Risk Factors for the Rupture of Bifurcation Intracranial Aneurysms Using CT Angiography

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INTRODUCTION
Ruptured intracranial aneurysms (RIAs) are the most common cause of subarachnoid hemorrhage (SAH), causing high mortality and morbidity rates up to 40–50% and 10–20%, respectively. However, only 1% of all intracranial aneurysms (IAs) actually rupture, and the surgical and endovascular treatments for unruptured intracranial aneurysms (UIAs) are not without risk. Thus, the ability to predict the rupture risk for UIAs would be of enormous clinical value.

AIs usually occur at Willis’ or arterial bifurcations, and many cases of SAH arise from bifurcation aneurysms. The International Study of Unruptured Intracranial Aneurysms (ISUIA) reported that treatment decisions regarding UIAs are to be based mainly on the size and location of the aneurysm. A recent study suggested that the risk factors of UIAs are related to a difference between sidewall- and bifurcation-type aneurysms, although they did not provide comprehensive results on the clinical parameters associated with the rupture of aneurysms. For this reason, the purpose of this study was to identify the relationships between personal factors and image characteristics and the rupture of bifurcation IAs.

MATERIALS AND METHODS
Patients
All protocols were reviewed and approved by the local institu-
national ethics committee. The clinical data for the study were extracted from the hospital medical records, including age, gender, history of hypertension, heart disease, diabetes mellitus, cerebral atherosclerosis, alcohol consumption, cigarette smoking, and history of SAH. The patients’ records/information were anonymized and de-identified prior to analysis, and the requirement for informed consent was waived.

From August 2011 and July 2014, a total of 246 consecutive patients with bifurcation aneurysms underwent computer tomography angiography (CTA) examinations. We included patients with bifurcation aneurysms that were managed with both treatment (coiling or clipping) and observation. Among these, 44 patients with mycotic, traumatic, extradural, or fusiform aneurysms, aneurysms with poor image quality, and aneurysms with a maximum diameter <1.8 mm (too small to measure accurately) were not eligible for this study. Thus, 202 patients (16 patients with multiple aneurysms) with 219 bifurcation aneurysms (129 ruptured and 90 unruptured aneurysms) were finally included. In cases with multiple aneurysms, the ruptured aneurysm was determined based on the location of the hemorrhage on CT, angiographic, or operative findings.

Computer tomography angiography

IAs were evaluated with CTA using a 64-slice CT machine (GE LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA) and a dedicated workstation (Advantage Windows 4.5). A total 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/s. Next, the images were obtained with a slice thickness of 0.625 mm and no overlap, and were transferred to the GE Advantix workstation to generate three-dimensional (3D) volume rendering (VR).

Image analysis

Bifurcation aneurysms were defined as lesions originating from major bifurcations, including the anterior cerebral artery (ACA), anterior communicating artery (ACoA), posterior communicating artery (PCoA), internal carotid artery (ICA), middle cerebral artery (MCA), and top of the basilar artery (TOBA). PCoA aneurysms were classified as bifurcations depending on the size of the PCoA relative to the ICA diameter (more than one-fifth the diameter). Based on the neck location, the neck types were classified into two types: Type C, the neck was located along the extension of the midline axis of the parent artery, and Type D, the neck deviated from the midline axis of the parent artery (Figs. 1 and 2).

The 3D VR images were manually measured independently by two neuro-radiologists. The mean values from two radiologists were used for analysis. Controversial cases were resolved through discussion. The diameters of the two daughter arteries of the bifurcation were measured: the larger daughter artery (DA) was defined as DA A, and the smaller one defined as DA B. Next, the DA ratio (diameter of DA A/diameter of DA B) was calculated. There are two angles on the lateral side of the bifurcation that are called lateral angles (LAs). The angle between the parent artery and DA A is defined as angle A, and the angle between the parent artery and DA B is defined as angle B; the LA ratio is defined as angle A/angle B. DA, daughter artery; LA ratio, lateral angle ratio; LA, diameter of DA A; LB, diameter of DA B.
another angle between the parent artery and DA B was defined as angle B; the LA ratio (angle A/angle B) was then calculated (Fig. 1).

The following four dimensions were measured in the plane parallel to the blood flow of the parent arteries: aneurysm depth, width, neck width, and maximum size (Dmax).\(^{5,10}\) The aspect ratio (AR), the depth-to-width ratio (DW), and the bottleneck factor (BF) were then calculated (Fig. 2).\(^{5,10-12}\) The aneurysm shapes were classified as simple lobed or irregular, and an aneurysm with lobular or daughter sacs was classified as irregular.\(^5\)

### Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 17.0). In the current study, rupture events were assessed as a dependent variable in the model. Independent t-test and chi-squared test were used to compare the means for continuous variables.

