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Morphological characteristics associated with rupture risk of multiple intracranial aneurysms

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ABSTRACT

Objective: To identify the morphological parameters that are related to intracranial aneurysms (IAs) rupture using a case-control model.

Methods: A total of 107 patients with multiple IAs and aneurysmal subarachnoid hemorrhage between August 2011 and February 2017 were enrolled in this study. Characteristics of IAs location, shape, neck width, perpendicular height, depth, maximum size, flow angle, parent vessel diameter (PVD), aspect ratio (AR) and size ratio (SR) were evaluated using CT angiography. Multiple logistic regression analysis was used to identify the independent risk factors associated with IAs rupture. Receiver operating characteristic curve analysis was performed on the final model, and the optimal thresholds were obtained.

Results: IAs located in the internal carotid artery (ICA) was associated with a negative risk of rupture, whereas AR, SR1 (height/PVD) and SR2 (depth/PVD) were associated with increased risk of rupture. When SR was calculated differently, the odds ratio values of these factors were also different. The receiver operating characteristic curve showed that AR, SR1 and SR2 had cut-off values of 1.01, 1.48 and 1.40, respectively. SR3 (maximum size/PVD) was not associated with IAs rupture.

Conclusions: IAs located in the ICA are associated with a negative risk of rupture, while high AR (>1.01), SR1 (>1.48) or SR2 (>1.40) are risk factors for multiple IAs rupture.

1. Introduction

Although most intracranial aneurysms (IAs) are usually asymptomatic and silent and the annual rupture rate is extremely low [1], aneurysmal subarachnoid hemorrhage is associated with a high morbidity and mortality rate when ruptures occur [2]. However, we cannot manage all unruptured IAs (UIAs) to prevent a potentially catastrophic hemorrhage because treatment (microsurgical clipping or endovascular coiling) is very costly and also associated with risks [2]. Thus far, the treatment of UIAs remains a controversial topic.

The question remains why a given aneurysm ruptures but another aneurysm remains stable. Therefore, identifying the risk factors for UIAs is of great clinical value. Previous studies have reported that clinical characteristics affecting aneurysm rupture can include old age [3], female gender [3], hypertension [4,5] and smoking [6]. Other researchers, however, have reported that these demographic variables were not associated with aneurysm rupture [7–9]. Morphological characteristics (*e.g.*, size) have been thought to play an important role in aneurysm ruptures [3,6,8,10,11]. However, many researchers have reported that most ruptured IAs (RIAs) are small [12–14]. These different results may be due to differences among individual patients, and such confounding clinical characteristics may lead to statistical bias. Identification of patients' clinical characteristics would be a more reliable basis for investigating the morphological characteristics associated with risk factors for the rupture of IAs. In this study, we use a case-control study model in patients with multiple IAs (MIAs, one ruptured and one or more unruptured) to identify rupture risk; then, the morphological characteristics can be directly compared between RIAs and UIAs without patient-related bias.

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2. Participants and methods

2.1. Patients

The present study was approved by our institutional ethics committee. All patients' family member signed written informed consent before participating in the experiments. At our institute from August 2011 to February 2017, 116 consecutive patients with the diagnosis of aneurysmal subarachnoid hemorrhage (SAH) and more than one IA on CT angiography (CTA) were selected. The ruptured aneurysm was determined based on the CT, angiographic or operative findings. Two chief neurosurgeons who were blind to the patients' conditions confirmed the ruptured aneurysm. If a disagreement occurred, a third chief neurosurgeon was consulted. Exclusion criteria were (1) mycotic, traumatic, fusiform aneurysms, or those associated with arteriovenous malformations (n = 4); (2) poor image quality (n = 3); or (3) an inability to identify which aneurysm ruptured (n = 2). Finally, 107 patients with 228 IAs (107 ruptured and 121 unruptured) were available for analysis. All RIAs were treated with microsurgical clipping or endovascular coiling.

2.2. CTA and image analysis

In our center, all patients except those with traumatic SAH undergo CTA to investigate the causes of SAH. All CTAs were performed on a 64-multidetector CT machine (GE Healthcare). All of the CT image data were transferred to the GE Advantix workstation (Advantage Windows 4.5) for postprocessing to generate three-dimensional (3D) volume rendering. The 3D volume rendering images could be rotated for assessment of IAs' characteristics. In addition to assessment of the locations, bifurcation (or not) and shape (simple lobed or irregular) of the IAs, two neuroradiologists found the best view angle to measure IAs morphological indices, including neck width (the largest cross-sectional diameter of the aneurysm neck), height (the largest perpendicular distance from the neck plane to the dome), depth (the longest diameter between the neck and dome), maximum size (Dmax, the largest measurement in terms of maximum dome diameter or width), flow angle (angle between the vector of depth of the aneurysm, and the vector of the centerline of the parent artery) and parent vessel diameter (PVD, the largest cross-sectional diameter of the vessel). Two secondary geometric indices were calculated: aspect ratio (AR, depth/neck width) and size ratio (SR1, height/PVD; SR2, depth/PVD; and SR3, maximum size/PVD). Notably, SR1, SR2 and SR3 were used for statistics and further analysis. These variables and measurement methods have been defined and depicted in previous literature [13–19]. Average values were used for subsequent statistical analyses.

