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Risk factors and predictive scoring system for twice or more strokes in patients with cerebral small vessel disease

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Abstract

Objectives: To explore the independent risk factors of twice or more strokes in patients with cerebral small vessel disease, and to construct a predictive scoring system. *Methods:* A retrospective study was carried out in patients with cerebral small vessel disease suffered from acute stroke and admitted to Neurology Department of Tangshan Gongren Hospital from January 2020 to June 2021. The patients were recruited and grouped according to whether they had a previous stroke history. Binary logistic regression models were used to investigate the independent risks for the occurrence of twice or more strokes in patients with cerebral small vessel disease, assigned scores to each factor, then established and evaluated the predictive efficacy of the predictive scoring system. *Results:* A total of 531 patients were analysed. Regression analysis showed that age, hypertension, diabetes, intracranial arterial stenosis, and total cerebral small vessel disease burden were independent risk factors. On the basis of each regression coefficient, a 10-point predictive scoring system selected the highest Jordon index as the cut-off value, which was 4 points. And the area under the receiver operating characteristic curve was 0.842 (95 %CI: 0.796~0.893, $P<0.001$).
Conclusions: The predictive scoring system based on age, hypertension, diabetes, intracranial arterial stenosis, and total cerebral small vessel disease burden can effectively predict whether patients with cerebral small vessel disease tend to have twice or more strokes.

Keywords: Cerebral small vessel disease, burden, stroke, risk factors, predictive scoring system

INTRODUCTION

Although with the many studies and improvement of medical treatment, great advancement have been achieved in the prevention, treatment, and early intervention of acute cerebrovascular disease, it still has high morbidity, mortality, and disability worldwide[1], which poses a serious threat to quality of life of patients. Therefore, prevention of stroke remains a continuous and difficult task. In recent years, the age of onset of stroke has gradually become younger[2], which seriously affects the quality of life, and also economic productivity. Multiple studies have found an association between stroke and cerebral small vessel disease (CSVD) in younger adults.[3-5] In both the younger adults and the elderly, CSVD can lead to decreased auto-regulation of cerebral blood flow leading to brain microstructure damage.[6] In addition, poor compensation of global function aggravates the acute stroke leading to a poor prognosis.

There have been a number of studies focusing on the association between CSVD and stroke, and found that CSVD worsened neurological function of stroke in both infarction and hemorrhage[7-8], and the impact of stroke on the global function is also aggravated by the total CSVD burden.[9-10] So there may be an interaction between CSVD and stroke, that progressively aggravate the CVSD. Although previous and current studies have helped to explore risk factors for CSVD and stroke, no clinical studies have been conducted in patients with CSVD to investigate the etiology of two or more strokes.

Although CSVD may have different pathogenesis and risk factors from stroke, in

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clinical practice, we found that many CSVD patients were exposed to risk factors such as hypertension (HT), diabetes (DM), and hyperhomocysteine (HCY), which are similar with the current recognized risk factors for acute stroke.[11-12] In this study, we explored the risk factors of twice or more strokes in patients with CSVD, we selected some of the most common risks as comparison parameters, and built a predictive scoring system based on those factors, quantified and displayed the contribution of each factor visually, so as to provide guidance for the prevention and treatment of stroke and clinical management of CSVD.

METHODS

This study was conducted in Tangshan City, Hebei Province, China. Patients with acute stroke who were admitted to the Department of Neurology of Tangshan Gongren Hospital from January 2020 to June 2021 were retrospectively selected.

The inclusion criteria were: 1. The diagnosis of CSVD[13] and stroke[14] was clear and non-controversial; 2. There was no systemic organ failure and other serious diseases; 3. There was no mental disorder to ensure good cooperation; 4. Willing to provide general information, past and personal history. The exclusion criteria were: 1. Incomplete or unavailable brain imaging data; 2. The acute stroke was critical; 3. Patients with other serious diseases, such as immune deficiency; 4. Reluctance to provide general information or medical history, or had an unclear medical history.

The following data of the study subjects were collected as variables for further analysis: 1. Demographic information: Age, gender; 2. Whether the patient was exposed to the most common risk factors of cerebrovascular disease; i.e., HT[15], DM[16], HCY[17], smoking (≥1 cigarette/day on average, and duration ≥1 year), alcohol drinking (≥30g/day on average, and duration≥6 months); 3. Imaging changes (Figure 1): MRA or CTA examination confirmed the presence of intracranial arterial stenosis; CSVD features displayed on MRI and SWI. The four most common markers: lacuna, white matter hyperintensity (WMH), perivascular space enlargement (EPVS), and cerebral microbleeds (CMBs) were selected. The total CSVD burden

