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ORIGINAL ARTICLE

Anatomical evaluation of intracranial aneurysm rupture risk in patients with multiple aneurysms

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Abstract

In patients with aneurysmal subarachnoid hemorrhage (aSAH) and multiple aneurysms, there is a need to objectively identify the ruptured aneurysm. Additionally, studying the intra-individual rupture risk of multiple aneurysms eliminates extrinsic risk factors and allows a focus on anatomical factors, which could be extrapolated to patients with single aneurysms too. Retrospective bi-center study (Department of Neurosurgery of the University Hospital Duesseldorf and Bern) on patients with multiple aneurysms and subarachnoid hemorrhage caused by the rupture of one of them. Parameters investigated were height, width, neck, shape, inflow angle, diameter of the proximal and distal arteries, width/neck ratio, height/width ratio, height/neck ratio, and localization. Statistical analysis and logistic regressions were performed by the *R* program, version 3.4.3. $N = 186$ patients with aSAH and multiple aneurysms were treated in either department from 2008 to 2016 (Bern: 2008–2016, 725 patients and 100 multiple aneurysms, Duesseldorf: 2012–2016, 355 patients, 86 multiple aneurysms). The mean age was 57 years. $N = 119$ patients had 2 aneurysms, $N = 52$ patients had 3 aneurysms, $N = 14$ had 4 aneurysms and $N = 1$ had 5 aneurysms. Eighty-four percent of ruptured aneurysms were significantly larger than the largest unruptured. Multilobularity of ruptured aneurysms was significantly higher than in unruptured. Metric variables describing the geometry (height, width, etc.) and shape are the most predictive for rupture. One or two of them alone are already reliable predictors. Ratios are completely redundant in saccular aneurysms.

Keywords Subarachnoid hemorrhage · Multiple intracranial aneurysms · Aneurysm anatomy · Aspect ratio · Bottleneck factor

Introduction

Aneurysmatic subarachnoid hemorrhage (aSAH) has a variable incidence depending on geographical area and race. It has been estimated that the worldwide incidence is about 9/100.000 [4]. In Japan and Finland, this number is much higher, whereas, in China, very low [8]. In the USA, the incidence is about 10/100.000 [12].

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Despite the advances in the management of subarachnoid hemorrhage, the mortality remains high. In general up to $^{1}/_{3}$ of patients with aSAH die before being admitted to the hospital, approximately $^{1}/_{4}$ die within 24 h [2]. Some studies report that half of the survivors remain dependent [7].

Because of the severe course of aSAH and its socioeconomic impact, it is of paramount importance to analyze risk factors for aneurysm rupture especially in cases of multiple aneurysms when not all can or should be treated.

In about ¼ of cases, patients have multiple aneurysms. The identification of ruptured aneurysm can be challenging, and the decision which aneurysm to treat in accordance to the distribution of subarachnoid blood alone can lead to a deleterious mistake. There is a significant number of cases where ruptured aneurysm can be poorly defined. Besides, known general risk factors for aneurysms rupture, anatomical aneurysm characteristics (in multiple aneurysms) might be helpful to objectively point out the ruptured aneurysm. We aim to identify such anatomical factors.

Material and methods

The study is a bi-center retrospective study of the neurosurgical departments of the University hospitals of Duesseldorf, Germany and Bern, Switzerland. Both departments are high volume centers for vascular neurosurgery. The data was collected in 2017 and all the parameters were added anonymized in a data bank. Afterwards, the data were handled by the data scientist. The data scientist has no neurosurgical background.

We evaluated $N = 1080$ patients with aneurysmatic subarachnoid hemorrhage and included those with multiple aneurysms (≥ 2). Data collected in Bern were from 2008 to 2016 (725 patients and 100 multiple aneurysms) and in Duesseldorf from 2012 to 2016 (355 patients, 86 multiple aneurysms).

In the evaluated cases, only patients with multiple aneurysms were taken into account. In every case, one of the aneurysms was ruptured. In this retrospective analysis, the ruptured aneurysm was identified in surgery (58% clipping) or by contrast leakage in angiography or through the distribution of the subarachnoid blood. The evaluated parameters for each aneurysm in each individual were height, width, neck, shape, inflow angle, diameter of the proximal and distal arteries and their ratios to each other, width/neck ratio, aspect ratio (height/width ratio), height/neck ratio, width/neck ratio, and localization (Fig. 1). We used the CTA and digital subtraction angiography for analysis. A neurosurgeon and a neuroradiologist made the analysis independent from each other, and the values were compared as to interindividual variance.

