ORIGINAL RESEARCH

Nomogram to Predict Cognitive Impairment in Patients with Asymptomatic Middle Cerebral Artery Stenosis

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Purpose: This study aims to investigate the characteristics and influencing factors of cognitive impairment in patients with asymptomatic middle cerebral artery stenosis (aMCAS) and to construct a nomogram to predict the risk of cognitive impairment in patients with aMCAS.

Patients and Methods: We collected 54 patients with aMCAS and 35 healthy controls to investigate the impaired cognitive domains and pathogenesis in patients with aMCAS. All patients underwent a cranial MRI, CT perfusion, transcranial Doppler ultrasound, blood tests, and a comprehensive neuropsychological evaluation. According to the MoCA score, patients were divided into cognitively normal and cognitively impaired groups. To construct the nomogram, we conducted univariate and multivariate logistic regression analyses to identify factors that affect cognitive function. And the performance of nomogram was evaluated by ROC curves, calibration curves, decision curve analysis (DCA), and clinical impact curve (CIC).

Results: In 54 patients with aMCAS, 24 patients presented with cognitive normal, and 30 patients presented with cognitive impairment. The results of multivariate logistic regression suggested that perfusion decompensation, middle cerebral artery mean flow velocity, and LDL-cholesterol levels were independent influencing factors of cognitive impairment. In the following step, a nomogram was constructed. The AUC of the nomogram is 0.862. Calibrating curves show good agreement between nomogram predictions and actual observations, while DCA and CIC show great clinical usefulness.

Conclusion: Patients with aMCAS have cognitive impairment in multiple cognitive domains, and impaired executive function was observed during the perfusion compensation period. Furthermore, a nomogram was constructed and validated to predict the risk of cognitive impairment in patients with aMCAS, which can help clinicians to identify at an early stage and improve the management of patients.

Keywords: cognitive impairment, asymptomatic middle cerebral artery stenosis, nomogram, predictive model

Introduction

Intracranial atherosclerotic stenosis (ICAS) is one of the most common causes of stroke worldwide as well as a significant contributor to the risk of cognitive impairment.[1,2] With the development of noninvasive imaging techniques, more and more patients can be diagnosed with asymptomatic ICAS before stroke or transient ischemic attack (TIA) occurs. Research has shown that the incidence of aICAS ranges from 5.9% to 24.5%. Moderate or above aICAS is associated with cognitive impairment, which affects the daily life and behavior of patients.[3]

Current research on aICAS is mainly focused on the carotid artery. Asymptomatic carotid artery stenosis (aCAS) is an independent risk factor for cognitive impairment,[4] mainly manifested as impairment in visuospatial ability, processing speed, short-delay recall, long-delay recall, executive function, attention, and language.[5–8] As an important branch of the carotid artery, the middle cerebral artery (MCA) mainly supplies blood to the front 2/3 of the dorsolateral of the cerebral hemisphere, including the frontal, parietal, temporal, and insular lobes. MCA stenosis may cause dysfunction in these brain areas and impair cognitive function. Current studies of cognitive impairment in patients with asymptomatic middle

cerebral artery stenosis (aMCAS) focus on the impaired cognitive domains. However, fewer studies have investigated the mechanisms of cognitive impairment, and the model to predict cognitive impairment in patients with aMCAS has not been constructed.

Therefore, this study used the 60-min protocol recommended in vascular cognitive impairment harmonization criteria[9] to comprehensively assess the cognitive function of patients with aMCAS. Additionally, CT perfusion (CTP) was used to assess the cerebral perfusion of patients, and transcranial Doppler ultrasound (TCD) was used to measure the blood flow velocity of MCA. We aimed to investigate the impaired cognitive domains and pathogenesis in patients with aMCAS, and constructed a nomogram for early recognition of cognitive impairment.

Materials and Methods

Participants

We collected 54 patients diagnosed with aMCAS admitted to the Department of Neurology of Shanxi Medical University First Hospital between July 2021 and November 2022. The inclusion criteria were: (1) patients with unilateral MCA stenosis of 50% or more as diagnosed by computed tomography angiography (CTA) or digital subtraction angiography (DSA), (2) stenosis caused by atherosclerosis and (3) patients can complete cognitive function tests independently. The exclusion criteria were: (1) stroke or TIA diagnosed by clinical and MRI, (2) stenosis of 50% or more in other large intracranial arteries (internal carotid artery, anterior cerebral artery, posterior cerebral artery, basilar artery, and vertebral artery), (3) intracranial vascular stenosis caused by other reasons (such as moyamoya disease, arteriovenous malformations, central nervous system (CNS) vasculitis, arterial dissection, cardiogenic embolism caused by atrial fibrillation, etc.), (4) cognitive impairment with other identifiable etiologies (such as Alzheimer's disease, epilepsy, Parkinson's disease, intracranial infections, mental illness, etc.), and (5) patient without cranial MRI, cranial CTP, TCD, and other blood tests. In addition, we also included 35 healthy controls to assess cognitive function as a comparison. This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University and followed the declaration of Helsinki. All patients and controls have signed informed consents.

