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Regional Cerebral Small Vessel Disease (rCSVD) Score: A Clinical MRI Grading System Validated in a Stroke Cohort

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Abstract

Background: Current methods for quantitative assessment of cerebral small vessel disease (CSVD) ignore critical aspects of the disease, namely lesion type and regionality. We developed and tested a new scoring system for CSVD, “regional Cerebral Small Vessel Disease” (rCSVD) based on regional assessment of magnetic resonance imaging (MRI) features.

Methods: 141 patients were retrospectively included with a derivation cohort of 46 consecutive brain MRI exams and a validation cohort of 95 patients with known cerebrovascular disease. We compared the predictive value of rCSVD against existing scoring methods. We determined the predictive value of rCSVD score for all-cause mortality and recurrent strokes.

Results: 46 (44 male) veteran patients (age: 66–93 years), were included for derivation of the rCSVD score. A non-overlapping validation cohort consisted of 95 patients (89 male; age: 34–91 years) with known cerebrovascular disease were enrolled. Based on ROC analysis with comparison of AUC (Area Under the Curve), “rCSVD” score performed better compared to “total SVD score” and Fazekas score for predicting all-cause mortality (0.75 vs 0.68 vs 0.69; p=0.046). “rCSVD” and total SVD scores were predictive of recurrent strokes in our validation cohort (p-values 0.004 and 0.001). At a median of 5.1 years (range 2–17 years) follow-up,

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Kaplan-Meier survival analysis demonstrated an rCSVD score of 2 to be a significant predictor of all-cause-mortality.

Conclusion: "rCSVD" score can be derived from routine brain MRI, has value in risk stratification of patients at risk of CSVD, and has potential in clinical trials once fully validated in a larger patient cohort.

INTRODUCTION

Metrics such as smoking, body weight, physical activity, diet, blood pressure, fasting blood glucose, and total cholesterol level, introduced by the American Heart Association can be used to measure cardiovascular health and predict risk of cardiovascular events and mortality. (1–4) Accurate assessment and monitoring of cardiovascular health and risk factors is difficult and time-intensive, since one must rely on subjective reports. This raises the need for an objective tool to measure cardiovascular health and predict outcomes such as cardiovascular events, stroke, dementia and mortality.

Cerebral microvascular disease (CSVD), an intrinsic disorder of the small perforating brain arterioles, is a known risk factor for stroke (both ischemic and hemorrhagic), dementia, and death and can be measured on routine brain MRI, making it a potential biomarker for cardiovascular health. (5–10) Previous efforts for quantitative assessment of CSVD have been promising. These include, scoring systems to measure burden of age-related white matter changes on MRI with the best established being Manolio, Fazekas and Schmidt, and Scheltens. (11–15) Subsequently, "total SVD score" was introduced as a clinically pragmatic visual assessment of four different manifestations of CSVD on MRI (i.e. white matter T2 hyperintensities, lacunar infarcts, cerebral microbleeds, and enlarged perivascular spaces. (5,16) Currently, "total small vessel disease" (total SVD) score is the reference standard for clinical measurement of CSVD burden and has been correlated with outcomes such as stroke and dementia. (5,16,17) However, "total SVD score" does not address the association of location of CSVD markers with variable pathophysiology, symptoms, prognosis and clinical outcomes.

The relationship between lesion location and clinical status of the patient have been addressed in numerous prior publications and are essential concepts, which are utilized in routine clinical practice and patient-care. (18–23) For example, CMBs in lobar regions are often seen in both familial and sporadic cerebral amyloid angiopathy, whereas deep CMBs are more common in sporadic deep perforator arteriopathy. (18, 19) Hypertension and lower LDL-C increase the risk of deep and infra-tentorial CMBs, but have no significant association with the presence of strictly lobar CMBs (18). Advanced age is independently associated with the prevalence of all CSVD markers, while the presence of hypertension increases the risk of lacunes, PVH/DWMH, and CMBs in deep or infratentorial locations. (18) Lacunar infarcts are associated with deep or infratentorial, and not lobar, CMBs and number and severity of lacunar infarcts are independent risk factors for deep CMBs (24).

