quality of the image

captured as “sufficient” or “insufficient”. The operator was alerted to take a better-quality image if the images were of insufficient quality. Two more attempts were made by the operator to obtain a sufficient-quality image. If the images were of sufficient quality, then those images were sent for glaucoma AI analysis. Depending upon the “fed” fundus images, AI is trained to output recommendations. It gives the vCDR along with referable glaucoma, disc suspect or no referable glaucoma for each eye separately (eye-level) and final referral (patient-level) based on the worse eye diagnosis. If the image quality was insufficient, then the eyes were dilated with 1% tropicamide solution (part of routine clinical care). After dilation, the operator made 2 attempts to get an image of sufficient quality. If the image was of sufficient quality, an estimated vCDR value along with the output of AI was obtained. The state in which the image was captured, whether dilated or undilated pupil status was recorded.

Glaucoma Artificial Intelligence System: The Medios Glaucoma AI is a proprietary, automated deep-learning-based tool integrated on the FOP NM10 fundus camera. The AI system includes two deep neural networks i.e an assistive network that detects the optic disc, crops the region of interest around it, outlines the disc and cup and finally outputs the cup-to-disc ratio. The network was trained using 4483 images in the train set (3700 images from South-Asian 172 population and 783 images from Caucasian population) and 560 images in the validation set. This also included images from the FOP NM10 camera. The detailed methodology followed in the development of Medios AI is previously published.[13,14] The final output includes vCDR along with the status of referral as “referable glaucoma”, “disc suspect or high vCDR” or “no referable glaucoma”.

Precision & Repeatability of Glaucoma AI: A precision sub-study was conducted where two different trained optometrists imaged the same patient independently (random participants from the main study) and generated AI reports. For repeatability, each optometrist captured two different images on the same eye of the same patient and ran glaucoma AI for those 2 images. This sub-study included an equal number of referable and no referable glaucoma (AI output) cases.

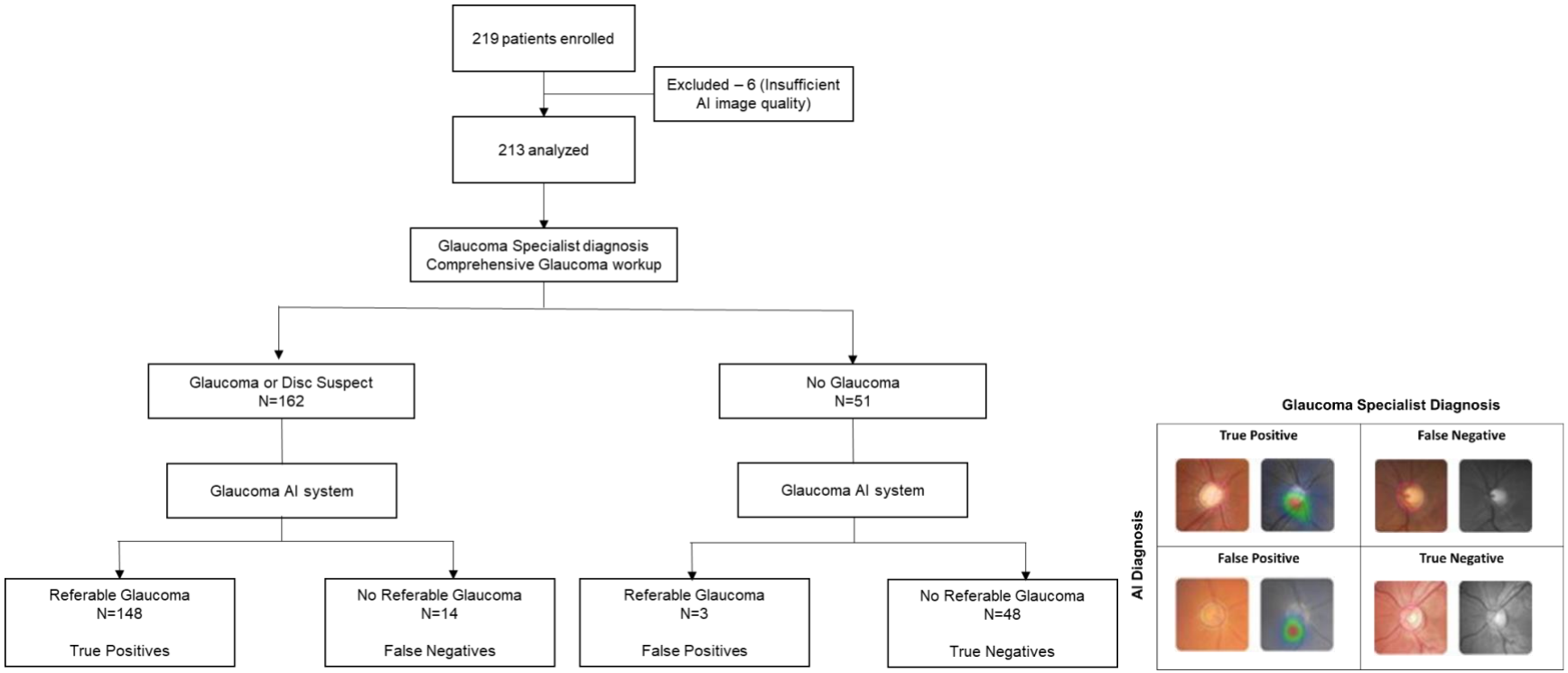
Statistical analysis: Sample size: Assuming an 80% sensitivity, 10% of precision, 40% glaucoma prevalence, 95% confidence level and anticipating 10% of poor image quality, the estimated sample size calculated was 200 patients.

