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Establishment and evaluation of a clinical prediction model for cognitive impairment in patients with cerebral small vessel disease

Fangfang Zhu^{1,2}, Jie Yao², Min Feng² and Zhongwu Sun^{1*}

Abstract

Background There are currently no effective prediction methods for evaluating the occurrence of cognitive impairment in patients with cerebral small vessel disease (CSVD).

Aims To investigate the risk factors for cognitive dysfunction in patients with CSVD and to construct a risk prediction model.

Methods A retrospective study was conducted on 227 patients with CSVD. All patients were assessed by brain magnetic resonance imaging (MRI), and the Montreal Cognitive Assessment (MoCA) was used to assess cognitive status. In addition, the patient's medical records were also recorded. The clinical data were divided into a normal cognitive function group and a cognitive impairment group. A MoCA score < 26 (an additional 1 point for education < 12 years) is defined as cognitive dysfunction.

Results A total of 227 patients (mean age 66.7 ± 6.99 years) with CSVD were included in this study, of whom 68.7% were male and 100 patients (44.1%) developed cognitive impairment. Age (OR = 1.070; 95% CI = 1.015 ~ 1.128, $p < 0.05$), hypertension (OR = 2.863; 95% CI = 1.438 ~ 5.699, $p < 0.05$), homocysteine (HCY) (OR = 1.065; 95% CI = 1.005 ~ 1.127, $p < 0.05$), lacunar infarct score (Lac_score) (OR = 2.732; 95% CI = 1.094 ~ 6.825, $P < 0.05$), and CSVD total burden (CSVD_score) (OR = 3.823; 95% CI = 1.496 ~ 9.768, $P < 0.05$) were found to be independent risk factors for cognitive decline in the present study. The above 5 variables were used to construct a nomogram, and the model was internally validated by using bootstrapping with a C-index of 0.839. The external model validation C-index was 0.867.

Conclusions The nomogram model based on brain MR images and clinical data helps in individualizing the probability of cognitive impairment progression in patients with CSVD.

Keywords Cerebral small vessel disease, Cognitive impairment, Nomogram, Clinical prediction models, Neuroimaging

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Introduction

Cerebral small vessel disease (CSVD) comprises a group of diseases involving cerebral arterioles, venules, and capillaries and is an important cause of cognitive dysfunction in elderly individuals [1–3]; lesions can be observed by neuroimaging or pathology [4]. Neuroimaging, represented by brain magnetic resonance imaging (MRI), plays an irreplaceable role in the diagnosis and classification of CSVD. Among the MRI features of CSVD, lacunar infarction (LI), cerebral microbleeds (CMBs), white matter hyperintensities (WMHs), and enlarged perivascular space (EPVS) are the four typical neuroimaging manifestations of CSVD [2]. Clinically, these neuroimaging changes that cause brain injury do not occur alone in the elderly population but mostly appear as two or more superimposed manifestations. Previous studies on the relationship between CSVD imaging markers and cognitive function have focused mainly on one or two imaging markers, which cannot comprehensively predict the risk of pathological changes in the brain during the progression of cognitive dysfunction [5, 6]. Klarenbeek et al. [7] first proposed the CSVD total burden score in 2013; that is, four findings (LI, WMH, CMBs, and EPVS) on the MRI of the same patient were scored separately, and the total burden score was subsequently calculated to more comprehensively assess CSVD-related brain injury, determine the severity of CSVD, and determine the importance of the severity of cognitive impairment.

Currently, there is no clear explanation for the disease pathogenesis. Many studies have focused on the relationship between the total burden of CSVD and the progression of cognitive decline [1, 6, 8], but it is not yet common to construct a more readable clinical prediction model of cognitive impairment from the perspective of the total burden of CSVD. The nomogram is a new statistical prediction model that transforms risk factors into continuous scoring graphs, which are highly readable [9]. A nomogram can graphically represent the impact of each predictor on the outcome, providing readers with a more specific interpretation of each predictor's impact on the outcome [10, 11]. The nomogram simplifies the prediction model into a numerical estimate of the probability of death or recurrence, which can guide clinical decision-making and is widely used for cancer prognosis, mortality in acute cerebrovascular disease, and risk of neurological deterioration [12–17]. This research aims to further enrich the necessary findings. In this study, risk factors for cognitive dysfunction in CSVD patients were investigated, and a predictive model was constructed for visualizing the nomogram from the perspective of the total burden of CSVD to provide a more efficient and convenient way for clinicians to predict the progression of cognitive dysfunction in patients with CSVD.

Materials and methods

Study design and patient selection

We included patients with cerebral small vessel disease in the Department of Neurology of the Second Affiliated Hospital of Bengbu Medical College. CSVD patients from September 2021 to October 2022 were included as training data. Patients with CSVD from October 2019 to September 2020 were included as test data. Demographic data, clinical history, relevant blood markers, and brain MRI images were recorded for all study subjects. Cognitive function was tested using the MoCA scale. The training data was a cross-sectional observational study based on retrospective analysis, and the data was based on electronic medical record acquisition, and the patient or family member had signed an informed consent form indicating that the medical record information could be used for clinical research. The test data was based on a prospective observational study in the past, and all subjects or family members also signed an informed consent form and agreed to join the clinical study. The inclusion criteria of the two sets of datasets are the same. Individuals with cognitive dysfunction due to metabolic, nutritional, or toxic factors, such as hypothyroidism, vitamin B deficiency, or alcoholism, were excluded from the study. Patients with traumatic brain injury, central nervous system infection, hydrocephalus, or tumors were also excluded. Furthermore, patients with severe psychiatric disease, delirium, hearing loss, visual impairment, or severe psychiatric symptoms that interfere with cognitive assessments were excluded. In this study, patients with WMH caused by demyelinating diseases, radiotherapy, or chemotherapy were excluded. Patients who suffered from large vessel infarctions or severe brain hemorrhages were also excluded. Finally, 227 patients met the criteria for the training data (Fig. 1). The test data included 70 participants, the average age was 67.71 (9.14) years, 16 cases of cognitive impairment appeared, and the incidence of cognitive impairment was 22.86%. Subjects with training data and test data underwent clinical evaluations, neurological examinations, and cognitive assessments conducted at the first visit, followed by an MRI within one week.

Clinical data collection

The following demographic characteristics and vascular risk factors were recorded: sex, age, years of education, previous or current smoking status (on average, one cigarette per day and a one-year history of smoking), history of alcohol consumption (an average of 50 ml of liquor consumed daily, 1 time a week, and a one-year drinking history), history of hypertension (any of the following conditions: ①rest quietly for 10 min, and blood pressure measurements on the same day are found to exceed the normal blood pressure standard at least 3

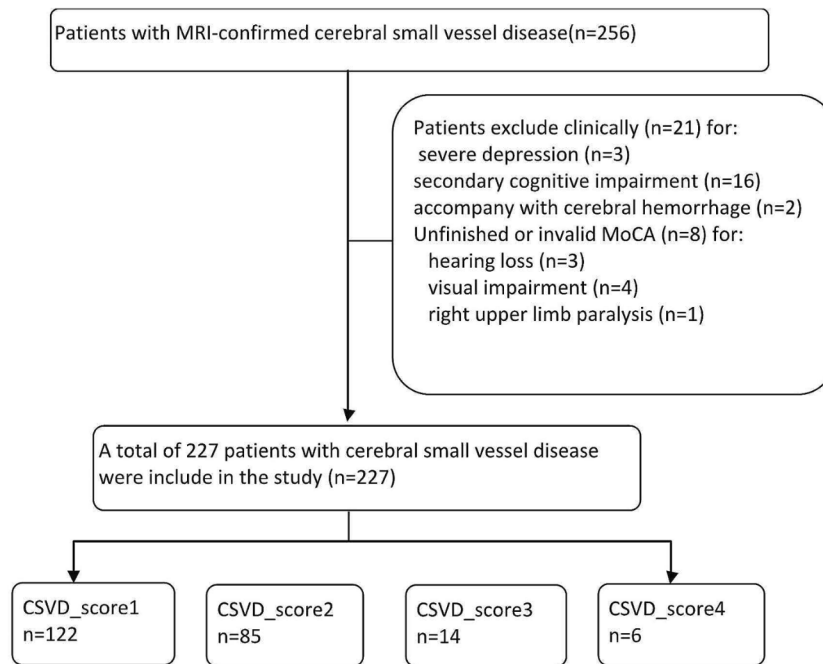


Fig. 1 Flowchart of patient selection. Note: Abbreviations: MRI, magnetic resonance imaging; CSVD, cerebral small vessel disease; MoCA, Montreal Cognitive Assessment

