A Web Based Dynamic MANA Nomogram for Predicting the Malignant Cerebral Edema

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Abstract

Background: For large hemispheric infarction (LHI), malignant cerebral edema (MCE) is a life-threatening complication with mortality approaching 80%. Establishing a convenient prediction model of MCE after LHI is vital for rapid identification of high-risk patients and understanding of the potential mechanism of MCE.

Methods: 142 consecutive patients with LHI within 24h of onset from January 1, 2016 to August 31, 2019 were retrospectively collected. MCE was defined as patient death or received DHC with obvious mass effect (≥ 5mm midline shift or Basal cistern effacement). Binary logistic regression was performed to evaluated the independent predictors of MCE. Independent prognostic factors were incorporated to build dynamic MANA nomogram to predict MCE.

Results: After adjustment for confounders, four independent factors were identified, including previously known atrial fibrillation (KAF), midline shift (MLS), National Institutes of Health Stroke Scale (NIHSS) and anterior cerebral artery (ACA) territory involvement. Furthermore, to facilitate the use of the nomogram for clinicians, we use “Dynnom” package to build dynamic MANA (acronym for MLS, ACA territory involvement, NIHSS and KAF) nomogram on web page (http://www.MANA-nom.com) to calculate the exact probability of developing MCE. The c-statistic of MANA nomogram was up to 0.887 ± 0.041 and AUC-ROC value in this cohort was 0.887 (95%CI, 0.828~0.934).

Conclusions: Independent predictors of MCE included KAF, MLS, NIHSS, and ACA territory involvement. The dynamic MANA nomogram is a convenient, practical and effective clinical decision-making tool for predicting MCE after LHI in Chinese patients.

Background

Large hemispheric infarction (LHI) is a severe ischemic stroke involving a large portion of MCA territory with significant morbidity and mortality(1). For LHI, malignant cerebral edema (MCE) is a life-threatening complication with mortality approaching 80%(2, 3). MCE is characterized by a malignant course of rapid neurological deterioration associated with massive cerebral swelling between the second and fifth day after stroke onset(4, 5), subsequent raised intracranial pressure (ICP), midline shift and brain herniation. To date, effective conservative treatment of MCE remains unsolved(6). Moreover, treatment of MCE had largely focused on symptomatic treatment rather than on edema prevention. Given the exceptionally high mortality rate associated with MCE, understanding underlying mechanisms and predictors in patients with MCE, thereby enabling the identification of patients who will benefit from early intervention and providing effective approaches for preventing the MCE, are important.

Previous clinical researches have indicated that MCE has demographic, clinical and radiographic predictors(7-10). Reported predictors of MCE included younger age, higher National Institutes of Health Stroke Scale (NIHSS)(7), larger parenchymal hypoattenuation on computed tomography (CT)(11), hyperdense artery sign and higher blood glucose(10). In recent years, diffusion weighted imaging (DWI)

has been extensively used in the prediction of MCE(7, 9). However, these indicators are not precise enough, not easy to obtain, or their predictive role in clinical settings is limited by their hysteresis(12). Meanwhile, many of the known predictors have been described in the western context. Although China has experienced rapid health transitions over the last four decades, the lifetime risk of stroke in China is significantly higher than the global average(13) and stroke is the first cause of death in China(14). Hence, MCE in Chinese patients are still worth exploring. Motivated by the above facts, we sought to establish a convenient and accurate risk model to forecast MCE in Chinese patients with LHI.

