



The global burden of cerebral small vessel disease related to neurological deficit severity and clinical outcomes of acute ischemic stroke after IV rt-PA treatment

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Abstract

Background and purpose Various types of cerebral small vessel diseases (CSVD) are commonly coexisting and the clinical outcome possibly is determined by their combined effect. The present study was designed to explore the possible relationship between the global burden of CSVD and clinical outcomes after recombinant tissue plasminogen activator (rt-PA) treatment of ischemic stroke.

Methods We enrolled patients with acute ischemic stroke (AIS) after IV rt-PA treatment between August 2016 and July 2018. According to the total burden rating scale of CSVD, we calculated the total CSVD score for white matter hyperintensities, lacunar infarction, cerebral microbleeds, and perivascular spaces. All patients were assessed on the basis of the National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin Scale (mRS) score at 90 days after stroke. We used multivariate logistic regression analysis to examine the associations between global burden of CSVD and degree of neurological deficit and clinical outcomes. ROC curve analysis was used to determine cut-off values of the total CSVD score in predicting poor outcomes.

Results The results showed that the total CSVD score was independently associated with moderate to severe stroke (OR 2.187, 95%CI 1.495–3.119, $P < 0.001$). Initial NIHSS (OR 1.23, 95%CI 1.144–1.330, $P < 0.001$), OTT (OR 1.007, 95%CI 1.000–1.014, $P = 0.037$), and CSVD score (OR 3.157, 95%CI 2.120–4.703, $P < 0.001$) was significantly related to poor functional outcome at 3 months. The total CVSD score cut-off value of 1.5 was determined at best to distinguish between good prognosis and poor outcome (AUC 0.7534 [95%CI 0.6883–0.8185]).

Conclusions The global burden of CSVD was independently associated with neurological deficit severity and clinical outcomes of AIS after IV rt-PA treatment. The total CVSD score is a reliable predictor for poor outcomes of AIS after IV rt-PA treatment.

Keywords Acute ischemic stroke · Intravenous thrombolysis · Cerebral small vessel disease · Neurological deficit severity · Outcomes

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Introduction

Stroke is the second most common cause of death and the leading cause of disability worldwide. Intravenous thrombolysis is regarded as the standard of therapy in acute ischemic stroke [1, 2].

Cerebral small vessel disease (CSVD) is a common finding among patients with acute ischemic stroke, which accounts for about 25% of all ischemic stroke patients, particularly if they are older or have vascular risk factors [3]. From a clinical point of view, CSVD contributes to a risk of cognitive decline, dementia, and stroke, and causes considerable worsening of cognitive function, balance, and gait [4]. The most common type of CSVD is age- and hypertension-related CSVD, which is recognized as a risk factor of ischemic stroke [5]. In general, CSVD has been associated with dysfunction of the blood–brain barrier (BBB), endothelial dysfunction, ischemia, hypoperfusion, amyloid deposition, and genetic factors [6–8].

In recent years, the development of neuroimaging has improved the diagnostic rate of CSVD and the number of neuroimaging spectrum ascribable to CSVD has been expanded including leukoaraiosis, microbleeds, lacunar infarcts, perivascular spaces, and brain atrophy. Magnetic resonance (MR) is the gold standard imaging for CSVD, and five closely correlated features are markers on brain MR: white matter hyperintensities (WMHs), lacunar infarction (LI), cerebral microbleeds (CMBs), perivascular spaces (PVS), and brain atrophy.

Previous studies showed that leukoaraiosis severity had been associated with the size of the acute ischemic tissue damage and degree of infarct expansion, as well as initial National Institutes of Health Stroke Scale (NIHSS) deficit severity [9–11]. Leukoaraiosis and infarct volume were independently associated with a greater NIHSS deficit in the fully adjusted multivariable model [12]. Leukoaraiosis severity may be associated with poor outcomes after successful recanalization for ischemic stroke with anterior large vessel occlusion [13]. However, these MRI markers of CSVD often occur together in individual people. Recently, efforts have been made to quantitatively assess specific CSVD markers. A lot of current evidence focuses on the effects of single features of CSVD on acute ischemic stroke treated with thrombolysis, and the results indicate that the presence of CSVD may increase the risk of symptomatic intracerebral hemorrhages and may be associated with poor functional outcomes [14, 15]. However, CSVD is a pathological process with heterogeneous etiologies, and whether the combinations of various imaging features of CSVD can better predict deficit severity and relevant clinical outcomes is little known. From the attempts to devise a joint CSVD score representative of the people's CSVD burden, a major effort has been made by Staals' Maastricht collaborative group, based on visually rated individual CSVD features which are combined into the "total

CSVD burden," yielding a 0 to 4 total CSVD score [16]. This CSVD score has been reported by multiple research groups to be related to cognitive function [17]. Few studies have combined these features to capture the total CSVD burden and to examine associations with stroke types or cerebrovascular risk factors [18, 19]. The global CSVD burden score might capture the overall effects of CSVD on the cerebral hemisphere better than by considering just one or two individual features separately [20], and provide a more complete estimate of the full impact of CSVD on the brain, in a simple and pragmatic way. This emphasizes the importance of considering total brain damage due to CSVD.