times: systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg; ② currently taking antihypertensive medications; ③ Denying a history of hypertension, but being diagnosed with hypertension by a clinician), history of diabetes (this study refers to type 2 diabetes mellitus, which meets any of the following criteria. The diagnostic criteria are as follows: ① fasting blood glucose ≥ 7.0 mmol/L; ② random blood glucose ≥ 11.1 mmol/L; ③ Previously diagnosed with diabetes, regardless of current hypoglycemic drugs or insulin therapy), coronary heart disease (patients with a previous clinical diagnosis of coronary heart disease (asymptomatic myocardial ischemia, angina, myocardial infarction, ischemic heart failure) or transcatheter angiography showing varying degrees of coronary artery stenosis), previous stroke (those who have had a transient ischemic attack or symptomatic ischemic stroke in the past), triglycerides, total cholesterol, high-density lipoprotein, low-density protein, serum homocysteine (HCY) and uric acid and serum glucose tests.

Neuropsychological assessment

On the first visit, a trained neuropsychologist evaluated cognitive function using the Chinese version of the Montreal Cognitive Assessment (MoCA) scale. An impairment in cognitive function was identified as a MoCA score < 26 (an additional 1 point for education < 12 years) [9, 18]. The MoCA score in the data analysis of this study was defined as MoCA_score.

Magnetic resonance imaging acquisition

All patients underwent an MRI scan within 7 days after the first visit. MRI was performed on a 1.5T scanner, and T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI) were performed for each individual.

Total MRI CSVD burden assessment

The CSVD imaging features and clinical information were independently evaluated by two neurologists and radiologists using a blinded method. If there were differences in scores, the authors negotiated to reach an agreement. We defined lacunes as small and involved the subcortical area with a diameter of 3 mm to 20 mm. Circular or ovoid lesions remaining after infarction tissue or bleeding absorption showed a CSF-like signal in a FLAIR sequence with a ring of high signal around it and a CSF-like signal in T1-weighted imaging and T2-weighted imaging. Some studies have referred to these lesions as asymptomatic lacunar infarction [1, 19]. White matter hyperintensities (WMHs) can be divided into periventricular WMHs and deep WMHs. MRI reveals a high signal density on T2-weighted imaging and no significantly low signal density on T1-weighted imaging [1, 19], and WMHs are graded using the modified Fazekas scale [20]. Cerebral microbleeds (CMBs) appear as well-defined circular or oval hypo-homogeneous signals with a diameter of 2 mm to 10 mm on magnetic resonance imaging (MRI) [19, 21]. Enlarged perivascular spaces (EPVs)

refer to circular or tubular spaces with a diameter < 2 mm in the subcortical area and no high signal surrounding the lesion on FLAIR sequence and no absorbent bleeding lesion on axial T2-weighted gradient echo sequence [1, 19].

The CSVD total burden refers to the score constructed by the CSVD for the 4 imaging signs on MR images (LI, CMBs, WMH, and EPVS) [22]. Previous studies have quantitatively assessed the severity of CSVD by constructing latent variable models and developed an overall CSVD burden score scale [23]. The scoring criteria [24] for the overall burden of CSVD were as follows: (1) a visual scoring system for the severity of white matter lesions, Fazekas scale score ≥ 2 points for 1 point; (2) one or more lacunar infarction counts as 1 score; (3) one or more deep cerebral microbleeds count as 1 point; and (4) 10 or more basal segment EPVS counts as 1 point. Among them, WMH was graded according to the Fazekas scale: (1) Periventricular WMH score: 0 points for no lesions, 1 point for a periventricular cap or pen-like thin-layer lesions, 2 points for smooth halo-shaped lesions, and 3 points for periventricular signals extending to deep white matter; (2) Deep WMH score: 0 points for no lesions, 1 point for punctate lesions, 2 points for lesion fusion at the beginning, and 3 points for large area fusion lesions. The sum of the two scores is the final score. In this study, the total burden of CSVD was defined as CSVD_score, the lacunar infarct score was defined as Lac_score, the CMBs score was defined as CMBs_score, the WMH score was defined as WMH_score, and the EPVS score was defined as EPVS_score. The overall CSVD burden was 4 points, with higher scores associated with more severe CSVD lesions. However, because the score for brain atrophy has not been widely validated, most studies did not include brain atrophy as an indicator of the overall burden of CSVD.

Statistical analysis

The “tableone” package of R software was used to construct clinical data tables. Continuous variables are represented by the mean (standard deviation) or median (interquartile range), and categorical variables are represented by use cases (percentages). Violin plots and Box plots were drawn with the “ggpubr” package to compare the 4 CSVD burden groups. The logistic regression equation was fitted using the “rms” package. We identified independent risk factors for cognitive impairment in CSVD patients via a nomogram model. We verified the accuracy and utility of the nomogram using bootstrapping, the conformity index (C-index), the calibration curve, and decision curve analysis (DCA). Values of $p < 0.05$ were considered to indicate statistical significance. All the above statistical analyses were performed using the R software package (version 4.1.1).

Results

Comparison of baseline data

Finally, among the 227 patients (mean age 66.7 ± 6.99 years) with CSVD in the present study, 68.7% were male. One hundred (44.1%) patients experienced cognitive impairment, the others composed the normal cognitive function group, and the differences in demographic data (age), risk factors for cerebrovascular disease (smoke, hypertension, total cholesterol, homocysteine), imaging markers of CSVD (lacuneus, cerebral microbleeds, white matter hyperintensities, total CSVD burden) and MoCA score were statistically significant ($p < 0.05$) (Table 1).

According to the total burden of CSVD, the patients were divided into groups according to their CSVD_score1, CSVD_score2, CSVD_score3, or CSVD_score4. CSVD_score1 represents patients with a CSVD total burden score of 1, similarly, CSVD_score2, CSVD_score3, and CSVD_score4 represent patients with CSVD total burden scores of 2, 3, and 4, respectively. The “tableone” package of the R software is invoked to plot the baseline feature table. For the variables with statistically significant ($P < 0.05$) for the overall comparison, we found that multiple sets of non-parametric tests were needed for the variables of these four groups of data, so the “Bonferroni” method was selected to perform non-parametric tests and intergroup comparisons for these four sets of data. The demographic data and clinical characteristics of the patients in the two groups are shown in Table 2. There were statistically significant differences in age, HCY, MoCA scores, and imaging markers of CSVD (LI, CMBs, WMH, and EPVS) among these groups ($p < 0.05$). The “ggpubr” package of the R software was invoked, and the “Kruskal-Wallis” method based on “ANOVA” was used to compare the differences between the four groups, and the “Bonferroni” method was used to compare the two groups in pairs, and the results were finally displayed as box plots and violin plots. The results of the intergroup comparisons are presented in Fig. 2. As time progressed, the MoCA score decreased, and the total burden of CSVD increased. There was a significant difference in age between the CSVD_score1 and CSVD_score3 groups ($p < 0.05$) (Fig. 2a). With the increase in the total burden of CSVD, the HCY level exhibited an increasing trend, and there were significant differences between the CSVD_score1 and CSVD_score2 groups and between the CSVD_score1 and CSVD_score3 groups ($p < 0.05$) (Fig. 2b). With the increase in the total burden of CSVD, the MoCA score showed a downwards trend, and there were significant differences among the multiple groups (CSVD_score1 and CSVD_score2, CSVD_score1 and CSVD_score3, CSVD_score1 and CSVD_score4, and CSVD_score2 and CSVD_score3) ($p < 0.05$) (Fig. 2c). The more imaging markers of CSVD were used, the more serious the total burden of CSVD was, and there were

