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Smartphone-based Ophthalmic Imaging Compared With Spectral-domain Optical Coherence Tomography Assessment of Vertical Cup-to-disc Ratio Among Adults in Southwestern Uganda

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Abstract

Precis: Using optical coherence tomography (OCT) measurements as a reference standard for vertical cup-to-disc ratio (vCDR), a smartphone-based ophthalmic camera has a sensitivity of 67.7% and specificity of 96.7% to detect a vCDR > 0.5.

Purpose: The purpose of this study was to assess the performance of a smartphone-based ophthalmic camera system using an Apple iPhone 6S and an adapter, Paxos Scope, to obtain adequate dilated fundus photos to measure clinically useful vCDR cutoffs.

Patients and Methods: Adult patients from a government tertiary level eye hospital in Southwestern Uganda were prospectively recruited from January to April 2019. All patients experienced a comprehensive eye examination, dilated posterior segment indirect ophthalmoscope imaging with the Paxos Scope, and spectral-domain OCT imaging with a Cirrus HD-OCT to measure vCDR. Patients' eyes excluded had media opacities or existing disease precluding a view of the fundus. Fundus images underwent a single masked review to assign vCDR at increments of 0.1. Descriptive statistics, parametric and χ^2 tests for significance, repeated measures correlation, κ, receiver operating characteristics curve, and Bland-Altman were used to assess the data.

Results: Among 467 (consecutive) individuals, fundus photographs acquired with the Paxos Scope demonstrated a 67.7% [95% confidence interval (CI), 63.0-72.0] sensitivity and 96.7% (95% CI, 94.2-98.3) specificity to detect a vCDR > 0.5, using OCT as the reference standard. A total of 138 eyes were excluded due to poor imaging acquisition, such as dense cataract, rendering

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796 eyes for analysis. The vCDR from graded Paxos Scope images and OCT correlated well with repeated measures correlation of 0.82 (95% CI, 0.77-0.86, $P < 0.001$) and agreement, dichotomized as > 0.5 or ≤ 0.5, was 80.9% ($\kappa = 0.63 \pm 0.034$, $P < 0.001$). Among glaucoma and glaucoma suspects (85 eyes), the sensitivity and specificity dichotomized using vCDR > 0.5 were 97.5% (95% CI, 91.3-99.7) and 80.0% (95% CI, 28.4-99.5), respectively. The area under the receiver operating characteristics curve was 0.92 (95% CI, 0.89-0.94) for all eyes and 0.98 (95% CI, 0.78-1.0) for glaucoma and glaucoma suspects.

Conclusions: The Paxos Scope produced images that can be reliably used to estimate vCDR, which is closely aligned with the automated algorithm from the OCT optic disc cube scan. The low-cost, ready-to-integrate adapter, and minimal training requirements make it a viable option for population-based screening in low-resource settings.

Keywords

cup-to-disc ratio; glaucoma; global ophthalmology; smartphone; teleophthalmology

Glaucoma is the third and fourth leading cause of global blindness and visual impairment below 6/18 best-corrected visual acuity, respectively.[1] The global prevalence of glaucoma among adults 40 to 80 years is 3.5% (~76 million in 2020) and expected to increase to 111.8 million in 2040.[2] The glaucoma burden is disproportionately high in Africa with the prevalence of primary open-angle glaucoma of 4.20%,[2] highest among all continents. Glaucoma is often detected at a more advanced stage of disease in sub-Saharan African countries; reasons for this include asymptomatic progression of many types of glaucoma, suboptimal infrastructure and human resources for eye health in sub-Saharan Africa, and lack of widespread knowledge of glaucoma among the general population.[3–5] Increasing the availability of mass screening is one measure to increase rates of early detection and preventing severe visual impairment.

Well-designed teleophthalmology systems can yield similar visual outcomes to traditional modes of care delivery with the added benefit of reaching a larger population.[6] It has the promise to bridge existing service delivery gaps for mass level screening along with more robust evaluation and management applications.[7,8] Fundus imaging is one component of a screening program[9] that can be financially viable with low-cost, appropriate applications of widespread technology, especially the smartphone. The vertical cup-to-disc ratio (vCDR) is a commonly evaluated clinical parameter that is assessed for glaucoma screening and baseline evaluation since it correlates with glaucomatous neuroretinal rim (NRR) loss.[10] An enlarged vCDR[11] or asymmetry > 0.2[12] should prompt a formal workup; though they are not definitively signs of glaucomatous damage, these signs are often used in conjunction with signs, such as rim notching, and assessments (eg, perimetry) to diagnose glaucoma. In Uganda, a lower threshold of vCDR > 0.5 is used as a criterion for referral-warranted cases by nonophthalmologists staffing large-scale screening camps.

Cost-effectiveness is a major argument for the implementation of teleophthalmology, especially for glaucoma.[13] Universal screening of adults in Ghana 5 times between age 45 and 85 can cost as much as USD 13,504 per disability-adjusted life-year averted, which is far above the 4.4 times the Ghanaian per capita gross domestic product to qualify as a cost-

effective intervention.[14] In rural India, a universal community-based screening and treatment program for individuals age 40 to 69 years has an incremental cost-effectiveness ratio of about USD 100 per quality-adjusted life-year, which is below the country's willingness-to-pay threshold making it cost-effective.[15] To help improve cost-effectiveness in a low-income country such as Uganda, judicious equipment purchasing can make a major difference when scaled nationally, since a Paxos Scope costs USD 150 to 200, whereas a conventional fundus camera costs a minimum of USD 8000 while second-hand spectral-domain optical coherence tomography (SD-OCT) systems cost USD 50,000. Thus, smartphone-based ophthalmic cameras are promising in that they allow nonophthalmic health care workers to deploy screening services at primary care and community levels, especially far away from the referral center.[16]

The Paxos Scope is a smartphone adapter that stabilizes a typical indirect ophthalmoscopic condenser lens and provides an intensity-adjustable paraxial light source[17,18]; as a United States Food and Drug Administration (FDA) Class II 510(k) exempt device, the Paxos Scope has been studied for diabetic retinopathy screening proving clinical utility.[19] Therefore, this present study was undertaken to assess Paxos Scope's clinical performance in successfully identifying eyes with a vCDR > 0.5 with the hope of applying this to community-level glaucoma screening in Uganda and other resource-limited settings.

