A nomogram to predict the risk of bleeding after discharge from stent-assisted aneurysm embolization in a Chinese population

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Abstract

Background

The occurrence of bleeding events may seriously affect the prognosis of patients with Stent-Assisted Coil (SAC) aneurysms. A nomogram can provide a personalized, more accurate risk estimate based on predictors. We, therefore, developed a nomogram to predict the probability of bleeding events in patients with stent-assisted aneurysm embolization.

Methods

We performed a single-center retrospective analysis of data collected from patients undergoing stent-assisted aneurysm embolization between January 2018 and December 2021. Forward stepwise logistic regression was performed to identify independent predictors of adverse events of bleeding after stent-assisted embolization and to establish nomograms. Discrimination and calibration of this model using the area under the ROC curve (AUC-ROC) and the calibration plot. The model is internally validated by using resampling (1000 replicates).

Results

A total of 131 patients were collected, and a total of 118 patients met the study criteria. The predictors included in the nomogram were Body Mass Index(BMI), AAi, and MA-ADP. The model showed good resolving power with a ROC area of 0.893 (95% CI: 0.834 ~ 0.952) for this model with good calibration.

Conclusion

The nomogram can be used to individualize, visualize and accurately predict the risk probability of bleeding events after stent-assisted embolization of aneurysms.

Introduction

Intracranial aneurysm (IA) is a pathological expansion of intracranial arteries under the influence of hemodynamics and other factors. Studies have shown that the incidence of IA in ordinary people is about 3%. The probability of rupture death and disability is extremely high [1–4]. There are two common treatment options for patients with intracranial aneurysms, surgical clipping, and endovascular coiling. In recent years, Stent-Assisted Coil (SAC) embolization has been widely reported for the treatment of aneurysms [5, 6]. The advent of SAC embolization has expanded the complexity of aneurysms amenable to interventional therapy, while additional stenting requires long-term dual antiplatelet therapy [7, 8]. Studies have shown that thrombotic events do not appear to be an important factor in poor prognosis in patients undergoing stent-assisted embolization of aneurysms[9, 10]. A study by Darkwah et al. showed that patients receiving dual antiplatelet therapy had a greater risk of bleeding events [11]. Therefore, identifying those at risk for bleeding events is the primary goal for this group of patients.

Thromboelastography (TEG) is a method to measure the kinetics of thrombosis and lysis, providing a comprehensive real-time analysis of coagulation and fibrinolysis status[12]. In addition to the standard TEG parameters, a modified TEG with a platelet map was used to assess platelet reactivity and the effect of antiplatelet drugs [13]. The nomogram is a tool to visualize the regression model, which is widely used in the research of intracranial aneurysms because of its simplicity and visualization[14–16]. However, there are few studies on the risk prediction of bleeding events in patients after stent-assisted embolization of aneurysms.

Therefore, we developed a diagram to predict the occurrence of bleeding events in patients after stent-assisted embolization by using TEG-related parameters and patient characteristic parameters. This model can help clinicians determine the risk of bleeding events after stent-assisted embolization, and provide evidence for the prevention of rebleeding and appropriate adjustment of treatment intervention.

Materials And Methods

Study design and patient characteristics

We conducted a retrospective study on patients with intracranial aneurysms who were diagnosed by cerebral angiography and received stent-assisted embolization in Gansu Provincial Hospital from January 2018 to January 2022. Patient data were extracted from the electronic medical record system of Gansu Provincial Hospital. This study was approved by the Ethics Committee of Gansu Provincial Hospital. Written informed consent was waived due to the retrospective nature of this study. All surgeries were performed by the World Medical Association Code of Ethics (Declaration of Helsinki). Inclusion criteria were as follows: 1) age ≥ 18 years; 2) Hunt-Hess ≤ grade 3 at admission. 3) Patients with ruptured intracranial aneurysms who received stent-assisted coil embolization in our hospital. At the same time, we excluded the following cases 1) patients with aneurysms without stent-assisted embolization (including simple coil embolization and microsurgical clipping) 2) severe end-organ failure, intracranial and systemic infections, and blood diseases (patients with serious end-organ failure, intracranial and systemic infections, and blood diseases;) 3) Those with incomplete clinical medical records.

