Morphological parameters and anatomical locations associated with rupture status of small intracranial aneurysms

Zhihui Duan1, Yuanhui Li4, Sheng Guan3, Congmin Ma1, Yuezhen Han1, Xiangyang Ren1, Liping Wei4, Wenbo Li4, Jiyu Lou2 & Zhiyuan Yang1

Characterization of the rupture risk factors for small intracranial aneurysms (SIAs, ≤ 5 mm) is clinically valuable. The present study aims to identify image-based morphological parameters and anatomical locations associated with the rupture status of SIAs. Two hundred and sixty-three patients with single SIAs (128 ruptured, 135 unruptured) were included, and six morphological parameters, including size, aspect ratio (AR), size ratio (SR), height–width ratio (H/W), flow angle (FA) and aneurysm width–parent artery diameter ratio, and the aneurysm locations were evaluated using three-dimensional geometry, and were used to identify a correlation with aneurysm rupture. Statistically significant differences were observed between ruptured and unruptured groups for AR, SR, H/W, FA, and aneurysm locations, from univariate analyses. Logistic regression analysis further revealed that AR (p = 0.034), SR (p = 0.004), H/W (p = 0.003), and FA (p < 0.001) had the strongest independent correlation with ruptured SIAs after adjustment for age, gender and other clinical risk factors. A future study on a larger SIA cohort need to establish to what extent the AR, SR, H/W and FA increase the risk of rupture in patients with unruptured SIAs in terms of absolute risks.

Intracranial aneurysm (IA) is a prevalent vascular disorder affecting 2–5% of the population worldwide1,2, and IA rupture frequently leads to fatal subarachnoid hemorrhage (SAH). With the widespread use of advanced imaging scanning, unruptured IAs are incidentally discovered with an increasing frequency. In a 5,720 cohort study, 91% of the IAs were identified incidentally, and close to 50% of them are <5 mm in diameter3, which are defined as small IAs by published reporting standards4,5. Results from the large cohort studies, including those of the International Study of Unruptured Intracranial Aneurysms (ISUIA), indicate that aneurysms smaller than 5 or 7 mm rarely rupture and thus surgical and endovascular treatments are rarely justified3,6,7. However, discrepant data shown that small IAs account for 13% of all ruptured IAs by two independent studies long time ago8,9, and more recent studies also reported a higher percentage of small IAs among their ruptured cases10–13. In addition, most of the ruptured IAs seen in daily clinical practice are small IAs10,14, and small IAs are a common cause of aneurysmal SAH15. To determine the most appropriate management plan for individual patients, we need to have a better understanding of the rupture risk of small IAs.

Numerous studies in analyzing the morphological characteristics of IAs have demonstrated that geometric parameters such as aspect ratio (AR)6,17, size ratio (SR)18,19, and aneurysm inflow angle (FA)20 are associated with aneurysm rupture status. However, most of these previous studies were not focused on evaluating the rupture-associated morphological parameters specific to small IAs (<5 mm). Additionally, reported results on the aneurysm locations associated with rupture status are conflicting for small IAs. Although most of the studies agreed that the most prevalent location of ruptured small IAs was anterior communicating artery (AcoA)10,12, in
were ruptured. None of the clinical risk factors showed significant correlation with the rupture status (\(p\) = 1.065 to 4.715, \(p\) vs flow angel (FA) (123.68 ± 112.19, \(p\) vs their values between the ruptured and unruptured groups (Table 2). Ruptured SIAs were associated with larger MR1 size (4.28 mm ± 4.21 mm, \(p\) = 0.191) and aneurysm width–parent artery diameter (W/L) ratio (1.50 ± 0.40, \(p\) = 0.061). Aneurysm size (4.28 mm ± 4.21 mm, \(p\) = 0.191) and aneurysm width–parent artery diameter (W/L) ratio (1.50 ± 0.40, \(p\) = 0.061) did not significantly differ between the ruptured and unruptured groups.