Table 1 Characteristics of cerebral small vessel disease between cognitive normal and cognitive impairment (n)**

Variables	Overall n = 227	Cognitive impairment n = 100	Cognitive normal n = 127	P value
Sex				1.000
male	156(68.7)	69(69.0)	87(68.5)	
female	71(31.3)	31(31.0)	40(31.5)	
Age, year, mean(SD)	66.7(6.99)	68.99(6.73)	64.84(6.66)	< 0.001
Education, year	9.00[7.00,12.00]	10.00[6.75,12.00]	9.00[7.00,12.00]	0.958
Smoke				0.023
no	122(53.7)	45(45.0)	77(60.6)	
yes	105(46.3)	55(55.0)	50(39.4)	
Alcohol				0.683
no	137(60.4)	62(62.0)	75(59.1)	
yes	90(39.6)	38(38.0)	52(40.9)	
Hypertension				0.005
no	122(53.7)	43(43.0)	79(62.2)	
yes	105(46.3)	57(57.0)	48(37.8)	
CHD				0.339
no	138(60.8)	57(57.0)	81(63.8)	
yes	89(39.2)	43(43.0)	46(36.2)	
Diabetes				0.681
no	139(61.2)	63(63.0)	76(59.8)	
yes	88(38.8)	37(37.0)	51(40.2)	
Stroke				0.345
no	129(56.8)	53(53.0)	76(59.8)	
yes	98(43.2)	47(47.0)	51(40.2)	
TG, mmol/l	2.13[1.65,2.47]	2.14[1.65,2.59]	2.06[1.65,2.42]	0.189
TC, mmol/l	4.63[3.69,5.46]	4.68[4.23,5.66]	4.29[3.68,5.29]	0.034
HDL-C, mmol/l	1.91[1.54,2.27]	1.93(0.51)	1.89[1.45,2.26]	0.578
LDL-C, mmol/l	2.45[1.60,3.26]	2.49(1.12)	2.44(1.02)	0.702
Hcy, ummol/l	15.00[11.00–19.00]	16.00[13.00,22.25]	13.00[10.00,16.50]	< 0.001
UA, mmol/l	388.00[346.00,425.00]	399.00[364.00,426.00]	368.00[324.50,423.00]	0.052
FBG, mmol/l	5.68[5.24,6.78]	5.73[5.24,6.88]	5.66[5.24,6.56]	0.410
Lac_score	1.00[0.00,1.00]	1.00[0.00,1.00]	0.00[0.00,1.00]	0.002
CMBs_score	0.00[0.00,0.00]	0.00[0.00,1.00]	0.00[0.00,0.00]	0.002
WMH_score	1.00[0.00,1.00]	1.00[0.00,1.00]	0.00[0.00,1.00]	< 0.001
EPVS_score	0.00[0.00,1.00]	0.00[0.00,1.00]	0.00[0.00,1.00]	0.837
CSVD_score	1.00[1.00,2.00]	2.00[1.00,2.00]	1.00[1.00,1.50]	< 0.001
MoCA_score	26.00[24.00,28.00]	23.00[22.00,24.00]	27.00[27.00,28.00]	< 0.001
MoCA				< 0.001
< 26	100(44.1)	100(100.0)	0(0.0)	
≥ 26	127(55.9)	0(0.0)	100(100.0)	

Note: **Reported as n (%), or median (interquartile range, IQR), unless indicated otherwise. Abbreviations: CHD, coronary heart disease; TG, triacylglycerol; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; Hcy, homocysteine; UA, uric acid; FBG, fasting blood glucose; Lac, lactate; CMBs, cerebral microbleeds; WMH, white matter hyperintensities; EPVS, enlarged perivascular spaces; CSVD, cerebral small vessel disease; MoCA, Montreal Cognitive Assessment

statistically significant differences between the different CSVD burden groups. There were statistically significant differences in the biomarkers of CSVD, such as lacunes, microbleeds, white matter hyperintensities, and enlarged perivascular spaces ($p < 0.05$), between the different CSVD burden groups (Fig. 2d, e, f and g). We further assessed the effect of confounders on cognitive impairment using analysis of covariance. The results showed that HDL, LDL, UA, FBG, and Education were not

correlated with the MoCA, and the CSVD burden had a significant effect on the MoCA scores. The results also showed that Age, Hcy, TG, CHOL, Lac_score, CMBs_score, EPVS_score, and WMH_score all affected MoCA scores. After controlling for these confounders, the effect of total CSVD burden on MoCA scores was more accurate (Supplementary Table and Supplementary Figure).

Table 2 Characteristics of cerebral small vessel disease between groups of total magnetic resonance burden (n)**

Variables	CSVD_score1 n=122	CSVD_score2 n=85	CSVD_score3 n=14	CSVD_Score4 n=6	P value
Sex					0.186
male	86(70.5)	53(62.4)	11(78.6)	6(100.0)	
female	36(29.5)	32(37.6)	3(21.4)	0(0.0)	
Age, year	65.11(6.69) [#]	68.00[63.00,74.00]	70.00(4.49) [#]	71.67(9.29)	0.004
Education, year	9.00[8.00,12.00]	9.12(3.33)	9.36(3.39)	8.00(3.95)	0.57
Smoke					0.103
no	74(60.7)	37(43.5)	8(57.1)	3(50.0)	
yes	48(39.3)	48(56.5)	6(42.9)	3(50.0)	
Alcohol					0.796
no	74(60.7)	50(58.8)	10(71.4)	3(50.0)	
yes	48(39.3)	35(41.2)	4(28.6)	3(50.0)	
Hypertension					0.058
no	68(55.7)	49(57.6)	4(28.6)	1(16.7)	
yes	54(44.3)	36(42.4)	10(71.4)	5(83.3)	
CHD					0.529
no	72(59.0)	54(63.5)	7(50.0)	5(83.3)	
yes	50(41.0)	31(36.5)	7(50.0)	1(16.7)	
Diabetes					0.325
no	71(58.2)	58(68.2)	7(50.0)	3(50.0)	
yes	51(41.8)	27(31.8)	7(50.0)	3(50.0)	
Stroke					0.398
no	72(59.0)	49(57.6)	5(35.7)	3(50.0)	
yes	50(41.0)	36(42.4)	9(64.3)	3(50.0)	
TG, mmol/l	2.10[1.65,2.45]	2.13[1.65,2.46]	2.17(0.67)	2.52(0.83)	0.507
TC, mmol/l	4.35[3.65,5.40]	4.73(0.94)	5.71[5.17,6.18]	4.25(1.02)	0.077
HDL-C, mmol/l	1.97[1.64,2.31]	1.88[1.36,2.24]	1.86(0.58)	1.78(0.29)	0.454
LDL-C, mmol/l	2.45(1.10)	2.51(1.07)	2.40(0.80)	2.20(0.82)	0.904
Hcy, ummol/l	14.00[10.00,17.75] [#]	15.00[12.00,20.00] [*]	18.00(6.96) [#]	18.33(5.35)	0.029
UA, umol/l	397.50[354.00,426.00]	379.09(67.79)	379.79(42.93)	380.83(42.69)	0.664
FBG, mmol/l	5.75[5.28,6.77]	5.65[5.12,6.56]	6.02(1.00)	6.39(1.25)	0.326
MoCA_score	27.00[26.00,28.00] [#] [§]	24.68(2.44) ^{*/%}	20.14(2.82) [#] [%]	18.33(3.50) [§]	<0.001
Lac_score	1.00[0.00,1.00] [#] [§]	1.00[0.00,1.00] [@]	1.00[1.00,1.00] [#]	1.00[1.00,1.00] [§] [@]	0.02
CMBs_score	0.00[0.00,0.00] [#] [§]	0.00[0.00,1.00] ^{*/%@}	1.00[0.25,1.00] [#] [%]	1.00[1.00,1.00] [§] [@]	<0.001
WMH_score	0.00[0.00,0.75] [#] [§]	1.00[1.00,1.00] [*]	1.00[1.00,1.00] [#]	1.00[1.00,1.00] [§]	<0.001
EPVS_score	0.00[0.00,0.00] [#] [§]	0.00[0.00,1.00] ^{*/@}	0.50[0.00,1.00] [#] ^{&}	1.00[1.00,1.00] [§] ^{@&}	<0.001