2.3. Statistical analysis

The data were analyzed using the SPSS 17.0 (IL, USA). $P < 0.05$ was considered statistically significant. Inter-observer agreement in morphological characteristics values was compared by using the chi-squared tests and Student's t tests or Mann–Whitney U tests. Categorical data were expressed as n (%) of aneurysms and were compared using *chi*-squared tests. Continuous data were expressed as the means ± standard deviation and were compared using Student's t tests (for normally distributed data) or Mann–Whitney U tests (for abnormally distributed data). Conditional, forward multiple logistic regression was used to calculate the independent risk factors associated with IAs rupture. Then, receiver operating characteristic curve analysis was performed on the final model to determine the optimal sensitivity and specificity and the cut-off point.

3. Results

A total of 107 patients with MIAs and aneurysmal SAH were available for analysis. Of these patients, 80 were female and 27 were male (a 3:1 ratio of females to males). The mean age was (57.33 ± 11.33) years for both genders, with (59.11 ± 11.48) years for females (range, 33–83 years) and (52.04 ± 9.00) years for males (range, 41–78 years).

The level of agreement between the two observers for numerical measurements was satisfactory ($P > 0.05$). The geometric and morphological characteristics of RIAs and UIAs are listed in Table 1. The following characteristics were all associated with rupture risk ($P < 0.05$): location in the posterior

Table 1

Morphological features of aneurysms.

Factors	Aneurysm groups		P
	Unruptured (n = 121)	Ruptured (n = 107)	
Location			
ACoA	10 (8.3%)	11 (10.3%)	0.651
ACA	4 (3.3%)	6 (5.6%)	0.601
MCA	38 (31.4%)	29 (27.1%)	0.560
PComa	29 (24.0%)	49 (45.8%)	0.001
ICA	36 (29.7%)	8 (7.5%)	<0.001
PCC	4 (3.3%)	4 (3.7%)	1.000
Bifurcation	60 (49.6%)	66 (61.7%)	0.083
Irregular shape	27 (22.3%)	70 (65.4%)	<0.001
Neck width	3.99 ± 1.41	4.79 ± 1.72	<0.001
Height	3.57 ± 1.90	6.36 ± 2.80	<0.001
Depth	3.84 ± 2.10	6.87 ± 2.95	<0.001
Maximum diameter	4.93 ± 2.43	7.98 ± 3.17	<0.001
Aspect ratio	0.96 ± 0.36	1.49 ± 0.56	<0.001
Flow angle	112.74 ± 28.33	115.64 ± 26.64	0.428
Parent vessel diameter	3.48 ± 0.89	3.29 ± 0.93	0.114
Size ratio1	1.06 ± 0.52	2.07 ± 1.02	<0.001
Size ratio2	1.13 ± 0.58	2.24 ± 1.10	<0.001
Size ratio3	1.47 ± 0.71	2.58 ± 1.15	<0.001

ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PComa, posterior communicating artery; ICA, internal carotid artery; PCC, posterior cerebral circulation.

Table 2

Multiple logistic regression model for prediction of aneurysm rupture.

Characteristics	*OR*	*P*	95% *CI*	β
Size ratio1 entered				
ICA	0.254	0.021	0.079–0.816	−1.372
Aspect ratio	4.303	0.004	1.601–11.567	1.459
Size ratio1	4.239	<0.001	2.153–8.348	1.444
Size ratio2 entered				
ICA	0.269	0.027	0.084–0.860	−1.314
Aspect ratio	4.211	0.005	1.538–11.525	1.438
Size ratio2	3.713	<0.001	1.982–6.954	1.312
Size ratio3 entered				
ICA	0.107	<0.001	0.033–0.353	−2.232
Depth	1.446	<0.001	1.187–1.760	0.369
Aspect ratio	4.968	0.003	1.745–14.147	1.603

CI, confidence interval; β, partial regression coefficient.

Table 3

Area under curve for aspect ratio and size ratio.

Characteristics	Area	Threshold value	*P*	Sensitivity (%)	Specificity (%)	95% *CI*
Aspect ratio	0.805	1.01	<0.001	85.0	66.1	0.748–0.862
Size ratio1	0.839	1.48	<0.001	73.8	84.3	0.786–0.891
Size ratio2	0.842	1.40	<0.001	80.4	76.9	0.789–0.894

CI, confidence intervals; threshold value, the cut off for the aspect ratio and size ratio.

communicating artery and internal carotid artery (ICA), irregular shape, neck width, perpendicular height, depth, maximum size, AR, SR1, SR2 and SR3. These variables were then entered into a forward conditional multiple logistic regression model (Table 2). When SR1 was used in this model, the model showed that IAs located in ICA [odds ratios (*OR*) 0.254] were associated with a negative risk of aneurysm rupture and that AR (*OR* 4.303) and SR1 (*OR* 4.239) increased the risk of aneurysm rupture. When SR2 was used in the model, the results were similar to those for SR1: ICA (*OR* 0.269), with AR (*OR* 4.211) and SR2 (*OR* 3.713) associated with IAs rupture. However, when SR3 was used in the model, SR3 was not significantly associated with rupture. In contrast, ICA (*OR* 0.107), depth (*OR* 1.446) and AR (*OR* 4.968) were independently significant parameters for rupture.