#### Table 1. Patient Characteristics with Ruptured and Unruptured Aneurysms

| Factors                  | Unruptured | Ruptured | p value |
|--------------------------|------------|----------|---------|
| Patients No.             | 73 (36.1%) | 129 (63.9%) | 0.371   |
| Female                   | 40 (54.8%) | 79 (61.2%)  | 0.028   |
| Age (≥ 60 yr)            | 24 (32.9%) | 63 (48.8%)  | 0.028   |
| Hypertension             | 37 (50.7%) | 45 (34.9%)  | 0.028   |
| Heart disease            | 4 (5.5%)   | 3 (2.3%)    | 0.437   |
| Diabetes mellitus        | 8 (11.0%)  | 2 (1.6%)    | 0.009   |
| Cerebral atherosclerosis | 30 (41.1%) | 8 (6.2%)    | 0.000   |
| Alcohol history          | 16 (21.9%) | 33 (25.6%)  | 0.560   |
| Cigarette smoking        | 16 (21.9%) | 34 (26.4%)  | 0.483   |
| Bleeding history         | 5 (6.9%)   | 3 (2.3%)    | 0.8     |
| Multiple aneurysms       | 5 (6.9%)   | 11 (8.5%)   | 0.671   |

#### Table 2. The Morphological Features of Aneurysms

| Factors                  | Unruptured | Ruptured | p value |
|--------------------------|------------|----------|---------|
| No. of aneurysm          | 90 (41.1%) | 129 (58.9%) | 0.000   |
| Location                 |            |          |         |
| ACoA                     | 21 (23.3%) | 57 (44.2%)  | 0.000   |
| ACA                      | 1 (1.1%)   | 3 (2.3%)    | 0.883   |
| MCA                      | 30 (33.3%) | 23 (17.8%)  | 0.008   |
| PCOMa                    | 31 (34.4%) | 38 (29.5%)  | 0.434   |
| ICA                      | 6 (6.7%)   | 3 (2.3%)    | 0.213   |
| PCC                      | 1 (1.1%)   | 5 (3.9%)    | 0.416   |
| Irregular shape          | 28 (31.1%) | 91 (70.5%)  | 0.000   |
| Daughter sac             | 18 (20.0%) | 65 (50.4%)  | 0.000   |
| Type C                   | 45 (50%)   | 63 (48.8%)  | 0.866   |
| DA ratio                 | 1.70±0.75  | 1.56±0.61   | 0.138   |
| LA ratio                 | 1.51±0.85  | 1.34±0.60   | 0.104   |
| Depth                    | 4.64±2.83  | 6.08±2.51   | 0.000   |
| Width                    | 4.85±2.40  | 5.27±2.53   | 0.068   |
| Neck width               | 4.55±1.90  | 4.08±1.51   | 0.044   |
| Maximum diameter         | 5.72±2.93  | 7.20±2.76   | 0.000   |
| Aspect ratio             | 1.03±0.45  | 1.60±0.70   | 0.000   |
| Depth/width ratio        | 1.00±0.31  | 1.24±0.40   | 0.000   |
| Bottleneck factor        | 1.02±0.30  | 1.33±0.52   | 0.000   |

#### Table 3. Univariate Logistic Regression Model for Prediction of Aneurysm Rupture

| Characteristic           | Odds ratio | p value | 95% CI | β     |
|--------------------------|------------|---------|--------|-------|
| Age (≥ 60 yr)            | 0.300      | 0.000   | 0.165–0.547 | -1.203 |
| Hypertension             | 0.521      | 0.029   | 0.291–0.935 | -0.652 |
| Diabetes mellitus        | 0.128      | 0.011   | 0.026–0.620 | -2.056 |
| Cerebral atherosclerosis | 0.095      | 0.000   | 0.040–0.223 | -2.356 |
| Location                 |            |          |        |       |
| ACoA                     | 6.810      | 0.000   | 3.385–13.698 | 1.918  |
| MCA                      | 0.798      | 0.477   | 0.427–1.488 | -0.226 |
| Irregular shape          | 4.864      | 0.000   | 2.717–8.671 | 1.580  |
| Daughter sac             | 3.679      | 0.046   | 1.994–6.790 | 1.303  |
| DA ratio                 | 0.836      | 0.000   | 0.701–0.997 | -0.179 |
| LA ratio                 | 0.650      | 0.000   | 0.546–0.773 | -0.431 |
| Depth                    | 1.125      | 0.000   | 1.077–1.174 | 0.118  |
| Width                    | 1.074      | 0.001   | 1.028–1.122 | 0.071  |
| Neck width               | 0.808      | 0.000   | 0.759–0.860 | -0.214 |
| Maximum diameter         | 1.132      | 0.046   | 1.086–1.180 | 0.124  |
| Aspect ratio             | 5.658      | 0.000   | 4.234–7.560 | 1.733  |
| Depth/width ratio        | 3.225      | 0.000   | 2.223–4.679 | 1.171  |
| Bottleneck factor        | 7.191      | 0.000   | 4.988–10.347 | 1.973  |