There are also genetic predispositions for specific regions of CSVD markers. Knol et al 2020 demonstrated that genetic variants in the APOE region are associated with the presence of CMB, most likely due to the APOE e4 allele count related to a higher number of strictly

lobar CMBs (20). The genetic risk factor profiles for lobar and deep hemorrhage have been shown to differ. (25)

From the symptomatic standpoint, lobar, but not deep or infratentorial, CMBs are associated with changes in cognitive function, especially in visuospatial executive functions. (26) C Miller Fisher's meticulous dissections confirmed by a more recent MRI study by Hernandez et al suggest that lesions, such as focal infarcts, in the internal capsule are more likely to have caused symptoms than those in other brain regions. (27, 28) White matter tracts in lobar white matter regions such as centrum semiovale are more multidirectional than in the internal capsule, possibly 'diluting' the impact of a small lesion across several functions. (28)

Pathophysiologic explanations for the clinical relevance of the location of CSVD markers have been discussed in prior publications. CSVD is associated with chronic end arteriolar insufficiency leading to vessel wall media lipohyalinosis and subsequent narrowing of deep perforating cerebral vessels. This in turn eventually leads to chronic tissue ischemia and results in above described CSVD imaging findings predominantly within watershed regions. (21) Ischemic perforating small vessels and reduced density of deep penetrating vessels may make deep and infratentorial regions susceptible to acute brain infarction. (21, 22) On the other hand, if micro-emboli are the predominant cause of acute infarction in these regions, it is conceivable that emboli are trapped in these narrowed lipohyalinized diseased vessels leading to acute lacunar infarctions or in the event of a large vessel occlusion, poor collateral flow to the penumbra. (21) For example, Obusez et al demonstrated that deep (and not total or periventricular) white matter T2 hyperintensities are a predictor of acute brain infarction after thoracic aortic replacement in a cohort of 5171 patients (23). The brainstem's primary role in central control of consciousness, cardiovascular, and respiratory functions also likely contributes to a worse prognosis in patients with CSVD in this region.

The location of CSVD has important clinical, pathophysiologic, symptomatic, and genetic ramifications and associations. Therefore, inclusion of the anatomic location of CSVD on MRI within a scoring system may give rise to a more accurate metric to measure cardiovascular health and predict risk of cardiovascular events, dementia, and mortality. To test this hypothesis, we derived and validated the "Regional CSVD" (rCSVD) scoring system and measured its predictive value for all-cause mortality and recurrent stroke. This scoring paradigm is grounded in cerebral microvascular disease pathophysiology and radiographic phenotypes and can be visually calculated on routine clinical brain MRI.

METHODS

This retrospective study was approved by the West Los Angeles Veterans Affairs (WLA VA) Medical Center Institutional Review Board (IRB) and Research and Development committee (#2019–040306). The VA IRB determined that this study is exempt from IRB oversite under "Category 4 (iii)".

We report our results according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) for reporting studies in CSVD (www.equatornetwork.org) (29).

Patient cohort

We used data from 2 nonoverlapping groups of patients.

