Review Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_9_23

A narrative review of retinal vascular parameters and the applications (Part II): Diagnosis in stroke

Yuan Gao[1,2], Lijun Xu[3], Ning He[4], Yuchuan Ding[5], Wenbo Zhao[6], Tingting Meng[7], Ming Li[6], Jiaqi Wu[1], Yazeed Haddad[5], Xuxiang Zhang[7], Xunming Ji[1,6]

[1]Department of Biomedical Engineering, Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, School of Biological Science and Medical Engineering, Beihang University, Departments of [2]Ophthalmology and [6]Neurology, Xuanwu Hospital, Capital Medical University, [3]School of Instrumentation and Optoelectronic Engineering, Beihang University, [7]Department of Ophthalmology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [4]Engineering Research Center of Molecular and Neuro Imaging, Ministry of Education, School of Life Science and Technology, Xidian University, Xi'an, Shaanxi, China, [5]Department of Neurosurgery, Wayne State University School of Medicine, Detroit, Michigan, USA

Address for correspondence:
Prof. Xunming Ji, Department of Biomedical Engineering, Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, School of Biological Science and Medical Engineering, Beihang University, No.37, Xueyuan Road, Haidian District, Beijing 100191, China.
E-mail: jixm@ccmu.edu.cn

Submission: 03-02-2023
Revised: 27-03-2023
Accepted: 12-04-2023
Published: 27-09-2023

Abstract:

The retina, as an external extension of the diencephalon, can be directly, noninvasively observed by ocular fundus photography. Therefore, it offers a convenient and feasible mode to study nervous system diseases. Caliber, tortuosity, and fractal dimension, as three commonly used retinal vascular parameters, are not only the reflection of structural changes in the retinal microcirculation but also capture the branching pattern or density changes of the retinal microvascular network. Therefore, it contributes to better reflecting the subclinical pathological changes (e.g., lacunar stroke and small cerebral vascular disease) and predicting the risk of incident stroke and recurrent stroke.

Keywords:

Caliber, fractal dimension, retina, stroke, tortuosity

Introduction

The retinal vascular system, which can be noninvasively visualized and measured its parameters from color fundus photography by computer-assisted analysis, supplies a distinctive and feasible "window" to study cerebrovascular diseases since it shares analogous anatomical traits and physiological characteristics to the brain.[1] Currently, many ophthalmologists and neurologists have studied the correlation between retinal abnormalities and cerebrovascular disease[2-4] and neurodegenerative diseases.[5,6] Novel parameters, including caliber, tortuosity, and fractal dimension (FD), can quantify branching patterns and reflect how effectively and efficiently blood is distributed and abnormalities in the retinal vascular system.[7] Retinal vascular diameter can indirectly reflex the blood flow and metabolism of vasculature in the retina.[8] It also has been associated with subclinical and clinical cerebrovascular diseases.[9-12] Increased tortuosity, a sign of damaged blood–retinal barriers and dysfunctional vessel walls[5,13] has been investigated in several diseases such as systemic hypertension,[14,15] diabetic retinopathy,[16] and retinopathy of prematurity.[17,18] Fractal analysis can quantify complex geometric patterns such as the retinal vascular tree.[19] Decreased vascular FD can be caused by the narrowing and collapse of retinal vessels, which is frequently linked to hypoxia.[20] Thus, those novel parameters may provide additional knowledge for cerebrovascular diseases beyond qualitative indicators.[20] Color fundus photography has a great number of advantages such as simplicity, accessibility, noninvasive, and economical when compared with neuroimaging tools such as computed tomography, magnetic resonance imaging, and positron emission tomography to study cerebrovascular diseases.[1] It offers an extra optional method for studying the

How to cite this article: Gao Y, Xu L, He N, Ding Y, Zhao W, Meng T, *et al*. A narrative review of retinal vascular parameters and the applications (Part II): Diagnosis in stroke. Brain Circ 2023;9:129-34.

pathophysiology of stroke and may offer a specific diagnosis by distinctive data on the condition of the cerebral microvasculature.

