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Original Article

Smartphone-enabled retinal arteriovenous imaging and correlation with coronary SYNTAX score

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ABSTRACT

Objective: To assess the feasibility of measurement of retinal arteriovenous (AV) ratio using a smartphone, we performed a comparative evaluation with fundus camera imaging and coronary SYNTAX score.
Method: Successive coronary artery disease (CAD) patients who underwent coronary angiography were recruited for smartphone retinal imaging. Following pupillary dilatation, fundus camera images and smartphone photography were performed. Video images were captured with a smartphone, edited and analysed. Retinal artery and vein size at 0.5 and 1 disc diameter (DD) were measured using DICOM software by two independent observers. Another observer calculated SYNTAX score.
Results: Analysable smartphone images were available in 91 (89.2%) of 102 patients. Tobacco use was found in 26%, hypertension in 54%, diabetes in 55%, and high LDL cholesterol in 50%. Median and 25–75 interquartile range (IQR) AV ratio at 0.5 and 1.0 DD, respectively, with smartphone were 0.48 (0.45–0.52) and 0.47 (0.45–0.52) and fundus camera were 0.48 (0.44–0.53) and 0.48 (0.45–0.53) (Spearman's correlation 0.80 and 0.79, $p < 0.001$). Coronary single vessel disease was in 21%, double vessel in 16%, triple vessel in 55%, normal angiogram in 8%, and median SYNTAX score was 18.0 (8.0–25.0). There was an inverse correlation of SYNTAX score with smartphone-derived AV ratio at 0.5 and 1.0 DD (rho −0.27,$p = 0.007$ and −0.26,$p = 0.009$) as well as with fundus camera (rho −0.37 and −0.38, $p < 0.001$). Trend-analysis showed an inverse association of smartphone AV ratio with increasing CAD (p_{trend} <0.001).
Conclusions: Smartphone-based retinal AV imaging is feasible and comparable to fundus-camera imaging. There is a significant inverse correlation with coronary angiographic severity.

1. Introduction

India has high prevalence of **c**oronary artery disease (CAD).[1] Major international guidelines recommend early CAD detection so that prevention strategies can be initiated.[2–4] For early detection of atherosclerosis, imaging technologies such as vascular ultrasound for measuring carotid-intima media thickness, sonographic plaque characterization in the carotid and other large arteries, coronary calcium estimation using electron beam computerised tomography (EBCT), and CT coronary angiography are helpful.[5,6]

Studies have reported that retinal arteriovenous (AV) imaging with reduced AV ratio is an important marker of cerebral and coronary atherosclerosis.[7–9] Ocular fundus cameras are used to evaluate the retinal vascular system. Significant correlations between retinal vascular alternations (branching, tortuosity and diameter) and various cardiac diseases, including coronary artery disease, heart failure, and conduction abnormalities were found in a comprehensive review of 42 studies using an ocular fundus camera (14 prospective, 26 cross-sectional and 2 retrospective).[9] Retinal AV ratio is also an important marker of hypertension and diabetes.[8,10] Artificial intelligence and machine learning tools are now available to classify retinal vascular changes.[11–14] Smartphone technology is

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rapidly evolving and has gained widespread acceptance for performing point-of-care evaluation of retinal diseases such as retinopathy of prematurity and diabetes.[15–17] There have been sporadic case reports of the use of hand-held smartphone devices in conjunction with an ophthalmoscope for fundus AV ratio assessment,[18,19] but it has not been systematically evaluated for CAD risk assessment. We performed a study to assess the feasibility of retinal AV imaging using a smartphone and compared the results with conventional fundus camera-based images and the extent of coronary artery disease on angiography.

2. Methods

The study protocol was approved by the institutional ethics committee (Government of India registration: CDSCO No. ECR/615/Inst/RJ/2014/RR-20) before the initiation of the study. Informed written consent was obtained from all the participants. Patient enrolment in the study is shown in a CONSORT diagram (Fig. 1). We approached 160 consecutive stable CAD patients hospitalised for coronary angiography from May to June 2022. Patients with unstable angina, recent acute myocardial infarction, moderate to severe congestive heart failure, recent stroke, post-coronary bypass surgery, uncontrolled hypertension, or diabetes, chronic renal or liver failure, unoperated cataract or known proliferative or severe retinopathy were excluded. After exclusions, informed consent was available from 112 patients. Of these, 10 patients were further excluded due to central cataract, significant diabetic retinopathy, or inadequate fundus images on routine ophthalmoscopic examination. Retinal imaging was performed either before or after the coronary angiography according to patient convenience.

