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Therapeutic Effects of Microsurgical Clipping at Different Time Points on Intracranial Aneurysm and Prognostic Factors

Ge Huang[1,2], Yang Sun[1], Jinhong Li[2], Zhengyuan Xie[2] and Xiaoguang Tong[1,3*]

Abstract

Background: Microsurgical clipping is effective for treating early rupture hemorrhage in intracranial aneurysm (IA) patients. We aimed to evaluate the therapeutic effects of microsurgical clipping at different time points on IA and to explore prognostic factors.

Methods: A total of 102 eligible patients were divided into good prognosis group ($n = 87$) and poor prognosis group ($n = 15$) according to Glasgow Outcome Scale (GOS) scores at discharge. The effects of microsurgical clipping at different time points (within 24 h, 48 h and 72 h) were compared. The incidence rates of postoperative complications in patients with different Hunt–Hess grades were compared. Prognostic factors were determined by multivariate logistic regression analysis. The nomogram prediction model was established based on independent risk factors and validated.

Results: The good recovery and success rates of complete aneurysm clipping were significantly higher in patients undergoing surgery within 24 h after rupture. The incidence rate of complications was significantly higher in patients with Hunt–Hess grade IV. Good and poor prognosis groups had significantly different age, history of hypertension, preoperative intracranial hematoma volume, aneurysm size, preoperative Hunt–Hess grade, later surgery, postoperative complications and National Institute of Health Stroke Scale (NIHSS) score, as independent risk factors for prognosis. The nomogram model predicted that poor prognosis rate was 14.71%.

Conclusion: Timing (within 24 h after rupture) microsurgical clipping benefits the prognosis of IA patients. Age, history of hypertension, preoperative intracranial hematoma volume, aneurysm size, preoperative Hunt–Hess grade, later surgery, postoperative complications and NIHSS score are independent risk factors for poor prognosis.

Keywords: Time point, Microsurgical clipping, Intracranial aneurysm, Prognosis

1 Introduction

As a cerebrovascular disease with abnormal tumor-like protrusions on the intracranial arterial walls [1], intracranial aneurysm (IA) is mainly caused by hypertension, atherosclerosis, vasculitis or local congenital defects in intracranial arterial walls [2]. IA will gradually develop and expand, ultimately resulting in rupture. The incidence rate of IA rupture is second only to that of cerebral thrombosis and hypertensive cerebral hemorrhage in patients with cerebrovascular diseases. The fatality rate of initial rupture hemorrhage can be up to 15% [3], seriously threatening the life health and significantly reducing the quality of life of patients. After IA diagnosis, the condition of disease should be assessed immediately, and complications should be avoided as far as possible through the most effective treatment means [4]. Currently, the major treatment methods for IA rupture are

*Correspondence: jaelynsandovalboey@yahoo.com
[1] Department of Graduate School, Tianjin Medical University, Tianjin 300350, China
Full list of author information is available at the end of the article

endovascular interventional therapy and microsurgical treatment, and aneurysm clipping is the preferred method in the latter, which is also regarded as the golden standard for the treatment of IA [5]. Early surgery refers to surgery performed within 72 h after IA rupture, and it can eliminate intracranial hematoma promptly and lower the incidence and risk of re-bleeding [6]. Microsurgical clipping is effective for treating early aneurysm rupture hemorrhage in IA patients, and the sooner it is performed after hemorrhage, the better the surgical effect will be, which can significantly reduce the incidence of postoperative complications, and produce a better prognosis [7]. In the present study, the effects of microsurgical clipping at different time points on IA were explored, and the influencing factors for the prognosis were analyzed.

2 Materials and Methods

2.1 General Data

A total of 102 IA patients undergoing microsurgical clipping from January 2017 to January 2019 in our hospital were selected as the objects, including 49 males and 53 females aged 33–72 years old, with an average of (56.54 ± 5.62) years old. All patients underwent aneurysm clipping within 72 h after IA rupture, including 21 cases within 24 h, 54 cases at 24–48 h, and 27 cases at 48–72 h. According to the postoperative treatment effect, the patients were divided into good prognosis group ($n=87$) and poor prognosis group ($n=15$).