- In the *derivation cohort (Cohort 1)*, we derived the rCSVD score from 46 consecutive veteran patients (44 Males; age range: 66–93 years, mean 74.6 ± 8.3 years) with brain MRI exams that had standard T1, T2, T2-FLAIR (FLuid Attenuated Inversion Recovery), T2* (i.e. gradient echo – GRE), and Diffusion Weighted Imaging (DWI) sequences performed in 2016). To create the derivation cohort, a retrospective database search was performed to identify consecutive patients who had brain MRI at West Los Angeles Veterans Medical Center in 2016. Search parameters included age between 65–100 years, and brain MRI scans between 1/1/2016 and 12/31/2016. Patients with incomplete sequences or significant motion, large intracranial lesions with significant mass effect such as mass or hemorrhage, or susceptibility artifact secondary to external causes were excluded. There were no other inclusion or exclusion criteria. Patients' demographics, risk factors, and imaging results divided in all-cause-mortality and "alive at 4 years follow-up" groups are summarized in Supplemental Table. Their comorbid conditions include 39% diabetes, 76% hypertension, 65% dyslipidemia.
- In the *validation cohort (Cohort 2)*, 95 veteran patients (89 Male; age range: 34–91 years, mean 72.35 years) with ischemic lacunar or cortical infarct detected between 2012–2018 were enrolled. This cohort was taken from a large stroke database at the West LA VA medical center accumulated by the senior author (JDH). All patients in Cohort 2 had at least one brain MRI with T1, T2, T2-FLAIR, GRE, and DWI sequences. Patients with incomplete sequences or significant motion, large intracranial lesions with significant mass effect such as mass or hemorrhage, or susceptibility artifact secondary to external causes were excluded. There were no other inclusion or exclusion criteria. Patient demographics, risk factors and imaging results reported by "all-cause-mortality" and "alive at 2–17 years follow-up" are summarized in Table 1. Their comorbid conditions include 31 (33%) patients with diabetes, 79 (83%) patients with hypertension, and 85 (89%) patients with dyslipidemia.

Medical record abstraction and outcomes

Review of medical records was performed by a fellowship trained stroke neurologist (JDH), a cardiologist (KLN), and a neuroradiologist (SH) to determine baseline demographics, vascular risk factors, and other details. Clinically relevant patient characteristics and outcomes (including all-cause mortality and recurrent strokes) were abstracted from medical records. In the derivation cohort, all-cause mortality at 5 years from the time point of brain MRI was obtained from the VA electronic medical records. In the validation cohort, 2 to 17-year follow-up from the oldest brain MRI containing all required sequences for the validation cohort. Recurrent stroke was defined as any type of stroke (lacunar, cortical, ischemic, or hemorrhagic) in a patient with known prior history of stroke as determined by the treating neurologist and reconfirmed by a board -certified stroke neurologist (JDH) through medical record review. Some diagnoses of stroke were symptomatic without

correlative imaging. Hypertension (blood pressure ≥ 140/90 mm Hg), diabetes mellitus (fasting blood glucose ≥ 6.1 mmol/L), hypercholesterolemia (total cholesterol ≥ 5.0 mmol/L) were defined by the treating physician.

Brain MRI acquisition and analysis

All patients had clinical brain MRI on a 1.5 Tesla (N= 123) (Aera, Siemens, Erlangen, Germany) or 3.0 Tesla (N= 18) magnet (Skyra, Siemens, Erlangen, Germany) at the West Los Angeles VA Medical Center. All brain MRI exams contain the following pulse sequences with scanning parameters as previously described (5, 29): Axial and/or sagittal T1-Weighted, axial T2-Weighted, axial T2 FLAIR, axial T2* Weighted GRE, and axial Echo Planar Diffusion Weighted Imaging (DWI). All scanners were operated by licensed technical staff and underwent daily quality assurance monitoring.

Subjects with significant motion artifact or missing one or more of the required sequences on their brain MRI were excluded at the outset and not included in the cohorts. Two board-certified neuroradiologists (S.H., A.Z.) reached consensus in determining rCSVD, total SVD, and Fazekas scores of brain MR images in 2016 for the derivation cohort (cohort 1) and the oldest brain MR images containing all required sequences for the validation cohort (cohort 2). All images were rated by two neuroradiologists for the presence of asymptomatic lacunar infarcts, white matter lesions, cerebral microbleeds, and enlarged perivascular spaces during collaborative image analysis. In cases of disagreement, a consensus was reached during the meeting. The neuroradiologists were blinded to clinical information and assessed all brain MRIs for the presence and location of Cerebral MicroBleeds (CMBs), Lacunar Infarcts (LI), white matter T2 hyperintensities, dilated PeriVascular Spaces (PVS) (29, 30), and cortical infarcts.

Definition of components of the rCSVD score

"rCSVD" score with maximum of 9 was determined by assigning 0–3 points to 3 categories: 1. white matter T2 Hyperintensities, 2. CMBs, and 3. lacunar infarcts as demonstrated in Figure 1. Total SVD and Fazekas scores were determined on each MRI as described in prior publications.