Examination And Operation

All patients underwent preoperative routine examination including blood routine, coagulation examination, blood biochemical examination, liver and kidney function examination, and head CT before the operation. The preoperative diagnosis is based on the results of computed tomographic arteriography(CTA) or Digital subtraction angiography(DSA), and the operation is performed by a neuro-interventional physician with a senior professional title. Interventional operations were performed under general anesthesia, and intravascular operations were performed after systemic heparinization. Whether to use stent-assisted aneurysm embolization was determined by two or more neuro-interventional physicians with senior professional titles based on the angiography results. After the operation, the patients were treated with a dual-antiplatelet regimen (dual-antibody regimen: clopidogrel 75 Mg daily, aspirin 100 Mg daily; oral or nasal feeding) after three days of treatment, blood was collected to complete thromboelastography testing, and venous blood samples for TEG were obtained by training Collected by a trained nurse and immediately transported to the hematology laboratory with sodium citrate tubes. The samples were stored at room temperature and detected within 2 hours, and the detection was completed by the Has-100 thromboelastometer from Haemonetics, USA. After double-antiplatelet therapy for 3 months, the patient was re-admitted to the hospital for re-examination, and the drug regimen was adjusted to single antiplatelet therapy (the single antiplatelet regimen was daily aspirin 100 Mg).

Data Acquisition

Demographic data (age, sex, BMI, smoking, prior hypertension (and hypertension grade), Previous type 2 diabetes, Hunt-Hess score for admission, Modified-Rankin-Scale(MRS) score for discharge, aneurysm location, number of aneurysms, Aneurysm size. TEG parameters were selected as important variables three days after the operation with double antibody: (1) reaction time (R, min), representing the time from activation of coagulation factors to initial clot formation; (2) coagulation time (K, min)), representing the time for clot formation to reach an amplitude of 20 mm; (3) angle (α, degrees), representing the speed of clot formation; (4) maximum amplitude (MA), representing the maximum strength of the clot; (5) MAADP, represents the blood clot intensity induced by adenosine diphosphate; (6) arachidonic acid (AA) inhibition rate (AAi%), represents the response to aspirin; (7) ADP inhibition rate (ADPi%), represents the response to clopidogrel. Patients were questioned or performed relevant physical examinations and related examinations during the three-month postoperative inpatient review. Gastrointestinal bleeding was defined as vomiting with coffee, hematemesis, melena, or a positive fecal occult blood test. Urinary tract bleeding was defined as gross hematuria or positive urine occult blood without obvious urinary tract injury. Oral and nosebleeds were defined as spontaneous mouth or nose bleeding without any apparent cause or history of spontaneous bleeding.

Statistical analysis

Categorical variables were expressed as numbers (percentages), and comparisons between groups were performed using chi-square or Fisher's exact test. Continuous variables that conformed to normality were expressed as the mean (standard deviation), and Student's t-test was used for comparison between groups; those that did not conform to normality were expressed as the median (quartile), and the Mann-Whitney U test was used for comparison between groups. Multivariate Logistic regression was used to investigate the influencing factors of bleeding adverse events after stent-assisted embolization. The relationship between the variables in Logistic regression is reflected by the nomogram. Predictive model variability was assessed using the area under the receiver operating characteristic curve (AUC-ROC). The calibration test used a bootstrap calibration curve resampling 1000 times, reflecting the agreement between the nomogram and actual observations. All statistical analyses were done using SPSS 26.0 (IBM, New York, NY) and R version 4.2.0, and P values < 0.05 were considered statistically significant.

