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Colour tone of retinal arterioles imaged with a colour scanning laser ophthalmoscope can be an indicator of systemic arterial stiffness

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ABSTRACT

Objective Colour scanning laser ophthalmoscope (cSLO) offers several advantages, including improved image quality and better visualisation of the retinal structures compared with colour fundus photograph (CFP). This study aimed to identify whether cSLO could be used to predict systemic arterial stiffness.

Methods and analysis We retrospectively analysed the data of 54 patients with 103 eyes. In addition to blood pressure and blood data, all patients had cardio-ankle vascular index (CAVI) measurements, as well as images of the fundus acquired using cSLO and CFP. We determined the retinal artery sclerosis (RAS) index from the colour of the retinal artery in cSLO images, the ratio of arterial to venous diameter (A/V ratio), and Scheie's classification in CFP images. The correlation between each parameter and CAVI was examined using Spearman's rank correlation coefficient, and the correlation between Scheie's classification and CAVI was examined using Steel-Dowass tests.

Results CAVI showed a significant positive correlation with the RAS index ($r=0.679$, $p<0.001$) but not with the A/V ratio or Scheie's classification. Multiple regression analysis showed that the RAS index was significantly and independently correlated with CAVI.

Conclusion cSLO is a non-invasive imaging modality that has the potential to accurately and instantaneously detect early systemic arterial stiffness.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Colour scanning laser ophthalmoscope (cSLO) offers several advantages, including improved image quality and better visualisation of the retinal structures compared with colour fundus photographs.

WHAT THIS STUDY ADDS

⇒ The cSLO has the potential to accurately and instantaneously detect early systemic arterial stiffness.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current method enables easy, non-invasive and accurate prediction of systemic arteriosclerosis and early detection of arteriosclerosis when compared with the conventional colour fundus photography.

INTRODUCTION

Arteriosclerosis is a lesion characterised by thickening, hardening and remodelling of the arterial wall caused by damage to endothelial cells and tunica media smooth muscle cells.[1 2] It has diverse aetiologies, including diabetes,[3] hypertension[3–6] and ageing.[7–9] Arteriosclerosis is associated with various systemic diseases, such as cerebrovascular and renal disorders. Early and appropriate detection of this condition is known to prolong the life expectancy of patients, with resulting economic benefits.[1 9–11]

The ocular fundus is an area where blood vessels can be directly observed. Colour fundus photographs (CFPs) show vascular narrowing as retinal arteriolosclerosis progresses. However, the retinal artery/vein ratio (A/V ratio)[12 13] and Scheie's classification,[14] which are conventional criteria for the subjective judgement of arteriosclerosis based on CFPs, evaluate the vessel diameter. Therefore, early detection of arteriosclerosis prior to changes in vessel diameter is difficult.

In recent years, research has been conducted on the use of CFPs to predict systemic diseases.[15–20] Poplin *et al* reported that many factors, including age, blood pressure and the presence of cardiovascular events, can be predicted from CFPs using artificial intelligence (AI).[21] This implies that fundus photographs contain much information that ophthalmologists are not yet aware of. Some studies predicted systemic arteriosclerosis from fundus photographs using AI; however, the accuracy is insufficient.[22 23] Another major limitation with AI is that the information in CFPs from which the results were obtained is unclear (black box AI). This poses a significant challenge in the medical field[24 25] because explaining to patients the reasons for decisions is necessary and can prevent misdiagnosis. Furthermore, revealing the decision-making process helps determine the disease mechanism.

We previously found that retinal capillary microaneurysms (MA) in diabetic retinopathy were more visible in a colour scanning laser ophthalmoscope (cSLO) than in CFPs.[26] The colour tone of MA could be classified as retinal haemorrhage because alteration of the vessel wall in MA was observed in green at the centre and red at the periphery.[26] This result was obtained using three wavelengths of laser light in cSLO to evaluate the properties of the vessel wall, providing a more direct assessment of blood vessels than black box AI. Since the histological findings between MA and retinal arterial sclerosis, such as hyaline substance deposition in the vessel wall and vascular smooth muscle cell damage, were similar,[1 2 27] we hypothesised cSLO could evaluate the arterial stiffness more accurately than the conventional CFP.