In considering that the FA of side-wall aneurysm is different from that of end-wall one (Fig. 1), and the percentages of each type SIAs were different between the ruptured and unruptured groups (71.6% vs. 49.3% for side-wall SIAs, and 27.4% vs. 50.7% for end-wall SIAs), we further separately analyzed whether the ruptured SIAs are associated with specific type of SIA. The results showed that a larger FA was associated with the end-wall SIAs (\(p\) < 0.05). The \(\chi^2\) test showed a significant relationship between the aneurysm location and aneurysm rupture (\(\chi^2 = 47.52, p < 0.001\)) (Table 3). Especially, 41.4% (53) and 39.1% (50) of the 128 ruptured SIAs were located at AcoA and PcoA, respectively. PcoA is usually defined as small arteries. However, we recognized that aneurysms at the origin of internal carotid-posterior communicating artery (IC-PC) are internal carotid artery (ICA) aneurysms. Demographic information and clinical risk factors for patients with ruptured and unruptured small intracranial aneurysms.

Table 1. Demographic information and clinical risk factors for patients with ruptured and unruptured small intracranial aneurysms.

|                      | Unruptured (n = 135) | Ruptured (n = 128) | \(P\) value |
|----------------------|----------------------|-------------------|-------------|
| Age (SD)             | 59.84 (7.26)         | 60.55 (7.11)      | 0.429       |
| Female (%)           | 74 (54.8)            | 57 (44.5)         | 0.095       |
| Smoking (%)          | 29 (23.2)            | 26 (20.3)         | 0.816       |
| Hypertension (%)     | 52 (38.5)            | 62 (48.4)         | 0.105       |
| SAH history (%)      | 6 (4.4)              | 11 (8.6)          | 0.171       |
| Family history (%)   | 6 (4.4)              | 4 (3.1)           | 0.813       |

Table 2. Univariate analyses for the morphological parameters measured for ruptured and unruptured small intracranial aneurysms.

|        | Unruptured (n = 135) | Ruptured (n = 128) | \(P\) value |
|--------|----------------------|-------------------|-------------|
| Size   | 4.21 ± 0.43          | 4.28 ± 0.42       | 0.191       |
| AR     | 1.49 ± 0.37          | 1.61 ± 0.39       | 0.008       |
| SR     | 1.70 ± 0.33          | 1.86 ± 0.34       | < 0.001     |
| FA     | 112.19 ± 16.523      | 123.68 ± 17.10    | < 0.001     |
| H/W ratio | 1.43 ± 0.24          | 1.50 ± 0.18       | < 0.008     |
| W/L ratio | 1.50 ± 0.32          | 1.58 ± 0.40       | 0.061       |

Results

263 patients with small IAs (<5 mm) were included in the study with 128 ruptured and 135 unruptured aneurysms. Demographic and clinical information of the study population is listed in Table 1. Mean age of the patients was 60.19 ± 7.18 years (range, 41–81 years), and 49.8% (131/263) were women. A total of 48.7% (128/263) SIAs were ruptured. None of the clinical risk factors showed significant correlation with the rupture status (\(p > 0.05\)).

We used univariate analysis to examine pre-defined morphological parameters individually and compared their values between the ruptured and unruptured groups (Table 2). Ruptured SIAs were associated with larger flow angel (FA) (123.68 ± 112.19, \(p < 0.001\)), higher aspect ratio (AR) and size ratio (SR) (1.61 vs. 1.49, \(p = 0.008\) and 1.86 vs. 1.71, \(p < 0.001\)), and higher height-width ratio (H/W) and (1.50 vs. 1.43, \(p = 0.008\)). Aneurysm size (4.28 mm ± 4.21 mm, \(p = 0.191\)) and aneurysm width–parent artery diameter (W/L) ratio (1.58 vs.1.51, \(p = 0.061\)) did not significantly differ between the ruptured and unruptured groups.