Statistical analysis was performed by paired, Fisher's exact test for count data, Welch's two-sample t test analysis, logistic regression analysis in the metric, and logarithmic space with a step-by-step elimination. We performed 20 tests (some maybe correlated). This led to the corrected significance level of 0.00256 (Sidak) or 0.0025 (Bonferoni). The level for trend was 0.00525 (Sidak) or 0.005 (Bonferoni).

Logistic regression analysis in metric space

We performed logistic regressions using all anatomical variables in their metric space. We started with all variables and eliminated step by step those, which are not significant, starting with the least significant values.

Logistic regression analysis in the logarithmic space

Again, we started with all variables in the logarithmic space and eliminated step-by-step those which are not significant, starting with the least significant. Using the logarithmic space allows a more normal distribution of the values and eliminates the skew deviation given the nature of the parameters measured.

Results

In total, we analyzed $N = 1080$ aSAH patients of which 186 (17.2%) had multiple aneurysms. One hundred nineteen patients had 2 aneurysms, 52 patients had 3 aneurysms, 14 had 4 aneurysms, and 1 had 5 aneurysms. In summary, we analyzed $N = 447$ aneurysms.

Table 1 gives the mean values and standard deviations for the evaluated parameters.

Comparison of the data between Duesseldorf and Bern

In order to exclude any significant differences of the collected aneurysms between the two centers, we performed a statistical analysis of all the parameters for the two centers. None of the evaluated parameters showed a significant difference in a center-to-center comparison. Demographically, the mean age of the patients in Duesseldorf was 55.4 and in Bern 57 years old. The WFNS grades had a mean value of 2.7 in Duesseldorf and 2.8 in Bern and the Fisher grade was 3.17 in Duesseldorf and 2.95 in Bern.

Paired analysis

Aneurysm height and rupture risk

In the paired analysis, the ruptured and the second largest aneurysm differed significantly in height (the critical size for rupture had a mean value of 6.3 mm, SD: 3.7 vs. 3.7 mm, SD: 2.7 mm for unruptured, Fig. 2b) with a p value of $< 2.2\text{e-}16$. As shown in Fig. 2, the aneurysm height (longest neck to dome distance) was