Although, the total CSVD score has been shown to predict cognitive impairment in the elderly population [17] and in patients with hypertension [21]. It remains uncertain whether the score also predicts neurological deficit severity and clinical outcomes after IV recombinant tissue plasminogen activator (rt-PA) treatment in patients with ischemic stroke or transient symptoms with infarction (TSI).

In the present study, we aimed to investigate whether the global burden of CSVD was associated with neurological deficit severity and clinical outcomes after IV rt-PA treatment.

Methods

Study population The present study was conducted in the Stroke Center of the First Hospital Affiliated to Soochow University and performed a retrospective analysis of prospectively collected data between August 2016 and July 2018. Two hundred eighteen consecutive patients with acute cerebral infarction were admitted to our study, treated with intravenous (IV) rt-PA within 4.5 h from symptom onset. They underwent admission and finished MR-based imaging. We excluded patients who were treated with combined endovascular thrombectomy and idiopathic ventricular tachycardia (IVT) or had a pre-morbid modified Rankin scale (mRS) score > 2. All patients gave informed consent to join in and all data were analyzed anonymously. Ethical approval for this study was obtained from the ethics committees of the First Hospital Affiliated to Soochow University (2018104).

Intravenous rt-PA thrombolytic therapy According to the stroke guidelines, the standard dosage was 0.9 mg/kg and 10% was given as intravenous injection for 1 min. The remaining dosage was continuous intravenous infusion for 60 min, and the maximum thrombolytic dose was no more than 90 mg.

Clinical information Clinical variates of interest including age, gender, and marital status were collected. Disease history of hypertension, diabetes, stroke, hyperlipidemia, and coronary heart disease were obtained. Onset to treatment time (OTT),

admission systolic blood pressure (SBP), admission diastolic blood pressure (DBP), admission glucose level, stroke severity assessed with NIHSS score, Trial of ORG 10172 in Acute Stroke Treatment (TOAST) subtypes, infarct volume, infarct location, and laboratory data were also systematically recorded. mRS score were assessed at 3 month post discharge.

Imaging The MR examination was performed within 48 h after thrombolysis. All MRIs were assessed blinded to clinical information by two experienced neuroradiologists for the presence, location, and size of the recent symptomatic infarct and any other vascular lesions. Structural MRI included diffusion-weighted imaging (DWI), 3d-TOF-MRA, FLAIR, T2-weighted, T1-weighted, and gradient echo/T2*/susceptibility-weighted sequences.

Lacunae infarctions (LI) were defined as rounded or ovoid lesions, > 3 and < 20-mm diameter, in the basal ganglia, internal capsule, centrum semiovale, or brainstem, of CSF signal intensity on T2 and FLAIR, generally with a hyperintense rim on FLAIR, and no increased signal on DWI. CMBs were defined as small (< 5 mm), homogeneous, round foci of low signal intensity on gradient echo images in cerebellum, brainstem, basal ganglia, white matter, or cortico-subcortical junction, differentiated from vessel flow voids and mineral depositions in the globi pallidi [22]. PVS were defined as small (< 3 mm) round or linear hyperintensities on T2 images in the basal ganglia or centrum semiovale, and they were rated using a five-point ordinal scale as follows: 0 = no EPVS, 1 = 1–10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = > 40 EPVS [23]. Deep and periventricular WMH were both coded according to the Fazekas scale from 0 to 3 [24].

Based on the recently described score, we rated the total MRI burden of CSVD on an ordinal scale from 0 to 4, by counting the presence of each of the 4 MRI features of CSVD. A point was awarded for each of the following: One point on the CSVD scale was awarded when one or more LI were present. The presence of one or more CMBs was given one point on the CSVD scale. Presence of PVS was counted if there were moderate to severe (grade 2–4) PVS in the basal ganglia (one point if present). One point was awarded on the CSVD scale when (early) confluent deep WMHs (Fazekas score 2 or 3) and/or irregular periventricular WMHs extending into the deep white matter (Fazekas score 3) were present. We therefore combined the scores of WMHs, CMBs, PVS, and LI [16, 20, 25].

Clinical assessment

All patients were assessed by two neurologists on the basis of the National Institutes of Health Stroke Scale (NIHSS). NIHSS scale was used to assess the degree of neurological deficit. Zero to five scores were mild stroke and > 5 scores

were moderate to severe stroke. Short-term functional outcomes at 3 months were determined based on the modified Rankin Scale. Poor outcome was defined as a modified Rankin Scale (mRS) score > 2. The follow-up was conducted by two trained neurological doctors who were blinded to the baseline information.

Statistical analysis

All analyses were done with SPSS version 18 (SPSS, Inc., Chicago, IL, USA).

