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Risk factors for ruptured intracranial aneurysms

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***Background & objectives*: The treatment of unruptured intracranial aneurysms (IAs) remains controversial; the ability to predict the risk of rupture for an aneurysm would be of clinical value. The aim of this study was to determine and evaluate the predictive value of the risk factors of IA rupture.**

***Methods*: This retrospective study involved 379 consecutive patients with 441 aneurysms between August 2011 and July 2014. Based on clinical data and computed tomography angiography findings, the potential of risk factors to predict the aneurysmal rupture was assessed using statistical methods.**

***Results*: Age, hypertension, heart disease, diabetes mellitus, cerebral atherosclerosis, aneurysms located at the internal carotid artery (ICA) and neck width (*N*) correlated negatively with rupture risk. Aneurysms located at the anterior communicating artery, bifurcation, irregularity, with a daughter sac, aneurysm height, maximum size, aspect ratio (AR), height-to-width ratio and bottleneck factor were significantly and positively correlated with rupture risk. The multivariate logistic regression model revealed that bifurcation aneurysm, irregular aneurysm and high AR increased the rupture risk, while cerebral atherosclerosis, aneurysm located on the ICA and greater *N* decreased the risk. Receiver operating characteristic analysis of AR curve values differed according to circumstances.**

***Interpretation & conclusions*: Cerebral atherosclerosis, location in the ICA and larger *N* were the protective factors against aneurysm rupture, and IAs located at bifurcations, irregular shape and increased AR indicated a greater rupture risk.**

Key words Angiography - computed tomography - intracranial aneurysm - risk factors - rupture - subarachnoid haemorrhage

Intracranial aneurysms (IAs) are abnormal dilations of the arteries in the brain that usually occur at Willis' circle or at arterial bifurcations[1]. The universal usage of non-invasive imaging methods has led to an increase in the number of unruptured intracranial aneurysms (UIAs) found by chance[2]. IAs affect 3-8 per cent of the world's population[3], with ruptured intracranial aneurysms (RIAs) being the most common cause of subarachnoid haemorrhage (SAH) and causing a mortality rate of 40-50 per cent and a morbidity rate of 10-20 per cent[4]. While this suggests that UIAs should be treated to prevent SAH, the surgical and endovascular treatments for UIAs are with risk, with mortality and morbidity rates of up to 5 per cent[5]. The optimal UIA management strategy remains open to debate. The decision to treat incidental UIAs must be balanced against the risk of rupture. Thus, the ability to predict the risk of rupture for a given incidentally detected aneurysm would be of enormous clinical value. A number of researchers have focussed on evaluating the role of dynamic blood flow[1,6]; however, this requires prospective follow up to monitor the haemodynamic changes of IAs, which is very difficult and often unavailable due to considerations of expense, time and ethical issues[6]. Therefore, it is important to consider other morphological indices and personal or familial factors when evaluating the risk factors for aneurysm rupture, including aspect ratio (AR), cigarette smoking, alcohol consumption and hypertension[7]. The imaging patterns of IAs in the Chinese population have been described that might be related to rupture[8].

The purpose of this study was to determine the patient-related factors and image characteristics of IAs to identify the risk factors of aneurysm rupture.

Material & Methods

The data included in this retrospective study were extracted from the hospital medical records of Xinqiao Hospital, Third Military Medical University, PR China. Details of age, sex, personal history of hypertension, heart disease, diabetes mellitus, cerebral atherosclerosis, alcohol consumption, cigarette smoking and history of SAH were extracted from clinical records. The patients' records/information was anonymized and de-identified before analysis. The study protocol was approved by the institutional ethics committee.

Between August 2011 and July 2014, a total of 9050 consecutive patients underwent head computed tomography angiography (CTA) examinations in Xinqiao Hospital, and a total of 435 patients were diagnosed with aneurysms. The patients with aneurysms were managed with both observation and treatment by coiling or clipping. Overall, 56 patients were excluded based on the following criteria: patients with traumatic, mycotic, fusiform or extradural aneurysms; aneurysms with poor-image quality and aneurysms with a maximum diameter <1.8 mm (too small to measure accurately). Thus, 379 patients with 441 aneurysms (326 patients with single aneurysm and 53 patients with multiple aneurysms; of the 53 patients, 45 patients had two aneurysms, seven patients had three aneurysms and one patient had four aneurysms) were included in the analysis. In cases with multiple aneurysms, the ruptured aneurysm was determined based on the location of the haemorrhage in CTA or operative findings.