Methods

Patient selection

This study continuously enrolled 157 adult patients diagnosed LHI and admitted within 24 hours to the neuro-intensive care unit (NICU) of Tongji Hospital at Huazhong University of Science and Technology between January 2016 and August 2019. This retrospective study was approved by our Institutional Review Board and written informed consent was waived. LHI was defined as infarction involving at least 50% of the territory of the middle cerebral artery (MCA) in computed tomography (CT) scan or DWI infarct volume >82mL within 24h of onset(15). Infarct volume was calculated by ABC/2 formula(16). MCE was defined as patient death or received DHC with obvious mass effect on follow-up imagological examination (≥ 5mm midline shift or Basal cistern effacement on CT or DWI). Patients were selected for DHC at our institution based on the criteria outlined in previously published trials(17). All patients completed the baseline CT scan or DWI at admission and had no primary intracranial hemorrhage. Other inclusion criteria for our study were: 1) Chinese ethnicity; 2) age 18 years or older; 3) first or recurrent acute stroke occurring within 24h before admission. The exclusion criteria included: 1) Patients with terminal illness such as tumor, severe trauma, or other life-threatening diseases before admission; 2) patients without follow-up Imaging examinations (CT scan or DWI) after 24h of onset; 3) death with secondary intracranial hemorrhage, acute myocardial infarction (AMI) or severe infection during hospitalization.

Table 1. Demographic and clinical characteristics of patients with and without MCE

Parameter	Non-ME (N=101)	ME (N=41)	*P*
Age, y, (IQR)	58 (51~67)	64 (57~71)	0.005*
Gender, male, N (%)	70 (69.3)	26 (63.4)	0.497
Smoke, N (%)	53 (52.5)	21 (51.2)	0.892
Drink, N (%)	44 (43.6)	14 (34.1)	0.302
Hypertension, N (%)	50 (49.5)	21 (51.2)	0.853
Diabetes mellitus, N (%)	18 (17.8)	9 (22)	0.570
Previous stroke, N (%)	16 (15.8)	13 (31.7)	0.037*
Preexisting coronary heart disease, N (%)	9 (8.9)	10 (24.4)	0.018*
KAF	8 (7.9)	13 (31.7)	0.001*
Treatment, N (%)			
Conservative (reference)	79 (78.2)	34 (82.9)	
Intravenous thrombolysis	16 (15.8)	4 (9.8)	0.362
Endovascular intervention	6 (5.9)	3 (7.3)	0.839
NIHSS (IQR)	18 (15~20)	21 (20~22)	< 0.001*
MLS, mm (IQR)	1.9 (3.6~5.1)	5.6 (4.9~8.1)	< 0.001*
Baseline temperature, ℃ (IQR)	36.5 (36.4~36.8)	36.5 (36.5~37.1)	0.170
ACA territory involvement, N (%)	9 (8.9)	18 (43.9)	< 0.001*
PCA territory involvement, N (%)	27 (26.7)	24 (58.5	< 0.001*
Basal ganglia involvement, N (%)	60 (59.4)	37 (90.2)	0.001*
Cerebral hemisphere, right, N (%)	56 (55.4)	15 (36.6)	0.044*
Systolic pressure, mmHg, (IQR)	145 (127~166)	141 (120~159)	0.168
Diastolic pressure, mmHg, (IQR)	83 (73~95)	80 (74~92)	0.871
FBG, mmol/L, (IQR)	5.9 (5.4~6.8)	7.1 (5.8~9.2)	0.002*
HbA1c (%)	5.6 (5.3~6.1)	5.7 (5.3~6.1)	0.378

MCE: Malignant cerebral edema; **IQR:** Interquartile range; **KAF:** Previously known atrial fibrillation; **NIHSS:** National Institutes of Health stroke scale; **MLS:** Midline shift; **ACA:** Anterior cerebral artery; **PCA:** Posterior cerebral artery; **FBG:** Baseline fasting blood glucose; **HbA1c:** Glycosylated hemoglobin; **OR:** Odds Ratio; **CI:** Confidence Interval; **SE:** Standard Error

*p < 0.05 in univariate analysis were included in multivariable logistic regression models for adjustment.