The normal distribution data were analyzed by independent sample *t* test, the non-normal distribution data were analyzed by Mann Whitney *U* test. Fisher's exact test or the chi-square test was used to compare categorical variables as appropriate. Statistical significance was determined as a bilateral test. Univariate analysis was used to compare the baseline, clinical data, and imaging evaluation between the mild stroke group and the moderate to severe stroke group. Adjusted for age, sex, and variables with *p* value < 0.1 in univariate analysis (admission DBP, TOAST subtype, infarction location, infarct volume, low-density lipoprotein (LDL), total glyceride (TG), creatinine, c-reactive protein (CRP), atrial fibrillation, coronary artery disease, smoking, antiplatelets/anticoagulation, radiological features, CSVD score) for neurological deficit severity, multivariate logistic regression analysis model was used to determine the relationship between the global burden of CSVD and the degree of neurological impairment in acute ischemic stroke (AIS). Univariate analysis was used to compare the baseline, clinical data, and imaging evaluation between the patients with good prognosis and those with poor outcomes. Then, multivariate logistic regression analysis was applied to identify clinical factors to predict short-term prognosis. Moreover, receiver operator characteristic curves (ROCs) were performed to find out the better clinical indicators and assess the sensitivity and specificity of CSVD score, NIHSS score, and OTT for predict clinical outcome of AIS after rt-PA treatment. *P* < 0.05 (bilateral) is defined as a statistically significant difference.

Results

Demographic data of the studied patient population

We collected a total of 309 patients and excluded patients who were with incomplete baseline information (*n* = 28) or had not completed the magnetic resonance examination (*n* = 63). Finally, we enrolled 218 patients with acute ischemic stroke who received intravenous thrombolysis in the present study. Baseline characteristics of the 218 patients were summarized

Table 1 Baseline characteristics of the studied patient population and the single factor analysis as stratified by neurological deficit severity

Characteristics	Total N= 218	Mild stroke N= 104	Moderate to severe stroke N= 114	χ^2/Z	P value
Age, mean	65.79 ± 11.99	62.73 ± 12.10	68.58 ± 11.25	3.695	< 0.001
Sex, male	144 (66.1)	68 (65.4)	76 (66.7)	0.040	0.842
Admission SBP mmHg	150.37 ± 20.66	148.56 ± 19.11	152.03 ± 21.93	1.240	0.216
Admission DBP mmHg	87.20 ± 14.61	83.94 ± 11.42	90.17 ± 16.50	3.162	0.002
Admission glucose mmol/L	6.66 ± 2.96	6.43 ± 2.95	6.86 ± 2.98	1.473	0.141
Infarct location				6.881	0.032
Anterior circulation	141 (64.7)	63 (60.6)	78 (68.4)		
Posterior circulation	47 (21.6)	30 (28.8)	17 (14.9)		
Both circulation	30 (13.8)	11 (10.6)	19 (16.7)		
TOAST subtype				31.759	< 0.001
Large artery atherosclerosis	80 (36.7)	32 (30.8)	48 (42.1)		
Cardioaortic embolism	29 (13.3)	3 (2.9)	26 (22.8)		
Small artery occlusion	65 (29.8)	44 (42.3)	21 (18.4)		
Other uncommon causes	14 (6.4)	10 (9.6)	4 (3.5)		
Undetermined	30 (13.8)	15 (14.3)	15 (13.2)		
Infarct volume cm ³	24.45 ± 48.45	6.48 ± 18.19	40.84 ± 60.31	7.063	< 0.001
Laboratory data					
LDL mmol/L	2.52 ± 0.81	2.63 ± 0.80	2.43 ± 0.81	1.791	0.075
TC mmol/L	4.42 ± 1.27	4.47 ± 0.96	4.38 ± 1.51	1.607	0.108
TG mmol/L	1.44 ± 0.95	1.60 ± 0.97	1.29 ± 0.90	2.739	0.006
Hcy umol/L	13.15 ± 11.53	13.22 ± 12.59	13.09 ± 10.55	0.863	0.388
Creatinine	71.67 ± 26.24	68.00 ± 16.01	75.05 ± 32.59	1.812	0.07
Uric acid mmol/L	298.95 ± 94.89	293.85 ± 88.32	303.60 ± 100.67	0.734	0.463
CRP mg/L	7.33 ± 7.77	4.90 ± 6.01	9.55 ± 8.52	4.810	< 0.001
Risk factors					
Previous stroke or TIA	39 (17.9)	19 (18.3)	20 (17.5)	0.019	0.889
Hypertension	147 (67.4)	66 (63.5)	81 (71.1)	1.427	0.232
Diabetes	46 (21.1)	23 (22.1)	23 (20.2)	0.123	0.726
Atrial fibrillation	49 (22.5)	10 (9.6)	39 (34.2)	18.880	< 0.001
Dyslipidemia	32 (14.7)	12 (11.7)	20 (17.5)	1.495	0.221
Smoke	69 (31.7)	31 (29.8)	38 (33.3)	0.312	0.576
Coronary artery disease	11 (5.0)	1 (1.0)	10 (8.8)	6.924	0.009
Congestive heart failure	10 (10.6)	2 (1.9)	8 (7.0)	2.166	0.141
Antiplatelets/anticoagulation	36 (16.5)	11 (10.6)	25 (21.9)	5.084	0.024
Radiological features					
WMHs	55 (25.2)	15 (14.4)	40 (3.1)	12.311	< 0.001
CMBs	54 (24.8)	16 (15.4)	38 (33.3)	9.402	0.002
PVS	76 (34.9)	26 (25)	50 (43.9)	8.518	0.004
LI	128 (58.7)	54 (51.9)	74 (64.9)	3.785	0.052
CSVD score				24.201	0.001
0	48 (22.0)	31 (29.8)	17 (14.9)		
1	77 (35.3)	43 (41.3)	34 (29.8)		
2	54 (24.8)	24 (23.1)	30 (26.3)		
3	29 (13.3)	4 (3.8)	25 (21.9)		
4	10 (4.6)	2 (1.9)	8 (7.0)		