Note: **Reported as n (%), or median (interquartile range, IQR); Italics indicate the mean (SD). * indicates the comparison of CSVD_score1 and CSVD_score2; # indicates the comparison of CSVD_score1 and CSVD_score3; % indicates the comparison of CSVD_score2 and CSVD_score3; § indicates the comparison of CSVD_score1 and CSVD_score4; @ indicates the comparison of CSVD_score2 and CSVD_score4; & indicates the comparison of CSVD_score3 and CSVD_score4. Abbreviations: CHD, coronary heart disease; TG, triacylglycerol; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; Hcy, homocysteine; UA, uric acid; FBG, fasting blood glucose; Lac, lactate; CMBs, cerebral microbleeds; WMH, white matter hyperintensities; EPVS, enlarged perivascular spaces; CSVD, cerebral small vessel disease; MoCA, Montreal Cognitive Assessment

Construction of predictive models

The MoCA score was used as the dependent variable, and the statistically significant variables shown in Table 1 (age, smoking status, hypertension, total cholesterol, homocysteine level, lacune, cerebral microbleeds, white matter hyperintensities, and CSVD score) were selected as the independent variables. The independent risk factors for cognitive impairment in patients with CSVD were identified by binary logistic regression. Age (OR=1.070; 95% CI=1.015~1.128, $p<0.05$), history of hypertension (OR=2.863; 95% CI=1.438~5.699, $p<0.05$), HCY (OR=1.065; 95% CI=1.005~1.127,

$p<0.05$), Lac_score (OR=2.732; 95% CI=1.094~6.825, $P<0.05$), and total CSVD burden (CSVD_score) (OR=3.823; 95% CI=1.496~9.768, $P<0.05$) were found to be independent risk factors for cognitive impairment in patients with CSVD, and a risk prediction model for cognitive impairment was established, which is displayed in Fig. 3 in the form of a nomogram.

Validation of predictive models

The nomogram was verified by using the “rms” package and bootstrap internal verification method, and the C-index was calculated as 0.839 (Fig. 4). Finally, the

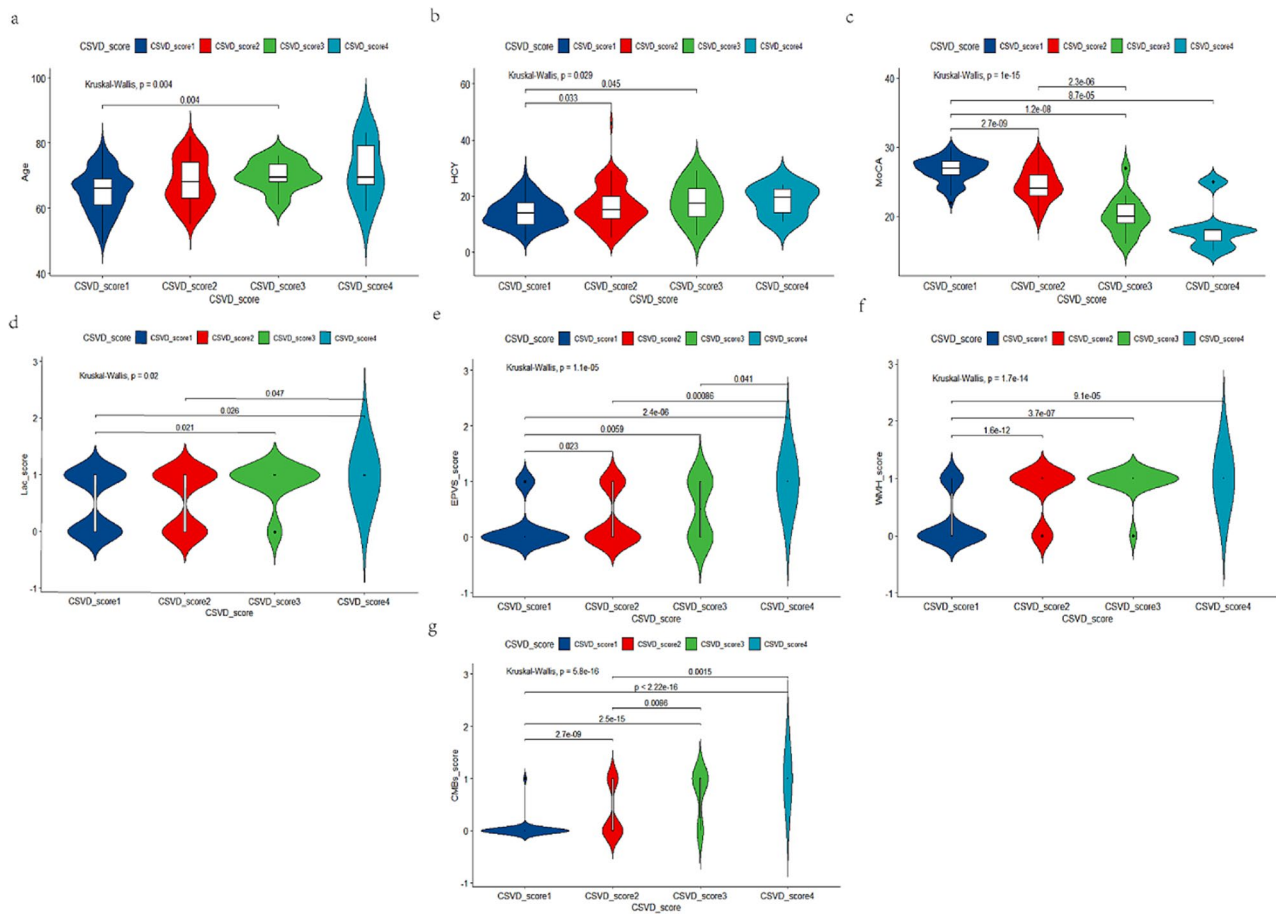


Fig. 2 Comparison of clinical characteristics between CSVD burden groups. Note: Abbreviations: Hcy, homocysteine; Lac, lacune; CMBs, cerebral microbleeds; WMH, white matter hyperintensity; EPVS, enlarged perivascular space; CSVD, cerebral small vessel disease; MoCA, Montreal Cognitive Assessment

model is verified against test data from other periods at our institute, as shown in Fig. 5, with a C index of 0.867. Both the predictive model and the validation model showed good performance. As shown in Fig. 6, according to the DCA of the nomogram of the predictive model, the prediction nomogram has a better net benefit in the threshold probability range of DCA. Similarly, the DCA of the test nomogram also revealed a greater net benefit of the test model for predicting cognitive impairment in patients with CSVD, as shown in Fig. 7.

Discussion

Currently, the etiology of CSVD-related cognitive deterioration has not been fully elucidated, and the underlying risk factors are controversial. The ability of the prediction model to predict CSVD-related cognitive impairment has become a hot topic in clinical research. The purpose of this study was to establish a clinical prediction model of cognitive dysfunction in patients with CSVD and guide clinicians in the individualized prevention and treatment of these patients. Research has shown [25–27] that CSVD is an important cause of stroke, cognitive decline, and

age-related disability. It is a comprehensive disease that includes brain atrophy, cerebral microbleeds, lacuna, and other pathological changes. Moreover, CSVD-related cognitive impairment is an important subtype of vascular cognitive impairment. According to this research, the probability of cognitive impairment in patients with CSVD has reached 41%, which is consistent with previous research results [28], suggesting that prevention and treatment of cognitive impairment in patients with CSVD have become the main goals of clinicians.

