



Prognostic Factors Influencing Interventional Embolization for Ruptured Intracranial Aneurysms

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Abstract

Background: Risk factors analysis affecting the prognosis of Ruptured Intracranial Aneurysms (RIA) patients is important to improve their clinical prognosis. The aim of this study was to investigate the risk factors affecting the prognosis of patients with RIA treated with interventional embolization.

Methods: Retrospective analysis of 123 patients with RIA treated by interventional embolization at the second affiliated Hospital of Nanjing Medical University from January 2016 to January 2022 were selected for the study. Patient admission general information, aneurysm factors, surgical factors, postoperative factors were collected from cerebrovascular images and medical records. Identification of independent risk factors affecting the prognosis of patients with interventional RIA using chi-square test and binary multifactorial logistic regression analysis.

Results: Of the 123 RIA patients, 43 were male and 80 were female, with an overall mean age of 62.43 ± 10.45 years, and the results were followed up from 3 months to 2 years. Based on the mRS score, 81 (65.9%) RIA patients had a good prognosis (mRS score 0-2) and 42 (34.1%) had a poor prognosis (mRS score 3-6). On univariate analysis, patient age, history of diabetes mellitus, smoking, alcohol consumption, Hunt-Hess (HH) score, Fisher score, regularity of RIA morphology, intraoperative use of stent-assisted embolization, and postoperative pulmonary infection were associated with patient prognosis. Later, by binary multifactorial regression logistic analysis, history of diabetes mellitus, HH score, Fisher score, and regularity of RIA morphology were independent risk factors affecting the prognosis of RIA treated by intervention?

Conclusion: The prognosis of patients with ruptured aneurysms is influenced by several factors. Patient history of diabetes mellitus, HH score, Fisher score, regularity of IA morphology were independent risk factors affecting the prognosis of interventional RIA.

Keywords: Ruptured intracranial aneurysm; Interventional therapy; prognosis; Risk factors

Abbreviations

IA: Intracranial Aneurysm; RIA: Ruptured Intracranial Aneurysm; DCI: Delayed Cerebral Ischemia; SAH: Subarachnoid Hemorrhage; aSAH: Aneurysmal Subarachnoid Hemorrhage; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; TIA: Transient Ischemic Attack; CCI: Charlson Comorbidity Index; AVM: Cerebral Arteriovenous Malformation; AVF: Cerebral Arteriovenous Fistula; DSA: Digital Subtraction Angiography; IRA: Irregular Aneurysm; RA: Regular Aneurysm; Hb: Hemoglobin; VSMC: Vascular Smooth Muscle Cell; WSS: Wall Shear Stress; MIA: Multiple Intracranial Aneurysms; SIA: Single Intracranial Aneurysm; ISS: Intra-Stent Stenosis; ICA: Internal Carotid Artery; AcomA: Anterior Communicating Artery; PcomA: Posterior Communicating Artery; MCA: Middle Cerebral Artery; VBA: Vertebrobasilar Artery

Introduction

Intracranial Aneurysm (IA) occurs in about 1% to 2% of the population, but accounts for about 80% to 85% of Non-Traumatic Subarachnoid Hemorrhage (SAH) [1]. Hughes et al. collected 58 studies from 31 different countries, and estimated that the worldwide prevalence of aneurysmal

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Subarachnoid Hemorrhage (aSAH) is approximately 6.67 per 100,000 people, and that nearly 500,000 people will suffer from aSAH each year, with nearly 2/3 of these patients occurring in low- and middle-income countries [2]. aSAH accounts for more than 25% of all deaths due to hemorrhagic stroke in people under 65 years of age [3]. Wang et al. concluded that patients of advanced age have an elevated risk of IA rupture compared to younger patients with the same aneurysm size [4]. Zhao et al. found that the majority of RIAs were 2 mm to 5 mm in size, followed by 5 mm to 10 mm, with 95.0% of RIAs occurring in the anterior circulation and 5.0% in the posterior circulation, with approximately 34.9% in the posterior communicating artery and 29.5% in the anterior communicating artery, and 14.6% of patients had multiple aneurysms [5].