We mainly summarized the applications of these parameters based on the 30° or 45° range of color fundus photography in subclinical and clinical stroke research, which provides the scientific basis for applying color fundus photography as a noninvasive approach to predict the risk of stroke occurrence, recurrent stroke, and stroke mortality in clinical practice in future.

Retinal Vascular Parameters and Cerebral Artery Stenosis

Cerebral artery stenosis, mainly including extracranial carotid atherosclerotic stenosis and intracranial artery stenosis, is the leading cause of stroke worldwide.[21-23] Extracranial internal carotid artery (ICA) stenosis was related to 8.0% of all ischemic strokes,[24,25] and a major cause of ischemic monocular visual loss.[26] Retinal vascular abnormalities are closely related to cerebral artery stenosis as a result of the ophthalmic artery deriving from the ICA.[27,28] A cross-sectional study recruited from three centers (Melbourne, Sydney, Singapore) found that retinal venous diameter was related to ipsilateral severe extracranial carotid disease (odds ratio [OR], 3.81; 95% confidence interval [CI], 1.80–8.07), and the association regardless of age and conventional vascular risk factors, indicating that patients with carotid stenosis or occlusion diseases may have the concurrent retinal and cerebral microvascular disease.[29] Wang *et al*. discovered that central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and arteriovenous ratio (AVR) have no significant differences in the normal group, mild stenosis group, moderate stenosis group, and severe stenosis group ($P > 0.05$, each).[30] However, Wu *et al*. found that smaller CRAE, AVR, and decreased mean retinal sensitivity were related to severe ICA stenosis, whereas CRVE has no relationship with the degrees of ICA stenosis.[31]

ICA stenosis can lead to both ocular and cerebral ischemia, while treatment with carotid endarterectomy (CEA) may contribute to restoring blood flow perfusion and may prevent ocular and cerebral complications.[32] Machalińska *et al*. observed that CRVE decreased both in the ipsilateral ($P = 0.01$) and contralateral ($P = 0.04$) eyes, CRAE decreased in the ipsilateral eyes ($P < 0.001$) of asymptomatic patients with hemodynamically significant ICA stenosis compared to healthy controls 3 months after CEA, which hints that microvascular dysfunction persists despite the recovery of carotid artery flow.[33] Recently, another study also reported that 6 months after CEA, CRVE decreased in the ipsilateral of patients' eyes (222 μm vs. 214 μm, $P = 0.024$), and arteriolar, venular tortuosity subsided in the macula ($P = 0.15$, $P = 0.10$, respectively), while CRAE was no significant difference preoperatively and postoperatively.[34]

Intracranial arterial stenosis (ICAS) can also lead to ischemic stroke, particularly in Asian patients.[35,36] De Silva *et al*. reported that any intracranial large artery disease was not related to ipsilateral retinal caliber (OR, 1.05; 95% CI 0.89–1.24, arteriolar caliber; OR, 1.00; 95% CI 0.84–1.18, venular caliber), but was related to severe enhanced arteriolar light reflex (OR, 1.74; 95% CI 1.18–2.57).[37] However, Rhee *et al*. found that ICAS subjects had larger CRAE and CRVE than those free of ICAS, particularly a large standard deviation of mean arterial width independently related to ICAS (OR, 22.1; 95% CI: 2.56–190.97) after adjusting for possible confounders.[38]