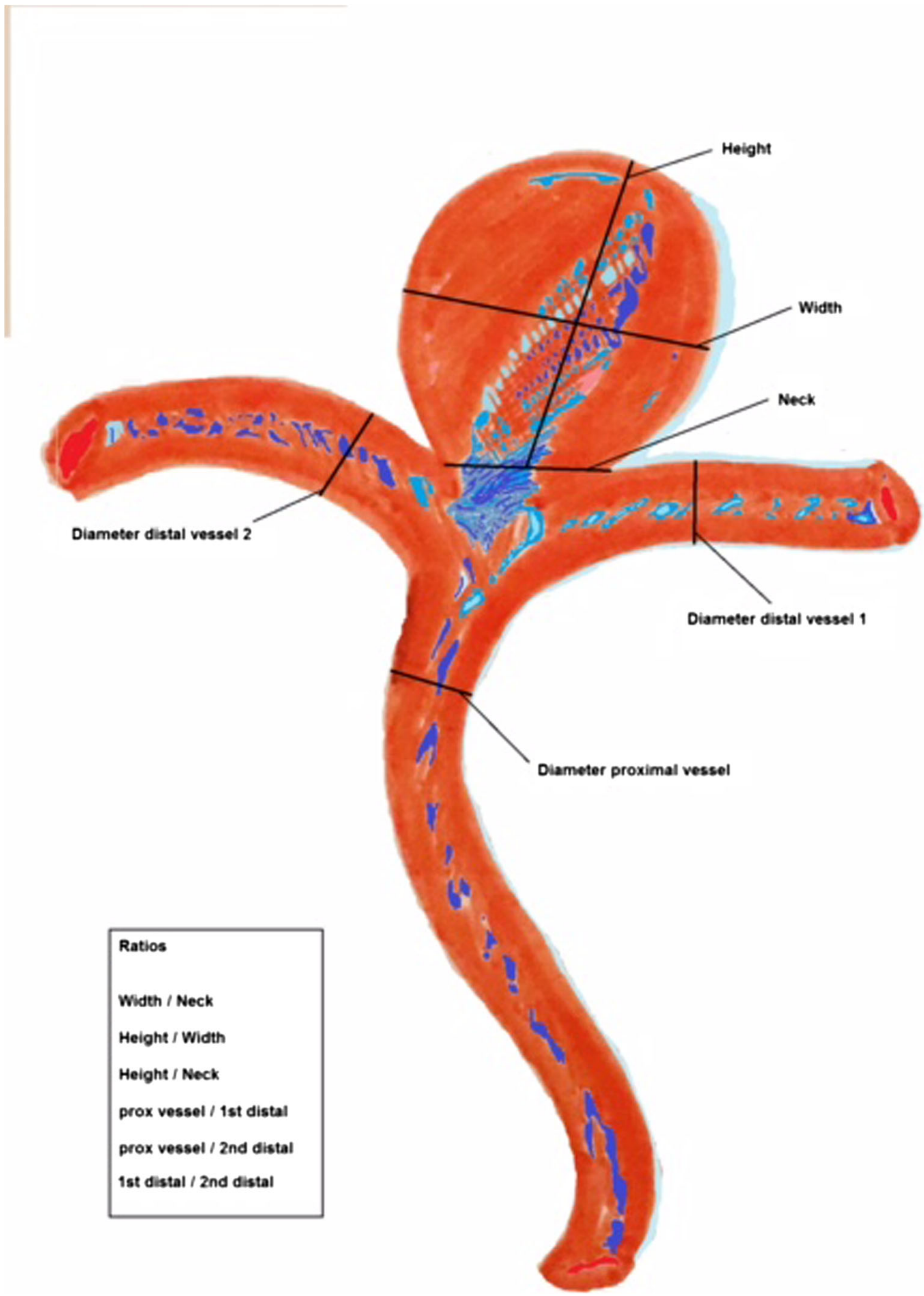

Fig. 1 Illustration of the analyzed parameters (drawing by A.K.Petridis)

significantly greater in the ruptured aneurysm in 83.24% of individuals compared to the second largest one. The distribution of the sizes of the ruptured to the nonruptured aneurysms for each pair is shown in Fig. 2a.

Aneurysm width, neck and rupture risk

The same results applied to the width of the ruptured aneurysm, which was greater compared to the unruptured one. For the width, the p value was < 2.2e-16. The same did not apply for the neck size, which did not reach significance. Correlation of "neck ruptured" and "neck unruptured" was not significant (3.2 mm, SD: 1.3 mm for ruptured vs. 2.5 mm, SD: 1.2 mm for unruptured, Fig. 3a). In 50 cases (27%), the neck of the unruptured aneurysms was larger than that of the ruptured ones. Figure 3b shows the results for the width of ruptured to unruptured aneurysms. The critical size for rupture had a mean width of 6.3 mm, SD: 3.7 mm (vs. 3.7 mm, SD: 2.8 mm for unruptured, Fig. 3c).

Table 1 Aneurysms characteristics between the ruptured and the second largest unruptured aneurysm

Aneurysm	Ruptured	Unruptured
Height***	6.29 ± 3.7 mm	3.69 ± 2.66 mm
Width***	6.34 ± 3.71 mm	3.71 ± 2.81 mm
Neck	3.23 ± 1.26 mm	2.46 ± 1.16 mm
Inflow angle	131 ± 31.7°	127.6 ± 28.7°
Diameter proximal vessel	2.49 ± 0.8 mm	2.64 ± 0.96 mm
Diameter 1st distal vessel	2.1 ± 0.72 mm	2.2 ± 0.93 mm
Diameter 2nd distal vessel	2.29 ± .75 mm	1.71 ± 0.58 mm
Dome/width ratio	1.17 ± 0.5	1.21 ± 0.4
Dome height/neck ratio (aspect)**	1.97 ± 0.82	1.53 ± 0.83
Width/neck ratio**	1.98 ± 0.8	1.49 ± 0.6

The height and width were highly statistical significant (***$p < 0.00\ldots1$), the width/neck and dome/neck ratios were statistically significant at (**$p < 0.01$) in the *t* test analysis for two independent variables and in the paired analysis

Aneurysm shape

Of the 100 multilobar aneurysms, 74 (74%) ruptured, whereas of the 370 unilobar aneurysms, 99 were ruptured (26%). The *p* value for this difference was < 5e-12. The height of the multilobar aneurysms reached a mean of 6.1 mm, whereas the unilobar aneurysms had a mean height of 4.2 mm. The difference in size was also statistical significant with a $p < 4e$-06.

The statistical analysis showed for multilobar aneurysms that the 50% boundary (odds ratio 1:1) was at a width of 3.1 mm and for unilobar at 5.7 mm (Fig. 4a). The odds ratio for multilobar/unilobar was 2.79 (Fig. 4b).

The rest of the analyzed parameters did not show any statistical significance in the paired analysis between ruptured and unruptured aneurysms pairs of each individual (Table 1). This means that the aneurysm angle, its cosine, the diameter of the proximal and distal vessels, and the ratios were insignificant. The localization of the aneurysms was also not significant.