Computed tomography angiography

IAs were diagnosed and evaluated with CTA using a 64-slice CT machine (GE LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA). A quantity of 80 ml of non-ionic contrast medium (Visipaque 320; GE Healthcare) was injected into the antecubital vein at a rate of 4-4.5 ml/sec with an 18G needle and an automatic injector (Medrad; Warrendale, PA, USA). Images were then obtained with a 0.625 mm slice thickness with no overlap and transferred to the GE Advantix Workstation (Advantage Windows 4.5) for three-dimensional (3D) volume rendering (VR).

Image analysis: Aneurysms were found in a variety of locations, including anterior cerebral artery, anterior communicating artery (ACoA), posterior communicating artery, internal carotid artery (ICA), middle cerebral artery and posterior cerebral circulation (consists of superior cerebellar artery, anterior inferior cerebellar artery, basilar artery, basilar top and posterior cerebral artery). Side-wall aneurysms were defined as lesions located in only one parent vessel or at a branch that was much smaller than the parent vessel (<1/5th of the diameter)[9]. Bifurcation aneurysms were defined as lesions originating from major bifurcations[10]. Aneurysm shapes were classified as simple lobed or irregular, with lobular aneurysms or aneurysms with daughter sacs classified as irregular[11].

The geometric indices of IAs on 3D VR images were measured independently manually by two neuroradiologists. The following four dimensions were measured in the plane parallel to the blood flow of the parent arteries: aneurysm depth (*D*, the longest diameter between the neck and dome); width (*W*, the maximum distance vertical to *D*); neck width (*N*)[10] and maximum size (*Dmax*, the largest measurement in terms of maximum dome diameter or width)[12]. Subsequently, the aspect ratio (AR, the ratio of *D*-to-*N*), the depth-to-width ratio (DW, the ratio of *D*-to-*W*) and the bottleneck factor (BF, the ratio of *W*-to-*N*) were calculated[7,10,11,13,14].

Statistical analysis: The size of sample was calculated according to the formula: $N=2\pi(1-\pi)(z_\alpha+z_\beta)^2/(p_1-p_0)^2$ (*N*, the size of the sample; α, probability of type-I error; β, probability of type-II error; z_α and z_β, the standard normal table value of α and β; p_1 and p_0, case and control group exposed to the factors of exposure rate)[15]. According to the results of the preliminary experiment and previous research[7,13,14], we made age (<60 yr), hypertension and cerebral atherosclerosis as the main indicators, $N_{age}=121$[13], $N_{hypertension}=153$[7], $N_{cerebral\ atherosclerosis}=108$[14]. There were 379 consecutive patients in the study. Statistical analysis was carried out using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Independent *t* test were used to compare the means of continuous data.

The Chi-square tests were used to compare categorical data. Multiple logistic regression analysis was applied considering ruptured (or unruptured) variable as dependent variable and patients' and morphological characteristics as independent variables selected by the step forward method[14]. The odds ratios (ORs) and 95 per cent confidence intervals (CIs) were also calculated. Receiver operating characteristic (ROC) analysis was performed on the final model, and the optimal sensitivity and specificity of competent parameters were obtained by determining the cut-off point using the maximizing Youden's index.

Results

The demographic characteristics of the patients are reported in Table I. The age of the 379 patients was 57.6±12.88 years Of the 379 patients, there were 188 patients with RIAs and 191 with UIAs. Two hundred and forty patients were women (mean age: 58.1±12.98 yr) and 139 (36.7%) were men (mean age: 56.9±12.71 yr). Age, hypertension, heart disease, diabetes mellitus and cerebral atherosclerosis were individually in univariate analyses and found to be related to RIAs (P<0.05).