Retinal Vascular Parameters and Cerebral Venous Stenosis

Cerebral venous stenosis (CVS), including internal jugular vein stenosis and cerebral venous sinus stenosis, is the major cause of poor cerebral venous return and cerebral venous sinus thrombosis.[39] Jugular venous reflux (JVR) occurs more frequently in patients with transitory monocular blindness (TMB) compared to the control group (57% vs. 30%, $P < 0.0001$), according to a study.[40] Moreover, JVR in TMB patients resulted in a greater retinal venule diameter of the right eyes and left eyes (184.5 ± 17.5 μm vs. 174.3 ± 16.2 μm, $P = 0.023$; 194.2 ± 24.6 μm vs. 176.6 ± 19.5 μm, $P = 0.017$, respectively).[41] The Valsalva maneuver (VM) studies revealed that patients with JVR have a higher rise in retinal venule diameters compared to the patients without JVR (14.27% ± 11.16% vs. 2.75% ± 3.51%, $P = 0.0002$, right eyes; 10.06% ± 6.42% vs. 1.80% ± 2.03%, $P = 0.0003$; left eyes) during VM.[41] The results demonstrated that JVR was related to TMB and impair ocular venous outflow. However, there is a lack of studies on retinal vascular parameter changes in non-TMB patients with CVS. Cerebral venous sinus thrombosis often leads to intracranial hypertension, presenting with ocular symptoms including papilledema, retinal hemorrhages, exudation, and venous tortuosity.[42]

Retinal Vascular Parameters and Subclinical Stroke

Lacunar strokes are small subcortical infarcts and are usually correlated with cerebral small vessel disease (CSVD).[43] Lindley *et al*. reported lacunar stroke was related to retinal arteriole narrowing (OR, 1.45; 95% CI, 0.84–2.51) and retinal venular widening (OR, 1.35; 95% CI, 0.80–2.26) after controlling the confounder factors, suggesting that it may be a presentation of nonatherothrombotic occlusive small-vessel

disease (SVD) and contribute to the recognition of this stroke subtype.[44] Dumitrascu *et al*. further demonstrated that venular widening was correlated with lacunar stroke (OR, 1.46; 95% CI 1.10–1.93).[45] Doubal *et al*. found that lacunar stroke subtype (lacunar stroke and cortical stroke) and older age were related to decreased both mono-FD ($P < 0.001$) and multi-FD ($P < 0.001$) after correcting confounding factors, hinting that it has a loss of branching complexity.[46]

Apart from lacunar stroke, CSVD is also distinguished by cerebral white matter hyperintensities (WMH), enlarged perivascular spaces (ePVSs), microbleeds, and cerebral atrophy on imaging.[43] McGrory *et al*. confirmed that reduced FD was related to WMH load and deep WMH scores (OR, 0.53; 95% CI, 0.32–0.87) in older people, supporting that retinal vasculature may be used in the study of brain microvascular disease.[47] Hilal *et al*. found that lower arteriolar FDs (OR, 1.89; 95% CI 1.27–2.82), larger venular calibers (OR, 2.29; 95% CI, 1.19–4.40), and narrower retinal arteriolar calibers (OR, 2.10; 95% CI, 1.06–4.15) were all related to multiple cerebral microbleeds (CMB), but not related to lacunar infarcts and white matter lesions (WML) volume.[3] They concluded that CMBs may be the early sign of CSVD in older people with a thinner and more convoluted retinal microvascular network, regardless of risk factors and other signs of SVD.[3] In addition, ePVSs influenced by vascular risk factors was closely linked to WMLs and lacunes. Mutlu *et al*. found that smaller artery and broader vein diameters were independently related to more ePVSs in the centrum semioval (arterioles, OR, 1.07; 95% CI, 1.01–1.14; venules, OR 1.08; 95% CI, 1.01–1.16) and hippocampal region (arterioles, OR 1.13; 95% CI, 1.04–1.22; venules, OR, 1.09; 95% CI, 1.00–1.18), further demonstrating the relationship between microvascular damage and ePVSs.[48] Ballerini *et al*. also confirmed that decreased CRAE and FD of the arterioles and venules were correlated with increased total perivascular space (PVS) volume and count ($P < 0.001$, $P < 0.01$, respectively), while CRVE has no associations of PVS.[49]

Retinal vascular parameters also have a vital mediation role in studying the relationship of other factors and stroke. Cheung *et al*. surveyed the correlation between arterial stiffness and retinal diameter to clear whether arterial stiffness being related to a high risk of stroke is interceded by small- or large-artery disease.[50] They found that decreased arterial wall compliance in large arterial beds was related to a smaller retinal arteriolar diameter, whereas the compliance in small arterial beds was related to a wider retinal venular diameter. The findings may offer additional information on the impacts of altered arterial stiffness on brain circulation.[50] Meanwhile, another study also confirmed that alterations in the retinal microvasculature, such as arteriolar constriction and arteriolosclerosis, were associated with aortic stiffening.[51] These changes may have indirect effects on the cerebral microvasculature.