Data collection

The admission characteristics was recorded for all patients, consisting of age, gender, history of smoke and history of drink, preexisting hypertension, diabetes mellitus, previous stroke, preexisting coronary heart disease, admission temperature, admission systolic pressure and admission diastolic pressure and previous atrial fibrillation (AF). AF was identified as previously known AF (KAF), differentiates from AF detected after stroke (AFDAS)(18). Recorded treatment including intravenous thrombolysis or endovascular intervention. The following laboratory tests on admission including baseline fasting blood glucose (FBG) and HbA1c. All 142 patients underwent CT/DWI within 24 hours of onset and the imaging data were evaluated by two experienced clinicians, blinded to the patients' outcome. Midline shift (MLS) was defined as the distance from the septum pellucida to the anatomic line anchored by the falx cerebri to the skull. Stroke severity was measured by National Institutes of Health stroke scale (NIHSS). The cases without recorded NIHSS (N=127, 89.4%) were not excluded from the analysis, and NIHSS were calculated from documented neurologic exams of all patients by two experienced raters, blinded to the patients' outcome. The intraclass correlation efficient (ICC) between calculated NIHSS and recorded NHISS was 0.897 (p< 0.001, 95%CI, 0.667~0.966). An intrarater reliability test was performed in 50 subjects, and the kappa values for MLS and NIHSS were 0.88 and 0.80, respectively.

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics 22 software (SPSS Inc., Chicago, IL, United States) and R version 3.5.2 software (Institute for Statistics and Mathematics, Vienna, Austria; http://www.r-project.org/). Continuous variables (including MLS) were expressed as the median and interquartile range (IQR). Categorical variables were presented as percentages. We performed binary logistic regression to determine predictors independently associated with the MCE. Variables with P<0.05 from the results of the univariate analyses were considered as potential confounders and included in multivariable model. The multivariable logistic regression using a backward stepwise method with input of variables if p-value < 0.05 and backward elimination if p-value > 0.05. All P-values were two-sided, P < 0.05 was considered statistically significant. Collinearity of variables that entered the multivariate logistic regression analysis was assessed by the variation inflation factors (<5 being considered nonsignificant) and tolerance (>0.2 being considered nonsignificant). The "rms" package and "Dynnom" package were used to construct dynamic nomogram model.

Table 2. Multivariate logistic regression model for MCE

Parameter	β	SE	*P*	OR (95%CI)
KAF	1.54	0.61	0.011*	4.68 (1.42~15.42)
MLS	0.26	0.11	0.023*	1.30 (1.04~1.62)
NIHSS	0.28	0.11	0.012*	1.33 (1.07~1.66)
ACA	1.54	0.55	0.005*	4.64 (1.59~13.60)

MCE: Malignant cerebral edema; **KAF:** Previously known atrial fibrillation; **NIHSS:** National Institutes of Health stroke scale; **MLS:** Midline shift; **ACA:** Anterior cerebral artery; **OR:** Odds Ratio; **CI:** Confidence Interval; **SE:** Standard Error

*Statistically significant at p <0.05 level, two-sided

Results

Patient characteristics

In total, 142 patients with LHI were consecutively recruited in this study. Of all these potential subjects, 41 (28.9%) finally developed MCE (39 died, 2 received DHC). As shown in Table 1, patients with MCE were older (median, 64 VS. 58y; mean, 65 VS. 58y; p=0.005), more likely to have preexisting coronary heart disease (24.4 VS. 8.9%; p=0.018), previous stroke (31.7 VS. 15.8%; p=0.037) or KAF (31.7 VS. 7.9%; p = 0.001), higher baseline NIHSS (median, 21 VS. 18; mean, 21 VS. 17; p < 0.001), higher baseline fasting blood glucose (median, 7.1 VS. 5.9mmol/L; mean, 7.9 VS.6.4mmol/L; p=0.002) and greater admission MLS (median, 5.6 VS. 1.9 mm; mean, 6.2 VS. 3.7mm; p < 0.001). In addition, patients with left hemisphere infarction (63.4 VS. 44.6%; p=0.044) and patients with concurrent ACA (43.9 VS. 8.9%; p < 0.001), PCA (58.5 VS. 26.7%; p < 0.001) territory or basal ganglia (90.2 VS. 59.4%; p=0.001) infarction were more likely to develop into MCE.

Table 3. Comparison of the risk of MCE among SR, AFDAS and KAF.