Retinal imaging was performed following pupillary dilatation, first using a standard fundus camera and then with a smartphone in a single eye in each patient.[8,15] Fundus camera-enabled photography was performed using standard techniques. [8,9] To maintain uniformity, we used a commercially available smartphone in conjunction with a 20D lens for image magnification in all patients by a single investigator (HCA) (Fig. 2, upper panel). The technique was adapted from available literature.[19] A video image was captured and subsequently edited for the identification of the most suitable retinal image. All the images were saved and stored on a computer. Retinal artery and vein size were measured using DICOM software by 2 independent observers (HCA and HC) who were blinded to the results of AV ratio measurement and coronary angiographic findings (Fig. 1). Measurements of retinal AV ratio with smartphone and fundus-camera images were performed at 0.5 and 1 disc diameter (DD). Details are shown in the lower panel of Fig. 2. The first observer (HCA) independently analysed the fundus camera images, and findings were re-evaluated by the second observer (HC) in 10% of the images. The coefficient of variation was 5.0%. Coronary angiography results were available for all the 102 patients, and the SYNTAX score was calculated using standard techniques by an interventional cardiologist (CC) unaware of the findings of retinal imaging.

Statistical analyses: The data were entered into a MS Office Excel work-sheet. Data analyses were performed with SPSS software (Version 22.0). Categorical variables are reported as percent and continuous variables as median and interquartile (25–75th quartile) range (IQR). Medians were used as most of the AV ratio data as well as SYNTAX scores followed a skewed distribution (Fig. 3). A non-parametric Spearman's test was performed to correlate the AV ratio obtained with fundus camera and smartphone as well as to determine their association with the coronary SYNTAX score. Intergroup comparisons were performed using the Mantel-Haenszel χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. *P* values of <0.05 are considered significant.

3. Results

The clinical characteristics of the study participants (n = 102) are shown in Table 1. The mean age was 58.7 ± 9 years, and 83.3% were men. Low educational attainment was reported by 29.4%, and tobacco use by 26.5%. Abdominal obesity was in 56.9%, overweight/obesity (BMI >25 kg/m2) in 62.7%, hypertension in 53.9%, diabetes in 54.9%, and hypercholesterolemia (LDL cholesterol >100 mg/dl) in 50.0%.

Analysable images from smartphone imaging were available in 91 patients (89.2%) of the 102 patients whose fundus camera images were available. Representative images are shown in Fig. 2. Significant skewness and kurtosis were observed for the retinal AV ratio using both the technologies (Fig. 3). For the smartphone images, the medians and 25–75 interquartile range (IQR) AV ratio at 0.5 and 1.0 DD, respectively, were 0.48 (0.45–0.52) and 0.47 (0.45–0.52) and with fundus camera were 0.48 (0.44–0.53) and

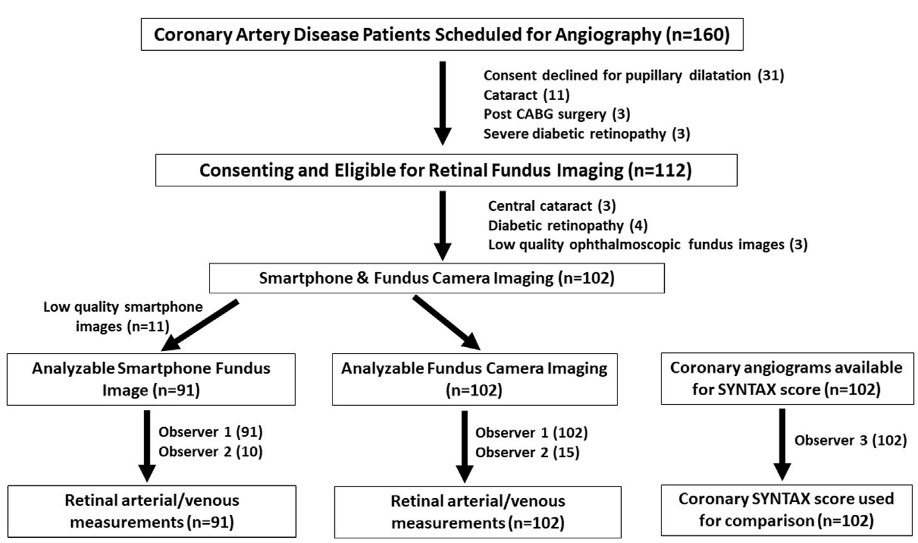

Fig. 1. Study flow chart and the CONSORT diagram.