In considering that the FA of side-wall aneurysm is different from that of end-wall one (Fig. 1), and the percentages of each type SIAs were different between the ruptured and unruptured groups (71.6% vs. 49.3% for side-wall SIAs, and 27.4% vs. 50.7% for end-wall SIAs), we further separately analyzed whether the ruptured SIAs are associated with specific type of SIA. The results showed that a larger FA was associated with the end-wall ruptured SIAs (\(p < 0.05\)).

The \(\chi^2\) test showed a significant relationship between the aneurysm location and aneurysm rupture (\(\chi^2 = 47.52, p < 0.001\)) (Table 3). Especially, 41.4% (53) and 39.1% (50) of the 128 ruptured SIAs were located at AcoA and PcoA, respectively. PcoA is usually defined as small arteries. However, we recognized that aneurysms at the origin of internal carotid-posterior communicating artery (IC-PC) are internal carotid artery (ICA) aneurysms, and these aneurysms’ SR is not so high because the ICAs diameter is usually big. In checking our dataset, we confirmed that the SR of aneurysms at PcoA was indeed higher in the ruptured group than that in the unruptured group (\(p < 0.05\)).

In the multivariate logistic regression model adjusted for both morphological and clinical risk factors, FA, SR, H/W ratio and AR were evaluated as independent variables and the results were summarized in Table 4. The analysis showed that greater SR (OR 3.586; 95% CI 1.518 to 8.474, \(p = 0.004\)), larger FA (OR 1.045; 95% CI 1.026 to 1.064, \(p < 0.001\)), higher H/W ratio (OR 8.023; 95% CI 2.011 to 32.008, \(p = 0.003\)), and AR (OR 2.241; 95% CI 1.065 to 4.715, \(p = 0.034\)) had the strongest independent correlation with ruptured SIAs.

Table 3. Demographic information and clinical risk factors for patients with ruptured and unruptured small intracranial aneurysms.

| Variable          | Unruptured (n = 135) | Ruptured (n = 128) | \(P\) value |
|-------------------|----------------------|-------------------|-------------|
| Age (SD)          | 59.84 (7.26)         | 60.55 (7.11)      | 0.429       |
| Female (%)        | 74 (54.8)            | 57 (44.5)         | 0.095       |
| Smoking (%)       | 29 (23.2)            | 26 (20.3)         | 0.816       |
| Hypertension (%)  | 52 (38.5)            | 62 (48.4)         | 0.105       |
| SAH history (%)   | 6 (4.4)              | 11 (8.6)          | 0.171       |
| Family history (%)| 6 (4.4)              | 4 (3.1)           | 0.813       |
Figure 1. Definition of the morphological parameters in end-wall aneurysm (A) and side-wall aneurysm (B). Aneurysm size is defined as the maximum distance of the dome from the aneurysm neck plane (W). Aspect ratio (AR) is defined as the maximum perpendicular height (H1) of the aneurysm divided by the average neck diameter of the aneurysm (N). D1: the diameter of the parent vessel at the edge of the neck, perpendicular to flow; D2: the diameter of the parent vessel perpendicular to flow, measured at 1.5D1 from D1; average diameter: (D1 + D2)/2; size ratio (SR) is defined as the maximum aneurysm height (H2) divided by the average diameter. Height–width (H/W) ratio is defined as the ratio of H2/W. Aneurysm width–parent artery diameter ratio is the ratio between W/D1. Flow angle (FA) is defined as the angle between the maximum height of the aneurysm and the parent vessel (α).

| Location          | Unruptured (n = 135) | Ruptured (n = 128) | χ² | P value |
|-------------------|----------------------|--------------------|----|---------|
| ACoA              | 16                   | 53                 | 47.526 | <0.001 |
| PCoA              | 56                   | 50                 |     |         |
| VA                | 9                    | 5                  |     |         |
| Ophthalmic artery | 30                   | 4                  |     |         |
| MCA               | 8                    | 3                  |     |         |
| ACA               | 8                    | 6                  |     |         |
| Cavernous carotid artery | 4              | 3                  |     |         |
| Others            | 4                    | 4                  |     |         |