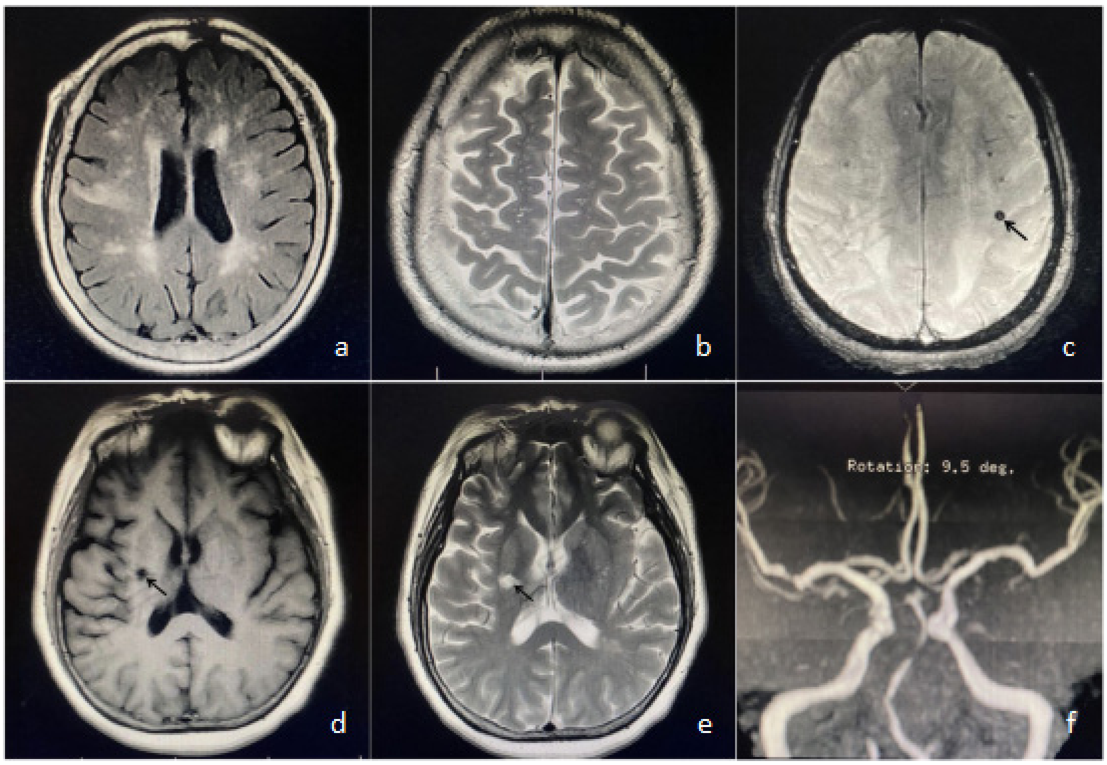

Figure1. Imaging features: Figure **a** shows WMH on T2 FLAIR. Figure **b** shows the EPVS on T2 FSE. Figure **c** shows CMBs on SWI. Figures **d** and **e** shows lacuna. Figure **f** shows basilar artery stenosis on MRA. (WMH: white matter hyperintensities; EPVS: perivascular space enlargement; CMBs: cerebral microbleeds)

The patients were divided into two groups according to whether they had a previous stroke.

based on whether the above-mentioned imaging characteristics was calculated, each feature was counted as 1 point.[18]

Statistical analysis

The statistical analysis was performed by SPSS 25.0. Continuous and categorical variables were represented and analyzed by $\overline{x}$ ± s and *t* test, component ratio and χ^2 test, respectively. Binary logistic regression models were used to find independent risk factors of twice or more strokes in patients with CSVD. Then extracted each regression coefficient, transformed and assigned scores to establish a predictive scoring system, and selected the highest Jordon index as the cut-off value. The receiver operating characteristic curve (ROC curve) was drawn and the area under the ROC curve (AUC) was calculated, and Hosmer-Lemeshow test were applied to verify the efficacy of the scoring system. P<0.05 was considered as statistically significant difference.

As for ethics, strict principle of confidentiality was observed in the handling of data. Informed consent was obtained from the participants before the investigation.

RESULTS

Baseline data

Table 1 shows the baseline data. A total of 531 patients with acute stroke complicated with CSVD were included. There were differences in age, gender, HT, DM, intracranial artery stenosis, total CSVD burden, WMH, EPVS, and CMBs between 2 groups (*P*<0.05).

