Total small vessel disease score and risk of recurrent stroke

Validation in 2 large cohorts

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ABSTRACT

Objective: In patients with TIA and ischemic stroke, we validated the total small vessel disease (SVD) score by determining its prognostic value for recurrent stroke.

Methods: Two independent prospective studies were conducted, one comprising predominantly Caucasian patients with TIA/ischemic stroke (Oxford Vascular Study [OXVASC]) and one predominantly Chinese patients with ischemic stroke (University of Hong Kong [HKU]). Cerebral MRI was performed and assessed for lacunes, microbleeds, white matter hyperintensities (WMH), and perivascular spaces (PVS). Predictive value of total SVD score for risk of recurrent stroke was determined and potential refinements considered.

Results: In 2,002 patients with TIA/ischemic stroke (OXVASC n = 1,028, HKU n = 974, 6,924 patient-years follow-up), a higher score was associated with an increased risk of recurrent ischemic stroke (adjusted hazard ratio [HR] per unit increase: 1.32, 1.16–1.51, $p < 0.0001$; c statistic 0.61, 0.56–0.65, $p < 0.0001$) and intracerebral hemorrhage (ICH) (HR 1.54, 1.11–2.13, $p = 0.009$; c statistic 0.65, 0.54–0.76, $p = 0.006$). A higher score predicted recurrent stroke in SVD and non-SVD TIA/ischemic stroke subtypes (c statistic 0.67, 0.59–0.74, $p < 0.0001$ and 0.60, 0.55–0.65, $p < 0.0001$). Including burden of microbleeds and WMH and adjusting the cutoff of basal ganglia PVS potentially improved predictive power for ICH (c statistic 0.71, 0.60–0.81, $p_{het} = 0.45$), but not for recurrent ischemic stroke (c statistic 0.60, 0.56–0.65, $p_{het} = 0.76$) on internal validation.

Conclusions: The total SVD score has predictive value for recurrent stroke after TIA/ischemic stroke. Prediction of recurrence in patients with nonlacunar events highlights the potential role of SVD in wider stroke etiology. *Neurology*® 2017;88:2260–2267

GLOSSARY

BG = basal ganglia; **CAA** = cerebral amyloid angiopathy; **CS** = centrum semiovale; **HKU** = University of Hong Kong; **HR** = hazard ratio; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **OXVASC** = Oxford Vascular Study; **PVS** = perivascular spaces; **SVD** = small vessel disease; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment; **WMH** = white matter hyperintensity.

Cerebral small vessel disease (SVD) is a common cause of stroke, cognitive impairment, and gait disturbances.[1,2] Recently, a total SVD score was proposed,[3–5] which incorporates 4 established neuroimaging biomarkers of SVD and aims to capture the overall burden of cerebral SVD. In this score, one point is allocated to each of the following: (1) presence of lacunes, (2) presence of microbleeds, (3) moderate to severe (>10) basal ganglia (BG) perivascular spaces (PVS), and (4) severe periventricular or moderate to severe deep white matter hyperintensity (WMH).[3] The score has been associated with age, male sex, hypertension, smoking, and lacunar stroke subtype in ischemic stroke patients.[3] In patients with lacunar infarct, the total SVD score has also been associated with increased ambulatory blood pressure[4] and cognitive impairment.[5]

Although the total SVD score has subsequently been shown to be associated with cognitive impairment,[6,7] its long-term prognostic implications for recurrent stroke in patients with TIA/ischemic stroke have yet to be determined.[3] Whether the score also predicts risk of recurrent stroke in nonlacunar stroke subtypes is unknown. Moreover, whether refinements to the score (e.g., by incorporating different weightings based on microbleed[8] and WMH burden) may improve its predictive value has not been explored.[3,9] Therefore, in 2 large prospective studies, 1 comprising predominantly Caucasian patients with TIA/ischemic stroke and 1 predominantly Chinese patients with ischemic stroke, we (1) validated the current total SVD score by determining its long-term prognostic implications and (2) determined whether minor refinements to the score might improve its prognostic value.