aSAH has an overall poor prognosis of 32% to 67% [6]. Based on long-term follow-up and cohort studies of patients with a SAH, a number of risk factors associated with poor prognosis in patients with RIA have been identified. They can be broadly classified into three main categories; patient factors, IA characteristics and surgery-related factors [7]. One study concluded that men; age \geq 65 years; presence of diabetes, congestive heart failure, hypertension, Chronic Kidney Disease (CKD), or End Stage Renal Disease (ESRD); history of prior stroke or Transient Ischemic Attack (TIA); and Charlson Comorbidity Index (CCI) score \geq 2 were independent risk factors for poor prognosis in patients with RIA [8], in addition, alcohol consumption [9], smoking [10], opioids [11], cocaine and methamphetamine [12] can also lead to poor prognosis in patients with RIA. Early surgery, bleeding, duration of surgery, surgeon familiarity and experience with microsurgical techniques, use of certain neuroesthetics, circulatory arrest, and hypothermia may also be associated with poor outcomes in patients with RIA [13].

This thesis focuses on the factors influencing the long-term prognosis of RIA treated with interventional embolization, with the aim of furthering the understanding of the prognosis of this disease in the course of clinical practice. The relevant influencing factors were screened out and included in binary multi-factor logistic regression analysis to screen out the independent risk factors affecting the prognosis after IA treated by interventional embolization.