PATIENTS AND METHODS

Study Design, Patient Recruitment, and Institutional Review Board Approval

This was a prospective comparative testing study performed at one institution, the Mbarara University and Referral Eye Centre (MURHEC), which is a tertiary level ophthalmology hospital with a catchment population of ~5 million serving 4 countries (Uganda, Democratic Republic of the Congo, Rwanda, and Tanzania). All adults aged 18 years and above seeking services at MURHEC were eligible for this study and were enrolled from January to April 2019. The sample size was estimate using Buderer formula based on anticipated sensitivity of an experiment test set a priori.[20] The parameters set were as follows: anticipated sensitivity = 0.90 from previous testing performance of Paxos Scope albeit for diabetic retinopathy,[19] $\alpha = 0.05$, absolute precision desired = 0.05, and prevalence of vCDR > 0.5 = 0.35 using normative assumptions from 2 sub-Saharan African countries for vCDR.[21,22] The targeted sample size needed was 400 divided into suspect and normal arms at 1:1 ratio. We set the minimum threshold to define a suspect as vCDR > 0.5 and a normal as vCDR ≤ 0.5. This seemingly lower threshold has long been used routinely in Uganda during screening eye camps as a one criterion for referral for formal evaluation; in an ongoing Lions diabetic retinopathy population screening program implemented in Southwestern Uganda, a vCDR of 0.5 and 0.6 is at the 90th percentile and 95th percentile, respectively in healthy adults over age 18 years (internal data). These data were not available at the time the present study was implemented, thus the prevalence of vCDR > 0.5 from previous studies was used in the sample size calculation.

On each clinic day at MURHEC, the principal investigator (B.R.I.) enrolled at least 20 patients aiming for 10 suspects and 10 normals per day. Patients were given numbers in the order they arrived per routine clinic flow management, and the numbers were pulled using a

random number generator. Exclusion criteria included: bilateral media opacities, bilateral postevisceration/enucleation, bilateral phthisis, or any other reason preventing a clear view of the optic nerve and posterior pole. If an individual only had one accessible eye, the patient was still eligible and asked for participation. After a dilated fundus examination per routine clinical practice, patients deciding to participate in the study signed a written form providing informed consent. This study was approved by the Mbarara University Research Ethics Committee (Ref 02/03-19). All research activities adhered to the tenants of the Declaration of Helsinki and the National Laws of the Republic of Uganda.

Examination

Patients underwent a comprehensive eye examination per routine standard of care, which pertain to this study included visual acuity, intraocular pressure (IOP) (acquired by applanation tonometry), slit-lamp biomicroscopy, dilated fundus examination by indirect ophthalmoscopy, and smartphone-based imaging with the Paxos Scope adapter after mydriasis using topical 1% phenylephrine and/or 0.5% tropicamide. Some patients needed > 1 drop for adequate dilation. For this study, the Paxos Scope was paired with an Apple iPhone 6S, which has a 12MP camera (Apple Inc., Cupertino, CA), and a 20 D condenser lens fixed at 20 cm from the iPhone's rear camera. This allowed for images with a 45-degree field of view. The digital zoom and focus features were used to acquire as clear of image sets as possible. The examiner's hand came into contact with the patient's brow and lateral cheek to stabilize the condenser lens at a distance of 4 to 5 cm from the patient's cornea In burst photography mode, the patient was asked to fixate on a target straight ahead in her/his line of view for an optic nerve—centered image; the patient was then asked to look directly at the Paxos's light source for macula-centered image (Fig. 1). For each eye, multiple image sets were taken until at least 1 set had the highest quality image that allows for a vCDR measurement. All comprehensive eye examinations and Paxos Scope imaging were performed by 1 examiner (B.R.I.) throughout the study.

Patients then underwent optical coherence tomography (OCT) imaging of the optic nerve head (ONH) using a Zeiss Cirrus HD-OCT 500 (Carl Zeiss AG, Oberkochen, Germany) in Optic Disc Cube 200 ×200 mode, acquiring 200 A scans and 200 B scans over a 6.0 mm^2 area centered at the ONH. In recent years, OCT has become a vital tool in detecting and monitoring glaucomatous changes to the optic nerve.[23,24] Measurements recorded were vCDR, optic disc area, and cup volume. All OCT scans were acquired by an experienced midlevel provider (ophthalmic clinical officer). Only optimal quality scans were used which had signal strength above 7 of 10 and no discontinuity, movement, drop-out or any other artifacts. Peripapillary retinal nerve fiber layer (RNFL) thickness was used in diagnosing glaucoma, which though beyond the purview of this study, was diagnosed by experienced attending ophthalmologists (J.O. or 3 other attendings). They used a combination of: First, slit-lamp biomicroscopy showing disc damage such as generalized NRR thinning, especially with asymmetry in VCDR > 0.2, focal NRR notching, or disc hemorrhage. Second, There had to be OCT evidence of disc damage correlating with clinical examination, for example, RNFL general or thinning in one of the quadrants. Third, perimetric field loss detected by a reliable performance on 24-2 SITA protocol automated perimetry with a reliable field absent of artifact, minimal fixation losses, <10% false-positive and false-negative errors; if the field

was reliable, it had to exhibit field loss in a glaucomatous pattern (eg, arcuate, nasal step, altitudinal) and the attending would apply Hoddap-Parish-Anderson criteria to borderline glaucoma suspects.[25] Fourth, if the individual had IOP > 21 mm Hg, this would further support the diagnosis. Fifth, gonioscopic assessment of the angle and patient's history were used to determine the mechanism of glaucoma, which led to categorization as primary or secondary. While the vast majority had primary open-angle glaucoma, all glaucoma was aggregated into one category. As we suspect is common in many other low-income country settings, nearly all glaucoma patients were diagnosed at more advanced stages in which filtering surgery was offered due to 1 month lost to follow-up rates of over 70% (internal data). A pilot with 10 patients was done to refine operating procedures before the start of this study but their data were not included.

Image Reading and Statistical Analysis

The Paxos-acquired images of the optic nerve were read by a senior specialist ophthalmologist (J.O.) who was blinded to any patient details or corresponding OCT-measured vCDR. The grader used a physical ruler overlying a desktop screen to more accurately reach a measurement; he then assigned a value with one significant figure after the decimal, for example, 0.3, and this value was then compared against the reference, which was the OCT-measured vCDR value with 2 significant figures (eg, 0.35). Images were processed and provided to the reader at a consistent pixel resolution, so the physical measurements were as close as possible among all images. Descriptive statistics, parametric and χ^2 tests for significance, repeated measures correlation, weighted κ, receiver operating characteristics, and Bland-Altman analyses were performed in STATA 16 (StataCorp, College Station, TX). Each eye was the unit of analysis, and intraindividual correlation was adjusted for in significance testing using 2-level generalized linear models where a random intercept was set for intereye correlation. Significance level was set at $P = 0.05$. The OCT-measured vCDR was not rounded in weighted κ analysis to make the comparison more conservative.

