Turk Neurosurg 34(4):624-639, 2024

Original Investigation

Received: 27.06.2023
Accepted: 26.07.2023

DOI: 10.5137/1019-5149.JTN.44866-23.2

Published Online: 01.08.2023

Risk Factors for Intracranial Aneurysm Rupture: A Clinical Case Series and Systematic Review of the Literature

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ABSTRACT

AIM: To evaluate the patients who underwent surgery for an anterior communicating artery (AcomA) aneurysm at our institution. We analyzed our case series and systematically reviewed the literature to identify factors that could predict the rupture of an intracranial aneurysm in patients with AcomA aneurysms or any intracranial aneurysm.

MATERIAL and METHODS: We conducted a cross-sectional analysis of prospectively collected data from patients who underwent surgery for AcomA aneurysms at a single institution between January 2014 and May 2023. Predictors for the rupture of intracranial aneurysm were systematically reviewed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Pubmed and MEDLINE databases.

RESULTS: Younger age (odds ratio (OR): 0.957, 95% confidence interval (CI): 0.920–0.995, p=0.028), presence of a daughter sac (OR: 3.209, 95% CI: 1.095–9.408, p=0.034), and ever-smoking (OR: 0.357, 95% CI: 0.137–0.930, p=0.035) were significant predictors of increased risk of rupture in patients with AcomA aneurysms. Several aneurysm- and patient-related risk factors for rupture of intracranial aneurysms were retrieved via the literature analysis.

CONCLUSION: Younger age, ever-smoking, and presence of a daughter sac increased the risk of AcomA aneurysm rupture. A systematic literature review revealed several more aneurysm- and patient-related risk factors for rupture of the intracranial aneurysms. Our results could aid neurosurgeons during their decision-making process when treating patients with unruptured intracranial aneurysms.

KEYWORDS: Aneurysm, Rupture, Subarachnoid hemorrhage, Risk factor, Anterior communicating, unruptured

ABBREVIATIONS: UIA: Unruptured intracranial aneurysm, **AcomA:** Anterior communicating artery, **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **OR:** Odds ratio, **CI:** Confidence interval, **SAH:** Subarachnoid hemorrhage, **DSA:** Digital subtraction angiography, **CT:** Computed tomography, **CTA:** Computed tomography angiography, **FOV:** Field of view, **GCS:** Glasgow coma score, **mRS:** Modified Rankin Scale, **GOS:** Glasgow outcome score, **SD:** Standard deviation, **RR:** Relative risk, **HR:** Hazards ratio, **IC:** Internal carotid artery, **PcomA:** Posterior communicating artery, **MCA:** Middle cerebral artery, **ACA:** Anterior cerebral artery.

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INTRODUCTION

Unruptured intracranial aneurysms (UIA) are vascular lesions formed by the outpouching of the arterial wall due to its thinning (78). UIAs are detected in 3%–8% of the general population with an annual rupture rate of 2% (68,87). Subarachnoid hemorrhage caused by the rupture of an aneurysm increases the patient's morbidity and mortality (27).

The exact pathogenesis of aneurysm rupture remains unclear, despite the identification of some pre-defined risk factors including smoking, alcohol consumption, and hypertension (9,10,41,84,87). Hemodynamic stress triggers a degenerative process by causing focal changes in the aneurysm wall (98). Studies regarding the morphological aneurysm parameters that are associated with the risk of rupture in specific locations are scarce (17). Thus, we aimed to evaluate the patients who underwent surgery for an anterior communicating artery (AcomA) aneurysm at our institution. We analyzed our case series and systematically reviewed the literature to identify predictors of aneurysm rupture in patients with AcomA aneurysms and any intracranial aneurysms.

MATERIAL and METHODS

Patient Cohort

We conducted a cross-sectional analysis of patients who were surgically treated for an AcomA aneurysm by the first author (E.C.) at a single institution between January 2014 and May 2023. The exclusion criteria were as follows: age of <18 years, aneurysms treated with endovascular methods, aneurysms associated with the Moyamoya disease, fusiform aneurysms, and aneurysms with poor image quality. The study was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments (IRB approval no: FSMEAH-KAEK 2021/87, 23.12.2021).

Imaging Modality

All aneurysms were confirmed either with digital subtraction angiography (DSA; Canon Medical Systems Corporation, Otawara, Tochigi, Japan) or computed tomography angiography (CTA; GE Healthcare, Chicago, Illinois, USA). Cerebral angiography was performed under local anesthesia or sedation depending on the patient's anxiety level and medical status. CTA was obtained using a dual-source CT scanner with a field of view (FOV) of 300 mm, slice thickness of 5 mm, and 384 slices.

Clinical and Radiological Evaluation

The following data were obtained from the patients' charts: Glasgow coma score (GCS) at the time of admission, post-operative GCS, and the modified Rankin Scale (mRS) and Glasgow Outcome Score (GOS) during the final follow-ups. The patient's age, sex, and smoking status were also recorded. The same researcher evaluated each patient's pre-operative DSA or CTA scan images (O.S.).

Literature Review

Predictors for the rupture of an intracranial aneurysm were systematically reviewed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (62). Pubmed and MEDLINE were searched for the systematic review using the following keywords: "intracranial" and "aneurysm" and "rupture" and "predictor" and "morphology." Relevant articles and their relevant references were included. A flow chart of the search is depicted in Figure 1. The search was conducted by two authors (M.S.E. and F.B.) and disagreements were settled by consensus. We retrieved 85 articles via the review process and have presented it with our clinical series (Table I).

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (version 25.0; IBM, Armonk, New York, USA) and Excel 2019 (Microsoft, Redmond, Washington, USA). Continuous variables are presented as means and standard deviations (SDs). Categorical variables are presented as absolute numbers and percentage. Categorical variables were compared using the Chi-square test. Continuous variables were analyzed using the independent samples t-test or Mann–Whitney U test depending on whether the data was normally or non-normally distributed based on the Kolmogorov–Smirnov and Shapiro–Wilk tests, respectively. Binary logistic regression analysis was conducted to identify significant predictors for the rupture of AcomA aneurysms; the data was presented as odds ratio (OR) and 95% confidence interval (CI). Predictive values from the literature review were recorded in their naïve form as OR, relative risk (RR), or hazards ratio (HR). An alpha value of <0.05 was statistically significant.

RESULTS

Demographics

A total of 107 patients with an AcomA aneurysm (women, 54 [50.5%]; men, 53 [49.5%]) with a mean age of 52.43 ± 10.48 years (range, 23–77 years) were included in the study. Of the 107 patients, 53 (49.5%) were ever-smokers (smoked formerly or were active smoker). Approximately 59.8% (n=64) of the patients presented with SAH. The mean maximum width of the aneurysms was 6.86 ± 2.67 mm (range, 2–18 mm). Daughter sacs were detected on the aneurysm domes in 22.4% (n=24) of the patients. The GCS score at admission was ≤ 8 in 5.6% (n=6) of the patients. Approximately 84.1% (n=90) of the patients had a good recovery following surgery and 81.3% (n=87) had good mRS scores (≤ 2) at their final follow-up. The mean GOS was 6.45 ± 2.39 (range, 1–8) at the final follow-up.