1. **Lacunar infarct (LI):** Acute or chronic lacunar infarcts are defined as 3–15 mm in size focal lesions with decreased diffusion (acute) or the same signal characteristics as cerebrospinal fluid on all MRI sequences, and surrounded by a hyperintense rim on T2-FLAIR images (chronic). (29, 31) For rCSVD scoring they were subdivided into: "strictly lobar" (1 point): within the cerebral hemispheres including frontal parietal, temporal and occipital lobes White matter and excluding deep gray nuclei and internal capsule; "Deep or Infratentorial (D/I)" (2 points): Within basal ganglia, thalamus, internal capsule, midbrain, pons, medulla, and cerebellum. "mixed lobar and D/I" (3 points). Please note that the definition of "deep" lesions of CSVD is variable in the literature in regards to the "deep and periventricular white matter regions." (18, 24) We followed the guidelines in paper by Hans et al (18), where deep and periventricular white matter regions are included in the "lobar" regions.

2. **Cerebral Microbleed (CMB):** CMBs are defined as 2 to 10 mm in diameter round or ovoid areas of homogeneous signal loss on GRE or Susceptibility Weighted Images with blooming effect. For rCSVD scoring they were subdivided into: “strictly lobar” (1 point); “Deep (D) or Infratentorial (I)” (2 points) and “mixed lobar and D/I” (3 points).

3. **White matter T2 Hyperintensities (WMH):** Initially, Fazekas grading was applied as described in prior publications. (11) “rCSVD” White matter T2 Hyperintensities component score was then calculated based on the following: Strictly lobar Fazekas grade Peri-Ventricular White Matter (PVWM) of 3 and/or Deep White Matter (DWM) of 2 or 3: “1 point”, Deep or Infratentorial (D/I) partially confluent T2-Flair hyperintensity (internal capsule, brain stem, or cerebellar white mater): “2 points”, mixed lobar Fazekas grade PVWM of 3 and/or DWM of 2 or 3 AND Deep or Infratentorial (D/I) partially confluent T2-Flair hyperintensity: “3 points”.

Statistical analysis

We used univariable ordinal regression analysis to determine predictive value of rCSVD score (independent variable) for all-cause mortality (dependent variable) in both of our cohorts and recurrent strokes (dependent variable) in 95 patients with known prior stroke. All analyses were Adjusted for age. We then compared the age-adjusted predictive value of rCSVD score with Total SVD and Fazekas scores by comparing the area under the Receiver Operating Curve (ROC) of each analysis. Finally, using Kaplan-Meier survival curves and log-rank tests, we tested the effect of the different cutoffs in the rCSVD score for determining survival by. All statistical analyses were performed with STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). A p-value of <0.05 was considered significant.

RESULTS

Prognostic value of rCSVD score:

“rCSVD score” demonstrates significant predictive value for mortality (OR 1.38, 95% CI 1.08–1.76, p-value 0.009), and recurrent strokes (OR 1.38, 95% CI 1.11–1.72, p-value 0.009).

“rCSVD score” performed slightly better, with statistical significance, for predicting all-cause mortality compared to “total SVD score” and Fazekas score in both cohorts (cohort 1 AUC’s: 0.75 vs 0.73 vs 0.67; cohort 2 AUC’s: 0.75 vs 0.68 vs 0.69; p-value <0.05 for both cohorts) (Figure 2). “rCSVD score” performed slightly better, without statistical significance, for predicting recurrent stroke compared to “total SVD score” and Fazekas score in cohort 2 (AUC’s: 0.75 vs 0.73 vs 0.66; p-value > 0.05).

