



# Aneurysmal Subarachnoid Hemorrhage Associated with Small Aneurysms in Smokers and Women: A Retrospective Analysis

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■ **BACKGROUND:** Previous studies have shown low rupture rates for small aneurysms (<10 mm), suggesting that the risk of treatment could exceed the benefits. However, evidence has changed, showing crescent rates of aneurysmal subarachnoid hemorrhage (aSAH) associated with small aneurysms. We report trends in size, localization, clinical characteristics, and outcomes of intracranial aneurysms (IAs).

■ **METHODS:** In this retrospective study, a total of 200 clinical histories of patients diagnosed with IAs over an 8-year period were analyzed. Variables considered included age, sex, tobacco consumption, morphological characteristics of the aneurysm, complications, vasospasm, and mortality. Qualitative variables were assessed by measurements of absolute and relative frequency. Smoking behavior, aneurysm size, and aneurysm rupture (AR) were compared using 1-way analysis of variance. Categorical variables were analyzed using Pearson's  $\chi^2$  test.

■ **RESULTS:** The average age at presentation was 58 years. The average size of ruptured aneurysms in the general group was 2.5–7.5 mm, and AR was most common in women (76%) and in patients age 50–60 years (33%). The rate of vasospasm was 19%, and mortality was 37%. Smokers composed 32% of the cohort. Heavy smokers had a 57% rate of aSAH, with an average size of rupture of 5 mm. The most common location of aneurysms and AR was the AComA (33%).

■ **CONCLUSIONS:** Our results suggest increasing AR rates in aneurysms smaller than 10 mm. This trend is seen

especially in individuals with heavy tobacco consumption and in women of perimenopausal age. Our findings show a tendency of AR in accordance with previous results and are expected to serve as basis for further research on aneurysm management.

## INTRODUCTION

Intracranial aneurysms (IAs) are potentially disabling and even life-threatening vascular dilations.<sup>1,2</sup> Repercussions depend largely on whether or not the aneurysm ruptures, and management of unruptured aneurysms is based on the risk of aneurysm rupture (AR).<sup>1,3</sup> The risk of AR varies according to the size and morphology of the aneurysm.<sup>4,5</sup> However, there are considerable variations in the reported prevalence of AR in small (<5 mm) to medium (6–10 mm) aneurysms.<sup>4,6</sup> Initial estimates considered a minimal risk of AR in aneurysms <7 mm, but new evidence suggests a higher prevalence of AR in this group than previously thought.<sup>6</sup>

Owing to this possibly higher prevalence of AR in small to medium aneurysms, earlier intervention than previously recommended may be called for. As technology improves, smaller aneurysms can be identified with more precision, providing an opportunity for early management, mainly in cases that coexist with known risk factors for AR,<sup>2,7</sup> which are related mostly to inflammatory processes, such as lack of estrogens and smoking.<sup>8–10</sup>

The possibly higher prevalence of AR in small aneurysms makes their characterization and analysis of potential associated risk factors of paramount importance. To address this, we sought to

## Key words

- Intracranial aneurysm
- Menopausal
- Small aneurysm
- Smoker

## Abbreviations and Acronyms

**AComA:** Anterior communicating artery

**ANOVA:** Analysis of variance

**AR:** Aneurysm rupture

**aSAH:** Aneurysmal subarachnoid hemorrhage

**IA:** Intracranial aneurysm

**ISUIA:** International Study of Unruptured Intracranial Aneurysms

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retrospectively analyze and describe trends in reported size, morphology, orientation, localization, clinical characteristics, and outcomes of IAs in a fourth-level university hospital over an 8-year period.

## METHODS

In this retrospective analytical study, with previous Institutional Review Board approval, 200 clinical histories of patients diagnosed with IAs who presented to our institution between the years 2008 and 2016 were analyzed. Patient consent was not required, owing to the anonymous nature of the information collected. The information used in this study did not pose a risk or potential risk to patients' personal integrity.

Computed tomography and computed tomography angiography scan data were analyzed. For patients who presented with several aneurysms, each symptom was characterized separately, morphology was described, and intraoperative records and outcomes were considered.