Predictors of AcomA Aneurysm Rupture

Patients with rupture-induced SAH were statistically younger than those with intact aneurysms at the same location (50.57 ± 10.32 vs. 55.21 ± 10.21 years, p=0.024). The ruptured AcomA aneurysms were smaller than the intact AcomA aneurysms; however, the difference was not statistically significant (6.53 ± 2.31 vs. 7.29 ± 3.06 mm, p=0.302). Men were more likely to have an AcomA aneurysm rupture than women. However, the

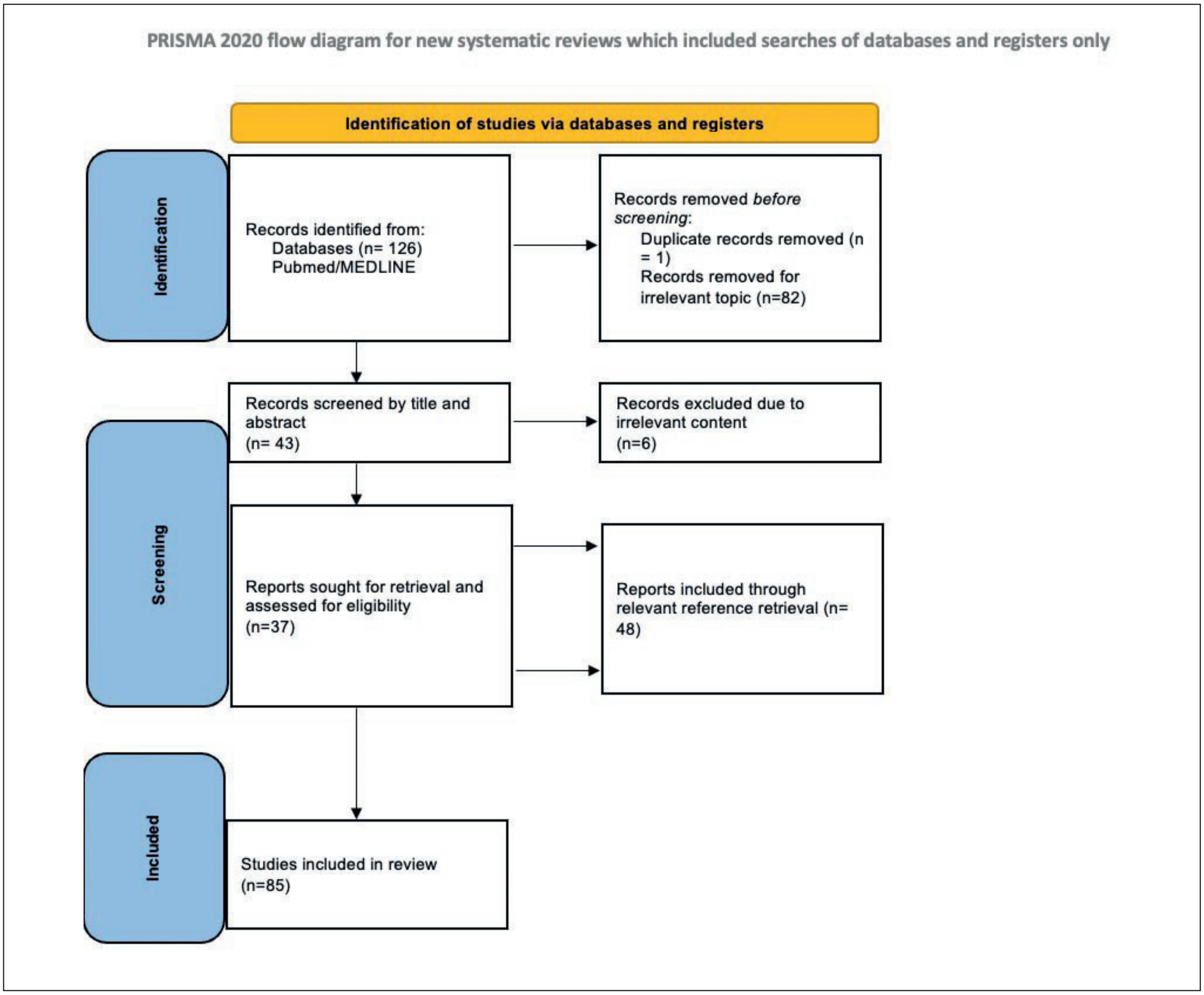

Figure 1: Flowchart of the PRISMA guidelines regarding the systematic review to determine the predictive risk factors for intracranial aneurysm rupture (62).

difference was not statistically significant (56.2% vs. 39.5%, p=0.09). The incidence of daughter sacs (29.7% vs. 11.6%, **p=0.028**) and history of smoking (76.7% vs. 54.1%, **p=0.032**) were higher in patients with an AcomA aneurysm rupture than in those with an intact AcomA. Younger age (OR: 0.957, 95% CI: 0.920–0.995, **p=0.028**), presence of daughter sacs (OR: 3.209, 95% CI: 1.095–9.408, **p=0.034**), and ever-smoking (OR: 0.357, 95% CI: 0.137–0.930, **p=0.035**) were significant predictors for the increased risk of AcomA aneurysm ruptures.

Literature Review

Aneurysm-Related Factors

Size ratio had an OR of 1.14–21.462; aspect ratio, 1.85–10.833; bottleneck ratio, 1.25–2.65; area ratio, 4.089; height-width ratio, 1.21–14.22; undulation index, 1.51; aneurysm size, 1.33–50; aneurysm volume, 0.98; aneurysm projection (for AcomA, anterior vs. posterior; for MCA, temporal) 1.91–6.0; inflow angle, 1.045–2.286; parent-daughter angle, 0.92–0.95; aneurysm width, 1.676–4.11; height > width, 9.067; aneurysm neck diameter, 1.30–3.52; deviated aneurysm neck, 2.11; aneurysm dome diameter, 4.35; energy loss, 1.497; daughter sac, 1.63–22.0; multilobulated aneurysm, 7.3–17.38; aneurysm fenestration, 4.135; aneurysm growth on follow-up, 55.93; enhancement on wall, 6.710; enhancement ratio, 6.638; irregular shape, 0.12–10.443; aneurysm location (any; specifically at bifurcations), 1.5–2.646; MCA location, 2.31–9.21; ACA location, 4.57; AcomA location, 2.02–6.28; PcomA location, 1.90–11.19; anterior circulation, 0.77–2.2; posterior circulation 2.9–5.33; multiple aneurysms, 4.87; right sidedness, 1.32; ICA diameter, 0.50; distance to ICA bifurcation (mm), 0.44; vessel size, 0.4–0.42; and dominant vessel (for AcomA), 2.26 (Table I) (1-6,8,11-23,25,26,28,29,31, 33-61,63-67,69-76,79-81,83,85,86,88-93,95-100).