Inclusion criteria were as follows: (1) patients diagnosed with IA by digital subtract angiography (DSA), CT angiography (CTA) or/and magnetic resonance angiography (MRA); (2) those in preoperative Hunt–Hess grade I–IV. The Hunt–Hess grading system, which describes the severity of subarachnoid hemorrhage due to intracerebral aneurysm rupture, is utilized to predict survival in clinical practice. Grade I: Asymptomatic or mild headache and neck stiffness; grade II: moderate to severe headache and neck stiffness, without neurologic deficit except for cranial nerve palsy; grade III: drowsy, with mild neurologic deficit; grade IV: stuporous, moderate to severe hemiparesis, with the possibility of early decerebrate rigidity and vegetative disturbances; grade V: deep coma, decerebrate rigidity and moribund; (3) those undergoing microsurgical clipping in our hospital; (4) those with complete medical records.

Exclusion criteria were as follows: (1) patients aged > 75 years old; (2) those with red blood cell, infectious, mental or other neurological diseases; (3) those with severe insufficiency of the heart, lung, liver, kidney or spleen. Seven cases were excluded, including one patient older than 75 years, three patients suffering from red blood cell, infectious, mental or other neurological diseases, and another three patients suffering from severe insufficiency of the heart, lung, liver, kidney or spleen.

This study was approved by the Ethics Committee of our hospital, and the patients and their families signed the informed consent.

2.2 Surgical Methods

All patients with IA underwent early surgery, namely microsurgical clipping within 72 h after aneurysm hemorrhage. The location of aneurysm was determined by CTA combined with DSA, the appropriate approach was selected, and the patient received general anesthesia with tracheal intubation in a supine position. If the patient had intracranial hypertension, mannitol was intravenously infused additionally. The lateral fissure cistern and the carotid cistern were dissected and separated under a microscope. The optic chiasm cistern was opened, and the cerebrospinal fluid was slowly released to fully expose the parent artery. Then, the aneurysmal neck was separated and clipped using appropriate clipping forceps, followed by wet dressing using papaverine cotton pads. During operation, the patient's blood pressure, blood gas and electrocardiogram were monitored.

2.3 Collection of Clinical Data

The general data of all patients were collected through the electronic medical record system, including age, gender, body mass index (BMI), preoperative Hunt–Hess grade (I, II, III and IV), history of hypertension, preoperative intracranial hematoma volume, aneurysm size, timing of surgery, length of hospital stay, postoperative complications (cerebral vasospasm, aneurysm rupture, cerebral edema, cerebral infarction, intracranial infection, and severe pulmonary infection), and the National Institute of Health Stroke Scale (NIHSS) score upon admission to hospital.

2.4 Assessment of Surgical Treatment Outcomes

The short-term prognosis of patients was assessed using the Glasgow Outcome Scale (GOS) score at discharge [8], as follows: 5 points (good recovery): the patient returned to normal life at discharge; 4 points (mild disability): the patient was disabled at discharge but could live independently; 3 points (severe disability): the patient was awake and disabled at discharge, and could act as instructed but needed daily care; 2 points (vegetative state): the patient could not interact with the outside world at discharge, and only had the least response; 1 point: death. 4–5 points indicate a good prognosis, while 1–3 points indicate a poor prognosis.

The postoperative clipping status (complete clipping, most clipping, and partial clipping) was recorded.

2.5 Statistical Analysis

SPSS 19.0 software was used for one-way analysis of variance of data. The *t* test and χ^2 test were performed to compare the differences between two groups. The factors affecting the prognosis of IA patients were explored through multivariable logistic regression analysis and the variables with statistically significant differences were assigned values. The nomogram prediction model was established using R software (R3.3.2) and rms software package. The discrimination of the model was evaluated using receiver operating characteristic (ROC) curves, and the area under the curve was calculated. Concordance index (*C*-index) ranges from 0.5 to 1, and the value closer to 1 indicates that the prediction result is closer to the truth. Bootstrap method was used for internal validation. The actual *C*-index was compared with the internally validated *C*-index, and the closer the difference is to 0, the better the conformance of the model. Besides, 80 patients undergoing microsurgical clipping from February 2019 to August 2019 in our hospital were selected for external validation, and *C*-index was calculated to assess the accuracy of the model. The inclusion and exclusion criteria were the same as those in this study. $P < 0.05$ suggested statistically significant difference.

3 Results

3.1 General Data

According to the GOS score at discharge, the patients were divided into good prognosis group and poor prognosis group, and the general data were compared between the two groups. There were statistically significant differences in age, history of hypertension, preoperative intracranial hematoma volume, aneurysm size, preoperative Hunt–Hess grade, timing of surgery, length of hospital stay, postoperative complications and NIHSS score between the two groups ($P < 0.05$) (Table 1).