Result

Participant characteristics

Of the 131 patients initially identified for stent-assisted embolization of aneurysms, 118 were included in the final analysis, and 8 of the 131 patients were not re-admitted for follow-up 3 months postoperatively; 2 elderly patients developed severe Complications and died in the hospital; 3 patients did not take antiplatelet drugs as prescribed by the doctor after discharge. Among the patients included in the analysis, the mean age was 55.2 years, 72 (61.02%) were female, and 22 patients had multiple aneurysms. Table 1 presents baseline information for patients with stent-assisted embolization of aneurysms. There were no significant differences in age, aneurysm size, BMI, pre-existing hypertension, and pre-existing type 2 diabetes between patients in the hemorrhagic group and non-hemorrhagic group, but patients with bleeding events were more likely than those without bleeding events. The mean age was greater but the difference was not statistically significant (P = 0.681).

Table 1
Baseline characteristics.

Characteristics	Bleeding		P value
	Yes(26)	No(92)	
Age (years), mean ± SD	56.15 ± 13.98	55.02 ± 11.89	0.681
Aneurysm size (mm), mean ± SD	5.31 ± 2.27	6.26 ± 3.53	0.198
BMI,mean ± SD	25.51 ± 2.14	24.84 ± 3.11	0.307
Aneurysm number, n (%)			0.903
1	20(76.92%)	76(82.61%)	
2 ~ 3	6(23.08%)	16(17.39%)	
Male, n (%)	6(23.08%)	25(27.17%)	0.061
Hypertension, n (%)	8(30.77%)	48(52.17%)	0.055
Type 2 diabetes, n (%)	2(7.69%)	4(4.35%)	0.172
Smoke,n (%)	4(15.38%)	12(13.04%)	0.759
Hunt-Hess grade on admission			0.297
1 ~ 3	26(100%)	92(100%)	
Aneurysm location			0.361
ACoA	10(38.46%)	20(21.74%)	
BA	0(0%)	4(4.35%)	
ICA	4(15.38%)	8(8.69%)	
MCA	4(15.38%)	24(26.09%)	
PCoA	8(30.77%)	32(34.78%)	
Vertebral artery	2(7.69%)	4(4.35%)	

Development Of The Bleeding-predicting Nomogram

In univariate analysis, the factors associated with bleeding events in patients were BMI, AAi, and MA-ADP. After multivariate logistic regression analysis, BMI (OR, 1.47295%CI, 1.127–1.921 P = 0.005), AAi (OR, 1.10895%CI, 1.043–1.178, P = 0.001), MA-ADP (OR, 1.10895%CI), 0.876–0.969, P = 0.002) remained an independent predictor of the occurrence of bleeding events (Table 2). The model was developed by combining the independent predictors identified above and is presented in Fig. 1 as a nomogram. Assign scores for each predictor in the nomogram by drawing a vertical line between the predictor break line and the preliminary score line. The total score was calculated by summing the scores for each predictor, and the predicted probability of the corresponding bleeding event was obtained by drawing a vertical line between the total score and the probability line. The area under the receiver operating characteristic curve (ROC) of the prediction model was 0.893 (95% CI: 0.834–0.952) (Fig. 2). In addition, the calibration curve of the nomogram for the likelihood of postoperative bleeding events in patients with stent-assisted embolization showed good agreement (Fig. 3), and the predictive model could predict the risk of postoperative bleeding events in patients with aneurysms. The calibration curve is shown in Fig. 3. Calibration curves for estimating bleeding events showed no significant deviation from a perfect match and good agreement between predicted and actual outcomes.

Table 2
Logistic regression analysis for symptomatic intracranial hemorrhage.