Table 3. Univariate analyses for the locations of the ruptured and unruptured small intracranial aneurysms.

| Risk Factor       | OR (95% CI)      | P value |
|-------------------|------------------|---------|
| SR                | 3.586 (1.518–8.474) | 0.004   |
| FA                | 1.045 (1.026–1.064) | <0.001 |
| H/W ratio         | 8.023 (2.011–32.008) | 0.003   |
| AR                | 2.241 (1.065–4.715) | 0.034   |
| Age               | 1.023 (0.983–1.065) | 0.255   |
| Smoking           | 1.158 (0.579–2.315) | 0.678   |
| Hypertension      | 1.505 (0.849–2.668) | 0.161   |
| SAH history       | 1.978 (0.591–6.625) | 0.269   |
| Family history    | 0.922 (0.223–3.816) | 0.911   |
| W/L ratio         | 1.100 (0.482–2.509) | 0.821   |
| Female            | 0.625 (0.350–1.118) | 0.113   |
| Diameter          | 1.513 (0.770–2.974) | 0.230   |

Table 4. Multivariate analysis (Logistic regression) after adjustment for clinical and morphological risk factors.
Discussion

In this study, we identified that aneurysm FA, SR, AR and H/W ratio were significantly different between ruptured and unruptured SIAs. Moreover, ruptured SIAs were more likely to locate at AcoA. To our best knowledge, there were only a few reports about morphological parameters of SIAs in evaluating the rupture risk, the results of the current study may imply that, for SIAs that are equally suitable for observation or endovascular treatment, having these morphological risks factors and being located at AcoA site may need closer monitoring or more prompt intervention.

Controversy exists in the management of patients with unruptured SIAs, and one of the reasons is because SIAs were generally considered benign or “safe” with a very low rupture risk (0–0.05% per year)\(^{3,6,7}\). However, Pavis et al. recently did a cross-sectional hospital-based study of aneurysmal SAH in emphasizing the aneurysm size at the time of rupture, and the results clearly indicate that SIAs are a common cause of aneurysmal SAH\(^{15}\). In addition, extensive data have demonstrated that the rupture risk of a IA depends on a number of biological factors in addition to aneurysm size\(^{25–27}\), implying that the prevailing notion of “the larger the IAs, the greater the rupture risks”, is not entirely true. From 2009 to 2017, we encountered total 310 ruptured IAs in our hospital, and about 41.3% (128/310) of them are SIAs, also indicating the prevalence of rupture from SIAs in the Chinese demographic setting. One possible explanation for the high rupture rate of SIAs is that aneurysm rupture occurs relatively soon after formation when the aneurysm wall is weaker and before healing processes takes place. After this initial stage, aneurysms may reach a somewhat stable condition. This is ascertained by the observation that rupture at a smaller size than those at other locations\(^{38,39}\). In our analysis of SIAs’ location, the results showed that 11.9% and 41.4% of the total SIAs located at PcoA and AcoA, respectively, and SIAs at these two locations are likely to rupture\(^{48,49}\). In the present study, we didn’t observe any SIAs with obvious daughter sacs, but many