RESULTS

A total of 467 individuals were enrolled yielding 934 possible eyes. A total of 138 eyes could not be analyzed; 135 eyes (14.5% of theoretically eligible eyes) could not be assessed clinically, imaged by Paxos Scope, or scanned with OCT for reasons provided in the methods (eg, most commonly mature cataracts), and 3 eyes (0.3%) yielded poor quality Paxos Scope images despite multiple repeat attempts. Reasons included inadequate dilation despite maximal topical mydriatics, excessive glare, and inability to acquire a focused image. Nine individuals of 476 individuals did not provide consent yielding a 98.1% response rate. Therefore, a total of 796 eyes were analyzed in which 436 eyes had a vCDR > 0.5 [54.8% of eyes, 95% confidence interval (CI), 51.3-58.2] by OCT.

Sample Characteristics

A summary of the study participants is provided in Table 1. The mean age was 46.1 ± 18.1, 53.7% were females, and participants came from 31 Districts of the total 134 nationwide. Because of the location of MURHEC near the city center, a near majority of patients live in

an urban environment, nearly one third were attaining/attained tertiary education or higher, 41.8% were subsistence farmers or manual laborers, and the main ethnic group in the Southwestern Uganda area is Banyankore (73.9%). Our sample's demographics differ from the national averages, in which, for example, 21.4% live in urban areas and 6.9% of adults over age 18 are attaining or have attained tertiary education or higher.[26] The mean distance presenting visual acuity with a pinhole was Snellen 6/9 [median, 6/7.5, interquartile range (IQR): 6/6 to 6/12] (Table 2). Median IOP was 12 (IQR: 10 to 13) and median vCDR by OCT was 0.54 (IQR: 0.43 to 0.70) (Table 2). Of the 796 eyes, 65.2% had normal or no significant ophthalmic pathology while 9.0% were eventually diagnosed with glaucoma and 1.6% were glaucoma suspects (Table 1). Among glaucoma patients, median vCDR was 0.8 (IQR: 0.7 to 0.9), which is significantly higher compared with age-matched normals at 0.6 (IQR: 0.5 to 0.7) ($P < 0.001$).

vCDR Agreement

The exact agreement for vCDR between the Paxos Scope images and the OCT-acquired measurements was 45.2% with a weighted κ of 0.62 ± 0.021 ($P < 0.001$). However, repeated measures correlation, which accounts for within-individual clustering, using generalized linear model was acceptable at 0.82 (95% CI, 0.77-0.86). The Bland-Altman plot in Figure 2 shows a mean bias of −0.05 [limits of agreement (LOA): −0.24 to 0.14]. This means the vCDR estimated from smartphone images were consistently slightly lower than the OCT automated measurement. Only 2 values fell outside the lower LOA and 13 were above the upper LOA, thus the outliers tended to involve an overestimation of vCDR by the smartphone-reviewed images. The 2 extreme outliers at 0.8 and 0.6 on the *y*-axis were due to the OCT measuring a near zero vCDR while the smartphone-reviewed vCDR estimates were 0.8 and 0.6, respectively.

Using OCT-acquired vCDR as the reference and dichotomized as vCDR > 0.5 (suspect) and vCDR ≤ 0.5 (normal), the Paxos Scope's sensitivity and specificity was 67.7% (95% CI, 63.0-72.0) and 96.9% (95% CI, 94.6-98.5), respectively (Table 3). The positive predictive value (PPV) was 96.4% (95% CI, 93.7-98.2) and negative predictive value was 71.2% (95% CI, 67.0-75.2). When dichotomized using vCDR > 0.5, the agreement improved to 80.9% with κ of 0.63 ± 0.034 ($P < 0.001$). If dichotomized using vCDR > 0.6 as the threshold, the agreement between Paxos Scope images and OCT was perfect at 100.0% with κ of 1.0 ± 0.035 ($P < 0.001$). If the analysis is restricted to eyes diagnosed with glaucoma after a formal evaluation and the eyes of glaucoma suspects (85 eyes total), the Paxos Scope's performance with the same vCDR threshold of 0.5 is as follows: sensitivity 97.5% (95% CI, 91.3-99.7), specificity 80.0% (95% CI, 28.4-99.5), PPV 98.7% (95% CI 93.1-100.0), negative predictive value 66.7% (95% CI, 22.3-95.7) (Table 4). Agreement was 96.5% with κ of 0.71 ± 0.11 ($P < 0.001$). The receiver operating characteristics curve is depicted in Figure 3; the area under the receiver operating characteristics (AROC) curve for all eyes is 0.92 (95% CI, 0.89-0.94) and increased to 0.98 (95% CI, 0.78-1.0) in glaucoma and glaucoma suspect eyes only. Among those with vCDR > 0.5, the proportion with glaucoma is 15.6% and increased to 52.4% at vCDR > 0.7.

Eyes with a vCDR > 0.5 were much more prevalent in adults age 50 years and older ($P < 0.001$, Table 5), which drove the expected increase in sensitivity at 70.4% versus all-age sensitivity of 67.7% and correlating decrease in specificity at 94.9% versus all-age specificity 96.9% (Table 5). Sensitivity and specificity were both higher among males than females: sensitivity 71.1% versus 63.9% ($P = 0.032$), specificity 99.4% versus 94.2% ($P < 0.001$). Therefore, the ArOC in females was lower at 0.89 (95% CI, 0.86-0.93) versus males at 0.96 (95% CI, 0.93-0.99) ($P < 0.001$, Fig. 4). The most likely contributing factor is a significantly lower sensitivity among females age 18 to 29 years compared with their similar age male counterparts: 37.8% (95% CI, 22.5-55.2) compared with 74.4% (95% CI, 57.9-87.0, $P < 0.001$).

DISCUSSION

In this prospective study of adults at a tertiary referral eye hospital in Southwestern Uganda, we assessed the performance of a low-cost smartphone adapter, the Paxos Scope, in producing quality photographs to estimate vCDR. To the best of our knowledge, comparing vCDR between a smartphone-based ophthalmic camera and another method has only been previously done using the D-EYE (D-EYE Srl, Padova, Italy) in a northern Italian population.[27] The simplicity of measuring vCDR and the lack of specialized equipment makes it a convenient and widely utilized parameter in large-scale screenings and population surveys[28]; however, we recognize the pitfall of high interobserver variability of vCDR among clinicians[29] and even from those grading fundus photography.[30] The Paxos Scope, paired with a 12MP camera of the iPhone 6S in our setup, produced useful images to enable vCDR measurement in which only 0.3% of eyes that could be examined clinically did not yield readable Paxos Scope images. As a screening test with vCDR threshold > 0.5 in Uganda, it has an acceptable sensitivity of 67.7%, the high specificity of 96.7%, and a good AROC of 0.92. By itself, the Paxos scope does not meet the recommended minimums of 85% sensitivity and 95% specificity for population-based glaucoma screening, though no single mode of evaluation by itself would meet these thresholds.[31] In Cameroon, a smartphone-based screening study using vCDR ≥ 0.5 and asymmetry ≥ 0.2 led to a referral rate of 9.87% but only 57% of the 14 successful referrals were eventually diagnosed with glaucoma.[32] Proactive screening in the community benefits from lower sensitivity and high specificity, some would argue 99%,[33] since it would curtail unnecessary referrals, especially since most tertiary eye hospitals in sub-Saharan Africa are already operating at full capacity and patients bear excessive direct and indirect costs despite publicly funded hospitals, such as MURHEC. A vCDR threshold of > 0.7 may be more reasonable for this population since about half of individuals above 0.7 have glaucoma in our sample. Historically in the Ugandan setting, the 0.5 threshold was used because of a known low rate of attendance after a primary level referral, so it would be safe to “over-refer.” A typical Ugandan patient screened at a lower level health facility during an eye camp would need to arrange for transport, pay nominal procedural fees, and if they need glaucoma eye drops other than timolol, these can be notoriously expensive. Even if the sensitivity is considered too low to facilitate referral of all possible glaucoma suspects, the use of a device like Paxos Scope and remote interpretation by ophthalmologists or trained ophthalmic technicians would yield higher referrals than the status quo. A study from Nepal’s rural screening eye camps using