Data Collection

Data collection included baseline assessments, imaging evaluations, and blood tests. Baseline assessments include sex, age, education, hypertension, diabetes, smoking history and drinking history. Imaging evaluations included the following parameters: (1) cranial CTA or DSA, including the degree of stenosis, the side of the stenosis and types of collateral compensation; (2) cranial MRI, including T1W1, T2W1, Flair, DWI, and then assessed the severity of white matter lesions using the revised Fazekas standard; (3) CTP, including time to peak (TTP), transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV), (4) TCD, including peak systolic velocity, end diastolic velocity and mean flow velocity (MFV) of MCA, and then calculated pulsatility index (PI). Blood tests included kidney function, coagulation, serum lipids, homocysteine, folic acid, vitamin B12, and thyroid function, which were completed in all patients on the first day after admission. Based on the CTP results, patients were further divided into normal, compensation, and decompensation subgroups according to their perfusion period. CTP normal patients had complete blood perfusion. In the CTP compensation group, cerebrovascular function was retained (delayed TTP and MTT, normal or increased CBF and CBV), while in the CTP decompensation group, hypoperfusion was evident and cerebrovascular function was diminished (decreased CBF, normal or decreased CBV).

Neuropsychological Assessment

All patients underwent a standard neuropsychological evaluation by a specialized neurologist. The Montreal cognitive assessment scale (MoCA) assesses overall cognitive function. The auditory verb learn test-Huashan version (AVLT-H) was used to measure memory functions, including short-delay recall, long-delay recall, cued recall, and recognition. Executive function, including working memory, attention, dominance inhibition, set shifting, and fluency, was assessed with digit span test (DST), Symbol-digit Modalities Test (SDMT), Stroop color-word task (SCWT), trail making test (TMT), and verbal fluency test (VFT), respectively. The modified Boston naming test (mBNT) was used to measure

language function and the Rey-Osterrieth complex figure test (RCFT) was used to measure visuospatial function. Patients were divided into cognitive normal (CN) group and cognitive impairment (CI) group according to MoCA score.

Statistical Analysis

SPSS 26.0 and R software were used for statistical analysis. The Kolmogorov–Smirnov test was used to analyze whether the data were normally distributed. For the data that passed the normality test, we used the two-sample independent *t*-test or analysis of variance, whereas for the data that failed it, we used the Mann–Whitney test or Kruskal–Wallis test. Chi-square test or Fisher's exact test was used to compare qualitative variables. Univariate logistic regression analysis was used to screen predictors of cognitive impairment in patients with aMCAS. Factors with P<0.1 were included in the multivariate logistic regression analysis, and a backward conditional method was used to determine the best model. Based on the predictors of cognitive impairment identified in the final model, a nomogram was constructed and internally validated using bootstrap method with 1000 resamples. Receiver operating characteristic (ROC) curves were used to evaluate discrimination. Calibration curves were used to test the consistency between predicted probability and observed probability. Decision curve analysis (DCA) and clinical impact curve (CIC) were employed to evaluate the clinical applicability.

Results

General Clinical Characteristics

According to the inclusion and exclusion criteria, 54 patients with aMCAS were finally included in the study. Among them, 30 patients were cognitively impaired and 24 patients were cognitively normal. The general clinical characteristics of the two groups of aMCAS patients are shown in Table 1. The CI group included 14 patients with MCA occlusions and 16 patients with severe MCA stenosis; the CN group included 6 patients with MCA occlusions, 16 patients with severe MCA stenosis and 2 patients with moderate MCA stenosis. In addition, in the CI group, the number of patients in the CTP normal, CTP compensated, and CTP decompensated groups were 3, 11, and 16, respectively. In the CN group, the

