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A nomogram to predict cognitive impairment after supratentorial spontaneous intracranial hematoma in adult patients

A retrospective cohort study

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Abstract

To establish a nomogram model to predict early cognitive impairment after supratentorial spontaneous intracranial hematoma in adult patients.

A retrospective cohort study was held between January 2016 and October 2018. One hundred twenty seven out of 170 consecutive patients with supratentorial spontaneous intracranial hematoma were enrolled in this study. They were divided into development (n = 92) and validation (n = 35) dataset according to their admission time. Mini-mental State Examination (MMSE) was conducted between the third and the sixth month after the onset of stroke. MMSE $\leq$ 24 was considered as cognitive impairment. Univariate and multivariate logistic regression was used to screen for independent risk factors which correlate with cognitive impairment on the development dataset. A nomogram was built based on Akaike Information Criterion (AIC). Receiver operating characteristic (ROC) curve and calibration curve on development and validation dataset was drawn with each area under the curves (AUC) calculated. The decision curve analysis was also conducted with the development dataset.

The bleeding volume, Glasgow Coma Scale (GCS), and intraventricular hemorrhage (IVH) are the most significant risk factors which may cause cognitive impairment both in the univariate and multivariate analysis. The finial model performed good discrimination ability on both development and validation dataset with AUC 0.911 and 0.919. Most patients would benefit from the model according to the decision curve analysis.

A nomogram, constructed based on bleeding volume, GCS, and IVH can provide a feasible tool to evaluate cognitive impairment after supratentorial spontaneous intracranial hematoma in adult patients.

Abbreviations: AIC = Akaike Information Criterion, AUC = area under the curves, CI = cognitive impairment, CT = computed tomography, DCA = decision curve analysis, DM = diabetes mellitus, GCS = Glasgow Coma Scale, ICH = intracranial hematoma, IVH = intraventricular hemorrhage, MMSE = Mini-mental State Examination, NIHSS = The National Institute of Health Stroke Scale score, ROC = receiver operating characteristic.

Keywords: cognitive impairment, supratentorial spontaneous intracranial hematoma, nomogram

1. Introduction

Cognitive impairment (CI) is a common complication after supratentorial spontaneous intracranial hematoma (ICH).[1] More than one thirds of the ICH patients suffer from various degree of cognitive problems.[2] Early recognition of CI is helpful for rehabilitation and recovery of cognitive function. However, the clinical data about CI after hemorrhagic stroke is extremely limited, and there is no feasible model to predict CI after ICH. To evaluate the probability of CI after supratentorial spontaneous ICH, we held a retrospective cohort study and developed a nomogram model to predict CI with internal validation.

2. Methods

From January 1, 2016 to October 31, 2018, 170 consecutive patients with intracranial hematoma were enrolled in this study. All participants were admitted in rehabilitation department and had received initial treatment at the onset of stroke in 1 hospital in southeast area of China. Eleven patients were excluded due to dementia past history. Nineteen patients with stroke history before and 23 patients with subtentorial hematoma were also excluded. We divided the remaining 127 patients into 2 datasets according their admission time, 92 patients who were admitted before 2018 were enrolled in development dataset. The other 35 patients were in validation dataset (see Fig., Supplemental Digital Content 1, http://links.lww.com/MD/D301, which illustrates patient management workflow).

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Variables including age, gender, preexisting diabetes mellitus (DM), hypertension, hyperlipidemia, and Glasgow Coma Scale (GCS) at the onset of stroke were recorded by the first clinicians in charge of the patients. Mini-mental State Examination (MMSE) score was evaluated after 3 months from the onset of the disease by 1 qualified rehabilitation physician. MMSE $\leq$ 24 was considered as cognitive impairment. To avoid potential observational bias, stroke related radiological findings including hemorrhage site, bleeding volume, and intraventricular hemorrhage (IVH) were evaluated by 2 neurosurgeons independently according to computed tomography (CT) using Tada formula known as a $\times$ b $\times$ c/2. Bleeding sites were categorized as deep location including ganglia region and thalamus, frontal lobe, parietal lobe, temporal lobe, and occipital lobe.