Exploration of independent factors of twice or more strokes in patients with CSVD

Multivariate binary logistic regression analysis showed that age, HT, DM, intracranial arterial stenosis, and total CSVD burden were independent risk factors (*P*<0.05) (Table 2). According to the corresponding coefficients, the clinical prediction model for the occurrence of twice or more strokes in patients with CSVD was established: logit(*P*) = -0.768 + 0.104*age + 1.455*HT + 1.237*DM + 1.402*intracranial arterial stenosis + 0.413*total CSVD burden.

Table 1: Baseline data

	Items	Whether twice or more strokes have occurred		Total (N = 531)	*P*
		Yes (N = 206)	**No (N = 325)**		
Demographic information	Age/Year	61.874±10.186	59.785±11.155	60.595±10.828	**0.031**
	Male/N,%	152(73.8)	216(66.5)	368(69.3)	**<0.001**
Risk factors	Hypertension/N,%	160(77.7)	206(63.4)	366(68.9)	**0.001**
	Diabetes/N,%	70(34.0)	74(22.8)	144(27.1)	**0.005**
	Hyperhomocysteine/N,%	94(45.6)	136(41.8)	230(43.3)	0.391
	Smoking/N,%	100(48.5)	145(44.6)	245(46.1)	0.376
	Drinking/N,%	78(37.9)	127(39.1)	205(38.6)	0.780
	Intracranial aortic stenosis/N,%	128(62.1)	166(51.1)	294(55.4)	**0.013**
Imaging features	Total cerebral small vessel disease burden/ Score	3.31±0.884	2.815±0.964	3.008±0.964	**<0.001**
	lacuna/N,%	205(99.5)	320(98.5)	525(98.9)	0.290
	White matter hyperintensity/N,%	199(96.6)	290(89.2)	489(92.1)	**0.004**
	Perivascular space enlargement/N,%	190(92.2)	277(85.2)	467(87.9)	**0.017**
	Cerebral microbleeds/N,%	146(70.9)	165(50.8)	311(58.6)	**<0.001**

Table 2: Multivariate binary logistic regression

Items	*B*	*S.E*	*Wald*	*P*	*Exp(B)*
Age/Year	0.094	0.009	0.185	**0.017**	1.099
Male/N,%	0.008	0.212	4.863	0.667	1.008
Hypertension/N,%	1.455	0.217	4.392	**0.036**	4.284
Diabetes/N,%	1.237	0.213	6.100	**0.014**	3.445
Intracranial aortic stenosis/N,%	1.402	0.194	4.298	**0.038**	4.063
Total cerebral small vessel disease burden/Score	0.413	0.213	3.758	**0.033**	1.511
White matter hyperintensity/N,%	0.744	0.464	2.571	0.109	2.104
Perivascular space enlargement/N,%	0.220	0.415	0.282	0.595	1.246
Cerebral microbleeds/N,%	0.233	0.334	0.489	0.484	1.262
Constant	-0.768	1.693	0.206	0.004	0.464

Construction of predictive scoring system and evaluation of prediction effect

Age, HT, DM, intracranial aortic stenosis, and total CSVD burden were included in the construction of the predictive scoring system. According to the clinical characteristics of the study subjects, divided age by 10 years, the minimum age was 25 years old and the maximum age was 88 years old. Total CSVD burden was divided into 5 segments, the lowest score of the subjects was 0 points, and the highest was 4 points. Then assigned scores according to the regression coefficients to form a scoring system with a total score of 10 points (Table 3). The cut-off value was 4 points based on the highest Jordon index. That was to say, CSVD patients with a score ≥ 4 are at risk of twice or more strokes, while the score of -1 to 3 is considered a safe range.

The ROC curve was constructed (Figure 2), and the AUC value was 0.842 (95 %CI: 0.796~0.893, P<0.001). Hosmer-Lemeshow was carried out to test the goodness of fit ($\chi^2 = 10.008$, $P = 0.264 > 0.05$, which indicated that the model had a high goodness of fit). The sensitivity and specificity of the model were calculated to be 79.6% and 87.4% respectively.

DISCUSSION

Based on our clinical data, we constructed a scoring system to predict the risk of twice or more strokes in patients with CSVD. We found that age, HT, DM, intracranial arterial stenosis, and total CSVD burden were independent risk factors for the occurrence of twice or more strokes in patients with CSVD. Statistical analysis showed that for patients with CSVD, the risk of twice or more strokes increased by 9.9% for each additional year of age, and the risk increased significantly when the age is over 60. In addition, patients with HT, DM, and intracranial arterial stenosis were 4.28 times, 3.45 times, and 4.06 times on average than those without HT, DM, or intracranial arterial stenosis, respectively. Furthermore, for each 1 point increase in total CSVD burden, the risk increases by 51.1% on average, and when the total CSVD burden reaches 3-4 points, its contribution to the occurrence of twice or more strokes will be more significant.