	Univariate logistic regression		**multivariate logistic regression**			
	OR(95%CI)	**P value**	**Regression Coefficient**	**SE**	**OR(95%CI)**	**P value**
Sex	6.089(0.870-42.636)	0.069				
Age	1.081(0.997–1.171)	0.060				
BMI	1.904(1.231–2.943)	**0.004**	0.386	0.136	1.472(1.127–1.921)	0.005
Previous hypertension	0.252(0.042–1.512)	0.132				
Angle	1.114(0.735–1.688)	0.320				
K	0.645(0.371–1.121)	0.120				
R	0.706(0.441–1.131)	0.148				
AAi	1.154(1.049–1.270)	**0.003**	0.103	0.031	1.108(1.043–1.178)	0.001
ADPi	0.995(0.963–1.028)	0.765				
MA-ADP	0.877(0.792–0.970)	**0.011**	-0.082	0.026	0.921(0.876–0.969)	0.002

Discussion

Although the occurrence of bleeding events may have a significant impact on the prognosis of patients with stent-assisted embolization of aneurysms, current studies have only pointed out the parameters that may be associated with TEG and bleeding events. We developed and internally validated a nomogram combining BMI, AAi, and MA-ADP to predict the probability of a patient's bleeding event after stent-assisted aneurysm embolization, internal validity, and discrimination Satisfactory power.

To our knowledge, this is the first study to use nomograms to predict postoperative bleeding events in patients with stent-assisted embolization of aneurysms. In this study, about 22% of patients experienced bleeding events, and our study showed that BMI, AAi, and MA-ADP could be used as predictors of bleeding events in Chinese patients. However, the incidence of allelic variants associated with clopidogrel activity is higher in Western populations than in East Asian populations, and at the same time, Western populations have more types of allelic variants[17, 18]. So for Western populations, the influencing factors may be different.

Studies have shown that for patients with intracranial stent placement, there is no statistically significant difference in MA-ADP between the bleeding event group and the non-bleeding event group. They believe that TEG-PM is almost no predictor of bleeding complications in such patients' roles [19]. Another study also pointed out that TEG parameters were not found to be associated with bleeding complications in patients [20]. This is in stark contrast to our findings, which suggest that the associated parameters combined with TEG can predict the probability of bleeding complications in this patient. A study by Ge, H et al. [21] showed that there was a statistically significant difference between ADPi and MA-ADP between the bleeding event group and the non-bleeding event group for patients with stent-assisted embolization of aneurysms. At the same time, the study of He, D et al. [22] suggested that for patients with ischemic stroke, the relationship between ADPi and MA-ADP and the occurrence of bleeding events was also shown after dual-antibody treatment. Contrary to our study, they considered no statistical difference in AAi between the two groups, whereas our study showed no significant difference in ADPi between the bleeding and non-bleeding groups. At the same time, Xu, R et al. [23]showed that R and MA-ADP were risk factors for bleeding events in patients with stent-assisted aneurysm embolization, and R and MA-ADP could be used as predictors of bleeding events. The study of Liang et al. [24] showed that for patients with acute ischemic stroke, the R-value can be used to assess bleeding events in such patients. Although studies have shown[25]that dual antiplatelet therapy can affect R and α angles, our study did not show that R values and α angles had a predictive effect on bleeding events in patients. Meanwhile, the study by He, Q et al. [26] showed that AAi and ADPi were independent risk factors for rebleeding in patients with aneurysmal subarachnoid hemorrhage, which was similar to our findings. In addition, other studies have demonstrated that TEG can predict bleeding tendencies [27, 28].

Various previous studies have shown that thromboelastometry parameters may be associated with bleeding events in a variety of patients, but our study is only for patients with ruptured aneurysms. Because most patients with intracranial aneurysms in our center have ruptured aneurysms due to clinical symptoms, we have constructed this diagram only for patients with ruptured aneurysms who have received stent-assisted embolization. Meanwhile, our nomogram has the following innovations. First, to our knowledge, no one has previously designed a nomogram for the patients. The nomograms we created enable individualized screening, and the effective identification of patients with possible bleeding events can provide evidence for appropriate adjustment of their treatment strategies.

Limitation

At the same time, this study has some limitations. Our study is a single-center retrospective study, and small sample size may affect the results. At the same time, we only analyzed patients with ruptured aneurysms, but the conclusions for patients with unruptured aneurysms are unknown. And all patients had only one TEG test, although it is common in clinical work, it may lead to the insufficient observation of the dynamic changes of related parameters. Finally, the subjects we included are all Chinese patients. Due to the existence of genetic problems, the promotion of the results may need further research.