Paxos Scope showed remotely located ophthalmologists identified more glaucoma suspects based on fundus photography, 49 eyes, than frontline midlevel ophthalmic providers using direct ophthalmoscopy, 2 eyes.[16] As with any technological solution, the users set the criteria and conditions in which the Paxos Scope can facilitate appropriate referrals balancing local health system resources with glaucoma epidemiology.

Using the vCDR > 0.5 threshold and restricting the analysis to glaucoma and glaucoma suspects, Paxos Scope's performance reflected an excellent screening test: high sensitivity (97.5%) and acceptable specificity (80.0%). Our cohort's glaucoma patients had a much higher vCDR than age-matched normals, explaining the performance improvement. If the threshold of vCDR is raised to 0.6, the sensitivity and specificity for Paxos Scope are perfect compared with SD-OCT for correctly delineating suspect from normals. With this vCDR > 0.6 threshold, the Paxos's performance is similar to slit-lamp biomicroscopy and traditional fundus cameras, which have been criticized for leading to excessively high specialist referrals even in high-income countries.[34] Yet, some conventional disc imaging methods have a sensitivity as low as 29%.[34] Using a vCDR threshold of 0.55, the sensitivity and specificity of color optic disc photographs from traditional fundus cameras are 59% and 73% for detecting glaucoma.[35] It is not surprising our study's κ for the exact agreement of vCDR between Paxos Scope images and OCT measurements was 0.36 ± 0.014; in a telemedicine-based glaucoma screening setup in Kenya, remotely graded photos for vCDR had a κ 0.55 (95% CI, 0.50-0.61) with clinical examination, in which the κ is expected to be higher since these are more comparable methods.[7] In another study assessing a different smartphone adapter, D-EYE, the κ for vCDR between smartphone images and a clinical examination was 0.63 (95% CI, 0.52-0.73) among 29 eyes.[27] Compared with a traditional fundus camera, D-EYE images yielded high correlation in vCDR ($\rho = 0.91$, $P < 0.001$).[36] Another smartphone adapter, Peek Retina (Peek Vision Ltd, Berkhamsted, UK), was compared against a traditional fundus camera and showed remarkable exact agreement in vCDR with only a mean difference of −0.02 (95% CI, −0.22 to 0.17).[37] Both D-EYE and Peek Retina produced magnified images with similar principles to direct ophthalmoscopy whereas Paxos Scope's optics is similar to indirect ophthalmoscopy. These 3 adapters among others have yet to be compared head to head. In principle, D-EYE and Peek Retina have greater magnification within a smaller field of view; this magnification may aid in evaluation of optic disc images. The Paxos Scope's advantage is its "posterior pole" larger field of view, FDA registration as an ophthalmic camera, external and adjustable LED light source, universal fit with virtually any type and sized smartphone, and low unit cost that readily integrates with ubiquitous condenser lenses used in indirect ophthalmoscopy, and like the other smartphone adapters, training requirements are low as nearly all individuals who are comfortable using a smartphone can eventually acquire quality images. The Paxos's limitation for posterior segment imaging is it requires dilation and as our study showed, glaucoma patients with a vCDR between 0.5 and 0.7 are less likely to be read as abnormal.

Small variations in vCDR are likely insignificant, but an exact agreement between smartphone imaging and OCT cube scans was difficult to achieve since OCT uses 3D nerve head information for more accurate measurements. Perhaps if compared with photos acquired by traditional fundus camera using the same grader, there would have been higher concordance. Our findings of increased sensitivity with increased vCDR threshold (a

surrogate for severity) is similar to another smartphone-based ophthalmoscopy study done at MURHEC. This study used the Panoptic (Welch Allyn, Skaneateles Falls, NY) and Samsung S6 (Samsung Electronics Co. Ltd, Suwon, South Korea) in diabetic retinopathy screening; overall sensitivity for any diabetic retinopathy was 70% but increased to 100% for proliferative diabetic retinopathy; the majority of false negatives were from mild nonproliferative diabetic retinopathy.[38] Within this context, the Paxos Scope's performance at a vCDR threshold of 0.5 is expectedly low on sensitivity. In community-based screening settings, frequency doubling technology (FDT)-based perimetries have a sensitivity and specificity of 55% and 90% for detecting an abnormal clinical examination. Using OCT to measure RNFL thinning can have sensitivities as low as 47.8% if the criterion is the stringent global RNFL thickness abnormalities at <1% or 65.2% thickness abnormalities at the <5% levels compared with age-matched normals.[39] If deployed in a community-based screening program, the Paxos Scope would not be relied upon solely. Indeed, adding tonometry and FDT perimetry raises sensitivity to over 90% at the detriment of specificity and PPV.[34] An ideal community-based screening in Uganda and similar settings could combine the Paxos Scope for imaging, portable tonometry devices including even smartphone-based,[40] and low-cost virtual reality headsets paired to a smartphone running FDT-based perimetry.[41] Screenings that can afford slit lamps and gonio lenses could incorporate iridocorneal angle imaging using more advanced smartphone models.[42,43]

Our study has several limitations. First, the study is not population-based and has a sample characteristic that reflects a tertiary eye hospital. Our sample has a higher mean vCDR than observed from studies elsewhere in East and West Africa; moreover, the 97.5th percentile is 0.8 in our setting versus 0.7 in studies from Ghana, Nigeria, South Africa, and Tanzania.[10,21,22,28] In a general population, the prevalence of a higher value vCDR and most likely glaucoma are lower. Traditionally, this would not affect sensitivity but if there are more individuals in the 0.4 to 0.6 range, the sensitivity of reading Paxos Scope images compared with OCT would likely decrease, thus the results of this study cannot be fully translated to a population screening setup. For Uganda, we advocate that having a trained reader review images, either at the screening site or remotely, can be a valuable addition to help alleviate the strain on overworked ophthalmic midlevel and nursing cadres. Second, only 1 senior ophthalmologist was grading the optic disc images. Given the known interobserver variability, we do not know those effects on the images produced in this setting. Yet since all images analyzed were high quality, the variability is most likely idiosyncratic and occurs daily in clinical practice among different ophthalmologists. The grader also used a physical ruler to arrive at the vCDR. A more precise measurement plan could have been done with digitally magnified images on a desktop running ImageJ to measure pixels (National Eye Institute, Bethesda, MD).