Age is the main risk factor for the development and progression of CSVD [28]. Our research also reached the same conclusion. In addition, this study confirmed that there was a statistically significant difference in age between different groups of participants according to the severity of the total burden of CSVD and that the total burden score of CSVD increased with age. This finding is highly consistent with previous research results [29]. We also showed that the prevalence of neuroimaging markers and cognitive decline in patients with CSVD increased with age and was found in most people older than 60 years. When we conducted a univariate analysis between

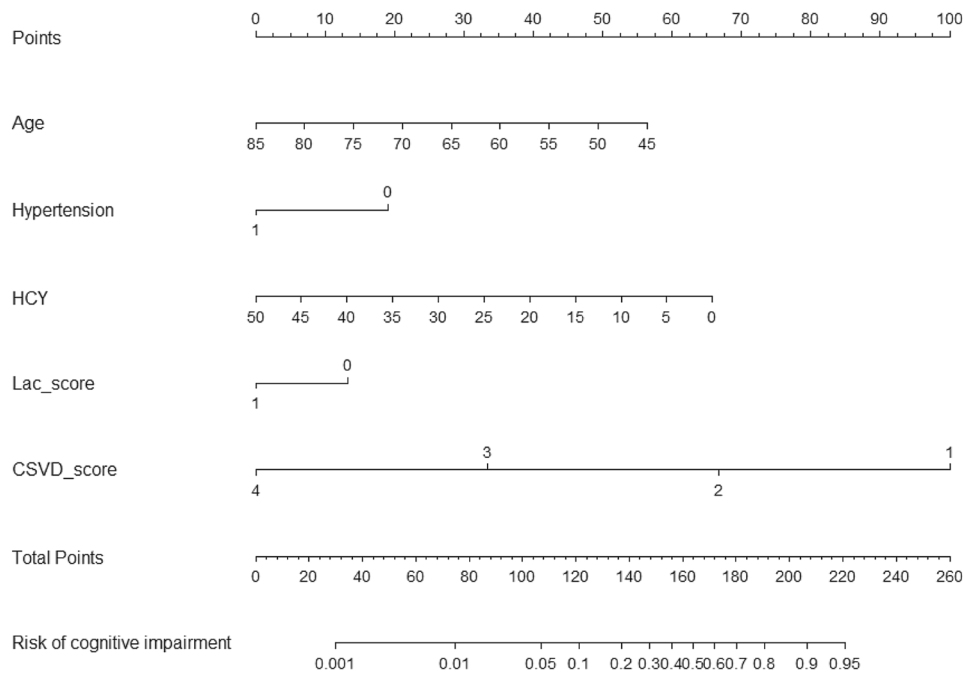


Fig. 3 The nomogram for assessing cognitive impairment. As shown in Fig. 3, a total score (0-100 points) for each independent variable was obtained by the use of a vertical line on the scoring scale at the top of the nomogram. The total score of all variables was added together to obtain the predicted risk value on the prediction line at the bottom of the nomogram. The assignment of categorical variables, without the disease or state, is represented by no and otherwise by yes. Of the two categorical variables, hypertension, and Lac_score, 0 is no, and 1 is yes. Note: Abbreviations: Hcy, homocysteine; Lac, lacune; CSVD, cerebral small vessel disease

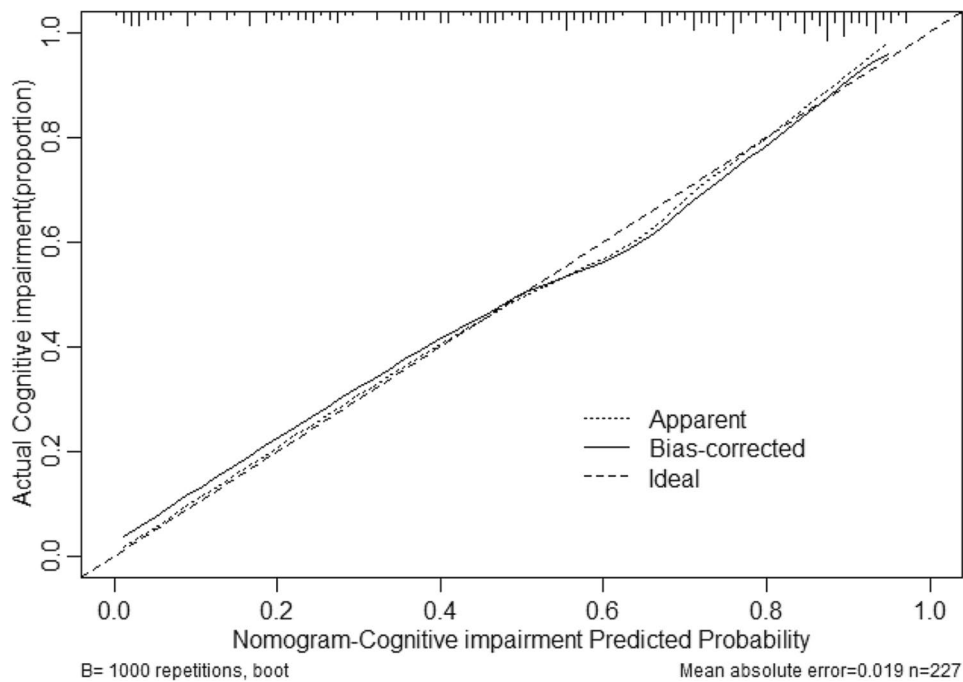


Fig. 4 The calibration curves for the prediction nomogram. As shown in Fig. 4, the x-axis represents the nomogram-predicted probability, and the y-axis represents the actual probability of cognitive impairment. A perfect prediction would correspond to the 45° ideal line. The dotted line represents the entire cohort ($n=227$), and the solid line represents the data bias-corrected by bootstrapping ($B=1000$ repetitions), indicating the performance of the observed nomogram. Note: C-index=0.839

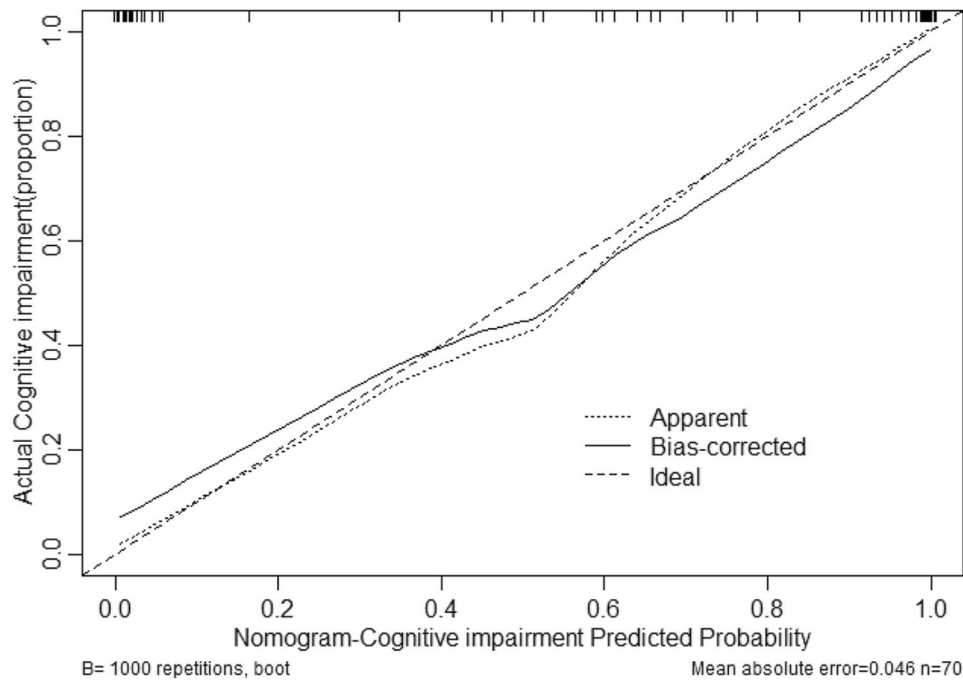


Fig. 5 The calibration curves for the test nomogram. As shown in Fig. 5, the x-axis represents the nomogram-predicted probability, and the y-axis represents the actual probability of cognitive impairment. A perfect prediction would correspond to the 45° ideal line. The dotted line represents the entire cohort ($n = 70$), and the solid line represents the data bias-corrected by bootstrapping ($B = 1000$ repetitions), indicating the performance of the observed nomogram. Note: C-index = 0.867

