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Original Article

ORIGINAL ARTICLE

A deep learning system for retinal vessel calibre improves cardiovascular risk prediction in Asians with chronic kidney disease

Cynthia Ciwei Lim [1], Crystal Chong[2], Gavin Tan[2,3], Chieh Suai Tan[1], Carol Y. Cheung [4], Tien Y. Wong [1], Ching Yu Cheng[2,3] and Charumathi Sabanayagam[2,3]

[1]Department of Renal Medicine, Singapore General Hospital, Singapore, [2]Singapore Eye Research Institute, Singapore National Eye Center, Singapore, [3]Eye-ACP, Duke-NUS Medical School, Singapore and [4]Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China

Correspondence to: Charumathi Sabanayagam; E-mail: charumathi.sabanayagam@seri.com.sg

ABSTRACT

Background. Cardiovascular disease (CVD) and mortality is elevated in chronic kidney disease (CKD). Retinal vessel calibre in retinal photographs is associated with cardiovascular risk and automated measurements may aid CVD risk prediction.

Methods. Retrospective cohort study of 860 Chinese, Malay and Indian participants aged 40–80 years with CKD [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2] who attended the baseline visit (2004–2011) of the Singapore Epidemiology of Eye Diseases Study. Retinal vessel calibre measurements were obtained by a deep learning system (DLS). Incident CVD [non-fatal acute myocardial infarction (MI) and stroke, and death due to MI, stroke and other CVD] in those who were free of CVD at baseline was ascertained until 31 December 2019. Risk factors (established, kidney, and retinal features) were examined using Cox proportional hazards regression models. Model performance was assessed for discrimination, fit, and net reclassification improvement (NRI).

Results. Incident CVD occurred in 289 (33.6%) over mean follow-up of 9.3 (4.3) years. After adjusting for established cardiovascular risk factors, eGFR [adjusted HR 0.98 (95% CI: 0.97–0.99)] and retinal arteriolar narrowing [adjusted HR 1.40 (95% CI: 1.17–1.68)], but not venular dilation, were independent predictors for CVD in CKD. The addition of eGFR and retinal features to established cardiovascular risk factors improved model discrimination with significantly better fit and better risk prediction according to the low (<15%), intermediate (15–29.9%), and high (30% or more) risk categories (NRI 5.8%), and with higher risk thresholds (NRI 12.7%).

Conclusions. Retinal vessel calibre measurements by DLS were significantly associated with incident CVD independent of established CVD risk factors. Addition of kidney function and retinal vessel calibre parameters may improve CVD risk prediction among Asians with CKD.

Keywords: artificial intelligence, cardiovascular disease, chronic kidney disease, microvascular disease, risk prediction

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INTRODUCTION

Chronic kidney disease (CKD) and CKD-related mortality and disability-adjusted life years (DALYs) increased worldwide and especially in Asia [1, 2]. Its prevalence doubled between 1990 and 2019 so that more than 430 million people in Asia are now living with CKD [2]. The growing burden of CKD may be attributed to aging populations and greater frequency of metabolic risk factors such as diabetes and hypertension [1, 3]. These chronic metabolic conditions are also well-established risk factors for cardiovascular disease (CVD) [4], hence it is unsurprising that CVD is prevalent among individuals with CKD. Indeed, the risk of incident CVD was significantly higher in people with lower estimated glomerular filtration rate (eGFR), a measure of CKD severity [5, 6], and CKD (defined as eGFR 15-59 ml/min/1.73 m^2 with or without albuminuria) is recognized as a CVD risk enhancer [7]. CVD is the most common cause of death among individuals with CKD [8], and the risk of cardiovascular mortality increased with lower eGFR. In a large population-based study of 81 064 deaths in Canada, the age- and sex-adjusted proportion of patients who died from cardiovascular disease increased as eGFR decreased (33.3%, 37.1%, and 39.9% of patients with eGFR 45–59.9, 30–44.9, and 15–29.9 ml/min per 1.73 m^2, respectively) [8]. Thus, CVD can be considered a bigger threat to health in people with CKD than even end-stage kidney failure [9].

Accurate CVD risk stratification and prediction may help identify individuals with CKD who may benefit most from aggressive risk factor control, primary prevention interventions, or screening for occult disease. Although several cardiovascular risk scores based on factors such as age, gender, smoking status, diabetes, body mass index (BMI), lipid and blood pressure levels, and/or use of anti-hypertensive medications exist [10], there remains residual risk not accounted for by these established risk factors for macrovascular disease [5, 10], especially in CKD [11]. It is postulated that CVD can be driven by microvascular disease that is mediated or exacerbated by CKD [12]. In animal models, reduced kidney function was associated with coronary microvascular structural and functional changes [13–15]. Among individuals with CKD without overt obstructive coronary artery disease, lower coronary flow reserve (indicating more severe microvascular dysfunction) predicted left ventricular dysfunction and adverse cardiovascular outcomes [16]. Therefore, in CKD, retinal vessel changes may reflect microvascular disease that mediate CVD [9], beyond the contributions of the traditional risk factors to macrovascular disease [11]. Prior studies in predominantly Caucasian populations have explored the addition of expensive and/or invasive clinical parameters such as apolipoproteins, high-sensitivity C-reactive protein (hs-CRP), troponins, N-terminal prohormone B-type natriuretic peptide (NT-proBNP), carotid intima-media thickness, pulse wave velocity, and coronary or aortic calcification to improve cardiovascular risk prediction in the general population and in CKD cohorts [10, 17, 18]. Instead, retinal vessel changes are reflective of microvascular disease [19], and were associated with established cardiovascular risk factors (such as hypertension) and CVD in various disease conditions [19]. Indeed, retinal microvascular changes may be more predictive of cardiovascular risk in groups where the microvascular contribution to CVD is prominent, such as in diabetes [19], and also possibly CKD [16]. For example, the addition of flickering light-induced dynamic retinal vessel changes improved cardiovascular mortality risk prediction among haemodialysis patients [20]. Additionally, retinal vessel changes can be interrogated via non-invasive image acquisition. Recent advances in retinal photographic methods can quantify even subtle retinopathy and retinal-vessel calibre abnormalities [19], while artificial intelligence, especially deep learning systems (DLS) with convolutional neural networks, can overcome the need for highly-trained human assessment of retinal-vessel calibre from retinal photographs and thus reduce the technical expertise, manpower and time required. Our team developed a DLS to automatically quantify retinal vessel calibres called SIVA-DLS, which highly correlated with validated human measurements [21].

