Cerebral Small Vessel Disease Burden and All-Cause Mortality: Mayo Clinic Florida Familial Cerebrovascular Diseases Registry

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Goal: Cerebral small vessel disease (CSVD) leads to cognitive decline, gait disturbances, mood changes, and an increased risk of stroke. The goal of this study is to describe the relationship between a composite radiographic CSVD score and all-cause mortality. *Materials and Methods:* Data were collected from a prospective registry of patients with and without cerebrovascular disease from November 2010 through April 2018. The radiographic Total CSVD Score (tSVD) ranges from 0 (minimal disease) to 4 (severe disease), based on detection of lacunar infarcts, cerebral microbleeds, perivascular spaces, and subcortical or periventricular white matter hyperintensities. All-cause mortality served as the primary endpoint. The independent relationship between CSVD burden and all-cause mortality was assessed using Cox regression models with significance being $P < .05$. *Findings:* Four hundred and forty-nine patients were included (mean age, 63 years; 50.1% [225 of 449] women). The hazard ratio for mortality significantly increased with advancing score (1.92, $P = .014$ score 1; 2.92, $P < .001$ score 2; 4.23, $P < .001$ combined scores 3 and 4). Significance remained despite adjustment for coexistent cerebrovascular risk factors aside from age. *Conclusions:* The clinically practical tSVD score may serve as a predictor for all-cause mortality in populations with high disease prevalence. Continued investigations are needed to better understand the effects of risk factor modification on mortality and pathogenesis with the goal of developing disease modifying therapies.
Key Words: Cerebrovascular disease—stroke—cerebral microangiopathy—mortality—stroke imaging

Introduction

Cerebral small vessel disease (CSVD) is a common heterogeneous disease affecting the small leptomeningeal and intraparenchymal arteries, arterioles, capillaries, and venules of the brain stemming from the subarachnoid or large intraparenchymal arterial ciruclations.[1] CSVD of varying degree occurs in as many as 90% of adults aged 60-90 years, contributing to about 45% of dementias and 20%-30% of strokes, as well as to progressive gait dysfunction and increased mortality.[2-7] Moreover, as evidenced by the Leukoaraiosis and Disability Study, the accumulation of CSVD over a period of 3 years increases the rate of disability from 9% for mild disease to 26% for severe disease as well as negatively affecting quality of life and autonomy.[8]

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Received November 1, 2018; revision received June 17, 2019; accepted July 3, 2019.
The Mayo Clinic Familial Cerebrovascular Diseases Registry is approved by the IRB # 08-003878.
Dr. James F. Meschia receives financial support from the following donor funds: the Earl and Nyda Swanson Neurosciences Research Fund and Harley N. and Rebecca N. Hotchkiss Endowed Fund in Neuroscience Research honoring Ken and Marietta.
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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.07.001

Given the significant clinical and societal implications of CSVD, surrogate scales of CSVD have been developed to stratify burden of disease to allow for clinical implementation. The total Cerebral Small Vessel Disease (tSVD) score was developed to grade several radiographic markers of CSVD burden, including lacunes, cerebral microbleeds, white matter hyperintensities (WMH) and enlarged perivascular spaces.[9] Several studies have previously examined the predictive value of the tSVD score with evidence for increased risk of first-time and recurrent stroke, onset of dementia or cognitive decline (in particular executive dysfunction), recurrent mixed-etiology intracranial hemorrhage and all-cause mortality.[9-14]

Though studies have found several associations between increasing ordinal tSVD and worsened cerebrovascular outcome, the majority of those studies were performed in East Asian and Western European cohorts. The goal of our study is to determine whether similar relationships exist between ordinal tSVD score and all-cause mortality, dementia, and recurrent stroke in a diverse North American cohort.

Materials and Methods

Study Population

Patient data were obtained via the Mayo Clinic Florida Familial Cerebrovascular Diseases Registry, which prospectively enrolls adults with more than 25 various cerebrovascular diseases in both inpatient and outpatient settings. A description of this Registry, has been previously published.[15] Participants or their surrogates provided written informed consent to participate in the Registry, and the Registry is approved by the Mayo Clinic Institutional Review Board (IRB No 08-003878). Inclusion criteria for this analysis were as follows: age older than or equal to 18 years and brain magnetic resonance imaging (MRI) with the necessary sequences for tSVD interpretation. Participants in this analysis were enrolled in the Registry from November 2010 to April 2018 following a systematic intake evaluation. Medical and surgical comorbidities, stroke severity (National Institutes of Health Stroke Scale), and cognitive status (Mini Mental State Exam) were documented upon enrollment into the Registry. Patient death status was obtained through the National Death Index, with all-cause mortality serving as the primary endpoint. Secondary outcomes including recurrent/new ischemic stroke, recurrent/new hemorrhagic stroke, and new diagnosis of dementia were abstracted from electronic medical records.