“rCSVD” score of 2 is most predictive for all-cause mortality. Upon 2–17 years (median: 5.08 yrs; IQR 0.9 yrs) follow-up, Kaplan- Meier survival analysis demonstrated statistically significant (p-values ranging 0.01–0.04) all-cause mortality for rCSVD score cut-offs of 1 through 5 suggesting a large impact by each incremental increase in the score (0=9). We then determined a cut-off score, which is most significant and appropriate for predicting all-cause mortality, for all three scoring systems. The most statistically appropriate rCSVD

score cut-off was at 2 (maximized sensitivity + specificity at 1.393) for predicting all-cause mortality. Similar analysis of total SVD and Fazekas scores determine total SVD cut-point of ≤1 (Youden index: 0.428, Sensitivity + Specificity: 1.428, Distance to corner: 0.5162) and Fazekas cut-point of ≤2 for the Youden index and sensitivity + specificity criteria (0.293, 1.293), and ≤3 for distance to the corner criterion (0.577). The Kaplan-Meier survival curve for an rCSVD score cutoff of 2 and 5 are shown in Supplemental Figure. P-value of 0.0061 at cut-off of 2 and 0.0206 at cut-off of 5 were calculated on Chi-square test.

There was a 30% reduction in survival in patients with rCSVD scores of 6–9 supporting the significant prognostic value of this scoring system. Numerically, median survival was 2987 days (~8.2 years) and 2091 days (~5.7 years) in patients with rCSVD score of 2–5 and greater than 5 (6–9) respectively. In patients with rCSVD score of 0–1 median survival was “too long” and could not be calculated. It’s interesting to note that known clinical comorbidities were not statistically different in the patients within each range of rCSVD score as demonstrated in table 1.

The difficulty of using clinical cardiovascular risk factors for determining cardiovascular health and predicting mortality is demonstrated in our data. Known clinical co-morbid risk factors such as diabetes, hypertension and dyslipidemia were overall not predictive of mortality or recurrent stroke, however we did not include the severity of these risk factors in each subject in our analysis.

Outcome prediction based on individual components of rCSVD score:

Our data demonstrate that cerebral microbleeds, especially in the deep or infra-tentorial locations, are highly predictive of mortality. Upon logistic regression microbleed scores were highly predictive of all-cause mortality (P-Value= 0.008), while lacunar infarcts and white matter T2 hyperintensity scores were not (p-value > 0.05).

Deep and infratentorial CMBs were a significant risk factor for all-cause mortality in our cohorts. In cohort 1, 5 out of 11 (45%), and in cohort 2, 8 out of 19 (42%) patients with mixed or “deep or infra-tentorial (D/I) microbleed” expired. Mortality rate in patients with “any microbleed” was 5 out of 17 (30%) in cohort 1 and 10 out of 31 (32%) in cohort 2. Mortality in patients with mixed or D/I CMB is significantly higher compared to the entire cohort mortality [8 out of 46 (17%) in cohort 1 and 17 out of 95 (18%) in cohort 2] with Fisher’s exact test p-values of 0.013 and 0.005 in cohort 1 and 2 respectively. The percentage of patients with mixed or D/I CMB who expired is greater than double the percentage of all patients death.

Lacunar infarcts were overall a poorer predictor for all-cause mortality in our cohorts. In cohort 1, 6/26 (23%) and in cohort 2, 11/48 (23%) of patients with any lacunar infarct (LI) expired, while 6/15 (40%) and 8/39 (21%) of patients with D/I or mixed LI expired. Fisher’s exact test, demonstrates that D/I or mixed LI is a significant predictor of mortality in cohort 1 (p-value = 0.01), however not in cohort 2 (p-value = 0.6).

Lacunar infarcts were a strong predictor for recurrent stroke in our validation cohort. In cohort 2, 26 out of 95 patients (27%) had recurrent stroke, of whom 18/26 (69%) had LI (2

strictly lobar, 5 D/I, 11 mixed), and out of 18 patients with LI 16 (89%) had D/I or mixed LI. Fisher's exact test, demonstrates that D/I or mixed LI is a significant predictor of recurrent strokes in cohort 2 (p-value = 0.000013).

Addition of perivascular spaces (0 or 1) to our scoring system did not significantly change the results of our study as described.