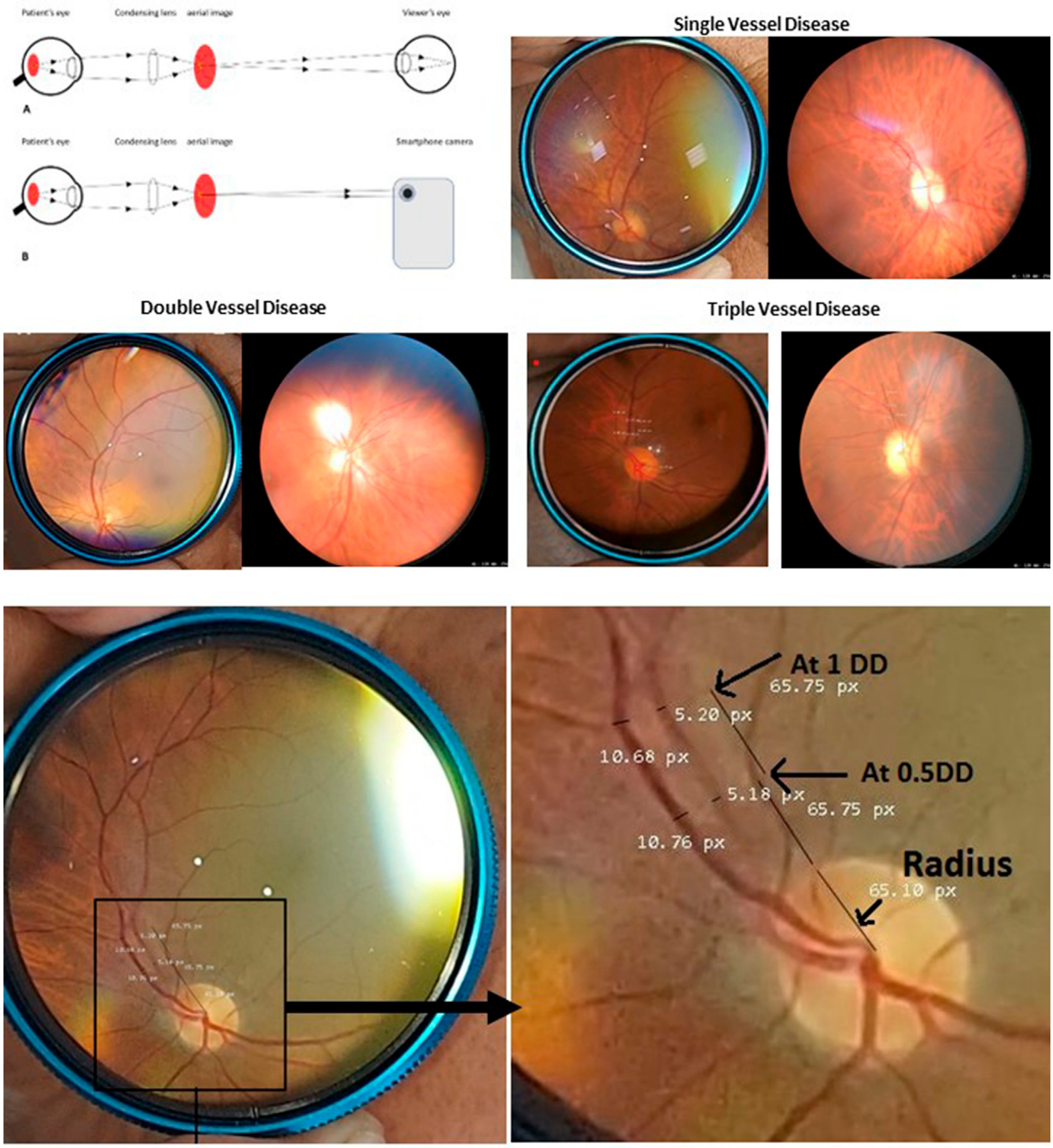

Fig. 2. The upper panel shows principles of fundus photography with a smartphone and representative images from the smartphone (images with lens margins) and fundus camera depicting images of single, double, and triple vessel coronary artery disease. The lower panel shows details of the measurement of retinal arterial and venous dimensions at 0.5 and 1.0 disc-diameter (DD) in a representative smartphone fundus image.