Brain MRI Interpretation

All patients were scanned using a 1.5-3 Tesla MRI either at Mayo Clinic in Florida or at a referring facility. Standard-of-care brain MRIs were obtained in either the inpatient or outpatient settings. The tSVD was calculated by 3 of the authors (E.D.G., M.K.B., and T.F.H.). The tSVD scores discretely range from 0 (no burden) to 4 (significant burden). Per the tSVD score, patients were given one point for each of the following categories: more than or equal to 1 lacunar infarct; more than or equal to 1 cerebral microbleed; presence of grade 2-4 perivascular spaces; or a Fazekas periventricular (PVWM) or deep white matter (DWM) grade of 3 and more than or equal to 2, respectively.[9] Lacunar infarcts were identified as 3-20 millimeter hyperintense, ovoid lesions on T2-weighted and T2-weighted fluid attenuation inverted recovery sequences within subcortical regions. Perivascular spaces were identified as rounded structures primarily within the basal ganglia of greater than 3 millimeter in width, of similar intensity to cerebrospinal fluid, and graded using a quantitative scale (grade 0 = none, grade 1 = <10, grade 2 = 11 to 20, grade 3 = 21 to 40, grade 4 = >40).[16] Differentiation of lacunar infarcts and perivascular spaces is aided by evidence of perilesional gliosis, T2 signal pattern, lesion width, and cerebral location. WMH were defined as T2 hyperintense lesions with increasing grade dependent on confluence of the lesions. Fazekas grade 3 for PVWM describes a nonuniform extension of T2 hyperintensity from the lateral ventricle into the adjacent subcortical white matter. The Fazekas DWM grades 2 and 3 describe beginning WMH confluence and advanced WMH confluence, respectively.[17] Susceptibility-weighted imaging and gradient recalled echo sequences were used to assess for presence of cerebral microbleeds, which are described as less than 5 millimeter rounded foci of hypointensity within subcortical regions.

Statistical Analysis

Single and multivariable Cox-proportional hazards models were used to assess the relationship between tSVD and all-cause mortality. This strategy was again used to evaluate tSVD score with the composite endpoint of stroke or dementia in both the overall registry and with those solely with a diagnosis of acute ischemic stroke. Time to death was calculated as the number of years from the individual's MRI to the recorded death, stroke and/or dementia. Grades 3 and 4 of tSVD were combined to achieve adequate variability. To reduce possible confounding, multivariable models were adjusted first for age at MRI and sex, and second for cerebrovascular risk factors (eg, atrial fibrillation, diabetes mellitus, coronary artery disease, and chronic arterial hypertension). The Kaplan-Meier method was used to estimate overall patient survival with their corresponding 95% confidence intervals for every one year following the patient's MRI. Continuous variables were summarized with median and range, and categorical variables were summarized with frequency and percent. Continuous differences between tSVD score groups were tested using the Krukal-Wallis Rank Sum test, and proportional differences were tested using the Pearson Chi-square test. All tests were 2-sided and P values less than .05 were considered statistically significant. Adjustment for multiple testing was not implemented due to high correlations between models assessed. All statistical analysis was

performed using R Statistical Software version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria.