### Patient Selection: Inclusion and Exclusion Criteria

Institutional yearly records between January 2008 and January 2016 from the neurosurgery department were reviewed for patients with diagnosed IA or aSAH. A total of 200 clinical histories were chosen for analysis. Patients for whom no postsurgical follow-up data were available were excluded from the study, after which 189 remained for our analysis.

### Database Construction

Data was obtained from our hospital's centralized patient history system. Variables considered were age and sex; admittance date; comorbidities; tobacco use; symptoms such as headache, nausea, hemiparesis, hemiplegia, sensitive disturbance, and consciousness diminishment before and after intervention for aneurysm; history of previous subarachnoid hemorrhage; Hunt and Hess grade and Fisher classification; morphological characteristics of the aneurysm (including orientation, lobulations, transverse diameter, anteroposterior diameter, and maximum reported diameter); intervention(s) provided; complications of intervention(s); vasospasm; prescribed medical treatment; and mortality.

Radiologic images were obtained from our institutional imaging database (IMPAX-AGFA Health Care; Agfa-Gevaert Group, Mortsel, Belgium). The Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines for observational studies were followed.<sup>11,12</sup>

### Statistical Analysis

Qualitative variables were assessed by measurements of absolute and relative frequency, and quantitative data were assessed using central tendency measures, data dispersion, mean  $\pm$  SD in normal distribution models. Smoking, aneurysm size, and AR were compared using 1-way analysis of variance (ANOVA). Categorical variables, including aneurysm location, were analyzed using Pearson's  $\chi^2$  test. All data analyses were done using GraphPad Prism 8 for Mac OS X, version 8.01 (GraphPad Software, La Jolla, CA, USA). Patients with missing data were not included in our analysis.

**Table 1.** Demographic Data

Characteristic	Value
Number of patients	189
Age, years, mean $\pm$ SD (range)	58 $\pm$ 15.1 (16–91)
Female sex, <i>n</i> (%)	138 (73)
Diabetes, <i>n</i> (%)	18 (9.5)
Hypertension, <i>n</i> (%)	97 (51.3)
Hypercholesterolemia, <i>n</i> (%)	37 (19.6)
Smoking, <i>n</i> (%)	61 (32.3)

## RESULTS

A total of 189 patients were included in the study. The average patient age was 59  $\pm$  15 years (range, 16–91 years). The majority of patients were female (73%; *n* = 138), and 32.3% (*n* = 61) reported tobacco consumption (Table 1).

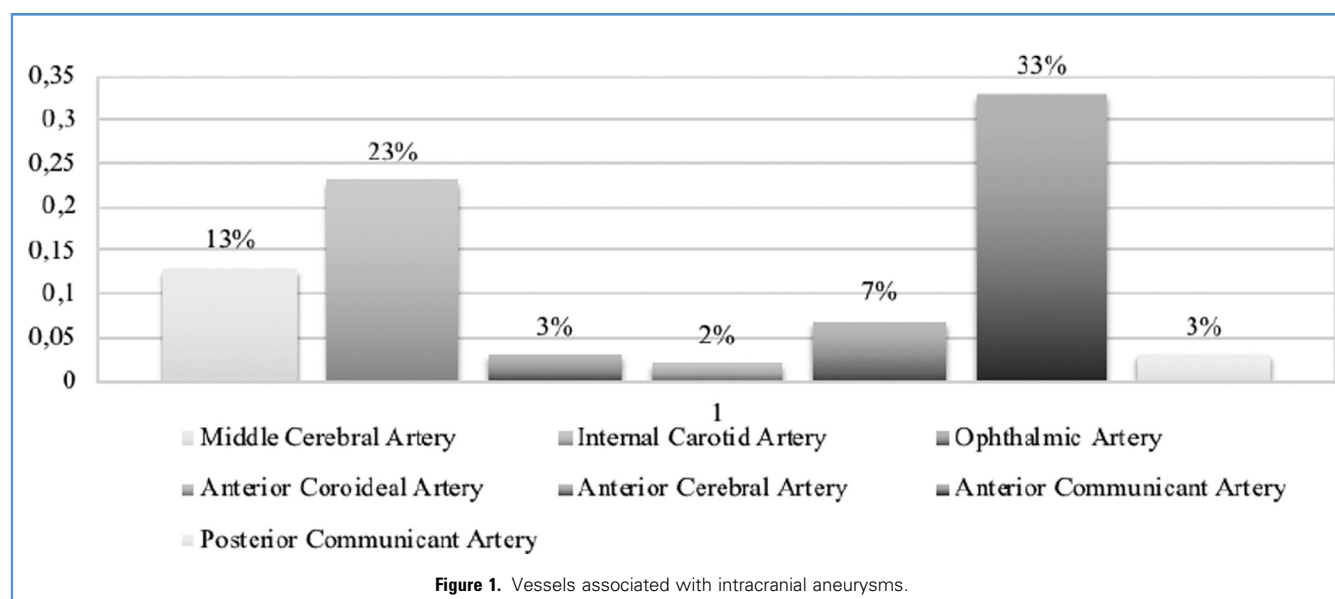
The most common vessel associated with aneurysm location was the anterior communicating artery (AcomA; 33%; *n* = 189), followed by the internal carotid artery (23%; *n* = 43) and middle cerebral artery (13%; *n* = 23) (Figure 1). The most common location of AR was the AComA (34.8%; *n* = 66), followed by the middle cerebral artery (20.3%; *n* = 38) (Figure 2). The orientation of the aneurysms in AComA was most often anterior (24%; *n* = 15).