Patient-Related Factors

Age had an OR of 0.17–5.23; male sex, 1.2; female sex, 0.52–0.7; headache, 0.75; hypertension, 2.1–7.93; diabetes mellitus, 0.32; dyslipidemia, 0.45–0.68; history of ischemic stroke, 0.28–3.4; history of ischemic heart disease, 0.26–0.57; history of carotid artery stenosis, 0.5; history of SAH, 7.3–10.83; statin treatment, 0.59; platelet aggregation inhibitor, 0.57; hormone therapy treatment, 0.59; allergy, 0.75; smoking, 0.3–4.435; alcohol consumption, 1.27; screening brain scan as a reason for imaging, 4.09; and history of familial intracranial aneurysms had an RR of 10.1 (Table I).

DISCUSSION

Intracranial aneurysms have been detected in 0.3%–4% of cadavers and 3%–8% of the general population (32,68,87). The prevalence of incidental aneurysms on magnetic resonance imaging is reportedly 0.31% (77). High rate of incidental intracranial aneurysms necessiates early diagnostic and preventive measures to be taken to prevent unintended consequences. In the present study, we evaluated the patients who underwent surgery for AcomA aneurysm at our institution. We analyzed our case series and systematically reviewed the literature to identify predictive factors for the rupture of an intracranial aneurysm (Table I). These factors could be categorized as aneurysm-related and patient-related factors.

Aneurysm-Related Factors

Reported, size ratio and aspect ratio were important predictive factors for the rupture of an aneurysm (42,47,95,98). Size ratio is calculated by dividing the maximum aneurysm height by the average diameter (16). Compared to the subjects that had aneurysms with smaller size ratio is a dominant predictor of aneurysm rupture with up to 21 times increased risk and a threshold of 1.4–1.6. However, Lauric et al. identified a limited utility of size ratio in predicting aneurysm rupture than that previously reported (45). In contrast, Kashiwazaki et al. determined that the OR for size ratio increased when the aneurysms were <5 mm in size (42). Aspect ratio is calculated by dividing the maximum perpendicular height of the aneurysm by the average neck diameter (16). Different threshold values have been defined for aspect ratio ranging between 1.01 and 1.6. Patients with values higher than the threshold had a greater risk (up to 11 times) of developing aneurysm rupture than those with values lower than the threshold. Bottleneck ratio is the ratio of the dome width to the neck width. The bottleneck ratio had an increased risk of rupture up to 2.7 times for every increment of 0.1 (26). Area ratio is the ratio of the area of the aneurysm to that of the parent artery in the neck plane (28). An area ratio of ≥1.5 led to a four times higher risk of rupture. Height-width ratio is the ratio of the maximum aneurysm height to the aneurysm width in the neck plane (16). A height-width ratio of >1 resulted in a 14 times increased risk of rupture. Undulation index has been defined by only one group. Dhar et al. defined undulation index as 1-V/Vch, where V is the volume of the aneurysm above the neck plane and Vch is the volume of the convex hull (15). An increased undulation index increases the likelihood of rupture by 1.5 times. Another commonly used parameter is the aneurysm size, which is the maximum perpendicular distance of the dome from the neck plane (15). An aneurysm of >4–7 mm in size increases the likelihood of rupture by 50 times (83). However, different thresholds have been defined as the critical size for aneurysm rupture; furthermore, increased aneurysm size is related to the higher aneurysm rupture rate (35,80,91). In contrast, a vessel size of <1.6 mm is the threshold for AcomA rupture (8). This may be because a small vessel might have a higher jet flow and thinner vessels might have greater tensile stress (53).

Projection of the aneurysm dome is a prognostic factor for AcomA aneurysms. Larger aneuryms, larger size ratios, and larger aspect ratios are observed more in the anteriorly projected AcomA aneurysms than in the posteriorly projected ones (55,73). Furthermore, AcomA aneurysms with a dominant A1 are more likely to rupture due to significant differences in the wall shear stress between the dominant and non-dominant A1 segments (94). Configuration of the AcomA aneurysms (symmetric, dominant or absent A1) might change the wall shear stress, flow velocity, and pressure of the AcomA complex (13,24). Other important parameters that can predict rupture status were inflow angle, parent-daughter angle, width, neck diameter, dome diameter, energy loss, multilobulation and/or fenestration, wall enhancement, and aneurysm growth (1,2,11 ,13,14,16,25,47,51,52,56,63,75,79,85,86,89,96,98).

Irregularity of the aneurysm wall is also a risk factor for the rupture of aneurysms (13). Irregular aneurysm shapes might indicate changes in the aneurysm wall. Hence, an unstable blood flow due to hypertension and atherosclerosis might lead to weakness of the wall and increase the risk of rupture. This theory was confirmed by the observation that aneurysms with irregular shapes increase in size (7). Irregularly shaped aneurysms increase the risk of rupture by up to 10 times compared to the regularly shaped aneurysms. Daughter sac, an irregular protrusion of the aneurysm wall, is reportedly a dominant predictive factor for aneurysm rupture, with an increased likelihood of rupture between 1.6 and 22 times (1, 12,14,36,37,41,47,48,50,55,71,80,96,98,100). In the present study, we found that the presence of a daughter sac increased the risk of rupture by 3.2 times, which is comparable with the findings of previous studies. Not only the aneurysm, but also the perianeurysmal environment is crucial in predicting the risk of rupture. Higher rates of unbalanced contract constraints increases the incidence of rupture (72).