METHODS We prospectively studied patients with TIA/ischemic stroke from 2 cohorts: the Oxford Vascular Study (OXVASC) and the University of Hong Kong (HKU). In brief, OXVASC is an ongoing population-based study of all acute vascular events occurring within a population of 92,728 individuals, irrespective of age, who are registered with 100 general practitioners in 9 general practices of Oxfordshire, UK.[10] This analysis includes 1,080 consecutive cases of TIA/ischemic stroke recruited from November 1, 2004, to September 30, 2014, who had a cerebral MRI. The imaging protocol of OXVASC has been described in detail elsewhere.[11,12] Briefly, from April 1, 2002, to March 31, 2010 (phase 1), MRI and magnetic resonance angiography (MRA) was performed in selected patients when clinically indicated. From April 1, 2010 onwards (phase 2), brain MRI and MRA became the first-line imaging methods.[11] A total of 1,076 consecutive patients who were predominantly Chinese with a diagnosis of acute ischemic stroke and received a brain MRI with MRA at the HKU MRI Unit were recruited during the period March 1, 2008, to September 30, 2014.

We collected demographic data, atherosclerotic risk factors, and details of hospitalization of index event during face-to-face interview and cross-referenced these with primary care records and hospital records in both cohorts. Cause of TIA/ischemic stroke was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[13]

TIA/ischemic stroke patients recruited from OXVASC were scanned predominantly (881/1,080) with 2 scanners: Achieva (Philips Healthcare, Best, the Netherlands) (493/630 patients who received a 1.5T MRI) and Magnetom Verio (Siemens health care, Munich, Germany) (388/450 patients who received a 3T MRI).[12] All patients from HKU were scanned using a single 3T MRI scanner. Details of scan parameters are documented in table e-1 at Neurology.org. PVS were defined as small (<3 mm) punctate (if perpendicular to the plane of scan) or linear (if longitudinal to the plane of scan) hyperintensities on T2 images in the BG or centrum semiovale (CS) based on a previously validated scale.[14] Burden of PVS was then stratified into 3 groups: <11, 11–20, and >20. The severity of white matter disease was

determined for each patient according to the Fazekas scale.[15] Cerebral microbleeds were defined as rounded, hypodense foci up to 10 mm and were differentiated from microbleed mimics based on current guidelines.[16] The location and number of microbleeds were scored according to the Microbleed Anatomical Rating Scale.[17] Lacunes were defined as rounded or ovoid lesions, >3 and <20 mm in diameter, in the BG, internal capsule, CS, or brainstem, with CSF signal density on T2 and fluid-attenuated inversion recovery and no increased signal on diffusion-weighted imaging.[18]

Two neuroradiologists (W.K. and H.K.F.M.) provided ongoing supervision of interpretation of the MRI throughout the study period. Definitions of neuroimaging biomarkers were based on STRIVE.[18] The intrarater κ for 50 randomly selected scans in each center was as follows: lacunes 0.85 (OXVASC), 0.82 (HKU); microbleed burden (0, 1, 2–4, ≥5) 0.88 (OXVASC), 0.81 (HKU); periventricular WMH burden (Fazekas grade 0, 1, 2, 3) 0.66 (OXVASC), 0.69 (HKU); subcortical WMH burden (Fazekas grade 0, 1, 2, 3) 0.75 (OXVASC), 0.71 (HKU); PVS burden (<11, 11–20, >20) 0.86 (BG), 0.84 (CS) in OXVASC and 0.86 (BG), 0.72 (CS) in HKU.

All patients in OXVASC were followed up regularly by a research nurse or physician at 1, 3, 6, 12, 24, 60, and 120 months after the index event. Patients recruited from HKU were followed up by a clinician every 3–6 months, or more frequently if clinically indicated. All patients were assessed for the development of recurrent ischemic stroke or ICH. Recurrent stroke was defined as a sudden new neurologic deficit fitting the definition of ischemic stroke or ICH, occurring after a period of unequivocal neurologic stability and not attributable to cerebral edema, mass effect, or hemorrhagic transformation of the incident cerebral infarction. Patients with suspected recurrent stroke received repeat neuroimaging in the form of cranial CT or MRI to support the diagnosis. Where needed, details of clinical outcomes were supplemented by electronic or paper medical records from primary care practices, hospitals, as well as the Deaths General Register Office. The modified Rankin Scale (mRS) score of recurrent strokes was determined at 1 month after recurrent event and a disabling stroke was defined as mRS ≥3.

