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A New Nomogram Model for Individualized Prediction of Cognitive Impairment in Patients With Acute Ischemic Stroke

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Abstract

Background: Cognitive impairment is common after ischemic stroke, which significantly affects patients' quality of life and rehabilitation. A reliable scoring tool to detect the risk of cognitive impairment after stroke is imperative. The present study was designed to investigate the risk factors of cognitive impairment in the acute phase and to develop and validate a new nomogram for individualized prediction of cognitive impairment in patients with acute ischemic stroke (AIS).

Methods: We enrolled patients who suffered from AIS and were hospitalized at the First Affiliated Hospital of Soochow University between October 2018 and June 2020. All patients

were assessed for cognitive impairment by the Montreal Cognitive Assessment (MoCA) scales within 14 days after the onset of AIS and MoCA score < 26 was defined as having cognitive impairment. The main outcome was the cognitive impairment. All patients were randomly (7:3) divided into two cohorts: the primary cohort and the validated cohort. On the basis of multivariate logistic model, the independent predictors of cognitive impairment in the acute phase were identified and the predictive nomogram was generated. The performance of the nomogram was evaluated by Harrell's concordance index (C-index) and calibration plot both in the training cohort and validation cohort, respectively.

Results:A total of 191 patients with complete data were enrolled, of whom 135 comprised the primary cohort and 56 comprised the validated cohort. Of pooled analyses, gender, age, baseline NIHSS score, hyperhomocysteinemia (HHcy) and multiple lesions were independently associated with acute cognitive impairment after stroke and included to construct the nomogram. The nomogram derived from the primary cohort had an Area Under Curve (AUC) of 0.764 and the validated cohort had AUC of 0.867. Besides, calibration plot revealed adequate fit of the nomogram in predicting the risk of immediate cognitive impairment in patients with ischemic stroke.

Conclusion: The new nomogram based on gender, age, baseline NIHSS score, HHcy and multiple lesions gave rise to an accurate and comprehensive prediction for cognitive impairment in AIS patients. After further validation, it could be potentially a simple and pragmatic tool for prediction of immediate cognitive impairment of patients suffered from AIS.

Keywords: Cognitive impairment; Ischemic stroke; Nomogram; Prediction

1. Background

Stroke patients have a significantly higher risk of dementia and cognitive impairment than the general population[1], contributing to decreased daily living abilities, mental health, as well as the quality of life. Current evidence shows that 25–30% of patients of acute ischemic stroke (AIS) develop immediate or delayed cognitive impairment or dementia[2]. All types of cognitive disorders may occur after stroke. Cognitive and psychological symptoms are tough

to detect before discharge from the hospital and may first be recognized when the stroke patient needs to meet demands in daily life.

Diagnosis of cognitive impairment after stroke relies on clinical judgment, defined by clinical, cognitive, and functional criteria for the lack of stable biomarkers of neurodegeneration[3, 4]. Therefore, methodological heterogeneities may explain why there is huge variability of the incidence of cognitive impairment after stroke in different researches[5]. Various tools are available to screen and assess cognition, the Montreal Cognitive Assessment (MoCA) is widely used to screen for mild cognitive impairment.

At present, studies on the epidemiology of cognitive impairment after stroke mainly focus on the time of 1 month, 3 months, 6 months,1 year or even longer after stroke, while there are just a few studies on cognitive dysfunction in the acute stage after stroke. Furthermore, despite the high morbidity of cognitive impairment after stroke, a clinical scoring tool predicting immediate cognitive impairment is absent.

Nomogram model is a graphical statistical tool and it has been generally used in medical decision-making. To date, there is no nomogram model to predict the risk of early-onset of post-stroke cognitive impairment. Therefore, the aim of this study was to investigate the independent risk factors for cognitive impairment in the acute phase of stroke, and to establish a simple and pragmatic nomogram to predict immediate cognitive impairment during the hospitalization.