This study aimed to identify the factors associated with arterial stiffness in ocular fundus images using cSLO. In addition to blood pressure and blood data, we used the cardio-ankle vascular index (CAVI) as a measure of arterial stiffness. The CAVI is widely used as an index of arterial stiffness in cardiology and is strongly correlated with arteriosclerosis.[28]

MATERIALS AND METHODS

Study design, patients and examination methods

This was a retrospective study of patients who underwent cataract surgery and postoperative cSLO (Mirante, NIDEK, Japan) imaging at our hospital between October 2020 and November 2021 and those who underwent physical examination and cSLO imaging from April to November 2022. Patients whose image evaluation was difficult owing to poor image quality and those with ocular fundus disease were excluded. The patients underwent perioperative blood tests (all fasted in the morning), blood pressure and CAVI measurements (Vasera VS-3000, FUKUDA DENSHI CO, Japan). Fundus photography (Triton, Topcon, Japan), cSLO (Mirante) and optical coherence tomography (OCT, Triton) were performed within 1 month of cataract surgery. Patients or the public were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Measurement of retinal arteriolosclerosis in photographed fundus images

In cSLO images, the colour tone of retinal arterioles located in the 60°–90° range with the macula as the centre point (intersection of the X–Y axis) and the line connecting the macula and optic nerve as the X axis (angle with the centre is 0°) was quantified as the red, green, blue (red, green, blue) signal intensity using Image J. The ratio of red to green (green/red) was defined as the retinal artery sclerosis (RAS) index (figure 1A).

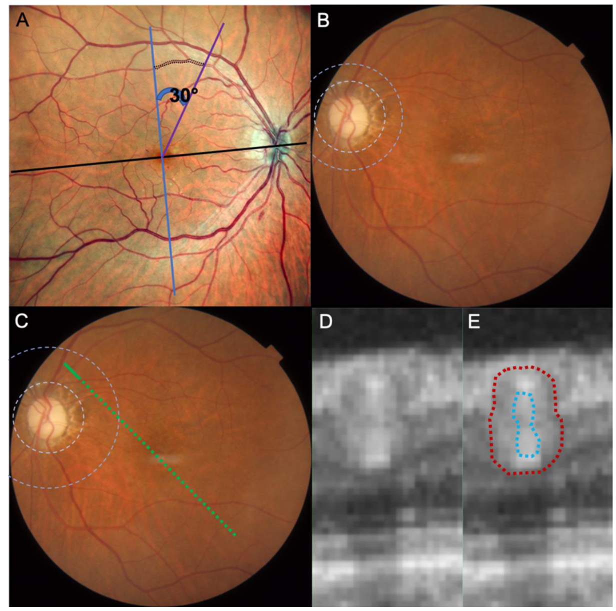

Figure 1 Measurement of retinal artery sclerosis index (RAS index), artery/vein diameter ratio and lumen/vessel wall ratio. (A) Measurement of RAS index. In a colour scanning laser ophthalmoscope image, the fovea is set as the central point (intersection of X–Y axis) and the line connecting the macula and centre of the optic nerve is the X axis (angle with the centre is 0°), the ratio of green to red of the colour tone (black dotted line circled area) of arcade vessels (arteries) in the 60°–90° range is measured. (B) Colour fundus photograph artery/vein ratio (A/V ratio) measurement method. The diameter of retinal arterioles and veins between 0.5 and 1.0 times the papillary diameter (green, dotted line) is measured and the A/V ratio is calculated. (C) Method of measuring the lumen/vessel ratio. An optical coherence tomography radial scan in the range of 0.5–2.0 times of the diameter of optic disc in the colour fundus photograph papillary diameter was analysed. (D and E) In the B-scan image of retinal arterioles, the area of red dotted line was defined as the arterial diameter and the one of blue dotted line was defined as the physiological blood flow range.

In CFPs, arterial and venous diameters were measured from the optic nerve papilla at 0.5–1.0 times the papillary diameter, based on the report by Seidelmann *et al*,[13] and the A/V ratio was calculated (figure 1B).

Scheie's classification was calculated by two retinal specialists (TSakono and HT) using CFPs. The correlation between the RAS index, A/V ratio and CAVI was examined using Spearman's rank correlation coefficient, and the correlation between Scheie's classification and CAVI was examined using Steel-Dowass tests.

Correlation between the RAS index and factors related to systemic arteriosclerosis

The correlation between the RAS index and factors related to arterial stiffness, such as blood pressure (systolic, diastolic and mean), CAVI and blood data (haemoglobin A1c (HbA1c), fasting blood sugar, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol) in the patients was examined. Similarly, we examined the correlation of the A/V ratio on fundus photographs, Schieie's classification and CAVI.