All the data was entered in Microsoft Excel and normality was tested for all the quantitative variables. The AI and glaucoma specialist diagnosis was categorized as “definite glaucoma”, “disc suspect” and “no glaucoma”. We defined referable glaucoma by combining those diagnosed as “disc suspect” and “definite glaucoma”. A patient-level analysis including the diagnosis of the worse eye for the presence of referable glaucoma was compared for AI and specialist diagnosis. A 2*2 confusion matrix was used to compute the sensitivity and specificity of the AI system against the ground truth. Additional metrics included the positive predictive value (PPV) and the negative predictive value (NPV), likelihood ratios (LR) and accuracy along with Wilson’s 95% Confidence Intervals (CI). For repeatability of measurements using funding images and glaucoma AI, Intraclass correlation (ICC) was used and categorized ICC values < 0.5 as poor correlation, values between 0.5 and <0.75 as moderate correlation, values between 0.75 and <0.90 as good correlation and values ≥0.90 as excellent correlation.[17] Kappa statistic was used to determine the interobserver agreement. Kappa of 0–0.20 was considered as slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement.[18]

Results:

The study included a total of 219 patients and 6 were excluded due to insufficient AI system image quality in both eyes. We analyzed 213 participants (419 eyes) with a mean age of 55±14.7 years (18 to 88 years) and 62% (n=131) were male. Undilated images were captured in 49% (n=104) patients. A total of 129 Glaucoma (23 Mild, 31 Moderate and 75 Advanced Glaucoma) and 33 Disc suspects were included. Figure 1 presents the Standard for Reporting Diagnostic Accuracy (STARD) flow diagram of participant disposition.

Figure 1. Standard for Reporting Diagnostic Accuracy (STARD) flow diagram of participant disposition: Glaucoma Artificial Intelligence against specialist diagnosis



Glaucoma AI vs Specialist vCDR

The average difference in vCDR of 402 eyes comparing AI vCDR output (0.68±0.16, range 0.15 – 0.97) with the glaucoma specialist vCDR measurements (0.65±0.20, range 0.10 – 0.95) was -0.03±0.11 (range 0.39, -0.35) and statistically significant ($p<0.001$). Supplementary Figure 1 shows the distribution of vCDR comparing AI with specialist based on (A) categories of vCDR (<0.6, 0.61 to 0.8 and >0.81) and (B) difference in vCDR based on the severity of glaucoma graded as Mild, Moderate and Advanced Glaucoma.