In this study, we aimed to assess the incremental value of retinal vessel calibres measured by SIVA-DLS in predicting incident CVD beyond established CVD risk factors in in a population-based cohort of multi-ethnic Asians with CKD.

MATERIALS AND METHODS

Study population

The Singapore Epidemiology of Eye Diseases (SEED) study is a large population-based prospective cohort study of Chinese, Malay, and Indian adults aged 40–80 years at enrollment that combined three independent studies: the Singapore Malay Eye Study (SiMES, 2004–2006), the Singapore Indian Eye Study (SINDI, 2007–2009), and the Singapore Chinese Eye Study (SCES, 2009–2011) [22]. Detailed methodology was previously reported by the Singapore Eye Research Institute [23–25]. Briefly, age-stratified random sampling from computer-generated random lists of individuals 40 to 80 years of age residing in the same geographical area in Singapore generated a sampling frame of 6350 Chinese, 5600 Malays, and 6350 Indians, then enrolled 10 033 participants comprising 3353 Chinese, 3280 Malays, and 3400 Indians [22]. All participants had data collection and retinal photography. For this analysis, we included 860 individuals with eGFR <60 ml/min/17.3 m^2 who (i) did not have self-reported or physician-diagnosed angina, myocardial infarction (MI) or stroke at baseline, and (ii) had complete information for all co-variates (Fig. 1).

Data collection

An interviewer-administered questionnaire was used to collect participants' socio-demographic and medical history as previously described [26]. Diabetes mellitus was defined in the presence of random serum glucose ≥11.1 mmol/L, glycosylated haemoglobin (HbA1c) ≥6.5%, self-reported physician-diagnosed diabetes or use of glucose-lowering treatment [27]. Hypertension was defined in the presence of systolic blood pressure (BP) ≥140 mmHg, diastolic ≥90 mmHg, self-reported physician-diagnosed hypertension or use of blood-pressure lowering therapy. Non-fasting serum lipid, HbA1c, and creatinine were evaluated. Serum creatinine was measured using an enzymatic method calibrated to the National Institute of Standard and Technology (NIST) Liquid Chromatography Isotope Dilution Mass Spectrometry (LC-IDMS) method [22]. eGFR was calculated using the Chronic Kidney Disease Epidemiology study (CKD EPI) equation [28]. Laboratory investigations were conducted at hospitals accredited by the College of American Pathologists.

Assessment of retinal vascular parameters

After pupil dilation, two-field color photographs [Early Treatment for Diabetic Retinopathy Study (ETDRS) field 1, centered on the optic disc; field 2, centered on the fovea] were obtained from each eye of all participants using a digital retinal camera

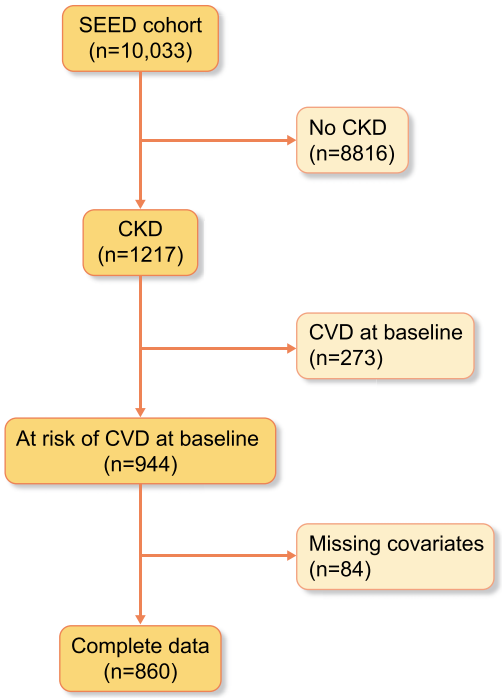

Figure 1: Participants selection flowchart.

(Canon CR-1 Mark-II Non-mydriatic Digital Retinal Camera; Canon, Tokyo, Japan). Retinopathy was present if any characteristic lesion including microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels were seen. Retinal arteriolar and venular calibers [central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively] were assessed by (i) human measurement and (ii) calculated automatically by SIVA-DLS at two regions: one from 0.5 to 1.0-disc diameters away from the disc margin (zone B: $CRAE_B$ and $CRVE_B$) and one from 0.5 to 2.0-disc diameters away from the disc margin (zone C: $CRAE_C$ and $CRVE_C$), as shown in Fig. 2. SIVA-DLS was developed and validated in several international datasets to specifically perform fully automated retinal-vessel calibre measurements from retinal photographs [21]. In addition to the usual assessment of retinal vessels within zone B, a larger area that included more vessels at zone C was assessed for a more representative sampling of retinal vascular calibre [29]. The DLS had previously showed high agreement (intraclass correlation coefficients between 0.82 and 0.95) with expert human graders for retinal vessel calibre measurements and performed comparably or better than expert human graders in identifying retinal abnormalities associated with CVD risk factors [21]. Participants gave written informed consent before enrolment. The study was conducted according to the Declaration of Helsinki Sixth Revision (2008) and approved by the Singapore Eye Research Institute Review Board and the SingHealth Centralised Institutional Review Board.