Correlation of lumen/vessel ratio of retinal arterioles between the RAS index and OCT B-scan

To determine whether the RAS index correlates with vessel wall thickening in actual retinal vessels, we used OCT B-scan images to examine the retinal arteriolar diameter in images sliced in the area between 0.5 and 2.0 times the papillary diameter, as described previously[29] (figure 1C). In the OCT image, the area of physiological blood flow was measured using Image J, and the ratio of the area of physiological blood flow to the arterial diameter was calculated and defined as the lumen/vessel wall ratio (L/V ratio, figure 1D).

Reproducibility of the RAS index and L/V ratio measurements

In 20 randomly selected cases, the intra-examiner and inter-examiner reproducibility of the RAS index and L/V ratio measurements were examined. For intra-examiner reproducibility, the order of measurements was randomly changed, and the measurements were performed on different days. For inter-examiner reproducibility, measurements were performed by two examiners (TSakono and NM).

Analysis of factors associated with CAVI

We examined the relationship between CAVI and age, systolic and diastolic blood pressure, total cholesterol and HbA1c in this study because CAVI has been reported as correlated with these factors.[30 31] First, the association between each factor and CAVI was examined using a single regression analysis. Subsequently, multiple regression analysis was conducted using factors significantly associated in the single regression analysis, previously reported explanatory variables, and CAVI as the explained variable to examine the association between the RAS index and CAVI after adjusting for other factors. We performed multiple regression analysis using: model 1, which used information obtained from the interview alone (such as age and sex) as the explanatory variable; model 2, which used non-invasive medical tests (such as axial length, blood pressure, body mass index (BMI) and smoking history) in addition to model 1; and model 3, which used invasive medical tests in addition to model 2 as the explanatory variable (figure 2). We examined the association between the RAS index and CAVI in different situations.

Statistical analysis

We performed statistical analyses using the statistical package for the social sciences software for Windows (SPSS, IBM, Somers, NY, USA) and the EZR software (Saitama Medical Center, Saitama Japan).[32]

Spearman's rank correlation coefficient and Steel-Dowass tests were used to examine correlations between cases, and the intra-rater correlation coefficient was calculated using a one-way random effects model to measure agreement. A two-way mixed effects model was used to calculate the number of intra-rater correlations to measure absolute agreement. Both simple and multiple linear regression analyses were performed using the R software (V.4.0.5).

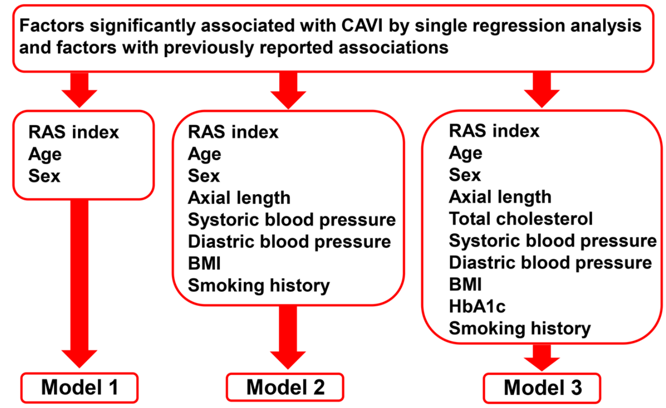

Figure 2 Flowchart on multiple regression analysis. We performed multiple regression analysis using: model 1, which used information obtained from the interview alone (such as age and sex) as the explanatory variable; model 2, which used non-invasive medical tests (such as axial length, blood pressure, body mass index (BMI) and smoking history) in addition to model 1; and model 3, which used invasive medical tests in addition to model 2 as the explanatory variable. CAVI, cardio-ankle vascular index; HbA1c, haemoglobin A1c; RAS index, retinal artery sclerosis index.

RESULTS

Patients

In total, 54 patients (26 men, 28 women) with 103 eyes were enrolled in this study. The mean age was 60.1±18.9 years. Mean corrected visual acuity (logMAR) was −0.08±0.33, mean refractive error was −1.75±2.70 dioptre and mean ocular axial length was 24.1±1.58 mm. There were 61 pseudophakic eyes and 42 phakic eyes. Seven participants reported a history of smoking. The mean CAVI was 8.28±1.33. The mean systolic and diastolic blood pressure, and average blood pressure were 124.9±18.7 (mm Hg), 74.2±8.4 (mm Hg) and 91.1±12.3 (mm Hg), respectively. Regarding lipid levels, the mean total cholesterol, triglycerides and HDL cholesterol were 196.5±34.7 (mg/dL), 103.0±55.7 (mg/dL) and 63.1±17.1 (mg/dL), respectively. The mean HbA1c, which was measured in 42 patients, was 5.86±0.8 (%), and the mean fasting blood glucose and BMI were 114.4±39.1 (mg/dL) and 22.9±3.5, respectively (table 1).