The average size of all (ruptured and nonruptured) aneurysms was 6  $\pm$  0.35 mm (range, 2–25 mm). The average size of ruptured aneurysms was 5  $\pm$  0.53 mm (range, 2.5–7.5 mm) (Figure 3). Of the 189 surgeries, 120 were elective procedures. AR occurred in 72 patients, who had an average age of 58  $\pm$  15.8 years (standard error, 1.9). The majority of these patients were female (76%; *n* = 55; *P* = 0.0752), with an average rupture size of 4  $\pm$  0.98 mm (Figure 4). In patients with AR, 15% (11 of 70) needed reintervention after rupture; 7 of these 11 patients required 1 additional surgery, and the other 4 required 2 or more interventions, including 1 decompressive craniotomy.

The mortality rate was 11.2% (8 of 71), predominantly in patients with an initial Hunt and Hess grade of 5 (38%; 3 of 8) and a Fisher scale score of 2 (25%; 2 of 8) (Table 2). Twenty-six patients had a Fisher scale score of 4, with a mortality rate of 2.55% (*P* = 0.5304) (Figure 5). Fisher scale score was also associated with the presence of vasospasm (*P* = 0.2670), with higher rates at Fisher 3 and 4 (Figure 6). Finally, the prevalence of hydrocephalus (*P* = 0.0132) was higher in the Fisher 4 group (18 of 26) (Figure 7). These findings are summarized in Table 3.

Patients who consumed tobacco composed 28% of the entire population (53 of 189) and 25% of the patients with aSAH (25 of 72) (Table 3). Heavy smokers (>16 packs/year) had an median AR size of 3 mm (range, 2–15 mm) (*R*<sup>2</sup> = 0.0128; *P* = 0.4988, ANOVA) (Figure 8).

In women, the average size of AR was nearly 5 mm for all groups (Figure 9). Finally, the evaluation for differences in ruptured aneurysm sizes between young smokers, young nonsmokers, old smokers, and old nonsmokers revealed a *P* value of 0.038 for