SIAs were generally considered benign or “safe” with a very low rupture risk (0–0.05% per year)\(^{3,6,7}\). However, Pavis et al. recently did a cross-sectional hospital-based study of aneurysmal SAH in emphasizing the aneurysm size at the time of rupture, and the results clearly indicate that SIAs are a common cause of aneurysmal SAH\(^{15}\). In addition, extensive data have demonstrated that the rupture risk of a IA depends on a number of biological factors in addition to aneurysm size\(^{25–27}\), implying that the prevailing notion of “the larger the IAs, the greater the rupture risks”, is not entirely true. From 2009 to 2017, we encountered total 310 ruptured IAs in our hospital, and about 41.3% (128/310) of them are SIAs, also indicating the prevalence of rupture from SIAs in the Chinese demographic setting. One possible explanation for the high rupture rate of SIAs is that aneurysm rupture occurs relatively soon after formation when the aneurysm wall is weaker and before healing processes takes place. After this initial stage, aneurysms may reach a somewhat stable condition. This is ascertained by the observation that rupture at a smaller size than those at other locations\(^{38,39}\). In our analysis of SIAs’ location, the results showed that 11.9% and 41.4% of the total SIAs located at PcoA and AcoA, respectively, and SIAs at these two locations are likely to rupture\(^{48,49}\). In the present study, we didn’t observe any SIAs with obvious daughter sacs, but many
of them were irregular shape, and the average H/W ratio of the ruptured SIAs was significant higher than that of the unruptured ones \( p = 0.003 \), indicating the potential value of using H/W ratio as a clinical predictor for SIA rupture risk.

Our study has important implications for clinical practice. Small IAs are more and more incidentally discovered in clinical screening, and they are not rare to rupture as underestimated before, but they were undervalued for proper management. Our study focused on identifying imaging-based measurable risk factors associated with rupture of SIAs, thus will provide clinical guidance in further differentiating the high-risk patients and make most appropriate management plan for individual patients. A future study on a larger SIA cohort need to establish to what extent the AR, SR, H/W ratio and FA increase the risk of rupture in patients with unruptured SIAs in terms of absolute risks.

Materials and Methods
The study was conducted in accordance with relevant guidelines and regulations, and was approved by the Ethics Committee of Affiliated Luoyang Central Hospital of Zhengzhou University. Written informed consent was obtained from each study patient.

Patient Population. From January 2009 to March 2017, angiography images of patients with single IAs that were diagnosed or treated in our database were carefully reviewed. The largest aneurysm size was measured by 2D or 3D angiography, and only patients with aneurysm size \( \leq 5 \) mm were included in the present study. Such criteria was based on the reporting standards of small IAs in most published studies.\(^4\)\(^5\) Subsequently, 263 patients with small IAs were included with 128 ruptured and 135 unruptured aneurysms. Medical records were reviewed to obtain demographic and clinical information, including age, gender, family history, smoking status, hypertension and prior history of SAH. Re-operated aneurysms, fusiform aneurysms, blood blister-like aneurysms, or those associated with arteriovenous malformations were excluded from the study.

Reconstruction of 3D models. Three-dimensional (3D) models of SIAs were reconstructed from digital subtraction angiography using Siemens Artise Zee software or TOSHIBA AQUILION ONE 320 CTA. Detailed methods of constructing and refining the 3D models have been described previously.\(^20\) All measurements were obtained independently by two observers, and the average value was used for subsequent statistical analyses.

Definition of parameters and calculation. Six morphological parameters and aneurysm locations were examined in 3D aneurysm models.

These parameters have been defined previously\(^16\)\(^–\)\(^20\) and are described briefly below (Fig. 1). Aneurysm size was defined as the maximum distance of the dome from the aneurysm neck plane. Aspect ratio (AR) was calculated from the maximum perpendicular height of the aneurysm divided by the average neck diameter of the aneurysm. Size ratio (SR) was calculated from the maximum aneurysm height divided by the mean vessel diameter of all branches associated with the aneurysm. The maximum height is the maximum distance from the cross-section of the aneurysm neck to any point on the aneurysm dome. In the case of a terminal aneurysm, the average diameter of the feeding artery and the other branching vessels was used for the ‘average vessel diameter’ in our study. Height–width (H/W) ratio was defined as the ratio of height (the maximum perpendicular distance of the aneurysm dome from the neck plane) to the width of aneurysm, where the aneurysm width was the maximum width parallel to the neck. Aneurysm width–parent artery diameter (W/L) ratio is the ratio between the aneurysm diameter and the associated vessel diameter. Flow angle (FA) was defined as the angle between the maximum height of the aneurysm and the parent vessel. In our study the SIAs were divided into eight location groups: PcoA, AcoA, MCA, ACA, cavernous carotid artery, ophthalmic artery (OA), basilar artery (BA) and other locations.