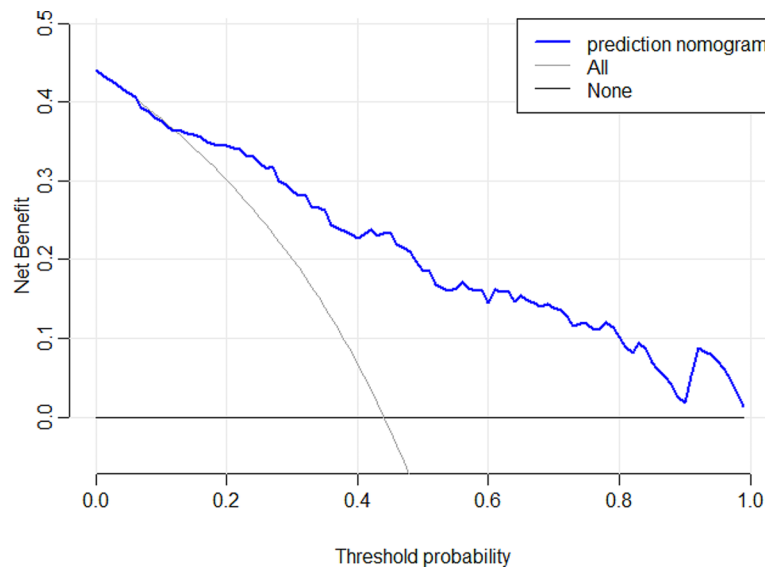


Fig. 6 Assessment of clinical usefulness of the prediction nomogram with a decision analysis curve. A horizontal straight line denotes a net benefit of 0, indicating that all CSVD patients have normal cognitive function and no treatment is needed; the gray line represents that all subjects have developed cognitive deterioration and are being treated; the blue curve represents the intervention of CSVD patients according to the outcomes in the predictive model; and the prediction nomogram has a better net benefit than the other two extreme curves in the threshold probability range of DCA.

the cognitive impairment group and the cognitively normal group, smoking was statistically different between the two groups ($p < 0.05$). However, we included it in logistic regression, and after adjusting for confounders, smoking was screened out, suggesting that smoking was not an independent risk factor for cognitive impairment

in CSVD in this study. The same conclusions have been found in the previous literature [30, 31]. According to a previous study, hypertension has been proven to be an important independent risk factor for cognitive impairment in patients with CSVD [7, 13, 28, 32]. Fortunately, our findings were consistent with those of our

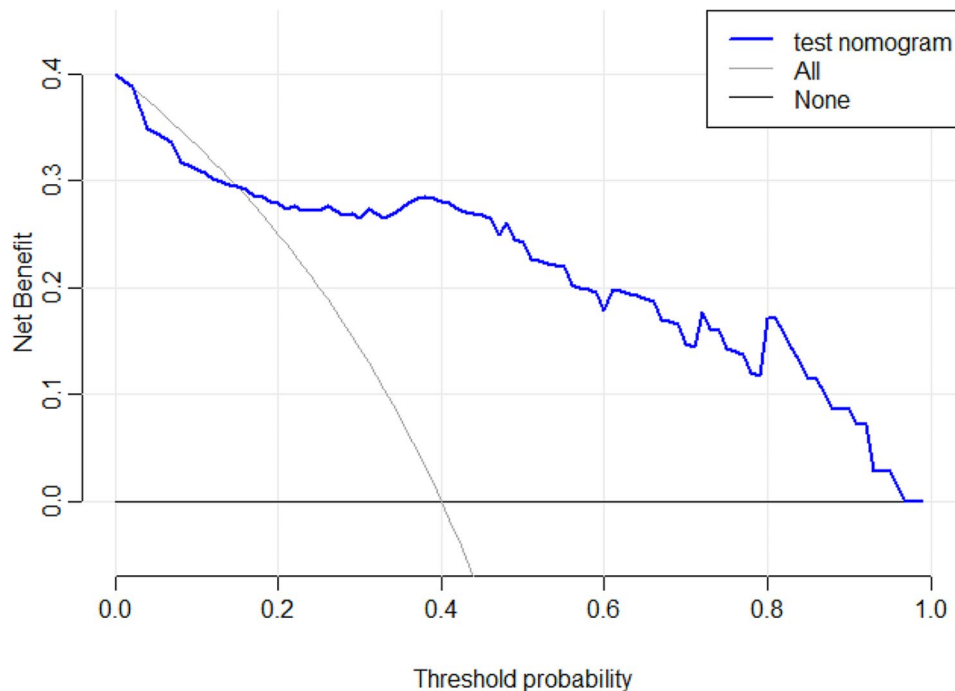


Fig. 7 Assessment of clinical usefulness with a decision analysis curve in the test nomogram. A horizontal straight line denotes a net benefit of 0, indicating that all CSVD patients have normal cognitive function and no treatment is needed; the gray line represents that all subjects have developed cognitive deterioration and are being treated; the blue curve represents the intervention of CSVD patients according to the outcomes in the test model; and the test nomogram has a better net benefit than the other two extreme curves in the threshold probability range of DCA.

predecessors. A cross-sectional study showed that age and hypertension were significantly and independently associated with the burden of CSVD [33]. Patients with CSVD and hypertension are prone to cognitive progress, possibly because hypertension can lead to successive oxidative stress and inflammatory responses, leading to changes in nerves and blood vessels; endothelial dysfunction; increased permeability of the blood-brain barrier; and accelerated pathological changes in CSVD, such as WMH, lacunar, EPVS, and CMBS [34]. Therefore, identifying and understanding the early subclinical stage of brain health deterioration and studying hypertension exposure may provide more in-depth insights into the role of hypertension in the pathophysiology of cognitive dysfunction.

In this study, we confirmed that homocysteine (Hcy) concentration was an independent risk factor for cognitive impairment in patients with CSVD. Moreover, the data showed that with increasing Hcy concentration, the total burden of CSVD and cognitive function tended to increase. As previously mentioned, Hcy produces oxygen-free radicals during metabolism and strongly oxidizes vascular endothelial cells [35]. An increase in Hcy levels has been proven to be related to cardiovascular disease, Alzheimer's disease, and cerebrovascular disease [36], suggesting that endothelial dysfunction is the main mechanism involved. Endothelial dysfunction has also been studied as the main mechanism of cognitive

impairment in patients with CSVD. The effect of the serum Hcy concentration on the development of CSVD was dose-dependent [37]. These findings provide clues for us to further study the pathophysiology of CSVD.

As previously mentioned, the total burden of CSVD was evaluated by neuroimaging to evaluate more complete and comprehensive brain injury in patients with CSVD, which represents the severity of brain injury and directly contributes to cognitive impairment [2, 38–40]. We confirmed that the greater the burden of CSVD was, the lower the MoCA score, and the greater the degree of brain damage; these results reaffirm the conclusions of the previous literature. Based on studies of neuroimaging features of CSVD, cognitive decline in patients with CSVD may be caused by pathological changes in the brain (LI, CMBS, WMH) that disrupt cortico-cortical, cortical-subcortical fibrous connections, especially when white matter hyperintensities predominate [32, 41]. During the one-year follow-up, the increase in enlarged perivascular spaces (EPVSs), especially in stroke patients, was closely related to other indicators of small vessel disease and cognitive impairment [42]. Enlarged perivascular spaces (EPVSs) are key to evaluating CSVD, but related research is insufficient. Although EPVS is associated with worse cognition, depression, and neurodegenerative diseases, its prognostic significance is unclear.

However, relying on pathological brain impairment does not directly predict the chance of cognitive decline.