Parameter	β	SE	*P*	OR (95%CI)
Rhythm				
SR (reference)				
AFDAS	-0.69	0.87	0.428	0.50 (0.09~2.77)
KAF	0.46	0.62	0.018*	4.29 (1.28~14.36)
MLS	0.25	0.11	0.026*	1.29 (1.03~1.61)
NIHSS	0.28	0.11	0.011*	1.33 (1.07~1.66)
ACA	1.63	0.57	0.004*	5.11 (1.68~15.54)

MCE: Malignant cerebral edema; **SR:** Sinus rhythm; **AFDAS:** Atrial fibrillation detected after stroke; **KAF:** Previously known atrial fibrillation; **NIHSS:** National Institutes of Health stroke scale; **MLS:** Midline shift; **ACA:** Anterior cerebral artery; **OR:** Odds Ratio; **CI:** Confidence Interval; **SE:** Standard Error

*Statistically significant at p <0.05 level, two-sided

Independent predictors and dynamic nomogram for predicting MCE

Variables with p < 0.05 in univariate logistic regression were included in multivariable logistic regression models for adjustment (Table 1). No significant statistical collinearity was observed for these variables. After adjusted by potential confounders, the KAF (aOR=4.68, 95%CI, 1.42~15.42), MLS (aOR=1.30, 95%CI, 1.04~1.62), NIHSS (aOR=1.33, 95%CI, 1.07~1.66) and ACA territory involvement (aOR=4.64, 95%CI, 1.59~13.60) were independent predictors (Table 2).

All independent predictors (Table 2) of MCE were recruited to construct a nomogram (Figure 1). This nomogram can predict MCE individually according to the different conditions of each patient. Each of the 4 independent predictors were projected upward to the value of the small ruler to get a score, with a point range from 0 to 100. Points assigned to the corresponding factors were summed to get the total points. The total score was then converted into an individual risk of MCE. The higher the total score, the higher the risk of MCE. The predictive accuracy of the nomogram was validated using 1000 bootstrap samples, with a Harrell's c-index value of 0.887 ± 0.041 (Figure 2). The model was also internally validated in this cohort with AUC-ROC value of 0.887 (95%CI, 0.828~0.934). Furthermore, to facilitate the use of the nomogram for clinicians, we use "Dynnom" package to build an operation interface on web page (www.MANAnom.com) to calculate the exact probability of developing MCE (Figure 3).

Discussion

We identified four independent predictors of MCE in this study, The three of which were consistent with previous studies, including NIHSS, MLS and ACA territory involvement(19, 20). The association between KAF and MCE are still controversial. On this basis we present a visual MANA (MLS, ACA territory involvement and KAF) nomogram to assess risk for development of MCE in Chinese patients with LHI. The c-statistic of MANA nomogram up to 0.887 ± 0.041 and AUC-ROC value in this cohort was 0.887 (95%CI, 0.828~0.934).

For the past few years, with the development of cardiac monitoring technologies, physicians have noticed atrial fibrillation (AF) after ischemic stroke or transient ischemic attack (TIA). About 23.7% patients without AF before the stroke later develop AF(21), termed AF detected after stroke (AFDAS). Nevertheless, the relationship between KAF and MCE has never been reported. Currently, the KAF is considered as the cardiogenic AF, which was mainly caused by cardiac remodeling, while AF detected after stroke (AFDAS) may composed of multiple types of AF, including the preexisting but newly diagnosed atrial fibrillation