Diagnostic performance of Glaucoma AI against specialist diagnosis:

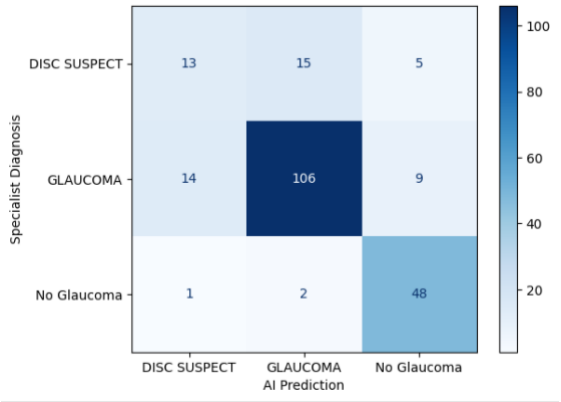
The glaucoma specialist (ground truth) diagnosed 129 as 'certain glaucoma', 33 as 'disc suspect' and 51 as 'no glaucoma' based on a comprehensive glaucoma workup (Figure 2). The sensitivity and specificity of the Glaucoma AI system in detecting referable glaucoma (certain glaucoma + disc suspect) against the glaucoma specialist diagnosis was 91.36% (95% CI 85.93% to 95.19%) and 94.12% (95% CI 83.76% to 98.77%) respectively (Table 1). Among the false negatives (n=14), 9 were diagnosed with certain glaucoma and 5 as disc suspects by the glaucoma specialists. Among the 9 with certain glaucoma missed by AI, 3 were early, 3 moderate and 3 advanced glaucoma severity levels and the specialist diagnosed POAG (n=3), PACG (n=4) or Secondary glaucoma (n=2). Overall, 3 out of 14 FNs (21%) had IOP >21mmHg. Among the disc suspects (n=5 FNs), one had IOP >21mmHg and angle was open in all. There were 3 false positives by AI. One was non-glaucomatous disc pallor, and one eye had a grossly tilted disc with PPA (2 recommended as referable glaucoma by AI) and one was normal disc flagged as disc suspect by AI. The glaucoma specialist's diagnosis was Ocular Hypertension (OHT), Primary Angle Closure (PAC) and normal. Table 1 and Figure 2 summarize the overall diagnostic performance of the glaucoma AI against specialist diagnosis and the 3x3 confusion matrix respectively.

Table 1. Diagnostic accuracy of Glaucoma AI system against glaucoma specialist diagnosis based on comprehensive glaucoma workup

Overall performance of Glaucoma AI (n=213)

Statistic	Value	95% CI
Sensitivity	91.36%	85.93% to 95.19%
Specificity	94.12%	83.76% to 98.77%
Positive Predictive Value	98.01%	94.30% to 99.59%
Negative Predictive Value	77.42%	65.03% to 87.07%
Accuracy	92.02%	87.53% to 95.28%

Figure 2. 3x3 Confusion matrix: Performance of Glaucoma AI against Specialist Diagnosis based on glaucoma workup



Sub-analysis: The study included 7 Juvenile Open-angle glaucoma (JOAG) and all were correctly identified as referable glaucoma by the AI system. Ocular Hypertension (OHT) was diagnosed in 12 participants (one/both) eyes and all were diagnosed correctly as no referable glaucoma by the AI system.

We analyzed the Intraocular pressure (IOP) of 419 eyes (213 patients) and 38 eyes (9%) had IOP >21mmHg. Comparing the AI and specialist diagnosis in those with high IOP, there were 8 false negatives i.e 6 eyes with glaucoma and 2 eyes diagnosed as disc suspect by the specialist were flagged as no referable glaucoma by the AI system.