All these variables were compared between the development and validation datasets. *t* test was used to compare continuous variables consistent with normal distribution. Skew distribution data was tested by Kruskal–Wallis test. Categorical data was text by Chi-Squared test and Fisher exact test was conducted if any theoretical frequency was expected less than 10.

We used logistic regression to build models on the development dataset. Cognitive impairment was chosen to be the response variable. Age, gender, hemorrhage sites, bleeding volume, GCS, IVH, DM, hypertension, hyperlipidemia were potential risk factors. We classified GCS into 3 categories: GCS $\geq$ 12, 9 $\leq$ GCS $<$ 12 and GCS $\leq$ 8. Bleeding volume was also divided into ordered categorical factors as volume $<$ 10 ml, 10 ml $\leq$ volume $<$ 20 ml, 20 ml $\leq$ volume $<$ 30 ml, 30 ml $\leq$ volume $<$ 40 ml, 40 ml $\leq$ volume $<$ 50 ml, 50 ml $\leq$ volume $<$ 60 ml and volume $\geq$ 60 ml. Risk factors which showed statistically significant in univariate logistic analysis would be enrolled in multiple logistic regression. Akaike Information Criterion (AIC) was used to determine which factors should be enrolled in the final model.

A nomogram was drawn according to the final logistic regression model. Receiver operating characteristic (ROC) curve and calibration curve on development and validation datasets were drawn separately. The area under the curves (AUC) were calculated with 95% confidence intervals. The decision curve analysis (DCA) was also conducted with development dataset.

All analyses were performed with R (https://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA). $P <$. 05 was considered as statistically significant. This study was approved by ethics committee in the first affiliated hospital of Xia'men University.

Table 1

Baseline characters.

Variable	Development set (n = 92)	Validation set (n = 35)	*P* value
Age (year)	57. 3 ± 12.2	53. 0 ± 16.9	.114
Gender (%)			.274
Male	64 (69.6%)	28 (80.0%)	
Female	28 (30.4%)	7 (20.0%)	
Site			
Deep location	70 (76.1%)	28 (80.0%)	.814
Frontal lobe	9 (9.8%)	4 (11.4%)	.752
Parital lobe	17 (18.5%)	2 (5.7%)	.095
Tempral lobe	10 (10.9%)	5 (14.3%)	.555
Occipital lobe	5 (5.4%)	3 (8.6%)	.683
Volume (ml)	28.0 (5.0–120.0)	28. 0 (5.0–112.0)	.261
GCS Score	12.5 (4.0–15.0)	12. 0 (4.0–15.0)	.728
IVH	46 (50.0%)	16 (45.7%)	.666
DM	12 (13.0%)	9 (25.7%)	.109
Hypertension	64 (69.6%)	26 (74.3%)	.601
Hyperlipidemia	27 (29.3%)	6 (17.1%)	.182
MMSE	24. 0 (0.0–30.0)	25. 0 (0.0–30.0)	.981

3. Results

The baseline characteristics were showed in Table 1. In all 127 patients, 69 patients got cognitive impairment according to MMSE. There was no significant difference between the development and the validation dataset.

In univariate logistic regression analyses, bleeding volume, GCS and IVH showed statistically significant with *P* value $<$ .001. These 3 risk factors still showed significant *P* value in multiple logistic regression with OR 1.610 for every 10 ml bleeding volume (P = .021), 4.103 for every GCS class (P = .004) and 8. 082 for IVH (P = .001). These results indicated that bleeding volume, GCS and IVH are strong risk factors to develop cognitive impairment after supratentorial spontaneous intracranial hematoma in adult patients (Table 2).

Table 2

Univariate and multivariate logistic regression analyses.