Patient-Related Factors

Age is a valid prognostic factor for intracranial aneurysm rupture (OR: 0.17–5.23). Younger age (<50 years) increases the risk of rupture (76). Similarly, in our study, we determined that a younger age was a significant predictive factor for the rupture of AcomA aneurysms. Furthermore, males had higher risk of developing a rupture than females. Although several comorbidities were associated with the risk of rupture, the most significant ones were hypertension, history of SAH, history of ischemic stroke, and familial history of intracranial aneurysms. Alcohol consumption (1.3 times higher risk) and smoking (up to 4.4 times higher risk) have significant predictive values for the rupture of intracranial aneurysm. Similarly, in our study we

Table I: Literature Review About Predictors of Intracranial Aneurysm Rupture

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Present study	RCS	64 SAH patients, 43 incidental patients	AcomA	Daughter sac had an OR of 3.2 (95% CI: 1.09-9.4), smoking had an OR of 0.3 (95% CI: 0.13-0.93) and younger age of the patient had an OR of 0.95 (95% CI: 0.92-0.99)
Chen et al. (11), 2023	RCS	62 SAH patients and 36 incidental patients	PcomA	Size ratio had an OR of 1.625 (95% CI: 1.034-2.553), inflow angle had an OR of 2.286 (95% CI: 1.417-3.690) in all patients; inflow angle had an OR of 3.223 (95% CI: 1.444-7.197) in patients with fetal circulation; size ratio had an OR of 2.378 (95% CI: 1.216-4.650), inflow angle had an OR of 2.086 (95% CI: 1.082-4.020) in patients with non-fetal circulation
Xu et al. (96), 2023	RCS	45 SAH patients with mirror unruptured aneurysm at PcomA	PcomA	Aneurysm width with an OR of 1.676, daughter sac with an OR of 7.775, aneurysm with height > width had an OR of 9.067
Zhang et al. (99), 2021	RCS	218 SAH patients, 35 incidental patients	AcomA	Aneurysm diameter had an OR of 4.11 (95% CI:1.601-16.07), younger age than 65 years had an OR of 0.17 (95% CI: 0.062-0.48)
Van der Kamp et al. (83), 2021	RCS	312 patients of 7.6% ruptured	ICA, MCA, PcomA, AcomA, ACA, VBA	Size of 7 mm or more had a HR of 3.1 (95% CI: 1.4-7.2), irregular shape had a HR of 2.9 (95% CI: 1.3-6.5)
Liu et al. (50), 2021	RCS	278 SAH patients and 125 incidental patients	MCA	Aneurysm size, aneurysm height, perpendicular height, aspect ratio, size ratio, bottleneck factor, height-width ratio all higher in ruptured aneurysms. Aneurysm angle, flow angle were significantly different. Unruptured aneurysm more frequently regular (70.4% vs. 46.4%), ruptured aneurysms more frequently had daughter sac (29.5% vs. 10.4%)
Rousseau et al. (69), 2021	PCS	994 SAH patients, 1511 incidental patients	ICA, MCA, ACA, PCC	Male sex had an OR of 1.2 (95% CI: 1.01-1.44), age of younger 60 had an OR of 0.7 (95% CI: 0.58-0.85), age of 60-69 had an OR of 0.42 (95% CI: 0.34-0.52), age of 70 or more had an OR of 0.28 (95% CI: 0.2-0.38), MCA had an OR of 2.31(95% CI: 1.79-3.00), ACA had an OR of 4.57 (95% CI: 3.58-5.86), posterior circulation had an OR of 5.33 (95% CI: 4.08-7.00) adjusted size ratio of 3 or more had an OR of 2.23 (95% CI: 1.89-2.62), headache had an OR of 0.75 (95% CI: 0.6-0.94), dyslipidemia had an OR of 0.68 (95% CI: 0.55-0.82), ischemic stroke history had an OR of 0.28 (95% CI: 0.19-0.41), ischemic heart disease history had an OR of 0.26 (95% CI: 0.13-0.47), carotid artery stenosis history had an OR of 0.5 (95% CI: 0.28-0.85), statin treatment had an OR of 0.59 (95% CI: 0.47-0.75), platelet aggregation inhibiting treatment had an OR of 0.57 (95% CI: 0.44-0.72), hormone therapy treatment had an OR of 0.59 (95% CI: 0.35-0.96), allergy had an OR of 0.75 (95% CI: 0.62-0.91)
Chen et al. (13), 2020	RCS	578 SAH patients, 72 incidental patients	AcomA	Vessel size had an OR of 0.41 (95% CI: 0.24-0.70), aneurysm size had an OR of 1.33 (95% CI: 1.14-1.55), projection (anterior vs. posterior) had an OR of 1.91 (95% CI: 1.13-3.24), dominant (vs. symmetric) had an OR of 2.26 (95% CI: 1.22-4.18), irregularity had an OR of 3.29 (95% CI: 1.23-8.82)
Ma et al. (54), 2020	RCS	72 SAH patients, 40 incidental patients	AcomA	Smoking had an OR of 4.435 (95% CI: 1.443-13.634), size ratio had an OR of 3.890 (95% CI: 1.574-9.617), flow angle had an OR of 1.054 (95% CI: 1.022-1.088), irregular shape had an OR of 1.068 (95% CI: 1.019-1.249)
Chen et al. (12), 2020	RCS	268 patients with 207 ruptured and 73 unruptured aneurysms	MCA	Size ratio had an OR of 1.324 (95% CI: 1.062-1.651), daughter sac had an OR of 2.462 (95% CI: 1.123-5.398)
Lv et al. (52), 2019	RCS	257 patients with unruptured 313 aneurysms	ICA, MCA, ACA, PcomA, PCC	Aneurysm wall enhancement had higher predictive value for rupture; size had an OR of 1.536 (95% CI: 1.312-1.798), location had an OR of 1.592 (95% CI: 1.237-2.049) for predicting aneurysm wall enhancement
Skodvin et al. (75), 2019	RCS	12 SAH patients, 24 incidental patients	AcomA, MCA, PcomA	Smaller inflow angle was predictor of rupture

Table I: Cont.