CI, confidence interval; ACoA, anterior communicating artery; MCA, middle cerebral artery; DA ratio, daughter artery ratio; LA ratio, lateral angle ratio.
data and categorical data, respectively. All variables with a $p$ value less than 0.2 were entered into a logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were also calculated. Binary logistic regression was performed separately, using forward stepwise regression to control for those features that achieved univariate statistical significance ($p<0.05$). Receiver operating characteristic (ROC) curve analysis was also performed to determine the sensitivity and specificity of the area under the curve values.

RESULTS

Of the 202 patients, 119 (58.9%) were women and 83 (41.1%) were men. The mean age of all of the patients was 58.2±11.91 years (range, 21–84 years), 56.7±12.01 years among the males (range, 21–84 years) and 59.3±11.77 years among the females (range, 31–84 years). Because the mean patient age was 58.2 years, 60 years was chosen to dichotomize the sample. Chi-squared test were used to compare means for the patient characteristics (Table 1). Independent t-test and chi-squared test were used to compare the means for the morphological features of aneurysms (Table 2). To determine the risk factors predisposing the patients to aneurysm rupture, 17 independent variables ($p\leq 0.2$) were entered into a univariate logistic regression model (Table 3). Of these variables, 16 independent variables were found to be significant predictors of aneurysm rupture ($p<0.05$). Next, these variables were entered into a forward stepwise binary logistic regression model (Table 4). Among these variables, the binary logistic regression model showed that aneurysms with an irregular shape (OR 6.598) and AR (OR 3.507) strongly increased the risk of aneurysm rupture. By contrast, age (OR 0.434), cerebral atherosclerosis (OR 0.125), neck width (OR 0.771), and the LA ratio (OR 0.267) were associated with a decreased risk of aneurysm rupture.

To identify optimal thresholds for RIAs, ROC analysis (excluding the outliers) was performed for AR, neck width, and LA ratio. The resulting curves are shown in Figs. 3, 4, and 5. The

Table 4. Binary Logistic Regression Model for Prediction of Aneurysm Rupture

| Characteristics         | Odds ratio | $p$ value | 95% CI          | $\beta$ |
|-------------------------|------------|-----------|-----------------|---------|
| Age                     | 0.434      | 0.042     | 0.194–0.971     | -0.835  |
| Cerebral atherosclerosis| 0.125      | 0.000     | 0.041–0.382     | -2.081  |
| Irregular shape         | 6.598      | 0.000     | 2.583–16.985    | 1.887   |
| Neck width              | 0.771      | 0.048     | 0.596–0.998     | -0.260  |
| Aspect ratio            | 3.507      | 0.004     | 1.494–8.234     | 1.255   |
| LA ratio                | 0.267      | 0.000     | 0.149–0.477     | -1.320  |

CI, confidence interval; LA ratio, lateral angle ratio.

Fig. 3. The area under the receiver operating characteristic curve for the neck width is 0.566 (95% confidence interval, 0.490–0.642). The cut point for the neck width is 4.35 mm, the sensitivity is 67.4%, and the specificity is 40%.

Fig. 4. The area under the receiver operating characteristic curve for the aspect ratio is 0.781 (95% confidence interval, 0.719–0.844). The cut point for the aspect ratio is 1.18, the sensitivity is 70.5%, and the specificity is 74.4%.
AUC, threshold value, and sensitivity and specificity values were calculated for a range of thresholds (Table 5). Our data showed that the threshold value of the neck width was 4.35 mm, although the AUC value was small (0.566, \(p=0.097\)). The threshold values of the AR and LA ratio were 1.18 and 1.50, respectively, and the corresponding AUC values were 0.781 and 0.622, respectively.

**DISCUSSION**

As an increasing number of UIAs are detected incidentally with the increased use of imaging, the treatment of asymptomatic UIAs continues to be debated. However, surgical and endovascular treatments for asymptomatic aneurysms are not always safe. In recent reports, many studies on UIAs have focused on rupture risk factors; however, results differ for different countries or regions, \(^1\),\(^2\),\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^9\),\(^10\),\(^11\),\(^12\),\(^13\), and few papers have described the patterns of IAs in Chinese populations.