Retinal Vascular Parameters and Clinical Stroke

Stroke can always lead to adult disability and death worldwide,[52] thus early screening for risk factors and intervention is extremely important. In a multi-ethnic cohort, Kawasaki *et al*. found that middle-aged people free of clinical cardiovascular disease who had narrower retinal arteriolar caliber and retinopathy throughout 6 years were more likely to experience a clinical stroke than those without them (42.3% vs. 27.8%; OR, 2.3, 95% CI 1.06–4.97), regardless of conventional cardiovascular risk factors and assessments of subclinical atherosclerosis.[53] Cheung *et al*. confirmed that retinopathy (hazard ratio [HR], 1.94; 95% CI, 1.01–3.72) and wider retinal vein diameter (HR, 3.28; 95% CI 1.30–8.26) were correlated with the risk of stroke and retinal microvascular signs assessment enhancing stroke risk identification and stratification superior to the established risk factors, which was consistent with previous findings in European and American populations.[54] Ong *et al*. also reported that decreased arteriolar (OR, 2.28; 95% CI, 1.80–2.87) and venular FD (OR, 1.80; 95% CI, 1.46–2.23), increased arteriolar tortuosity (OR, 1.56; 95% CI, 1.25–1.95), and venular tortuosity (OR, 1.49; 95% CI, 1.27–1.76), narrower arteriolar caliber (OR, 2.79; 95% CI, 2.21–3.53), and larger venular caliber (OR, 1.57; 95% CI, 1.27–1.95) were related to stroke and those results were similar to stroke subtypes, suggesting that ischemic stroke has a sparser and more tortuous vessels in retinal microvascular network.[12] Pial collateral blood flow is a significant predictor of stroke outcomes. Khan *et al*. reported that increased multifractal FD (1.673 ± 0.028 vs. 1.652 ± 0.025, $P = 0.028$) was associated with poor pial collaterals, and they hoped to develop a classifier to identify patients with either poor or good pial collaterals noninvasively.[55] Zhuo *et al*. reported that every unit increase in CRAE and CRVE would raise stroke risk recurrent by 4.28 times in patients with coronary heart diseases.[56] Apart from that, every additional unit of the arterial and venous angles would raise stroke risk recurrent in atrial fibrillation patients by 3.9 and 13.7 times, respectively.[56] These findings demonstrated that retinal vascular parameters contain numerous information for assessing the risk of recurrent cerebral infarction and may be developed as a tool for stroke management in large population screening in the future.[56] Besides, Liew *et al*. confirmed that decreased FD was related to a higher long-term risk of stroke mortality (HR, 2.42; 95% CI, 1.15–5.07), indicating relative hypoxia existing in retinal and cerebral tissue and thus raised the risk of stroke mortality.[57]

Retinal Vascular Parameters and Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH), as a subtype of stroke, can make up 10% to 15% of stroke patients each year, and have high rates of death and disability in older people.[58,59] Prevention seems the most effective method due to the present treatment limitation and poor prognosis.[60] New risk indicators and risk factors screening is becoming increasingly important in identifying people at risk of ICH. A study of acute stroke patients discovered that those with deep ICH had smaller arterioles (131.9 vs. 138.7 μm; $P = 0.0004$) and larger venules (212.5 vs. 205.9 μm; $P = 0.03$) than those with nonlacunar stroke.[61] During an average follow-up of 11.5 years, wider venular caliber was independently correlated with an increased risk for stroke (HR, 1.2; 95% CI, 1.09–1.33), ICH (HR, 1.53; 95% CI: 1.09–2.15), particularly with lobar hemorrhages (HR, 2.02; 95% CI 1.28–3.19) and oral anticoagulant-related hemorrhages (HR, 2.48; 95% CI: 1.30–4.76).[62] The results imply that in the general population, larger retinal vein diameter was related to an increased risk of stroke, particularly ICH. Besides, a diagnosis of Wyburn–Mason syndrome should be taken into consideration when retinal vascular tortuosity covering both arteries and veins, manifests unilaterally but does not result in hemorrhage.[63]