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Kocur et al. (43), 2019	RCS	140 ruptured aneurysms, 285 unruptured aneurysms	AcomA, MCA, ICA, PCC	Aspect ratio, aneurysm location higher rupture risk for AcomA
Feng et al. (18), 2019	RCS	121 SAH patients, 386 incidental patients	ICA, AcomA, PcomA, ACA, MCA, PCA	Moderate (50-70%) cerebrovascular stenosis had an OR of 3.4 (95% CI: 1.8-6.5), lobulation of aneurysm had an OR of 2.6 (95% CI: 1.1-5.8), aneurysms at bifurcation locations of the arteries had an OR of 2.4 (95% CI: 1.5-3.8)
Zhang et al. (98), 2019	RCS	106 SAH patients and 455 incidental patients	MCA	Temporal projection of MCA aneurysm had an OR of 2.16 (95% CI: 1.16-4.00), irregular aneurysm shape had an OR of 6.42 (95% CI: 3.50-11.78), daughter sac had an OR of 5.19 (95% CI: 2.84-9.48), higher bottleneck ratio had an OR of 2.65 (95% CI: 1.15-6.07), size ratio had an OR of 9.98 (95% CI: 3.50-23.08)
Vergouwen et al. (85), 2019	PCS	57 incidental patients	ICA, PcomA, AcomA, ACA, pericallosal artery, MCA, VBA, PCC	Contrast enhancement on aneurysm wall on MRI signifies increased rupture risk
Ikawa et al. (31), 2019	PCS	5720 aneurysm patients	MCA, AcomA, ICA, PcomA, VBA	Past history of SAH had an OR of 10.83 (95% CI: 2.29-51.13), uncontrolled hypertension had an OR of 5.21 (95% CI: 1.77-15.30), AcomA had an OR of 4.98 (95% CI: 1.60-15.52), screening brain checkup as a reason for imaging had an OR of 4.09 (95% CI: 1.16-14.40) for predicting rupture of small aneurysms (of 4 mm or less in size)
Fung et al. (20), 2019	RS	1080 SAH patients	N/A	Metric variables escribing the geometry of the aneurysm and shape were the most predictive factors
Shojima et al. (74), 2018	PCS	25 SAH patients	MCA, AcomA, ICA, PcomA, VBA	Size had an OR of 5.7 (95% CI: 1.8-17.3)
Duan et al. (16), 2018	RCS	128 SAH patients, 135 incidental patients	AcomA, PcomA, VBA, ophthalmic artery, MCA, ACA, ICA	Size ratio had an OR of 3.586 (95% CI: 1.518-8.474), inflow angle had an OR of 1.045 (95% CI: 1.026-1.064), height/width ratio had an OR of 8.023 (95% CI: 2.011-32.008), aspect ratio had an OR of 2.241 (95% CI: 1.065-4.715)
Wang et al. (90), 2018	RCS	379 patients with 441 aneurysms	AcomA, ACA, MCA, PcomA, ICA, PCC	Bifurcation had an OR of 2.646, irregularity had an OR of 3.478, aspect ratio had an OR of 2.484
Mocco et al. (57), 2018	PCS	57 SAH patients, 198 incidental patients	ICA, ACA, AcomA, MCA, VBA, PcomA, PCC	Perpendicular height was predictor of rupture
Grochowski et al. (21), 2018	RCS	96 SAH patients, 169 incidental patients	ICA, AcomA, MCA, VBA, PCC, ACA	Aneurysms with a size of 5-10 mm and AcomA location had higher risk rupture, in multiple aneurysm group two-concomitant aneurysm had higher rupture risk than other multiple aneurysms
Wang et al. (89), 2018	RCS	91 patients (19 ruptured & 87 unruptured aneurysms)	N/A	Partial enhancement on wall had an OR of 6.710 (95% CI: 1.805-24.938), enhancement ratio had an OR of 6.638 (95% CI: 1.919-22.967)
Qin et al. (63), 2017	RCS	36 SAH patients, 31 incidental patients	MCA	Longest dimension from the aneurysm neck to dome tip/dome width had an OR of 6.760, energy loss had an OR of 1.497

Table I: Cont.

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Xu et al. (95), 2017	RCS	474 SAH patients, 45 incidental patients	AcomA	Vessel size had an OR of 0.4 (95% CI: 0.2-0.8), size ratio had an OR of 3.9 (95% CI: 1.6-9.1) for very small aneurysms; vessel size had an OR of 0.4 (95% CI: 0.2-0.8), aneurysm size had an OR of 1.8 (95% CI: 1.3-2.5), aneurysm height had an OR of 1.6 (95% CI: 1.2-2.3), perpendicular height had an OR of 1.5 (95% CI: 1.1-2.2), size ratio had an OR of 3.2 (95% CI: 1.8-5.8) for small aneurysms
Abboud et al. (1), 2017	RCS	301 SAH patients, 204 incidental patients	ACA, PCA, MCA, ICA	OR of 3 from single sac with regular margin to irregular margin (95% CI: 1.6-5.3), OR of 5.5 with daughter sac (95% CI: 2.8-11), OR of 7.3 with multilobulated aneurysm (95% CI: 4.1-13.1)
Qiu et al. (65), 2017	RCS	41 SAH patients, 22 incidental patients	MCA, ICA, PcomA, ACA, ophthalmic artery	High and low wall shear stress predict rupture
Wang et al. (88), 2017	RCS	107 SAH patients (107 ruptured & 121 unruptured aneurysms)	AcomA, ACA, MCA, PcomA, ICA, PCC	Aneurysms located in the ICA had a negative risk of rupture, whereas high AR (>1.01), size ratio (>1.40) had higher risks for multiple aneurysm rupture
Huhtakangas et al. (29), 2017	RCS	258 SAH patients, 155 incidental patients	PcomA	Irregular shape had an OR of 0.12 (95% CI: 0.07-0.22), neck diameter had an OR of 1.30 (95% CI: 1.07-1.61), aspect ratio > 1.5 had an OR of 2.26 (95% CI: 1.26-4.04), ICA diameter had an OR of 0.50 (95% CI: 0.32-0.75)
Lv et al. (51), 2016	RCS	68 SAH patients, 40 incidental patients	PcomA	Size ratio had an OR of 1.67 (95% CI: 1.12-2.50), inflow angle had an OR of 2.01 (95% CI: 1.32-3.05) for small (< 7mm) PcomA aneurysms
Choi et al. (14), 2016	RCS	68 SAH patients, 187 incidental patients	AcomA	Superior direction of dome had an OR of 2.802 (95% CI: 1.151-6.818), daughter sac had an OR of 5.998 (95% CI: 2.763-13.020), aspect ratio >1.6 had an OR of 3.138 (95% CI: 1.334-7.384), size of > 7 mm had an OR of 3.356 (95% CI: 1.295-8.696), fenestration had an OR of 4.135 (95% CI: 1.334-14.371)
Shao et al. (73), 2016	RCS	461 SAH patients, 42 incidental patients	AcomA*	Size ratio had an OR of 1.46 (95% CI: 1.12-1.91), vessel size had an OR of 0.42 (95% CI: 0.18-0.98)
Huang et al. (28), 2016	RCS	63 ruptured aneurysms, 63 unruptured aneuryms	PcomA, MCA, ACA, ICA, VBA	Aspect ratio of 1.6 or more had an OR of 9.521 (95% CI: 2.182-41.535), area ratio of 1.5 or more had an OR of 4.089 (95% CI: 1.247-13.406), irregular shape had an OR of 10.443 (95% CI: 3.394-32.135)
Hao et al. (23), 2016	RCS	34 SAH patients, 40 incidental patients	AcomA, PcomA, MCA, ICA	Aspect ratio had an OR of 10.833 (95% CI: 2.606-45.039)
Zheng et al. (100), 2016	RCS	68 SAH patients, 82 incidental patients	MCA, AcomA, PcomA, ophthalmic artery	Size ratio had an OR of 1.66 (95% CI: 1.05-2.64), height-width ratio had an OR of 14.22 (95% CI: 2.67-75.88), shape had an OR of 4.68 (95% CI: 2.44-8.98), irregular shape had an OR of 5.76 (95% CI: 1.64-20.26), daughter sac had an OR of 14.56 (95% CI: 3.44-61.67), location had an OR of 1.60 (95% CI: 1.15-2.23), MCA had an OR of 9.21 (95% CI: 1.89-44.80), AcomA had an OR of 6.28 (95% CI: 1.57-25.02), PcomA had an OR of 11.19 (95% CI: 3.12-40.10)
Jiang et al. (37), 2016	RCS	58 SAH patients, 39 incidental patients	ICA, ACA, MCA, AcomA	Current smokers smoked more than 20 cigarettes per day, those with hypertension with an irregular use of anti-hypertensive medications were more prone to rupture; aneurysm location, daughter sac and size ratio were predictors of rupture
Lindgren et al. (49), 2016	Observa-tion	4074 aneurysms (2784 ruptured & 3030 unruptured)	AcomA, PcomA, MCA, ICA	Irregular shape had an OR of 7.1 (95% CI: 6.0-8.3), smoking had an OR of 0.7 (95% CI: 0.6-0.9); population, hypertension, age, aneurysm size, history of SAH, site of aneurysm score had an OR of 1.5 (95% CI: 1.4-1.6)