Statistical analysis. Data are presented as mean and SD for quantitative parameters, and as frequency for categorical parameters. The Kolmogorov–Smirnov test for normal distribution was performed for all quantitative parameters. Student’s t-test was used if a parameter was normally distributed; otherwise, a Mann–Whitney U test was used to compare differences between ruptured and unruptured lesions. For categorical parameters, the chi-square test was used to analyze the data. Univariate analysis was performed to compare the value of each morphological parameter between the ruptured and unruptured groups. Multivariate logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CI) for the likelihood of aneurysm rupture after adjusting for age, sex, smoking status, family history, hypertension, and prior history of SAH. Results were considered statistically significant at \( p < 0.05 \). Statistical analysis was carried out using SPSS, Version 17.0 (SPSS, Chicago, IL, USA).

References
1. Rinkel, G. E., Dzijbuti, M., Algra, A. & van Gijn, J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke; a journal of cerebral circulation* 29, 251–256 (1998).
2. Vernooij, M. W. et al. Incidental findings on brain MRI in the general population. *The New England journal of medicine* 357, 1821–1828, https://doi.org/10.1056/NEJMoat070972 (2007).
3. Investigators, U. J. et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *The New England journal of medicine* 366, 2474–2482, https://doi.org/10.1056/NEJMoai1113260 (2012).
4. Meyers, P. M. et al. Reporting standards for endovascular repair of saccular intracranial cerebral aneurysms. *J Neurointerv Surg* 2, 312–323, https://doi.org/10.1136/jnis.2010.002337 (2010).
5. Stellert, W. R. Jr et al. Conventional endovascular treatment of small intracranial aneurysms is not associated with additional risks compared with treatment of larger aneurysms. *J Neurointerv Surg* 7, 262–265, https://doi.org/10.1136/neurintsurg-2014-011133 (2015).
6. Unruptured intracranial aneurysms--risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. *The New England journal of medicine* 339, 1725–1733, https://doi.org/10.1056/NEJM1998121039292401 (1998).
47. Cebral, J. R. et al. Characterization of cerebral aneurysms for assessing risk of rupture by using patient-specific computational hemodynamics models. AJNR Am J Neuroradiol 26, 2550–2559 (2005).
48. Abboud, T. et al. Morphology of Ruptured and Unruptured Intracranial Aneurysms. World Neurosurg 99, 610–617, https://doi.org/10.1016/j.wneu.2016.12.053 (2017).
49. Lindgren, A. E. et al. Irregular Shape of Intracranial Aneurysm Indicates Rupture Risk Irrespective of Size in a Population-Based Cohort. Stroke 47, 1219–1226, https://doi.org/10.1161/STROKEAHA.115.012404 (2016).
50. Lin, N. et al. Differences in simple morphological variables in ruptured and unruptured middle cerebral artery aneurysms. J Neurosurg 117, 913–919, https://doi.org/10.3171/2012.7.JNS111766 (2012).

Acknowledgements
This work was supported by the Research Funds for Young Physician Scientist of Luoyang Central Hospital to ZD.

Author Contributions
Conceived and designed the experiments: Z.D., Y.L., J.L., and Z.Y. Performed the experiments: Z.D., S.G., Y.L., C.M., Y.H. Analyzed the data: Z.D., X.R., L.W., W.L. Wrote the paper: Z.D., Y.L., and J.L.

Additional Information
Competing Interests: The authors declare no competing interests.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018