	Univariate analysis		Multiple analysis	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age	0.973 (0.939, 1.008)	.130		
Gender				
Female	1.0			
Male	1.028 (0.419, 2.523)	.952		
Site				
Deep location	0.719 (0.268, 1.932)	.513		
Frontal lobe	2.815 (0.552, 14.369)	.213		
Parital lobe	1.440 (0.482, 4.303)	.513		
Tempral lobe	3.289 (0.658, 16.444)	.147		
Occipital lobe	1.110 (0.176, 6.982)	.911		
Volume	2.148 (1.548, 2.980)	**<.001**	1.610 (1. 074, 2.412)	.021
GCS Score	5.445 (2.733, 10.851)	**<.001**	4. 103 (1. 577, 10. 675)	.004
IVH	7.708 (2.987, 19.893)	**<.001**	8. 082 (2. 307, 28. 314)	.001
DM	1.556 (0.433, 5.589)	.498		
HBP	1.560 (0.637, 3.818)	.330		
Hyperlipidemia	0.888 (0.359, 2.196)	.797		

Table 3

Comparison of different models.

	Enrolled variables	AUC (95%CI)	AIC
Model1	GCS + Volume + IVH	0.912 (0. 856, 0.967)	77.704
Model2	GCS + IVH	0.881 (0. 809, 0.951)	81.662
Model3	Volume + IVH	0.873 (0. 806, 0.940)	86.466

As we noticed that GCS have a relatively strong correlation with bleeding volume (Spearman Correlation Coefficient 0.6620, $P < .001$), we built multiple models with different combinations to compare their AUCs and AICs (Table 3). According to AIC, model 1 which combined these 3 variables together showed the smallest AIC (77.704) and the largest AUC (0.912) value. We used model 1 to develop our final nomogram model (Fig. 1).

ROC analyses on both development and validation dataset were showed on Figure 2, and the AUC were 0.911 and 0.919. The model showed good discrimination ability on both development and validation datasets.

We drew calibration curve on both datasets (see figure, Supplemental Digital Content 2, http://links.lww.com/MD/D301, which showed calibration ability). The model showed good calibration ability on development dataset and less excellent calibration ability on validation dataset. This might be caused by a relatively small validation sample amount. Clinical decision curve analysis was showed on Figure 3. Most patients can benefit from the prediction.

4. Discussion

Our results showed bleeding volume, GCS and IVH have strong associations with cognitive prognosis after supratentorial ICH. The nomogram based on these 3 risk factors shows considerable discrimination ability to recognize patients with great risks to develop cognitive impairment. As all these factors can be easily evaluated at the onset of stroke, our study provided a feasible tool for the clinical physicians to identify potential cognitive disorder patients who need further cognitive rehabilitation at the initial stage of the disease, thus may improve the cognitive prognosis.

Although cognitive dysfunction is frequently associated with ICH, few studies ever focused on the prognostic factors for CI and its prediction.[3] Ignorance of cognitive function evaluation can have a great negative impact on rehabilitation and outcome.[4] Some factors such as previous stroke, transient ischemic attack, preexisting cognitive impairment, and severity of cortical atrophy may have a strong relationship with long term CI, but how to predict CI in the acute stage remains unclear.[5]

Recognizing potential CI patients is quite helpful for early rehabilitation. Some treatment such as cognitive rehabilitation training, acupuncture,[6] computer-assisted cognitive training,[7] or even music listening[8] may improve the cognitive function at early stage of stroke. Moreover, a quantitative tool can help the patients' families to establish more reasonable anticipation about the prognosis and may be helpful for averting disputes.