Data are presented as mean ± standard deviation values or n (%)

SBP systolic blood pressure, DBP diastolic blood pressure, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG total glyceride, Hcy homocysteine, CRP C-reactive protein, WMH white matter hyperintensities, LI lacunes infarction, CMB cerebral microbleeds, PVS perivascular spaces, CSVD cerebral small vessel disease

in Table 1. The mean age was 66 (65.79 ± 11.99) years old and 144(66.1%) were men. One hundred seventy (78%) were accompanied with CSVD. WMHs were found in 25.2% of the subjects (55/218), CMBs in 24.8% (54/218), PVSs in 34.9% (76/218), and LIs in 58.7% (128/218). Total CSVD score assessment showed that 77 cases (35.3%) were 1, 54 cases (24.8%) were 2, 29 cases (13.3%) were 3, and 10 cases(4.6%) were 4.

Association of CSVD burden with severity of neurological deficit

Among the enrolled 218 patients, mild neurological deficit was in 104 (47.71%) patients and moderate to severe was in 114 (52.29%) patients. When comparing patients with mild stroke, those with moderate to severe stroke were older, more frequently with higher admission DBP, CRP,

Table 2 Multivariate logistic regression analysis of factors independently associated with neurological deficit severity

Variables	Age- and sex-adjusted OR (95%CI)	P value	Multivariate adjusted OR (95%CI)	P value
Admission DBP	1.042 (1.019–1.066)	0.000	1.050 (1.020–1.081)	0.001
TOAST subtype				
Large artery atherosclerosis	–	–	–	–
Cardioaortic embolism	5.778 (1.613–20.699)	0.007	4.494 (1.040–19.415)	0.044
Small artery occlusion	0.318 (0.160–0.632)	0.001	0.725 (0.305–1.726)	0.468
Other uncommon causes	0.267 (0.077–0.924)	0.037	0.499 (0.110–2.256)	0.366
Undetermined	0.667 (0.287–1.550)	0.346	–	–
Infarct location				
Anterior circulation	–	–	–	–
Posterior circulation	0.450 (0.223–0.907)	0.026	0.577 (0.253–1.316)	0.191
Both circulation	1.116 (0.480–2.594)	0.799	–	–
Infarct volume	1.036 (1.018–1.054)	< 0.001	1.031 (1.011–1.051)	0.002
LDL	0.778 (0.550–1.099)	0.154	–	–
TG	0.751 (0.520–1.083)	0.126	–	–
Creatinine	1.013 (0.999–1.027)	0.064	–	–
CRP	1.088 (1.039–1.141)	< 0.001	1.062 (1.008–1.118)	0.023
Atrial fibrillation	3.685 (1.658–8.189)	0.001	1.049 (0.304–3.616)	0.940
Coronary artery disease	9.210 (1.134–74.775)	0.038	11.012 (1.068–113.548)	0.044
Antiplatelets/anticoagulation	1.982 (0.905–4.344)	0.087	–	–
WMHs	2.522 (1.259–5.052)	0.009	0.966 (0.113–8.272)	0.975
CMBs	2.367 (1.201–4.665)	0.013	0.574 (0.191–1.723)	0.322
PVS	2.284 (1.260–4.141)	0.007	0.977 (0.300–3.187)	0.970
LI	1.467 (0.834–2.580)	0.184	–	–
CSVD score	1.716 (1.290–2.282)	< 0.001	2.187 (1.495–3.119)	< 0.001

DBP diastolic blood pressure, LDL-C low-density lipoprotein cholesterol, TG total glyceride, CRP C-reactive protein, WMHs white matter hyperintensities, LI lacunes infarction, CMBs cerebral microbleeds, PVS perivascular spaces, CSVD cerebral small vessel disease

infarct volume, TG and histories of atrial fibrillation, coronary artery disease, and antiplatelets/anticoagulation. Infarct location, TOAST subtype, radiological features, and the total CSVD score were correlated with the severity of stroke. In univariable analysis, old age, higher DBP, infarct location, more infarct volume, TOAST subtype, TG, CRP, atrial fibrillation, coronary artery disease, and antiplatelets/anticoagulation were associated with moderate to severe stroke (Table 1).