Table 1 Characteristics of All Patients in the CN and CI Groups

	CN (n=24)	CI (n=30)	Z/t	P
Baseline characteristics				
Sex (Male)	16	17	0.561[c]	0.454
Age	51.5±10.70	55±11.26	−0.796[a]	0.430
Education (>9 years)	13	18	0.186[c]	0.667
Hypertension	14	14	0.727[c]	0.394
Diabetes	8	6	1.234[c]	0.267
Smoking history	11	15	0.093[c]	0.761
Drinking history	8	7	0.665[c]	0.415
Degree of stenosis			2.684[c]	0.101
Moderate to severe	18	16		
Occlusion	6	14		
Side of the stenosis (Left)	12	9	2.244[c]	0.134
Perfusion period			9.966[c]	0.007*
Normal	6	3		
Compensation	15	11		
Decompensation	3	16		
Fazekas grade			3.477[c]	0.324
Fazekas grade 0	6	3		
Fazekas grade 1	7	7		
Fazekas grade 2	7	10		
Fazekas grade 3	4	10		

(*Continued*)

Table 1 (Continued).

	CN (n=24)	CI (n=30)	Z/t	P
Collateral compensation				0.905[d]
None	6	8		
AcoA	4	7		
PcoA	5	5		
AcoA+PcoA	6	4		
Pial collateral	2	4		
Neovascularization	1	1		
TCD parameters				
MCA MFV	109(53.25, 189.5)	58.3(41.9, 90.75)	−2.995[b]	0.003*
MCA PI	0.70(0.52, 1.13)	0.80(0.65, 1.11)	−1.306[b]	0.192
Blood tests				
PT	12.05(11.25, 12.4)	11.85(11.40, 13.58)	−0.479[b]	0.632
APTT	28.85±3.96	26.59±5.80	1.628[a]	0.11
TT	18.1(17.65, 18.5)	17.75(17.3, 19.4)	−0.322[b]	0.747
AT-III	87.07±23.76	93.82±15.18	−1.268[a]	0.21
FDP	2.5(0.54, 2.5)	1.47(0.93, 2.5)	−0.354[b]	0.724
D-D	0.25(0.17, 36.69)	0.57(0.14, 32.08)	−0.331[b]	0.741
FT3	4.76±0.83	4.79±0.60	−0.187[a]	0.85
FT4	16.60±2.63	16.62±3.43	−0.029[a]	0.98
TSH	2.25±1.33	2.00±1.07	0.762[a]	0.45
TC	3.55±0.91	4.18±1.13	−2.174[a]	0.03 *
TG	1.34(0.84, 1.54)	1.49(1.15, 2.47)	−1.889[b]	0.059
HDL-c	0.88(0.80, 1.06)	1.06(0.85, 1.11)	−1.376[b]	0.169
LDL-c	2.24±0.75	2.80±0.76	−2.717[a]	0.01 *
CRE	64.65±8.62	66.09±17.82	−0.39[a]	0.70
UA	332.9(245.03, 372.95)	304.2(251.76, 432.15)	−0.548[b]	0.583
Urea	4.3(3.96, 5.60)	5.05(4.16, 6.17)	−1.122[b]	0.262
HCY	13.6(11.93, 21.2)	14.2(10, 17.95)	−0.583[b]	0.560
FA	17.50±7.24	23.66±15.11	−1.969[a]	0.060
B12	113.5(88, 166)	146(109, 279)	−1.550[b]	0.121

Notes: *P<0.05; [a]The t value of the two-sample independent *t*-test; [b]The Z value of t Mann–Whitney *U*-test; [c]The P value of chi-square test exact test; [d]The P value of Fisher exact test.

Abbreviations: AcoA, anterior communicating artery; PcoA, posterior communicating artery; MFV, mean flow velocity; PI, pulsatility index; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; AT-III, antithrombin III; FDP, fibrin degradation products; D-D, D-dimer; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, triglyceride.; HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; CRE, Creatinine; UA, uric acid; HCY, homocysteine; FA, folic acid; B12, vitamin B12.

number of patients in the CTP normal, CTP compensated, and CTP decompensated groups were 6, 15, and 3, respectively. According to univariate analysis, there was a statistically significant difference between the two groups in terms of perfusion, MCA MFV, total cholesterol levels and LDL-c (P<0.05).