Materials and Methods

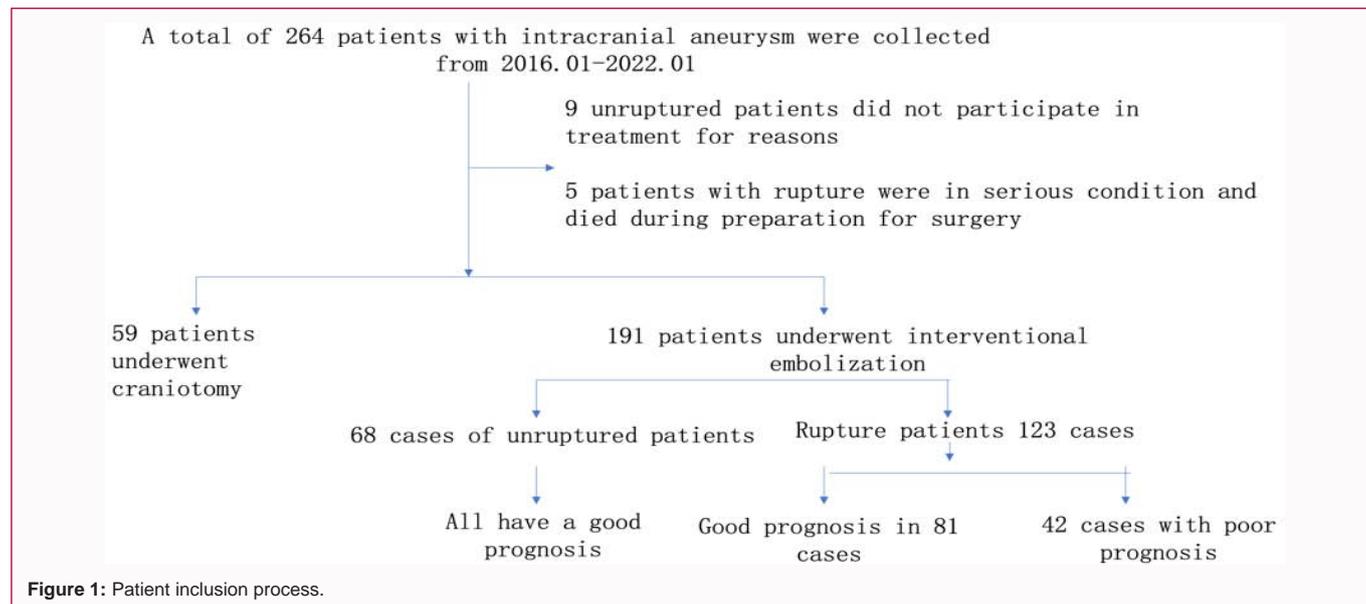
Study population and data collection

With the approval of our hospital (the second affiliated Hospital of Nanjing Medical University) ethics committee, we retrospectively analyzed 264 patients with IA treated at our center from January 2016 to January 2022. Patients with RIA treated by interventional embolization were selected for the study (Figure 1).

Inclusion criteria were showed as followed: Patients with at least IIA confirmed by CTA, MRA, and DSA; treated by interventional embolization. Patients with unexplained SAH or genetic disorders (polycystic kidney disease, Marfan's syndrome); presence of other intracranial vascular malformations, such as cerebral Arteriovenous Malformation (AVM) or Cerebral Arteriovenous Fistula (AVF) and other malignant diseases or poor general condition; intracranial and other malignant tumors; cloacal, traumatic, fungal or anatomic IA were excluded. Patients without a complete medical record were also excluded.

Collect information on patient gender, age, Hunt-Hess (HH) score, Fisher score, history of smoking, history of alcohol consumption, previous history of hypertension, history of diabetes, aneurysm size, aneurysm neck width, aneurysm location, single or multiple aneurysms, whether the aneurysm is regular, timing of surgery, intraoperative rupture, intraoperative acute cerebral ischemia, intraoperative stent use, postoperative pulmonary infection, postoperative Delayed Cerebral Ischemia (DCI), postoperative hydrocephalus, and postoperative epilepsy. Preoperative grading was performed using HH score and Fisher score, with HH (1-3) or Fisher (0-2) as low grading and HH (4-5) or Fisher (3-4) as high grading; postoperative follow-up was performed using the mRS scale [14], with mRS (0-2) as good prognosis and mRS (3-6) as poor prognosis [15].

All patients were reviewed by CTA, MRA or DSA at 3 months after discharge. Patient information was obtained by telephone follow-up, and clinical events such as ischemic events (cerebral infarction during postoperative follow-up), hemorrhagic events (cerebral hemorrhage during postoperative follow-up), whether the postoperative aneurysm recurred, and patient survival were recorded



during follow-up. Detailed assessment using the mRS scale with a good prognosis (mRS score of 0-2) and a poor prognosis (mRS score of 3-6).

Performance of Interventional Embolization Treatment

In patients with RIA, blood pressure was controlled before surgery (140/90 mmHg), and a loading dose of 300 mg each of Aspirin and Clopidogrel was administered orally or intranasally 1.5 h to 3 h before surgery. After general anesthesia, the femoral artery was punctured by Seldinger method, 6F arterial sheath was placed, whole brain angiography was performed, and 3D imaging of the responsible vessels was performed to clarify the number, morphology, size, and location of the aneurysm, and to select appropriate working angle, deliver the guiding catheter to the rocky bone segment of the internal carotid artery under the road map, and then perform systemic heparinization (50 U/kg, intravenous push), and choose simple embolization or stent-assisted embolization according to the measured data. Postoperatively, according to the cranial CT, if the ventricular blood accumulation was severe or the lateral ventricles appeared dilated, extra-ventricular puncture and drainage was performed; if the patient showed intracerebral hematoma, subdural hematoma or cranial hypertension, cranial hematoma removal was performed in combination with postoperative CT results, and if necessary, decompression with debridement was performed. In patients with stent-assisted embolization, oral clopidogrel (75 mg/day) was administered for 6 weeks and aspirin (100 mg/day) for at least 6 months after discharge, during which the clotting time was monitored and the drug dose was adjusted promptly.

Statistical methods

The Pearson chi-square test, continuously corrected chi-square test or Fisher's exact test were used for the counting data in this study. The relevant influencing factors were screened at P<0.05 and then included in a binary multivariate logistic regression analysis to screen for independent risk factors affecting the prognosis of RIA treated with interventional embolization.