Outcome definition and ascertainment

The primary outcome was incident CVD defined as fatal and non-fatal myocardial infarct (MI), stroke and other CVD. Secondary outcomes were (i) stroke and stroke-related mortality, (ii) MI and MI-related mortality.

MI was defined as either (i) definitive or clinical MI; (ii) death cases signed up by pathologists or physicians as MI, with or without necropsy done. MI was identified by linkage with the Singapore Myocardial Infarction Registry (SMIR), a nation-wide registry under the purview of the National Registry of Diseases Office (NRDO). The epidemiological data in SMIR included all MI diagnosed and coded with International Classification of Diseases 9th Revision (ICD-9) 410 in all hospitals, thus data capture is estimated to be 100%. Stroke data was obtained from the Singapore Stroke Registry gathered from medical claims records and case finding from public hospital electronic medical records using ICD-9 codes 430 to 437, while excluding 432.1 and 435 (subdural hemorrhage, transient cerebral ischemia, respectively). Data capture is estimated to be 95% as cases from private hospitals were not included. Cardiovascular mortality was ascertained by linkage with the Registry of Births and Deaths for death due to cardiovascular causes that included acute myocardial infarction, coronary heart disease, hypertensive and other heart disease, heart failure, and stroke (Table S1, see online supplementary material). It is mandatory to report all deaths in Singapore, thus this registry is 100% complete in recording all reported deaths.

To assess the secondary outcomes, we excluded participants who had cardiovascular events other than the secondary outcome of interest (Table S2, see online supplementary material). All outcomes were censored at death or 31 December 2019.

Statistical analysis

Statistical analyses were performed using STATA statistical software (Version 14.1, StataCorp, College Station, TX, USA). Categorical data were reported as number (percentage) and continuous data presented as mean (standard deviation). Demographic and clinical characteristics at baseline of those who had incident CVD and those who did not were compared using *t*-test or chi-square test for continuous and categorical variables, respectively. Established risk factors (age, gender, ethnicity, body mass index, total cholesterol, high density lipoprotein (HDL)-cholesterol, smoking status, systolic BP, HbA1c, and use of blood pressure-lowering medication) [30] were included in Model 1, while kidney function (as an ASCVD risk enhancer [7]) and retinal features were added in a series of multi-variable models and assessed using Cox proportional-hazards regression. Discrimination was assessed using the receiver operating characteristic (ROC) curve and area under the receiver operating curve (AUC) [31]. The Akaike Information Criterion (AIC) was computed to compare the goodness of fit between the various models after accounting for model complexity, with a difference in AIC >10 considered to be significant [32]. We then performed (i) subgroup analyses by gender, ethnicity, diabetes status, and severity of kidney disease for the models that included established cardiovascular risk factors, kidney function, and retinal features, (ii) sensitivity analyses in (a) participants with retinal vessel caliber assessment by both DLS and expert human graders and (b) participants with albuminuria results and (iii) supplementary analysis evaluating the associations between the incident CVD and retinal vessel calibres assessed by both human measurements and DLS.

The improvement in risk prediction by addition of eGFR and retinal vascular parameters to established cardiovascular risk factors was assessed by net reclassification improvement (NRI). The NRI_e is the net proportion of events assigned a higher risk category, while the NRI_{ne} is the net proportion of non-events assigned a lower risk category. While the American College of

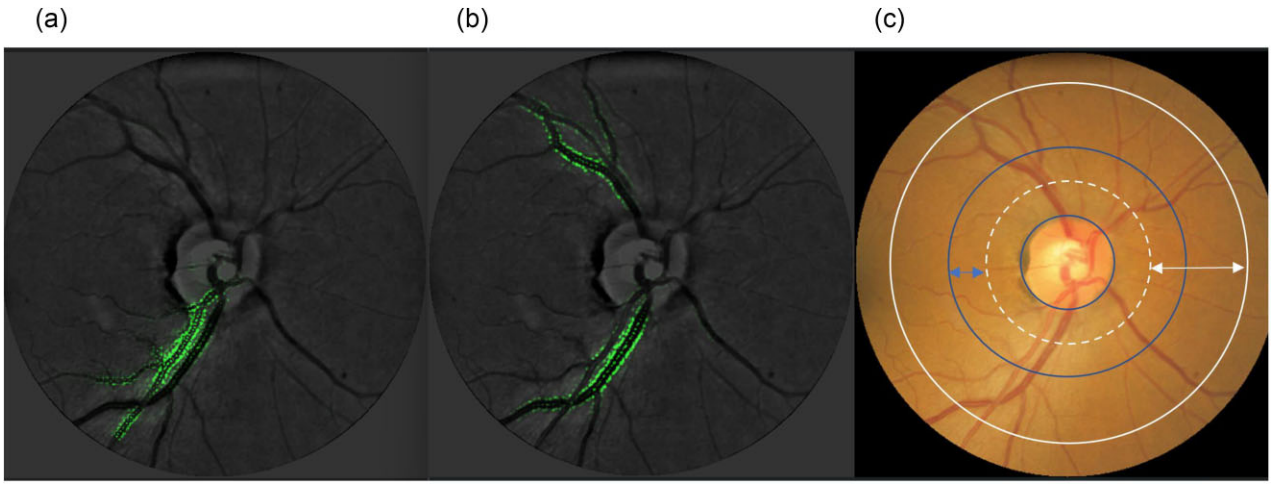

Figure 2: Heat maps for (**a**) central retinal arteriolar equivalent (CRAE) and (**b**) central retinal venular equivalent (CRVE) were generated by SIVA-DLS using integrated gradients at selected layers of the neural network to show features identified by the predicted attributions (with positive attributions indicated by the green dots), based on (**c**) retinal image captured by digital camera labelled with Zone B (0.5 to 1.0-disc diameters away from the disc margin, between dashed white line and solid blue line as shown by blue arrow) and Zone C (0.5 to 2.0-disc diameters away from the disc margin, between dashed white line and solid white line as shown by white arrow).