After adjusting for confounders, in multivariable logistic regression analysis, admission DBP, infarct volume (OR = 1.031, 95%CI = 1.011–1.051, P = 0.002), atrial fibrillation,

coronary artery disease, and the total CSVD score (OR = 2.187, 95%CI = 1.495–3.119, P = 0.000) were independently associated with moderate to severe stroke (Table 2). Distribution of total CSVD score and comparison of infarct volume in mild and moderate to severe stroke groups were showed in Figs. 1 and 2.

Univariable and multivariable analyses of functional outcomes at 3 months

After 3 months from the index stroke, 96 (44%) patients had a mRS of 3–6. Poor functional outcomes at 3 months were more

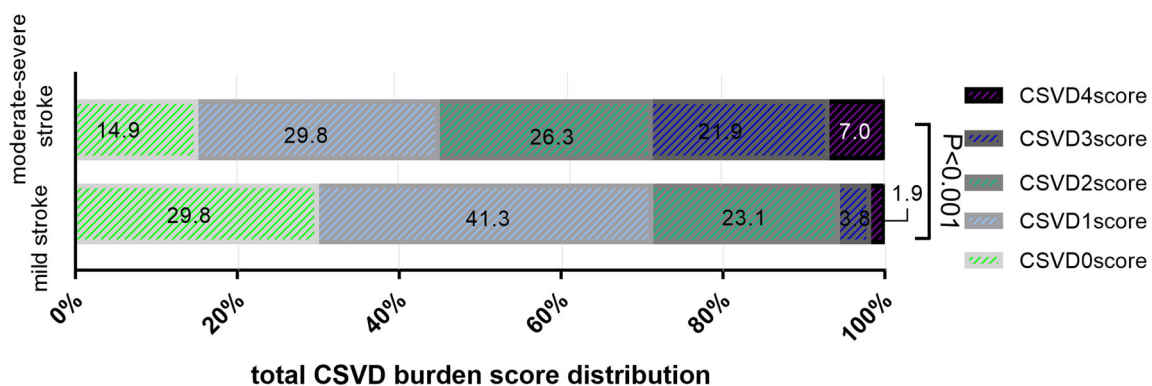
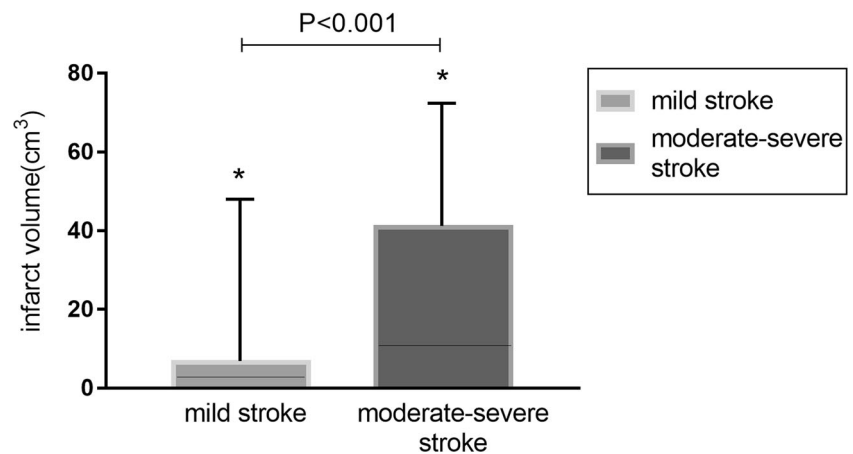


Fig. 1 (GraphPad Prism 7.00 was used to create the artwork.). Distribution of the total CSVD burden scores as stratified by degree of neurological deficit.

Fig. 2 Comparison of infarct volume between mild stroke group and moderate to severe stroke group.



common in higher CSVD score (Fig. 3). In univariable analyses, old age, initial stroke severity, admission DBP, TOAST subtypes, infarct volume, CRP, hypertension, atrial fibrillation, radiological features, and the total CSVD score were associated with short-term outcomes in AIS after rt-PA treatment (Table 3). A number of predictors of poor outcomes were shown in logistic regression model (Table 4). However, after age, sex, and multivariate adjustment, only initial NIHSS (OR = 1.23, 95%CI = 1.144–1.330, $P < 0.001$), OTT (OR = 1.007, 95%CI = 1.000–1.014, $P = 0.037$), and CSVD score (OR = 3.157, 95%CI = 2.120–4.703, $P < 0.001$) were significantly related to poor functional outcomes at 3 months of discharge.