Diagnostic Performance of the Glaucoma AI based on Glaucoma Severity: The AI performance against glaucoma specialist diagnosis for advanced glaucoma (n=75) was higher compared to moderate (n=31) and early glaucoma (n=23). The diagnostic performance of the AI system against glaucoma specialist diagnosis of 'certain glaucoma' based on the glaucoma severity is summarized in Figure 3 & Table 2. The false negatives (any severity level) commonly included POAG, PACG, and secondary/steroid-induced glaucoma. At least one in three of these glaucoma cases (every severity level) missed by the AI system had IOP >21mmHg. Those missed by the AI system included both undilated and dilated imaging for any severity of glaucoma.

Figure 3. Diagnostic performance of Glaucoma AI based on severity of Glaucoma

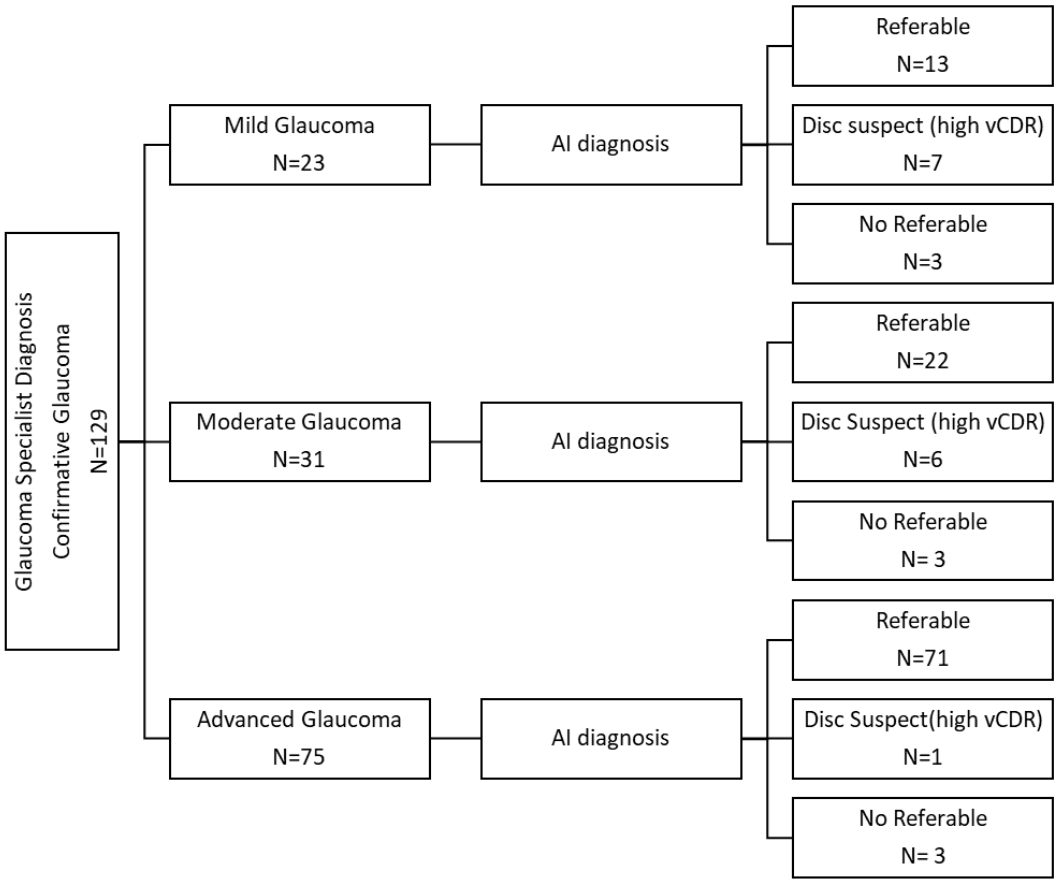


Table 2. Diagnostic accuracy of Glaucoma AI system against specialist diagnosis based on glaucoma severity

Glaucoma severity	Sample	Sensitivity
Mild	23	86.96% (66.41% to 97.22%)
Moderate	31	90.32% (74.25% to 97.96%)
Advanced	75	96.00% (88.75% to 99.17%)

Precision & Repeatability of Glaucoma AI: A subset of 30 patients (consisting of 16 Glaucoma cases, 5 Disc Suspects, and 9 No Glaucoma cases) underwent a repeatability assessment for fundus imaging along with Glaucoma AI analysis performed twice by two different operators. The calculated intraclass correlation (ICC) indicated an excellent correlation, with ICC values of 0.93 and 0.87 for operators 1 and 2, respectively, in their respective repeated measurements. Additionally, Cohen's kappa statistic comparing the AI output from both operators demonstrated excellent agreement, with a value of 0.85.