Comparison of Cognitive Function in Patients with aMCAS Under Different Perfusion Conditions

After grouping according to different perfusion periods, we compared the cognitive function of each group. There was no significant difference between the groups in VFT, mBNT, DSF, and RCFT (P > 0.05), while there was a significant difference in MoCA scores, AVLT-H, DSB, SDMT, TMT, and SCWT (P < 0.05). Compared with healthy controls, the CTP normal group had no significant difference in all cognitive tests, whereas the CTP compensation group had a significant difference in cued recall and executive function. The CTP decompensation group had significant differences in MoCA score, memory function, and executive function. In comparison among subgroups with different perfusion

periods, patients in the CTP compensation group and decompensation group showed a significant decrease in attention, set shifting and dominance inhibition compared with the CTP normal group (P<0.05). And as the degree of hypoperfusion increased, the patients' overall cognitive function and long-delayed recall ability gradually decreased (Table 2).

Screening of Predictors and Construction of Prediction Model

Univariate logistic regression was used to screen predictors with a screening criterion of P<0.1. The results showed that CTP decompensation (OR=10.667, 95% CI 1.669–68.183), MCA MFV (OR=0.354, 95% CI 0.174–0.722), TC (OR=1.879, 95% CI 1.03–3.43), TG (OR=2.215, 95% CI 1.121–4.378), LDL-c (OR=2.239, 95% CI 1.178–4.257), FA (OR=1.748, 95% CI 0.933–3.275) and Fazekas grade 3 (OR=5, 95% CI 0.821–30.461) were included in further analysis. As a result of multivariate logistic regression, CTP decompensation (OR=15.220, 95% CI 1.461–158.606, P=0.023), MCA MFV (OR=0.412, 95% CI 0.191–0.893, P=0.025), and LDL-c (OR=2.409, 95% CI 1.11–5.228, P=0.026) were independent influencing factors of cognitive impairment in patients with aMCAS, which were included in the final model (Table 3).

Table 2 Comparison of Cognitive Function in Patients with aMCAS Under Different Perfusion Periods

	Healthy Control	Normal	Compensation	Decompensation	F/H	P
Number	35	9	26	19		
MoCA	26.31±1.87	25.22±2.39	24.07±4.05	19.31±4.41*#'	17.034	0.001
Short-delay recall	9.03±1.42	8.56±2.07	8.27±1.89	7.74±1.63	2.625	0.056
Long-delay recall	7.46±1.46	7.00±2.06	6.50±1.70	5.21±1.23*#'	8.769	0.001
Cued recall	10(10, 11)	10(9, 11)	10(8.75, 11)*	9(8, 10)*	19.623	0.001
Recognition	11(11, 12)	11(10.5, 12)	11(10, 11)	10(10, 11)	7.541	0.057
VFT	17.29±1.79	16.56±1.42	16.54±1.61	16.47±1.50	1.543	0.209
mBNT	15(14, 15)	15(14.5, 15)	15(14, 15)	14(14, 15)	6.969	0.073
DSF	8(7, 9)	8(7, 8)	8(7, 9)	8(7, 9)	1.507	0.681
DSB	5(4, 6)	4(4, 6)	4(4, 5)*	4(3, 4)*	21.474	0.001
SDMT	42(38, 43)	41.5(39.5, 43.5)	40(37.88, 41.25)*#	39(38, 40)*#	9.894	0.019
RCFT	35(35, 36)	35(35, 36)	35(34, 36)	35(34, 36)	2.827	0.419
TMT-A	29.43±3.85	31±5.68	32.08±4.37	33.47±7.40*	2.908	0.039
TMT-B	57(52, 63)	59(55, 63.5)	70(64.75, 75.25)*#	71(67, 95)*#	42.383	0.001
SCWT-A	43.94±7.99	43.01±8.12	48.81±8.86	48.71±8.98	2.624	0.056
SCWT-B	56.61±6.97	57.81±6.79	64.50±8.00*	66.35±7.74*#	9.804	0.001
SCWT-C	97.16±7.84	97.76±5.37	121.08±15.86*#	123.92±12.02*#	35.349	0.001
SIE	40.9(34.02, 45.77)	41.33(36.55, 42.91)	58.73(45.37, 65.25)*#	63.92(43.47, 67.23)*#	39.637	0.001

Notes: *Compared with healthy control, P<0.05; #Compared with CTP normal group, P<0.05; 'Compared with CTP compensation group, P<0.05.
Abbreviations: MoCA, Montreal cognitive assessment scale; VFT, verbal fluency test; mBNT, the modified Boston naming test; DSF, digit span forward; DSB, digit span backward; SDMT, Symbol-digit Modalities Test; RCFT, Rey-Osterrieth complex figure test; TMT, trail making test; SCWT, Stroop color-word task; SIE, stroop interference ensues.