Table I: Cont.

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Kang et al. (41), 2015	RCS	103 patients with SAH (one ruptured and one unruptured aneurysm in each patient)	AcomA, PcomA, others	Daughter sac had an OR of 13.8 (95% CI: 1.65-115.87), maximum aneurysm height of 7 mm or more had an OR of 4.8 (95% CI: 1.21-18.98), PcomA or AcomA aneurysm had an OR of 3.09 (95% CI: 1.34-7.11), maximum aneurysm height/average parent diameter had an OR of 2.13 (95% CI: 1.16-3.91)
Orz & AlYamany (60), 2015	RCS	76 SAH patients, 5 incidental patients	AcomA, MCA, PcomA, AChA, ACA, VBA, ophthalmic artery, ICA, PCC	Small aneurysms presented at AcomA and distal ACA
Cai et al. (8), 2015	RCS	50 SAH patients, 30 incidental patients	AcomA	Size ratio had an OR of 411.08 (95% CI: 5.636-29998.329)
Qiu et al. (64), 2014	RCS	34 patients (34 ruptured & 42 unruptured aneurysms)	N/A	Size ratio of 1 or more and of 1.6 or less had an OR of 10.931 (95% CI: 1.98-60.39), size ratio > 1.6 had an OR of 21.462 (95% CI: 4.11-111.96), height-width ratio > 1 had an OR of 8.954 (95% CI: 2.32-34.60)
Backes et al. (4), 2014	PCS	124 ruptured aneurysms, 178 unruptured aneurysms	ACA, ICA, PcomA, MCA, PCC	Aspect ratio of 1.3 or more had an OR of 3.3 (95% CI: 1.3-8.4)
Ho et al. (25), 2014	RCS	40 SAH patients, 23 incidental patients	PcomA	Volume had an OR of 0.98 (95% CI: 0.95-0.99), neck diameter had an OR of 3.52 (95% CI: 1.01-17.9), distance to ICA bifurcation (mm) had an OR of 0.44 (95% CI: 0.19-0.80)
Mehan et al. (56), 2014	RCS	152 incidental patients	ACA, MCA, ICA, VBA, PCC	Growth had an OR of 55.93 (95% CI: 4.469-700.084), multilobulated structure had an OR of 17.38 (95% CI: 1.522-198.422)
Jeon et al. (36), 2014	RCS	85 SAH patients with multiple aneurysms (85 ruptured, 104 unruptured aneurysms)	ICA, ACA, AcomA, MCA, VBA	Height-to-width ratio with an OR of 1.21 (95% CI: 1.05-1.41), daughter sac with an OR of 3.12 (95% CI: 1.05-9.27), size ratio type I had an OR of 1.14 (95% CI: 1.05-1.22)
Tykocki et al. (79), 2014	RCS	31 SAH patients, 27 incidental patients	PCC	Inflow angle had an OR of 1.05 (95% CI: 1.01-1.1), size ratio had an OR of 3.53 (95% CI: 1.09-11.5)
Korja et al. (44), 2014	PCS	118 incidental patients	N/A	Current smoking had an OR of 3.44 (95% CI: 1.11-10.68), aneurysm size of 7 mm or more had an OR of 4.02 (95% CI: 1.14-14.19)
Villablanca et al. (86), 2013	RS	165 incidental patients	AcomA, PcomA, VBA	Aneurysm growth, size, smoking status
Elsharkawy et al. (17), 2013	RCS	1009 patients (902 unruptured & 407 ruptured aneurysms)	MCA	Height-width ratio had an OR of 3.44 (95% CI: 1.07-11.05), wall regularity had an OR of 8.39 (95% CI: 6.13-11.49), aneurysm location had an OR of 1.56 (95% CI: 1.09-2.23)
Kashiwazaki et al. (42), 2013	PCS	854 SAH patients, 180 incidental patients	ICA, MCA, AcomA, ACA,	Aneurysm size had an OR of 3.2 (95% CI: 2.3-14.1), size ratio had an OR of 5.1 (95% CI: 2.1-19.1) for all aneurysms; size ratio had an OR of 9.1 (95% CI: 3.1-15) for small aneurysms < 5 mm
Juvela et al. (40), 2013	Observation	142 patients with 181 aneurysms	ICA, ACA, AcomA, MCA, VBA	Cigarette smoking had a HR of 2.44 (95% CI: 1.02-5.88), AcomA had a HR of 3.73 (95% CI: 1.23-11.36), aneurysm diameter of 7 mm or more had a HR of 2.60 (95% CI: 1.13-5.98), alcohol consumption had a HR of 1.27 (95% CI: 1.05-1.53)

Table I: Cont.