Cardiology (ACC) and American Heart Association (AHA) guideline defined high cardiovascular risk as 20% or greater at 10 years [7], the World Health Organization (WHO)/International Society of Hypertension (ISH) suggested that a risk cut-off of 30% [33], and our previous study noted that incident CVD occurred in 15–30% in Asians with kidney disease [5]. Thus, the risk categories were defined as low (risk <15%), intermediate (15–29.9%) and high (30% or more), and according to the observed risk tertiles.

SEED was conducted in accordance with the Declaration of Helsinki and was approved by the SingHealth Centralised Institutional Review Board (2018/2717, 2018/2921, 2012/487/A, 2015/2279, 2018/2006, 2018/2594, 2018/2570). Informed consent was obtained from all participants.

RESULTS

Table 1 showed the characteristics of 860 participants with CKD without CVD at baseline. The mean age was 67.7 (8.8) years and eGFR was 47.4 (11.8) ml/min/1.73 m^2. Most (783 participants, 91.0%) had eGFR between 30–59.9 ml/min/1.73 m^2 (CKD Stage G3), while 49 (5.7%) and 28 (3.3%) had eGFR between 15–29.9 ml/min/1.73 m^2 (CKD Stage G4) and <15 ml/min/1.73 m^2 (CKD Stage G5), respectively. Established cardiovascular risks such as older age, diabetes, hypertension, and higher BMI were frequent. Detailed characteristics of the three cohorts (SiMES, SINDI, and SCES) are further described in Table S3 (see online supplementary material). CRAE and CRVE in Zones B and C were similar (Table 1; Fig. S1, see online supplementary material). CRAE and CRVE were not significantly different between the groups with and without (i) diabetes, (ii) eGFR <45 ml/min/1.73 m^2, and (iii) albuminuria (Fig. S2a–S2c, see online supplementary material).

Incident CVD occurred in 289 (33.6%) over mean follow-up of 9.3 (4.3) years. Incident CVD occurred in 33.1%, 32.7%, and 50.0% of participants with CKD Stage G3, G4, and G5, respectively. Table 1 showed that those with incident CVD were significantly older, more likely to be Malay, current smokers, and have diabetes and retinopathy. They also had significantly higher systolic BP, total cholesterol, low density lipoprotein (LDL)-cholesterol, and HbA1c, but lower eGFR and narrower central retinal arterioles (at both zones B and C), than those without incident CVD.

Multivariate Cox regression in Table 2 noted that older age, Indian ethnicity, current smoking, higher systolic BP, and higher HbA1c independently associated with incident CVD, while sex, BMI, total cholesterol, HDL-cholesterol, and use of BP-lowering medications were not (Model 1). Model 2 additionally included eGFR and Models 3 and 4 further included both kidney and retinal features at Zone B and Zone C, respectively. After adjusting for established cardiovascular risk factors, eGFR [adjusted HR 0.98 (95% CI: 0.97–0.99) in Models 3 and 4] and smaller CRAE [adjusted HR 1.40 (95% CI: 1.17–1.68) in Model 3 and 1.41 (1.17–1.69) in Model 4], were independently associated with CVD. $CRVE_B$ and $CRVE_C$ were not associated with incident CVD. In subgroup analyses (Fig. 3), like the main analyses, smaller CRAE remained strongly associated with incident CVD in diabetes, male, female, Malay, Indian, CKD Stage G3A, and CKD Stage G3B or worse.

Sensitivity analysis for 843 participants with complete caliber measurements by both DLS and human graders were performed (Table 3). The associations between incident CVD and retinal features at Zone B assessed by DLS and expert human graders were similar in both magnitude and direction. Smaller CRAE, but not CRVE, measured by both expert human graders and DLS were independently associated with incident CVD in the multivariable model that included kidney and retinal parameters.

Table S4 (see online supplementary material) showed the addition of albuminuria to the kidney-enhanced Cox regression model for 496 participants with albuminuria data. After adjusting for the established cardiovascular risk factors and eGFR, albuminuria was not independently associated with incident CVD (Model 2). Despite the addition of albuminuria to models that included established cardiovascular risk factors, kidney function and retinal features (Model 3 and 4), eGFR and smaller CRAE were independently associated with CVD.

Table 2 compared the model that used established risk factors [age, gender, ethnicity, body mass index, total cholesterol, high density lipoprotein (HDL)-cholesterol, smoking status, systolic BP, HbA1c, and use of blood pressure-lowering medication]

Table 1: Sociodemographic and clinical characteristics of study cohort.