Standard protocol approvals, registrations, and patient consents. Patients gave written informed consent after an event or assent was obtained from relatives for patients who were unable to provide consent. Both cohorts were approved by the local research ethics committee.

Statistical analysis. We compared differences in baseline and imaging characteristics in OXVASC and HKU using Student t test for continuous variables and χ^2 test for categorical variables. We determined, by Cox regression analysis, the unadjusted and adjusted (for age, sex, and vascular risk factors) risks of recurrent ischemic stroke and ICH in patients with (1) lacunes, (2) increasing burden (1, 2–4, and ≥5 vs 0) of microbleeds, (3) increasing burden (11–20 and >20 vs <11) of BG and CS PVS, and (4) increasing burden (Fazekas grade 1, 2, and 3 vs 0) of periventricular and subcortical WMH. We calculated the total SVD score for all patients[3,4] and determined the unadjusted and adjusted (for age, sex, and vascular risk factors) odds of TIA/ischemic stroke due to SVD and subsequent risks of recurrent ischemic stroke and ICH with increasing total SVD score. The c statistic for area under the receiver operating characteristic curve for prediction of a recurrent stroke based on the total SVD score was calculated. Prediction of a nondisabling and disabling or fatal recurrent stroke based on increasing total SVD score was also determined.

Table 1	Clinical and imaging characteristics of the study populations		
	OXVASC, UK, n = 1,028 (542 TIA, 486 ischemic stroke)	HKU, HK, n = 974 (974 ischemic stroke)	p
Baseline clinical characteristics			
Age, y	68 ± 14	69 ± 12	0.25
Male	538 (52.3)	583 (59.9)	0.001
Hypertension	563 (54.8)	640 (65.7)	<0.0001
Diabetes	136 (13.2)	275 (28.2)	<0.0001
Hyperlipidemia	381 (37.1)	249 (25.6)	<0.0001
Ever-smokers	521 (50.7)	291 (29.9)	<0.0001
Atrial fibrillation	160 (15.6)	128 (13.1)	0.12
Prior TIA/stroke	187 (18.2)	154 (15.8)	0.16
Imaging characteristics			
Magnet strength, T	1.5T, n = 582; 3T, n = 446	3T, n = 974	
With DWI-positive lesion	233 (22.7)	759 (77.9)	<0.0001
With basal ganglia PVS			
<10	527 (51.3)	659 (67.7)	<0.0001
10-20	271 (26.4)	246 (25.3)	
>20	230 (22.4)	69 (7.1)	
With centrum semiovale PVS			
<10	226 (22.0)	410 (42.1)	<0.0001
10-20	331 (32.2)	463 (47.5)	
>20	471 (45.8)	101 (10.4)	
With lacunes	182 (17.7)	430 (44.1)	<0.0001
With microbleeds	156 (15.2)	441 (45.3)	<0.0001
1	79 (7.7)	179 (18.4)	
2-4	44 (4.3)	145 (14.9)	
≥5	39 (3.8)	117 (12.0)	
Strictly deep	14 (1.4)	60 (6.2)	<0.0001
Strictly lobar	73 (7.1)	157 (16.1)	<0.0001
Strictly infratentorial	16 (1.6)	38 (3.9)	0.001
Mixed location	53 (5.2)	186 (19.1)	<0.0001
With periventricular WMH			
Grade 1	386 (37.5)	213 (21.9)	<0.0001
Grade 2	201 (19.6)	75 (7.7)	
Grade 3	96 (9.3)	30 (3.1)	
With subcortical WMH			
Grade 1	338 (32.9)	475 (48.8)	<0.0001
Grade 2	177 (17.2)	278 (28.5)	
Grade 3	117 (11.4)	155 (15.9)	
Total small vessel disease score[a]	1.12 ± 1.11	1.67 ±1.15	<0.0001
Modified total small vessel disease score[b]	1.01 ± 1.31	1.27 ± 1.31	<0.0001
Outcome			
Follow-up time, mo	45 ± 26	37 ± 19	
Patient-years follow-up	3,884	3,040	

Continued

All analyses were done with SPSS version 20 (SPSS Inc., Chicago, IL).