Intra-rater and inter-rater correlations between the measurement of the RAS index and physiological blood flow area/arterial diameter

The intra-rater correlation coefficients for the RAS index and physiological blood flow area/arterial diameter were significantly high (0.914 and 0.887, respectively; p<0.001, online supplemental table 1). Inter-rater correlation coefficients in the RAS index and physiological blood flow

Table 1 Demographic characteristics of the included patients

	Mean±SE	Range
Age	60.1±18.9	24–82
Right/left	51/52	
Sex (male/female)	26/28	
BCVA (logMAR)	−0.08±0.33	−1.69 to 0.18
Refractive error (dioptre)	−1.75±2.70	−11.5 to 2.0
Axial length (mm)	24.1±1.58	21.8–28.2
Smoking history (yes/no)	7/47	
CAVI	8.28±1.33	8.4–10.6
Systolic blood pressure (mm Hg)	124.9±18.7	94.0–167
Diastolic blood pressure (mm Hg)	74.2±8.4	60.0–113
Mean blood pressure (mm Hg)	91.1±12.3	70.0–117.3
Total cholesterol (mg/dL)	196.5±34.7	100–271
Triglyceride (mg/dL)	103.0±55.7	61.0–274
HDL cholesterol (mg/dL)	63.1±17.1	33.0–109.0
Fasting blood glucose (mg/dL)	114.4±39.1	79.0–240.0
HbA1c (%)*	5.86±0.8	4.7–8.2
BMI	22.9±3.5	18.0–30.1

*HbA1c was measured in 42 subjects.
BCVA, best corrected visual acuity; BMI, body mass index; CAVI, cardio-ankle vascular index; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein.

area/arterial diameter were also high (0.860 and 0.894, respectively, p<0.001, online supplemental table 2).

Correlation between CAVI and RAS index in cSLO, artery/vein diameter ratio and Scheie's classification in CFPs

The highest correlation with CAVI was observed for the RAS index, which showed a significant correlation (correlation coefficient (r)=0.679, p<0.001; figure 3A). Additionally, no significant correlation was identified between the A/V ratio (r=0.054, p=0.590, figure 3B). Although there was a significant correlation between CAVI and Scheie's classification (r=0.852, p<0.001), the Steel-Dowass test showed a significant difference between Scheie's classification 0 and Scheie's classifications 1, 2 and 3, but not between Scheie's classifications 1, 2 and 3 (*p<0.05, figure 3C).

Correlation of the RAS index with blood pressure, lipids and blood glucose

Simple regression analysis showed that the RAS index, systolic blood pressure (r=0.426, p<0.001, online supplemental figure 1A) and mean blood pressure (r=0.195, p=0.048, online supplemental figure 1C) were significantly correlated, whereas diastolic blood pressure was not (r=−0.051, p=0.612, online supplemental figure 1B). All blood lipid levels including total cholesterol (r=0.069, p=0.490, online supplemental figure 1D), triglycerides (r=0.000, p=0.996, online supplemental figure 1E) and HDL cholesterol (r=−0.014, p=0.996, online supplemental figure 1F) were not significantly correlated with the RAS index. Fasting blood glucose (r=0.425, p<0.001, online supplemental figure 1G) and HbA1c (r=0.425, p<0.001, online supplemental figure 1H) levels were significantly correlated with the RAS index. BMI was not significantly correlated with the RAS index (r=0.048, p=0.629, online supplemental figure 1I).

Correlation between the RAS index and physiological blood flow area/arterial diameter area

The RAS index was significantly correlated with the physiological blood flow area/arterial diameter area (r=−0.652, p<0.001, online supplemental figure 2).