Characteristics	All participants ($n = 860$)	Incident CVD ($n = 289$)	No Incident CVD ($n = 571$)	*P* value*
Age, mean (SD), years	67.70 (8.81)	69.45 (8.64)	66.82 (8.77)	<0.001
Ethnicity, *n* (%)				
Chinese	171 (19.9)	38 (13.1)	133 (23.3)	0.002
Malay	510 (59.3)	182 (63.0)	328 (57.4)	
Indian	179 (20.8)	69 (23.9)	110 (19.3)	
Female sex, *n* (%)	412 (47.9)	128 (44.3)	284 (49.7)	0.150
BMI	26.23 (4.68)	26.02 (4.75)	26.34 (4.65)	0.346
Current smoking, yes (%)	105 (12.2)	52 (18.0)	53 (9.3)	<0.001
Diabetes mellitus, yes (%)	381 (44.3)	154 (53.3)	227 (39.8)	<0.001
Hypertension, yes (%)	770 (89.7)	267 (92.4)	503 (88.4)	0.089
Systolic BP, mean (SD), mmHg	151.96 (24.32)	157.36 (23.81)	149.23 (24.14)	<0.001
Diastolic BP, mean (SD), mmHg	79.02 (11.40)	80.03 (11.97)	78.52 (11.07)	0.073
Total cholesterol, mean (SD), mmol/L	5.51 (1.31)	5.65 (1.34)	5.44 (1.28)	0.024
HDL-cholesterol, mean (SD), mmol/L	1.25 (0.36)	1.22 (0.34)	1.26 (0.36)	0.079
LDL-cholesterol, mean (SD), mmol/L	3.34 (1.07)	3.47 (1.10)	3.28 (1.05)	0.015
HbA1c, % (mmol/mol)	6.62 (1.49)	6.87 (1.74)	6.50 (1.33)	0.001
Glucose-lowering medication, yes (%)	243 (28.4)	97 (33.8)	146 (25.6)	0.015
BP-lowering medication, yes (%)	492 (57.2)	169 (58.5)	323 (56.6)	0.644
Lipid-lowering medication, yes (%)	296 (34.8)	95 (33.6)	201 (35.4)	0.654
eGFR, mean (SD), mL/min/1.73 m^2	47.37 (11.79)	45.72 (12.55)	48.21 (11.30)	0.005
Presence of retinopathy, yes	120 (14.0)	54 (18.7)	66 (11.6)	0.006
$CRAE_B$, mean (SD), μm	132.47 (13.93)	129.99 (15.07)	133.72 (13.15)	<0.001
$CRVE_B$, mean (SD), μm	190.20 (26.33)	188.00 (30.75)	191.32 (23.74)	0.108
$CRAE_C$, mean (SD), μm	131.68 (15.43)	128.96 (17.43)	133.06 (14.14)	<0.001
$CRVE_C$, mean (SD), μm	195.35 (24.17)	193.34 (28.66)	196.37 (21.49)	0.114
Follow up duration, years	9.31 (4.33)	6.19 (3.77)	10.89 (3.68)	<0.001

BP: blood pressure; $CRAE_B$: central retinal arteriolar equivalent at $Zone_B$; $CRVE_B$: central retinal venular equivalent at $Zone_B$; $CRAE_C$: central retinal arteriolar equivalent at $Zone_C$; $CRVE_C$: central retinal venular equivalent at $Zone_C$; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; Hba1c: glycated haemoglobin (A1c); HDL: high density lipoprotein; SD: standard deviation.

*Bivariate comparison of participants who had incident CVD and participants who did not have incident CVD

[30], and the models with kidney and retinal parameters. The addition of eGFR to established cardiovascular risk factors in the kidney-enhanced model (Model 2) improved model discrimination with significantly lower AIC and hence better-fit. Addition of retinal features such as retinopathy, CRAE and CRVE (Models 3 and 4) further improved discrimination with better-fit, compared to the established-risk model (Fig. 4) and the kidney-enhanced model (Table 2). Tables S5a–c and S6a–c (see online supplementary material) assessed reclassification for low- (<15%), intermediate- (15 to 29.9%) and high-risk (≥30%) categories. The addition of kidney and retinal features to established cardiovascular risk factors resulted in NRI of 5.9% (P <0.001) regardless of the retinal zone assessed: Model 3 (Table S5a, see online supplementary material) and Model 4 (Table S6a, see online supplementary material) both reclassified more patients who did not have the event to lower risk categories (NRI_{ne} were 6.7% and 7.2%, respectively). The addition of retinal features at Zones B and C (without eGFR) to established cardiovascular risk factors resulted in NRI of 2.8% ($P = 0.04$; Table S5b, see online supplementary material) and 2.2% ($P = 0.10$; Table S6b, see online supplementary material), respectively, while the addition of retinal features at Zone B and C to established cardiovascular risk factors and eGFR did not alter NRI significantly (Tables S5c and S6c, respectively, see online supplementary material). When higher risk thresholds were used (0–48.7%, 48.8–63.0% and ≥63.1%), the addition of kidney and retinal features to established cardiovascular risk factors resulted in greater NRIs (12.7% for Model 3 in Table S7 and 10.3% for Model 4 in Table S8, see online supplementary material), suggesting better model calibration for patients with very high risk of incident CVD.

For the secondary outcomes, fatal and non-fatal stroke and MI occurred in 107 participants (15.8%) and 160 participants (21.9%), respectively. Multivariate Cox regression in Table S9 (see online supplementary material) noted that older age, Indian ethnicity, current smoking, higher systolic BP and HbA1c, smaller CRAE and larger CRVE were independently associated with fatal and non-fatal stroke in CKD. In contrast, lower eGFR but not CRVE, in addition to older age, Indian ethnicity, current smoking, higher systolic BP and HbA1c, and smaller CRAE, were independently associated with incident fatal and non-fatal MI in CKD (Table S10, see online supplementary material). The risk models for incident fatal and non-fatal stroke (Fig.S3, see online supplementary material) and MI (Fig. S4, see online supplementary material) that added kidney function and retinal vessel calibre to established cardiovascular risk factors had better discrimination for the outcomes than models with only established cardiovascular risk factors.