0.48 (0.45–0.53). Non-parametric Spearman's test showed significant inter-correlation of retinal AV ratio between the two technologies at 0.5 DD (rho = 0.80, $p < 0.001$) and 1.0 DD (rho = 0.79, $p < 0.001$).

Coronary angiography showed single vessel disease in 21 (20.6%), double vessel disease in 16 (15.7%), triple vessel disease in 56 (54.9%) and normal coronary angiogram in 9 (8.8%) (Table 1). The median SYNTAX score was 18.0 (IQR 8.0–25.0) and 51.0% patients had score of $\leq$18. The coronary SYNTAX score followed a skewed distribution (Fig. 3) with a skewness index of 0.20 $\pm$ 0.24 and a kurtosis of -0.58 ± 0.47. Scatter plots showing the association of smartphone and fundus camera derived AV ratio with coronary SYNTAX scores are shown in Fig. 4. Non-parametric correlation (rho) was calculated for assessing the association of retinal AV ratio with coronary SYNTAX score (Table 2). There is a significant inverse correlation of smartphone derived AV ratio with SYNTAX score at both 0.5 DD (rho = −0.27, $p = 0.007$) and 1.0 DD (rho = −0.26, $p = 0.009$). The correlation is slightly greater with fundus camera derived AV ratio at 0.5 DD (rho = −0.37, $p < 0.001$) and 1.0 DD (rho = −0.38, $p < 0.001$).

CAD patients have been categorised according to CAD severity (Table 3) into single-, double- and triple-vessel disease. Insignificant differences in various risk factors are observed in CAD categories, although there is slightly lower prevalence of hypertension