Table I. Patient characteristics with ruptured and unruptured aneurysms

Factors	Patient groups	
	Unruptured (n=191), n (%)	Ruptured (n=188), n (%)
Female	116 (60.7)	124 (66.0)
Age (<60 yr)	94 (49.2)	125 (66.5)***
Hypertension	89 (46.6)	62 (33.0)**
Heart disease	13 (6.8)	4 (2.1)*
Diabetes mellitus	16 (8.4)	4 (2.1)**
Cerebral atherosclerosis	60 (31.4)	8 (4.3)***
Alcohol history	35 (18.3)	44 (23.4)
Cigarette smoking	43 (22.5)	45 (23.9)
Bleeding history	7 (3.7)	6 (3.2)
Multiple aneurysms	23 (12.0)	30 (16.0)

P *<0.05 **<0.01 ***<0.001 compared to unruptured group

The morphologic features of aneurysms are listed in Table II. ACoA, bifurcation, irregular

Table II. The morphological features of aneurysms

Factors	Aneurysm groups		P
	Unruptured (n=253)	Ruptured (n=188)	
Categorical data			
Location, n (%)			
ACoA	21 (8.3)	57 (30.3)	<0.001
ACA	13 (5.2)	15 (8.0)	0.226
MCA	36 (14.2)	26 (13.8)	0.905
PCoA	67 (26.5)	63 (33.5)	0.109
ICA	105 (41.5)	17 (9.1)	<0.001
PCC	11 (4.3)	10 (5.3)	0.636
Bifurcation	91 (36.0)	128 (68.1)	<0.001
Irregular shape	77 (30.4)	127 (67.6)	<0.001
Daughter sac	52 (20.6)	93 (49.5)	<0.001
Continuous data			
Depth (mm)	5.49±4.2	6.39±3.34	<0.001
Width (mm)	5.42±4.07	5.48±3.51	<0.001
Neck width (mm)	4.77±2.24	4.14±1.69	<0.001
Maximum diameter (mm)	6.74±4.63	7.51±3.72	<0.001
AR	1.12±0.54	1.61±0.67	<0.001
Depth/width ratio	1.04±0.32	1.26±0.43	<0.001
Bottleneck factor	1.09±0.44	1.34±0.55	<0.001

Data are expressed as the number of patients (%) or as mean±SD. 326 patients with single aneurysms and 53 patients with multiple aneurysms. ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCoA, posterior communicating artery; ICA, internal carotid artery; PCC, posterior cerebral circulation; SD, standard deviation; AR, aspect ratio

Table III. Multiple logistic regression model for prediction of aneurysm rupture

Characteristics	OR	*P*	95% CI	*B*
Cerebral atherosclerosis	0.107	<0.001	0.046-0.248	−2.237
ICA	0.798	0.002	0.692-0.920	−0.226
Bifurcation	2.646	0.001	1.518-4.613	0.973
Irregular shape	3.478	<0.001	1.942-6.229	1.246
Neck width	0.755	<0.001	0.653-0.873	−0.281
AR	2.484	<0.001	1.576-3.917	0.910

CI, confidence interval; ICA, internal carotid artery; *B*, partial logistic coefficient; OR, odds ratio; AR, aspect ratio

shape, daughter sac, *D*, *Dmax*, AR, DW and BF were significantly ($P<0.001$) higher among ruptured aneurysms compared to unruptured ones. ICA and *N*, on the contrary, were significantly ($P<0.001$) higher in unruptured aneurysms.

The 17 variables ($P<0.05$) were entered into the forward stepwise multiple logistic regression model. This analysis revealed that bifurcation (OR 2.646), irregularity (OR 3.478) and AR (OR 2.484) strongly affected the risk of aneurysm rupture, while cerebral atherosclerosis (OR 0.107), ICA (OR 0.798) and *N* (OR 0.755) were associated with a decreased risk of aneurysm rupture ($P<0.05$) (Table III).

