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Risk Factors Associated with Rupture of Multiple Intracranial Aneurysms

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Abstract: *Objective:* To identify risk factors associated with multiple intracranial aneurysm (MIA) rupture. *Methods:* This retrospective study included patients with MIAs diagnosed at the center between February 2010 and December 2015. Patients were grouped based on their history of aneurysmal subarachnoid hemorrhage (aSAH) into ruptured and unruptured categories. In the ruptured group, aneurysms were further classified as ruptured MIAs (R-MIAs) and unruptured MIAs (U-MIAs). Patient- and aneurysm-related factors were analyzed using univariate analysis to determine their significance in rupture risk. Receiver operating characteristic (ROC) analysis was employed to calculate the area under the curve (AUC) and identify optimal thresholds for five morphological parameters distinguishing R-MIAs from U-MIAs. *Results:* Of 368 enrolled patients, 327 (86 with ruptured aneurysms and 241 unruptured) were included in the analysis. Among the ruptured group, 66 patients had R-MIAs and 96 had U-MIAs. Univariate analysis identified statistically significant factors associated with rupture, including BMI, irregular aneurysm shape, size, aspect ratio, size ratio, and bottleneck ($P < 0.05$). Size, size ratio, and bottleneck exhibited high AUC values (AUC > 0.7). ROC analysis determined an optimal threshold of 4.6 mm for MIA rupture size. *Conclusions:* Lower BMI, irregular aneurysm shape, larger size, larger size ratio, and bottleneck are associated with an increased risk of MIA rupture. Notably, MIAs may rupture at smaller sizes compared to single intracranial aneurysms.

Keywords: Multiple intracranial aneurysms; Rupture; Risk factors

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1. Introduction

Unruptured intracranial aneurysms (UIAs) are increasingly detected in clinical practice due to the widespread use of computed tomography (CT) and magnetic resonance imaging (MRI), with a prevalence of approximately 1–2% in the population [1]. The rupture of intracranial aneurysms is the leading cause of subarachnoid hemorrhage (SAH) in 80–85% of cases, resulting in high morbidity and mortality rates of 40–50% and 10–20%, respectively [2,3]. Only about 40% of patients achieve independent recovery following SAH.

Studies indicate that 15–35% of patients with aSAH have multiple intracranial aneurysms (MIAs) [4-6], which are more likely to rupture and result in poorer outcomes compared to single intracranial aneurysms. Although several studies have explored the risk factors for aneurysm rupture, only two small-sample studies have specifically focused on MIAs, comparing ruptured and unruptured patients, with inconclusive results [7,8].

To address this gap, this study investigates patient-related risk factors for MIA rupture using a larger sample size and further examines aneurysm-related factors by comparing ruptured MIAs (R-MIAs) and unruptured MIAs (U-MIAs) in the same patient cohort. Findings suggest that lower BMI, irregular shape, larger aneurysm size, larger size ratio, and bottleneck are potential risk factors for MIA rupture, warranting further investigation in prospective follow-up studies.

2. Methods

2.1. Study design and ethics

This retrospective study was approved by the Institutional Review Board of Beijing Tiantan Hospital. Written informed consent was obtained from all patients, and privacy was strictly protected.

2.2. Patient selection

Data from consecutive patients with MIAs admitted to the institution between February 2010 and December 2015 were retrospectively collected. Diagnoses of aSAH were confirmed via CT, and aneurysm parameters were measured using three-dimensional rotational angiography (3DRA).

Exclusion criteria included:

(1) Arteriovenous malformation, arteriovenous fistula, or Moyamoya disease.

(2) Dissecting aneurysms.

(3) Intracranial hemorrhage of unknown origin.

Additional exclusions for the ruptured group were:

(1) Inability to identify ruptured aneurysms.

(2) Inability to obtain imaging for aneurysms clipped during surgery.

2.3. Definition of parameters

Body mass index (BMI) was calculated as weight/height^2. According to Chinese standards, obesity is defined as BMI ≥ 28 kg/m^2. Patients were categorized as obese (BMI ≥ 28) or non-obese (BMI < 28). Cardio-cerebral vascular incident (CCVI) was defined for patients with a history of acute coronary syndrome, transient ischemic attack, or stroke.