2. Methods

2.1 Study population

The present study was a retrospective analysis of prospectively collected data from the First Affiliated Hospital of Soochow University between October 2018 and June 2020. All patients suffered from AIS within 14 days. Patients who were with depression and anxiety disorder or diagnosed with other mental diseases before the stroke or had complicated diseases such as severe infection, cardiopulmonary dysfunction, malignant tumor or autoimmune disease, or had previous history of severe brain injury, spontaneous cerebral hemorrhage, brain tumor, Parkinson's disease or other central nervous system diseases were excluded. All the enrolled patients in our study signed informed consent.

2.2 Data Collection and Baseline evaluation

We collected the baseline and demographic characteristic, laboratory data and imaging information of the enrolled patients during hospitalization. Demographic and clinical baseline data, including gender, age, education level, smoking and alcohol consumption, past disease history (including stroke, hypertension, diabetes, hyperlipidemia and atrial fibrillation), baseline NIHSS score[6], baseline systolic and diastolic blood pressure, baseline blood glucose and lipid levels, homocysteinemia and other relevant laboratory data, were collected within 48 hours of admission. All the enrolled patients completed MRI or CT examination within 1 week after admission. According to the number of new lesions, the lesions were recorded as single or multiple, single lesion was recorded as 0, and multiple lesions as 1.

2.3 Clinical assessment

MoCA score was adopted to evaluated cognitive function of the patients, the results were related to the educational level. The classification criteria[7] were: 1 point would be added to the total points if years of schooling were less than 12 years, the highest total score was 30 points. A score of less than 26 was defined as cognitive impairment. Hamilton Depression Rating (HAMD) was conducted to evaluate the patients mental status. A score of equal or greater than 7 points indicated the presence of depression. MoCA and HAMD-17 score were conducted by two independent neuropsychological experts.

2.4 Statistical analysis

Continuous variables were compared using the Mann-Whitney U test for non-normally distributed variables or Student's t-test for normally distributed variables. Differences between proportions were assessed by Fisher's exact test or Chi-square test, where appropriate. Continuous variables were reported as the mean ± SD or median (interquartile range), and categorical variables were described by constituent ratio. To identify the independent predictors of immediate cognitive impairment at the early phase of ischemic stroke, a multivariable logistic regression model was performed and the variables with a P value < 0.05 in the univariate analysis were included. The SPSS 23.0 was used for statistical analysis of baseline data.

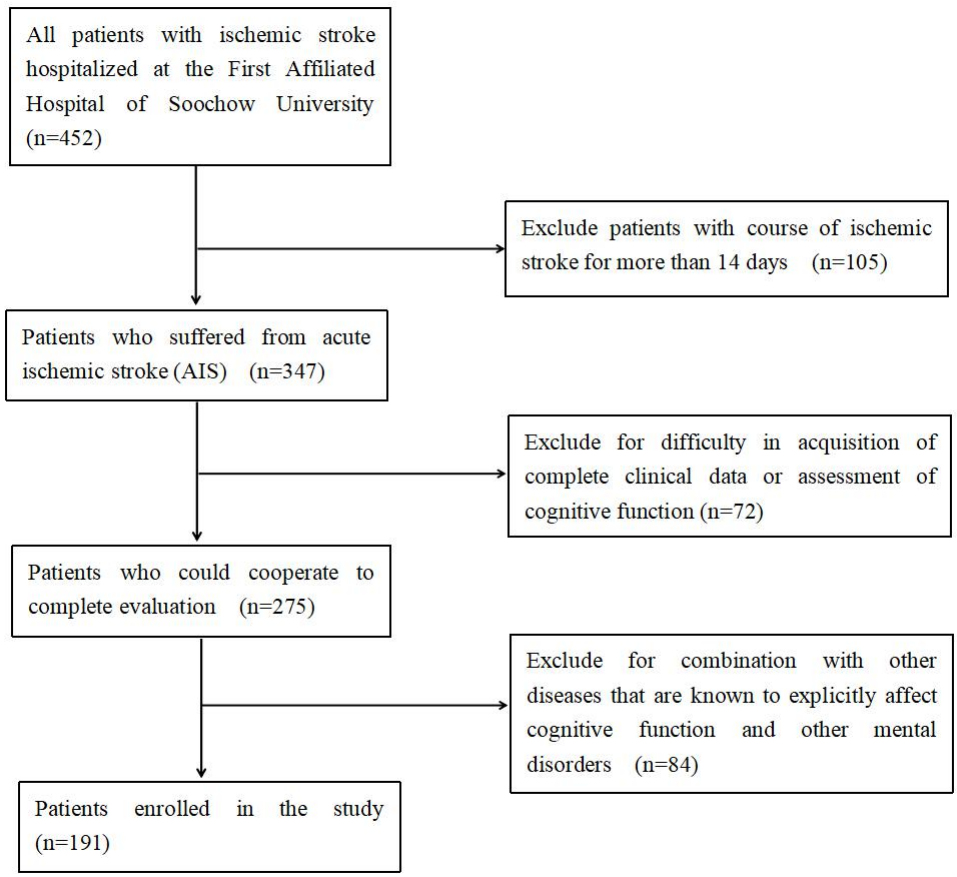
The nomogram was constructed by R version 3.6.0. Included patients were randomly assigned into two cohorts (7:3): 67% of the patients to the training cohort and 33% to the validation cohort. Nomogram model was developed from the primary cohort and evaluated in the validated cohort. Variables with P values that were less than 0.05 in the multivariable