DISCUSSION

Accurate assessment and monitoring of cardiovascular health by using clinical co-morbid risk factors such as diabetes, hypertension and dyslipidemia is difficult, frequently inaccurate, and time-intensive. This dictates the need for an objective, precise, and accurate biomarker such as an imaging-based scoring system. In this study we showed that rCSVD score can be determined on routine brain MRI and has construct validity in a retrospective cross-sectional study of 46 patients. We validated the score in a cohort of 95 patients with stroke. "rCSVD score" is predictive of all-cause mortality in both cohorts with slightly better performance, with statistical significance, compared to "total SVD" and Fazekas scores. While these differences may not be clinically significant, they suggest "rCSVD score" as the initial building block for a more accurate and clinically relevant scoring system.

Our results, utilizing a total of 141 subjects, are congruent with prior studies with larger cohorts. In a meta-analysis of 94 studies (with up to 14,529 patients for white matter hyperintensities, 16,012 patients for "MRI-defined brain infarcts", and 15,693 patients for CMBs), extensive white matter hyperintensity burden, "MRI-defined brain infarcts" defined as usually asymptomatic small subcortical infarcts, and CMBs were associated with higher risk of incident stroke and death. (32)

Based on the information presented in this paper, we believe that the location of different CSVD MRI markers should be considered when assessing the total burden of CSVD. These characteristics signify variable pathophysiology of CSVD as discussed in the introduction section. A larger score range (for example 0–9 in rCSVD vs. 0–4 in Total SVD) will allow more finely-tuned cutoff points for outcome studies. For example, in our cohort of 95 patients with stroke we determined cut-off rCSVD score of 2 for predicting all-cause mortality maximized the sum of sensitivity and specificity compared to other cut-off points.

Limitations:

This study has several limitations. First, our scoring system is derived solely from cross-sectional data of predominantly male veterans, who are known to have a high rate of co-morbid vascular risk factors, CSVD and stroke, for both derivation and validation. Prior studies have demonstrated sex difference in stroke, brain aging, Alzheimer's disease and dementia. (33–35) In addition, the epidemiology of cerebral vascular disease is variable across countries and ethnicities. For example, Asians have a two-times higher proportion of intracranial hemorrhage, and a different distribution of ischemic stroke subtypes compared with white populations of European and US origin. (18, 36, 37) Hence, prospective, longitudinal, large cohort, prospective studies that encompass men and women and various ethnicities and countries are required to explore the predictive ability and association of

rCSVD score at single and multiple time points with outcomes such as stroke risk and death. Second, we report all-cause mortality as our main outcome in this study. In future studies with a larger cohort, cardiovascular mortality should be separate from other causes of mortality. Third, since lobar, but not deep or infratentorial, abnormalities such as CMB's are associated with changes in cognitive function (26), a modified rCSVD score may be more appropriate for prediction of cognitive decline and dementia. For example, a scoring platform in which lobar abnormalities are assigned a higher grade than deep and infratentorial ones.

Future directions:

Currently, there are no proven and established guidelines for management of CSVD (18, 19, 25, 32, 38–46). For example, the utility and risk/benefit ratio of aspirin, antiplatelet therapy, and extent of blood pressure control in patients with CSVD features such as lacunar infarcts, CMBs, or white matter T2 hyperintensities remain elusive. These challenges contribute to a wide variation in clinical practice (32). An important feature of a clinical trial to address this gap is quantitative measurement of CSVD. Quantitative measures are essential to reduce the variability seen in multicenter clinical trials, determining the utility and consequence of experimental transitional treatments, and developing and evaluating new diagnostic tools. An easy to calculate, pragmatic, and physiologically sensible scoring system relying on imaging features that can be obtained on routine clinical MRIs is ideal for this purpose. This type of scoring system can improve communication amongst clinicians, radiologists, and researchers, stratify patients in clinical trials, and contribute to early outcome prediction. For example, instead of new stroke or death being the endpoint of an experimental preventative or treatment modality, a quantitative radiologic metric such as progressive CSVD score can serve as a surrogate endpoint.

