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Exploration of a comprehensive index for predicting cognitive impairment in patients with cerebral small vessel disease and white matter lesions

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Abstract

Background & Objective: The objective of this study was to explore the risk factors for cognitive impairment in patients with cerebral small vessel disease (CSVD), and to construct a predictive model for cognitive impairment in CSVD patients, providing personalized diagnostic and treatment strategies for patients. *Methods:* Clinical data and blood indicators of CSVD patients admitted to the Department of Neurology at the Second Affiliated Hospital of Shandong First Medical University from February 2022 to February 2023 were collected. Additionally, these patients underwent cranial MRI examinations and completed neurological and psychological assessments, including the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). Based on the MoCA and MMSE results, the patients were divided into the cognitive impairment group and the normal cognitive group. Clinical data, blood indicators, and white matter lesion (WML) grades were compared between the two groups. Univariate logistic regression analysis was performed to identify the risk factors for cognitive impairment in CSVD patients. Using MoCA assessment results as the gold standard and several clinical indicators as independent variables, a logistic regression model was constructed. Predicted values were calculated based on this model, and a receiver operating characteristic (ROC) curve for the comprehensive diagnosis of multiple variables was plotted to evaluate the model's accuracy. *Results:* A total of 134 CSVD patients were included, and cognitive impairment occurred in 98 cases, with an incidence rate of 73.13%, while 36 patients did not have cognitive impairment. Univariate logistic regression analysis of the collected variables identified eight factors: age, education level, hypertension, diabetes, cerebral hemorrhage, low-density lipoprotein cholesterol (LDL-C), hyperhomocysteine (HHCY), and WML grading. Multivariate logistic regression analysis identified age, LDL-C, and WML grading as the final predictive factors, establishing a combined diagnostic model to predict the probability of cognitive impairment in patients. The constructed ROC curve for the comprehensive diagnosis of multiple variables yielded an area under the curve of 0.870, indicating good accuracy. To facilitate clinical diagnosis, the combined diagnostic model was simplified into an L score calculation formula, with the optimal cutoff value of 5.223. When the L score is <5.223, the patient can be considered not having cognitive impairment, while an L score >5.223 indicates cognitive impairment, allowing for the prediction of the risk of cognitive impairment in patients.
Conclusion: Age, education level, hypertension, diabetes, cerebral hemorrhage, LDL-C, HHCY, and WML grading are related risk factors for cognitive impairment in CSVD patients. Age, LDL-C, and WML grading are independent risk factors for cognitive impairment in CSVD patients. The clinical predictive model for cognitive impairment in cerebral small vessel disease, constructed using the final predictive factors, showed good performance and clinical utility. It facilitates individualized risk assessment for cognitive impairment in CSVD patients and allows for targeted follow-up observation for high-risk individuals.

Keywords: Cerebral small vessel disease, cognitive impairment, predictive factors, combined diagnostic model.

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INTRODUCTION

Cerebral small vessel disease (CSVD) is a comprehensive syndrome characterized by a series of clinical, cognitive, imaging, and pathological manifestations resulting from various pathogenic influences on the small arteries, arterioles, capillaries, venules, and small veins within the brain. It has become a hot research topic in the field of stroke both domestically and internationally in recent years.[1] CSVD mainly includes several different magnetic resonance imaging changes, such as lacunar infarcts, cortical subcortical infarcts, white matter lesions (WML), enlarged perivascular spaces, cerebral microbleeds, and brain atrophy.[2] Among these, white matter lesions (also known as white matter hyperintensities, WMHs) are considered the main pathological factor and marker of subcortical ischemic vascular dementia. Recent studies have shown a close association between white matter lesions and cognitive impairment, attracting significant attention from scholars.[3,4]

Currently, in clinical practice, there are numerous cognitive assessment scales for detecting cognitive impairment, but there is a lack of standardized evaluation criteria. In practice, the assessment can be influenced by factors such as the patient's education level, environment, compliance, and the subjectivity of the investigator, leading to an inability to accurately and effectively assess the risk of cognitive impairment in CSVD patients. Cognitive function assessment using these scales is also retrospective, which seriously affects its clinical application for screening cognitive impairment in CSVD patients. Therefore, early establishment of a predictive model to determine the prevalence of cognitive impairment is essential for evaluating the potential disease burden. In this study, relevant clinical data, laboratory indicators, and imaging data were used to screen for related risk factors for cognitive impairment and establish a comprehensive diagnostic model to predict the risk of cognitive impairment, guiding the clinical identification of high-risk groups and the formulation of individualized intervention measures.