Aneurysm localization

As can be seen in the Supplemental Figure 1, aneurysms of the ICA showed a tendency to be more common in the unruptured group than in the ruptured one (64 vs. 14), and PcomA aneurysms were more in the ruptured group (34 vs. 27). The rest of the aneurysms seemed to be equally distributed in both groups. Although, in the multivariate analysis, the localization of the aneurysm did not reach a statistical significant level; in the chi-square analysis, it reached a high statistical significance with $p < 0.00003$. In our study, there was a tendency of the aneurysms of the PcomA to rupture more than aneurysms of the ICA in general. Nonetheless, in cases of multiple aneurysms, the localization failed to predict which of the aneurysms would rupture.

Statistical analysis of multiple parameters

Logistic regression analysis in metric space

Having to analyze a large number of parameters, we approached the data in following manner: we performed logistic regressions using all anatomical variables in their metric space. We started with all variables and eliminated step-by-step those, which are not significant, starting with the least significant values. At the end, only width and shape remained significant as shown in Fig. 4.

Logistic regression analysis in the logarithmic space

After step-by-step elimination, we were left with only three variables: width, height, and shape (Fig. 5; cave: the dimensional variables are on the log scale!)

When the dimensional variables are excluded and only the ratios and shape were taken into account, the step-by-step elimination of variables left us only with the width/neck ratio (bottleneck factor) and shape, which were highly statistically significant (wnr: 1.98, SD:0.8 (ruptured) vs. 1.5, SD: 0.68 (unruptured), $p < 1e$-9) (Fig. 5a). Especially, for the width/

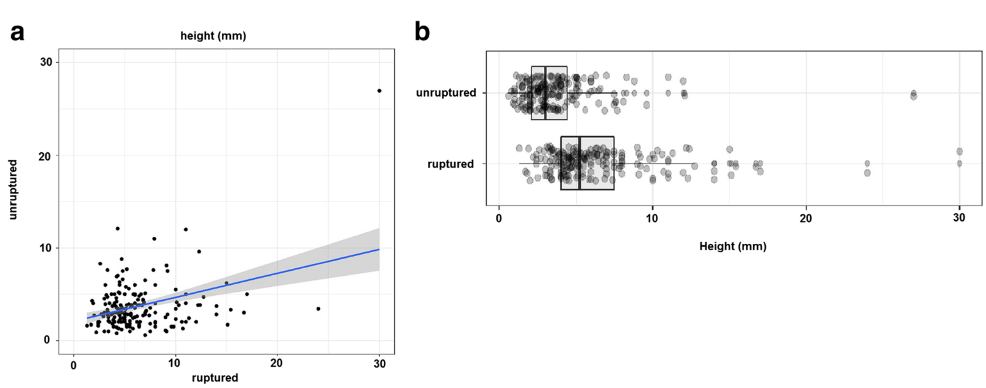

Fig. 2 Correlation of aneurysm height and ruptured aneurysm. **a** In the paired analysis, the ruptured aneurysm had a significantly greater height (neck to dome distance in mm) compared to the second largest unruptured in patients with multiple aneurysms. **b** As shown in the box plot analysis, the critical height for rupture was 6.3 ± 3.7 mm