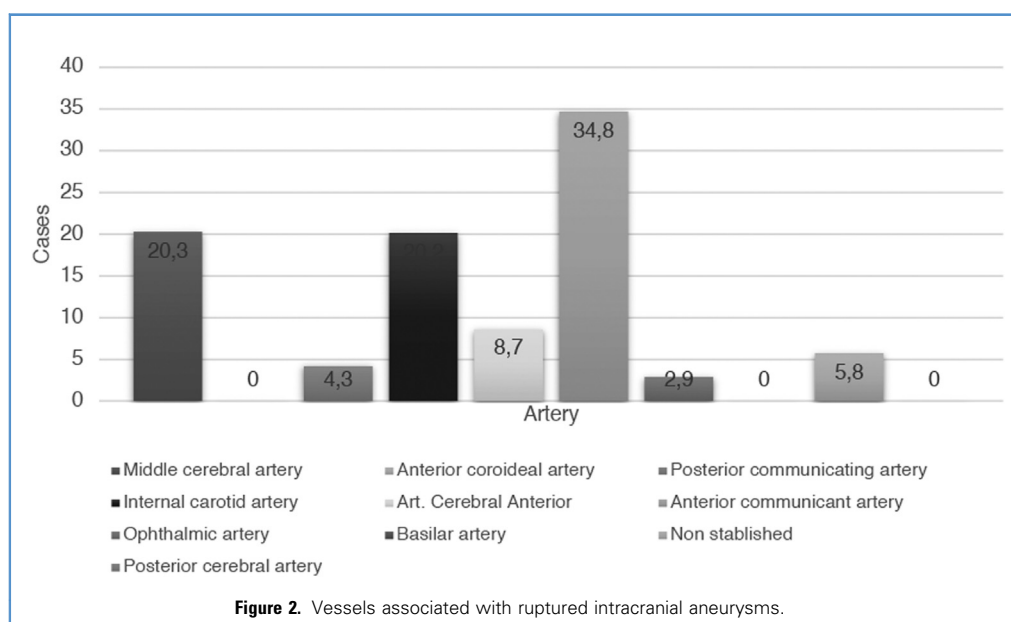


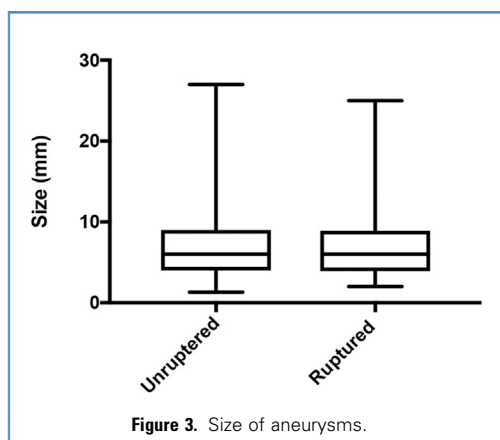
differences between young smokers and young nonsmokers, but a *P* value of 0,36 for differences in all groups. Bartlett's test for symmetry was 0,0088 (Figure 10). Vasospasm was reported in 17% of the patients (32 of 189). The internal carotid artery was the most prevalent location associated with vasospasm (37%), followed by the anterior cerebral artery (22%) (Table 4).

## DISCUSSION

In this 8-year retrospective descriptive study that included 189 patients presenting with IAs, most ruptures were observed in heavy smokers and women at the sixth decade of life. Age showed

a wide range of distribution (16–91 years), with a parametric behavior at a mean of  $59 \pm 15$  years. Vlak et al.<sup>13,14</sup> described a similar distribution, with a high incidence at age 50 years. In addition, a monomodal behavior was observed for aneurysms frequency, with a peak in the sixth decade of life. This pattern could be associated with higher mortality by other causes in the older population, which may potentially present a confounding bias by obscuring potential AR later in life, which is supported by data reported by the World Bank in 2015, where the life expectancy for the study population was 74 years with mortality predominantly associated with coronary events, supporting the idea that the increased mortality due to other events (not aneurysms) could





contribute to a bias for the risk of AR past the sixth decade of life. In addition, the International Study of Unruptured Intracranial Aneurysms (ISUIA) study found a relationship between increasing age and the risk of AR, essentially associated with aging mechanisms<sup>15</sup> related mainly to vascular fragility and the accumulation of reactive oxygen species.<sup>16,17</sup>

We found a higher prevalence of aneurysms in females, 73%, compared with males. Similar results were found by Vlák et al.,<sup>13,14</sup> who reported a prevalence of 6% (95% confidence interval [CI], 4.5%–8%) in females, compared with 1.57% (95% CI, 1.04%–2.37%) in males. Ghods et al.,<sup>18</sup> the ISUIA study,<sup>4</sup> and Rincon et al.<sup>19,20</sup> have reported similar findings.