(cardiogenic AF) and newly emerged atrial fibrillation (neurogenic AF)(22). The neurogenic AF is the main type of AFDAS, which may be caused by inflammatory response and dysfunction of the autonomic regulation of cardiac rhythm(22, 23). Based on this difference between mechanisms of KAF and AFDAS, the effect of AFDAS on stroke severity may also vary from that of KAF. Previous research has found that stroke patients with KAF have higher rate of death or stroke recurrence (including hemorrhagic and ischemic stroke) than patients with AFDAS, but the difference was unadjusted(23). In order to verify this supposition, we set up another multivariable regression to assess the differences in the risk of MCE among the SR, AFDAS and KAF (Table 3). After adjusting for confounders, we found that compared to patients with sinus rhythm (SR) or AFDAS, patients with KAF had significantly higher risk of MCE (adjusted OR 4.29, 95%CI, 1.28~14.36). However, the risk between SR and AFDAS had no significant difference. One possible reason is that patients with KAF had more severe hypoperfusion, which lead to greater infarct growth and larger infarcts(24). Our research also suggests that patients with KAF may have more severe stroke than patients with AFDAS (mean NIHSS 20 vs 18 & mean infarct volume 231.1mL vs 191.5mL). Additionally, it is noticeable that the risk factors of cardiac remodeling, such as endothelin-1 and matrix metalloproteinase, are also associated with brain edema(25-28). Furthermore, neurogenic AF as the “functional AF”, may have less AF burden than cardiogenic AF, which can also influence the prognosis of patients(29). It’s also worth noting that only 2.7% patients with AF in China received anticoagulant treatment(30), which may also associated with the more severe ischemic stroke and brain edema.

For patients with LHI, ACA territory involvement often hints the existence of larger infarction or more proximal vascular occlusion (such as the carotid T occlusion or ICA occlusion), less hemispheric collateral flow and greater volume of edematous brain tissue(31). The NIHSS score is correlated with stroke severity and infarct volume(10, 32), and MLS is a visual indicator on CT or MRI images, even Sonographic monitoring, for assessing severity of brain edema(33, 34). Previous study enrolled NHISS and MLS as categorical variables into scoring models of malignant brain edema for the convenience of clinical use(10, 20). However, compared to continuous use of NIHSS and MLS, the categorical use will lose some precision. Although the nomogram can get rid of that limitation, its practicability is less than scoring models. To make up for these deficiencies, we establish a web operation interface (http://www.MANA-nom.com) for MANA nomogram, which combines practicality and accuracy. Additionally, we did not collect data from CTA, DWI or special measurement techniques(19, 35-37), considering the model needed to be available and propagable.

Unlike previous nomogram that only roughly calculate an approximation, the dynamic MANA nomogram can provide an exact value. Furthermore, it's convenient for neurologists all over the world. After entering a patient’s NIHSS, MLS, infarct area (ACA territory or not) and KAF (Yes or No) on http://www.MANA-nom.com, the neurologist can get the patient’s corresponding probability of developing MCE. Furthermore, the MANA nomogram can also be used to identify patients who need early surgical treatment, or to aid in establishing of reasonable decisions for patients with immense likelihood of MCE of LHI.

Limitations

This study has several limitations. First, since the data of this study was retrospectively collected from single center in China, some information may not be accurate enough. Most patients didn't have recorded NIHSS, and the calculated NHISS may have discrepancy with the actual situation. Second, because through history and ECG during hospitalization to distinguish the KAF and AFDAS is not sufficiently rigorous. Moreover, limited by current ECG monitoring technologies, quite a few paroxysmal AF was undetected, which underestimated the number of patients with AFDAS. Third, defining the primary outcome as death with brain edema or received DHC might make us ignore the fact that some patients developed severe brain edema but pulled through without DHC at discharge. Additionally, there is a slight problem with this network prediction model, sometimes you will encounter a system crash, and all you have to do is clicking "Quit" and log in again. Despite these limitations, our study provided a widely available prediction model for neurologists to assess the risk of MCE in patients with LHI.

Conclusion

KAF in patients with LHI is worthy of attention. The dynamic MANA nomogram is a convenient and practical model that predicts MCE development in patients with LHI in the first 24 hours with high c-statistic and AUC-ROC value. It can help neurologists assess the patient's condition, discuss prognosis with patients' families and make clinical decisions. In addition, further external validation through prospective, multi-center, large-scale trials of this model are also necessary.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by Review Board of Tongji Hospital at Huazhong University of Science and Technology and written informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Authors' contributions

WS: writing-original draft. GL, YS, JM, YL, XQ: collected, analyzed and interpreted the data. ZY, WS: analyzed all imaging data. YF, ZZ, SZ: contributed substantially to study design and revised the manuscript.