Table 3 Univariate and Multifactor Logistic Regression Results of Cognitive Impairment in Patients with aMCAS

Variables	Univariate Regression		Multivarate Regression	
	OR (95% CI)	P	OR (95% CI)	P
Baseline characteristics				
Sex	1.275(0.425, 3.819)	0.665		
Age	1.021(0.971, 1.073)	0.422		
Education	1.224(0.373, 4.017)	0.739		
Hypertension	0.653(0.202, 2.114)	0.477		
Diabetes	0.428(0.097, 1.895)	0.264		

(Continued)

Table 3 (Continued).

Variables	Univariate Regression		Multivarate Regression	
	OR (95% CI)	P	OR (95% CI)	P
Smoking history	2.145(0.558, 8.255)	0.267		
Drinking history	0.760(0.197, 2.938)	0.691		
Degree of stenosis				
Moderate to severe	0.381(0.118, 1.227)	0.106		
Occlusion	NA	NA		
Side of the stenosis	0.429(0.14, 1.311)	0.137		
Perfusion period		0.014		
Normal	NA	NA		
Compensation	1.467(0.299, 7.188)	0.637	1.545(0.233, 10.258)	0.653
Decompensation	10.667(1.669, 68.183)	0.012	15.220(1.461, 158.606)	0.023*
Fazekas grade		0.348		
Fazekas grade 0	NA	NA		
Fazekas grade 1	2 (0.352, 11.364)	0.434		
Fazekas grade 2	2.528(0.528, 15.473)	0.223		
Fazekas grade 3	5(0.821, 30.461)	0.081		
Collateral compensation		0.792		
None	NA	NA		
AcoA	1.867(0.444, 7.852)	0.394		
PcoA	1.778(0.316, 10.013)	0.514		
AcoA and PcoA	5.333(0.506, 56.236)	0.164		
Pial collateral	6.667(0.659, 67.463)	0.108		
Neovascularization	0.667(0.052, 8.549)	0.755		
TCD parameters				
MCA MFV	0.354(0.174, 0.722)	0.004	0.412(0.191, 0.893)	0.025*
MCA PI	1.446(0.75, 2.785)	0.271		
Blood tests				
PT	1.522(0.826, 2.805)	0.178		
APTT	0.625(0.349, 1.12)	0.114		
TT	1.336(0.69, 2.588)	0.391		
AT-III	1.452(0.799, 2.638)	0.221		
FDP	0.826(0.454, 1.503)	0.531		
D-D	0.815(0.468, 1.42)	0.471		
FT3	1.054(0.613, 1.812)	0.849		
FT4	1.008(0.586, 1.733)	0.977		
TSH	0.807(0.466, 1.397)	0.443		
TC	1.879(1.03, 3.43)	0.040		
TG	2.215(1.121, 4.378)	0.022		
HDL-c	1.2(0.693, 2.078)	0.515		
LDL-c	2.239(1.178, 4.257)	0.014	2.409(1.110, 5.228)	0.026*
CRE	1.108(0.642, 1.912)	0.712		
UA	1.296(0.736, 2.283)	0.368		
Urea	1.248(0.709, 2.195)	0.443		
HCY	0.819(0.467, 1.436)	0.486		
FA	1.748(0.933, 3.275)	0.081		
B12	1.591(0.793, 3.193)	0.191		

Notes: *P<0.05. Variables with P<0.1 in univariate regression were subject to multivariate stepwise backward logistic regression.
Abbreviations: AcoA, anterior communicating artery; PcoA, posterior communicating artery; MFV, mean flow velocity; PI, pulsatility index; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; AT-III, antithrombin III; FDP, fibrin degradation products; D-D, D-dimer; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, triglyceride.; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; CRE, Creatinine; UA, uric acid; HCY, homocysteine; FA, folic acid; B12, vitamin B12.

Construction of a Nomogram for Predicting Cognitive Impairment in Patients with aMCAS

Nomogram was plotted in R software based on the independent influences shown in the results of multivariate logistic regression (Figure 1). To validate the performance of the nomogram, the ROC curve was used to evaluate the ability of the predictive model and its components to discriminate cognitive impairment. The results showed that the AUC of perfusion period was 0.719 (sensitivity53.3%, specificity=87.5%, P<0.05), the AUC of MFV was 0.739 (sensitivity=90%, specificity=50%, P<0.05), and the AUC of LDL-c was 0.712 (sensitivity=63.3%, specificity=75%, P<0.05). The AUC for combined perfusion period, MFV, and LDL-c was 0.862 (sensitivity=73.3%, specificity=87.5%, P<0.05), which confirmed the good discriminatory ability of the nomogram (Figure 2A).