3.2 Therapeutic Effect of Surgery at Different Time Points

The therapeutic effect of microsurgical clipping at different time points after aneurysm rupture on IA patients was compared. It was found that the good

Table 1 General data

Group	Good prognosis group ($n = 87$)	Poor prognosis group ($n = 15$)	t/χ^2	*P*
Age (years)	51.32 ± 7.25	63.58 ± 6.87	6.092	0.000
Male/female (*n*)	42/45	7/8	0.001	0.982
BMI (kg/m^2)	22.59 ± 2.42	23.12 ± 2.18	0.794	0.429
History of hypertension [*n* (%)]	23 (26.44)	11 (73.33)	1.278	0.046
Preoperative intracranial hematoma volume (mL)	18.16 ± 3.56	23.42 ± 4.37	5.107	0.000
Aneurysm size (mm)	5.43 ± 1.72	16.38 ± 5.43	15.163	0.000
Preoperative Hunt–Hess grade [*n* (%)]			6.480	0.002
I	17 (19.54)	1 (6.67)	–	–
II	34 (39.08)	4 (26.67)	–	–
III	32 (36.78)	7 (46.67)	–	–
IV	4 (4.60)	3 (20.00)	–	–
Timing of surgery [*n* (%)]			14.903	0.001
< 24 h	20 (22.99)	1 (6.67)	–	–
< 48 h	47 (54.02)	7 (46.67)	–	–
< 72 h	20 (22.99)	7 (46.67)	–	–
Length of hospital stay (days)	11.42 ± 6.42	21.58 ± 9.84	5.192	0.000
Postoperative complications [*n* (%)]			29.271	0.000
Cerebral vasospasm	2 (2.30)	3 (20.00)	–	–
Aneurysm rupture	1 (1.15)	2 (13.33)	–	–
Cerebral edema	1 (1.15)	2 (13.33)	–	–
Cerebral infarction	2 (2.30)	3 (20.00)	–	–
Intracranial infection	0 (0)	2 (13.33)	–	–
Severe pulmonary infection	1 (1.15)	3 (20.00)	–	–
NIHSS score	10.13 ± 2.42	16.12 ± 3.68	8.137	0.000

recovery rate was significantly higher among patients undergoing surgery within 24 h (85.71%) than that among patients undergoing surgery within 48 h (74.07%) and 72 h (59.26%) ($P<0.05$). There were 87 cases with a good prognosis and 15 cases with a poor prognosis. Patients undergoing surgery within 24 h had a significantly higher good prognosis rate and a significantly lower poor prognosis rate than those undergoing surgery within 48 h and 72 h ($P<0.05$) (Table 2).

3.3 Status After Microsurgical Clipping at Different Time Points

The aneurysm clipping status after microsurgical clipping at different time points was compared among patients. The results showed that the proportion of complete clipping was significantly higher among patients undergoing surgery within 24 h than that among patients undergoing surgery within 48 h and 72 h, showing statistically significant differences ($P<0.05$). Patients undergoing surgery within 24 h had significantly lower proportions of most clipping and partial clipping than those undergoing surgery within 48 h and 72 h, and there were statistically significant differences ($P<0.05$) (Table 3).

3.4 Postoperative Complications Among Patients with Different Hunt–Hess Grades

The incidence rate of complications was significantly higher among patients in preoperative Hunt–Hess grade IV than that among patients in Hunt–Hess grade I–III, and the difference was statistically significant ($P<0.05$) (Table 4).

3.5 Multivariable Logistic Regression Analysis Results of Prognostic Factors

With the general data with statistically significant differences in both groups as independent variables (Table 1), and the prognosis (0 = good prognosis, 1 = poor prognosis) of patients as the dependent variable, the influencing factors for the prognosis of IA patients were analyzed through logistic regression analysis. The results manifested that age, history of hypertension, preoperative intracranial hematoma volume, aneurysm size,

Table 2 Therapeutic effects of surgery at different time points

Timing of surgery	*n*	Therapeutic effect (*n*)					Good rate (%)	Good prognosis [*n* (%)]	Poor prognosis [*n* (%)]
		Good	Mild disability	Severe disability	Vegetative state	Death			
< 24 h	21	18	2	1	0	0	85.71	20 (95.23)	1 (4.76)
< 48 h	54	40	7	4	2	1	74.07*	47 (87.04)*	7 (12.96)*
< 72 h	27	16	4	2	2	3	59.26*#	20 (74.07)*#	7 (25.93)*#
Total	102	74	13	7	4	4	72.55	87 (85.29)	15 (14.71)