Results

We collected a total of 123 patients with interventional RIA who met the inclusion criteria from January 2016 to January 2022 were selected for the study. There were 43 males and 80 females, with an overall mean age of 62.43 ± 10.45 years. Based on the mRS scale, there were 22 patients (17.9%) with grade 0, 50 patients (40.7%) with grade 1, 9 patients (7.3%) with grade 2, 3 patients (2.4%) with grade 3, 17 patients (13.8%) with grade 4, 18 patients (14.6%) with grade 5, and 4 patients (3.3%) with grade 6 at 3 months to 2 years of follow-up.

Patient admission general information

During the follow-up period of 3 months to 2 years, 81 patients had a good prognosis and 42 patients had a poor prognosis. By univariate analysis, patient age ($\chi^2=8.854$, P=0.004), history of diabetes ($\chi^2=33.391$, P<0.001), smoking ($\chi^2=9.656$, P=0.002), alcohol consumption ($\chi^2=4.397$, P=0.039), HH score ($\chi^2=38.476$, P<0.001), Fisher score ($\chi^2=13.179$, P=0.001) were associated with poor prognosis, and gender and history of hypertension were not significantly associated with whether patients had a good prognosis (Table 1).

Table 1: Relationship between patient factors and prognosis of RIA treated by intervention.

	Good prognosis	Poor prognosis	χ^2	P-value
Gender			0.016	0.899
	Male	28 (22.8%)	15 (12.2%)	
	Female	53 (43.1%)	27 (22.0%)	
Age			8.854	0.004
	<65 years	44 (35.8%)	11 (8.9%)	
	≥ 65 years	37 (30.1%)	31 (25.2%)	
Hypertension			0.048	0.827
	No	16 (13.0%)	9 (7.3%)	
	Yes	65 (52.8%)	33 (26.8%)	
Diabetes			33.391	<0.001
	No	63 (51.2%)	10 (8.1%)	
	Yes	18 (14.6%)	32 (26.0%)	
Smoking			9.656	0.002
	No	49 (39.8%)	13 (10.6%)	
	Yes	32 (26.0%)	29 (23.6%)	
Drinking			4.397	0.039
	No	47 (38.2%)	16 (13.0%)	
	Yes	34 (27.6%)	26 (21.1%)	
Hunt-Hness Grade			38.476	<0.001
	1,2,3	61 (46.9%)	7 (5.7%)	
	4,5	20 (15.4%)	35 (28.5%)	
Fisher Grade			13.179	0.001
	0,1,2	45 (36.6%)	37 (30.1%)	
	3,4	36 (29.3%)	5 (4.1%)	

Table 2: Relationship between IA factors and prognosis of interventional RIA.

		Good prognosis	Poor prognosis	χ^2	P-value
Aneurysm size				3.762	0.154
	Small	48 (39.0%)	30 (24.4%)		
	General	27 (22.0%)	12 (9.8%)		
	Large	6 (4.9%)	0 (0%)		
Aneurysm neck				0.007	0.931
	Narrow	14 (11.4%)	7 (5.7%)		
	Wide	67 (54.5%)	35 (28.5%)		
Location				6.429	0.162
	ICA	20 (16.3%)	9 (7.3%)		
	AcomA	14 (11.4%)	6 (4.9%)		
	PcomA	34 (27.6%)	15 (12.2%)		
	MCA	12 (9.8%)	7 (5.7%)		
	VBA	1 (0.8%)	5 (4.1%)		
Number				1.355	0.345
	SIA	67 (54.5%)	31 (25.2%)		
	MIA	14 (11.4%)	11 (8.9%)		
Characteristic				8.838	0.004
	RA	46 (37.4%)	12 (9.8%)		
	IRA	35 (28.5%)	30 (24.4%)		

Table 3: Prognostic relationship between surgical factors and interventional treatment of ruptured aneurysms.