Third, we recognized the inherent limitations of a technology-driven study to assess an imaging method since smartphone camera technology improves at such a rapid pace. Future iterations of the iPhone and Android devices will only improve quality of imaging to provide stereoscopic and higher resolution views of the optic nerve, and perhaps newer smartphones can produce quality comparable to much more expensive traditional stereoscopic fundus cameras.[44] To address this, we initially sought video recordings to provide contours and evaluation of venous pulsations, but this was untenable for our aimed sample size and the

pilot study showed it would have added 6 to 8 minutes per patient. In a busy tertiary eye hospital, it was not feasible with our human resources constraints. Our grader did not report of any images where image resolution and clarity could have led to a vCDR error > ± 0.1.

Despite these limitations, our study achieved a larger sample size than targeted and rigorously compared a smartphone adapter to the automated SD-OCT ONH algorithm for vCDR. Although the sensitivity at a vCDR threshold of 0.5 was modest at high specificity among all eyes for referral-warranted cases, the Paxos Scope's performance improved markedly at higher vCDR thresholds, and agreement with OCT was acceptable despite inherent limitations comparing the 2 disparate modalities. As such, this smartphone adapter and similar adapters have the potential to play an important role in glaucoma screenings in rural, remote villages far from a tertiary eye hospital. To improve sensitivity, adding additional measurements, such as IOP and pachymetry, and consideration of risk factors for screened individuals could help without adding too much additional cost.

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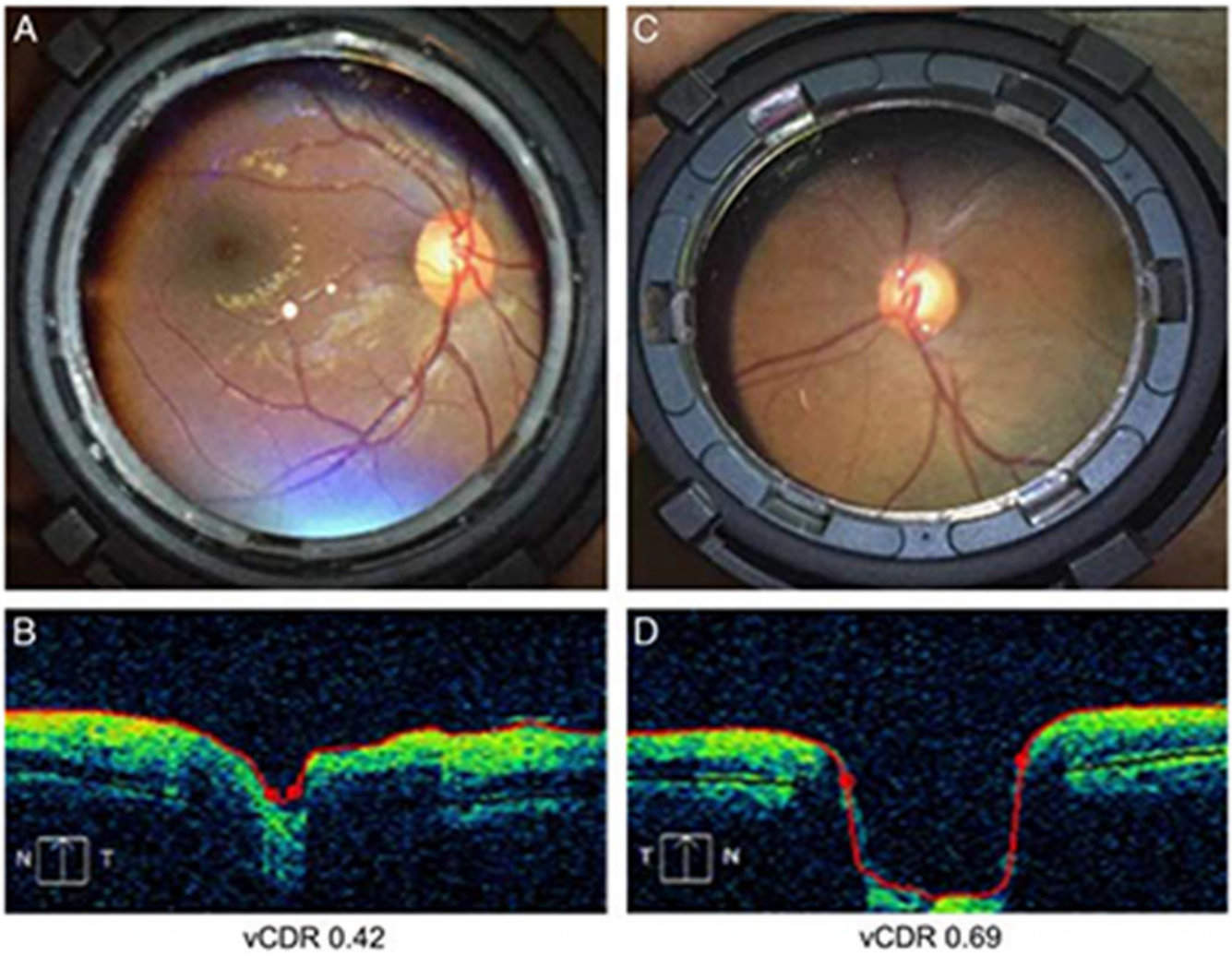

FIGURE 1.

Example suspect [vertical cup-to-disc ratio (vCDR) > 0.5] and control (vCDR ≤ 0.5). A and B, Control: optical coherence tomography (OCT)-acquired measurement was 0.43. A, Fundus photograph acquired by the smartphone-based camera (Paxos Scope) of the right eye is inverted since this is the unedited view the examiner sees as one would see with the indirect ophthalmoscope. The masked reviewer provided a vCDR value of 0.4. For extracted tomograms produced by the Zeiss Cirrus HD-OCT 500 system, the red line is the internal limiting membrane and the black line is the Bruch membrane opening. B, Vertical tomogram both showing an enlarged cup. C and D, Suspect: OCT-acquired vCDR was 0.69 and the masked reviewer read the fundus image as 0.7. C, Fundus photograph of the left eye. D, Vertical tomogram. For fundus imaging with the Paxos Scope, photographs were acquired in the highest illumination setting, iPhone camera in burst photo mode, fit-to-screen calibrated digital zoom, and use of the digital focus function in Apple iOS's native camera app.