The heavy smokers in our cohort had an AR prevalence of 56%. Previously, Can et al.<sup>21</sup> reported a similarly high prevalence (45%–75%) of aSAH in heavy smokers compared with a 30% rate in nonsmokers, which was also associated with small aneurysm size (median, 6 mm; range, 1–27 mm).<sup>21</sup> Similar results have been published in *Stroke*, reporting that patients smoking >15 packs/year have a 43% risk of aSAH ( $P = 0.05$ ).<sup>22</sup> In our cohort, the average size of AR in women with a history of smoking

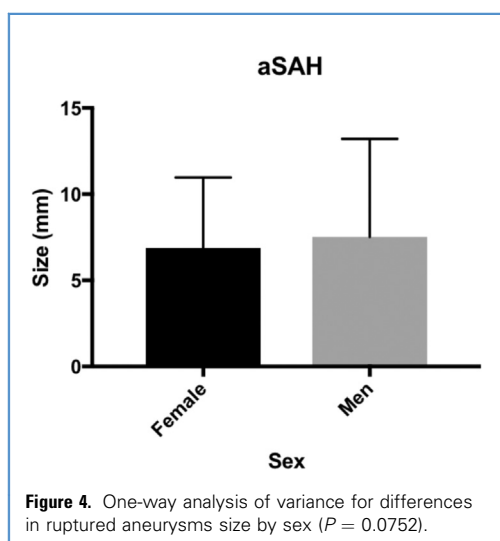
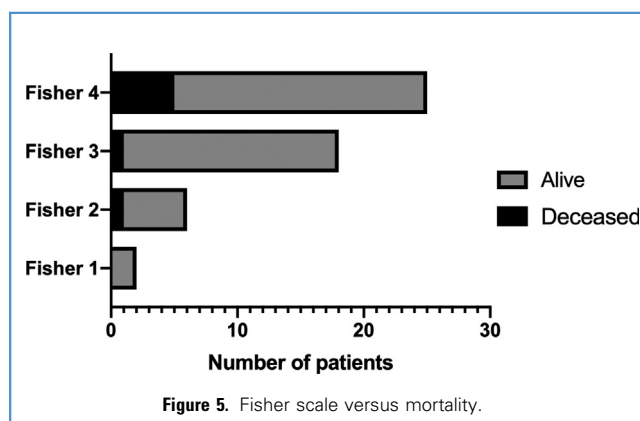


Table 2. Demographic Data for Patients with aSAH

Characteristic	Value
Number of patients	71
Age, years, n (%)	
10–30	4 (5.6)
31–40	3 (4.2)
41–50	12 (16.9)
51–60	23 (32.4)
61–70	13 (18.3)
>70	16 (22.5)
Sex, n (%)	
Female	54 (76)
Male	17 (24)
Mortality, n (%)	8 (11.2)
Hunt and Hess 1	1 (13)
Hunt and Hess 2	2 (25)
Hunt and Hess 3	1 (13)
Hunt and Hess 4	1 (13)
Hunt and Hess	3 (38)

suggests a higher incidence for smaller ruptures (4 mm in smokers vs. 5 mm in nonsmokers); however, these results were not statistically significant ( $P = 0.877$ , ANOVA) (Figure 5). The mechanisms behind this behavior may be related to tumor necrosis factor (TNF)- $\alpha$ , as a critical member of the immune system, associated with the activation of endothelial cells and macrophages.<sup>23,24</sup> In other studies, a high phenotypic modulation in smooth muscle cells was observed, specifically in genes associated with vascular remodeling, such as MMP-3, VCAM-1, and IL-1 $\beta$ .<sup>8,17,25</sup> These results are in accordance with the reported decrease in the Aneurysm Rupture Index after treatment with a TNF- $\alpha$  inhibitor.<sup>23</sup>

The average AR size in our population was smaller than that reported in previous studies (2.5 to 5 mm CI 95% 1.3 SD). These