Results

Patient Population

A total of 1034 patients were included in the Registry from November 2010 through April 2018. Of the 1034 patients screened, 43.4% (449 of 1034) patients had a brain MRI with the necessary sequences and available mortality data (Fig 1). Inter-rater reliability was acceptable ($k = .7$ based on 50 independently evaluated overlapping cases). The median age was 63 years at the time of MRI, ranging 18-100 years ($p < .001$). The cohort was 86% (386 of 449) white and 50.1% (225 of 449) women. Further demographic information including common cerebrovascular comorbid risk factors is included in Table 1. A primary diagnosis of acute ischemic infarct was recorded for 55.7% (250 of 449) of individuals; 6.3% (28 of 449) had a diagnosis of symptomatic intracerebral hemorrhage; 4.7% (21 of 449) had aneurysmal subarachnoid hemorrhage; 19.8% (89 of 449) had cerebral microbleeds, and 6.2% (28 of 449) had grade 2-4 enlarged perivascular spaces. The remaining 33 individuals had various miscellaneous cerebrovascular diagnoses. A Fazekas DWM grade of 0 was found in 36% (164 of 449), grade 1 in 37% (165 of 449), grade 2 in 15% (68 of 449), and grade 3 in 12% (52 of 449). A Fazekas PVWM grade of 0 was found in 25% (112 of 449); grade 1 in 42% (188 of 449); grade 2 in 22% (99 of 449); and grade 3 in 11% (50 of 449). Among those with a primary diagnosis of acute ischemic stroke (AIS), a Fazekas DWM grade of 0 was found in 26% (66 of 250); grade 1 in 40% (100 of 250); 2 in 21% (52 of 250); and grade 3 in 13% (32 of 250) and a Fazekas PVWM grade of 0 in 19% (48 of 250); grade 1 in 40% (99 of 250); grade 2 in 26% (66 of 250); and grade 3 in 13% (32 of 250).

Of the total 449 individuals, 29.8% (134 of 449) were enrolled as outpatients and 70.2% (315 of 449) were enrolled as inpatients. Inpatients had a median age of 66 years (range: 23-100 years), were mostly male (55.6%, 175 of 315) and had a lower median body mass index than outpatients (27.9 versus 29.0, $P \leq .016$). A plurality of the inpatient cohort were diagnosed with acute ischemic stroke (25.4%, 80 of 315, $P \leq .001$) and had ordinal values on Fazekas DWM and PVWM grading greater than or equal to 2 ($P \leq .001$). Amongst the 250 individuals with acute ischemic stroke, 86.4% (216 of 250) had the MRI performed while inpatient.

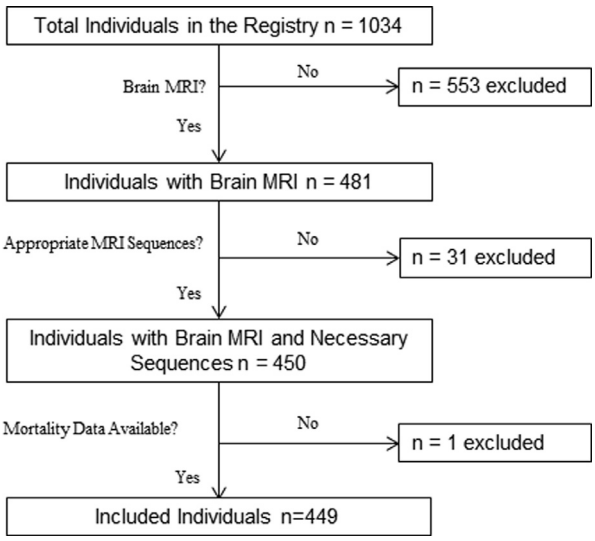

Figure 1. *Flowchart of patient selection.*

Total Cerebral Small Vessel Disease Scores

Of the 449 patients included 48.1% (216 of 449) scored 0 on the tSVD scale; 26.9% (121 of 449) scored 1; 16.5% (74 of 449) scored 2; 8.4% (38 of 449) scored either 3 or 4. Increasing age was associated with an increase on the tSVD grading scale, with mean ages of 55 (range: 18-87), 64 (range: 22-100), 72 (range: 25-95), and 75 (range: 60-96) for tSVD scores 0, 1, 2, and combined 3 and 4, respectively (Fig 2). With increasing tSVD score, there was an association with the presence of other systemic findings of vasculopathy or its risk factors including coronary artery disease ($P = .002$), congestive heart failure ($P = .005$), pack-years tobacco use ($P = .028$), chronic arterial hypertension ($P < .001$), and advancing age ($P < .001$) (Table 1). Evaluation of only those with AIS revealed 43% (109 of 250), 25% (64 of 250), 19% (48 of 250), and 12% (30 of 250) with scores of 0, 1, 2, and combined 3 to 4, respectively.