Historical difficulty in accurately assessing the severity of CSVD on imaging has not been appropriately addressed by the currently introduced scoring systems. However, the need for a quantitative measure of CSVD and specific cut-offs for clinical outcomes are crucial in measuring cardiovascular health, guiding patient counseling, risk factor modification, and treatment selection. We believe that computerized automation of CSVD assessment on routine brain MRI sequences or utilization of novel imaging techniques such as vessel size imaging (VSI) (47) can eventually lead us towards precise and accurate assessment of CSVD. In the meantime, we hope that our rationale and scoring system serves as a steppingstone for an ideal standardized scoring system for CSVD, that will enhance the progress of treatment-seeking clinical trials, patient counseling, and preventative medicine.

CONCLUSION

"rCSVD" score can be calculated on routine brain MRI and provides a pragmatic and physiologically relevant estimate of the full impact of CSVD on the brain especially in setting of stroke care and prevention. We hope that our rationale and scoring system serve as steppingstones for an ideal standardized scoring system for CSVD and cardiovascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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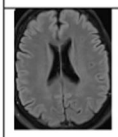
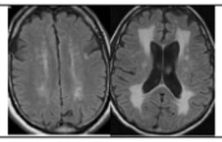
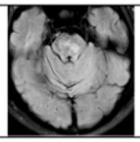
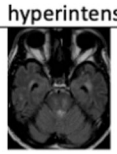
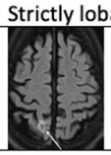
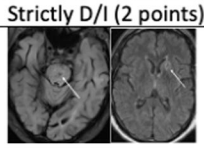
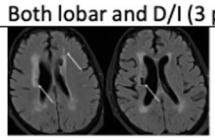
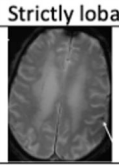
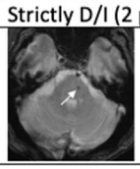
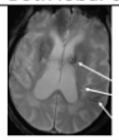
White matter T2 hyperintensities	Fazekas grade PVWM of <3 and/or DWM of <2 (0 point)	Strictly lobar Fazekas grade PVWM of 3 and/or DWM of 2 or 3 (1 point)	D/I partially confluent T2-Flair hyperintensity (rare) (2 points)	Combined lobar Fazekas grade PVWM of 3 and/or DWM of 2 or 3 AND D/I partially confluent T2-Flair hyperintensity (3 points)
				
Small focal or lacunar infarcts*	Absent (0 point)	Strictly lobar (1 point)	Strictly D/I (2 points)	Both lobar and D/I (3 points)
				
Micro-bleeds	Absent (0 point)	Strictly lobar (1 point)	Strictly D/I (2 points)	Both lobar and D/I (3 points)
				

Figure 1.

Regional Assessment of Cerebral Microvascular Disease (rCSVD) Score features and categories. PVWM: Peri-Ventricular White Matter, DWM: Deep White Matter, D/I: Deep or Infratentorial.