METHODS

Data collection

Clinical data, laboratory indicators, and imaging data of patients with cerebral small vessel disease and white matter lesions were collected. Clinical data included gender, age, education level, body mass index (BMI), smoking history, alcohol consumption history, diabetes history, hypertension history, hyperlipidemia history, coronary heart disease history, and stroke history. Fasting blood samples were collected in the morning for laboratory indicators, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fibrinogen (FIB), uric acid (UA), glycosylated hemoglobin A1c (HbA1c), and hyperhomocysteine (HHCY).

Imaging data were obtained using a GE Discovery 750 3.0T MRI scanner, including T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging, and T2 fluid-attenuated inversion recovery (FLAIR) sequence. The Fazekas scale scoring method was used to assess the grade of white matter lesions in patients with cerebral small vessel disease, classified as follows: no WML group (score of 0), mild WML group (score of 1-2), moderate WML group (score of 3-4), and severe WML group (score of 5-6).

All cases underwent cognitive impairment assessment using the Montreal Cognitive Assessment (MoCA) by trained researchers. The MoCA has a total score of 30, with an additional point for individuals with an education level of ≤12 years. Scores of 26-30 are considered normal, while scores <26 indicate cognitive impairment. Based on MoCA and MMSE results, the enrolled patients were divided into the cognitive impairment group and the normal cognitive group.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software. Normally distributed continuous data were expressed as mean ± standard deviation and compared between groups using the *t*-test. Categorical data were presented as *n* (%) and compared between groups using the chi-square test. Logistic regression models were constructed using MoCA assessment results as the gold standard and several clinical indicators as independent variables. Predicted values were calculated based on these models, and receiver operating characteristic (ROC) curves were plotted to evaluate the accuracy of the comprehensive diagnostic model. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical characteristics

A total of 134 patients with cerebral small vessel disease were included in the study, and their cognitive function was assessed. Among them, 98 patients had cognitive impairment, with an incidence rate of 73.13%, while 36 patients had normal cognitive function, with an incidence rate of 26.87%.

The cognitive impairment group showed significant differences from the normal cognitive group in terms of age, education level, hypertension history, diabetes history, cerebral hemorrhage history, LDL-C, and WML grading ($P < 0.05$), while there were no significant differences in other indicators. Please refer to Table 1 for details.

Single-factor logistic regression analysis

The results of the single-factor logistic regression analysis are shown in Table 2. The analysis indicates that age, education level, hypertension, diabetes, cerebral hemorrhage, LDL-C, HHCY, and WML grading are significantly associated with cognitive impairment ($P<0.05$). However, gender, BMI, hyperlipidemia, coronary heart disease, stroke, smoking history, alcohol consumption history, FIB, uric acid, HbA1c, TC, TG, and HDL-C are not significantly associated with cognitive impairment ($P>0.1$).

Multivariate logistic regression and joint diagnostic model establishment

The factors "age," "LDL-C," and "WML grading" that are significantly associated with cognitive impairment (P<0.05) were included in

Table 1: A comparison of various indicators between the Cognitive Impairment Group (n=98) and the Normal Cognitive Group (n=36) in patients with cerebral small vessel disease. The statistical significance (P-value) for each indicator is also provided.