All-Cause Mortality

All-cause mortality occurred over a 6-year period of enrollment in 13% (28 of 216), 24% (29 of 121), 33% (24 of 74), and 44% (17 of 38) patients with tSVD scores 0, 1, 2, and combined groups 3 and 4, respectively. Advancing tSVD score resulted in increased all-cause mortality: tSVD score 1 (unadjusted hazard ratio [HR] 1.92; 95% confidence interval [CI] 1.14-3.23; $P = .014$), score 2 (unadjusted HR 2.92; CI 1.69-5.03; $P < .001$), combined scores 3 and 4 (unadjusted HR 4.23; CI 2.31-7.75; $P < .001$). Significance was maintained when adjusted for common comorbid cerebrovascular risk factors ($P < .001$, Fig 3). Adjustment of all-cause mortality to composite age at time of brain MRI and gender resulted in loss of significance. The estimated Kaplan-Meier survival curve revealed a time-dependent association between all-cause mortality and advancing unadjusted tSVD score (Fig 3). An increasing rate of all-cause mortality was also noted within the AIS cohort: tSVD score 1 (HR = 1.93; CI 0.99-3.74, $P = .05$), score 2 (HR = 2.91; CI 1.51-5.59, $P = .001$), and score 3 to 4 (HR = 4.01; CI 1.97-8.19, $P < .001$), with survival differences appearing 2 years postenrollment.

Secondary Outcomes

Roughly 19% (85 of 449) of patients experienced a secondary outcome following enrollment. Specifically, 37.6% (32 of 85) developed dementia (Mini Mental State Exam <23),

Table 1. *Patients' baseline demographics in relation to the tSVD score % (n)*

	0 (N = 216)	1 (N = 121)	2 (N = 74)	3 and 4 (N = 38)	Total (N = 449)	*P* value
Ethnicity % (n)						.97
East Asian	2.3 (5)	2.5 (3)	1.4 (1)	2.6 (1)	2.2 (10)	
Black or African American	12.9 (28)	8.3 (10)	12.2 (9)	10.5 (4)	11.3 (51)	
More than one race	0.5 (1)	0.8 (1)	0 (0)	0 (0)	0.4 (2)	
White	84.3 (182)	88.4 (107)	86.5 (64)	86.8 (33)	86 (386)	
Sex % (n)						.831
Female	49.3 (107)	52.1 (63)	52.7 (39)	44.7 (17)	50.2 (226)	
Male	50.7 (110)	47.9 (58)	47.3 (35)	55.3 (21)	49.8 (224)	
Enrollment age						<.001
Mean (SD)	55 (±16)	64 (±16)	72 (±15)	75 (±9)	62 (±17)	
Median (Range)	55 (18, 87)	64 (22, 100)	72 (25, 95)	76 (60, 96)	63 (18, 100)	
Atrial fibrillation % (n)	11.1 (24)	17.4 (21)	18.9 (14)	28.9 (11)	15.5 (70)	.126
DMII* % (n)	20.7 (45)	22.3 (27)	29.7 (22)	28.9 (11)	23.3 (105)	.57
CAD† % (n)	12 (26)	14.9 (18)	29.7 (22)	26.3 (10)	16.9 (76)	.002
CHF‡ % (n)	4.6 (10)	3.3 (4)	14.9 (11)	5.3 (2)	6 (27)	.006
BMI§, mean (SD) kg/m^2	29.9 (10.4)	28.9 (5.9)	28.8 (5.9)	27.0 (4.8)	29.209 (8.321)	.202
Former/current tobacco user % (n)	51.2 (111)	52 (63)	59.4 (44)	42.1 (16)	52 (234)	.30
Pack-years tobacco use, mean (SD)	13 (±22)	20 (±28)	19 (±26)	11 (±21)	16 (±25)	.093
Chronic arterial hypertension % (n)	51.4 (110)	68.3 (82)	80.8 (59)	86.8 (33)	63.8 (284)	<**.001**

*Diabetes mellitus type II.
†Coronary artery disease.
‡Congestive heart failure.
§Body mass index.

56.5% (48 of 85) developed stroke and 5.9% (5 of 85) developed both stroke and dementia. Of those with the primary diagnosis of AIS, 13.6% (34 of 250) had recurrent AIS and 0.8% (2 of 250) developed an intracranial hemorrhage. The unadjusted tSVD score significantly predicted time to recurrent stroke (ischemic and hemorrhagic) and dementia: tSVD score 1 had a HR of 1.31 (CI .75-2.26); score 2, HR = 1.74 (CI 0.95-3.2); and score 3 to 4, HR = 2.25 (CI 1.10-4.61); (Fig 4).