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Figures

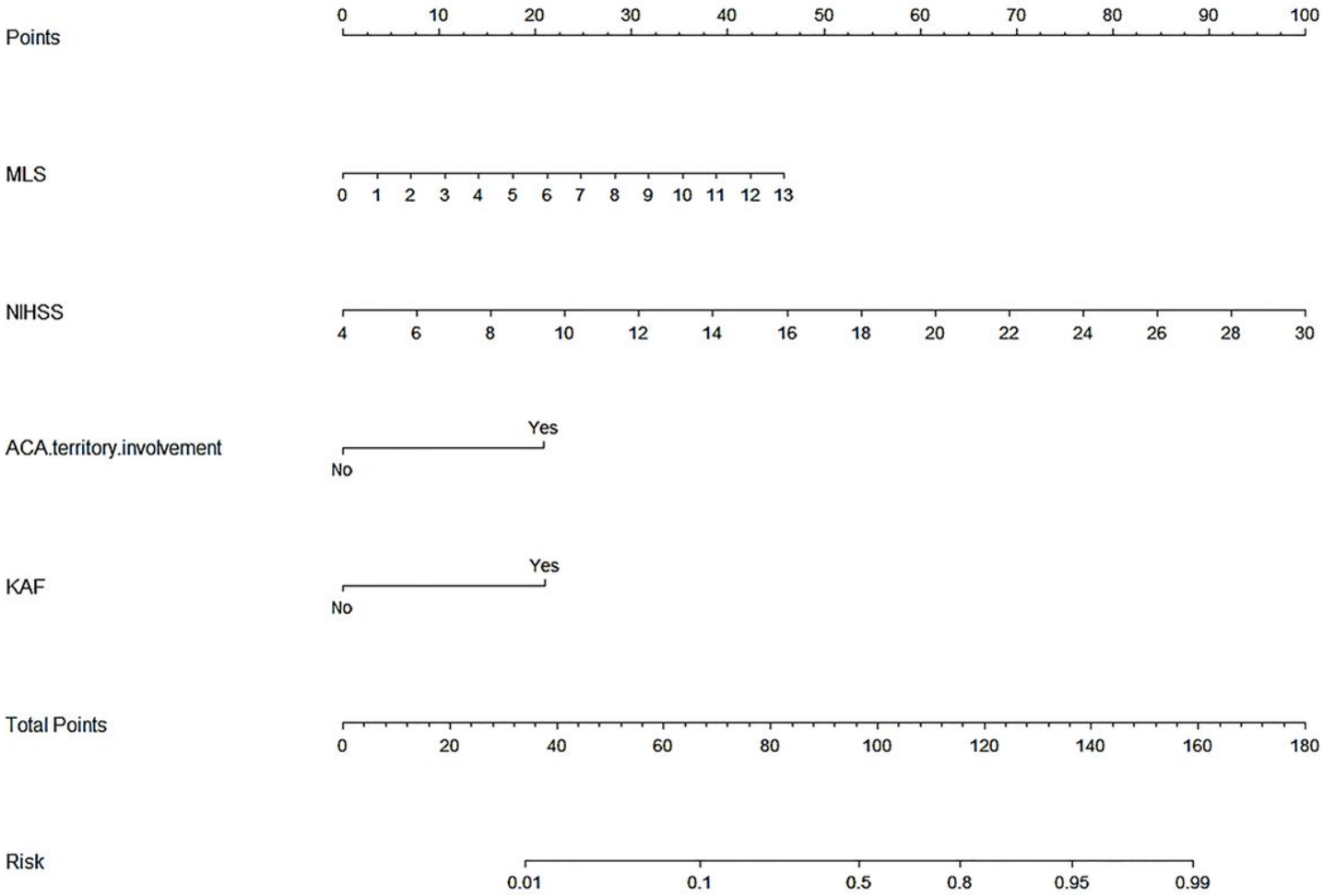

Figure 1

Nomogram for predicting malignant cerebral middle artery infarction; KAF: Previously known atrial fibrillation; NIHSS: National Institutes of Health stroke scale; MLS: Midline shift; ACA: Anterior cerebral artery.