		Cognitive Impairment	Normal Cognitive	t/z/χ^2value	P-value
Male [n(%)]		56(57.14%)	20(55.56%)	0.027	0.869c
Age (±s, years)		65±6.46	58±6.21	5.627	0.000b
Education Level (±s, years)		7±4.43	9±2.67	3.017	0.003b
BMI/(±s,kg/m2)		25.5±3.13	26.4±4.30	0.675	0.500b
Hypertension History [n(%)]		55(56.12%)	12(33.33%)	5.469	0.019c
Diabetes History [n(%)]		36(36.73%)	5(13.89%)	6.471	0.011c
Hyperlipidemia History [n(%)]		22(22.45%)	6(16.67%)	0.533	0.466c
Coronary Heart Disease [n(%)]		38(38.78%)	8(22.22%)	3.200	0.074c
Stroke History [n(%)]		19(19.39%)	5(13.89%)	0.541	0.462c
Cerebral Hemorrhage [n(%)]		2(2.04%)	4(11.11%)	5.064	0.024c
Smoking History [n(%)]		48(48.98%)	15(41.67%)	0.565	0.452c
Alcohol Consumption [n(%)]		22(22.45%)	5(13.89%)	1.199	0.274c
FIB/(±s,g/L)		2.95±0.57	2.82±0.49	1.501	0.133b
UA/(±s,umol/L)		299±79.38	293±60.45	0.459	0.646b
HbA1C/(,%)		6.1±0.83	6.0±0.96	-0.747	0.455b
TC/(±s,mmol/L)		4.48±1.03	4.09±1.09	-1.886	0.062a
TG/(±s, mmol/L)		1.7±0.85	1.5±0.74	-1.308	0.191b
HDL-C/(±s,mmol/L)		1.19±0.24	1.22±0.40	0.488	0.628a
LDL-C/(±s, mmol/L)		2.59±0.74	2.26±0.70	2.274	0.025a
HHCY/(±s,umol/L)		15.6±3.41	14.0±2.94	1.870	0.061b
WMLGrading	Mild	26(26.53%)	24(66.67%)	18.965	0.000c
	Moderate	48(48.98%)	10(27.78%)		
	Severe	24(24.49%)	2(5.56%)		

Note: BMI = Body Mass Index, FIB = Fibrinogen, UA = Uric Acid, HbA1C = Glycosylated Hemoglobin A1c, TC = Total Cholesterol, TG = Triglycerides, HDL-C = High-Density Lipoprotein Cholesterol, LDL-C = Low-Density Lipoprotein Cholesterol, HHCY = Hyperhomocysteine, WML = White Matter Lesions. SD = Standard Deviation. a: *t*-test, b: Mann-Whitney U test, c: Chi-square test. *P*-values < 0.05 are considered statistically significant.

Table 2: Results of single-factor logistic regression

Indicator	B	S.E.	Wald	Significance	Exp(B)
Gender	0.065	0.393	0.027	0.869	1.067
Age	-0.197	0.042	22.262	0.000	0.821
Education Level	0.146	0.054	7.341	0.007	1.157
BMI	0.076	0.055	1.909	0.167	1.079
Hypertension	0.939	0.408	5.301	0.021	2.558
Diabetes	1.281	0.526	5.941	0.015	3.600
Hyperlipidemia	0.370	0.509	0.529	0.467	1.447
Coronary Heart Disease	0.796	0.451	3.111	0.078	2.217
Stroke	0.400	0.545	0.536	0.464	1.491
Cerebral Hemorrhage	-1.792	0.890	4.055	0.044	0.167
Smoking History	0.296	0.394	0.563	0.453	1.344
Alcohol Consumption	0.585	0.539	1.176	0.278	1.795
FIB	-0.471	0.369	1.632	0.201	0.624
UA	-0.001	0.003	0.212	0.645	0.999
HbA1c	-0.066	0.231	0.081	0.775	0.936
TC	-0.371	0.201	3.419	0.064	0.690
TG	-0.358	0.256	1.956	0.162	0.699
HDL-C	0.414	0.672	0.379	0.538	1.512
LDL-C	-0.628	0.285	4.870	0.027	0.534
HHCY	-0.169	0.072	5.607	0.018	0.844
WML Grading	-1.334	0.342	15.185	0.000	0.263