logistic regression were entered into the nomogram. The nomogram was created by assigning a graphic preliminary score to each of the predictors with a point ranging from 0 to 100, which was then summed to generate a total score, finally converted to the logit and then to an individual probability (from 0 to 100%) of cognitive impairment in the acute phase of stroke. The area under the receiver operating characteristic curve (AUC-ROC) was used to evaluate the differentiation of the prediction model. Calibration was tested using a calibration curve with bootstraps of 1000 resamples, which reflexed the agreement between nomogram and actual observation.

3. Results

3.1 Clinical features and baseline characteristics

Figure 1. Flow diagram of included and excluded patients



The flow diagram of patient inclusion and exclusion was shown in Fig.1. A total of 191 patients were included in the study. The baseline characteristics of patients in the primary and

validated cohorts are shown in the Table 1. Of the 135 individuals comprising the primary cohort, the median age was 61(51.5–69) years, and 65.9% were male, including 69 (51.1%) cognitive impairment patients. The validation cohort consisted of 42 men (75%) and 14 women (25%) with a median age of 64.5 (51.5-71.5) years, and the overall proportion of cognitive impairment was 58.9%. The difference between the two cohorts was not statistically significant generally (except for LAA, SOE subtypes and creatinine, all P>0.05).

Table 1. Baseline characteristics of the primary cohort and the validation cohort. Abbreviations: SBP systolic blood pressure, DBP diastolic blood pressure, NIHSS National Institutes of Health Stroke Scale, LAA large artery atherosclerosis, CE cardio embolism, SAO small artery occlusion, SOE stroke of other demonstrated etiology, SUE stroke of other undetermined etiology, Reperfusion treatment including intravenous thrombolysis, thrombectomy, intravenous thrombolysis and bridging thrombectomy, HDL-C high-density lipoprotein, LDL-C low-density lipoprotein, H-hcy hyperhomocysteinemia.

Baseline	Primary cohort(n=135)	Validation cohort(n=56)	Test statisic	P value
Age	61(51.5-69)	64.5(51.5-71.5)	-1.217[a]	0.224
Gender,male	89(65.9)	42(75.0)	1.227	0.219
Hypertension	94(69.6)	42(75.0)	0.744	0.456
Admission SBP mmHg	145(136-158)	145.5(131-156)	-0.607[a]	0.544
Admission DBP mmHg	82.13±14.53	80.66±13.83	-0.653[a]	0.514
Admission glucose mmol/l	5.3(4.8-6.2)	5.1(4.7-6.6)	-0.634[a]	
Diabetes	51(37.8)	21(37.5)	-0.036	0.971
Dyslipidemia	9(6.7)	2(3.6)	-0.834	0.621
Atrial fibrillation	9(6.7)	8(14.3)	1.679	0.160
NIHSS score	2(1-5)	2.5(1-5)	-0.455[a]	0.649
Advancing stroke	9(6.7)	1(1.8)	-1.375	0.307
TOAST				
LAA	64(47.4)	17(30.4)	-2.165	0.030
CE	15(11.1)	7(12.5)	0.273	0.784
SAO	47(34.8)	21(37.5)	0.352	0.724
SOE	2(1.5)	5(8.9)	2.487	0.038
SUE	7(5.2)	6(10.7)	1.378	0.287
Reperfusin treatment	35(25.9)	15(26.8)	0.123	0.902
Multiple lesions	71(52.6)	23(41.1)	-1.446	0.147