RESULTS The 2 study populations contributed a total of 2,156 patients. After excluding 154 patients with incomplete clinical or imaging data, 2,002 patients (OXVASC n = 1,028, 542 TIA, 486 ischemic stroke; HKU n = 974, all ischemic stroke) were included in the final analysis. Baseline clinical and imaging characteristics of patients are shown in table 1. HKU patients had a higher proportion of male participants ($p = 0.001$) and were more likely to have hypertension and diabetes ($p < 0.0001$), while patients from OXVASC were more likely to have hyperlipidemia or a history of smoking ($p < 0.0001$).

Patients from OXVASC had a higher burden of BG PVS, CS PVS, and periventricular WMH ($p < 0.0001$) (table 1). In contrast, those from HKU had a greater burden of lacunes, microbleeds, and subcortical WMH ($p < 0.0001$) (table 1). As expected, the total SVD score was higher in the HKU cohort than in the OXVASC cohort ($p < 0.0001$, table e-2), mainly due to a higher prevalence of microbleeds in the Asian population. These differences remained in analyses confined to OXVASC and HKU patients who received an MRI with a 3T scanner (table e-3). There were also no differences in mean total SVD scores among OXVASC patients scanned on different MRI scanners ($p = 0.69$) (table e-2).

A total of 26.8% of the study population (OXVASC n = 124/1,028, HKU n = 413/974) were classified to have TIA/ischemic stroke due to small vessel disease or occlusion by TOAST criteria (table e-4). An increasing total SVD score was associated with a greater odds of having presented at baseline with a small vessel TIA/ischemic stroke (TOAST classification) in both cohorts (OXVASC: age, sex, and vascular risk factor adjusted odds ratio per unit increase in score 2.02, 95% confidence interval 1.66–2.46, $p < 0.0001$; HKU: 1.25, 1.11–1.42, $p = 0.0004$) (table e-5).

A total of 199 recurrent strokes occurred (85.4% ischemic) after a mean follow-up of 42 ± 23 months (OXVASC: 45 ± 26 months, HKU: 37 ± 19 months, total 6,924 patient-years) (table 1). The hazard ratios (HR) of recurrent ischemic stroke and ICH based on individual markers of SVD are shown in tables e-6 through e-9 and summarized in the figure.

An increasing total SVD score was associated with an increased risk of recurrent stroke in OXVASC and HKU (OXVASC c statistic: 0.60,

Table 1   Continued

	OXVASC, UK, n = 1,028 (542 TIA, 486 ischemic stroke)	HKU, HK, n = 974 (974 ischemic stroke)	p
Recurrent stroke	90 (8.8)	109 (11.2)	0.069
Ischemic stroke	81 (7.9)	89 (9.1)	0.31
Disabling or fatal	26 (32.1)	52 (58.4)	0.001
Fatal	6 (7.4)	12 (13.4)	0.13
Intracerebral hemorrhage	9 (0.9)	20 (2.1)	0.027
Disabling or fatal	6 (66.7)	17 (85.0)	0.015
Fatal	3 (33.3)	6 (30.0)	0.28

Abbreviations: DWI = diffusion-weighted imaging; HKU = University of Hong Kong; OXVASC = Oxford Vascular Study; PVS = perivascular space; WMH = white matter hyperintensity.

Values are mean ± SD or n (%).

[a] One point allocated for presence of lacunes, microbleeds, moderate to severe (>10) PVS in basal ganglia, periventricular WMH Fazekas 3, or deep WMH Fazekas 2-3.

[b] One point allocated for presence of lacunes, 1-4 microbleeds, frequent to severe (>20) PVS in basal ganglia, moderate WMH (total periventricular + subcortical WMH grade 3-4), 2 points allocated for ≥5 microbleeds and severe WMH (total periventricular + subcortical WMH grade 5-6).