Note: BMI = Body Mass Index, FIB = Fibrinogen, UA = Uric Acid, HbA1c = Glycosylated Hemoglobin A1c, TC = Total Cholesterol, TG = Triglycerides, HDL-C = High-Density Lipoprotein Cholesterol, LDL-C = Low-Density Lipoprotein Cholesterol, HHCY = Hyperhomocysteine, WML = White Matter Lesions. B = Regression coefficient, S.E. = Standard Error, Wald = Wald statistics. Exp(B) represents the odds ratio. *P*-values < 0.05 are considered statistically significant.

the multivariate logistic regression analysis. The results of this model show that "age," "LDL-C," and "WML grading" are all statistically associated with "cognitive impairment" (P<0.05). For each increase in age level, the risk of cognitive impairment increases by 1.206 times; for each unit increase in LDL-C, the risk of cognitive impairment increases by 3.221 times; for each increase in WML grading, the risk of cognitive impairment increases by 3.716 times. The results are presented in Table 3.

ROC curve construction and diagnostic performance comparison

Both the univariate and multivariate ROC curves were constructed, and from Figure 1, it is evident that the area under the curve (AUC) of the multivariate diagnostic model is significantly larger than that of the univariate diagnostic models. The AUC of the multivariate diagnostic model is 0.870, indicating good accuracy. The AUC values for the three univariate diagnostic models (age, LDL-C, and WML grading) are 0.817, 0.634, and 0.721, respectively. From the statistical values and their 95% confidence intervals (CIs) for each AUC, it can be observed that the AUC of the univariate diagnostic models is significantly smaller than that of the multivariate diagnostic model. The detailed results are shown in Table 4.

To facilitate the convenient clinical application of the model, the model coefficients are divided by the coefficient of WML grading to simplify the model, resulting in the L score calculation formula: L score = -89.856 + age + 6.257×LDL-C + 7.021×WML grading. The L score is calculated for each patient in the original dataset, and then an ROC curve is generated to find the optimal L score corresponding to the model. This diagnostic method yields a Youden Index of 0.609, sensitivity of 0.776, and specificity of 0.833. The cutoff value for the L score is determined as 5.223. By calculating the L score of each patient, disease diagnosis can be performed. When the L score is less than 5.223, it indicates that the patient is not affected by the disease, whereas an L score greater

Table 3: Results of multivariate logistic regression

	B	S.E,	Wals	Sig.	Exp (B)	EXP(B) 的 95% C.I.	
						Lower	Upper
Age	0.187	0.046	16.604	0.000	1.206	1.102	1.320
LDL-C	1.170	0.393	8.849	0.003	3.221	1.490	6.961
WML Grading	1.313	0.409	10.323	0.001	3.716	1.668	8.276
Constant	-16.803	3.341	25.299	0.000	0.000		

Based on the multivariate logistic regression model, a risk score Logit(P) for "cognitive impairment" can be calculated for each patient using the following formula:

Logit(P) = -16.803 + 0.187 × age + 1.170 × LDL-C + 1.313 × WML Grading.

Then, the predicted probability of each patient having cognitive impairment can be calculated using the following formula:

$$P = \frac{e^{\text{logit}(P)}}{1 + e^{\text{logit}(P)}}$$

This variable represents the probability of disease predicted by the multivariate diagnostic model. Next, ROC analysis will be conducted using this variable to evaluate the model's predictive performance.

than 5.223 suggests the presence of cognitive impairment in the patient.

DISCUSSION

Cognitive impairment is a globally significant concern, as it not only leads to a decline in the daily and functional abilities of patients but also imposes a heavy physical and psychological burden on caregivers, exacerbating the societal burden.[5,6] In countries like the United States and Japan, the prevalence of mild cognitive impairment (MCI) in the elderly population ranges from 6.5% to 39.1%.[7] The specific mechanisms by which cerebral small vessel disease (CSVD) causes cognitive impairment are not yet fully understood. Therefore, early diagnosis and identification of MCI stage, along with early intervention to control modifiable risk factors, hold crucial theoretical and clinical significance in enhancing patients' quality of life and reducing the burden on families.