White blood cell *10^9/L	7.0(5.5-8.6)	7.0(5.6-8.4)	-0.122[a]	0.903
Neutrophil *10^9/L	4.4(3.3-5.7）	4.6(3.7-5.8)	-0.837[a]	0.403
Lymphocyte *10^9/L	1.8(1.4-2.2)	1.5(1.2-2.1)	-1.510[a]	0.131
Platelet *10^9/L	197.0(156.0-232.0)	192.5(153.0-246.0)	-0.019[a]	0.985
Hemoglobin g/L	138.38±18.58	135.75±19.34	-0.531[a]	0.596
Total cholesterol mmol/l	4.2(3.6-5.0)	4.3(3.7-5.0)	-0.178[a]	0.859
Triglyceride mmol/l	1.5(1.1-2.0)	1.4(1.0-2.0)	-0.404[a]	0.686
HDL-C mmol/l	0.9(0.8-1.1)	0.9(0.8-1.1)	-0.006[a]	0.995
LDL-C mmol/l	2.6(2.1-3.1)	2.5(1.8-3.0)	-0.607[a]	0.544
Total bilirubin(μmol/l)	13.7(10.6-18.7)	15.4(11.4-22.0)	-1.326[a]	0.185
Uric Acid(μmol/l)	317.74±96.38	311.22±96.16	0.426[b]	0.671
Blood urea nitrogen (mmol/l)	4.5(3.8-5.3)	4.8(4.1-5.8)	-1.614[a]	0.107
Creatinine (μmol/l)	65.2(56.7-78.0)	69.9(62.6-83.1)	-2.149[a]	0.032
Albumin(g/l)	40.93±3.55	40.90±3.12	0.049[b]	0.961
Prealbumin (g/l)	242.65±50.24	234.64±51.22	0.998[b]	0.320
H-hcy	34(25.2)	19(33.9)	1.225	0.219
Fibrinogen g/l	2.4(1.9-3.2)	2.7(2.1-3.2)	-0.530[b]	0.597
HAMD-17 score	0(0-1）	0(0-2)	-0.197[a]	0.844
Depression	19(14.1)	6(10.7)	-0.625	0.531
Cognitive impairment	69(51.1)	33(58.9)	0.983	0.324

3.2 The risk factors of cognitive impairment at the acute phase of ischemic stroke

Multivariable logistic regression analysis showed that gender, age, NIHSS scores, multiple lesions, hyperhomocysteinemia (HHcy) were important determinant of cognitive impairment in the acute phase of stroke (Table 2). Sensitivity and specificity of the above variables were provided in a data supplement (Table 1).