0.54–0.67, p = 0.001; HKU: 0.61, 0.56–0.67, p = 0.0001; p_{het} = 0.82) (table e-10). When the 2 cohorts were pooled, patients with increasing total SVD score were at greater risk of recurrent stroke, recurrent ischemic stroke, and ICH. The multivariate adjusted HR of developing a recurrent stroke, ischemic stroke, and ICH per unit increase in score was 1.36 (1.21–1.54, p < 0.0001), 1.32 (1.16–1.51, p < 0.0001), and 1.54 (1.11–2.13, p = 0.009) (table 2). The c statistic was 0.62 (0.57–0.66, p < 0.0001), 0.61 (0.56–0.65, p < 0.0001), and 0.65 (0.54–0.76, p = 0.006), respectively (table 2). Patients with an increasing total SVD score were at increased risk of a recurrent nondisabling ischemic stroke (age, sex, and vascular risk factor adjusted HR per unit increase: 1.28, 1.07–1.54, p = 0.008) and recurrent disabling or fatal ischemic stroke (1.39, 1.14–1.69, p = 0.001) (table e-11). They were also at increased risk of nondisabling ICH (2.34, 1.15–4.74, p = 0.019). However, the risk association of total SVD score with disabling or fatal ICH did not reach statistical significance (1.42, 0.99–2.05, p = 0.060) (table e-11).

When all patients were stratified by their baseline TOAST subtype, the total SVD score predicted risk of recurrent stroke in both individuals presenting with a baseline TIA/ischemic stroke classified as SVD (537/2,002) (age- and sex-adjusted HR for recurrent stroke per unit increase in score in SVD subtype: 1.43 [1.12–1.83], p = 0.004) or non-SVD (1,465/2,002) (HR 1.39 [1.19–1.61] p < 0.0001 [p_{het} = 0.85]), the relationship of which was significant among patients with baseline TIA/ischemic stroke due to large artery atherosclerosis (large artery atherosclerosis 1.32 [1.03–1.69],
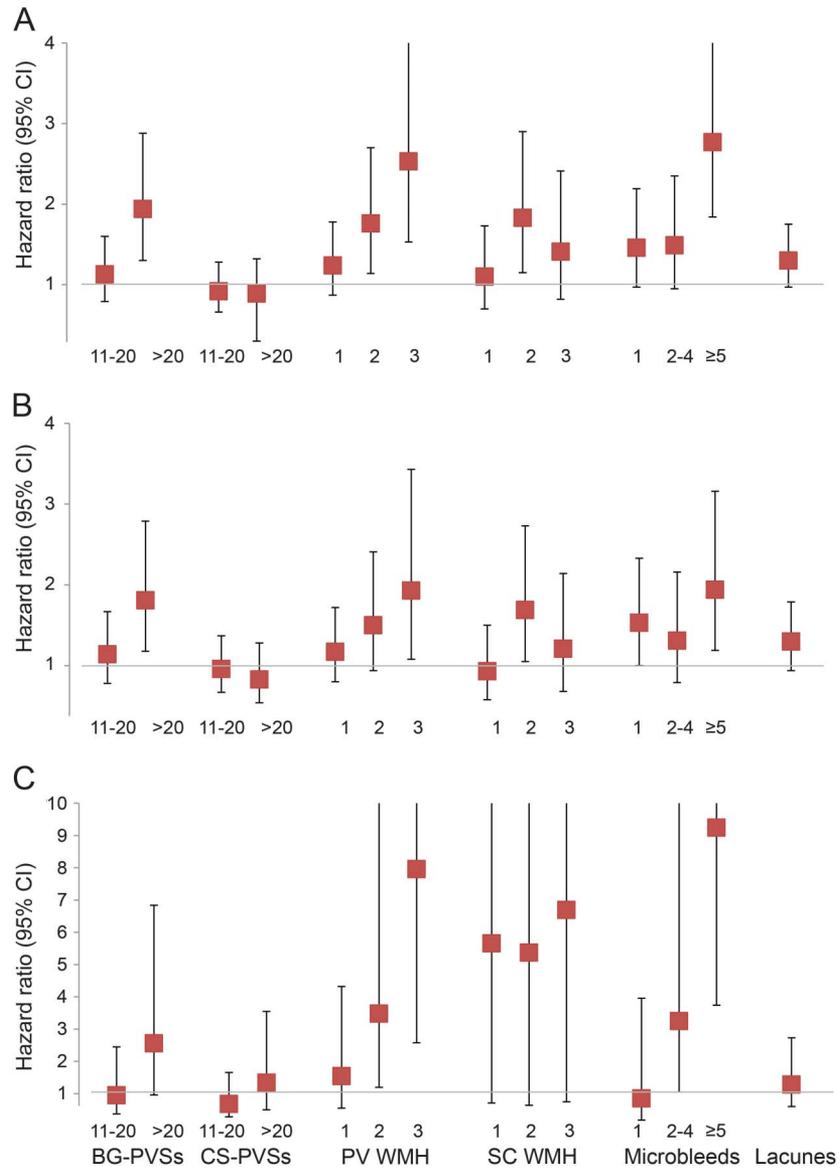
cardioembolic 1.27 [0.91–1.75], undetermined 1.40 [1.00–1.95]) (table 3). Furthermore, among 1,028 OXVASC patients, the prognostic value of the total SVD score did not differ for the prediction of recurrent ischemic strokes that were classified as SVD (8/81) or non-SVD (73/81) (p = 0.72).