This study identified age, LDL-C, and WML grading as important influencing factors for the occurrence of cognitive impairment in CSVD patients. Reviewing the current global research, the main risk factors identified in our study are generally consistent with previous studies.[8-10]

The findings in this research provide valuable

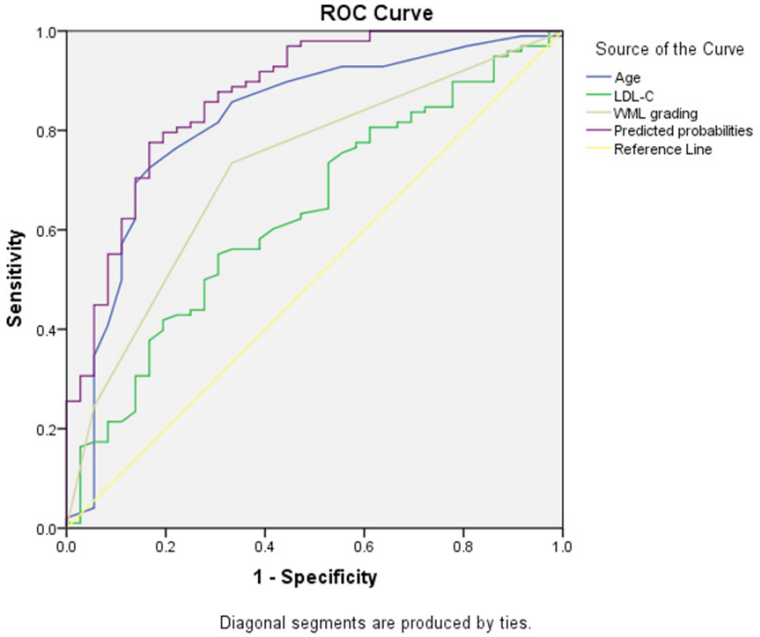

Figure 1.

Table 4: AUC (Area Under the Curve) of the corresponding ROC curves for each method

Variable	AUC	Standard Error	Asymptotic Significance	Asymptotic 95% Confidence Interval	
				Lower	Upper
Age	0.817	0.045	0.000	0.730	0.905
LDL-C	0.634	0.053	0.017	0.530	0.738
WML Grading	0.721	0.049	0.000	0.625	0.817
Predicted Probability	0.870	0.036	0.000	0.799	0.941

The table presents the AUC values with their standard errors and corresponding asymptotic significance for each method. The AUC is a measure of the model's predictive performance, ranging from 0.5 to 1. A higher AUC indicates better predictive accuracy. Based on the results, the predicted probability method has the highest AUC of 0.870, which is significantly greater than the AUC values for age (0.817), LDL-C (0.634), and WML grading (0.721). These findings indicate that the multivariate joint diagnostic model has superior predictive accuracy in assessing the risk of cognitive impairment in patients with cerebral small vessel disease.

insights into the risk factors associated with cognitive impairment in CSVD patients. The established predictive model and L score calculation formula offer a practical and convenient way to identify individuals at high risk of cognitive impairment. Early identification of at-risk patients allows for targeted interventions, potentially reducing the burden of cognitive impairment and improving the overall well-being of patients and their caregivers.

Although the study has made significant progress, there are still some limitations that need to be acknowledged. Firstly, the sample size may be relatively small, which could limit the generalizability of the results. Secondly, the study focused on a specific population from a single medical center, and the influence of other confounding factors may not have been fully accounted for. Therefore, future research with larger and more diverse samples is warranted to validate and further refine the predictive model.

In brief, this study contributes to the growing body of knowledge on cognitive impairment in CSVD patients and highlights the importance of early detection and intervention. By identifying and addressing modifiable risk factors, clinicians can potentially mitigate the impact of cognitive impairment on patients' lives and improve overall outcomes in this population.