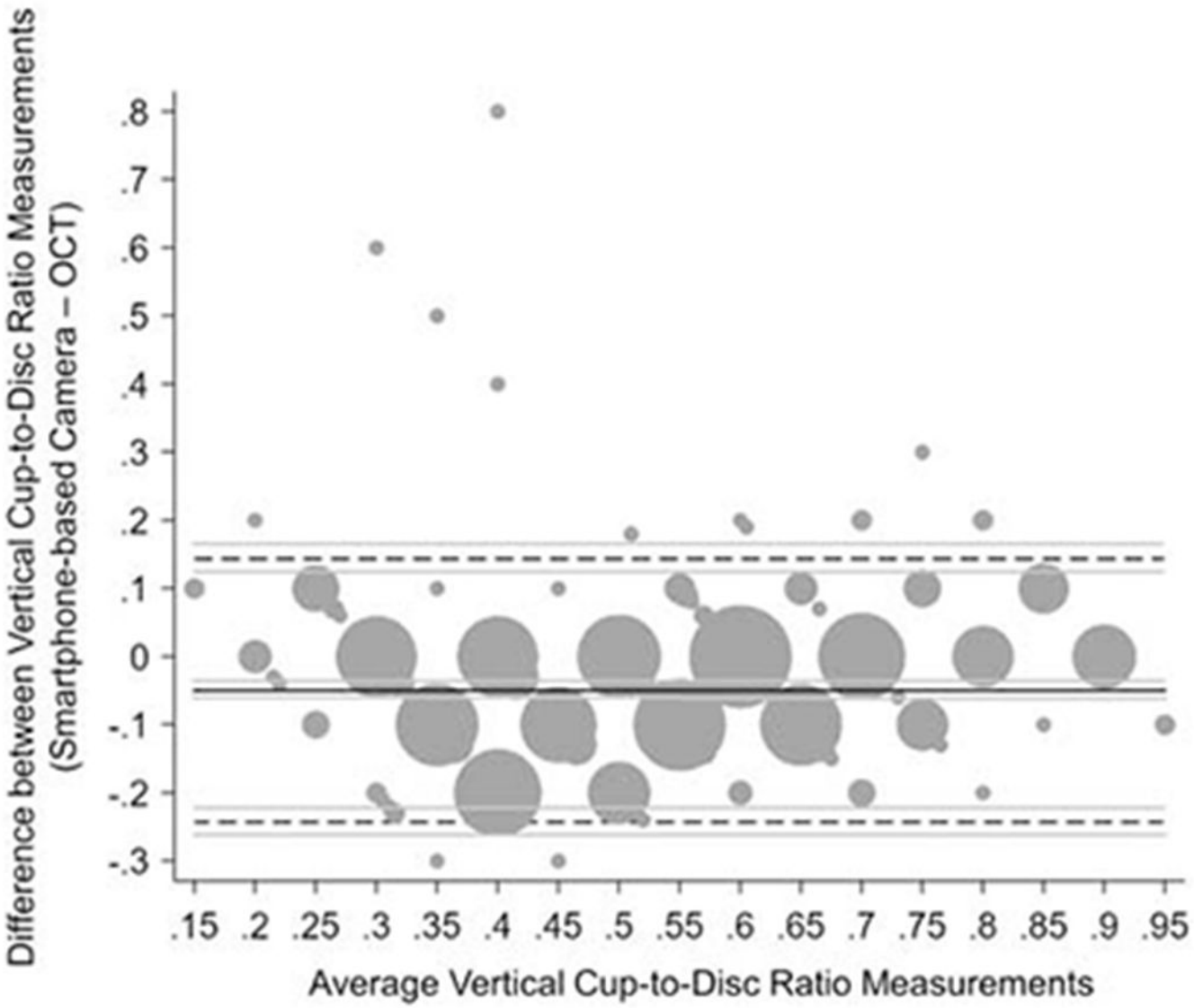

FIGURE 2.

Bland-Altman of vertical cup-to-disc ratio (vCDR) measurements. The average of the smartphone-based camera (Paxos Scope) and optical coherence tomography (OCT)-acquired vCDR is on the *x*-axis. The difference between OCT and Paxos Scope is on the *y*-axis (Paxos Scope estimated vCDR minus OCT-acquired vCDR), thus a value below 0 means the OCT-acquired measurement is larger than read by the masked reviewer using Paxos Scope images. The gray circles represent the data points with area proportional to number of data points. The mean bias (black solid line): −0.05 (95% confidence interval, −0.057 to −0.043); upper limit of agreement (black dashed line): 0.14 (95% confidence interval, 0.13-0.16); lower limit of agreement: −0.24 (95% confidence interval, −0.26 to −0.23). The gray lines represent the upper and lower confidence limits for all 3 measures.