Compared with <11 BG PVS, patients with 11–20 BG PVS were not at increased risk of recurrent stroke (adjusted HR 1.13, 0.79–1.60) (table e-9). However, risk of recurrent stroke was approximately doubled (1.94, 1.30–2.88) in patients with >20 BG PVS (table e-9 and figure). Risk of recurrent stroke was also greater with increasing burden of microbleeds (p_{trend} < 0.0001), especially those with ≥5 microbleeds (table e-7 and figure). Similarly, risk of recurrent stroke was also greater in patients with more severe WMH, especially those with periventricular WMH (p_{trend} = 0.0001) (table e-8 and figure). We therefore considered the following 3 refinements to the total SVD score: first, we allocated 1 point to those with >20 BG PVS rather than >11 BG PVS. Second, burden of microbleeds was accounted for by assigning 1 point to patients with 1–4 microbleeds and 2 points to those with ≥5 microbleeds. Third, burden of total WMH (combined periventricular and subcortical WMH) was also accounted for by allocating 1 point to those with a moderate degree of WMH (combined score of 3 or 4) and 2 points to those with severe WMH (combined score of 5 or 6).

The corresponding c statistic for the modified total SVD score in predicting recurrent stroke (0.62, 0.58–0.66, p < 0.0001) and recurrent ischemic stroke (0.60, 0.56–0.65, p < 0.0001) did not differ from the total SVD score in prediction of recurrent stroke (p_{het} = 1.00) or recurrent ischemic stroke (p_{het} = 0.76) (table e-12). The modified total SVD score also did not improve the prediction of nondisabling vs disabling or fatal events compared with the total SVD score (table e-11). However, the modified total SVD score might be better at identifying patients at high risk of ICH (adjusted HR per unit increase: 1.65, 1.34–2.02, p < 0.0001; c statistic 0.71, 0.60–0.81, p = 0.0001), but on comparison of c statistics, this difference was far from statistically significant (p_{het} = 0.45) (table e-12).

DISCUSSION We validated the prognostic value of the total SVD score in TIA/ischemic stroke patients in 2 large prospective cohorts involving over 2,000 Caucasian and Chinese participants with approximately 7,000 patient-years follow-up. Similar to an earlier report,[3] the total SVD score was strongly associated with TIA/ischemic stroke due to SVD in both of these cohorts. In addition, we demonstrated that patients with a higher score were at increasing risk of a recurrent ischemic stroke and ICH and that

Risk of (A) recurrent stroke, (B) recurrent ischemic stroke, and (C) intracerebral hemorrhage with increasing burden of small vessel disease. Hazard ratios adjusted for age, sex, vascular risk factors, and center and compared with patients with <11 basal ganglia (BG) perivascular spaces (PVS), <11 centrum semiovale (CS) PVS and no periventricular (PV) white matter hyperintensity (WMH), subcortical (SC) WMH, microbleeds, or lacunes, respectively. CI = confidence interval.

the total SVD score predicted both nondisabling and disabling recurrent ischemic strokes. We also showed that the total SVD score predicted recurrent strokes in patients with both SVD and non-SVD subtype of TIA/ischemic stroke at baseline.