*$P<0.05$ vs. < 24 h; #$P<0.05$ vs. < 48 h

Table 3 Status after microsurgical clipping at different time points

Timing of surgery	< 24 h (*n* = 21)	< 48 h (*n* = 54)	< 72 h (*n* = 27)	χ^2	*P*
Complete clipping [*n* (%)]	20 (95.24)	39 (72.22)	11 (40.74)	17.128	0.000
Most clipping [*n* (%)]	1 (4.76)	12 (22.22)	10 (37.04)	8.4819	0.014
Partial clipping [*n* (%)]	0 (0)	3 (5.56)	6 (22.22)	10.199	0.006

Table 4 Postoperative complications among patients with different Hunt–Hess grades

Complication	Grade I (*n* = 18)	Grade II (*n* = 38)	Grade III (*n* = 39)	Grade IV (*n* = 7)	χ^2	*P*
Cerebral vasospasm	0	1	1	3	23.437	0.000
Aneurysm rupture	0	0	1	2	17.825	0.000
Cerebral edema	0	0	1	2	17.825	0.000
Cerebral infarction	0	0	2	3	24.523	0.000
Intracranial infection	0	0	0	2	27.686	0.000
Severe pulmonary infection	0	0	2	2	13.725	0.003

Table 5 Multivariable logistic regression analysis results of prognostic factors

Item	β	SE	Wald χ^2	P	OR (95%CI)
Age	1.845	1.214	4.689	0.012	1.398 (1.241–2.876)
History of hypertension	1.218	1.342	5.398	0.001	2.325 (1.138–3.425)
Preoperative intracranial hematoma volume	1.352	1.217	3.285	0.002	2.469 (1.214–3.425)
Aneurysm size	1.167	1.438	2.568	0.000	1.397 (1.261–4.125)
Preoperative Hunt–Hess grade	1.043	0.872	2.194	0.002	1.983 (1.204–2.475)
Later surgery	1.586	1.369	4.102	0.000	1.241 (1.068–3.105)
Postoperative complications	1.460	0.942	3.619	0.001	1.402 (1.269–3.874)
NIHSS score	1.652	1.151	3.618	0.001	2.341 (1.145–3.628)

preoperative Hunt–Hess grade, later surgery, postoperative complications and NIHSS score were all independent risk factors for the poor prognosis of IA patients (Table 5).

3.6 Establishment of Nomogram Prediction Model

Variables affecting the prognosis of patients were assigned values (Table 6), and the nomogram prediction model was established using R software. Age ≥ 58 years old, presence of history of hypertension, preoperative intracranial hematoma volume ≥ 20 mL, aneurysm size ≥ 8 mm, preoperative Hunt–Hess grade IV, surgery performed within 72 h, presence of postoperative complications and NIHSS score ≥ 13 points were scored 20 points, 25 points, 27 points, 25 points, 24 points, 32 points and 25 points, respectively. The value corresponding to the total score (196 points) indicated the incidence rate of poor prognosis of patients (14.71%) predicted by the model (Fig. 1).

3.7 Validation of Nomogram Prediction Model

The discrimination of the model was detected to assess the conformance of the model. The actual *C*-index of the model was 0.815, the internally validated *C*-index was 0.809, and the externally validated *C*-index was 0.805. It can be seen that the difference between the actual *C*-index of the model and the internally validated *C*-index was 0.006, indicating good concordance and high accuracy (Fig. 2).

4 Discussion

As a common neurosurgery disease, IA seriously affects the lives of patients after rupture, with extremely high mortality and disability rates [9]. IA is commonly treated by clipping after craniotomy and endovascular embolization in clinical practice [10]. The treatment outcomes of clipping have been markedly improved using microscopes. Compared with microsurgical clipping, endovascular embolization is safer and less traumatic [11]. Additionally, endovascular embolization can be used to treat patients for whom surgical clipping is unsuitable. For instance, endovascular embolization is the first choice for elderly patients, those with complicated IA or narrow necks, or those intolerable to surgery [12]. However, the coils for embolization are irregularly shaped, which may cause blood flow disorder, aggravate histological defects and lead to IA recurrence. In addition, placing coils may induce IA rupture hemorrhage [13]. Moreover, microsurgical clipping has the advantages of high early clearance rate and low incidence rate of vasospasm.