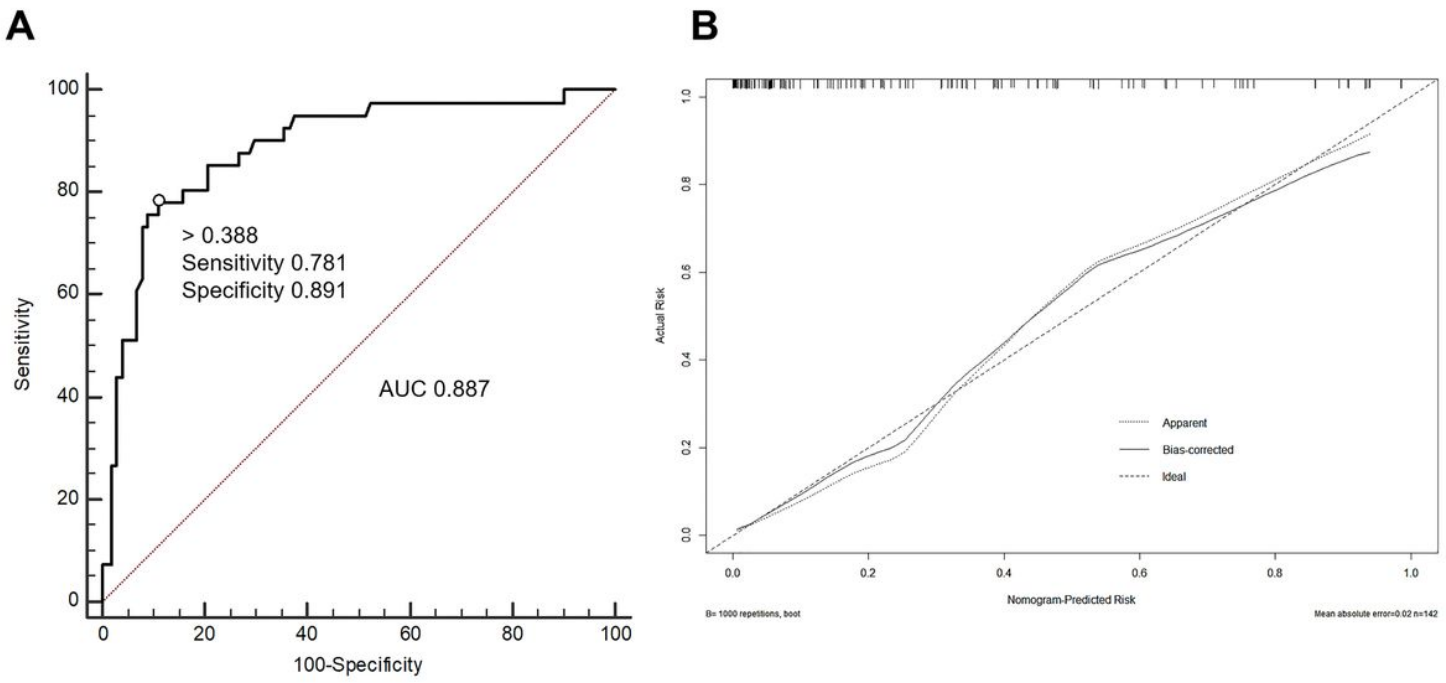

Figure 2

A: ROC curve of the nomogram used for predicting malignant cerebral edema; B: Calibration curves for the nomogram used for predicting malignant cerebral middle infarction. AUC: Area under curve.