Although previous studies have demonstrated that BG PVS are markers of hypertensive angiopathy,[19,20] the need for data on long-term prognostic implications of BG PVS has been highlighted.[18] Our results demonstrated that compared with patients with <11 BG PVS, those with 11–20 BG PVS were not at significantly increased risk of recurrent ischemic stroke or ICH. In contrast, TIA/ischemic stroke

patients with >20 BG PVS were at 1.8-fold increased risk of recurrent ischemic stroke and 2.6-fold increased risk of ICH, potentially justifying adjustment of cutoff for BG PVS in the total SVD score from >11 to >20. We also found that the risk of recurrent stroke, in particular ICH, varied substantially with burden of microbleeds, consistent with previous studies.[8] Rather than dichotomizing the grading of microbleeds as present or absent, we considered allocating different weightings for patients with increasing burden of microbleeds. Similarly, we considered increasing the points attributed for WMH, in view of the clear stepwise increase in risk

Table 2 Prognostic value of the total small vessel disease score[a] (external validation)

Total small vessel disease score	Events/ patients	Unadjusted HR (95% CI)	p_{trend}	Age- and sex-adjusted HR (95% CI)	p_{trend}	Multivariate[b] adjusted HR (95% CI)	p_{trend}	c Statistic (95% CI)	p
Recurrent stroke									
0	40/559	1	<0.0001	1	<0.0001	1	<0.0001	0.62 (0.57–0.66)	<0.0001
1	38/579	1.08 (0.69–1.69)		0.90 (0.57–1.42)		0.89 (0.57–1.41)			
2	53/478	1.88 (1.24–2.85)		1.43 (0.93–2.21)		1.38 (0.89–2.13)			
3	47/302	2.71 (1.77–4.15)		2.02 (1.29–3.17)		2.02 (1.29–3.18)			
4	21/84	4.58 (2.69–7.78)		3.32 (1.91–5.78)		3.20 (1.83–5.59)			
Recurrent ischemic stroke									
0	35/559	1	<0.0001	1	<0.0001	1	<0.0001	0.61 (0.56–0.65)	<0.0001
1	32/579	1.03 (0.63–1.66)		0.86 (0.53–1.42)		0.86 (0.53–1.41)			
2	48/478	1.93 (1.24–2.99)		1.48 (0.93–2.35)		1.43 (0.90–2.28)			
3	40/302	2.60 (1.65–4.12)		1.96 (1.21–3.18)		1.98 (1.22–3.23)			
4	15/84	3.60 (1.96–6.60)		2.65 (1.41–4.98)		2.60 (1.38–4.91)			
Intracerebral hemorrhage									
0	5/559	1	0.0004	1	0.004		0.009	0.65 (0.54–0.76)	0.006
1	6/579	1.42 (0.43–4.65)		1.13 (0.34–3.79)		1.10 (0.33–3.69)			
2	5/478	1.43 (0.41–4.94)		1.03 (0.28–3.74)		0.94 (0.26–3.43)			
3	7/302	3.20 (1.01–10.09)		2.25 (0.67–7.55)		2.11 (0.62–7.11)			
4	6/84	9.97 (3.03–32.81)		6.79 (1.93–23.93)		5.86 (1.62–21.23)			

Abbreviations: CI = confidence interval; HR = hazard ratio; PVS = perivascular space; WMH = white matter hyperintensity.
[a] One point allocated for presence of lacunes, microbleeds, moderate to severe (>10) PVS in basal ganglia, periventricular WMH Fazekas 3, or deep WMH Fazekas 2–3.
[b] Adjusted for age, sex, hypertension, hyperlipidemia, diabetes, atrial fibrillation, and smoking.

noted for increasing burden of WMH, in particular periventricular WMH. However, rather than having different cutoffs for periventricular and subcortical WMH, which may overcomplicate the score, we decided to attribute points to moderate or severe total WMH, by combining the total burden of periventricular and subcortical WMH.

Our results also support the initial decision of not incorporating CS PVS within the total SVD score.