In conclusion, retinal vascular parameters have a definite association with cerebral artery stenosis, ICH, either subclinical or clinical stroke, and offer new perception into the organization and pattern of stroke-related microcirculation changes. It has vital clinical significance for reflecting the subclinical pathological changes, stroke risk stratification, and the risk estimation of stroke recurrent and stroke mortality.

Conclusion and Future Directions

Retinal vascular parameters from ocular fundus photography are significantly associated with subclinical and clinical stroke and can be regarded as a complementary tool in brain circulation research, which have been demonstrated by many studies. However, the present studies were mainly cross-sectional studies but lack of longitudinal studies. Besides the relationship between retinal vascular parameters and intracranial aneurysm, the intracranial arteriovenous malformation is still unclear, and thus, it requires further research. Finally, further research into the performance and clinical utility of retinal vascular parameters in risk stratification and prediction for subclinical or clinical stroke may be warranted, especially in the age of artificial intelligence.

Financial support and sponsorship

This study was supported by the National Natural Science Foundation of China (No. 82071312 and 81971114).

Conflicts of interest

Prof. Xunming Ji is an Editor-in-Chief, Prof. Yuchuan Ding is an Editorial Board member of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

References

1. Cheung CY, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. Prog Retin Eye Res 2017;57:89-107.
2. Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, Hubbard LD, *et al*. Retinal microvascular abnormalities and incident stroke: The atherosclerosis risk in communities study. Lancet 2001;358:1134-40.
3. Hilal S, Ong YT, Cheung CY, Tan CS, Venketasubramanian N, Niessen WJ, *et al.* Microvascular network alterations in retina of subjects with cerebral small vessel disease. Neurosci Lett 2014;577:95-100.
4. Zhang Y, Shi C, Chen Y, Wang W, Huang S, Han Z, *et al.* Retinal structural and microvascular alterations in different acute ischemic stroke subtypes. J Ophthalmol 2020;2020:8850309;1-10.
5. Czakó C, Kovács T, Ungvari Z, Csiszar A, Yabluchanskiy A, Conley S, *et al.* Retinal biomarkers for Alzheimer's disease and vascular cognitive impairment and dementia (VCID): Implication for early diagnosis and prognosis. Geroscience 2020;42:1499-525.
6. Szegedi S, Dal-Bianco P, Stögmann E, Traub-Weidinger T, Rainer M, Masching A, *et al.* Anatomical and functional changes in the retina in patients with Alzheimer's disease and mild cognitive impairment. Acta Ophthalmol 2020;98:e914-21.
7. Sherman TF. On connecting large vessels to small. The meaning of Murray's law. J Gen Physiol 1981;78:431-53.
8. Bek T. Diameter changes of retinal vessels in diabetic retinopathy. Curr Diab Rep 2017;17:82.
9. Cheung CY, Wong WL, Hilal S, Kan CN, Gyanwali B, Tham YC, *et al.* Deep-learning retinal vessel calibre measurements and risk of cognitive decline and dementia. Brain Commun 2022;4:fcac212.
10. Zhou X, Li T, Qu W, Pan D, Qiu Q, Wu L, *et al.* Abnormalities of retinal structure and microvasculature are associated with cerebral white matter hyperintensities. Eur J Neurol 2022;29:2289-98.
11. van Dinther M, Voorter PH, Schram MT, Berendschot TT, Houben AJ, Webers CA, *et al.* Retinal microvascular function is associated with the cerebral microcirculation as determined by intravoxel incoherent motion MRI. J Neurol Sci 2022;440:120359.
12. Ong YT, De Silva DA, Cheung CY, Chang HM, Chen CP, Wong MC, *et al.* Microvascular structure and network in the retina of patients with ischemic stroke. Stroke 2013;44:2121-7.
13. Hammes HP, Feng Y, Pfister F, Brownlee M. Diabetic retinopathy: Targeting vasoregression. Diabetes 2011;60:9-16.
14. Cheung CY, Tay WT, Mitchell P, Wang JJ, Hsu W, Lee ML, *et al.* Quantitative and qualitative retinal microvascular characteristics and blood pressure. J Hypertens 2011;29:1380-91.
15. Cheung CY, Zheng Y, Hsu W, Lee ML, Lau QP, Mitchell P, *et al.* Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. Ophthalmology 2011;118:812-8.
16. Tapp RJ, Owen CG, Barman SA, Strachan DP, Welikala RA, Foster PJ, *et al*. Retinal microvascular associations with cardiometabolic risk factors differ by diabetes status: Results from the UK Biobank. Diabetologia 2022;65:1652-63.
17. Pour EK, Pourreza H, Zamani KA, Mahmoudi A, Sadeghi AM, Shadravan M, *et al*. Retinopathy of prematurity-assist: Novel software for detecting plus disease. Korean J Ophthalmol 2017;31:524-32.
18. Gelman R, Jiang L, Du YE, Martinez-Perez ME, Flynn JT, Chiang MF. Plus disease in retinopathy of prematurity: Pilot study