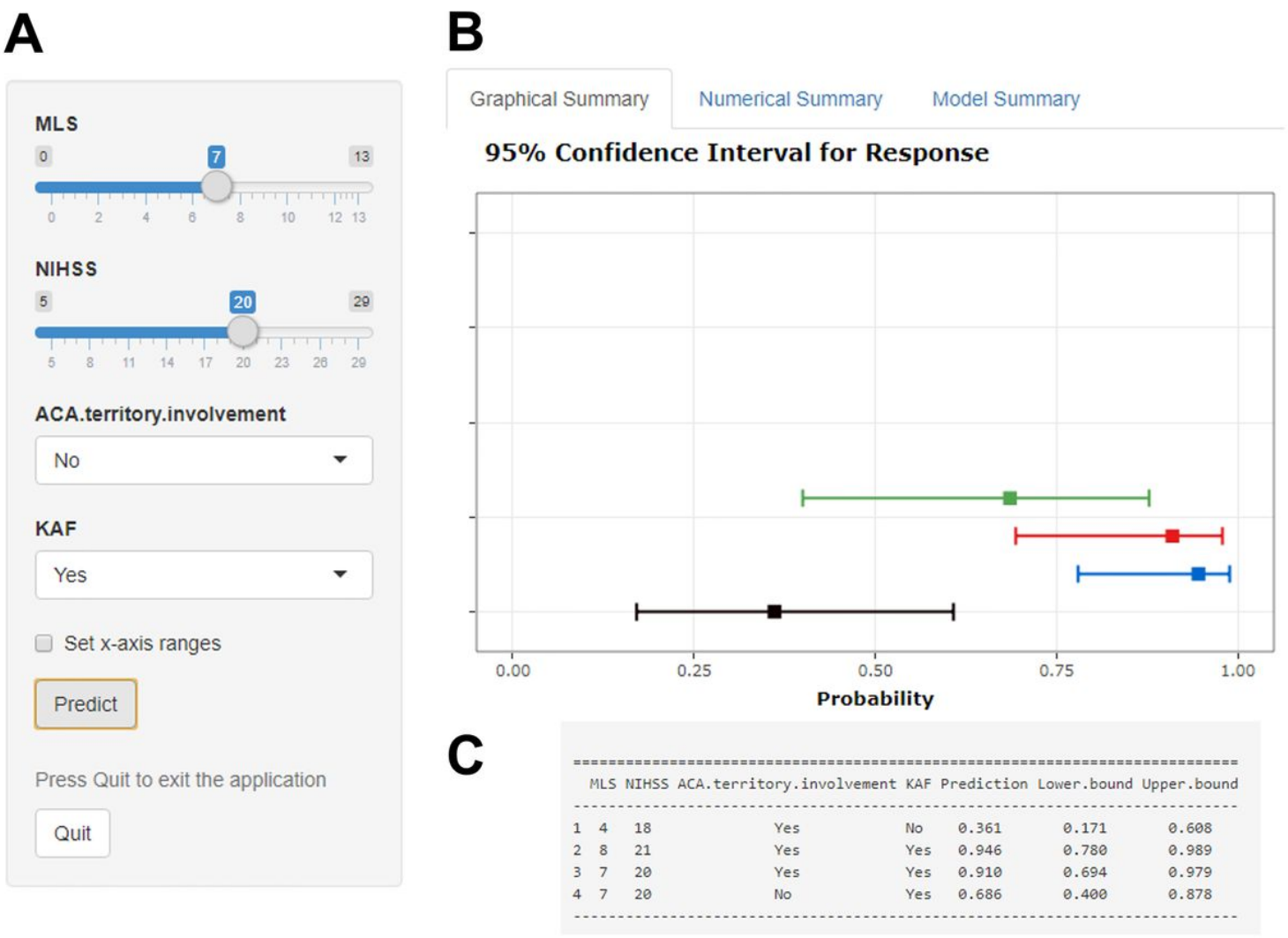

Figure 3

Operation interface of nomogram on web page. A: Input interface; B: Graphical summary; C: Numerical summary; MLS: Midline shift; NIHSS: National Institutes of Health stroke scale; ACA: Anterior cerebral artery; KAF: Previously known atrial fibrillation.