ROC analysis predictive of 90-day functional outcome

In ROC curve analysis, the total CSVD score cut-off value of 1.5 was determined at best to differentiate between favorable prognosis and poor outcome (AUC 0.7534 [95%CI 0.6883–0.8185]). The total CSVD score cut-off value presented 65% sensitivity and 76% specificity. Besides, an NIHSS score cut-off of 6.5 was used as the best cut-off value for evaluating the prognosis (AUC 0.7496 [95%CI 0.6828–0.8165]). The NIHSS cut-off score presented 68% sensitivity and 75% specificity. However, there was no obvious predictive value of OTT (AUC 0.5564 [95%CI 0.4794–0.6334]) in ROC analysis. (Table 5; Fig. 4).

Discussion

In this study, we demonstrated that (1) CSVD were substantial in older patients, (2) the total CSVD burden and infarct volume were independently associated with moderate to severe neurological deficit in the fully adjusted multivariable model, and (3) initial NIHSS (OR = 1.23, CI = 1.144–1.330, $P < 0.001$) and CSVD score (OR = 3.157, CI = 2.120–4.703,

$P < 0.001$) were independent predictors of poor functional outcome at 3 months.

CSVD imaging features commonly occur together. A total CSVD measure might better enclose the global effect of CSVD on the brain than the individual MRI feature separately as we described before. Actually, the results on total CSVD burden and the degree of neurological deficit have not been validated. So we tried to quantify the cumulative effect of

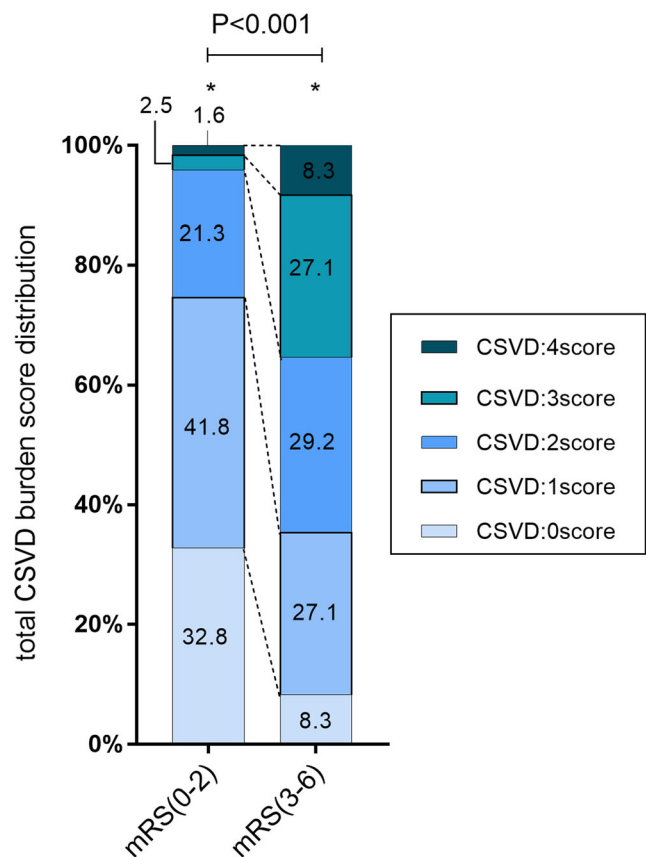


Fig. 3 Distribution of the total CSVD burden scores as stratified by 90-day functional outcome.