of computer-based and expert diagnosis. J AAPOS 2007;11:532-40.
19. Blindbæk SL, Torp TL, Lundberg K, Soelberg K, Vergmann AS, Poulsen CD, *et al.* Noninvasive retinal markers in diabetic retinopathy: Advancing from bench towards bedside. J Diabetes Res 2017;2017:2562759;1-10.
20. Rim TH, Teo AW, Yang HH, Cheung CY, Wong TY. Retinal vascular signs and cerebrovascular diseases. J Neuroophthalmol 2020;40:44-59.
21. Wang Y, Zhao X, Liu L, Soo YO, Pu Y, Pan Y, *et al.* Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: The Chinese Intracranial Atherosclerosis (CICAS) study. Stroke 2014;45:663-9.
22. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-73.
23. Li G, Liu P, Gong W, Zhang X, Zhang Y, Wang N. Endovascular recanalization for symptomatic intracranial internal carotid and middle cerebral artery occlusion lasting longer than 72 h: Experience in a single center. Brain Circ 2021;7:259-64.
24. Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, *et al.* Carotid artery stenosis as a cause of stroke. Neuroepidemiology 2013;40:36-41.
25. Bir SC, Kelley RE. Carotid atherosclerotic disease: A systematic review of pathogenesis and management. Brain Circ 2022;8:127-36.
26. Cheng SF, Zarkali A, Richards T, Simister R, Chandratheva A. Carotid artery stenosis, an underestimated cause of strok0065 recurrence in patients with ischaemic monocular visual loss. Ann R Coll Surg Engl 2019;101:579-83.
27. Michelson EL, Morganroth J, Nichols CW, MacVaugh H 3rd. Retinal arteriolar changes as an indicator of coronary artery disease. Arch Intern Med 1979;139:1139-41.
28. Alnawaiseh M, Ertmer C, Seidel L, Arnemann PH, Lahme L, Kampmeier TG, *et al.* Feasibility of optical coherence tomography angiography to assess changes in retinal microcirculation in ovine haemorrhagic shock. Crit Care 2018;22:138.
29. De Silva DA, Liew G, Wong MC, Chang HM, Chen C, Wang JJ, *et al.* Retinal vascular caliber and extracranial carotid disease in patients with acute ischemic stroke: The Multi-Centre retinal stroke (MCRS) study. Stroke 2009;40:3695-9.
30. Wang H, Li H, Zhang X, Qiu L, Wang Z, Wang Y. Ocular image and haemodynamic features associated with different gradings of ipsilateral internal carotid artery stenosis. J Ophthalmol 2017;2017:1842176;1-10.
31. Wu DH, Wu LT, Wang YL, Wang JL. Changes of retinal structure and function in patients with internal carotid artery stenosis. BMC Ophthalmol 2022;22:123.
32. Pierro L, Arrigo A, De Crescenzo M, Aragona E, Chiesa R, Castellano R, *et al.* Quantitative optical coherence tomography angiography detects retinal perfusion changes in carotid artery stenosis. Front Neurosci 2021;15:640666.
33. Machalińska A, Kawa MP, Babiak K, Sobuś A, Grabowicz A, Lejkowska R, *et al.* Retinal vessel dynamic functionality in the eyes of asymptomatic patients with significant internal carotid artery stenosis. Int Angiol 2019;38:230-8.
34. Ala-Kauhaluoma M, Ijäs P, Koskinen SM, Nuotio K, Vikatmaa P, Silvennoinen H, *et al.* Retinal vessel diameters and microvascular abnormalities in patients with carotid stenosis before and 6 months after carotid endarterectomy: A prospective study. Acta Ophthalmol 2023;1-10.
35. Gutierrez J, Turan TN, Hoh BL, Chmowitz MI. Intracranial atherosclerotic stenosis: Risk factors, diagnosis, and treatment. Lancet Neurol 2022;21:355-68.
36. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: Risk factors, diagnosis, and treatment. Lancet Neurol 2013;12:1106-14.
37. De Silva DA, Manzano JJ, Woon FP, Liu EY, Lee MP, Gan HY, *et al.* Associations of retinal microvascular signs and intracranial large artery disease. Stroke 2011;42:812-4.