Among CI risk factors, large bleeding volume is a primary concern which causes early dementia after ICH.[9] Our results were consistent with such finding. GCS is commonly used for evaluating conscious state in stroke patients.[10] Along with hematoma size, GCS reflects the severity of the primary stroke. Our results indicated that hematoma volume combined with GCS can obtain a higher AUC and a lower AIC value. The National Institute of Health Stroke Scale score (NIHSS) is also highly correlated with cognitive function according to the INTERACT-

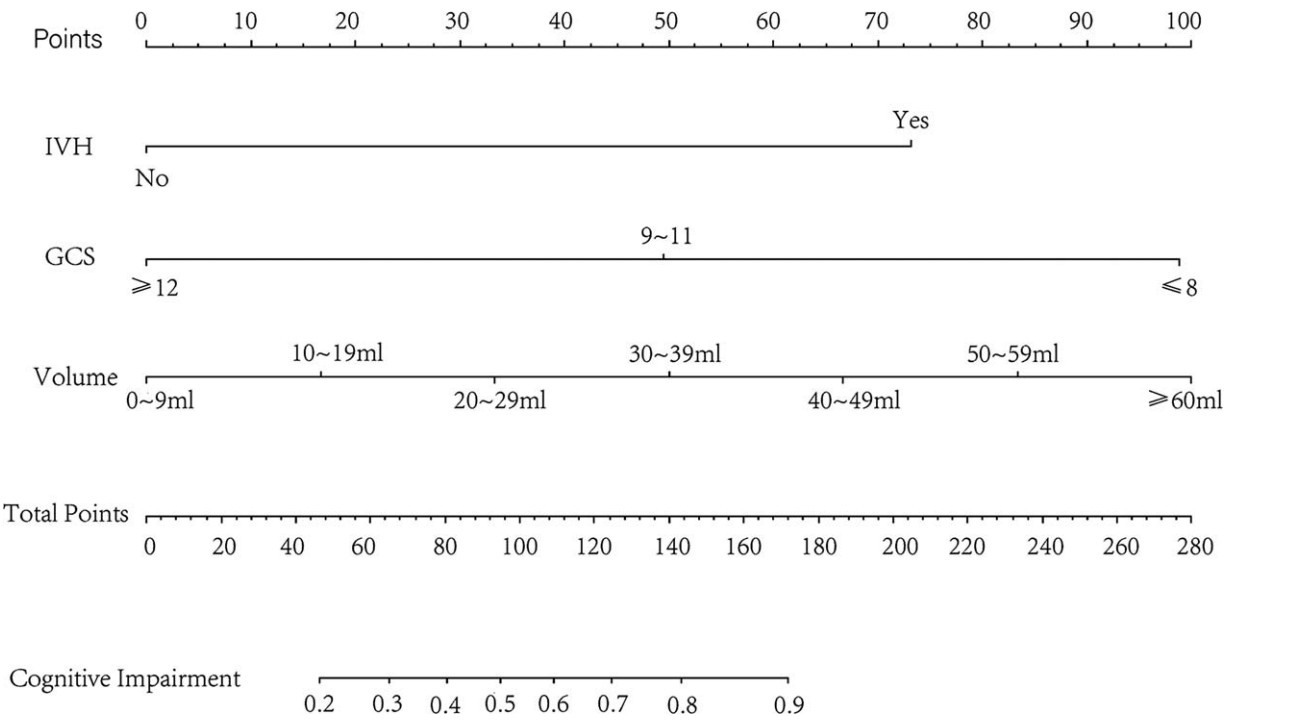

Figure 1. The nomogram to predict the cognitive impairment risks after supratentorial spontaneous intracranial hematoma in adult patients. The linear part of the logistic regression model is Logit (*P*) = -2.70914 + 2.08963 × IVH + 1.41172 × GCS + 0.47597 × Volume, where *P* stands for the probability of cognitive impairment.