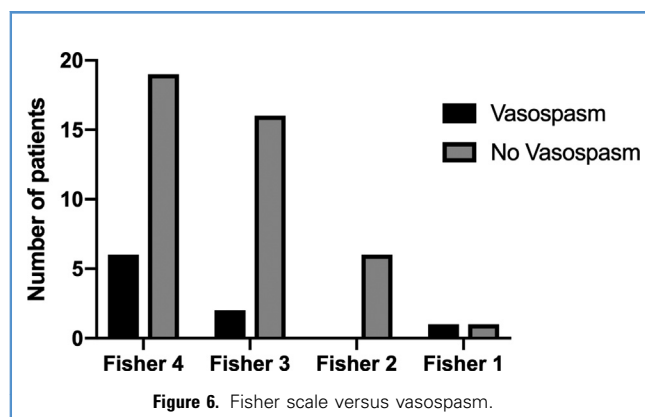


Figure 6. Fisher scale versus vasospasm.

findings are in disagreement with previous studies such as that by Nabaweesii et al.,<sup>26</sup> who reported ARs of 1–27 mm, with an average size of 7–8 mm, but are supported by others, such as the Cooperative Aneurysm Study, which reported that 20% of ruptured aneurysms were <5 mm.<sup>27</sup> A literature review was performed (Table 5). The International Subarachnoid Aneurysm Trial (ISAT) reported an AR incidence of 53% ( $P < 0.0001$ ) in surgically managed aneurysms measuring <5 mm and 40% in those measuring 6–10 mm.<sup>36</sup> In that same study, results for endovascular intervention showed an AR rate of 51% for aneurysms <5 mm. Some interesting results have been reported in the Japanese population. Morita et al.<sup>29</sup> reported an AR rate of 37% for aneurysms measuring 3–4 mm and 32.6% for those measuring 5–6 mm, with a total AR rate of almost 70% for aneurysms <7 mm. Ohashi et al.<sup>32</sup> also reported a high prevalence of AR (74.3%) for aneurysms <10 mm (mean, 7.6 mm).<sup>32</sup> Finally, Weir<sup>34</sup> reported a mean AR size of 5 mm. These findings suggest a trend toward smaller ruptured aneurysms than previously reported; however, possible confounding factors, including the tendency of the aneurysm wall to collapse after rupture, must be taken into account when considering this tendency. Bender et al.<sup>6</sup> reported a decrease in average aneurysm size over a 25-year

Table 3. Smoking Characterization by Amount of Calculated Packs/Year ( $N = 53$ )

Smoking Characterization	Size (mm)	Prevalence in the Population, % (n/N)	Prevalence of aSAH, %
Mild (0–5 packs/year)	6 (1–18)	13 (25/189)	25
Moderate (6–15 packs/year)	6.5 (1–18)	9 (15/189)	28
Severe (>16 packs/year)	3 (2–15)	7 (13/189)	56
No smokers	6 (1–27)		26

period, with an average size of 6 mm in 2012–2016, compared with 10.1 mm in 1991–1996, which may contribute to the lower average size of AR reported in more recent studies.

Hypotheses explaining the increasing rate of small ruptured aneurysms include improved aneurysm identification and endovascular innovations for treatment of large and giant aneurysms,<sup>37</sup> along with the recent more proactive approach to treating larger aneurysms with elective interventions, owing to the high risk associated with rupture.<sup>6</sup>

In our center, which is classified as a reference center for neurosurgery in our country, the management of aneurysms includes an early intervention for aneurysms <10 mm, mainly in patients with such risk factors as hypertension and family history of AR. The choice between an endovascular treatment or a surgical approach is based on the feasibility of embolization, and difficult cases are revised weekly in an interdisciplinary meeting, including interventional radiology, to evaluate the best option available to the patient.

In the present study, the most common artery associated with symptomatic vasospasm was the internal carotid artery (37%; 10 of 27). In our cohort, mortality and the rate of vasospasm were higher at higher Fisher scale grades. However, in contraposition of the literature, the worst prognosis was found at Fisher grade 4 ( $P = 0.2670$ ).