Discussion:

The global burden of Glaucoma underscores the need for a viable screening approach to enable the early identification of this irreversible cause of blindness and visual impairment and its timely intervention. In developing countries, where access to eye care is constrained and several seek specialist care only at the end-stage of the disease, community-based eye outreach initiatives could potentially facilitate early detection. The Glaucoma Artificial Intelligence algorithm integrated on a smartphone-based fundus camera evaluated in this prospective study demonstrated a robust performance with a sensitivity and specificity of 91.4% and 94.1% respectively when compared to glaucoma specialist diagnosis based on a comprehensive glaucoma workup. The performance of the AI system based on the severity of glaucoma demonstrated a sensitivity of 96% for advanced, 90.32% for moderate and 86.96% for mild glaucoma. . This innovation which also incorporates offline AI capabilities (operating without internet) addresses the challenge of accessibility by bringing glaucoma screening to the point of

care, enabling early detection and intervention in remote or resource-limited settings. In clinical settings, this technology can assist in photo documentation, monitoring follow-up visits and the development of glaucoma prediction models.

The smartphone-based fundus camera used in the study captures monoscopic images and the offline Glaucoma AI algorithm identifies characteristic signs of glaucoma, such as structural changes in the optic disc, retinal nerve fiber layer, and cup-to-disc ratio. The major strength of the study included a stringent ground truth or reference standard of glaucoma specialist diagnosis based on a comprehensive glaucoma evaluation. The Glaucoma AI showed a robust performance with sensitivity and specificity of 91.36% (95% CI 85.93% to 95.19%) and 94.12% (95% CI 83.76% to 98.77%) respectively. The false negatives included nine glaucoma and 5-disc suspects missed by the AI. Looking closely at nine glaucoma patients missed by the AI, there was no specific pattern based on the type of glaucoma or its severity.

The AI also demonstrated few false positives, labelling 3 out of 51 eyes with no glaucoma. Minimizing false positives holds significance for an AI system as it can help alleviate the burden caused by unnecessary referrals, the economic burden and the psycho-social implications of overdiagnosis. It can also lead to loss of trust and uptake of such screening programs. While missed glaucoma suspect or an early glaucoma may be picked up during the next screening visit, hoping that the condition is not progressed. The performance measures are comparable to other glaucoma AI algorithms. The previously published validation of various other glaucoma AI algorithms has reported a similar range of sensitivities and specificities.[19-23] Glaucoma encompasses a spectrum of disorders, and incorporating additional assessments such as intraocular pressure (IOP) and anterior chamber angle measurements can significantly enhance the AI system's sensitivity for detecting glaucoma cases that warrant referral. Including IOP measurements as part of the screening would have identified an additional 2%, i.e 8 out of 419 eyes, which exhibited elevated IOP >21 mmHg and glaucomatous changes but were missed by the AI system. The key strength of this study is that it was a prospective study yielding an in-depth understanding of the performance of the AI along with a comprehensive glaucoma workup as a reference standard and including patients with different severity of glaucoma. This was not done in other studies. The AI could better detect those with advanced glaucoma (sensitivity of 96.00%