		Good prognosis	Poor prognosis	χ^2	P-value
Timing of surgery				2.141	0.586
	Ultra Early	63 (51.2%)	29 (23.6%)		
	Early	10 (8.1%)	7 (5.7%)		
	Mid to late stage	7 (5.7%)	6 (4.9%)		
	Late stage	1 (0.8%)	0 (0%)		
Intraoperative rupture				1.641	0.179
	No	79 (64.2%)	38 (30.9%)		
	Yes	2 (1.6%)	4 (3.3%)		
Intraoperative cerebral ischemia				0	1
	No	72 (58.5%)	37 (30.1%)		
	Yes	9 (7.3%)	5 (4.1%)		
Stent Assist				5.711	0.018
	No	35 (28.5%)	9 (7.3%)		
	Yes	46 (37.4%)	33 (26.8%)		

Aneurysm factors

Intraoperative measurement of IA morphology, size, number, aneurysm neck width and aneurysm location, and assessment of IA characteristics in relation to prognosis of patients with RIA. After univariate analysis, the regularity of IA morphology ($\chi^2=8.838$, $P=0.004$) was associated with patient prognosis, while IA size, number, tumor neck width and location were not significantly associated with patient prognosis (Table 2).

Surgical factors

To document the timing of surgery, intraoperative re-rupture, intraoperative cerebral ischemia and intraoperative use of stent-assisted embolization after aSAH in 123 patients with RIA. After

univariate analysis, intraoperative use of stent-assisted embolization ($\chi^2=5.711$, $P=0.018$) was associated with patient prognosis, whereas timing of surgery after aSAH, intraoperative re-rupture, and intraoperative cerebral ischemia were not significantly associated with patient prognosis (Table 3).

Postoperative factors

Postoperative pulmonary infection, DCI, hydrocephalus, and seizure complications were present in 123 RIA patients during their post-interventional hospitalization. By univariate analysis, pulmonary infection ($\chi^2=29.854$, $P<0.001$) was associated with patient prognosis, and DCI, hydrocephalus, and seizure complications during the patient's hospitalization were not significantly associated

Table 4: Relationship between postoperative factors and prognosis of interventional RIA.

		Good prognosis	Poor prognosis	χ^2	P-value
Postoperative Pneumonia				29.854	<0.001
	No	72 (58.5%)	18 (14.6%)		
	Yes	9 (7.3%)	24 (19.5%)		
Postoperative DCI				2.354	0.125
	No	69 (56.1%)	31 (25.2%)		
	Yes	12 (9.8%)	11 (8.9%)		
Postoperative hydrocephalus				1.509	0.219
	No	81 (65.9%)	0 (0%)		
	Yes	40 (32.5%)	2 (1.6%)		
Postoperative epilepsy				0	1
	No	80 (65.1%)	42 (34.1%)		
	Yes	1 (0.8%)	0 (0%)		

Table 5: Interventional treatment of RIA Binary multifactorial logistic analysis of prognosis.

Clinical Indicators	B	SE	Wald	df	P-value	OR (95% CI)
Age	-2.025	1.206	3.344	1	0.067	0.110 (0.010, 1.172)
Diabetes	4.098	1.437	8.127	1	0.004	60.208 (3.599, 1007.316)
Smoking	1.244	1.096	1.288	1	0.256	3.469 (0.405, 29.731)
Drinking	-0.090	1.025	0.008	1	0.930	0.914 (0.123, 6.820)
HH	4.124	1.413	8.517	1	0.004	61.817 (3.874, 986.344)
Fisher	-6.366	1.409	20.422	1	<0.001	0.002 (0.000, 0.027)
IA Size	4.400	1.088	16.354	1	<0.001	81.422 (9.655, 687.019)
Stent Assist	1.458	1.006	2.102	1	0.147	4.299 (0.599, 30.865)
Pulmonary Infection	1.500	1.201	1.560	1	0.212	4.483 (0.426, 47.188)
Constants	-14.315	2.941	23.683	1	0.000	0.000

with prognosis (Table 4).