38. Rhee EJ, Chung PW, Wong TY, Song SJ. Relationship of retinal vascular caliber variation with intracranial arterial stenosis. Microvasc Res 2016;108:64-8.
39. Ding J, Guan J, Rajah G, Dornbos D II, Li W, Wang Z, *et al.* Clinical and neuroimaging correlates among cohorts of cerebral arteriostenosis, venostenosis and arterio-venous stenosis. Aging (Albany NY) 2019;11:11073-83.
40. Cheng CY, Chang FC, Chao AC, Chung CP, Hu HH. Internal jugular venous abnormalities in transient monocular blindness. BMC Neurol 2013;13:94.
41. Chung CP, Hsu HY, Chao AC, Cheng CY, Lin SJ, Hu HH. Jugular venous reflux affects ocular venous system in transient monocular blindness. Cerebrovasc Dis 2010;29:122-9.
42. Guan J, Song S, Wang W, Ji X, Meng R. Cerebral venous sinus thrombosis due to external compression of internal jugular vein. J Int Med Res 2021;49:1-7;3000605211006609.
43. Traylor M, Persyn E, Tomppo L, Klasson S, Abedi V, Bakker MK, *et al.* Genetic basis of lacunar stroke: A pooled analysis of individual patient data and genome-wide association studies. Lancet Neurol 2021;20:351-61.
44. Lindley RI, Wang JJ, Wong MC, Mitchell P, Liew G, Hand P, *et al.* Retinal microvasculature in acute lacunar stroke: A cross-sectional study. Lancet Neurol 2009;8:628-34.
45. Dumitrascu OM, Demaerschalk BM, Valencia Sanchez C, Almader-Douglas D, O'Carroll CB, Aguilar MI, *et al.* Retinal microvascular abnormalities as surrogate markers of cerebrovascular ischemic disease: A meta-analysis. J Stroke Cerebrovasc Dis 2018;27:1960-8.
46. Doubal FN, MacGillivray TJ, Patton N, Dhillon B, Dennis MS, Wardlaw JM. Fractal analysis of retinal vessels suggests that a distinct vasculopathy causes lacunar stroke. Neurology 2010;74:1102-7.
47. McGrory S, Ballerini L, Doubal FN, Staals J, Allerhand M, Valdes-Hernandez MD, *et al.* Retinal microvasculature and cerebral small vessel disease in the Lothian birth cohort 1936 and mild stroke study. Sci Rep 2019;9:6320.
48. Mutlu U, Adams HH, Hofman A, Lugt AV, Klaver CC, Vernooij MW, *et al.* Retinal microvascular calibers are associated with enlarged perivascular spaces in the brain. Stroke 2016;47:1374-6.
49. Ballerini L, McGrory S, Valdés Hernández MD, Lovreglio R, Pellegrini E, MacGillivray T, *et al.* Quantitative measurements of enlarged perivascular spaces in the brain are associated with retinal microvascular parameters in older community-dwelling subjects. Cereb Circ Cogn Behav 2020;1:100002.
50. Cheung N, Islam FM, Jacobs DR Jr., Sharrett AR, Klein R, Polak JF, *et al.* Arterial compliance and retinal vascular caliber in cerebrovascular disease. Ann Neurol 2007;62:618-24.
51. De Silva DA, Woon FP, Manzano JJ, Liu EY, Chang HM, Chen C, *et al.* The relationship between aortic stiffness and changes in retinal microvessels among Asian ischemic stroke patients. J Hum Hypertens 2012;26:716-22.
52. Wolf VL, Ergul A. Progress and challenges in preclinical stroke recovery research. Brain Circ 2021;7:230-40.
53. Kawasaki R, Che Azemin MZ, Kumar DK, Tan AG, Liew G, Wong TY, *et al.* Fractal dimension of the retinal vasculature and risk of stroke: A nested case-control study. Neurology 2011;76:1766-7.
54. Cheung CY, Tay WT, Ikram MK, Ong YT, De Silva DA, Chow KY, *et al.* Retinal microvascular changes and risk of stroke: The Singapore Malay eye study. Stroke 2013;44:2402-8.
55. Khan A, De Boever P, Gerrits N, Akhtar N, Saqqur M, Ponirakis G, *et al.* Retinal vessel multifractals predict pial collateral status in patients with acute ischemic stroke. PLoS One 2022;17:e0267837.
56. Zhuo Y, Yu H, Yang Z, Zee B, Lee J, Kuang L. Prediction factors of recurrent stroke among Chinese adults using retinal vasculature