Table 3 the single factor analysis as stratified by clinical outcome at 3 months

Variables	mRS (0–2) N = 122	mRS (3–6) N = 96	χ^2/Z	P value
Age	63.25 ± 12.102	69.01 ± 11.106	3.589	< 0.001
Sex, male	78 (63.9)	66 (68.8)	0.556	0.456
Admission NIHSS	4 (2–7)	10 (5–15)	6.340	< 0.001
OTT	160.03 ± 56.407	169.42 ± 55.070	1.430	0.153
Admission SBP mmHg	149.49 ± 19.716	151.49 ± 21.845	0.378	0.480
Admission DBP mmHg	85.32 ± 12.250	89.58 ± 16.907	2.235	0.025
Admission glucose mmol/L	6.37 ± 2.87	7.02 ± 3.06	2.520	0.012
Infarct location			1.626	0.444
Anterior circulation	75 (61.5)	66 (68.8)		
Posterior circulation	30 (24.6)	17 (17.7)		
Both circulation	17 (13.9)	13 (13.5)		
TOAST subtype			17.943	0.001
Large artery atherosclerosis	39 (32)	41 (42.7)		
Cardioaortic embolism	9 (7.4)	20 (20.8)		
Small artery occlusion	40 (32.8)	25 (26.0)		
Other uncommon causes	11 (9.0)	3 (3.1)		
Undetermined	23 (18.9)	7 (7.3)		
infarct volume cm ³	12.75 ± 40.780	39.31 ± 53.328	5.700	< 0.001
Laboratory data				
LDL mmol/L	2.51 ± 0.81	2.55 ± 0.82	0.083	0.710
TC mmol/L	4.35 ± 0.99	4.51 ± 1.56	0.485	0.628
TG mmol/L	1.44 ± 0.78	1.44 ± 1.23	0.614	0.539
Hcy umol/L	13.31 ± 14.25	12.95 ± 6.91	2.144	0.032
Creatinine umol/L	68.59 ± 16.20	75.58 ± 34.80	1.539	0.124
Uric acid mmol/L	293.14 ± 99.46	306.32 ± 88.69	1.523	0.128
CRP mg/L	5.73 ± 6.56	9.38 ± 8.69	3.852	< 0.001
Risk factors				
Previous stroke or TIA	17 (13.9)	22 (22.9)	2.951	0.086
Hypertension	69 (56.6)	78 (81.3)	14.916	< 0.001
Diabetes	24 (19.7)	22 (22.9)	0.340	0.560
Atrial fibrillation	19 (15.6)	30 (31.3)	7.577	0.006
Dyslipidemia	13 (10.7)	19 (19.8)	3.486	0.062
Smoke	31 (25.4)	38 (39.6)	4.989	0.026
Coronary artery disease	2 (1.6)	9 (9.4)	5.193	0.023
Congestive heart failure	5 (4.1)	5 (5.2)	0.004	0.950
Antiplatelets/anticoagulation	11 (9.0)	25 (26)	11.095	< 0.001
Radiological features				
WMHs	16 (13.1)	39 (40.6)	21.554	< 0.001
CMBs	19 (15.6)	35 (36.5)	12.575	< 0.001
PVS	31 (25.4)	45 (46.9)	10.901	0.001
LI	53 (43.4)	75 (78.1)	26.660	< 0.001
Intracerebral hemorrhages	6 (4.9)	26 (27.1)	21.075	< 0.001
CSVD score			48.961	< 0.001
0	40 (32.8)	8 (8.3)		
1	51 (41.8)	26 (27.1)		
2	26 (21.3)	28 (29.2)		
3	3 (2.5)	26 (27.1)		
4	2 (1.6)	8 (8.3)		

Data are presented as mean ± standard deviation values or *n* (%)

NIHSS the National Institutes of Health Stroke Scale, OTT onset to treatment time, SBP systolic blood pressure, DBP diastolic blood pressure, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG total glyceride, Hcy homocysteine, CRP C-reactive protein, WMH white matter hyperintensities, LI lacunes infarction, CMB cerebral microbleeds, PVS perivascular spaces, CSVD cerebral small vessel disease

combined signs and used the total CSVD burden to assess its relationship with clinical outcomes after IV rt-PA treatment. Considerably, our study found signs of two or more severe CSVD features in around about half of our patients. We investigated initial NIHSS and CSVD score in relation to poor functional outcomes at 3 months, especially the predictors of

CSVD score. Arba's results also suggested that CSVD negatively affected stroke outcomes after intravenous thrombolysis and global burden of CSVD quantified with a combined score was associated with disability and functional dependency [26]. Previous studies demonstrated that patients with a higher score were at increasing risk of a recurrent

Table 4 Multivariate logistic regression analysis for poor outcomes predictors at 3 months (mRS score 3–6)

Variables	Age- and sex-adjusted OR (95%CI)	P value	Multivariate adjusted OR (95%CI)	P value
Admission NIHSS	1.172 (1.103–1.246)	< 0.001	1.233 (1.144–1.330)	< 0.001
OTT	1.004 (0.999–1.010)	0.087	1.007 (1.000–1.014)	0.037
Admission DBP	1.027 (1.005–1.048)	0.014	1.026 (0.997–1.056)	0.081
Admission glucose	1.086 (0.982–1.202)	0.107	–	–
TOAST subtype				
Large artery atherosclerosis	–	–	–	–
Cardioaortic embolism	1.867 (0.746–4.676)	0.182	–	–
Small artery occlusion	0.733 (0.366–1.467)	0.380	–	–
Other uncommon causes	0.362 (0.089–1.462)	0.154	–	–
Undetermined	0.370 (0.139–0.990)	0.048	0.239 (0.066–0.867)	0.029
Infarct volume	1.013 (1.005–1.021)	0.001	1.003 (0.993–1.014)	0.537
Hcy	0.999 (0.974–1.025)	0.946	–	–
CRP	1.052 (1.010–1.095)	0.014	1.000 (0.944–1.060)	0.987
Previous stroke or TIA	1.731 (0.839–3.572)	0.138	–	–
Hypertension	3.161 (1.663–6.008)	< 0.001	1.705 (0.743–3.914)	0.208
Atrial fibrillation	1.733 (0.856–3.509)	0.126	–	–
Dyslipidemia	2.140 (0.972–4.713)	0.059	–	–
Smoke	2.094 (1.099–3.991)	0.025	1.219 (0.495–3.005)	0.667
Coronary artery disease	5.294 (1.069–26.201)	0.041	4.608 (0.576–36.846)	0.150
Antiplatelets/anticoagulation	3.184 (1.438–7.048)	0.004	1.512 (0.330–6.916)	0.594
Intracerebral hemorrhages	7.276 (2.731–19.384)	< 0.001	1.116 (0.262–4.749)	0.882
CSVD score	2.521 (1.823–3.486)	< 0.001	3.157 (2.120–4.703)	< 0.001

NIHSS the National Institutes of Health Stroke Scale, OTT onset to treatment time, DBP diastolic blood pressure, Hcy homocysteine, CRP C-reactive protein, CSVD cerebral small vessel disease

ischemic stroke and ICH and that the total CSVD score predicted both asymptomatic and disabling recurrent ischemic strokes [27].