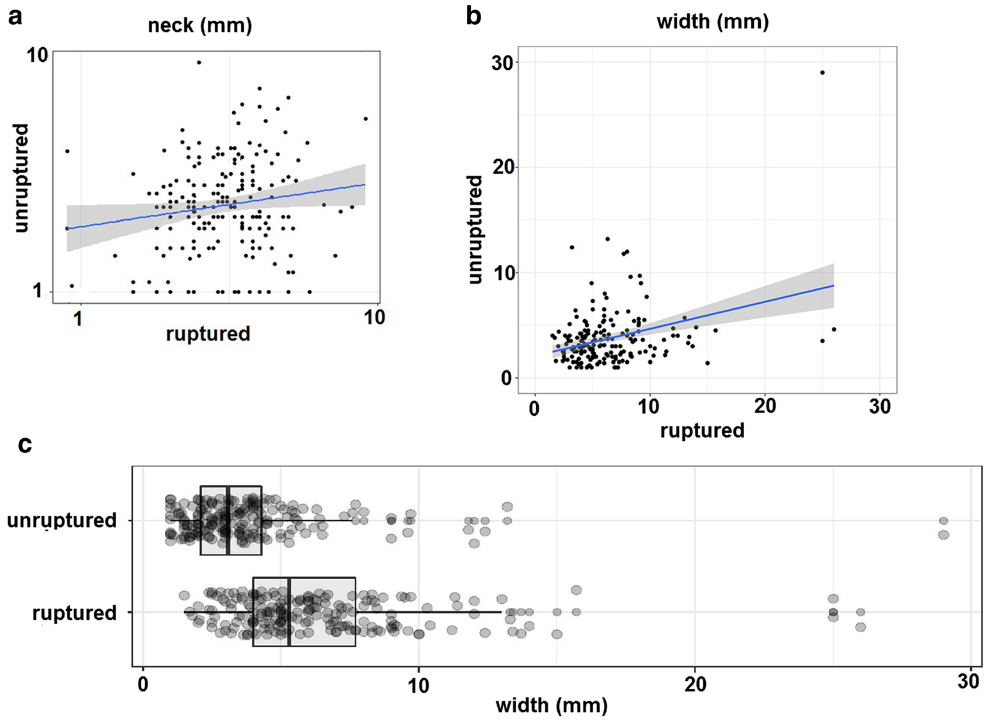

Fig. 3 Correlation of aneurysm neck and width with ruptured aneurysms. **a** The neck of the ruptured and the unruptured aneurysms show no correlation in the paired analysis. The neck of the ruptured aneurysms was 3.2 ± 1.3 mm and in the unruptured 2.5 ± 1.2 mm. **b** The width on the other side was significantly greater in ruptured aneurysms. **c** The box plot shows the critical width for rupture to be 6.3 ± 3.7 mm

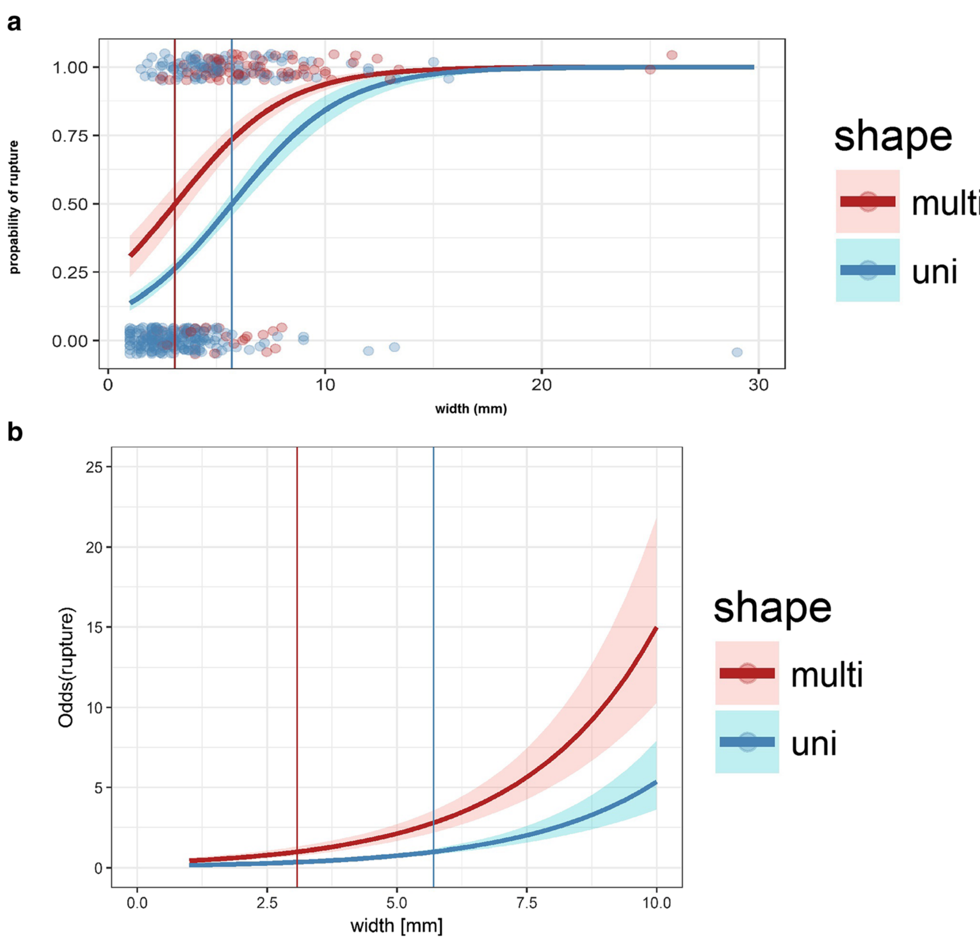

Fig. 4 Shape and width determine the probability of rupture. The regression analysis for the metric values shows that by "step-by-step" elimination, the shape and width correlate with a higher probability of rupture. Multilobar aneurysms are highly significant prone to rupture. **a** For multilobar aneurysms, the 50% boundary (odds ratio 1:1) was at a width of 3.1 mm and for unilobar at 5.7 mm. **b** The odds ratio for multilobar/unilobar was 2.79