Validation of the Nomogram

The bootstrap method was used to internally validate the constructed model. Calibration curves for the nomogram showed good agreement between prediction and observation (Figure 2B). In addition, the DCA showed that the nomogram has great clinical applicability (Figure 2C). To more intuitively evaluate the clinical effect of the model, CIC was plotted on the basis of DCA (Figure 2D). The red curve represents the number of people classified as high risk by the nomogram at each threshold probability, and the blue dotted line represents the number of true positives at each threshold probability. With risk thresholds exceeding 60%, people at high risk of cognitive impairment judged by the nomogram were highly matched to people actually experiencing cognitive impairment.

Discussion

Vascular cognitive impairment is the second commonest type of dementia after Alzheimer's disease. Most risk factors for vascular stenosis can be controlled, early diagnosis and effective treatment can delay the deterioration of cognitive function. Cognitive functions are jointly performed by multiple brain structures, and the frontal lobe is the key node of memory function.[10] Executive functions depend on neural networks including structures such as the frontal lobe, parietal lobe, and basal ganglia,[11] which are closely associated with the MCA. This study showed that aMCAS could impair multiple cognitive domains, including overall cognitive function, memory function and executive function. It is basically consistent with the results of previous studies.[12,13] In addition, both the CTP compensation group and the CTP decompensation group showed significant impairment in subdomains of executive function and cued recall. This
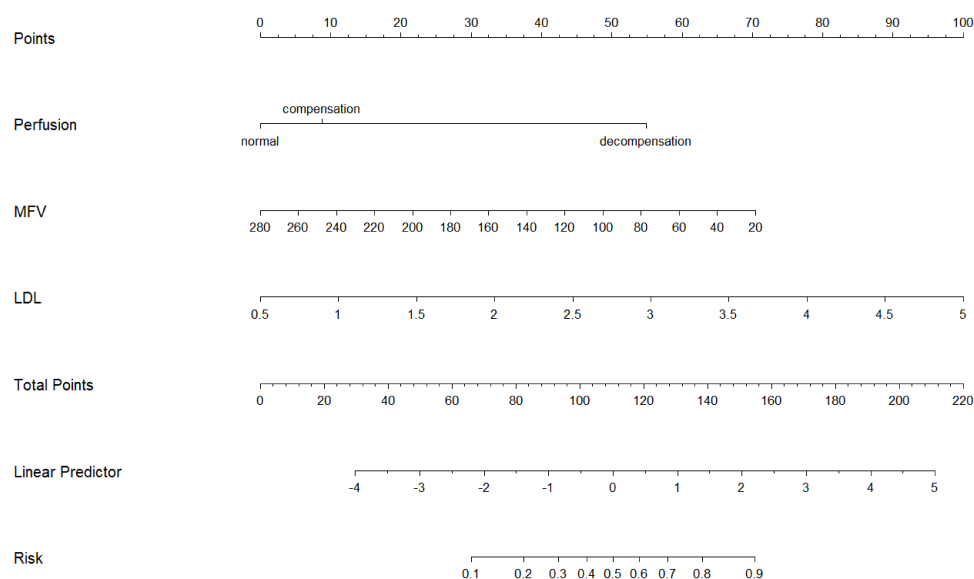