The threshold values of AR, SR1 and SR2 were 1.01, 1.48 and 1.40, respectively, and the AUC values for these variables were 0.805, 0.839 and 0.842, respectively (Table 3).

4. Discussion

Selecting a unique risk factor for predictive IAs rupture remains extremely difficult. The treatment decisions made for an unruptured aneurysm should consider referring to many factors, such as patient's age, history of hypertension, smoking and alcohol consumption, and especially the size and location of the IAs. In this study, we investigate ruptured aneurysms among MIAs. The advantages of this case-controlled model were that the patients acted as their own controls and that all of the IAs were exposed to the same internal milieu. We found that IAs located in the ICA were negatively correlated with rupture, while a high AR or SR was associated with rupture.

Most previous studies have reported a higher AR in RIAs than in UIAs [13,14,19–24] but not all studies showed that a high AR was associated with IAs rupture [15,25]. Additionally, there is no consensus on the common threshold value of AR. One previous study reported that 52.44% of RIAs showed a higher AR (>1.6) and that 66.22% of UIAs showed a small AR (<1.6), whereas 19.82% of RIAs had an AR <1.6, and 33.78% of UIAs had an AR >1.6 [23]. Similar to our study, four previous studies investigating MIAs with aneurysmal SAH demonstrated that a high AR was associated with aneurysm rupture; the AR threshold values were 1.3 [19], 1.064 [20], 1.3 [21], and 1.6 [24]. In this study, AR was an independently significant parameter for rupture; our data showed that AR >1.01 was associated with aneurysm rupture, which is consistent with a Chinese study [20]. Although used 3D reconstructed images nowadays, the AR threshold value was not yet confirmed. The reason for this may be associated with regional factors.

A previous study reported that the treatment decision regarding UIAs is based mainly on size and location [26]. Some studies believed that IAs located in the posterior communicating artery or anterior communicating artery were significantly associated with rupture [15,25]. In this study, IAs location in the posterior communicating artery was significantly associated with rupture by *chi*-squared test analysis; however, this factor was no longer significant upon multiple analysis. In contrast, IAs located in the ICA correlated negatively with rupture risk. This finding seems to be because the ICA has a larger diameter than other sites; IAs arising from a smaller artery have a thinner wall and may experience greater wall tension, thus being more prone to rupture [14,27]. SR is known to reflect not only the size but also the vessel geometry of the IAs. However, the SR measurement is not uniform. Recently, two studies using a case-control model indicated that SR2 (depth/PVD) is an important risk factor for rupture, with threshold values of 1.8 and 1.5 [15,19]. Previous studies have shown that SR3 (maximum size/PVD) > 3 was associated with IAs rupture and that sensitivity and specificity were 69% and 75%, respectively [7]. In this study, we found that SR1 and SR2 were significant parameters and that threshold values were 1.48 and 1.40, which are smaller than those reported in previous studies [15,19], but with higher sensitivity and specificity. However, this study showed that SR3 was not significantly associated with IAs rupture in a multiple logistic regression model, which is consistent with a previous study [19]. If SR is an independent risk factor, the calculation methods of SR1 and SR2 may be more accurate than those for SR3.

In summary, we compared morphological characteristics of RIAs and UIAs in the same patients with MIAs in this case-control model. This model allowed us to exclude the patients' own risk factors. We found that IAs located in the ICA correlated negatively with rupture risk, on the other hand, since aneurysms with a high AR and a high SR (SR1 or SR2) were independently associated with the rupture status of MIAs.

A significant limitation of this study is that it is a retrospective study with a small sample size, and certain IAs have already ruptured, so we cannot be certain whether the aneurysm size or shape has changed after rupture, though a previous study reported that aneurysms do not shrink in size after rupture [27]. Another limitation to our analysis is that RIAs may lead to parent vessel vasospasm and over-valuated SR, possibly resulting in bias. However, one previous study showed that the parent vessel vasospasm occurred approximately 5 days after rupture [28]. Additionally, we used CTA data in this study and did not compare it with digital subtraction angiography, which has been considered the gold standard for IAs detection and evaluation. However, given its non-invasive nature and similar sensitivity and specificity for the detection and evaluation of IAs, CTA is being used increasingly [24]. Thus, we believe that the chances of misdiagnosis and misevaluation of IAs by CTA should be acceptably small. In the future, a further self-control model and prospective study with a large multicenter sample size is needed. All these are under our investigation.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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