DISCUSSION

In a multi-ethnic Asian population with CKD, retinal arteriolar narrowing was consistently associated with incident CVD, MI and stroke, and venular dilation independently predicted for stroke. It was previously thought that associations between retinal vessel calibre changes and cardiovascular risk factors may explain the predictive role of retinal vessel calibre for CVD, as

Table 2: Relationship of established risk factors, serum biomarkers and retinal microvascular measures and the risk of incident cardiovascular disease.

	Participants, N = 860 Incident cardiovascular events, *n* = 289 (33.6%)			
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Age per 1 year increase	1.05 (1.03–1.06)	1.05 (1.03–1.06)	1.05 (1.03–1.06)	1.05 (1.03–1.06)
Female sex, yes	0.81 (0.62–1.06)	0.81 (0.62–1.06)	0.86 (0.65–1.13)	0.84 (0.64–1.10)
Ethnicity				
Malay	Reference	Reference	Reference	Reference
Indian	1.66 (1.21–2.26)	1.86 (1.36–2.56)	1.62 (1.16–2.26)	1.69 (1.21–2.36)
Chinese	0.96 (0.65–1.43)	1.04 (0.70–1.54)	0.94 (0.63–1.39)	0.99 (0.67–1.47)
BMI	0.99 (0.96–1.01)	0.98 (0.96–1.01)	0.98 (0.95–1.01)	0.98 (0.95–1.01)
Total cholesterol per 1 mmol/L increase	1.07 (0.97–1.18)	1.09 (0.99–1.20)	1.08 (0.98–1.20)	1.08 (0.98–1.19)
HDL cholesterol per mmol/L increase	0.87 (0.59–1.28)	0.95 (0.65–1.40)	0.96 (0.65–1.41)	0.97 (0.66–1.42)
Current smoking	2.27 (1.62–3.19)	2.51 (1.78–3.54)	2.36 (1.67–3.32)	2.38 (1.69–3.35)
Systolic blood pressure per 1 mmHg increase	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.01 (1.01–1.02)
HbA1c, per 1% increase	1.19 (1.11–1.28)	1.18 (1.10–1.27)	1.16 (1.07–1.26)	1.16 (1.07–1.26)
BP-lowering medication, yes	1.27 (0.98–1.64)	1.16 (0.90–1.50)	1.20 (0.92–1.55)	1.16 (0.89–1.50)
eGFR per 1 mL/min/1.73 m^2 increase		0.97 (0.96–0.98)	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Presence of retinopathy, yes			1.24 (0.85–1.81)	1.24 (0.85–1.81)
$CRAE_B$ [a]			1.40 (1.17–1.68)	
$CRVE_B$ [b]			1.15 (0.96–1.37)	
$CRAE_C$ [a]				1.41 (1.17–1.69)
$CRVE_C$ [b]				1.17 (0.98–1.41)
AUC	0.720 (0.680–0.758)	0.743 (0.704–0.779)	0.760 (0.722–0.797)	0.760 (0.722–0.797)
Akaike Information Criterion	3572	3550	3538	3538

[a]per standard deviation decrease in arteriolar caliber.
[b]per standard deviation increase in venular caliber.
CI: confidence interval; $CRAE_B$: central retinal arteriolar equivalent at $Zone_B$; $CRAE_C$: central retinal arteriolar equivalent at $Zone_C$; $CRVE_B$: central retinal venular equivalent at $Zone_B$; $CRVE_C$: central retinal venular equivalent at $Zone_C$; eGFR: estimated glomerular filtration rate; Hba1c: glycated haemoglobin; HDL: high density lipoprotein; HR: hazard ratio.
Model 1: Established risk factors.
Model 2: Established risk factors + eGFR.
Model 3: Model 2 + retinal features (presence of retinopathy, retinal arteriolar and retinal venular calibers assessed by SIVA-DLS at Zone B).
Model 4: Model 2 + retinal features (presence of retinopathy, retinal arteriolar and retinal venular calibers assessed by SIVA-DLS at Zone C).

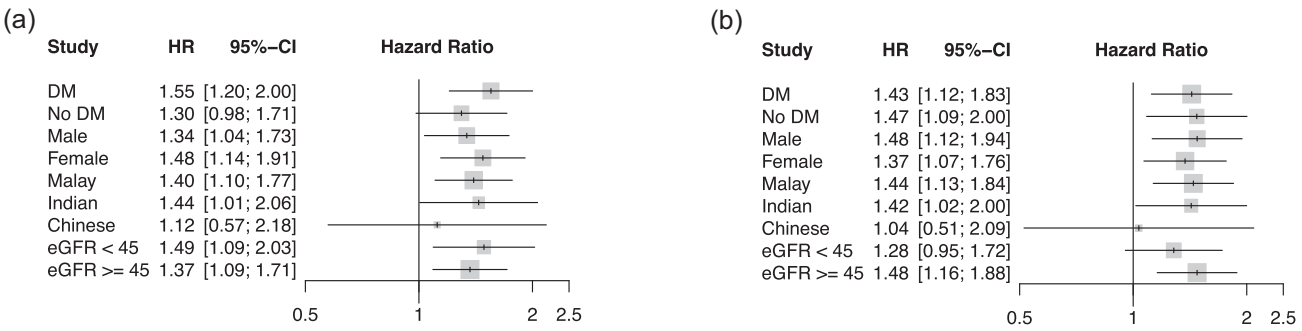

Figure 3: Forest Plots showing hazard ratio (HR) and 95% confidence interval (CI) of (**a**) $CRAE_B$ and (**b**) CRAEc for incident cardiovascular disease.

retinal arteriolar narrowing was associated with hypertension [34, 35], large arterial function and structure [36]; while venular dilation was associated with hypertension [35], atherosclerosis [37], hypercholesterolemia [37], and hyperglycemia [38]. Our study found that retinal arteriolar and venular calibres assessed by SIVA-DLS were significantly associated with incident CVD in CKD, even after accounting for established CVD risk factors and kidney function. The study findings support the hypothesis that retinal vessel changes may reflect microvascular disease that mediate CVD in CKD [9], beyond the predictive value of established risk factors that are usually involved in the pathogenesis of macrovascular disease. These findings are consistent with known literature, including a recently published systematic review of 42 publications focusing on acute coronary syndrome and coronary artery disease [39], that linked retinal vessel parameters with CVD risk in various disease cohorts [19, 39].