Figure 1 Nomogram for predicting cognitive impairment in patients with aMCAS.
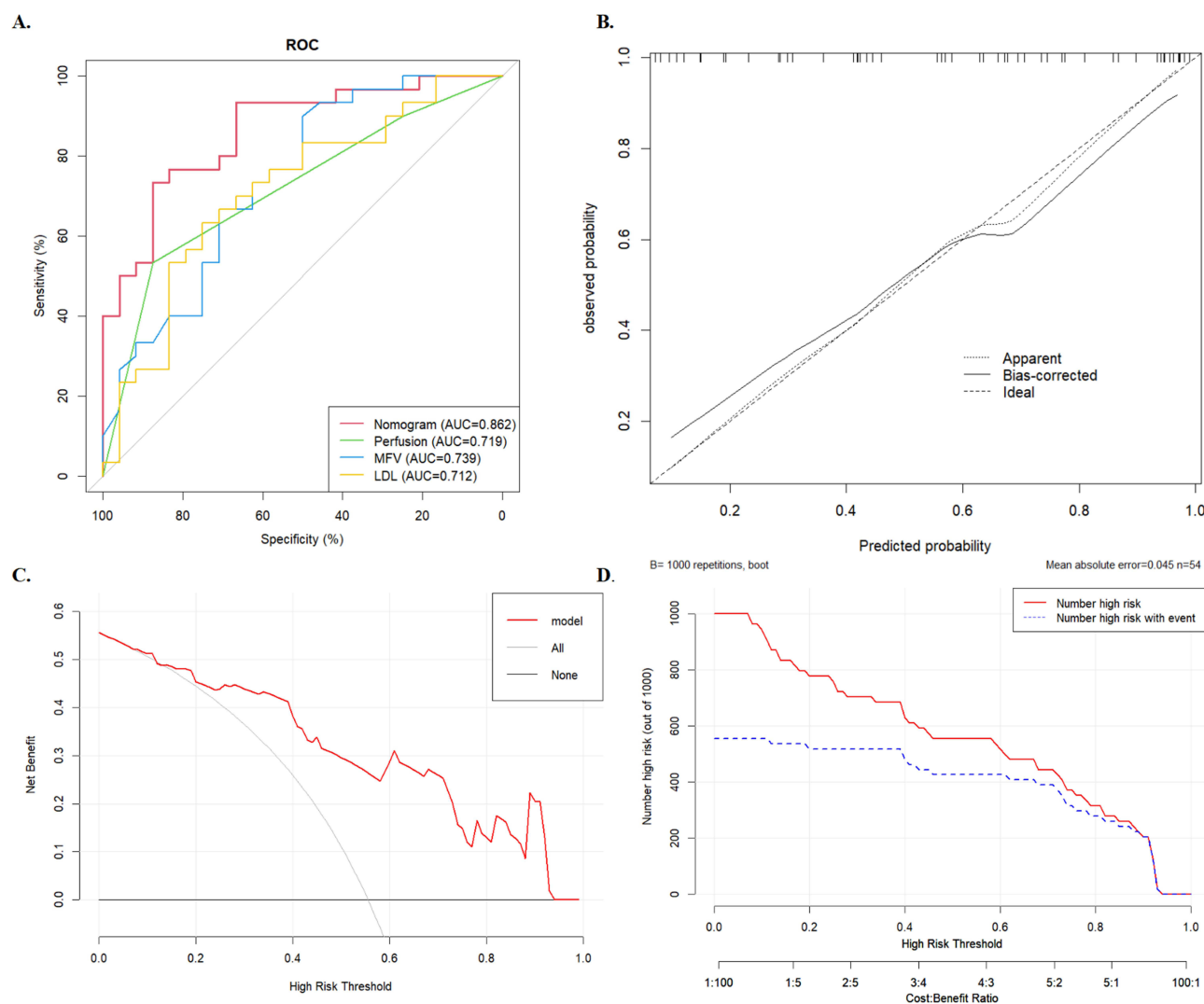
Figure 2 ROC curves (**A**), calibration curves (**B**), DCA curve (**C**) and CIC (**D**) of the nomogram.

suggested that cognitive impairment existed even in the early stages of aMCAS when blood flow was able to maintain perfusion through collateral substitution. It further demonstrates the importance of early diagnosis.

Recently, there has been a focus on predicting patients' risk of cognitive impairment and personalised treatment. Previous studies typically focused on analyzing the relationship between a single risk factor and cognitive impairment, overlooking the complex interplay of multiple risk factors. In this study, we analyzed various factors including baseline characteristics, vascular conditions, haemodynamic characteristics, and vascular risk factors in patients. Our study is the first to combine these factors and the results showed that CTP loss of compensation, MCA-MFV, and LDL-c levels were independent risk factors for cognitive impairment. And the nomogram was subsequently developed to assess the risk of cognitive impairment in patients, which has good discrimination, calibration and clinical applicability. Our study is the first to construct a predictive model to predict the risk probability of cognitive impairment in patients with aMCAS. The model serves as a tool to predict the risk probability of cognitive impairment in patients, enabling clinicians to identify and apply interventions early on.