Table 6 Variable assignment

Variable	Assignment
Age	< 58 *Y* = 0, ≥ 58 *Y* = 1
History of hypertension	No = 0, Yes = 1
Preoperative intracranial hematoma volume	< 20 mL = 0, ≥ 20 mL = 1
Aneurysm size	< 8 mm = 0, ≥ 8 mm = 1
Preoperative Hunt–Hess grade	Grade I = 1, grade II = 2, grade III = 3, grade IV = 4
Later surgery	Within 24 h = 1, within 48 h = 2, within 72 h = 3
Postoperative complications	No = 0, Yes = 1
NIHSS score	< 13 points = 0, ≥ 13 points = 1

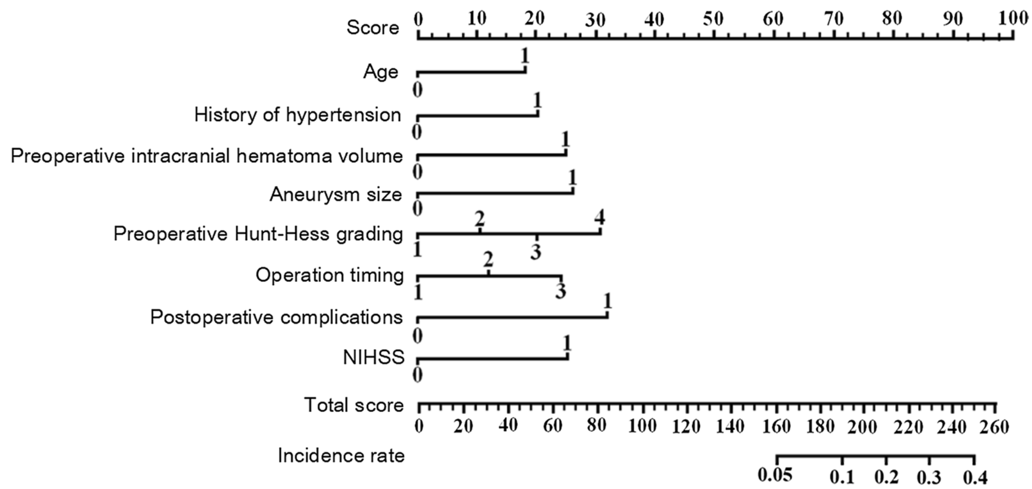

Fig. 1 Nomogram prediction model of prognostic factors. According to the influence of factors on prognosis, corresponding points were assigned, and those of all factors were summed up to predict the probability of poor prognosis

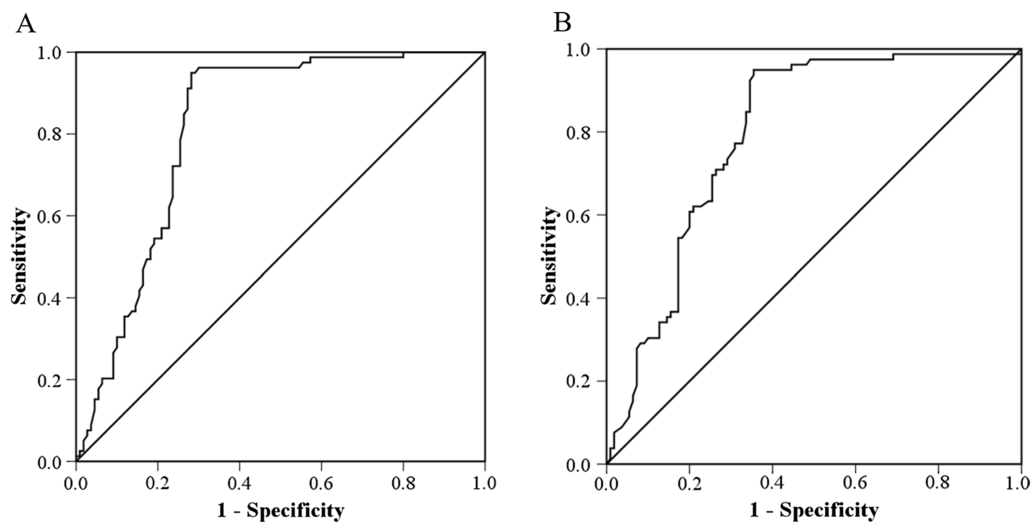

Fig. 2 Evaluation of nomogram prediction model for poor prognosis. **A** ROC curve of internal validation for 102 IA patients undergoing microsurgical clipping from January 2017 to January 2019, which compares the established model and actual results. **B** ROC curve of external validation for 80 patients undergoing microsurgical clipping from February 2019 to August 2019, which assesses the accuracy of this model

Notably, microsurgical clipping is preferable for patients with anterior circulation aneurysms or failed history of endovascular embolization [14].