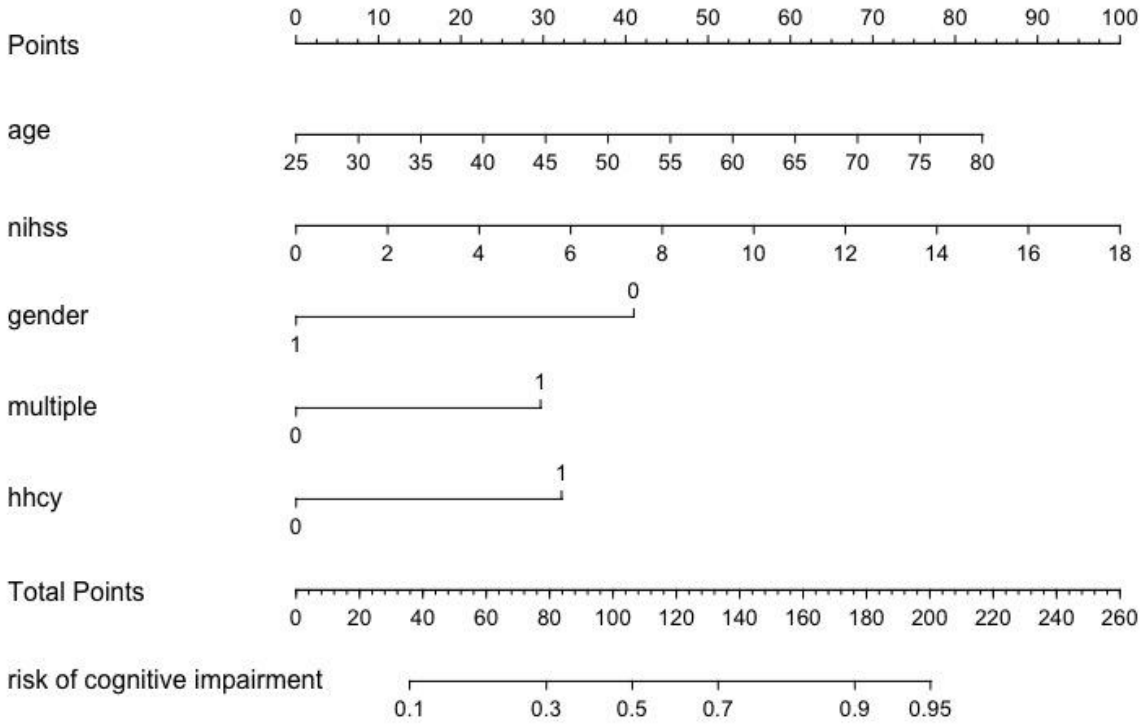
Table 2. Univariable and multivariable logistic regression of early-onset post-stroke cognitive impairment. Abbreviations: NIHSS National Institutes of Health Stroke Scale, H-hcy hyperhomocysteinemia.

	Univariable models		Full multivariable model	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.049(1.017-1.082)	0.003	1.038(1.001-1.077)	0.045

NIHSS score	1.202(1.058-1.365)	0.005	1.187(1.029-1.368)	0.018
Gender, male	0.416(0.199-0.869)	0.020	0.275(0.114-0.664)	0.004
Multiple lesions	2.542(1.270-5.089)	0.008	2.539(1.133-5.689)	0.024
HHcy	2.500(1.103-5.667)	0.028	2.873(1.075-7.676)	0.035
ALB	0.874(0.788-0.970)	0.011	0.903(0.800-1.019)	0.099

3.3 Prediction nomogram for cognitive impairment at the acute phase of ischemic stroke

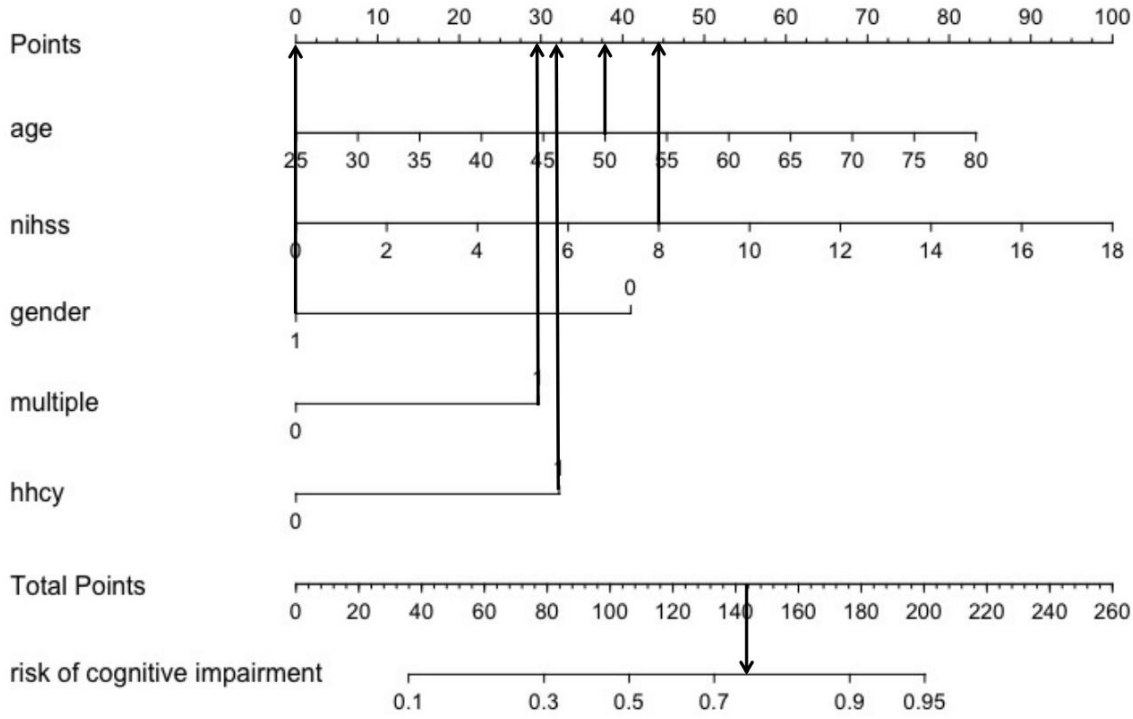
Figure 2. Nomogram predicting cognitive impairment in patients with acute ischemic stroke. Abbreviations: multiple: whether it was multiple lesions; hhcy: Hyperhomocysteinemia