In this retrospective study, we find that HT has a higher weight on the occurrence of twice or more strokes in patients with CSVD. Current studies had confirmed that HT is a risk factor for not only cerebrovascular disease but also CSVD[19], which is related to the pathophysiological damage of cerebral vessels caused by HT. HT-induced hyaline degeneration reduces the elasticity and brittleness of the arterial wall, which not only leads to abnormal hemodynamics, but also promotes the formation of atherosclerotic plaques.[20] Abnormal fluctuations in blood pressure can also cause intracranial hemorrhage due to rupture of the blood vessel walls. What is more, the blood pressure variability is related to varieties of CSVD imaging markers, such as the increase in the volume of WMH, the existence of lacunas, and deep CMBs.[21] However, whether systolic blood pressure, diastolic blood pressure and pulse pressure have a unique effect on CSVD or its different imaging characteristics is still unclear.

Compared with isolated CSVD imaging markers, total CSVD burden has a more comprehensive and objective value on the evaluation of global function.[22] In the pathogenesis

Table 3: The predictive scoring scale for the occurrence of twice or more strokes in patients with CSVD

Items		*B*	Scores
Years of age		0.094	
	<30		-1
	30-39		0
	40-49		0
	50-59		0
	60-69		1
	70-79		2
	⩾80		3
Hypertension		1.455	
	Yes		1
	No		0
Diabetes		1.237	
	Yes		1
	No		0
Intracranial aortic stenosis		1.402	
	Yes		1
	No		0
Total cerebral small vessel disease burden		0.413	
	0		0
	1		0
	2		0
	3		1
	4		1

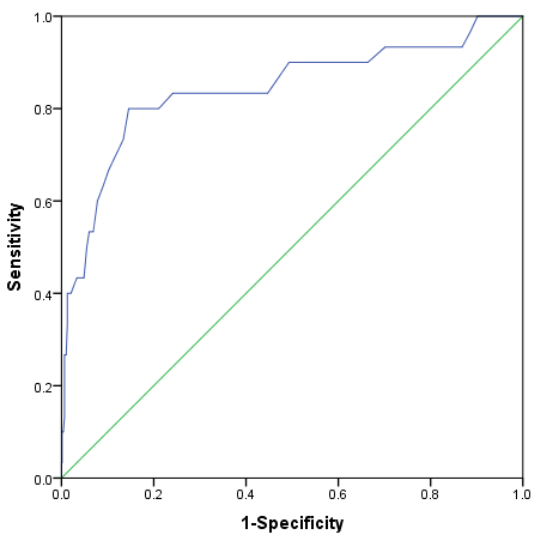

Figure 2. ROC curve: The clinical prediction model predicts the occurrence of twice or more strokes in patients with CSVD, the AUC value was 0.842 (95 %CI: 0.796~0.893, P<0.001).

of sporadic arteriosclerosis related to CSVD, the total CSVD burden is an important predictor of stroke, cognitive dysfunction, and abnormal mental behavior, and it has a significant impact on the quality of life in later years.[23] Our study find that total CSVD burden is an independent risk factor for twice or more stroke events. Since the damages of the neural network caused by CSVD is irreversible, increased efforts on management of HT and other potential risk factors is a key approach to improve the prognosis.

We also find DM and intracranial arterial stenosis are important risk factors in the occurrence of twice or more strokes in patients with CSVD. Though the current researches of DM on the occurrence and development of CSVD have not yet reached a consistent conclusion[24-25], it is no doubt that long-term poor blood glucose control could cause damage to vascular endothelial cells and increase blood viscosity, thereby promoting the process of intracranial aortic stenosis.[11] Based on our findings, we speculate that for CSVD patients with intracranial large artery stenosis, taking early and timely measures to improve vascular stenosis is an effective means to prevent twice or more strokes, and these include conservative treatments such as drugs to improve collateral circulation, and surgical procedures such as stenting and endarterectomy. However, the indications and efficacy of the above interventions need to be explored and verified by clinical studies.

There are limitations to our study. On the one hand, although the data were all from clinical sources, the study was a single-center, retrospective cross-sectional study, which may not reflect the overall demographic characteristics comprehensively. On the other hand, other potential risk factors, such as body mass index, abdominal circumference, and family history, were not included due to insufficient patient cooperation.

In summary, we find that aging, HT, DM, intracranial arterial stenosis, and increased total CSVD burden are independent risk factors for twice or more strokes in patients with CSVD, and the clinical prediction model and predictive scoring system established based on the above factors have effective prediction function, which can be used as assessment tools for the comprehensive management of cerebrovascular disease, and to identify high-risk patients early for individualized interventions.

DISCLOSURE

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Conflict of interest: None

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