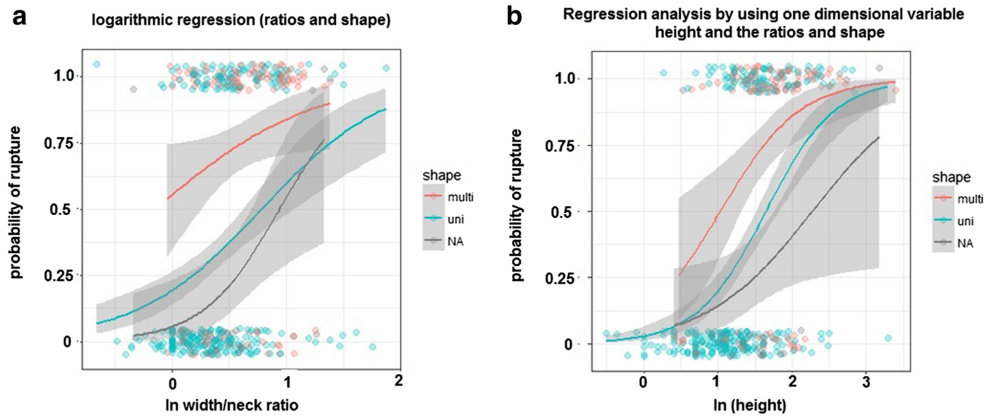

Fig. 5 Logistic regression analysis. **a** The logistic regression analysis and a step-by-step elimination for the ratios shows that the probability to rupture depends again on shape and the width/neck ratio. Aspect ratio and dome/neck ratio showed only a statistical trend. **b** The logistic regression analysis by using the metric value height and the ratios and shape showed that height and shape alone determine the risk of rupture

neck ratio and shape for multilobar aneurysms, the 50% boundary (odds ratio 1:1) was at a ratio of 1 and for unilobar aneurysms at a ratio of 2.2 (Fig. 6a). The odds ratio for the width/neck ratio for multilobar to unilobar aneurysms was 4.26 (Fig. 6b). The dome height/neck ratio (aspect ratio) showed statistical significance at $p < 0.01$ in the t test for two independent variables and in the paired analysis (Table 1).

At the end, we used the highly significant parameter "height," and the ratios and the only significance seen was again height with shape (Fig. 5b).

Table 1 gives the mean values and standard deviations for the evaluated parameters, and Fig. 7 illustrates the anatomic appearance of the aneurysm that is prone to rupture vs. the unruptured in accordance with the metric mean values of the statistical parameters (height, width, neck, height/width ratio, width/neck ratio, height/neck (aspect ratio), diameter of proximal vessel, diameter of distal vessels, angulation).

Discussion

The International Study of Unruptured Intracranial Aneurysms (ISUIA) showed that the size of an aneurysm either in the anterior or posterior circulation is a significant factor correlating with the rupture risk. The same study demonstrated that aneurysms of the posterior circulation are more prone to rupture than those of the anterior circulation [28]. Other researchers presented data supporting the fact that small aneurysms (< 10 mm) could bleed more frequently as we might expect [5, 14]. It became with time clear that size alone is not sufficient to direct our decision as to when to treat and when to opt for follow-up. In our series, we could demonstrate that the ruptured aneurysms were bigger than the unruptured ones. The critical size for rupture was 6.3 mm (SD: 3.7 mm). Regarding the shape of the aneurysms, the UCAS study and others demonstrated that irregularity in shape (daughter sacs) was a risk factor for rupture [6, 23, 25]. In our series, multilobar aneurysms ruptured more often than unilobar ones. As mentioned previously, the multilobar ones usually have a bigger size, a parameter already identified as a risk factor [15].

In our study, we found statistical significance between width of aneurysm and rupture risk but not between the size of the neck of the aneurysm and the rupture risk. Wang et al. found that ruptures associated with all other continuous data, but not with neck size either [26]. Kim and Hwang in a series of 130 aneurysms (86 ruptured) could not demonstrate a statistically significant correlation of neck width to rupture risk [11].