Therefore, it is necessary to construct a cognitive risk decline prediction system. Although a large number of studies have focused on the risk factors for and pathogenesis of cognitive impairment in CSVD patients [40, 43], they still cannot guide doctors to individualize and forecast the probability of deterioration of cognitive function in patients with CSVD. Currently, there are few clinical predictive models of cognitive deterioration risk in patients with CSVD. The strength of the present study compared to previous studies is that we established and verified a more readable nomogram that can easily display the risk of cognitive impairment in each individual with CSVD, confirming that the predictive model has good clinical application value and extrapolation. In this study, a nomogram for predicting risk factors for cognitive impairment in patients with CSVD was established, and the accuracy and usefulness of the model were verified by calibration curves and decision analysis curves. The results showed that the predictive model had good performance, as indicated by its calibration, discrimination, and clinical utility. Another highlight of the study is that compared with that of previous studies, the reliability of the model was further verified by using external data. The validation model also showed good performance. In conclusion, the results of double verification showed that the nomogram model has good stability and good generalizability. Therefore, we can conclude that except for a small subset of patients with low preferences, treatment strategies that intervene in patients with cognitive impairment based on predictive models have greater benefits than strategies that intervene in all patients and do not intervene in all patients. For patients with CSVD, the conclusion is that using this model to determine whether cognitive function interventions should be performed on patients will improve clinical outcomes. The results of the present study have dual clinical significance. First, the findings of this study could lead to more convenient predictions of the incidence of cognitive impairment in individuals with CSVD, and this topic is worth promoting for clinical application. The second important finding of this study is that additional attention and targeted efforts are needed to better understand the pathogenesis of vascular injury to the brain caused by small vessel disease and to thoroughly define the clinical consequences of these diseases.

Regarding these shortcomings, the study has certain limitations. First, the study included single-center data, and there was a certain bias in the selection of participants. Second, this was a retrospective cross-sectional study, and there was no further follow-up of the study cohort or further observation of the impact of time on the total burden of MRI and cognitive function. Third, the study was limited to assessing global cognitive function and did not evaluate specific cognitive domains;

therefore, the impact of different brain pathological changes on the cognitive domain could not be assessed. In addition, the distribution of CSVD burden in this sample was skewed, with a low frequency of severe CSVD, which is also consistent with clinical reality. This may have led to bias in the strength of the associations that we observed for the total CSVD load with the MoCA scores. Therefore, we emphasize the need to replicate our findings in different cohort studies. Because of the above limitations, we will improve upon these findings in subsequent studies, and in the future, prospective cohort studies will be performed to further evaluate the damage caused by the total magnetic resonance burden to specific cognitive domains and further verify the reliability of the CSVD-related cognitive impairment model.

Conclusion

Overall, our research provides further evidence that there is a significant association between the total MRI burden of CSVD patients and cognitive impairment. The nomogram model based on brain MR images and clinical data helps in individualizing the probability of cognitive decline progression in patients with CSVD.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12868-024-00883-y>.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Fangfang Zhu collected, analyzed, and interpreted the patient data and was a major contributor to writing the manuscript. Fangfang Zhu designed and provided financial support for this study. Jie Yao and Min Feng contributed to the acquisition of the data. Zhongwu Sun revised the manuscript and helped interpret the data. All the authors have read and approved the final version of this manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the First author on reasonable request.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed by the Ethics Committee of the Second Affiliated Hospital of Bengbu Medical College and were exempt from ethics. Written informed consent for participation was not required for this study following the national legislation and the institutional requirements. The study of the test data followed the principles of the Declaration of Helsinki, and the study of human subjects involved was reviewed and approved by the Ethics Committee of the Second Affiliated

Hospital of Bengbu Medical College ([2020] No. 248). According to the requirements of Chinese national legislation and institutions, the participants in the test data or their family members have signed a written informed consent form or oral consent form and have a detailed understanding of the process, benefits, and risks of the experiment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare no conflicts of interest.