The ROC analysis was performed for continuous data. The resulting curves are presented in Figs 1 and 2. Since the area of *N* under the ROC curve was small, only the threshold values of the AR were calculated. For AR of all aneurysms, bifurcation aneurysms, irregular aneurysms and irregular aneurysms located at bifurcations, the threshold values and the corresponding area under the curve values of the AR are listed in Table IV.

Discussion

Our results showed that cerebral atherosclerosis, location in the ICA and larger *N* were the protective factors against aneurysm rupture, while IAs located at bifurcations, irregular shape and high AR indicated a greater rupture risk. Calcified and atherosclerotic walls are known to decrease the risk of IA rupture[16]. This study also demonstrated an inverse relationship between cerebral atherosclerosis and IA rupture. The reason may be that cerebral atherosclerotic or calcified walls slow the flow rates entering the aneurysm and reduce wall shear stress[17].

The International Study of UIAs showed that decisions regarding UIAs treatment are based mainly

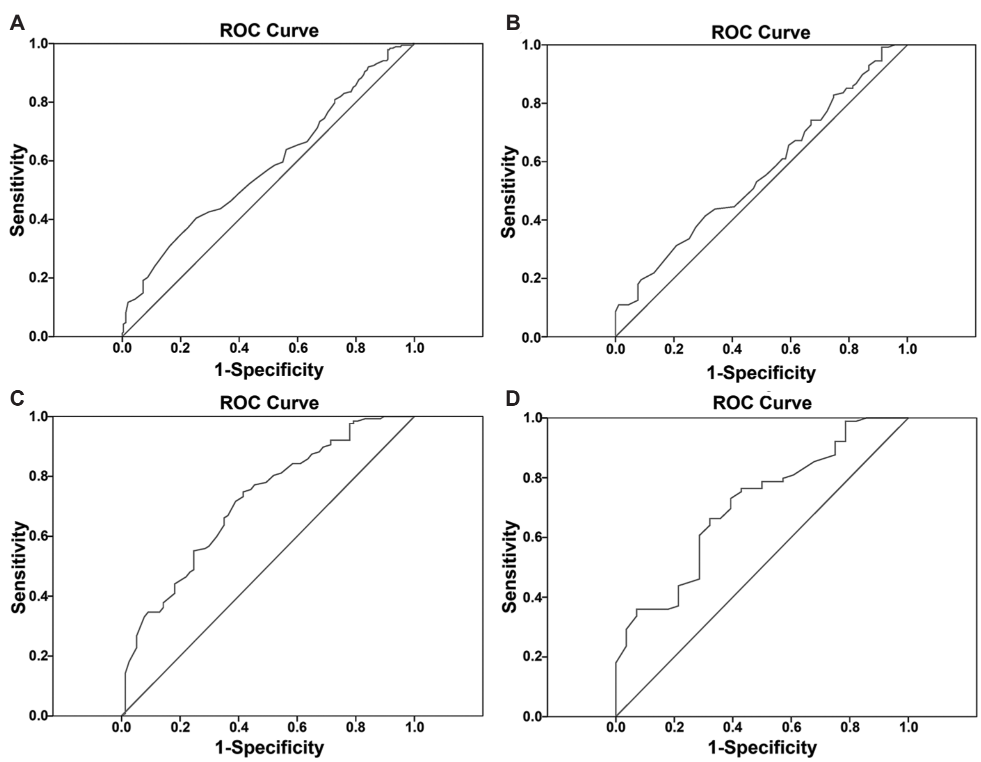

Fig. 1. Receiver operating characteristic curves for binary logistic regression analysis of neck width. Data for (**A**) all aneurysms, (**B**) aneurysms located at bifurcations, (**C**) irregular aneurysms, and (**D**) irregular aneurysms located at bifurcations. The corresponding area under the curve values are 0.583 for (**A**), 0.563 for (**B**), 0.714 for (**C**) and 0.706 for (**D**).