Other factors associated with CVD were older age, Indian ethnicity, current smoking, higher systolic BP, higher HbA1c, and lower eGFR. Age, smoking, systolic BP, and diabetes status or control were similarly featured in several cardiovascular risk scores such as the Framingham score [30], ACC/AHA Atherosclerotic

Table 3: Associations between incident CVD and retinal vessel caliber assessed by expert human graders and DLS.

	Patients with complete retinal caliber measurements, N = 843 Incident CVD, *n* = 284 (33.7%) Adjusted HR (95% CI) in multivariable model[c]
[a]Human-CRAE$_B$ per SD decrease	1.31 (1.13–1.51)
[b]DLS-CRAE$_B$ per SD decrease	1.44 (1.20–1.73)
[a]Human-CRVE$_B$ per SD increase	1.17 (1.00–1.37)
[b]DLS-CRVE$_B$ per SD increase	1.19 (1.00–1.42)

CI: confidence interval; CRAE$_B$: central retinal arteriolar equivalent at Zone$_B$; CRVE$_B$: central retinal venular equivalent at Zone$_B$; HR: hazard ratio; s.d.: standard deviation.
[a]Retinal vessel caliber assessed by expert human grader.
[b]Retinal vessel caliber calculated by SIVA-DLS.
[c]Multivariable model adjusted for established risk factors + eGFR + retinal features (presence of retinopathy, retinal arteriolar calibre and retinal venular calibre).

Cardiovascular Disease (ASCVD) risk estimator [7, 40], WHO/ISH risk [33] and SCORE [41], while kidney function was predictive of CVD and mortality [5, 6, 17]. Although albuminuria may be a cardiovascular risk indicator [5, 6, 12], its addition to our models did not significantly alter the predictive value of eGFR and CRAE on incident CVD. Albuminuria has been postulated to be a manifestation of systemic microvascular disease driven by inflammatory endothelial injury [12]. In such a hypothesis, the retinal vascular parameters used in our models would provide direct assessment of the severity of microvascular disease and thus obviate the use of albuminuria as an indirect indicator of microvascular disease. Notably, in this cohort with reduced eGFR and therefore possibly more severe or advanced glomerular microvascular disease and sclerosis, retinal vessel calibres were not significantly different regardless of the presence of albuminuria. Our findings thus support the 2019 ACC/AHA clinical practice guideline on the primary prevention of cardiovascular disease that recognized CKD in the form of reduced eGFR (15–59 ml/min/1.73 m^2, regardless of albuminuria) as an ASCVD risk enhancer [7].

While kidney disease was recognized as a risk modifier, most cardiovascular risk prediction models did not include kidney function [7, 33, 40, 41], hence the impact of kidney function on cardiovascular risk prediction was not quantified. In this study reported according to the STROBE checklist (Table S11, see online supplementary material), the addition of kidney function and SIVA-DLS to established cardiovascular risk factors improved the prediction of incident CVD among Asians with CKD, with increased predicted risk for events and reduced predicted risks for non-events. The incremental improvement in prediction by our model was especially marked at higher risk thresholds. Prior studies had evaluated a variety of biomarkers and imaging for cardiovascular risk prediction in the general population and in CKD [10, 17, 18]. However, model discrimination was only marginally increased in when multiple expensive novel biomarkers, compared to eGFR and UACR, were added to standard laboratory tests [17], thus raising concerns about the

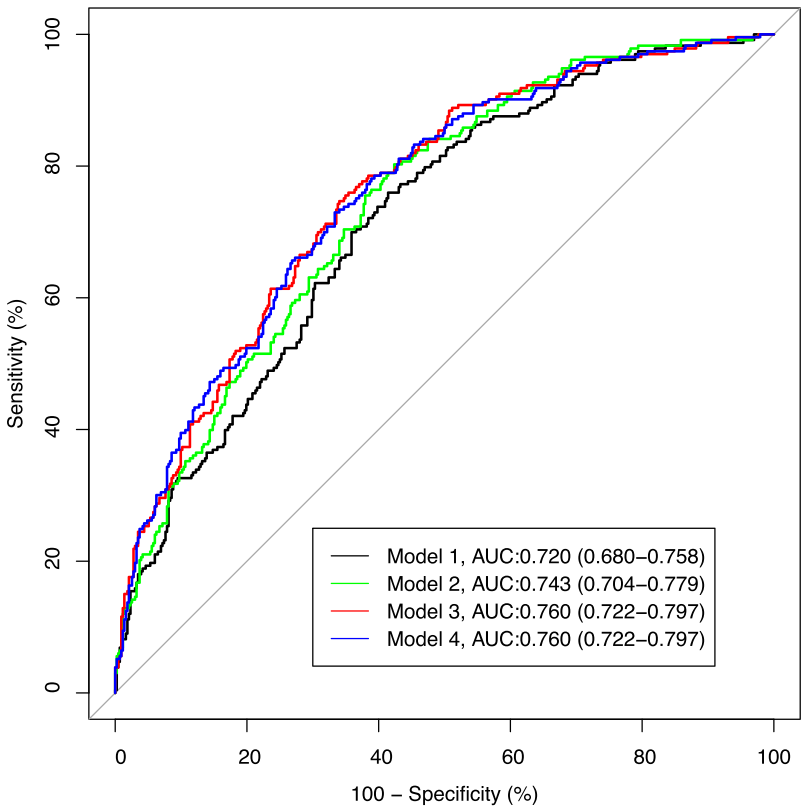

Figure 4: Area under the receiver operating characteristic curve for Model 1 (Established risk factors), Model 2 (Established risk factors + eGFR), and Model 3 and 4 (Model 2 + retinal features including retinal vessel calibers at Zone B and C, respectively).