Our data indicated that patients with increasing total CSVD score were more likely to be with poor outcome at 3 months. The total CSVD score cut-off value of ≥ 2 might indicate poor clinical outcomes after IV rt-PA treatment. The total CSVD score cut-off value presented 65% sensitivity and 76% specificity. Low sensitivity and specificity might attribute to the small sample and retrospective analysis of our study.

Our study also showed that patients with increasing admission NIHSS score were more likely to have poor outcomes, with a suggested NIHSS score ≥ 7 . Similar to previous studies, higher NIHSS proved an independent predictor of unfavorable clinical outcome and death [28]. The NIHSS score strongly predicted the likelihood of a patient's recovery after a stroke; a score of ≤ 6 forecasts a good recovery [29, 30].

A large number of studies suggested that symptomatic intracerebral hemorrhage was an independent risk factor for poor prognosis of thrombolysis [31, 32]. Nevertheless, our study was likely underpowered to demonstrate an independent association between ICH and poor outcomes.

The reason might be that it is not specifically classified as symptomatic intracerebral hemorrhage or asymptomatic hemorrhage.

Although the clinical impact of our findings needs further exploration, a quantitative definition of CSVD could lead to a chart of risk stratification for an acute stroke patient. The results might have significant implications for future research to improve patient selection for acute stroke therapies.

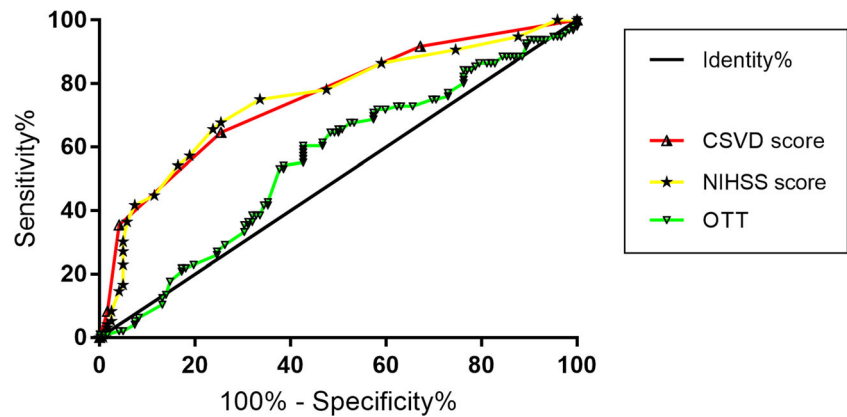
However, this study was subject to some limitations. Firstly, the present study was a retrospective one, which made it impossible to exclude the possibility of bias.

Table 5 Area under ROC curve and cut-off values of predictors for poor outcomes at 3 months

Independent variable	AUC	95%CI	P value	Cut-off value
CSVD score	0.7534	0.6883–0.8185	< 0.0001	1.5
NIHSS score	0.7496	0.6828–0.8165	< 0.0001	6.5
OTT	0.5564	0.4794–0.6334	0.1528	–

CSVD cerebral small vessel disease, NIHSS the National Institutes of Health Stroke Scale, OTT onset to treatment time

Fig. 4 Receiver operator characteristic (ROC) curve analysis comparing CSVD score, NIHSS score and OTT for prediction of poor outcome at 3 months



Subsequently, our sample size was relatively small, and we recognize that the conclusions need further investigation in larger cohorts. We did not follow up on the recurrence and long-term prognosis of stroke, so it was uncertain whether the patients with a higher burden of CSVDs might suffer from higher stroke recurrence, poor long-term prognosis, and higher mortality rate. Also, a few patients with severe symptomatic intracranial hemorrhage and subarachnoid hemorrhage who could not bear MR imaging were not included in the study, so this might lead to bias in case selection.

In conclusion, this study has shed light on the association of the global burden of CSVD score with neurological deficit severity and clinical outcomes after IV rt-PA treatment in acute ischemic stroke patients. The simple scoring system that combines the various types of CSVD in a single scale is easy to use. Our study suggested that this scoring system could have potential value of risk stratification or early efficacy assessment of CSVD progression and might have a useful role in future clinical practice and research.

Conclusions

The global burden of CSVD was independently associated with neurological deficit severity and clinical outcomes of AIS after IV rt-PA treatment. The total CVSD score is a reliable predictor for poor outcomes of AIS after IV rt-PA treatment with a suggested CSVD score ≥ 2 .

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