Multi-factor logistic regression analysis

After univariate analysis, the risk factors associated with the prognosis of patients with RIA, including age ($\chi^2=8.854$, $P=0.004$), history of diabetes ($\chi^2=33.391$, $P<0.001$), smoking ($\chi^2=9.656$, $P=0.002$), alcohol consumption ($\chi^2=4.397$, $P=0.039$), HH score ($\chi^2=38.476$, $P<0.001$), Fisher score ($\chi^2=13.179$, $P=0.001$), and whether IA morphology was regular ($\chi^2=8.838$, $P=0.004$), intraoperative use of stent-assisted embolization ($\chi^2=5.711$, $P=0.018$), and pulmonary infection ($\chi^2=29.854$, $P<0.001$) were assigned. This was followed by a binary multi-factor logistic regression analysis. Patient history of diabetes (OR=60.208, 95% CI=3.599 to 1007.316, $P=0.004$) HH score (OR=61.817, 95% CI=3.874 to 986.344, $P=0.004$), Fisher score (OR=0.002, 95% CI=0.000 to 0.027, $P<0.001$), and the regularity of IA morphology (OR=81.422, 95% CI=9.655 to 687.019, $P<0.001$) were independent risk factors for the prognosis of patients with RIA treated with intervention, and patient age, history of smoking, history of alcohol consumption, intraoperative stent use, and postoperative pulmonary infection were not independent risk factors (Table 5).

Discussion

There is a strong relationship between the rupture of IA and its clinical prognosis, and in clinical practice, it has been found that the morbidity and mortality rates are significantly higher in RIA compared to unruptured IA. In clinical practice, analysis of risk factors affecting the prognosis of RIA patients is important to

improve the clinical prognosis of RIA patients. It has been suggested that history of diabetes, HH score, Fisher score at admission, timing of intervention, and location and size of IA are risk factors for RIA prognosis [16]. However, the specific risk factors that affect patient prognosis are still controversial and need to be further explored.

The IA reviews, survival status and scores using the mRS scale were recorded during the follow-up period, and the risk factors affecting the patients' prognosis were analyzed. By univariate analysis, age, history of diabetes, smoking, alcohol consumption, HH score, Fisher score, regularity of IA morphology, intraoperative stent use, and postoperative pulmonary infection were found to be risk factors for poor prognosis. Later by binary multivariate logistic regression analysis, patients' history of diabetes, HH score, Fisher score, and regularity of IA morphology were found to be independent risk factors for poor prognosis.

It is believed that the patient's symptoms and state of consciousness at admission directly affect the prognosis [17]. The HH score is an important tool to assess the intraoperative and postoperative status of patients with RIA [18]. Previous studies reported mortality rates close to 100% in patients with HH grade 5 [19]. Ogden et al. [20] found that 91% of patients with HH grade 0% and 89% of patients with HH grade 1 were satisfied with the results of interventional embolization for RIA; 77% of RIA patients with HH grade 4 or higher had a poor prognosis or died after interventional embolization. Our study is also consistent with this finding that the HH score is significantly associated with whether the patient has a good prognosis and is an

independent risk factor for the prognosis of patients with RIA. Chen et al. [21] investigated 730 patients with aneurysms, of which 104 patients with HH grade 4 to 5 had a poor prognosis of 77.8%, and further analysis revealed that compared to preoperative patients with HH grade 0 to 1, patients with HH grade 4 to 5 had at least a 20- to 30- fold increase in poor prognosis. Qi et al. [22], in a retrospective study of 49 elderly patients with HH grade 3 to 5, found that patients with higher HH scores had increased postoperative complications, while there were no statistical differences in other general clinical information, and concluded that HH grading was an independent risk factor affecting the prognosis of elderly patients with severe aSAH. However, with advances in treatment techniques, more and more reports show that patients with HH grade 3 or higher have a good prognosis.