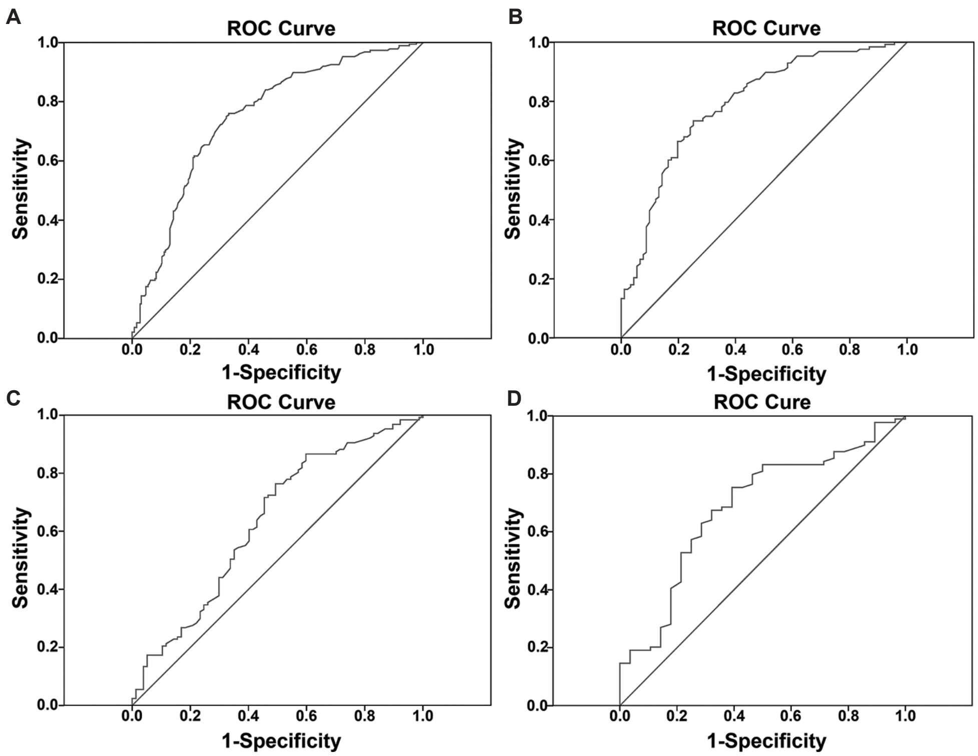

Fig. 2. Receiver operating characteristic curves for binary logistic regression analysis of the aspect ratio. Data for (**A**) all aneurysms, (**B**) aneurysms located at bifurcations, (**C**) irregular aneurysms, and (**D**) irregular aneurysms located at bifurcations. The corresponding area under the curve values are 0.750 for (**A**), 0.792 for (**B**), 0.634 for (**C**) and 0.685 for (**D**).

Table IV. Area under the curve for aspect ratio

Characteristics	AUC	SEs	*P*	95% CI	Threshold	Sen (%)	Spe (%)
All data	0.750	0.023	<0.001	0.705-0.796	1.135	76.1	66.8
Bifurcation	0.792	0.031	<0.001	0.731-0.853	1.14	73.4	74.7
Irregular shape	0.634	0.041	0.001	0.554-0.715	1.305	76.4	50.6
Bifurcation and irregular shape	0.685	0.058	0.003	0.572-0.798	1.265	75.3	60.7

SE, SD of its sampling distribution, or sometimes an estimate of that standard deviation. Threshold value, the cut-off for the AR in different situations, the criteria of cut-point selection are when the value of (sensitivity + specificity − 1) reaches its maximum. Sen, sensitivity, true positive rate; Spe, specificity, true negative rate; CI, confidence interval; AR, aspect ratio; SEs, standard errors; AUC, area under the curve; SD, standard deviation

on the size and location of the aneurysm[18]. It is well known that most UIAs are located in the ICA. In our study, IAs located in the ICA correlated negatively with rupture risk. These results also confirmed that IAs in the ICA seldom rupture. The reason seems that ICA with bigger diameter than other sites and IAs arising from ICA have thicker wall and maybe experience smaller wall tension[19].

Our study showed that aneurysms located at bifurcations ruptured more frequently than those located at the side wall; the reason may be that bifurcation areas of arteries are known to be vulnerable sites, where the wall is weak and haemodynamic stress is changed[20]. An aneurysm with lobular or daughter sacs was classified as having an irregular shape[11] and reported to be associated with a higher rupture risk[21,22]. Our results also showed that irregular IAs were more prone to rupture, possibly because the irregular shape leads to instability of the blood flow pattern.