Multiple regression analysis

The results of the multiple regression analysis using the three analysis models are presented in table 2. Model 1 demonstrated that the RAS index (β=5.346, p<0.001), age (β=0.048, p<0.001) and female (β=−0.113, p=0.427) were significantly and independently correlated with CAVI. Model 2 showed that the RAS index (β=4.330, p=0.002), age (β=0.041, p<0.001), systolic blood pressure (β=0.015,

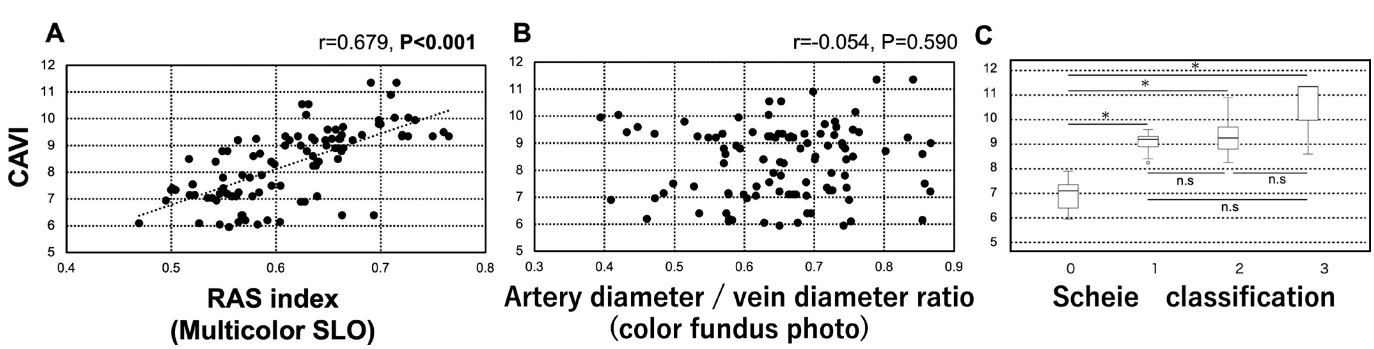

Figure 3 Correlation between CAVI and RAS index in colour SLO, artery/vein diameter ratio and Scheie classification in colour fundus photographs. The highest correlation with the CAVI was observed with the RAS index, which showed a significant correlation (correlation coefficient (r)=0.679, p<0.001 (A)). No significant correlation was found between the artery diameter/vein diameter ratio (r=0.054, p=0.590 (B)). The Steel-Dowass test showed a significant difference between Scheie's classification 0 and Scheie's classifications 1, 2 and 3, but not between Scheie's classifications 1, 2 and 3 (*p<0.05 (C)). CAVI, cardio-ankle vascular index; RAS index, retinal artery sclerosis index; SLO, scanning laser ophthalmoscope.

Table 2 Multiple regression analysis

	Regression coefficient	P value	Model 1 Partial regression coefficient	Model 1 P value	Model 2 Partial regression coefficient	Model 2 P value	Model 3 Partial regression coefficient	Model 3 P value
RAS index	13.26	<0.001	5.346	<0.001	4.330	0.002	4.281	0.018
Age	0.058	<0.001	0.048	<0.001	0.041	<0.001	0.034	<0.001
Female*	0.056	0.833	−0.113	0.427	−0.200	0.250	−0.034	0.870
Axial length	−0.457	<0.001			−0.103	0.086	−0.049	0.508
Total cholesterol	0.004	0.279					0.003	0.398
Systolic blood pressure	0.030	<0.001			0.015	0.008	0.016	0.025
Diastolic blood pressure	0.004	0.737			0.002	0.839	0.001	0.915
BMI	0.019	0.606			−0.046	0.042	−0.069	0.016
HbA1c	0.961	<0.001					0.136	0.329
Smoking history	1.020	0.002			0.193	0.377	0.253	0.402

*Males were used as references.
BMI, body mass index; HbA1c, haemoglobin A1c; RAS index, retinal artery sclerosis index.

p=0.008) and BMI (β=−0.046, p=0.042) were significantly and independently correlated with CAVI. Model 3 showed that the RAS index (β=4.281, p=0.018), age (β=0.034, p<0.001), systolic blood pressure (β=0.016, p=0.025) and BMI (β=−0.069, p=0.016) were independently and significantly correlated with CAVI.

DISCUSSION

In this study, we found an independent and statistically significant correlation between the RAS index and CAVI. Since the A/V ratio of fundus photographs and Scheie's classification showed no correlation with CAVI, analysis of the colour tone of retinal arterioles in cSLO is more useful than conventional methods for predicting systemic arterial sclerosis.

In the present study, cSLO showed a stronger green tint in the retinal arterioles of patients with higher CAVI. This is similar to the changes in retinal capillary aneurysms that we previously reported.[26] In retinal capillary aneurysms, the centre of the lesion is the colour green, and the periphery is the colour red in cSLO. This may be because the vessel wall in capillary aneurysms is thick and reflects the green laser of the cSLO more strongly in the centre. Arrigo *et al* reported that capillary wall thickening and fibrosis in retinal capillary aneurysms result in a stronger green tint in cSLO.[33] Histologically, both arteriosclerosis in retinal arteries and capillary aneurysms share the common finding of vessel wall thickening.[1 2 27] Thus, the present results are reasonable based on these reports.