Aneurysm measurement parameters included neck width, height, aneurysm width, and parent artery diameter, all measured in millimeters using 3DRA evaluations performed by two experienced neurosurgeons. Aneurysm size was defined by its height. Morphological parameters included aspect ratio (AR), size ratio (SR), height-to-width ratio (H/W), and bottleneck factor (BNF). Irregularly shaped aneurysms exhibited blebs, wall protrusions, or multiple lobes. Aneurysms were classified as sidewall (SW) or bifurcation (Bif).

Potential patient-related risk factors included sex, age, BMI, smoking status, alcohol intake, hypertension, hyperlipidemia, diabetes mellitus, and history of CCVI. Aneurysm-related risk factors encompassed irregular shape, location, type, and morphology.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS software (version 20, Chicago, IL, USA). Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range). Comparisons between categorical variables were performed using Pearson's χ^2 test or Fisher's exact test, and continuous variables were analyzed using Student's t-test or the Mann–Whitney U test.

Receiver operating characteristic (ROC) analysis was conducted to determine the area under the curve (AUC) and optimal thresholds for morphological parameters. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study population

Out of 368 consecutive patients, 327 were included in the study: 86 with aSAH and 241 without aSAH. Exclusions comprised cases with arteriovenous malformation, arteriovenous fistula, or Moyamoya disease (n = 11); dissecting aneurysms (n = 20); and intracranial hemorrhage of unknown origin (n = 10). Among the 86 patients with aSAH, an additional 20 were excluded due to the inability to identify ruptured aneurysms (n = 17) or the unavailability of imaging (n = 3). The remaining 66 patients presented with 66 R-MIAs and 96 U-MIAs.

3.2. Baseline characteristics

The analysis of MIA rupture risk factors was conducted in two steps. In the first step, patients were divided into ruptured and unruptured groups, and univariate statistics were performed. Demographic characteristics and results of the univariate analysis for patient-related factors associated with MIA rupture are presented in **Table 1**.

Table 1. Patient characteristics and univariate analysis for patient-related factors associated with MIA rupture

Variable	Ruptured (*n* = 86)	Unruptured (*n* = 241)	Univariate analysis *P*-value
Gender			0.163
Female	69 (80.2)	175 (72.6)	
Male	17 (19.8)	66 (27.4)	
Age (years)			
Mean ± SD	55.7 ± 10.5	56.3 ± 10.1	0.608
< 45	11 (12.8)	31 (12.9)	0.341
45–60	47 (54.7)	111 (46.1)	
≥ 60	28 (32.6)	99 (41.1)	
Body mass intake (kg/m²)			
Mean ± SD	24.6 ± 2.9	25.3 ± 3.5	0.125
< 28	78 (90.7)	182 (75.5)	0.003
≥ 28	8 (9.3)	59 (24.5)	

Table 1 (Continued)

Variable	Ruptured (*n* = 86)	Unruptured (*n* = 241)	Univariate analysis *P*-value
Smoking			0.872
Yes	20 (23.3)	54 (22.4)	
No	66 (76.7)	187 (77.6)	
Alcohol intake			0.202
Yes	20 (23.3)	41 (17.0)	
No	66 (76.7)	200 (83.0)	
Hypertension			0.137
Yes	54 (62.8)	129 (53.5)	
No	32 (37.2)	112 (46.5)	
Hyperlipidemia			0.073
Yes	5 (5.8)	31 (12.9)	
No	81 (94.2)	210 (87.1)	
Diabetes mellitus			0.915
Yes	10 (11.6)	27 (11.2)	
No	76 (88.4)	214 (88.8)	
Cardio-cerebral vascular incident			0.179
Yes	10 (11.6)	43 (17.8)	
No	76 (88.4)	198 (82.2)	

Abbreviation: SD, standard deviation.

In the ruptured group, characteristics were further compared between R-MIAs and U-MIAs.

3.3. Univariate analysis

Univariate analysis (**Table 2**) revealed significant associations between the rupture risk of MIAs and BMI (P = 0.014), irregular shape (P = 0.026), size (P < 0.001), AR (P = 0.014), SR (P < 0.001), and BNF (P < 0.001).