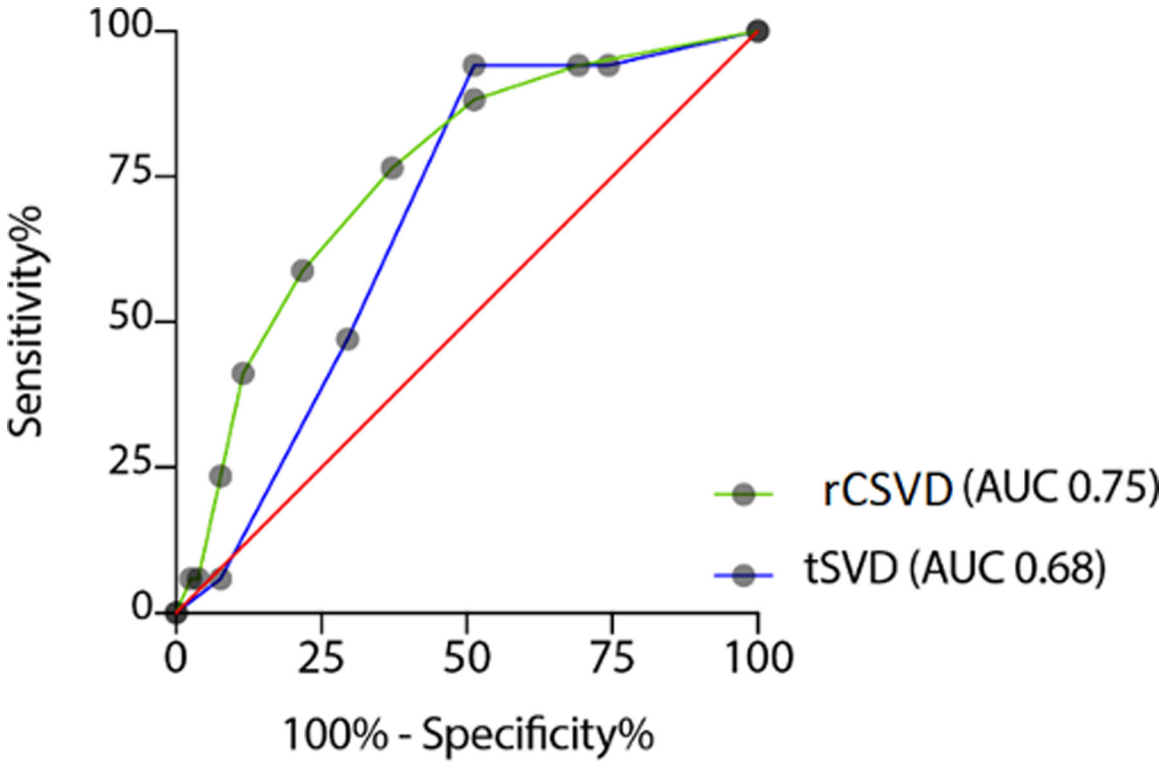


Figure 2.

Comparison of all-cause mortality receiver operating characteristic curves for rCSVD score and total SVD score (tSVD) adjusted for age, demonstrate superiority of rCSVD performance score for predicting all-cause mortality (0.75 vs 0.68; p-value 0.046). Define the color of lines here.

Table 1.

Patient demographics, risk factors and MRI attributes of Cohort 2 (validation of rCSVD).

	All Subjects N = 95	**All-Cause mortality N = 17**	**Alive at 2–17 years follow-up N = 78**
Traditional Cardiovascular Risk Factors			
Sex, male, *n (%)*	89 (94%)	17 (100%)	72 (92%)
Age, years, *mean (SD)*	66.7 (10.4)	71.4 (10.1)	65.7 (10.3)
Hypertension, *n (%)*	79 (83%)	14 (82%)	65 (83%)
Diabetes, *n (%)*	31 (33%)	6 (35%)	25 (32%)
Dyslipidemia, *n (%)*	85 (89%)	17 (94%)	68 (87%)
Smoking, n (%)	47 (49%)	9 (53%)	38 (49%)
MRI Risk Factors			
All Lacunar Infarcts (LI), *n (%)*	48 (51%)	11 (65%)	37 (47%)
"strictly lobar" LI, *n (%)*	9 (9%)	3 (18%)	6 (8%)
"Deep/Infratentorial (D/I)" LI, *n (%)*	20 (21%)	5 (29%)	15 (19%)
"Mixed Lobar and D/I" LI, *n (%)*	19 (20%)	3 (18%)	16 (21%)
All Cerebral Microbleed (CMB), *n (%)*	31 (33%)	10 (59%)	21(27%)
"strictly Lobar" CMB, *n (%)*	12(13%)	2(12%)	10 (13%)
"Deep/Infratentorial (D/I)" CMB, *n (%)*	9 (10%)	3 (18%)	6 (8%)
"Mixed lobar and D/I" CMB, *n (%)*	10(11%)	5 (30%)	5 (6%)
Scoring Systems			
Fazekas Score, *median (range)*	3 (0–6)	3 (2–6)	3 (0–6)
Total SVD Score, *median (range)*	2 (0–4)	2 (0–4)	2 (0–4)
rCSVD score, *median (range)*	2 (0–9)	4(0–9)	2 (0–9)