Early CT performance is important in the assessment of aSAH. Fisher grade is commonly used to evaluate CT scan findings in patients with aSAH. Our statistical results suggest that CT Fisher score is an independent risk factor affecting the prognosis of patients with RIA. Zhang et al. [16] showed that the more hemorrhage in the brain pool shown by CT, the greater the likelihood of vasospasm, and that patients with Fisher grade 1-2 were much more likely to heal than those with Fisher grade 3-4. Rivero et al. [23] concluded that patients with greater bleeding after IA rupture are usually in poorer clinical condition and may develop rebleeding, hydrocephalus, vasospasm and more serious surgical complications, which in turn lead to poor prognosis. It has been shown that patients with a higher Fisher score performed significantly better in terms of attention and memory than those with a lower Fisher score, which may be related to the neurotoxicity of intracerebroventricular blood [24]. It was found that Hb can exert direct contractile spasmogenic effects on VSMC, as well as irreversible cytotoxic effects. Moreover, it has been found that Hb can enhance the neurotoxic effects of activated glutamate receptors in cultured neuronal cells [25]. It is certain that the greater the amount of bleeding, the more severe the impairment of neurological function and the worse the prognosis.

A study by Zhang et al. [16] showed that abnormal blood glucose has a significant adverse effect on the prognosis of patients with RIA and that there is a significant association between abnormal fluctuations in blood glucose and cerebral metabolic distress and mortality in patients with RIA [26]. Diabetes mellitus predisposes to cerebrovascular tortuosity and cerebrovascular stenosis, and these complications increase the risk of cerebral embolism and cerebral vasospasm. Gu et al. [27] found that elevated blood glucose levels were associated with the formation of IA and that multifactorial logistic regression analysis showed a poorer prognosis in diabetic patients with aSAH [28]. Lanzino [29] also confirmed that blood glucose levels were associated with a poorer state of consciousness and high mortality in patients with aSAH. Our study similarly concluded that patients' previous history of diabetes was an independent risk factor for poor prognosis in patients with RIA.

The shape of aneurysms has been classified into monocystic aneurysms with regular margins and irregular margins, aneurysms with daughter sacs, and lobulated aneurysms, and the latter three morphological subtypes have been considered as Irregular Aneurysm (IRA) [30]. And IRA has been shown to be a major risk factor for aSAH [30]. In a study by Goertz et al. [31], ruptured IRAs were at higher risk of intraoperative re-rupture than ruptured Regular Aneurysms (RAs). Feng et al. [32] concluded that IRAs are significantly larger and

more often located at the bifurcation of the vessel compared to RAs, and that IA at the bifurcation is often exposed to high WSS, and that blood flow at the bifurcation often flows at right angles, increasing the kinetic energy transferred to the aneurysm wall [33]. These factors contribute to the degeneration of the IA wall and make it more prone to the formation of a blistered IA [34]. Abboud et al. [30] reported a 5-fold increased risk of aneurysm rupture in aneurysms with a subcyst and a 7-fold increased risk of rupture in lobulated aneurysms with an increased poor prognosis compared to single sac aneurysms. Our findings support that the regularity of IA morphology is an independent risk factor for patient prognosis.

Limitation

This study is a retrospective observational study, the results of which may be influenced by a variety of other factors in addition to the variables included in our study. This study is a single-center retrospective study with a single source of cases and a small sample size, the results may be biased, and the findings still need to be further validated by a multicenter, large sample of prospective randomized clinical trials.

Conclusion

The prognosis of patients with ruptured aneurysms is influenced by several factors. Patient age, history of diabetes, smoking, alcohol consumption, HH score, Fisher score, regularity of IA morphology, intraoperative use of stent-assisted embolization, and postoperative pulmonary infection are associated with patient prognosis. History of diabetes, HH score, Fisher score, and regularity of IA morphology are independent risk factors affecting the prognosis of interventional RIA.

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