Some studies examined *N*, with most UIAs and RIAs being 2-3 mm wide at the neck and with no significant difference observed between UIAs and RIAs[21,23]. The previous study showed that among aneurysms of the same depth in the same patient, the aneurysm with a larger N was less likely to rupture[24]. Our data showed that N was negatively correlated with rupture. One reason for this result may be that when the neck is larger, the blood flow is more sluggish.

The AR has been widely studied and shown to correlate with IA rupture. Many researchers have attempted to select an optimal AR threshold value to predict IA rupture. Previous study reported a mean AR of 1.89 in RIAs and 1.39 in UIAs[10]. In contrast, other study reported that the AR of UIAs was greater than that of RIAs (2.3 vs. 1.8)[22]. In our study, the threshold value of AR was smaller than the values reported in the literature[22,24] but close to that reported by Dhar *et al*[25]. In the present study, it was found that in different situations, the AR had different thresholds; these results were more accurate, practical and conducive to treatment than a general threshold.

Although many previous studies have reported that size ratio (SR) was associated with aneurysm rupture[10,25], the calculation method of the parameter is not unified. This ratio was defined as the maximum aneurysm height divided by the mean vessel diameter of all branches associated with the aneurysm[10,25,26]. However, Etminan *et al*[27] defined SR as the *Dmax* divided by parent artery diameter. Our data included side-wall and bifurcation aneurysms, so we did not consider SR as a risk factor in the study.

One limitation of this study was that RIAs might have changed in size or shape after rupture and would therefore, not reflect the data captured before rupture. Another limitation was that this was a retrospective analysis of the medical records from one hospital. In addition, the possibility that the UIAs would rupture in the future could not be excluded, and patients with IAs <1.8 mm were not included. Furthermore, family history was not used as a risk factor to predict IA rupture because this information was not obtained for some patients with SAH.

In conclusion, cerebral atherosclerosis, IAs location in the ICA and larger N were the protective factors against aneurysm rupture. On the other hand, since IAs located at bifurcations, with an irregular shape and a high AR indicated a greater likelihood of rupture, more attention should be paid to the aneurysm with these characteristics during the clinical practice.

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***Conflicts of Interest*:** None.

References

1. Lu G, Huang L, Zhang XL, Wang SZ, Hong Y, Hu Z, *et al*. Influence of hemodynamic factors on rupture of intracranial aneurysms: Patient-specific 3D mirror aneurysms model computational fluid dynamics simulation. *AJNR Am J Neuroradiol* 2011; *32* : 1255-61.
2. Gabriel RA, Kim H, Sidney S, McCulloch CE, Singh V, Johnston SC, *et al.* Ten-year detection rate of brain arteriovenous malformations in a large, multiethnic, defined population. *Stroke* 2010; *41* : 21-6.
3. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: A systematic review and meta-analysis. *Lancet Neurol* 2011; *10* : 626-36.
4. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007; *369* : 306-18.
5. Greving JP, Wermer MJ, Brown RD Jr., Morita A, Juvela S, Yonekura M, *et al.* Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: A pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; *13* : 59-66.
6. Nixon AM, Gunel M, Sumpio BE. The critical role of hemodynamics in the development of cerebral vascular disease. *J Neurosurg* 2010; *112* : 1240-53.
7. You SH, Kong DS, Kim JS, Jeon P, Kim KH, Roh HK, *et al.* Characteristic features of unruptured intracranial aneurysms: Predictive risk factors for aneurysm rupture. *J Neurol Neurosurg Psychiatry* 2010; *81* : 479-84.
8. Lai HP, Cheng KM, Yu SC, Au Yeung KM, Cheung YL, Chan CM, *et al.* Size, location, and multiplicity of ruptured intracranial aneurysms in the Hong Kong Chinese population with subarachnoid haemorrhage. *Hong Kong Med J* 2009; *15* : 262-6.
9. Xiang J, Natarajan SK, Tremmel M, Ma D, Mocco J, Hopkins LN, *et al.* Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. *Stroke* 2011; *42* : 144-52.
10. Baharoglu MI, Lauric A, Gao BL, Malek AM. Identification of a dichotomy in morphological predictors of rupture status between sidewall- and bifurcation-type intracranial aneurysms. *J Neurosurg* 2012; *116* : 871-81.
11. Ryu CW, Kwon OK, Koh JS, Kim EJ. Analysis of aneurysm rupture in relation to the geometric indices: Aspect ratio, volume, and volume-to-neck ratio. *Neuroradiology* 2011; *53* : 883-9.
12. Rahman M, Ogilvy CS, Zipfel GJ, Derdeyn CP, Siddiqui AH, Bulsara KR, *et al.* Unruptured cerebral aneurysms do not shrink when they rupture: Multicenter collaborative aneurysm study group. *Neurosurgery* 2011; *68* : 155-60.
13. Matsukawa H, Uemura A, Fujii M, Kamo M, Takahashi O, Sumiyoshi S, *et al.* Morphological and clinical risk factors