In recent years, microsurgical clipping has become the golden standard for the microsurgical treatment of IA, which can eliminate the aneurysm from the normal blood circulation in patients, ensuring the sufficient blood perfusion in brain tissues [15]. However, fatal complications may also be caused in IA patients during and after microsurgical clipping. As the most common and serious complications during microsurgical clipping, cerebral vasospasm and aneurysm rupture greatly disturb the operation process, prolong the duration of operation and even threaten the life of patients [16]. Therefore, it is of great importance to analyze the complications during microsurgical clipping for IA, take targeted prevention measures and develop reasonable therapeutic regimens for reducing the disability and mortality rates of patients.

Early surgery refers to microsurgical clipping performed within 72 h after IA rupture [17]. Currently, the timing of microsurgical clipping for IA has always been controversial [18], but it has been confirmed that early surgery can avoid the worsening of conditions and prevent IA re-rupture and re-bleeding [19]. Early surgery can promptly remove blood clots or hematomas in the cistern, thereby effectively lowering the incidence rate of complications such as cerebral vasospasm. However, the risk of death and disability in patients may also be raised by early surgery [20]. It has been reported that the mortality rate greatly declines in patients above preoperative Hunt–Hess grade IV after early surgery, suggesting that severely ill patients with IA should receive operation promptly after aneurysm rupture and bleeding [21]. In the present study, the effect of microsurgical clipping at different time points on IA was compared. The results manifested that patients undergoing surgery within 24 h after aneurysm rupture had a significantly higher good recovery rate and a good prognosis rate, and a significantly lower poor prognosis rate than those undergoing surgery within 48 h and 72 h. It has been found that the sooner the microsurgical clipping is performed after aneurysm rupture in IA patients, the higher the success rate of complete aneurysm clipping will be [22]. In this study, the success rate of complete aneurysm clipping was significantly higher among patients undergoing surgery within 24 h than that among patients undergoing surgery within 48 h and 72 h. It can be inferred that the sooner the microsurgical clipping is performed after aneurysm rupture, the better the effect on IA patients will be.

After microsurgical clipping, severe complications, such as aneurysm re-rupture, cerebral vasospasm, cerebral infarction, cerebral edema, pulmonary infection and intracranial infection, easily occur among IA patients [23]. It can be seen that the preoperative Hunt–Hess grade of IA patients has a close correlation with the incidence of postoperative complications.

Many factors are involved in the prognosis of IA patients after microsurgical clipping. It has been confirmed that age, preoperative Hunt–Hess grade, aneurysm size, and presence or absence of complications are all independent risk factors for the prognosis of IA patients [24]. In this study, age, history of hypertension, preoperative intracranial hematoma volume, aneurysm size, preoperative Hunt–Hess grade, later surgery, postoperative complications and NIHSS score were all independent risk factors for the poor prognosis of IA patients. Besides, the established model can effectively predict the risk factors for the death of patients, with high accuracy.

5 Conclusion

In conclusion, timing (within 24 h after aneurysm rupture) microsurgical clipping benefits the prognosis of IA patients. Age, history of hypertension, preoperative intracranial hematoma volume, aneurysm size, preoperative Hunt–Hess grade, later surgery, postoperative complications and NIHSS score are all independent risk factors for the poor prognosis of IA patients.

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Author contribution
GH & XT designed this study and prepared this manuscript; YS, JL & ZX collected and analyzed clinical data. All authors approve the publication of this manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author, X.T., upon reasonable request.

Declarations

Conflict of interest
The authors declare they have no conflicts of interest.

Author details
[1]Department of Graduate School, Tianjin Medical University, Tianjin 300350, China. [2]Department of Neurosurgery, Jiangmen Central Hospital, Jiangmen 529030, Guangdong Province, China. [3]Department of Neurosurgery, Tianjin Huanhu Hospital, Tianjin 300350, China.

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