Previous study found that patients with poor and moderate collateral circulation in aMCAS had worse cognitive function than patients with good collateral circulation,[13] which suggested that cognitive impairment in patients with aMCAS may be associated with hypoperfusion. This was further confirmed in this study that perfusion decompensation was an independent risk factor for cognitive impairment in patients with aMCAS. Severe hypoperfusion can lead to

irreversible atrophy and death,[14] deposition of neurotoxic substances and exacerbation of neuronal dysfunction.[15] In addition, hypoperfusion can also induce white matter damage and lead to cognitive impairment.[16] However, in our study white matter lesions were associated with cognitive impairment, but logistic regression showed that it was not an independent influencing factor of cognitive impairment. This may be because our study mainly includes asymptomatic patients, but a variety of symptoms may develop as white matter lesions progress. As a result, most patients have a low level of white matter lesions, which may affect the results of the study. Apart from directly affecting brain structures dominated by MCA, research has shown that MCA occlusion can lead to delayed death of hippocampal neurons.[17] This may be because the gap junction communication action of astrocytes propagates neurotoxic molecules or damage signals produced in the ischemic area to the hippocampus, expanding the ischemic damage.[18] In summary, hypoperfusion can impair cognitive function through multiple pathways, and our study confirms for the first time that perfusion decompensation is an independent risk factor for cognitive function in patients with aMCAS. Therefore, identifying the perfusion period of patients with aMCAS is necessary for predicting cognitive impairment in patients.

In addition, we found that decreased MCA MFV was an independent risk factor for cognitive impairment in patients with aMCAS. When vascular stenosis occurs, the flow velocity of the artery is inversely proportional to the diameter, but the reduction in cerebral perfusion leads to a decrease in blood flow velocity at a certain degree of stenosis. Decreased MCA MFV was found strongly associated with cognitive impairment in patients with asymptomatic carotid stenosis and mild cognitive impairment.[19,20] It is basically consistent with our results. Apart from MFV, PI is also one of the important parameters of TCD, which reflects cerebrovascular resistance and compliance. However, there was no significant correlation between PI and cognitive impairment in our study. The reason for this may be that in addition to cerebral blood flow resistance, PI can also be affected by arterial blood pressure, cerebral arterial elastic resistance, heart rate, and other factors.[21] A community-based follow-up study also found no significant association between MCA-PI and cognitive decline.[22] Therefore, monitoring MCA MFV in patients with aMCAS is important for assessing changes in cognitive function.

Apart from perfusion period and MCA MFV, LDL-c is also an independent risk factor for cognitive function in patients with aMCAS. As an important part of the neuron, cholesterol is essential for maintaining neuronal function.[23] However, low LDL levels in the periphery do not affect normal brain function because the cholesterol required by the CNS is resynthesized in brain cells.[24] Studies have shown that low LDL levels are associated with a slowed rate of cognitive decline.[25–27] Peripheral cholesterol can enter the CNS as 27-hydroxycholesterol (27-OHC), which can accelerate Aβ accumulation, increase hyperphosphorylated tau levels, decrease brain antioxidant enzyme activity, involve in inflammatory responses to promote neurodegeneration and reduce brain glucose uptake.[28] There is a close relationship between circulating cholesterol and 27-OHC levels, and high plasma cholesterol can lead to increased plasma levels of 27-OHC.[29] Therefore, reduced peripheral blood cholesterol levels may be beneficial to improving cognitive function. The development of PCSK9 inhibitors has made it possible to lower LDL-c to very low levels without causing adverse neurocognitive events.[30] Our findings provide evidence that low levels of LDL-c are beneficial for cognitive function. Therefore, early intervention to lower LDL-c is crucial in preventing and delaying cognitive function deterioration in patients with aMCAS.

Although our findings suggest that hypoperfusion and decreased mean middle cerebral artery flow velocity are independent risk factors for patients with aMCAS, it is controversial whether cognitive function can be improved after revascularization by surgery to relieve stenosis. Neuronal damage is permanent under conditions of chronic occlusion and long-term chronic ischemia may be irreversible.[31] Recent studies have shown that endovascular therapy may not improve cognitive function or decrease the 1-year risk of stroke and death in patients with aMCAS.[32–34] Therefore, drug therapy alone is a critical treatment for patients with aMCAS. This further emphasizes the importance of early diagnosis and treatment. Using nomogram for individualized assessment of aMCAS patients can help clinicians better evaluate patients' conditions and develop more accurate treatment plans.

The limitations of this study are as follows: (1) This study had a relatively small sample size, which may have influenced the results. (2) This study was a cross-sectional study and did not longitudinally follow up the change in cognitive function of the patients. (3) Since this study included inpatients mainly with more than severe stenosis, our findings may not be generalized to patients with mild degrees of aMCAS.

Conclusion

This study showed that CTP decompensation, MCA-MFV, and LDL-c were independent risk factors for cognitive impairment in patients with aMCAS. Afterwards, a nomogram was constructed with good discrimination, calibration, and clinical validity for predicting cognitive impairments. It can help clinicians to identify patients with cognitive impairment as early as possible to delay or even stop the deterioration of cognitive function in patients with aMCAS.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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