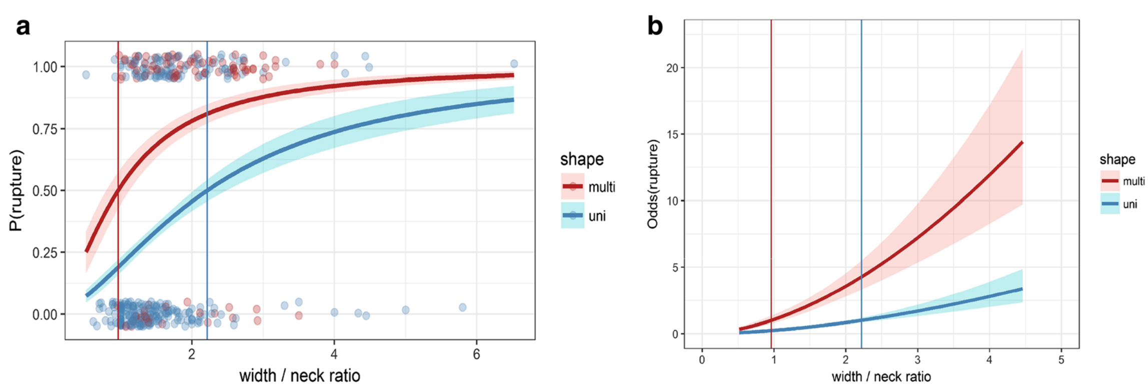

Fig. 6 The width/neck ratio. **a** Especially for the width/neck ratio and shape for multilobar aneurysms, the 50% boundary (odds ratio 1:1) was at a ratio of 1 and for unilobar aneurysms at a ratio of 2.2. **b** The odds ratio for the width/neck ratio for multilobar to unilobar aneurysms was 4.26

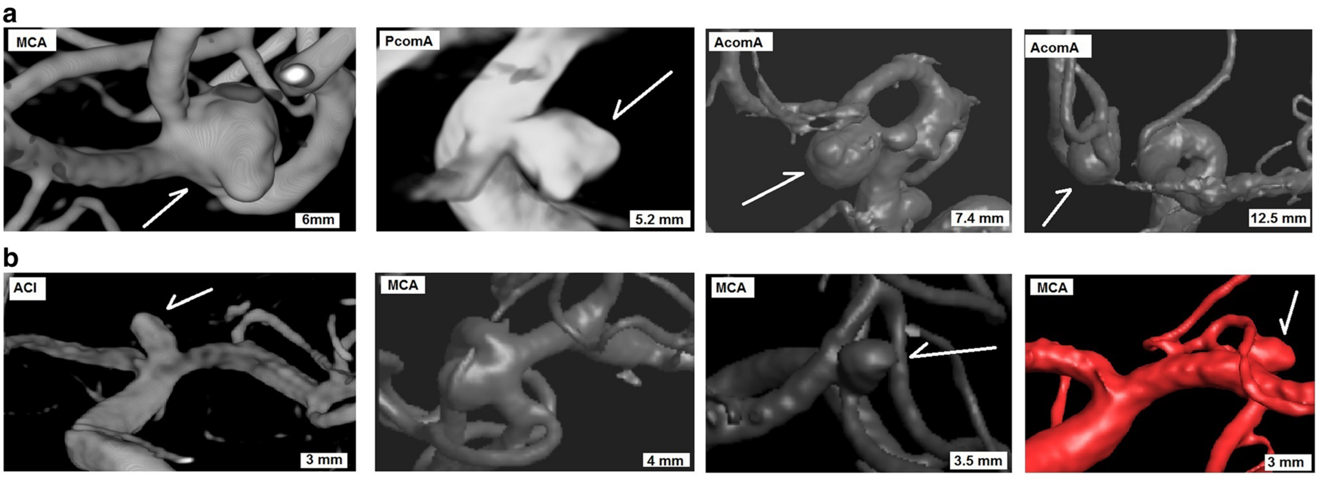

Fig. 7 Illustration of an aneurysm prone to rupture (**a**) vs. an aneurysm, which is not at risk (**b**). **a** Four examples with localization and height of the ruptured aneurysm. **b** Typical unruptured aneurysms

Regarding location, Clarke et al. reviewed the literature and reported that the ICA is the commonest site for unruptured aneurysms, whereas aneurysms of the posterior circulation demonstrate an annual rupture risk of 1.8% in comparison to 0.49% for anterior circulation aneurysms [3]. The same authors report, however, that the bleeding rate of posterior communicating artery aneurysms is almost similar to those of the anterior circulation. In our series, we could not draw this conclusion, since posterior communicating artery aneurysms reached statistical significance in the chi-square analysis in terms of tendency to rupture. This result would be in line with those of the ISUIA study; although, ISUIA did not focus solely on multiple aneurysms Nehls et al. from the Barrow Neurological Institute reported many years ago that anterior communicating artery aneurysms had the highest probability to rupture (62%) [17]. However, this analysis does not include logistic regression. In other words, in our opinion, one has to start with many variables and step-by-step identifying the significant ones. By doing so, in our study, we did not find a statistical difference for rupture risk of anterior communicating aneurysms. As stated in the same paper of Nehls et al., in many series, no posterior fossa angiography was performed making it difficult to assess differences in anterior vs. posterior circulation aneurysms [17].