Variables with P values that were less than 0.05 in the multivariable logistic regression were used to generate the nomogram (Fig. 2). The nomogram was generated by assigning a graphic preliminary score to each of the 5 predictors with a point ranging from 0 to 100, which was then summed to generate the total score, finally converted into an individual probability of the onset of cognitive impairment at the acute phase of stroke (from 0 to 100%).

To use the nomogram, you should identify the patient's value for each predictive variable at first, then draw a straight line upwards from each predictive value to the top point reference line and sum the points from each predictor, and finally find the location of the sum on the total points reference line and draw a straight line from total points line down to the bottom probability line to get the patient's likelihood of cognitive impairment. The applicability of the nomogram could be illustrated through a clinical example (Fig. 3).

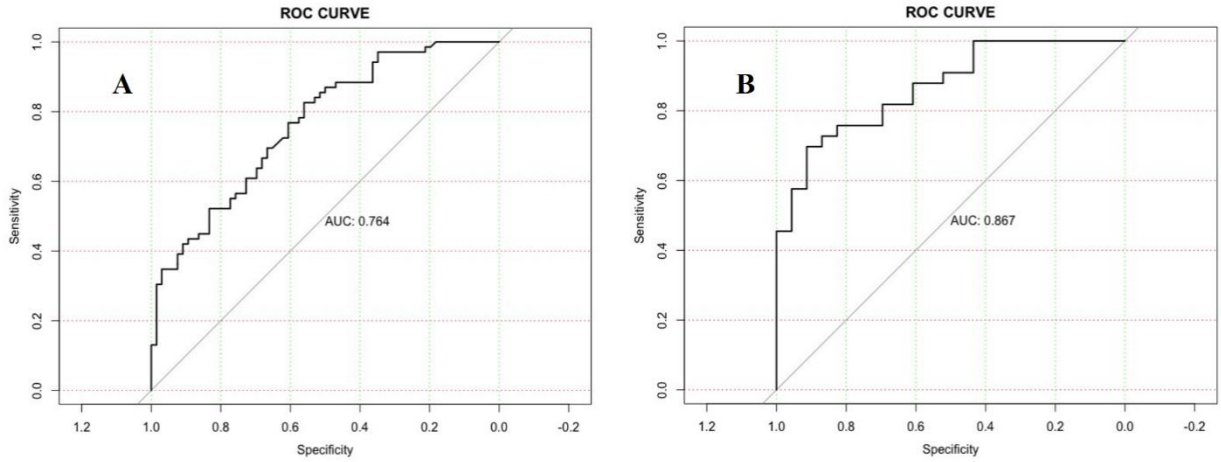
Figure 3. An example of how to use the nomogram. In this example, we calculated the predicted probability of cognitive impairment in a 50-years-old male patient suffered from AIS with a NIHSS score of 8, MRI of cranial showing multiple lesions, a high level of serum homocysteine. Points are assigned for each feature: 37.7 for the age of 50, 0 for the gender of male, 44.5 for NIHSS score of 8, 29.5 for multiple lesions, and 32 for the high level of homocysteine. The total of 143.7 points correspond to a nearly 75% chance of early cognitive impairment after stroke.