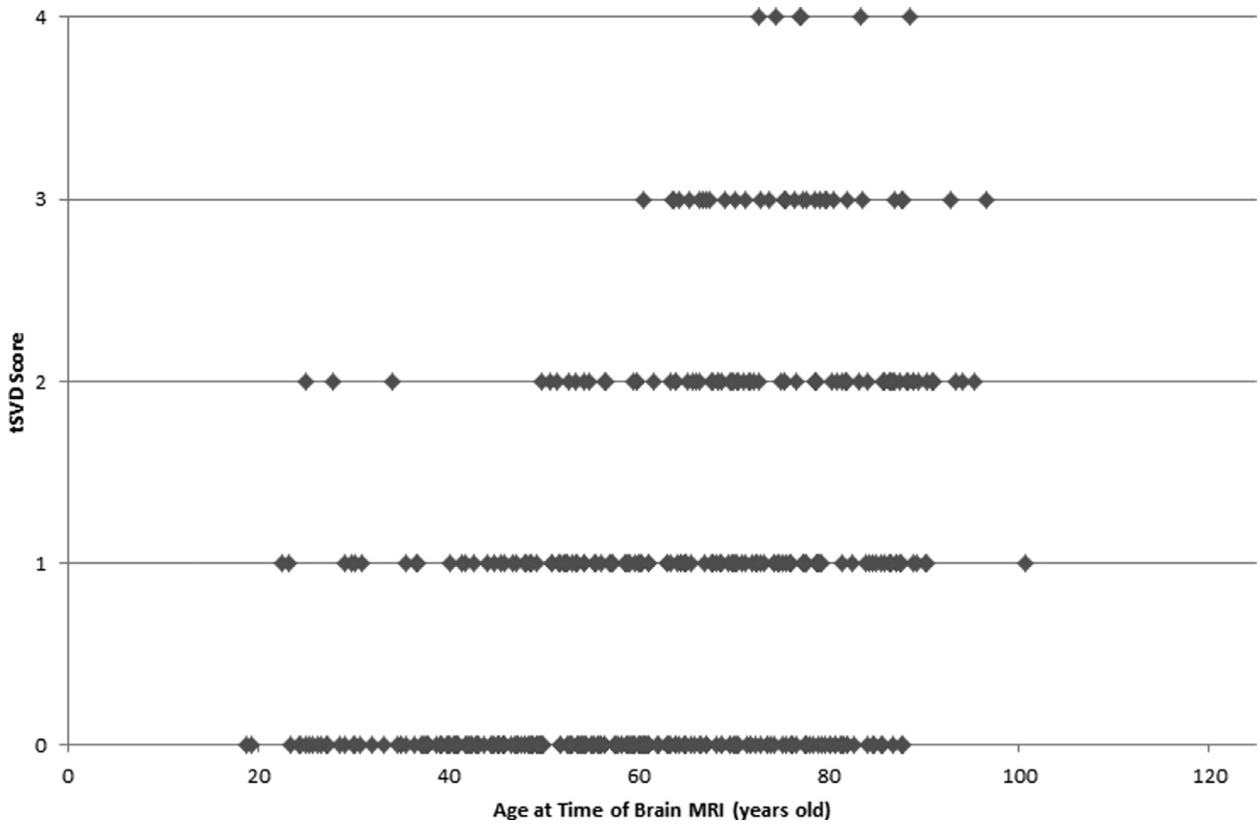

Figure 2. *Age plotted against tSVD at the time of MRI. Abbreviations: MRI, magnetic resonance imaging; tSVD, Total Cerebral Small Vessel Disease.*