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Matsukawa et al. (55), 2013	RCS	78 SAH patients, 62 incidental patients	AcomA	Anterior dome direction had an OR of 6.0 (95% CI: 2.1-19), daughter sac had an OR of 22 (95% CI: 7.8-72), size of 5 mm or more had an OR of 3.2 (95% CI: 1.1-9.4)
Lin et al. (47), 2013	RCS	42 SAH patients and 37 incidental patients	AcomA	Size ratio had an OR of 1.28 (95% CI: 1.15-1.76), flow angle had an OR of 1.05 (95% CI: 1.004-1.11), parent-daughter angle had an OR of 0.95 (95% CI. 0.91-0.99)
Li et al. (46), 2013	RCS	52 SAH patients with mirror incidental aneurysms	PcomA, MCA, ICA, ACA	No significant predictor
Lin et al. (48), 2012	RCS	40 ruptured aneurysm, 39 unruptured aneurysm	MCA	Aspect ratio had an OR of 1.85 (95% CI: 1.58-4.54), parent-daughter angle had an OR of 0.92 (95% CI: 0.82-0.97), flow angle had an OR of 1.06 (95% CI: 1.02-1.12)
Amenta et al. (2), 2012	RCS	1792 ruptured aneurysms, 3342 unruptured aneurysms	ICA, AcomA, ACA, MCA, VBA, PCC	Dome diameter > 10 mm had an OR of 4.35 (95% CI: 3.79-4.99), aspect ratio > 1.6 had an OR of 2.81 (95% CI: 2.45-3.22), deviated neck had an OR of 2.11 (95% CI: 1.72-2.59), anterior circulation aneurysms (including PcomA) had an OR of 0.77 (95% CI: 0.67-0.89), right sidedness had an OR of 1.32 (95% CI: 1.15-1.52)
Lauric et al. (45), 2012	RCS	98 ruptured aneurysms, 169 unruptured aneurysms	AcomA, ICA, PcomA, MCA, VBA, ACA, AchA, PCC	Size ratio had a more limited utility than previously reported ones
UCAS Japan Investigators (80), 2012	PCS	5720 patients with 6697 aneurysms of 91% discovered incidentally	MCA, AcomA, ICA, PcomA, VBA	Aneurysm size with 7-9 mm with a HR of 3.35 (95% CI: 1.87-6.00), 10-24 mm with a HR of 9.09 (95% CI: 5.25-15.74), 25 mm or larger with a HR of 76.26 (95% CI: 32.76-177.54), AcomA had a HR of 2.02 (95% CI: 1.13-3.58), PcomA had a HR of 1.90 (95% CI: 1.12-3.21), daughter sac had a HR of 1.63 (95% CI: 1.08-2.48)
Baharoglu et al. (5), 2012	RCS	101 ruptured, 170 unruptured aneurysms	AcomA, ICA, PcomA, MCA, VBA, oprthalmic artery, AChA, PCC	Height-width ratio had an OR of 2.69 (95% CI: 1.37-5.51), size ratio had an OR of 1.33 (95% CI: 1.07-1.68)
Ryu et al. (70), 2011	RCS	195 patients (105 ruptured & 109 unruptured aneurysms)	ACA, AcomA, MCA, PcomA, AChA, ICA, VBA, PCC	Height-width ratio, aspect ratio, bottleneck ratio, and volume-to-neck area ratio correlated with rupture
Rahman et al. (67), 2010	PCS	16 SAH patients, 24 incidental patients	Ophthalmic artery, ICA, VBA, MCA, PcomA, AcomA, PCC, ACA	Size ratio had an OR of 2.12 (95% CI: 1.09-4.13)
Sonobe et al. (76), 2010	PCS	72 SAH patients, 374 incidental patients	ICA, MCA, AcomA, ACA, VBA	Patient younger than 50 years of age had a HR of 5.23 (95% CI: 1.03-26.52), size of 4 mm or larger had a HR of 5.86 (95% CI: 1.27-26.95), hypertension had a HR of 7.93 (95% CI: 1.33-47.42), multiple aneurysms had a HR of 4.87 (95% CI: 1.62-14.65)
You et al. (97), 2010	RCS	167 ruptured aneurysms, 123 unruptured aneurysms	AcomA, ACA, PcomA, ICA, MCA, VBA, PCC	Maximum diameter of aneurysmal neck had an OR of 2.56 (95% CI: 1.402-4.552), aspect ratio had an OR of 2.939 (95% CI: 1.834-4.710)

Table I: Cont.

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Ma et al. (53), 2010	RCS	16 SAH patients, 22 incidental patients	N/A	Size ratio had an OR of 3.52 (95% CI: 1.035-11.938)
Inagawa (33), 2010	RCS	858 SAH patients, 285 incidental patients	ICA, ACA, MCA	Diabetes mellitus had an OR of 0.32 (95% CI: 0.19-0.53), hearth disease had an OR of 0.57 (95% CI: 0.38-0.86), hypercholesterolemia had an OR of 0.45 (95% CI: 0.33-0.61), smoking had an OR of 1.99 (95% CI: 1.26-3.14)
Ishibashi et al. (35), 2009	Observa-tion	419 patients with 529 aneurysms	ICA, ACA, MCA, VBA	A history of SAH had a HR of 7.3 (95% CI: 2.5-21.2), posterior circulation aneurysm had a HR of 2.9 (95% CI: 1.1-8), a size of 10-24.9 mm had a HR of 12.3 (95% CI: 3.9-38.8), a size of more than 25 mm had a HR of 50 (95% CI: 12.8-196)
Sadatomo et al. (71), 2008	RCS	41 patients (24 ruptured & 20 unruptured aneurysms)	MCA	Neck type (type C) showing central axis of the parent artery crossing the line of the neck, equality of the diameters of two daughter arteries, together with high aspect ratio were associated with rupture
Dhar et al. (15), 2008	RCS	20 SAH patients, 25 incidental patients	ICA, AcomA, MCA, PcomA, ACA, PCC	Undulation index had an OR of 1.51 (95% CI: 1.08-2.11), size ratio had an OR of 1.41 (95% CI: 1.03-1.92)
Hoh et al. (26), 2007	RCS	30 patients (30 ruptured & 37 unruptured aneurysms)	N/A	Bottleneck factor had an OR of 1.25 (95% CI: 1.11-1.41), height-width ratio had an OR of 1.23 (95% CI: 1.03-1.47)
San Milan Ruiz et al. (72), 2006	RCS	174 patients (124 ruptured & 66 unruptured aneurysms)	PcomA, AcomA, ICA, ophthalmic artery, MCA, PCC	Larger size, more irregular shape, more contact constraints with perianeurysmal environment, higher rates of unbalanced contact constraints
Beck et al. (6), 2006	PCS	83 ruptured aneurysms, 72 unruptured aneurysms	ACA, AcomA, MCA	Aneurysms located at anterior circulation diagnosed as ruptured more, MCA aneurysms diagnosed as unruptured more
Wermer et al. (93), 2006	PCS	93 patients (2 had SAH)	AcomA, ACA, ICA, MCA, VBA	History of SAH and familial intracranial aneurysms had a relative risk of 10.1 (95% CI: 1.3-81.9)
Raghavan et al. (66), 2005	RCS	9 SAH patients, 18 incidental patients	MCA, VBA, ophthalmic artery, AcomA, ACA, ICA, PcomA	Quantified shape was more important than size in discriminating between ruptured and unruptured aneurysms
Ohashi et al. (59), 2004	RCS	280 SAH patients	ICA, AcomA, MCA, ACA	AcomA/distal ACA had an OR of 2.2, female sex had an OR of 0.7, poorly controlled hypertension had an OR of 2.1, smoking had an OR of 0.5
Nader-Sepahi et al. (58), 2004	RCS	75 SAH patients with ruptured and unruptured aneurysms concomitantly	AcomA, PcomA, MCA, ICA	Size of the aneurysm and aspect ratio were predictive factors for rupture
Weir et al. (91), 2003	RCS	405 SAH patients, 127 incidental patients	Ophthalmic artery, ICA, AcomA, MCA, PcomA, PCC	Female sex had an OR of 0.52 (95% CI: 0.37-0.73), AcomA vs. cavernous ICA had an OR of 5.06 (95% CI: 1.69-15.1), MCA vs. cavernous ICA had an OR of 3.21 (95% CI: 1.06-9.65), PcomA vs. cavernous ICA had an OR of 5.86 (95% CI: 1.88-18.3), PCC vs. ICA had an OR of 5.83 (95% CI: 1.88-18.1), size of > 4 mm to 6 mm or less vs. 4 mm or less had an OR of 2.95 (95% CI: 1.94-4.47), size of > 6 mm to 8.2 mm or less vs. 4 mm or less had an OR of 3.66 (95% CI: 2.27-5.90), size of >8.2 mm vs. 4 mm or less had an OR of 3.67 (95% CI: 2.34-5.75)