Table 2. Univariate analysis for aneurysm-related factors associated with MIA rupture [*n* (%)]

Variables	R-MIAs (*n* = 66)	U-MIAs (*n* = 96)	*P*-value
Irregular shape			0.026
Yes	20 (30.3)	15 (15.6)	
No	46 (69.7)	81 (84.4)	
Types			0.200
Bif	18 (27.3)	18 (18.8)	
SW	48 (72.7)	78 (81.2)	
Locations			0.086
AC	51 (77.3)	84 (87.5)	
PC	15 (22.7)	12 (12.5)	

Abbreviations: Bif, aneurysms located at major bifurcations in the cerebral vessel; SW, aneurysms originating from only one parent vessel or from the origin of a small branch whose caliber was less than one-fifth of the parent vessel; AC, anterior circulation; PC, posterior circulation.

3.4. ROC analysis

ROC analysis for aneurysm morphological parameters is summarized in **Table 3**. Size (AUC = 0.722; 95% CI, 0.640–0.803), SR (AUC = 0.735; 95% CI, 0.656–0.815), and BNF (AUC = 0.708; 95% CI, 0.622–0.794) emerged as superior morphologic predictors of MIA rupture compared to AR (AUC = 0.628; 95% CI, 0.540–0.715) and H/W (AUC = 0.507; 95% CI, 0.416–0.598).

Table 3. Results from univariate and ROC analyses for aneurysm morphological parameters

Variables	Aneurysms			ROC analysis		
	R-MIAs	U-MIAs	*P*-value	AUC (95% CI)	Threshold	*P*-value
Size (mm)	6.5 ± 3.8	4.1 ± 3.0	< 0.001	0.722 (0.640–0.803)	4.6	< 0.001
AR	1.3 ± 0.7	1.1 ± 0.6	0.014	0.628 (0.540–0.715)	1.1	0.006
SR	2.0 ± 1.3	1.1 ± 0.8	< 0.001	0.735 (0.656–0.815)	1.7	< 0.001
H/W	1.1 ± 0.6	1.1 ± 0.6	0.877	0.507 (0.416–0.598)	1.4	0.875
BNF	1.2 ± 0.4	1.0 ± 0.3	< 0.001	0.708 (0.622–0.794)	1.1	< 0.001

Abbreviations: ROC, receiver operating characteristic; AUC, the area under the receiver operating characteristic curve; R-MIAs, ruptured multiple intracranial aneurysms; U-MIAs, unruptured multiple intracranial aneurysms; AR, aspect ratio; SR, size ratio; H/W = height/width; BNF, bottleneck factor.

4. Discussion

This study identifies lean BMI, aneurysms with an irregular shape, larger size, increased size ratio (SR), and greater bottleneck factor (BNF) as significant predictors of MIA rupture. These findings suggest that patients exhibiting these risk factors face an elevated risk of rupture, which is crucial for evaluating rupture risk and guiding treatment decisions in clinical practice.

4.1. Patient-related factors of MIA rupture

Gender is a recognized risk factor for both aneurysm formation and rupture. Juvela *et al.* [9] found that aneurysms in females grow significantly more than those in males. Similarly, De Rooij *et al.* [10] reported a higher incidence of aSAH in females, particularly those over 55 years old, likely linked to hormonal changes affecting collagen formation in blood vessels. Consistent with prior studies on MIAs [11,12], the findings confirm that females experience higher rates of aSAH. However, no significant differences were observed in rupture rates between sexes, possibly due to variations in age and geographical distribution among studies.

Smoking has been identified as a significant risk factor for ruptured aneurysms [6,7,13-16]. Mechanisms for this relationship include increased systemic coagulability, arterial inflammation, acute blood pressure spikes, and elastin degradation [13,16,17]. However, no association between smoking and MIA rupture was found in this study, which may be attributed to information bias or confounding factors. Flor *et al.* [17] reported a strong positive association between cigarette smoking and aSAH, especially in females, which was virtually eliminated within a few years of smoking cessation. The proportion of female smokers and the confounding effect of current or previous smoking may have influenced the results.