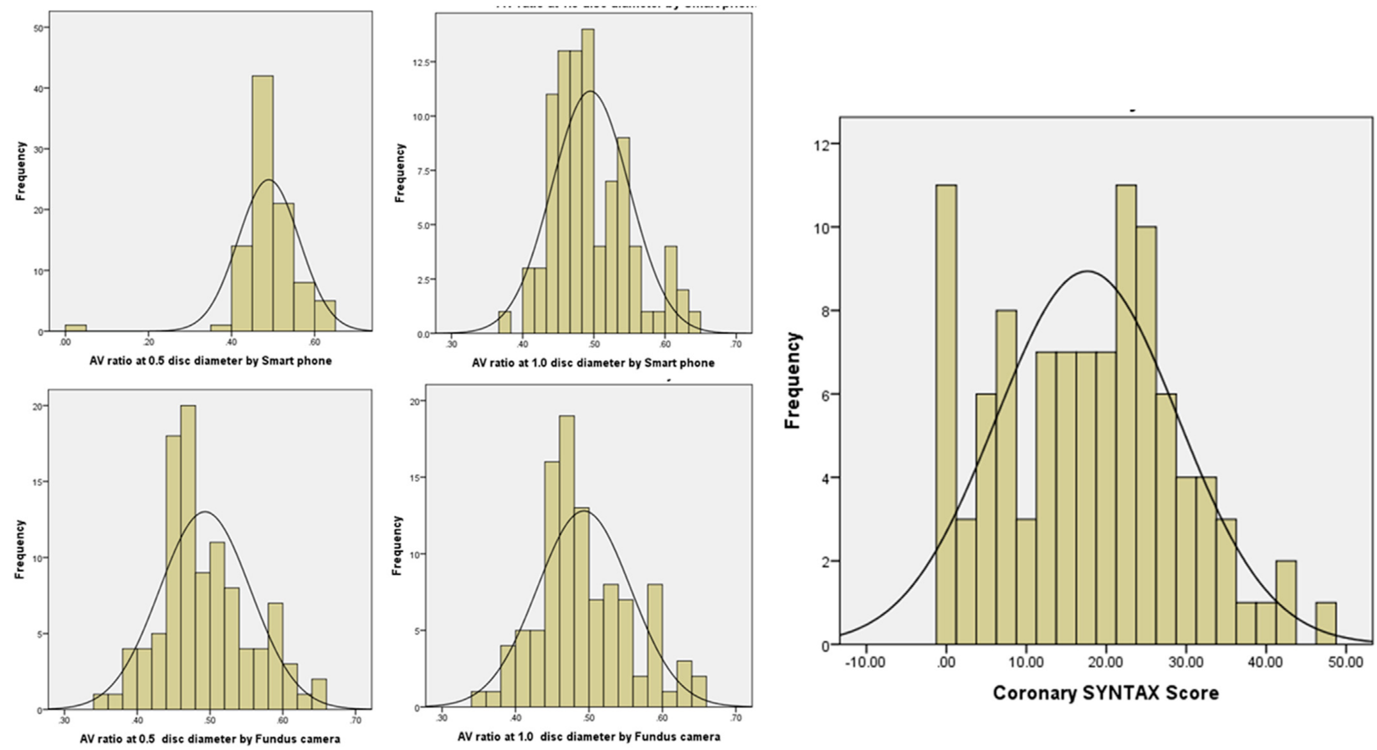

Fig. 3. Frequency distribution of retinal arteriovenous ratio measured using smart-phone imaging (n = 91, upper panels) and fundus camera imaging (n = 102, lower panel) at 0.5 and 1.0 disc-diameters showing a skewed distribution (Kurtosis −0.11 ± 0.47 to 20.72 ± 0.50). The Coronary SYNTAX score also has a skewed distribution (Kurtosis −0.58 ± 0.48).

Table 1
Clinical characteristic of the study participants.

	Total (N = 102)
Age (mean years)	58.7 ± 9.0
Men	85 (83.3)
Women	17 (16.7)
Low educational status (illiterate or < primary)	30 (29.4)
Urban	60 (58.8)
Rural	42 (41.2)
Any Tobacco	27 (26.5)
Waist circumference >90 men/80 women	58 (56.9)
Body mass index ≥25 kg/m^2	64 (62.7)
Alcohol	9 (8.8)
Hypertension	55 (53.9)
Diabetes	56 (54.9)
Hypothyroid	6 (5.9)
Previous stroke	5 (4.9)
Total cholesterol ≥200 mg/dl	20 (19.6)
HDL cholesterol <40 mg/dl men, <50 mg/dl women	73 (71.6)
Triglycerides ≥150 mg/dl	53 (52.0)
LDL cholesterol ≥100 mg/dl	51 (50.0)
Coronary angiography	
Single vessel disease	21 (20.6)
Double vessel disease	16 (15.7)
Triple vessel disease	56 (54.9)
Coronary SYNTAX score	
≤18	52 (51.0)
19-27	30 (29.4)
≥28	18 (17.6)

Numbers in parentheses are percent.
HDL high density lipoprotein; LDL low density lipoprotein.

and diabetes in normal angiography group. Coronary SYNTAX score shows graded increase with more severe CAD. There is a significant inverse correlation of retinal AV ratio with increasing CAD (Table 3).

Data were also stratified according to presence or absence of coronary risk factors-hypertension, diabetes, hypercholesterolemia, overweight/obesity and smoking/tobacco use. The median AV ratio using either smartphone or fundus camera imaging were not significantly different in various risk-factor categories (Supplementary Table 1).

4. Discussion

This study demonstrates the feasibility and utility of using smartphone-enabled imaging for calculating retinal arteriovenous dimensions. The results are comparable with conventional fundus camera-based retinal imaging. The study shows a significant inverse association of smartphone derived retinal AV ratio with coronary angiographic severity. Replication of these findings among various ethnic groups, men, women, and in different age groups using larger samples and prospective design is important before widespread use of this technology to non-invasively stratify CAD severity in asymptomatic and symptomatic patients.