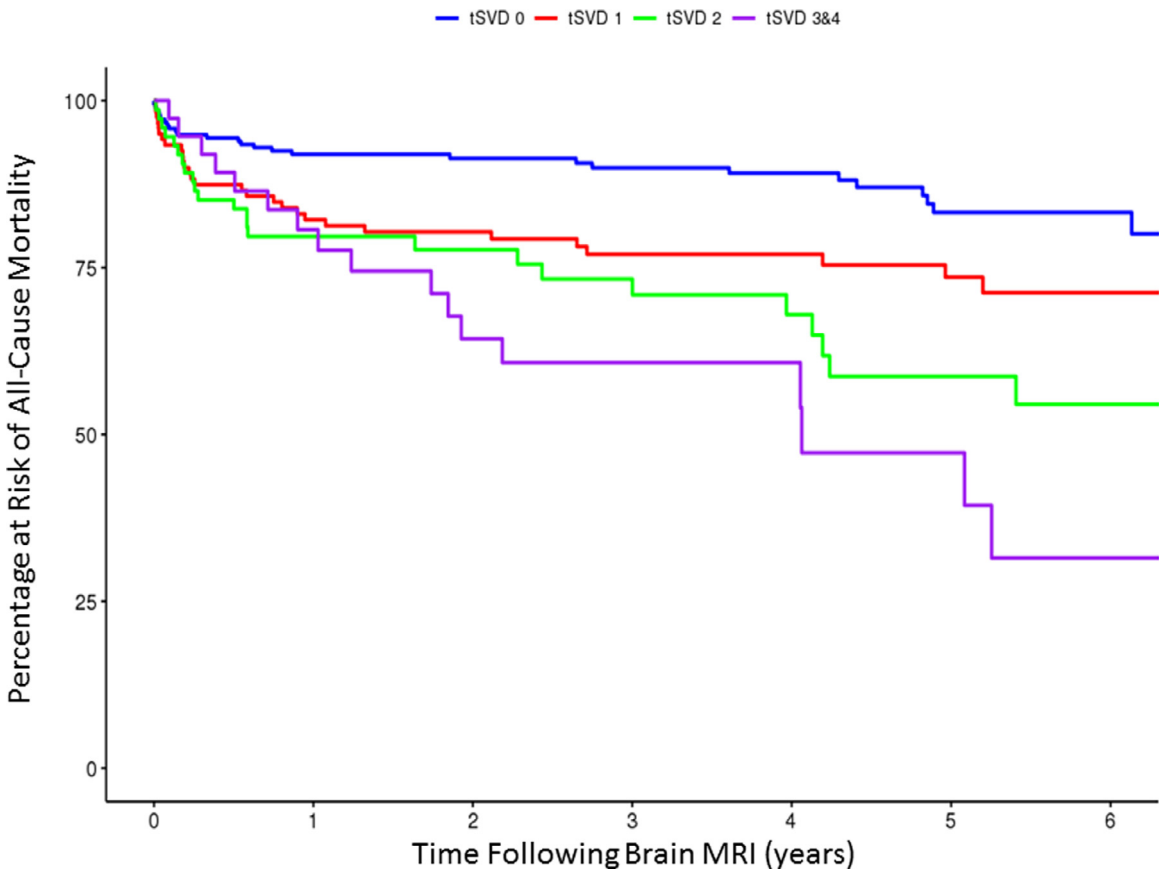

Figure 3. *Estimated Kaplan-Meier survival curve for all-cause mortality based on tSVD score. Abbreviations: tSVD, Total Cerebral Small Vessel Disease.*

Once adjusted for age at MRI and sex or common cerebrovascular risk factors, tSVD was no longer significant (P = .054). The tSVD score was not a significant predictor of composite end point within AIS patients ($P \leq .18$).

Discussion

Our study revealed a predictable time-dependent increase in all-cause mortality with advancing grade of tSVD score. Most notably a tSVD score of 3 or 4 resulted in a 4-fold increase in risk of mortality. For those with an enrollment diagnosis of AIS, there was a slightly elevated HR when compared to the larger cohort; however the comparative survival difference was shorter (2-years versus 6-years). These results are consistent with available data correlating burden of CSVD and mortality by various means.[4,10-15,18,19] In our heterogeneous North American cohort, we did find that statistical adjustment for age led to lack of statistical significance of the tSVD score. A previous study had shown continued significance of the tSVD score when adjusting for Framingham risk factors though did not report a result adjusted solely based on age.[14] The tSVD score may serve as a simple, reliable method for visually scoring several indicators of CSVD and aid as a general clinical tool for providers in counseling patients.[8]

Limitations include the assumption that each of the tSVD data points are of equal weight, which may artificially increase or decrease the total score as well as the heterogeneity of MRI protocols used amongst varying sites (eg, 1.5T versus 3T and susceptibility-weighted imaging versus gradient recalled echo). Factors outside the scope of the tSVD score may be of influence, including poor mural integrity of native intracerebral vessels, extracranial vessel disease (eg, coronary, aortic arch, and carotid), antithrombotic therapy and the underlying pathogenic nature of the individual's CSVD. Additionally, other neuroimaging characteristics of CSVD may influence mortality and functional outcomes, such as location of the WMH (eg, gray-white interface, periventricular based, and pontine), severity and/or pattern of cortical atrophy, rate of WMH accumulation, and presence of intracerebral large- or medium-vessel atherosclerosis. Future studies are needed to focus on correlations between the tSVD scale and rates of hospitalization or rehospitalization, economic burden of advanced scoring patients, hereditary risk stratification, and effects of disease modifying strategies on all-cause mortality.