for the rupture of anterior communicating artery aneurysms. *J Neurosurg* 2013; *118* : 978-83.

14. Wang GX, Zhang D, Wang ZP, Yang LQ, Zhang L, Wen L, *et al*. Risk factors for the rupture of bifurcation intracranial aneurysms using CT angiography. *Yonsei Med J* 2016; *57* : 1178-84.
15. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. *Methods in observational epidemiology*. New York: Oxford University Press; 1996. p. 332-4.
16. Inagawa T. Risk factors for the formation and rupture of intracranial saccular aneurysms in Shimane, Japan. *World Neurosurg* 2010; *73* : 155-64.
17. Castro MA, Putman CM, Sheridan MJ, Cebral JR. Hemodynamic patterns of anterior communicating artery aneurysms: A possible association with rupture. *AJNR Am J Neuroradiol* 2009; *30* : 297-302.
18. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr., Piepgras DG, *et al*. Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003; *362* : 103-10.
19. Wang GX, Yu JY, Wen L, Zhang L, Mou KJ, Zhang D, *et al*. Risk factors for the rupture of middle cerebral artery bifurcation aneurysms using CT angiography. *PLoS One* 2016; *11* : e0166654.
20. Kang HG, Kim BJ, Lee J, Kim MJ, Kang DW, Kim JS, *et al*. Risk factors associated with the presence of unruptured intracranial aneurysms. *Stroke* 2015; *46* : 3093-8.
21. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: Sifting through the sands of data. *Neurosurg Focus* 2009; *26* : E2.
22. Rahman M, Smietana J, Hauck E, Hoh B, Hopkins N, Siddiqui A, *et al*. Size ratio correlates with intracranial aneurysm rupture status: A prospective study. *Stroke* 2010; *41* : 916-20.
23. Hoh BL, Sistrom CL, Firment CS, Fautheree GL, Velat GJ, Whiting JH, *et al*. Bottleneck factor and height-width ratio: Association with ruptured aneurysms in patients with multiple cerebral aneurysms. *Neurosurgery* 2007; *61* : 716-22.
24. Nader-Sepahi A, Casimiro M, Sen J, Kitchen ND. Is aspect ratio a reliable predictor of intracranial aneurysm rupture? *Neurosurgery* 2004; *54* : 1343-7.
25. Dhar S, Tremmel M, Mocco J, Kim M, Yamamoto J, Siddiqui AH, *et al*. Morphology parameters for intracranial aneurysm rupture risk assessment. *Neurosurgery* 2008; *63* : 185-96.
26. Lin N, Ho A, Gross BA, Pieper S, Frerichs KU, Day AL, *et al*. Differences in simple morphological variables in ruptured and unruptured middle cerebral artery aneurysms. *J Neurosurg* 2012; *117* : 913-9.
27. Etminan N, Brown RD Jr., Beseoglu K, Juvela S, Raymond J, Morita A, *et al*. The unruptured intracranial aneurysm treatment score: A multidisciplinary consensus. *Neurology* 2015; *85* : 881-9.

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