Use of smartphone technology to evaluate the retinal AV dimension has been available for many years, but is not frequently done as it is labour intensive.[20,21] In the present study we performed video recording of retinal image with minimal discomfort to the patient and selected the most suitable image from the recorded image. The technology is simpler, quicker to learn, less invasive, has high patient compliance, observation of a larger retinal field at any one time is possible compared with routine ophthalmoscopy, pupillary dilation may not be required (although we used pupillary dilatation in all our patients), images can be saved for review later, and progression of disease can be monitored. Other strengths of the study are use of two methods of measuring retinal AV dimensions and the significant correlation of retinal AV

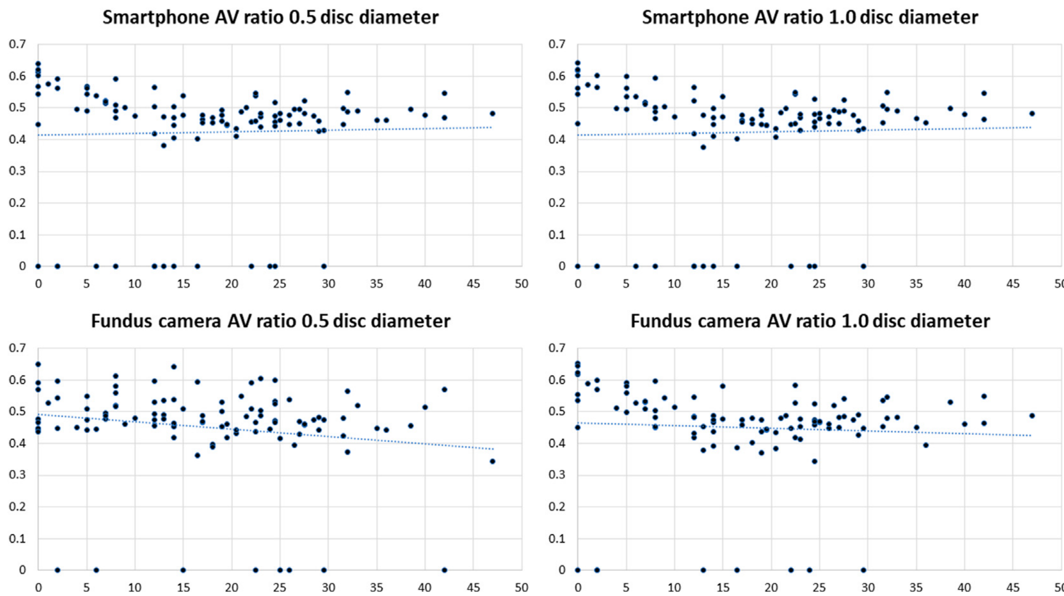

Fig. 4. Scatter plots showing the association of coronary SYNTAX score (*x*-axis) with smartphone and fundus camera derived arteriovenous (AV) ratio.

Table 2
Non-parametric correlation (Spearman's rho) of retinal vascular arteriovenous ratio with smartphone and fundus camera imaging with coronary angiographic SYNTAX score.

	Non-parametric correlation, Spearman's rho (*p* value)
Smartphone and fundus camera correlation	
0.5 disc diameter	0.800 (<0.001)
1.0 disc diameter	0.796 (<0.001)
Smart phone Imaging and SYNTAX score (n = 91)	
0.5 disc diameter	−0.267 (=0.007)
1.0 disc diameter	−0.257 (0.009)
Fundus camera imaging and SYNTAX score (n = 102)	
0.5 disc diameter	−0.369 (<0.001)
1.0 disc diameter	−0.381 (<0.001)

ratio with the extent of CAD using the gold-standard technique of coronary angiography.

Reduced retinal AV ratio is a known risk factor for coronary artery disease, and prospective studies have found significant association. In the Atherosclerosis Risk in Communities study, 9155 participants were followed for 16 years and it was reported that lower central retinal AV ratio, lower retinal arteriolar diameter, and higher central retinal venous diameter were associated with incident acute coronary syndrome in women but not in men.[7] Two other prospective studies reported that wider venular and narrower arteriolar diameters in both genders were associated with a higher incidence of acute coronary syndrome.[22,23] Systemic reviews have also reported a significant correlation of retinal microvascular changes and a reduced AV ratio with CAD.[7–9]

Imaging techniques are supplementing coronary risk assessment algorithms for more precise estimation of risk by visualisation of sub-clinical atherosclerosis in low and intermediate risk groups.[5,6,24] Traditional risk estimation tools estimate the risk of a first event using clinical data such as age, blood pressure, diabetes, smoking status, and cholesterol levels. However, there is inherent uncertainty in these tools and, therefore, there is substantial interest in improving existing tools by incorporating other factors.[5,24,25] Although existing imaging technologies provide

Table 3
Association of extent of coronary artery disease with risk factors and retinal vascular imaging.