Table I: Cont.

Author(s), Year	Study type	Cohort size	Aneurysm location(s)	Predictors of rupture
Weir et al. (92), 2002	RCS	337 ruptured aneurysms, 170 unruptured aneurysms	ICA, ophthalmic artery, PcomA, AcomA, MCA, ACA, VBA	Size, patient age
Ujiie et al. (81), 2001	RCS	129 SAH patients, 72 incidental patients	AcomA, MCA, ICA, PcomA	Aspect ratio of 1.6 or more
Forget et al. (19), 2001	RCS	245 SAH patients, 117 incidental patients	AcomA, PcomA, MCA, VBA, PCC, ICA, ophthalmic artery	AcomA location and an aneurysm size of < 10 mm had higher rupture risk
Juvela et al. (39), 2000	Observa-tion	142 incidental patients	ICA, ACA, AcomA, MCA, VBA	Aneurysm diameter of 10-26 mm had an OR of 3.38 (95% CI: 1.05-10.93), age of 41-50 years had an OR of 0.33 (95% CI: 0.12-0.91)
Hademenos et al. (22), 1998	RCS	40 SAH patients, 34 incidental patients	MCA, ICA, AcomA, PcomA, VBA, PCC	Shape and location of the aneurysms were the predictive factors
The International Study of Unruptured Intracranial Aneurysms Investigators (34), 1998	Ambi-spective	1449 incidental patients	ICA, AcomA, ACA, MCA, PcomA, VBA, PCC	Size and location were predictors of rupture
Orz et al. (61), 1997	RCS	1248 SAH patients, 310 incidental patients	MCA, AcomA, PcomA, ACA, ICA, Optalmic artery, AchA, VBA,	Small aneurysms < 6mm
Asari & Ohmoto (3), 1993	Observa-tion	54 patients with 72 aneurysms	ICA, AcomA, Aca, MCA, PCC, VBA	Aneurysms arising from MCA and VBA of 10-19 mm size and of multilobes had higher risk of rupture
Juvela et al. (38), 1993	RCS	142 patients with 181 unruptured aneurysms	ICA, AcomA, ACA, MCA	Aneurysm size

***SAH:** Subarachnoid hemorrhage**, RCS:** Retrospective comparative study, **RS:** Retrospective study, **PCS:** Prospective cohort study, **ACA:** Anterior cerebral artery, **AchA:** Anterior choroidal artery, **CMA:** Callosomarginal artery, **MCA:** Middle cerebral artery, **PCA:** Posterior cerebral artery, **AcomA:** Anterior communicating artery, **PcomA:** Posterior communicating artery, **ICA:** Internal carotid artery, **VBA:** Vertebrobasilar artery, **PCC:** Posterior cerebral circulation, **Or:** Odds ratio, **HR:** Hazard ratio, 95% **CI:** 95% confidence interval, size ratio type **I:** Ratio between the maximal height of the aneurysm and the parent vessels mean diameter, **N/A:** Not available, ***:** predictors of rupture status in the anterior projection aneurysms.*

found that smoking was a significant predictive factor for the rupture of AcomA aneurysm.

Clinical Significance of the Current Findings

Identifying the predictive factors for intracranial aneurysm rupture would yield better clinical counseling for the patients. Despite annual rupture rates of intracranial aneurysms being low, the morbidity and mortality following aneurysm rupture are high. Patients with UIAs have an overall estimated prevalence of 28% for anxiety and 21% for depression (30). This is mostly caused by the uncertainty of the natural progress of their diseases, more specifically, the rupture of their aneurysms. In the present study, we not only determined the significant predictive factors for the rupture of AcomA aneurysm in our community, but have also summarized the literature findings to provide a general idea regarding UIAs to neurosurgeons and patients.

Limitations

This study had some limitations. This study was a cross-sectional analysis of a prospectively collected database. Some clinical parameters such as comorbidities, time lapse between the first diagnosis and final clinical status, and lifestyle patterns (sedentary or active) were missing. We focused more on the aneurysm morphology nature rather than other confounding parameters, which could be evaluated in future studies. The aneurysms were evaluated using either CTA or DSA. DSA is superior to CTA in detecting aneurysms or any other vascular malformations (82). These could have caused some disparities between the evaluation modalities. The number of study participants were limited as the study was conducted at only one tertiary clinic. Another limitation of the study was that various definitions for the morphological parameters of intracranial aneurysms have been defined in the literature (43). The strength of the present study was that we have not only presented the findings of the present cohort, but have also reviewed the literature and updated the current knowledge regarding the risk factors for rupture of intracranial aneurysms.

CONCLUSION

Younger age, ever-smoking, and presence of a daughter sac increases the risk of AcomA aneurysm rupture. Furthermore, we identified several aneurysm- and patient-related risk factors for rupture of the intracranial aneurysms via a systematic literature review. Our results could enlighten neurosurgeons during their decision-making process in patients with UIAs.

ACKNOWLEDGEMENTS

We send our condolences for the loss of Juha Hernesniemi, who opened the doors of intracranial vascular neurosurgery, treated many patients and trained many neurosurgeons. He has become a legendary vascular neurosurgeon and idol for many of us. We dedicated this manuscript to his memory.

AUTHORSHIP CONTRIBUTION

Study conception and design: EC, MSE, TH
Data collection: FB, JH, MSE, AB, AT, OS, GB, RAK
Analysis and interpretation of results: EC, MSE, TH
Draft manuscript preparation: EC, MSE
Critical revision of the article: EC, MSE, TH
All authors (EC, MSE, FB, JH, AB, AT, OS, GB, RAK, TH) reviewed the results and approved the final version of the manuscript.

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