**Clinical characteristics**

In the current study, we revealed that patient characteristics including age and cerebral atherosclerosis are associated with a decreased risk of aneurysm rupture. It is well known that atherosclerotic or calcified walls will lower the risk of IA rupture.\(^14\) With increased age, the risk of cerebral atherosclerosis will be higher. Popular factors, such as smoking, alcohol consumption, and hypertension, were not significantly associated with the risk of RIAs. The reasons for these findings may possibly be that most patients in this study had healthy lifestyles and mild to moderate hypertension.

**Morphological characteristics**

At the same time, we showed that irregular aneurysms and AR strongly increased the risk of aneurysm rupture; neck width and LA ratio lowered the risk of aneurysm rupture. Aneurysm wall irregularity has been associated with a higher rupture risk.\(^15\) The reason may be that an irregular shape leads to instability of the blood flow pattern. Traditionally, aneurysm size, including the height, width, and maximum size, has been reported to be an unquestionable factor regarding rupture risk. It is generally believed that larger aneurysms are more prone to rupture than smaller ones. The ISUIA showed a near-zero rupture risk for aneurysms <10 mm in diameter.\(^16\) However, smaller aneurysms may also rupture. In fact, in 94.4% of ACoAs and 87.5% of PCoAs, the RIA size was less than 10 mm,\(^17\) a finding that was concordant with our data and explained why size is not a rupture risk factor. Neck width has also been reported in many studies, most of which showed no significantly statistical difference.\(^15\),\(^18\) Our data indicated that the mean neck width for unruptured and ruptured aneurysms was 4.55 mm and 4.08 mm, respectively, and there was a slight inverse correlation with aneurysm rupture (\(p=0.048\)), possibly indicating that small necks induce small inflow jets and small concentrated impaction zones. The AR has been studied widely, and was shown to correlate with IA rupture.\(^11\),\(^16\),\(^20\) Different studies have varying threshold values of the AR. Our data showed that the threshold value of the AR was 1.18, a value that was significantly smaller than that for most of Caucasian and Japanese populations,\(^20\),\(^21\) but concordant with that reported by Dhar, et al.\(^22\)

This study focused on aneurysms located in bifurcating arteries. Of all aneurysms, ACoA is the most common site and ACoA aneurysms account for the largest percentage of ruptured aneurysms. Although, the ISUIA showed that location is correlated with aneurysm rupture in multivariate logistic regression, we found no differences in relation to location. Recent studies have indicated that location is not associated with

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**Fig. 5.** The area under the receiver operating characteristic curve for the lateral angle ratio is 0.622 (95% confidence interval, 0.493–0.711). The cut point for the lateral angle ratio is 1.50, the sensitivity is 73.6%, and the specificity is 48.9%.

**Table 5. Area Under the Curve for Neck Width, Aspect Ratio, and Lateral Angle Ratio**

| Characteristics | Area | Threshold value (mm) | \(p\) value | Sen (%) | Spe (%) | 95% CI         |
|-----------------|------|----------------------|-------------|---------|---------|---------------|
| Neck width      | 0.566| 4.35                 | 0.097       | 67.4    | 40      | 0.490–0.642   |
| Aspect ratio    | 0.781| 1.18                 | 0.000       | 70.5    | 74.4    | 0.719–0.844   |
| LA ratio        | 0.622| 1.50                 | 0.002       | 73.6    | 48.9    | 0.543–0.711   |

CI, confidence interval; LA ratio, lateral angle ratio.
increased rupture risk after a long period of follow-up,\textsuperscript{12,23-25} which is consistent with our study. Comparing the results of previous literature,\textsuperscript{6-8} we investigated neck position, DA ratio, and LA ratio. In contrast, our results showed that neck type and DA ratio do not show significant differences between RIAs and UIAs, and that LA ratio significantly lowers the risk of aneurysm rupture. The reasons might be that our cases numbered more than those in the previous studies, and they studied single location. Not with standing, the present data need to be confirmed in further studies.

Limitations of the study
Our study has some limitations. First, it was a retrospective analysis of patients at a single institution. Second, the shape or size of the RIAs might have changed owing to the rupture. Third, we did not perform a long-term follow up examination, and the UIAs may be ruptured at some point in the future. Fourth, we focused on bifurcation aneurysms, not including sidewall aneurysms, and did not study the relationships between multiple aneurysms. We will further strengthen our study in the future.

In conclusion, selecting a unique risk factor for predictive aneurysm rupture remains difficult. From clinical records and CTA findings from patients with bifurcation aneurysms, we found that advanced age, cerebral atherosclerosis, a large neck width, and a large LA ratio were protective factors against bifurcation aneurysm rupture; bifurcation aneurysm with an irregular shape and a high AR were more prone to rupture.

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