Many decades ago Taveras and Wood in their textbook described criteria that could predict rupture, for example, aneurysm size, irregular configuration, and focal vasospasm [22]. These parameters are still relevant today; although, some are also infrequent and thus do not always apply. It is obvious that we need parameters present in every aneurysm so that we draw safe conclusions. In order to overcome possible discrepancy with some simple metric anatomic variables incorrectly correlating with risk to rupture, researchers have introduced ratios like height of dome/neck (aspect ratio), maximum height of aneurysm/mean diameter of all vessels, proximal and distal, (size ratio), as well as vessel to vessel angles with the hope to identify more accurately which aneurysms are in higher risk to rupture. Ujiie et al. introduced the aspect ratio in literature and found that aneurysm with an aspect ratio of 1.6 were more prone to rupture, thus warranting treatment [24]. Nader-Sepahi et al. report a mean aspect ratio of 2.7 for ruptured and 1.8 for unruptured aneurysms, which was statistically significant [16]. In our study, we could also find a statistical trend in the height/neck (aspect ratio) ratio among the ruptured and unruptured aneurysms (2 ± 0.8 vs. 1.5 ± 0.8 respectively). In the same line is Weir et al. who found 20 times greater odds of rupture when the height of dome/neck ratio was > 3.7 [27]. Wang et al. concluded that irregular shape and a height of dome/neck ratio > 0.96 are better predictors (threshold of receiver operating characteristic) of rupture in middle cerebral artery bifurcation aneurysms [25]. Further studies have demonstrated that dome/neck (aspect) ratio correlate with rupture [9, 10]. In our study, we evaluated most of the parameters, which are thought to be of value.

The bottleneck factor is defined as the width/neck ratio. As shown in Table 1, we found a statistically significant difference between ruptured and unruptured aneurysms (2 ± 0.8 vs. 1.5 ± 0.6 respectively). Jiang et al. could also demonstrate statistical significance of this parameter between the two groups [9]. Lv et al. investigated multiple parameters and ratios in small posterior communication artery aneurysms. They found no significance of bottleneck factor ($p = 0.154$) [13].

In our study, the inflow angle did not correlate with rupture risk. Baharoglu et al. found that increasing inflow angle (IA) in sideways aneurysms resulted in greater wall shear stress inside the dome. According to the authors, IA is a significant predictor of aneurysm rupture [1]. Ye et al. investigated the A1–A2 angle and found that it could help predict the formation of AcomA Aneurysms but not the rupture [29]. In basilar tip aneurysms, a bifurcation angle could be a significant predictor of rupture [19].

The results of our study show that size of aneurysm, irregularity in shape, height of dome/neck, and width/neck correlate with rupture risk and are, as discussed above, supported by the literature. A limitation in this study is that the aneurysms were evaluated with CT or CT angiography. A 3D rotational DSA is considered superior to other imaging modalities especially in aneurysms with irregular shape [18]. The anatomical characteristics of the aneurysm after rupture could also change [20]. Ideally, we would like to have anatomical measurements before the bleeding. Skodvin et al. demonstrated that aspect ratio and bottleneck ratio were significantly altered after rupture. If aneurysms change in morphology after the rupture, it is not very accurate to extrapolate the data for the pre-rupture status. Intracranial vessel wall MRI might be a useful tool in identifying unstable aneurysms [21].

A strength of our study is that we compared ruptured to unruptured aneurysms in the same person in order to eliminate confounding parameters related to patients' characteristics.

Conclusion

Metric variables like height and the morphology of aneurysms have been established as very reliable predictors of rupture. Ratios are dependent on these variables, and are therefore redundant in saccular aneurysms. We cannot say this for sausage-like aneurysms with abnormal ratios since they are rare; here, another study would be needed. Saccular aneurysms reaching the given critical size are prone to rupture and should be treated. Because of the redundancy, we do not routinely use primarily the ratios in decision-making in our practice. We focus instead more on size and irregularity of shape.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics committee (Nr.: 5817R).

Informed consent Informed consent (oral) was obtained from all individual participants included in the study. Patients who did not consent were not included.

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