	Normal (N = 9)	Single vessel (N = 21)	Double vessel (N = 16)	Triple vessel (N = 56)	X^2 for trend (*p* value)
Risk factors					
Tobacco use	1 (11.1)	4 (19.0)	4 (25.0)	18 (32.1)	0.107
Body mass index ≥25 kg/m^2	4 (44.4)	14 (66.7)	11 (68.8)	35 (62.5)	0.647
Hypertension	4 (44.4)	12 (57.1)	8 (50.1)	31 (55.4)	0.771
Diabetes	3 (33.3)	11 (52.4)	8 (50.1)	34 (60.7)	0.467
Cholesterol ≥200 mg/dl	2 (22.2)	5 (23.8)	5 (12.5)	11 (19.8)	0.750
HDL cholesterol: <40 mg/dl men, <50 mg/dl women	5 (55.6)	15 (71.4)	10 (62.5)	43 (76.8)	0.220
Triglycerides ≥150 mg/dl	7 (77.8)	10 (47.6)	10 (62.5)	26 (46.4)	0.195
LDL cholesterol ≥100 mg/dl	5 (55.6)	15 (71.4)	7 (43.8)	24 (42.9)	0.072
Coronary artery disease					
Coronary SYNTAX score (median, IQR)	0.0 (0.0–0.0)	7.0 (5.0–13.0)	16.7 (9.7–22.5)	24.2 (18.0–29.0)	<0.001
Retinal arteriovenous ratio					
Smart phone Imaging					
0.5 disc diameter (median, IQR)	0.60 (0.49–0.62)	0.54 (0.49–0.56)	0.50 (0.46–0.52)	0.47 (0.45–0.49)	<0.001
1.0 disc diameter (median, IQR)	0.61 (0.54–0.62)	0.54 (0.49–0.57)	0.49 (0.45–0.52)	0.47 (0.45–0.49)	<0.001
Fundus camera Imaging					
0.5 disc diameter (median, IQR)	0.61 (0.55–0.63)	0.51 (0.47–0.58)	0.49 (0.47–0.54)	0.46 (0.44–0.49)	<0.001
1.0 disc diameter (median, IQR)	0.62 (0.54–0.63)	0.51 (0.47–0.58)	0.49 (0.47–0.54)	0.46 (0.44–0.48)	<0.001

HDL high density lipoprotein; IQR interquartile range 25th-75th percentile; LDL low density lipoprotein.

incremental information regarding cardiovascular risk, they are cumbersome and expensive.[6] Machine learning models and artificial intelligence tools that combine conventional risk factors with imaging-based strategies may be more useful.[11–13] but needs ethnicity-specific risk factor data in view of varied proportionate attributable fractions in different populations.[26] Validation of such technologies also needs prospective evaluation and randomised clinical trials before they are widely implemented.[25,27]

Other limitations of the study include a small number of patients, controls without CAD, cross-sectional design of the study, and examination of one eye in each patient. It is likely that if we had used both eyes for obtaining data, better data granularity could have emerged, but that would only enhance the significance of the conclusions. Larger sample size and prospective studies to evaluate the sensitivity and specificity of this tool and comparison with clinical and imaging tools are needed. Most of the CAD patients in the study had associated cardiovascular risk factors that are known to influence retinal vasculature: hypertension, diabetes, smoking, and hypercholesterolemia.[8,10] However, this is a real-world study and finding CAD patients without risk factors is challenging. Furthermore, we could not find statistically significant differences in AV ratio in patients with or without these risk factors (Supplementary Table 1). Although we did not use machine learning tools, successful use of artificial intelligence algorithms in evaluation of diabetic retinopathy confirms the utility of this technology.[28]

In conclusion, this study suggests that smartphone-enabled retinal AV imaging is feasible and is comparable to fundus camera-based imaging. Although, the study shows that there is a significant inverse correlation of smartphone derived retinal AV ratio with coronary angiographic severity, use of this technology as a marker of CAD severity beyond usual risk factors needs larger studies. India has one of the highest penetrations of cell-phones in the world,[29] and this technology can potentially be widely implemented. However, prospective studies are needed to evaluate its association with CAD and assess clinical outcomes with use of this technology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- All the data are presented in the article. There are no additional data available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.11.005.

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