(88.75% to 99.17%) followed by moderate and early stages (sensitivity 90.32% (74.25% to 97.96%) and 86.96% (66.41% to 97.22%) respectively). The detection of early glaucoma can be challenging with variations in normal optic nerve head appearance. Subjective assessment of ONH using stereo photographs has shown inter- and intra-observer variation and moderate agreement has been noted among expert observers.[19,20] This emphasizes the need for an objective measurement that can aid in monitoring the progression. The Glaucoma AI used in the study provides an objective assessment of the optic disc and has been previously evaluated for the vCDR.[13] The study showed that the glaucoma AI demonstrated a good agreement and correlation with the vCDR from the spectral-domain optical coherence tomography (SD-OCT) and manual grading by glaucoma experts. In the present study, the vCDR measurements of AI and glaucoma specialist showed good agreement and no discernible distinctions were observed irrespective of the severity of glaucoma. The reliability of the automated measurements is a pivotal metric for evaluating the tool's effectiveness and multiple attempts may be required to capture an image of satisfactory quality. The repeatability of glaucoma AI showed excellent correlation and also demonstrated excellent agreement between two different operators in using the device.

Fundus photography has undergone a transformative evolution, resulting in numerous advancements over the course of 150 years. The study device (monoscopic) used is smartphone-based and has shown image quality similar to standard desktop cameras. Modern fundus cameras are characterized by their portability, non-mydriatic capability, user-friendliness, and improved cost-effectiveness suitable for photo documentation, screening and teleophthalmology models. Numerous studies have corroborated the reliability of portable, non-mydriatic fundus cameras when compared to the gold standard of dilated fundus examination for assessing the optic disc (cup-to-disc ratio measurements) for glaucoma demonstrating substantial agreement. [24,25] Monoscopic images have shown comparable and good agreement similar to stereoscopic imaging in the evaluation of optic disc photographs for morphological features and glaucoma likelihood.[26,27] Capturing good-quality fundus images is critical and it is known that with increasing age, pupil diameter reduces and there is a high risk of lenticular changes. This becomes crucial when deploying such technology in eye screening programs at the

population or community level, where it may not be feasible to dilate the eyes. Previous reports on the utilization of the study device and other non-mydriatic fundus cameras have indicated that these devices exhibit feasibility, image quality, image gradability, and diagnostic sensitivity comparable to that of desktop cameras.[28,29] Additionally, the utilization of fundus cameras, especially portable models, offers significant benefits owing to their cost-effectiveness, rendering them valuable instruments for screening eye conditions. Initiatives extend beyond hospital settings to encompass communities, vision centres, and primary health facilities. Diabetes is correlated with a substantially elevated risk of developing glaucoma. Including Glaucoma screening among diabetes individuals is essential. Our study group included 25% (54 out of 219) with diabetes and among them, almost 83% (45 out of 54) were diagnosed to have glaucoma or disc suspect by the specialists. An AI-powered glaucoma detection approach utilizing fundus imaging could be implemented for large-scale, cost-effective screening.

To the best of our knowledge, this is the first offline fundus image-based glaucoma screening software requiring no internet to run the AI. The majority of AI algorithms typically necessitate internet access and substantial computational resources, and they are designed to function exclusively with high-end and costly tabletop fundus cameras. This limitation restricts their ability in settings with limited resources. Furthermore, the device offers the capability to integrate data into a cloud-based platform and establish connections with teleglaucoma services, thereby improving patient care and facilitating additional interventions. The main objective of the study was to compare the performance based on the glaucoma severity. Including various forms or classifications of glaucoma would enable gaining additional insights into its applicability across a diverse spectrum of glaucoma types. To enhance its global utility, it would be beneficial to validate the glaucoma AI on different ethnic populations for generalizability of the glaucoma AI across different populations.

Conclusion

The study adds value in assessing the performance of glaucoma AI by including various glaucoma severity levels. In a population-based setting, the Glaucoma AI tool can be used either independently or along with teleophthalmology as a clinical assist tool to screen for undetected

glaucoma. It can act as a robust, fast, minimal training and easy-to-use triaging tool making Glaucoma screening affordable and scalable in resource-constrained communities. Within hospital-based settings, glaucoma AI and fundus imaging can be effectively employed for patients who come for follow-up visits. This data can prove invaluable in the development of a glaucoma prediction model, which could incorporate information from various other structural and functional assessments. Further, there is a scope for improvement of the tool in the early stages with the use of OCT information and by automatically referring those with par image quality.

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