cost-efficiency of incorporating novel biomarkers in a tool that should be made accessible to individuals with CKD globally in healthcare systems with variable resources and capabilities [11]. Furthermore, the addition of multiple biomarkers improved reclassification of non-events (NRI_{ne} 10.0%, 95% CI 6.8–13.3%), but not for events (NRI_e –1.4%, 95% CI: –8.9–6.4%) compared to established cardiovascular risk models (ACC/AHA Pooled Cohort Equations) [17]. In contrast, smartphone-based retinal photography and the SIVA-DLS may offer a new paradigm in cardiovascular risk screening [42]. Patient empowerment tools to self-manage their health, including cardiovascular risks, are increasingly leveraging on health information technology, such as publicly accessible websites that provide patients with online information on lifestyle modifications and targets for blood pressure, lipid, and weight [43]. We can potentially enhance patient self-management among the technology-savvy generation by incorporating smartphone-based retinal photography and the SIVA-DLS in mobile device applications to provide individualized risk assessment and tailored health advice. Such health technology can become cost-efficient by reducing the technical expertise, manpower and time required in the assessment of retinal vessel calibre [21] and optimizing the volume to be performed for cardiovascular risk assessment.

The strengths of this study are the inclusion of a large, well-characterised, population-based cohort with relatively little missing data, and the use of a well-established measurement to determine retinal vessel caliber. There are some limitations. The adoption of the enhanced risk model that includes SIVA-DLS will need to be externally validated in other cohorts, as the burden of CVD and its risk factors are likely to differ in different populations. Interestingly, the predictive values of the retinal vessel changes for clinical cardiovascular events have differed among different populations [39, 44], depending on the risk profile (general population versus disease cohorts), gender, age, and type of cardiovascular event (coronary heart disease versus stroke versus cardiovascular mortality). For example, arteriolar and venular diameters did not predict cardiovascular mortality in hemodialysis patients whose all-cause mortality risk was very high [44]. The incidence of CVD was higher in our cohort compared to other cohorts that were recently utilized to develop and validate cardiovascular risk prediction in CKD [17]. This was possibly because our study population was older and had more severe kidney disease. In contrast, the observed 10-year cardiovascular risks were 10.5% and 15.5% in the Chronic Renal Insufficiency Cohort (CRIC) cohort (mean age 55.8 $\pm$ 11.7 years, eGFR 56.0 $\pm$ 24.7 ml/min/1.73 m^2) and the combined Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA) cohort mean age 67.2 $\pm$ 8.5 years, eGFR 70.1 $\pm$ 24.3 ml/min/1.73 m^2), respectively [17]. Although there may be concern that the addition of SIVA-DLS to established cardiovascular risk models moderately increased discrimination for incident CVD and may not offer substantially greater prognostic information in populations with high baseline CVD risk, this study found that the predictive value of SIVA-DLS remained consistent in subgroups at greater risk of CVD, such as males, diabetes and lower eGFR <45 ml/min/1/73 m^2. This concurs with the postulation that retinal microvascular changes may be more predictive of cardiovascular risk in CKD where microvascular disease contributes significantly to CVD. Moreover, for a condition like cardiovascular disease that is prevalent in CKD, a risk predictor that accounts for even a modest proportion of risk may significantly impact public health services such as preventive care [45]. Given the greater NRIs when higher risk criteria were applied, the model incorporating kidney function and retinal-DLS, compared to the established risk model, may better identify individuals with very-high cardiovascular risk who can derive the greatest benefit from interventions to reduce cardiovascular morbidity and mortality in CKD. Further research can examine the value and cost-effectiveness of applying the eGFR- and retinal DLS-enhanced cardiovascular risk prediction model in clinical algorithms or decision-making for strategies such as aggressive risk factor control targeted at CKD with intermediate 10-year incident cardiovascular risk, or potentially more contentious and higher-stakes interventions such as high-intensity lipid-lowering pharmacotherapy or prophylactic antiplatelet therapy [7], and screening for occult CVD in CKD with high and very-high 10-year incident cardiovascular risk. Although cohort effect may be a potential confounder, the impact is unlikely to be significant. The macroenvironment such as economy and policies were largely similar for the cohorts so that healthcare access would not have differed significantly. The local and international recommendations for cardiovascular risk screening and primary prevention were also not dramatically different for the study periods. The multivariable models were adjusted for ethnicity and therefore by cohort (that were based on ethnicity) so that the study findings were independent of intrinsic differences between the cohorts.

In conclusion, adding kidney function and retinal vessel calibre assessed by DLS to established cardiovascular risk factors may better predict incident CVD in Asians with CKD. While this study adds to the potential role of retinal vessel calibre in cardiovascular risk prediction in CKD, future work in external validation, including comparison with prediction tools that incorporate biomarker panels, and costs analysis will be required before the incorporation of the eGFR- and retinal DLS-enhanced cardiovascular risk prediction model in clinical practice to reduce incident CVD in CKD.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests relevant to the manuscript.

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