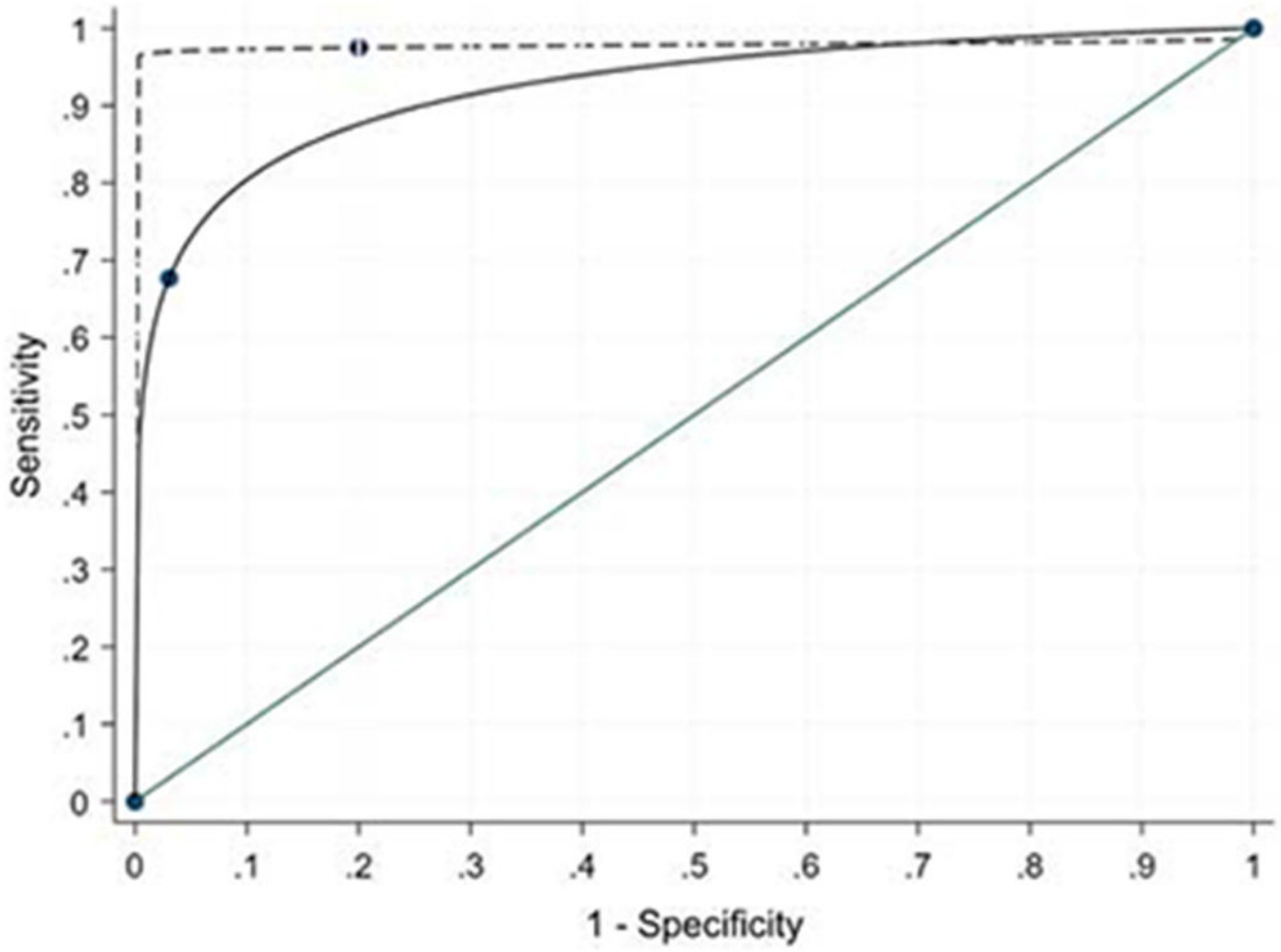

FIGURE 3.

Receiver operating characteristics curve for vertical cup-to-disc ratio (vCDR) measurements from smartphone-based camera reading and optical coherence tomography. Using optical coherence tomography—acquired vCDR as the gold standard, the sensitivity (*y*-axis) and 1-specificity (*x*-axis) use vCDR > 0.5 as cutoff for definition of a suspect. The solid line includes all eyes (N = 796): area under the receiver operating characteristics curve was 0.92 (95% confidence interval, 0.89-0.94). The dotted line only applies to eyes diagnosed with glaucoma or were glaucoma suspects (n = 85): area under the receiver operating characteristics curve was 0.98 (95% confidence interval, 0.78-1.0).

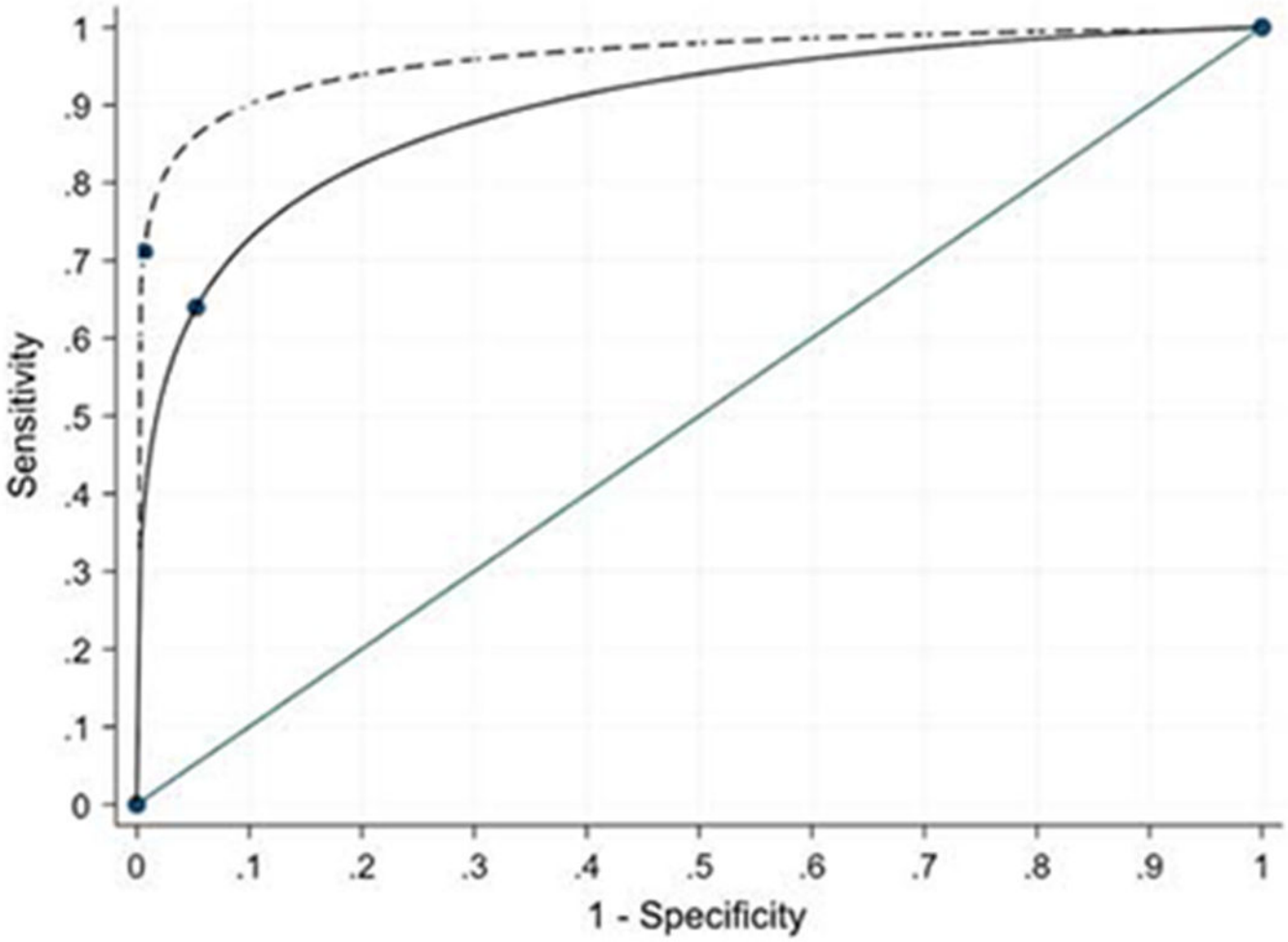

FIGURE 4.