In summary, the tSVD score is associated with long-term morbidity and mortality despite the fact that it summarizes heterogeneous pathologies. A general sense of CSVD burden may be quantified using the brain MRI-based tSVD

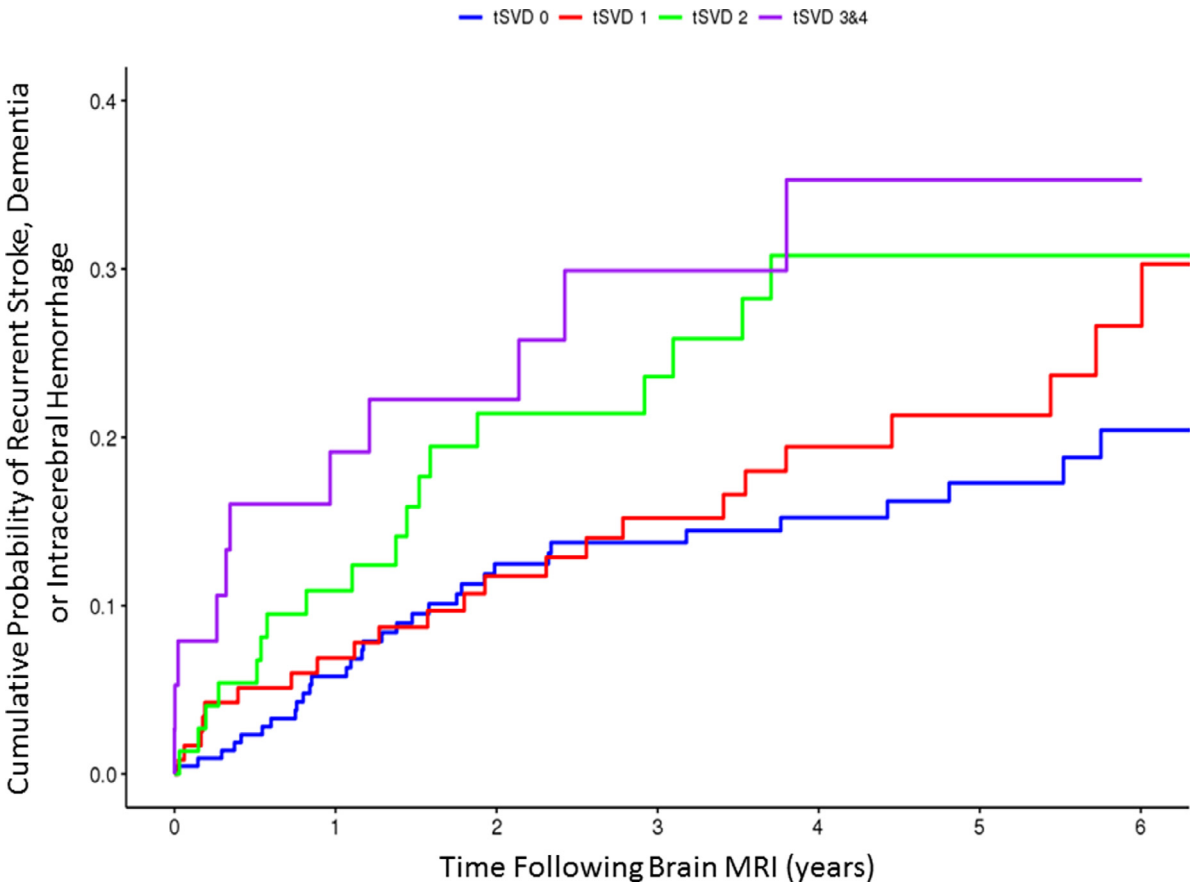

Figure 4. *Cumulative probabilities of ischemic stroke, intracerebral hemorrhage, or dementia with Total Cerebral Small Vessel Disease (tSVD) score.*

scoring system. Our data reveal that with increasing unadjusted tSVD score there is an increase in all-cause mortality, rate of recurrent stroke and dementia. The results of this study may be used as an aid in broad prognostication of all-cause mortality in patients with CSVD.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

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