3.4 The discrimination and calibration performance of the model

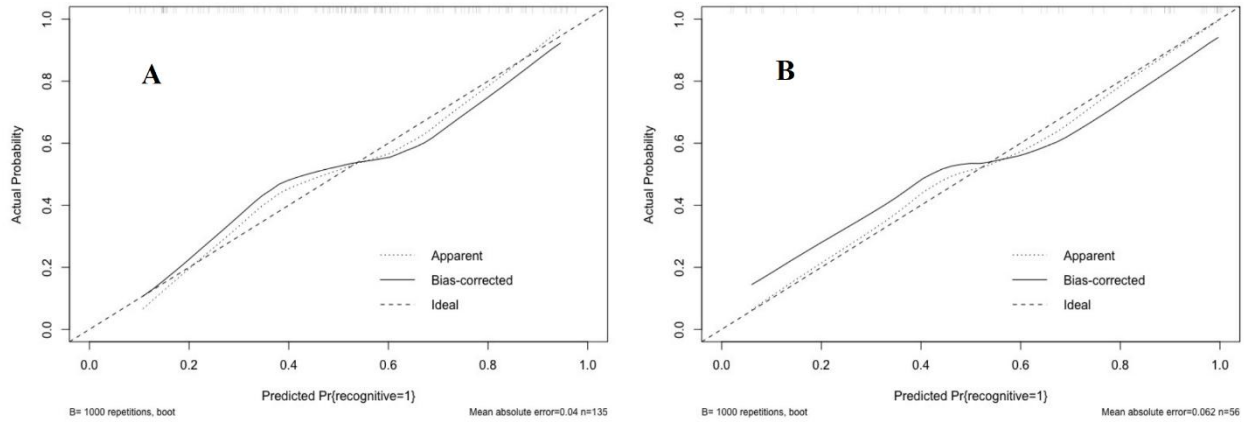
The C-Statistics was used to assess the discriminative capacity of the nomogram (Figure. 4A and B). The Area Under Curve (AUC) of the training cohort and the validation cohort were 0.764 (95%CI, 0.686-0.842) and 0.867 (95% CI,0.776-0.958), respectively.

Figure 4. Receiver operating characteristic (ROC) curve analysis for the nomogram, in the primary cohort (A) and validation cohort (B).



The calibration curves were demonstrated in the Fig.5. The x-axis represented the predicted possibility of immediate cognitive impairment, and the y-axis exhibited the actual possibility of immediate cognitive impairment. The calibration plot revealed general fit of the nomogram predicting the risk of immediate cognitive impairment both in the primary cohort and validated cohort.

Figure 5. The calibration curves for the nomogram, in the primary cohort (A) and validation cohort (B).



4. Discussion

The prevalence of stroke in China is 1114.8/100 000, the annual incidence is 246.8/100 000, and the mortality attributing to stroke is 149.49/100 000[8]. The present investigation suggests that 25–30% of AIS survivors develop immediate or delayed vascular cognitive

impairment or dementia[9], the cumulative prevalence of cognitive impairment after stroke increases linearly at an annual rate of 3%[10]. With a decreased risk of death after stroke[11], more lights have been shifted towards cognitive dysfunction. Cognitive impairment after stroke is mainly defined as dementia that occurs within three months after stroke onset. However, in the acute phase of stroke, 78% of patients have impairments in one or more cognitive domains, including attention, linguistic function, short-term memory, executive function. It follows that immediate cognitive impairment in patients after acute ischemic stroke is common, the identification of cognitive impairment in the acute stage after stroke is vital. It can provide clinicians with significant messages of early cognitive damage and promote rehabilitation through appropriate treatment to a certain extent[12].

Clinicians often make a fair diagnosis by using the most acceptable DSM IIIR or IV criteria and scale assessments, such as the Mini-mental State Examination (MMSE) and MoCA. MOCA is sensitive to the cognitive domains of memory and language[13]. Compared with MMSE, MoCA has higher sensitivity and specificity for the identification of mild cognitive impairment[14].