Conclusion

By combining 3 patient characteristic indicators, a nomogram was constructed. This model provides an effective method to assess the risk of bleeding events in patients after stent-assisted embolization of aneurysms, and can easily calculate the probability of bleeding events.

Declarations

Ethical Approval and Consent to participate

For this type of study, formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

Human and Animal Ethics

Not applicable

Consent for publication

Not applicable

Competing interests

The authors have no conflicts of interest to declare.

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Authors' information

Not applicable

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Figures

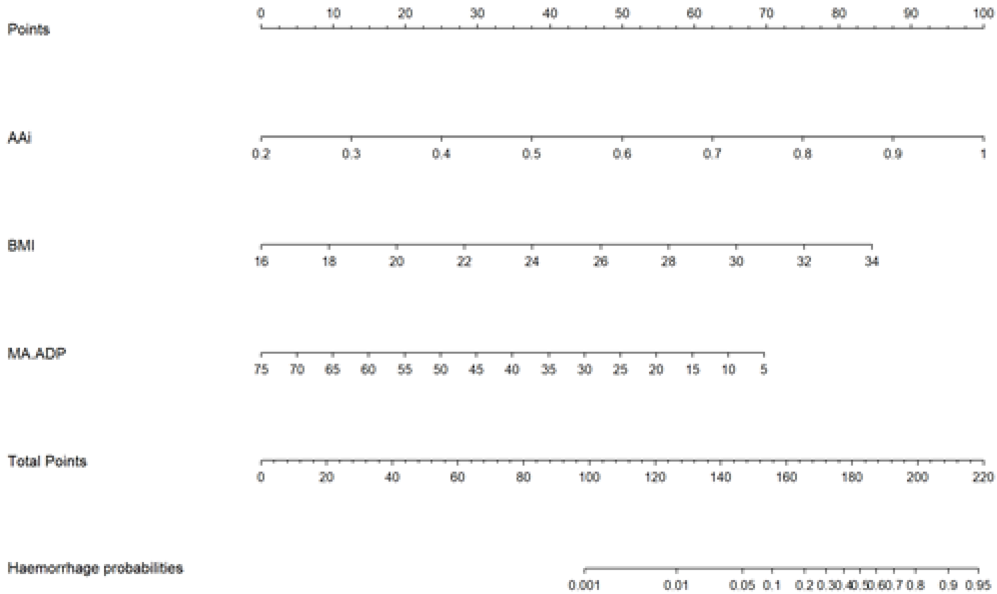

Figure 1

A nomogram consisting of the BMI, AAi, MA-ADP. Draw a line perpendicular from the corresponding axis of each predictor until it reaches the top line labeled “Points” . Sum up the number of points for all predictors then draw a line descending from the axis labeled “Total points” until it intercepts the predicted probability of Haemorrhage probabilities axes to determine probabilities of haemorrhage probabilities.