To prove this, we used OCT B-scan to examine the relationship between the L/V ratio and RAS index and found a significant correlation between them. This indicates that as the ratio of the vessel wall increases in the retinal artery on the OCT B-scan, which indicates the thickening of the arterial wall, the green tone of the retinal artery becomes stronger in cSLO. This result supports the above discussion (online supplemental figure 3).

Arteriosclerosis begins with thickening of the vessel wall, and as it progresses, the inner diameter (lumen) becomes narrower.[34–36] Therefore, fundus photographs show vascular narrowing as retinal arteriolosclerosis progresses. The conventional A/V ratio and Scheie's classification based on fundus photographs are the criteria for evaluating arteriosclerosis based on vessel diameter. Thus, these methods cannot be used to determine arteriosclerosis unless arterial narrowing occurs during the advanced stage of arteriosclerosis. Therefore, this evaluation method made early detection of arteriosclerosis difficult. Furthermore, Scheie's classification is a subjective evaluation, and its reproducibility is challenging.

The RAS index would be useful for the early detection of arteriosclerosis because it evaluates vessel colour tone, which is not affected by vessel diameter. The RAS index is a non-invasive and simple method of obtaining information from cSLO and is an innovative indicator for the early detection of arterial stiffness in the daily practice of ophthalmology.

Atherosclerosis is an important condition associated with many systemic diseases. CAVI and carotid echocardiography were performed for the early detection of the disease. However, because arteriosclerosis is asymptomatic, it is impossible for all patients to undergo these tests since they are difficult in terms of human resources and medical economics.

Moreover, blood pressure, lipids, blood glucose and BMI are factors that influence arteriosclerosis.[30 31] Some studies have shown statistically significant correlations with CAVI. However, many of these tests have diurnal variations, and their values change with treatment, and in some cases normalise. This makes it difficult to determine the presence or absence of arterial stiffness based on these values alone, and patients undergoing treatment may underestimate the degree of arterial stiffness.

Multiple regression analysis showed that the RAS index had a statistically significant correlation with CAVI even after adjusting for other factors. More importantly, the coefficient of determination between the RAS index and CAVI was higher in the multiple regression analysis than in the single regression analysis (simple regression analysis: r^2=0.436; multiple regression analysis, model 1: r^2=0.747; model 2: r^2=0.778; and model 3: r^2=0.7724). Since we perform interviews, and sometimes blood tests, in ophthalmology, the combination of the RAS index and other non-invasive test results may be a more accurate way to determine arterial stiffness. Future studies involving a larger number of participants are needed to clarify this issue and to predict the arterial stiffness by cSLO.

This study had several limitations. First, this was a retrospective study with a small sample size. However, the data were highly reliable because all patients had good visual function. Additionally, imaging equipment, CAVI and blood tests were performed at the same institution. Second, the eyes in this study were either healthy or had postoperative cataracts. Although this method has the advantage of providing clear images, future studies are required to determine whether the results are applicable to phakic eyes. In addition, there are retinal diseases such as uveitis and retinal vasculitis that can affect retinal vessels independently from systemic atherosclerosis. In the present cases, the analysis was performed on patients with no vitreoretinal disease. Thus, the effect was limited in the results of this study. However, it should be considered when interpreting the results examining systemic arterial stiffness in cases with a history of retinal disease.

Finally, we evaluated a limited range of retinal arterioles in fundus images. Even within this measurement range, a significant correlation was observed between the RAS index and CAVI. However, localising the best area in cSLO for predicting CAVI remains a subject for future research.

cSLO can be examined within a few seconds during a medical or ophthalmological check-up and can be performed non-invasively. It has the potential to accurately evaluate systemic arterial stiffness. This method is useful for detecting early arterial stiffness, which to date has not been given the attention due.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this study was approved by the Ethics Committee of Kagoshima University Hospital (approval number: 180243) and performed according to the tenets of the Declaration of Helsinki. The requirement for patient consent was waived owing to the retrospective nature of the study. We published the research plan on the homepage of our hospital's website and guaranteed participants an opt-out opportunity based on the committee's instructions.

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Data availability statement Data are available upon reasonable request.

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