Systematic reviews have reported that a variety of risk factors are closely bound up with cognitive impairment after stroke[5, 15] such as hypertension, diabetes mellitus, hyperlipidemia and previous history of stroke[16-18]. This study revealed higher age and female gender were independent risk factors of immediate cognitive impairment after stroke, which were consistent with Takahashi Y's and Umarova RM's researches[18, 19]. Higher age has been proved to be related to the development of Alzheimer's disease or vascular dementia because of the increased concentrations of total amyloid beta (Aβ) and Aβ-42[20]·[21]. Furthermore, the elderly stroke patients have more underlying diseases, hypoxic-ischemic brain damage and poorer vascular conditions, which finally contribute to the impaired cognitive function. Our study also indicated that baseline NIHSS score, HHcy and multiple lesions contributed to cognitive impairment in the acute phase of stroke. Jaillard A revealed that the size, location and number of lesions of the ischemic injury were closely related with immediate cognitive impairment which was concordant with our results[22].Larger and multiple infarcted lesions were more likely to damage cortex or cognitive functional areas, destroy more association fibers, causing the decline of brain function, and then leading to cognitive dysfunction[23]. HHcy increased the risk of stroke by at least 2.5 times[24]. Jixia Wu found out that elevated homocysteine was highly related to cognitive impairment after stroke[25]. The study of Lee JH also demonstrated that high level

of homocysteine could aggravate cognitive dysfunction[26]. As an independent risk factor for dementia after stroke, HHcy may affect cognitive dysfunction through mechanisms such as leading to white matter lesions[27, 28], increasing the density of intracranial neurofibrillary tangles[29] and accelerating brain atrophy[30]. Therefore, detection of serum Hcy level in AIS patients could help find out the high-risk population of immediate cognitive impairment. Timely supplementation of folic acid vitamin B12 could reduce the occurrence of cognitive impairment after stroke[31].

Two predictive models for cognitive impairment at 3–6 months and 6-12 months poststroke were published[32, 33]. Nagaendran Kandiah reported a 15-point model based on age, education, white matter hyperintensity, acute cortical infarcts, chronic lacunes, global cortical atrophy, and intracranial large vessel stenosis. The risk score had a good performance on prediction of cognitive impairment at 3-6 months after stroke. Another functional model published by Ding MY which consisted of age, years of education, periventricular hyperintensity grading, diabetes mellitus and the number of infarcts was used to predict post-stroke cognitive impairment at 6-12 months. However, a simple model to predict immediate cognitive impairment in the patients with AIS is still absent.

Nomogram, which integrates different prognostic and determinant variables, is able to generate an individual probability of a clinical event. Here, we presented a new nomogram based upon age, gender, NIHSS score, the number of lesions and the level of homocysteine to predict the probability of early cognitive impairment for patients suffered from acute ischemic stroke. Our nomogram gave rise to an accuracy of 0.764 (95%CI, 0.686-0.842), and the discriminatory and calibration capacity of the model that were confirmed by a validation cohort showed a good performance.

The best standard of image evaluation of the ischemic injury of the brain is cranial MRI, which can give a complete assessment of the extent of brain atrophy, the site and number of cerebral infarction and the extent of white matter lesions[34, 35]. But many primary hospitals can’t afford such kind of facilities leading to delayed recognition and the underestimate of cognitive impairment. According to our study, multiple lesions which may contribute to early cognitive impairment can be seen on cranial CT scan easily. Thus, our nomogram model has the advantages of high adaptability and efficiency in the primary medical organizations.

Our study was a single center research with a small sample size. In the later stage, it is necessary to scale up the study population, increase the sample size, and conduct multi-center

research. After further validation, our nomogram model could potentially be a simple and pragmatic tool to detect cognitive impairment at the acute stage of ischemic stroke for the clinicians even from the primary hospitals.

5. Conclusion

We proposed and validated a nomogram model that included age, gender, NIHSS score, multiple lesions, HHcy, which reliably assessed the probability of early cognitive impairment in AIS patients.

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