Age is an independent risk factor for cognitive impairment in patients with cerebral small vessel disease (CSVD).[11] As patients age, the narrowness and stiffness of cerebral small vessels lead to insufficient perfusion in the deep penetrating arterioles, resulting in cerebral white matter lesions and an increase in the prevalence of CSVD.[12,13] The low-density lipoprotein receptor (LDLR), a membrane glycoprotein, plays a role in the transport and metabolism of cholesterol lipoproteins. It is widely expressed in various cell types, including astrocytes and oligodendrocytes[14,15], and is involved in regulating brain glucose metabolism, which is closely related to cognitive function.[16] LDL-C has been confirmed as an independent risk factor for cognitive impairment in CSVD patients in several domestic studies.[17]

The Fazekas rating scale has been proven to be highly correlated with the severity of white matter lesions (WMLs). In this study, the Fazekas scale was used to assess the severity of WMLs, and patients were classified into mild, moderate, and severe WML groups based on their scores. The severity of WMLs in CSVD patients predicts the progression and adverse outcomes of cognitive impairment.[18-20]

Previous studies have shown that hypertension, hyperglycemia, and hyperhomocysteinemia (HHCY) are correlated with cognitive impairment in CSVD patients.[21-24] However, in this study, these factors were not identified as independent influencing factors, possibly due to the limited sample size. In future research, increasing the sample size could lead to more rigorous and comprehensive results.

It is noteworthy that while hypertension is a known factor closely associated with cerebral white matter hyperintensities and small vessel disease, it was not identified as an independent risk factor in this study. Apart from the small sample size, other potential influencing factors include the duration of hypertension, interactions with other variables (such as diabetes and lipid levels), genetic predispositions, and individual variations in blood pressure control. Future studies should not only expand the sample size

to enhance statistical power but also explore other potential confounding factors, including antihypertensive treatment, to more accurately assess the relationship between hypertension and cognitive impairments caused by small vessel disease.

Overall, this study provides valuable insights into the independent risk factors for cognitive impairment in CSVD patients. Understanding these risk factors allows for targeted interventions to prevent or delay cognitive decline and improve the overall management and outcomes of CSVD patients. Further research with larger samples is warranted to confirm and expand on these findings.

This study established a predictive model for cognitive impairment in patients with cerebral small vessel disease (CSVD) based on clinical risk factors, with the outcome variable being the occurrence of cognitive impairment. The model demonstrated good predictive performance, effectively estimating the risk probability of cognitive impairment in CSVD patients. The quantification and individualized prediction of the risk for cognitive impairment have significant implications for the prevention of cognitive decline.

From the perspective of hospital clinical practice, this predictive model can enhance diagnostic accuracy and efficiency, adding value to clinical decision-making. At a societal level, it can be used to screen high-risk populations for CSVD, identify and prevent cognitive impairment, and implement early intervention measures. With the continuous advancement of medical technology, new techniques can be incorporated to explore the mechanisms and influencing factors of cognitive impairment in CSVD. Collecting additional data and investigating potential mechanisms will contribute to the development of more accurate, comprehensive, and convenient predictive models for clinical practice in the future.[25]

In conclusion, objective factors such as age, LDL-C, and WML grading are statistically associated with cognitive impairment and serve as independent risk factors. Regular medical check-ups can help identify modifiable risk factors at an early stage, allowing for timely intervention.

The proposed joint diagnostic model for predicting cognitive impairment demonstrates good accuracy and has potential clinical applicability in guiding diagnosis and early intervention.

This study innovatively developed a joint diagnostic model to predict the occurrence of cognitive impairment, guiding clinical diagnosis and facilitating early intervention to delay the progression to dementia.

However, the predictive model has some limitations. Being a single-center retrospective study with a limited number of cases, there may be issues related to sensitivity and specificity. Further multi-center and large-sample clinical studies are needed to provide an ideal predictive model for clinical practice and better guide clinical decision-making.

DISCLOSURE

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