Similar to BG PVS, CS PVS have been associated with age, hypertension, WMH, and lacunes.[19–21] However, CS PVS have also been associated with lobar microbleeds[19] and cerebral amyloid angiopathy (CAA)[22] and hence been hypothesized to be a neuroimaging marker of CAA by representing fluid and metabolic waste clearance dysfunction due to vascular amyloid deposition.[19,23] While a high burden of CS PVS may be associated with subsequent risk of ICH

Table 3 Risk of recurrent stroke in patients with increasing total small vessel disease score[a] stratified by TIA/ischemic stroke TOAST subtype at baseline

TOAST classification	Events/patients	Unadjusted HR (95% CI)	p	Age- and sex-adjusted HR per unit increase in score (95% CI)	p	c Statistic (95% CI)	p
Small vessel disease	54/537	1.60 (1.27–2.01)	<0.0001	1.43 (1.12–1.83)	0.004	0.67 (0.59–0.74)	<0.0001
Non-small vessel disease	145/1465	1.47 (1.28–1.69)	<0.0001	1.39 (1.19–1.61)	<0.0001	0.60 (0.55–0.65)	<0.0001
Large artery atherosclerosis	53/471	1.37 (1.08–1.74)	0.011	1.32 (1.03–1.69)	0.030	0.59 (0.51–0.67)	0.031
Cardioembolic	35/278	1.34 (1.00–1.78)	0.048	1.27 (0.91–1.75)	0.16	0.57 (0.46–0.68)	0.17
Undetermined	33/556	1.48 (1.11–1.97)	0.008	1.40 (1.00–1.95)	0.049	0.57 (0.46–0.68)	0.18

Abbreviations: CI = confidence interval; HR = hazards ratio; PVS = perivascular space; TOAST = Trial of Org 10172 in Acute Stroke Treatment; WMH = white matter hyperintensity.
[a] One point allocated for presence of lacunes, microbleeds, moderate to severe (>10) PVS in basal ganglia, periventricular WMH Fazekas 3, or deep WMH Fazekas 2–3.

in healthy individuals[19] and in patients with cognitive impairment,[24] our results demonstrate that a high burden of CS PVS was not predictive of recurrent ischemic stroke or ICH in TIA/ischemic stroke patients. Indeed, interpretation of CS PVS is often affected by the presence of concomitant subcortical WMH, which was present in 77% of patients in our cohort, and hence the usefulness of CS PVS would without doubt be limited in a TIA/ischemic stroke population.

Our study has a number of limitations. First, our 2 cohorts were different in several respects. OXVASC consists of predominantly Caucasian participants with 50% having TIA, while the HKU cohort comprises predominantly Chinese participants with ischemic stroke. Although this would probably explain some differences in stroke subtypes between the 2 populations, and there was inevitably some selection in both cohorts in relation to MRI, particularly in the earlier stages of the studies when the 2 cohorts were analyzed separately (table e-10), we were able to demonstrate that the total SVD score had very similar prognostic value in predicting risk of recurrent stroke (c statistic 0.60 and 0.61) with no heterogeneity. Similarly, when our results were stratified according to period of recruitment (first 5 vs latter 5 years), the total SVD score had similar prognostic value in prediction of recurrent stroke with no significant heterogeneity ($p_{het} = 0.25$). These analyses suggest that the utility of the total SVD score is robust to ethnicity and is applicable to patients with TIA and ischemic stroke. Second, our study was limited by the small number of some clinical outcomes, with only 29 ICH on long-term follow-up, among 199 total recurrent strokes. Third, the TOAST subtypes of recurrent strokes were only available among OXVASC patients. Whether the total SVD score predicts recurrent strokes of different subtypes would require further study. Fourth, patients in OXVASC were scanned on 4 different scanners over the 10-year study period. However, although this could have been a potential source of heterogeneity, total SVD scores were similar across the 4 scanners and appeared to have similar predictive value for recurrent stroke ($p_{het} = 0.42$), accepting the limited statistical power to address this for individual scanners. Overall, therefore, the robustness of our findings to different scanner types is a potential strength of the total SVD score. Fifth, any modifications to the total SVD score require further external validation in other much larger cohorts. Finally, although the total SVD score has been shown to predict cognitive impairment in the elderly population[6] and in patients with hypertension,[7] whether the score also predicts cognitive decline in patients with TIA/ischemic stroke remains uncertain.

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