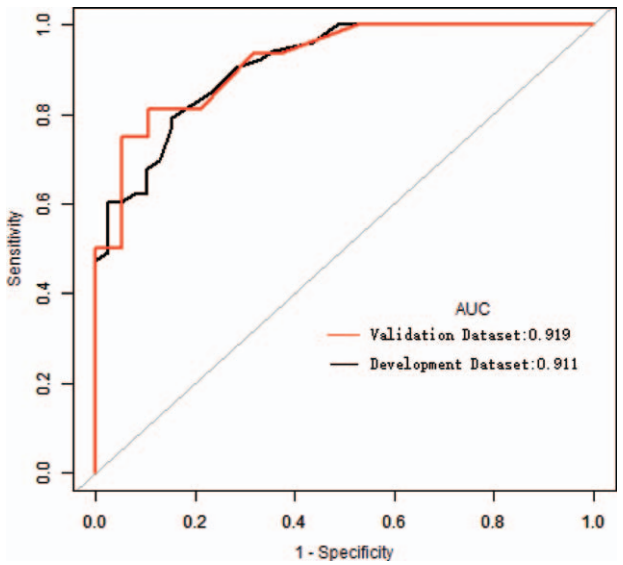

Figure 2. The ROC curves and AUC values for the nomogram model on both datasets. The AUC was 0.911 on the development dataset and 0.919 on the validation dataset.

1 trial data.[11] Future researches may compare these 2 score systems and confirm their relationship with CI.

Due to limited data, the impact of IVH on CI has not been highlighted in the previous studies.[12] Our results showed IVH is a significant risk factors to rise CI. This may be affected by the fact that large-size hematoma is more likely to rupture into ventricle system. Su et al found that nearly 92% hemorrhagic moyamoya disease patients with pure IVH presented mild CI after 1 year.[13] This indicated that IVH may play an independent role on CI occurrence. In addition, IVH is a main cause of hydrocephalus,[14] thus affect cognitive function. The effect of IVH on CI in adult ICH patients still needs to be tested in coming studies.

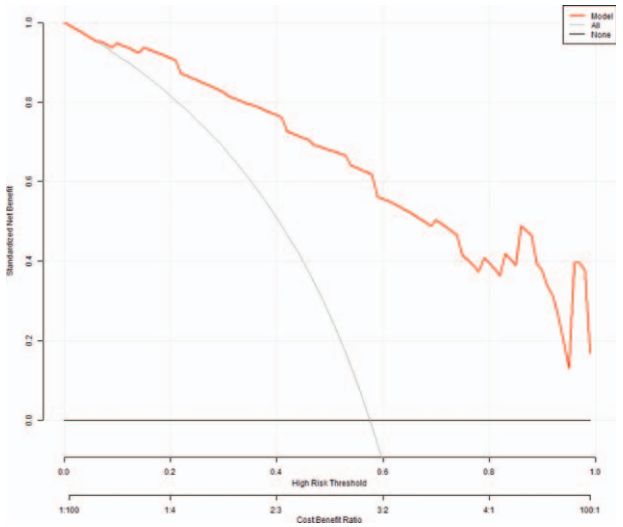

Figure 3. Clinical decision curve of the predictive model on development dataset. The red line indicates the decision curve of the clinical model. The y axis measures the net benefit; the x-axis represents the predictive probability threshold.

There are articles which demonstrated that Neutrophil-to-lymphocyte ratio,[15] delirium behavior,[16] blood pressure control,[11] and lobar intracerebral hemorrhage[17] may have positive effects on CI development. Admission Blood Glucose is not an independent risk factor according to previous study.[18] Further studies are needed to check these risk factors.

Our research has some limitations. Firstly, this is a single center retrospective study with internal validation. Cognitive function might be affected by regional culture, average education level, local stroke treatment level, and other factors.[19] Whether our nomogram suits for patients in other situations still needs to be tested. Secondly, our data was collected in rehabilitation department. Patients without obvious neurological deficits might escape from our collection, resulting in potential selective bias. Thirdly, the sample amount is relatively small. Some potential risk factors did not reach statistically significant in our study. Finally, MMSE is not sensitive enough for mild cognitive impairment especially in old patients (≥60 years old).[20] More precise instruments (such as Montreal Cognitive Assessment) may be needed to evaluate cognitive function.

More prospective observational studies form multiple centers are needed in the further to provide more clinical data about cognitive impairment after supratentorial ICH. And a more precise model with better generalization capacity would be developed.

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