Receiver operating characteristic curve for vertical cup-to-disc ratio (vCDR) measurements from smartphone-based camera reading and optical coherence tomography stratified by sex. Using optical coherence tomography—acquired vCDR as the gold standard, the sensitivity (*y*-axis) and 1-specificity (*x*-axis) use vCDR > 0.5 as cutoff for definition of a suspect. The solid line represents eyes from females (n = 422): area under the receiver operating characteristics curve was 0.89 (95% confidence interval, 0.86-0.93). The dotted line represents eyes from males (n = 364): area under the receiver operating characteristics curve was 0.96 (95% confidence interval, 0.93-0.99).

TABLE 1.

Study Participants (N = 467 Individuals)

	n (%)
Age [mean (SD)]	46.1 (18.1)
Age range (y)	
18-29	110 (23.5)
30-49	162 (34.7)
50-100	195 (41.8)
Female sex	251 (53.7)
Locality	
Urban	213 (45.6)
Peri-urban	8 (1.7)
Rural	241 (51.6)
Education	
None	13 (2.8)
Primary	153 (32.8)
Secondary	136 (29.1)
Tertiary	153 (32.8)
Occupation	
Subsistence farmer or manual laborer	195 (41.8)
Professional	139 (29.8)
Business	62 (13.3)
Student	50 (10.7)
Unemployed	4 (0.9)
Tribe	
Banyankore	345 (73.9)
Baganda	37 (7.9)
Bakiga	21 (4.5)
Others	64 (13.7)
Diagnoses (n = 796)	
Normal or allergic conjunctivitis or presbyopia	519 (65.2)
Dry eye syndrome	81 (10.2)
Primary open-angle glaucoma	72 (9.0)
Refractive error	47 (5.9)
Uveitis	31 (3.9)
Glaucoma suspect	13 (1.6)
Maculopathy	12 (1.5)
Postcataract surgery changes	11 (1.4)
Retinal vein occlusion	2 (0.3)
Macular edema	2 (0.3)
Optic neuritis or optic atrophy	2 (0.3)
Postpenetrating keratoplasty changes	2 (0.3)

	n (%)
Strabismus	2 (0.3)

TABLE 2.

Visual Acuity, Intraocular Pressure, Vertical Cup-to-disc Ratio (N = 796 Eyes)

	Right Eye (n = 403)	Left Eye (n = 393)
PVA (Snellen metric) [n (%)]		
6/5-6/12	318 (78.9)	318 (81.0)
6/18-6/60	72 (17.9)	63 (16.0)
6/75-3/60	4 (1.0)	4 (1.0)
< 3/60	9 (2.2)	8 (2.0)
Intraocular pressure (mm Hg)		
1.0st percentile	10	10
2.5th percentile	10	10
25.0th percentile	10	10
50.0th percentile	11	12
75.0th percentile	13	13
97.5th percentile	18	18
99.0th percentile	22	24
Vertical cup-to-disc ratio		
1.0st percentile	0.10	0.20
2.5th percentile	0.30	0.20
25.0th percentile	0.43	0.41
50.0th percentile	0.60	0.53
75.0th percentile	0.70	0.70
97.5th percentile	0.80	0.80
99.0th percentile	0.90	0.90

Vertical cup-to-disc ratios are acquired from optical coherence tomography and correlated with clinical examination.

PVA indicates presenting visual acuity.

TABLE 3.

Contingency Table Dichotomized as Eyes With vCDR > 0.5 and vCDR ≤ 0.5 (N = 796 Eyes)

	OCT-measured vCDR > 0.5	OCT-measured vCDR ≤ 0.5
Smartphone image-graded vCDR > 0.5	295	12
Smartphone image-grade vCDR ≤ 0.5	141	348

$\kappa = 0.63 \pm 0.034$ ($P < 0.001$). Sensitivity = 67.7%, specificity = 96.9%, positive predictive value = 96.4%, negative predictive value = 71.2%, positive likelihood ratio 22.1, negative likelihood ratio 0.33.

OCT indicates optical coherence tomography; vCDR, vertical cup-to-disc ratio.

TABLE 4.

Contingency Table Dichotomized as Eyes With vCDR > 0.5 and vCDR ≤ 0.5 Among Glaucoma and Glaucoma Suspects (N = 85 Eyes)

	OCT-measured vCDR > 0.5	OCT-measured vCDR ≤ 0.5
Smartphone image-graded vCDR > 0.5	78	1
Smartphone image-graded vCDR ≤ 0.5	2	4

$\kappa = 0.71 \pm 0.11$ ($P < 0.001$). Sensitivity = 97.5%, specificity = 80.0%, positive predictive value = 98.7%, negative predictive value = 66.7%, positive likelihood ratio 4.88, negative likelihood ratio 0.03.

OCT indicates optical coherence tomography; vCDR, vertical cup-to-disc ratio.

TABLE 5.

Performance of Paxos Stratified by Age and Sex (N = 796 Eyes)

	Age-specific [% (95% CI)]				Sex [% (95% CI)]		
	18-29 y	**30-49 y**	**≥ 50 y**	***P***	**Female**	**Male**	***P***
Prevalence of vCDR > 0.5	41.7 (34.6-49.1)	50.2 (44.0-56.4)	65.6 (60.3-70.6)	< 0.001	55.2 (50.3-60.0)	54.1 (48.8-59.3)	0.759
Sensitivity	57.7 (46.0-68.8)	68.4 (59.8-76.2)	70.4 (63.9-76.3)	0.004	63.9 (57.4-70.1)	71.1 (64.2-77.3)	0.032
Specificity	98.2 (93.5-99.8)	97.0 (92.4-99.2)	94.9 (89.2-98.1)	0.062	94.2 (89.8-97.1)	99.4 (96.7-100.0)	< 0.001
PPV	95.7 (85.5-99.5)	95.8 (89.6-98.8)	96.3 (92.2-98.6)	0.733	93.1 (88.0-96.5)	98.3 (96.1-100.0)	< 0.001
NPV	76.4 (68.5-83.2)	75.3 (68.1-81.6)	62.7 (55.1-69.9)	0.001	67.9 (61.9-73.5)	74.4 (68.2-80.0)	0.045
LR(+)	31.4 (7.86-125.8)	22.58 (8.54-59.68)	13.73 (6.27-30.07)	< 0.001	10.99 (6.14-19.7)	118.68 (16.78-839.38)	< 0.001
LR(−)	0.43 (0.33-0.56)	0.33 (0.25-0.42)	0.31 (0.25-0.38)	0.05	0.38 (0.32-0.46)	0.29 (0.23-0.36)	0.063

Prevalence of vCDR > 0.5 depended on optical coherence tomography measurements.

CI indicates confidence interval; LR(−), negative likelihood ratio; LR(+), positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics; vCDR, vertical cup-to-disc ratio.