characteristics. J Stroke Cerebrovasc Dis 2017;26:679-85.
57. Liew G, Gopinath B, White AJ, Burlutsky G, Yin Wong T, Mitchell P. Retinal vasculature fractal and stroke mortality. Stroke 2021;52:1276-82.
58. Yang G, Fan X, Mazhar M, Yang S, Xu H, Dechsupa N, *et al.* Mesenchymal stem cell application and its therapeutic mechanisms in intracerebral hemorrhage. Front Cell Neurosci 2022;16:898497.
59. Wang H, Cao X, Wen X, Li D, Ouyang Y, Bao B, *et al.* Transforming growth factor-β1 functions as a competitive endogenous RNA that ameliorates intracranial hemorrhage injury by sponging microRNA-93-5p. Mol Med Rep 2021;24:499.
60. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: Current approaches to acute management. Lancet 2018;392:1257-68.
61. Baker ML, Hand PJ, Liew G, Wong TY, Rochtchina E, Mitchell P, *et al.* Retinal microvascular signs may provide clues to the underlying vasculopathy in patients with deep intracerebral hemorrhage. Stroke 2010;41:618-23.
62. Wieberdink RG, Ikram MK, Koudstaal PJ, Hofman A, Vingerling JR, Breteler MM. Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: The Rotterdam study. Stroke 2010;41:2757-61.
63. Ledesma-Gil G, Essilfie J, Freund KB, Yannuzzi LA, Fisher YL. Detection of occult arteriovenous malformation with annular array ultrasonography. Ophthalmic Surg Lasers Imaging Retina 2020;51:239-43.