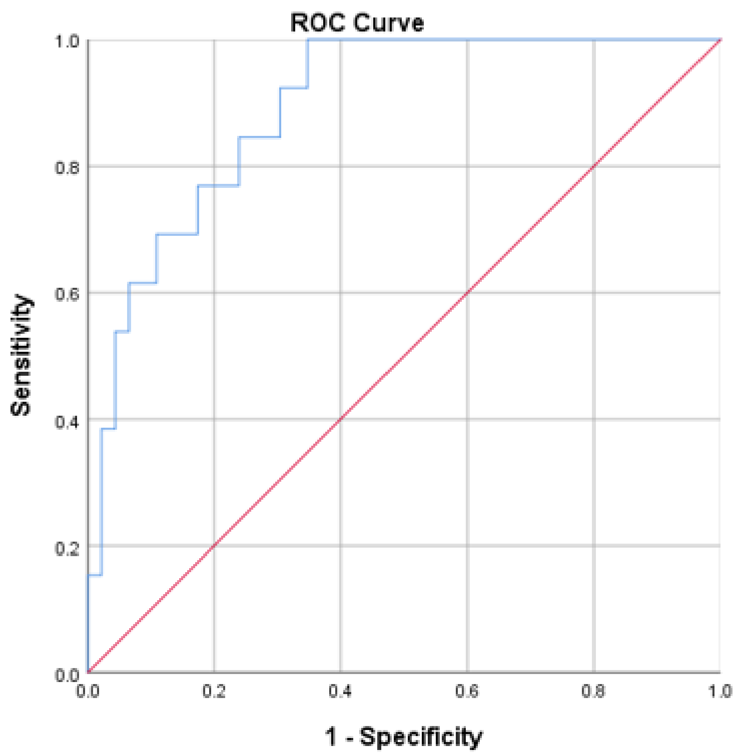

Figure 2

A receiver operating characteristic curve to evaluate the discriminating capability of the nomogram

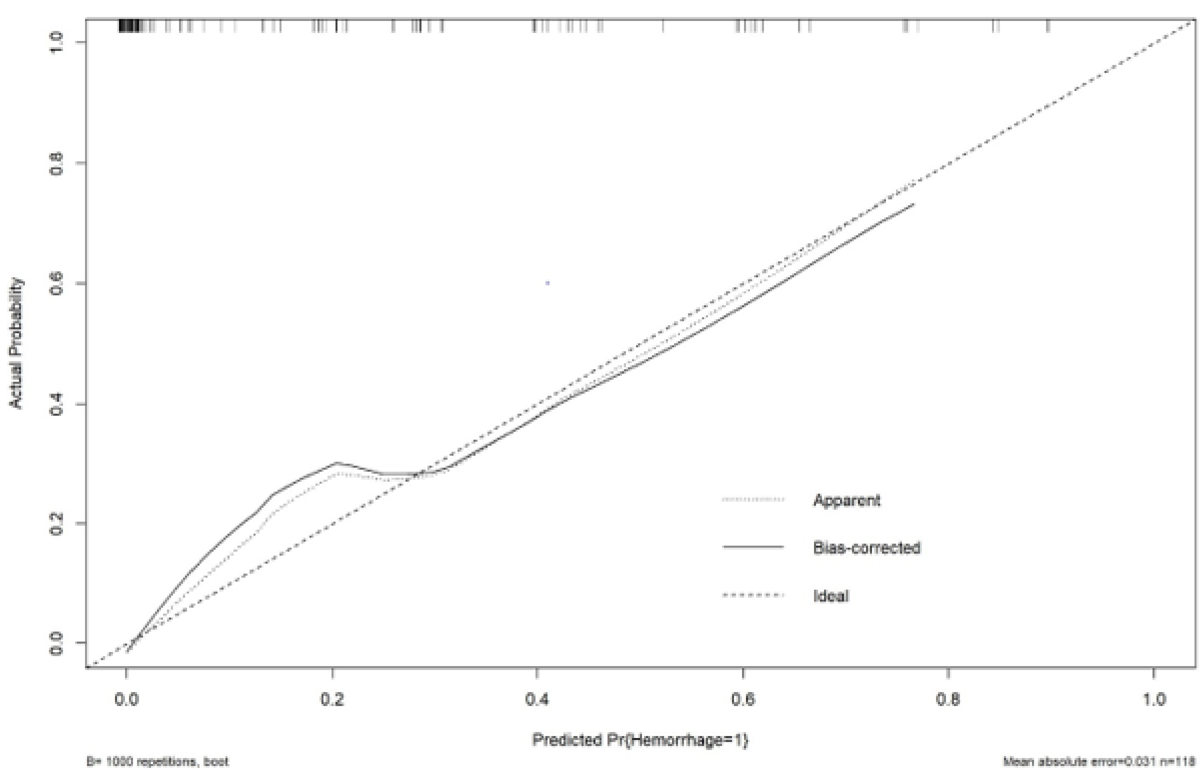

Figure 3

A calibration plot to evaluate the fitting performance of the nomogram