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References

- Hamilton OKL, Cox SR, Okely JA, Conte F, Ballerini L, Bastin ME, et al. Cerebral small vessel disease burden and longitudinal cognitive decline from age 73 to 82: the Lothian Birth Cohort 1936. *Transl Psychiatry*. 2021;11(1):376. <https://doi.org/10.1038/s41398-021-01495-4>.
- Fan Y, Xu Y, Shen M, Guo H, Zhang Z. Total Cerebral Small Vessel Disease Burden on MRI Correlates With Cognitive Impairment in Outpatients With Amnesic Disorders. *Frontiers In Neurology*, 2021. 12: p. 747115. <https://doi.org/10.3389/fneur.2021.747115>.
- Markus HS, de Leeuw FE. Cerebral small vessel disease: recent advances and future directions. *Int J Stroke*. 2023;18(1):4–14. <https://doi.org/10.1177/17474930221144911>.
- Jansen MG, Griffanti L, Mackay CE, Anatórk M, Melazzini L, Lange AG, et al. Association of cerebral small vessel disease burden with brain structure and cognitive and vascular risk trajectories in mid-to-late life. *J Cereb Blood Flow Metab*. 2022;42(4):600–12. <https://doi.org/10.1177/0271678X211048411>.
- Tang J, Zhang M, Liu N, Xue Y, Ren X, Huang Q, et al. The Association between Glymphatic System Dysfunction and Cognitive Impairment in Cerebral Small Vessel Disease. *Front Aging Neurosci*. 2022;14:916633. <https://doi.org/10.3389/fnagi.2022.916633>.
- Jokinen H, Koikkalainen J, Laakso HM, Melkas S, Nieminen T, Brander A, et al. Global burden of small Vessel Disease-related brain changes on MRI predicts cognitive and functional decline. *Stroke*. 2020;51(1):170–8. <https://doi.org/10.1161/STROKEAHA.119.026170>.
- Klarenbeek P, van Oostenbrugge RJ, Rouh RP, Knottnerus IL, Staals J. Ambulatory blood pressure in patients with lacunar stroke: association with total MRI burden of cerebral small vessel disease. *Stroke*. 2013;44(11):2995–9. <https://doi.org/10.1161/STROKEAHA.113.002545>.
- Jiang Y, Wang Y, Yuan Z, Xu K, Zhang K, Zhu Z, et al. Total cerebral small Vessel Disease Burden is related to worse performance on the Mini-mental State Examination and Incident Dementia: a prospective 5-Year Follow-Up. *J Alzheimers Dis*. 2019;69(1):253–62. <https://doi.org/10.3233/JAD-181135>.
- Zhang L, Gao F, Zhang Y, Hu P, Yao Y, Zhang Q, et al. Analysis of risk factors for the development of cognitive dysfunction in patients with cerebral small vessel disease and the construction of a predictive model. *Front Neurol*. 2022;13:944205. <https://doi.org/10.3389/fneur.2022.944205>.
- Park SY, Nomogram. An analogue tool to deliver digital knowledge. *J Thorac Cardiovasc Surg*. 2018;155(4):1793. <https://doi.org/10.1016/j.jtcvs.2017.12.107>.
- Wu J, Zhang H, Li L, Hu M, Chen L, Xu B, et al. A nomogram for predicting overall survival in patients with low-grade endometrial stromal sarcoma: a population-based analysis. *Cancer Commun (Lond)*. 2020;40(7):301–12. <https://doi.org/10.1002/cac2.12067>.
- Cappellari M, Zivelonghi C, Turcato G, Forlivesi S, Micheletti N, Tomelleri G, et al. A nomogram to predict the probability of mortality after first-ever acute manifestations of cerebral small vessel disease. *J Neurol Sci*. 2018;385:92–5. <https://doi.org/10.1016/j.jns.2017.12.020>.
- Gong P, Zhang X, Gong Y, Liu Y, Wang S, Li Z, et al. A novel nomogram to predict early neurological deterioration in patients with acute ischaemic stroke. *Eur J Neurol*. 2020;27(10):1996–2005. <https://doi.org/10.1111/ene.14333>.
- Jin C, Cao J, Cai Y, Wang L, Liu K, Shen W, et al. A nomogram for predicting the risk of invasive pulmonary adenocarcinoma for patients with solitary peripheral subsolid nodules. *J Thorac Cardiovasc Surg*. 2017;153(2):462–e4691. <https://doi.org/10.1016/j.jtcvs.2016.10.019>.
- Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*. 2008;26(8):1364–70. <https://doi.org/10.1200/JCO.2007.12.9791>.
- Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol*. 2015;16(4). [https://doi.org/10.1016/S1470-2045\(14\)71116-7](https://doi.org/10.1016/S1470-2045(14)71116-7). p. e173–80.
- Tang TY, Jiao Y, Cui Y, Zhao DL, Zhang Y, Wang Z, et al. Penumbra-based radiomics signature as prognostic biomarkers for thrombolysis of acute ischemic stroke patients: a multicenter cohort study. *J Neurol*. 2020;267(5):1454–63. <https://doi.org/10.1007/s00415-020-09713-7>.
- Wang T, Sun ZW, Shao LQ, Xu XB, Liu Y, Qin M, et al. Diagnostic Values of Serum Levels of Homocysteine and Uric Acid for Predicting Vascular mild cognitive impairment in patients with cerebral small Vessel Disease. *Med Sci Monit*. 2017;23:2217–25. <https://doi.org/10.12659/msm.901652>.
- Jiang J, Huang X, Zhang Y, Deng W, Shen F, Liu J. Total MRI burden of cerebral vessel disease correlates with the progression in patients with acute single small subcortical strokes. *Brain Behav*. 2019;9(1):e01173. <https://doi.org/10.1002/brb3.1173>.
- Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, et al. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci*. 1993;114(1):7–12. [https://doi.org/10.1016/0022-510x\(93\)90041-v](https://doi.org/10.1016/0022-510x(93)90041-v).
- Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease leading to cognitive impairment. *Chin Med J*. 2018;131(5):615–9. <https://doi.org/10.4103/0366-6999.226069>.
- Shu L, Liang J, Xun W, Yang H, Lu T. Prediction for the total MRI Burden of Cerebral Small Vessel Disease with Retinal Microvascular abnormalities in ischemic Stroke/TIA patients. *Front Neurol*. 2020;11:268. <https://doi.org/10.3389/fneur.2020.00268>.
- Staals J, Booth T, Morris Z, Bastin ME, Gow AJ, Corley J, et al. Total MRI load of cerebral small vessel disease and cognitive ability in older people. *Neurobiol Aging*. 2015;36(10):2806–11. <https://doi.org/10.1016/j.neurobiolaging.2015.06.024>.
- Gu Y, Zhao P, Feng W, Xia X, Tian X, Yan Y, et al. Structural brain network measures in elderly patients with cerebral small vessel disease and depressive symptoms. *BMC Geriatr*. 2022;22(1):568. <https://doi.org/10.1186/s12877-022-03245-7>.
- Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689–701. [https://doi.org/10.1016/S1474-4422\(10\)70104-6](https://doi.org/10.1016/S1474-4422(10)70104-6).
- Zanon Zotin MC, Sveikata L, Viswanathan A, Yilmaz P. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. *Curr Opin Neurol*. 2021;34(2):246–57. <https://doi.org/10.1097/WCO.0000000000000913>.
- Smith EE, Beaudin AE. New insights into cerebral small vessel disease and vascular cognitive impairment from MRI. *Curr Opin Neurol*. 2018;31(1):36–43. <https://doi.org/10.1097/WCO.0000000000000513>.
- Hamilton OKL, Backhouse EV, Janssen E, Jochems ACC, Maher C, Ritakari TE, et al. Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis. *Alzheimers Dement*. 2021;17(4):665–85. <https://doi.org/10.1002/alz.12221>.
- Hou Y, Li Y, Yang S, Qin W, Yang L, Hu W. Gait Impairment and Upper Extremity Disturbance are Associated with total magnetic resonance imaging cerebral small Vessel Disease Burden. *Front Aging Neurosci*. 2021;13:640844. <https://doi.org/10.3389/fnagi.2021.640844>.
- Zhou H, Hu J, Xie P, Dong Y, Chen W, Wu H, Jiang Y, Lei H, Luo G, Liu J. Lacunes and type 2 diabetes mellitus have a joint effect on cognitive impairment: a retrospective study. *PeerJ*. 2022;10:e13069. <https://doi.org/10.7717/peerj.13069>.
- Li X, Yuan J, Qin W, Yang L, Yang S, Li Y, Hu W. Higher total cerebral small Vessel Disease Burden was Associated with mild cognitive impairment and overall cognitive dysfunction: a propensity score-matched case-control study. *Front Aging Neurosci*. 2021;13:695732. <https://doi.org/10.3389/fnagi.2021.695732>.
- Jiménez-Balado J, Riba-Llena I, Abril O, Garde E, Penalba A, Ostos E, et al. Cognitive impact of Cerebral Small Vessel Disease changes in patients with hypertension. *Hypertension*. 2019;73(2):342–9. <https://doi.org/10.1161/HYPERTENSIONAHA.118.12090>.
- Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228–34. <https://doi.org/10.1212/WNL.0000000000000837>.

34. Amier RP, Marcks N, Hooghiemstra AM, Nijveldt R, van Buchem MA, de Roos A, et al. Hypertensive exposure markers by MRI in relation to Cerebral Small Vessel Disease and Cognitive Impairment. *JACC Cardiovasc Imaging*. 2021;14(1):176–85. <https://doi.org/10.1016/j.jcmg.2020.06.040>.
35. Zhang X, Bi X. Post-stroke Cognitive Impairment: a review focusing on molecular biomarkers. *J Mol Neurosci*. 2020;70(8):1244–54. <https://doi.org/10.1007/s12031-020-01533-8>.
36. Nam KW, Kwon HM, Jeong HY, Park JH, Kwon H, Jeong SM. Serum homocysteine level is related to cerebral small vessel disease in a healthy population. *Neurology*. 2019;92(4):e317–25. <https://doi.org/10.1212/WNL.0000000000006816>.
37. Teng Z, Feng J, Liu R, Ji Y, Xu J, Jiang X, et al. Cerebral small vessel disease mediates the association between homocysteine and cognitive function. *Front Aging Neurosci*. 2022;14:868777. <https://doi.org/10.3389/fnagi.2022.868777>.
38. Zhou LW, Panenka WJ, Al-Momen G, Gicas KM, Thornton AE, Jones AA, et al. Cerebral small Vessel Disease, Risk factors, and cognition in tenants of precarious housing. *Stroke*. 2020;51(11):3271–8. <https://doi.org/10.1161/STROKEAHA.120.030446>.
39. Yu C, Lu W, Qiu J, Wang F, Li J, Wang L. Alterations of the whole cerebral blood Flow in patients with different total cerebral small Vessel Disease Burden. *Front Aging Neurosci*. 2020;12:175. <https://doi.org/10.3389/fnagi.2020.00175>.
40. Xiang L, Zhang T, Zhang B, Zhang C, Hou S, Yue W. The associations of increased cerebral small vessel disease with cognitive impairment in neurosyphilis presenting with ischemic stroke. *Brain Behav*. 2021;11(6):e02187. <https://doi.org/10.1002/brb3.2187>.
41. Zhu W, Huang H, Yang S, Luo X, Zhu W, Xu S, et al. Cortical and Subcortical Grey Matter Abnormalities in White Matter Hyperintensities and subsequent cognitive impairment. *Neurosci Bull*. 2021;37(6):789–803. <https://doi.org/10.1007/s12264-021-00657-0>.
42. Williamson BJ, Khandwala V, Wang D, Maloney T, Sucharew H, Horn P, et al. Automated grading of enlarged perivascular spaces in clinical imaging data of an acute stroke cohort using an interpretable, 3D deep learning framework. *Sci Rep*. 2022;12(1):788. <https://doi.org/10.1038/s41598-021-04287-4>.
43. Yu X, Yu Y, Wei C, Wang L, Jiang J, Zhang R, et al. Association between small dense low-density lipoprotein cholesterol and neuroimaging markers of cerebral small vessel disease in middle-aged and elderly Chinese populations. *BMC Neurol*. 2021;21(1):436. <https://doi.org/10.1186/s12883-021-02472-6>.

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