The relationship between hypertension and aneurysm formation or rupture remains controversial [11]. While some studies suggest hypertension contributes to aneurysm rupture, others report no significant long-term impact [7]. No significant differences in hypertension prevalence were observed between ruptured and unruptured groups in this study, possibly reflecting improved management of hypertension in patients with unruptured MIAs. Additionally, saccular lesions may form and rupture even in the absence of persistent hypertension [18]. Experimental studies by Signorelli *et al.* [19] demonstrated that sudden, temporary spikes in blood pressure, rather than chronic hypertension, could be significant triggers for aSAH.

Few studies have investigated BMI as a risk factor for aSAH. Vlak *et al.* [20] found that lower BMI was associated with a higher risk of aSAH, a conclusion supported by this research. A large population study in Finland similarly reported that overweight (BMI 25.0–29.9) and obese (BMI ≥ 30.0) individuals had a lower risk of developing aSAH during follow-up, with hazard ratios of 0.6 and 0.7, respectively, compared to individuals with a BMI of 18.5–24.9 [21]. Further studies are necessary to validate this relationship and explore the underlying pathological mechanisms.

4.2. Aneurysm-related factors in MIA rupture

Previous studies have identified aneurysm-related factors associated with rupture by comparing ruptured and unruptured aneurysms. However, patient-related factors such as sex and hypertension can introduce confounding effects. This study mitigated such confounding by analyzing characteristics of ruptured and unruptured aneurysms within the same cohort of MIA patients.

The irregular shape is widely recognized as a predictor of rupture risk. A follow-up study of 6,606 unruptured aneurysms in Japan reported that irregular aneurysms had a 1.48-fold higher rupture risk than regular ones [22]. Similarly, a self-controlled study [23] found a 16.45-fold increase in rupture risk for irregularly shaped aneurysms, even after controlling for demographic factors. Hemodynamic analyses [24] have demonstrated that blebs often localize in the inflow jet region, leading to lower wall shear stress and higher oscillatory shear index, both of which contribute to the rupture process.

Aneurysm size is another critical factor in rupture risk. In this study, the mean sizes of ruptured MIAs (R-MIAs) and unruptured MIAs (U-MIAs) were 6.5 mm and 4.1 mm, respectively, with a critical rupture size of 4.6 mm. Jagadeesan *et al.* [25] reported that aneurysms ≤ 7 mm accounted for 75.3% of ruptured MIAs, while the International Study of Unruptured Intracranial Aneurysms (ISUIA) found only 2.5% of ruptured aneurysms were ≤ 7 mm [26]. This suggests that MIAs may rupture at smaller sizes compared to single intracranial aneurysms, a conclusion supported by additional studies [7,27].

Among morphological parameters, size ratio, and bottleneck factor had the highest predictive value (AUC > 0.7) [7,28]. Higher size ratios were associated with increased rupture risk, consistent with prior research [7]. The bottleneck factor has also emerged as a promising parameter for rupture risk assessment. A larger bottleneck factor may indicate a higher rupture risk, a finding corroborated by Pei *et al.* [7]. Further studies are required to validate the role of the bottleneck factor in intracranial aneurysms.

4.3. Strengths and limitations

This study benefits from a large patient cohort and detailed assessments of ruptured aneurysms by experienced neurologists, ensuring representative and objective analyses. However, limitations must be noted. The retrospective design and single-center nature of the study may introduce selection bias. Additionally, factors such as size, aspect ratio, size ratio, height-to-width ratio, bottleneck factor, and irregularity could have been altered by the rupture event itself. Nevertheless, previous research suggests that aneurysm size and shape remain largely unaffected by rupture [29,30]. Lastly, the calculation of size ratios may be influenced by parent vessel vasospasm, leading to potential bias. Prospective, multicenter studies with larger sample sizes are necessary to confirm these findings.

5. Conclusions

Lean BMI, irregular shape, larger size, increased size ratio, and greater bottleneck factor were identified as significant predictors of MIA rupture. These risk factors require further validation through prospective, multicenter studies with larger cohorts.

Disclosure statement

The authors declare no conflict of interest.

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