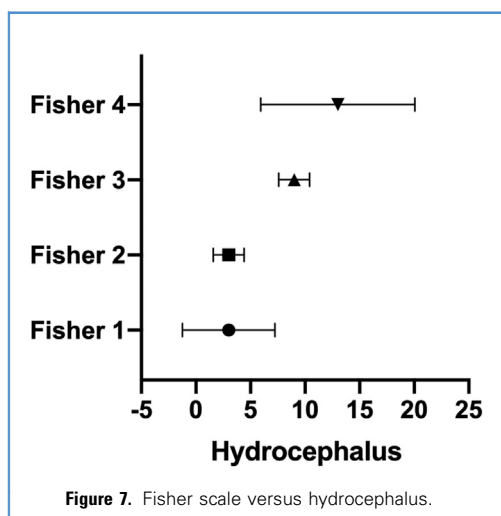
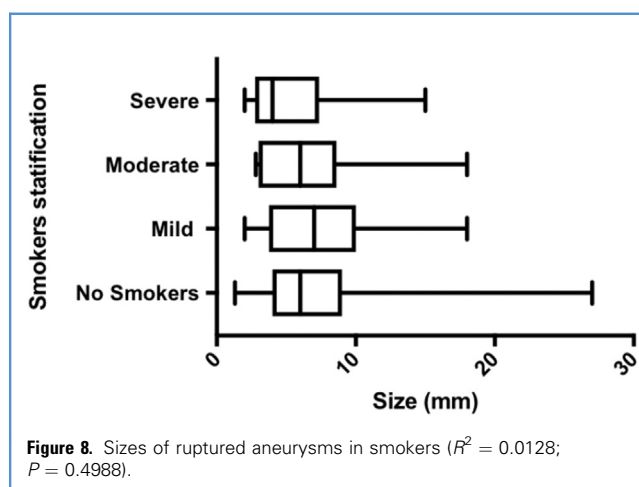
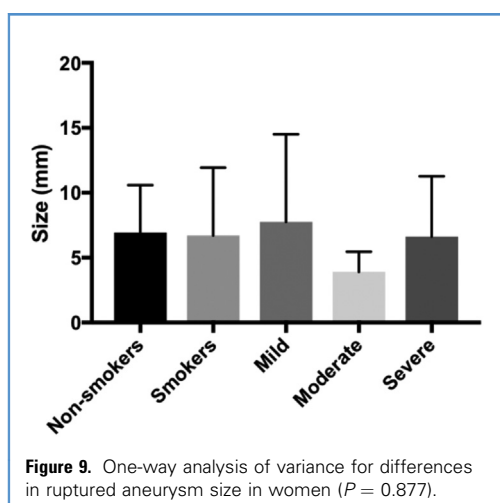


Figure 7. Fisher scale versus hydrocephalus.

Figure 8. Sizes of ruptured aneurysms in smokers ( $R^2 = 0.0128$ ;  $P = 0.4988$ ).

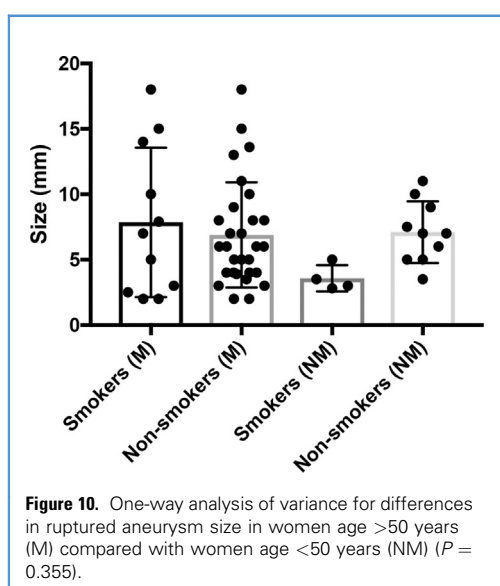




Among pathological risk factors, hypertension was the most significant in our cohort (occurring in 51% of cases), in agreement with results reported by Tada et al.<sup>9</sup> The ISUIA study reported a 43.6% prevalence of hypertension for the population with aneurysms in Europe, the United States, and Canada.<sup>4</sup> A possible explanation for the relationship between hypertension and aneurysm formation could be associated with the nature of hypertension as a systemic inflammatory process in which endothelial remodeling is strongly affected<sup>9,15,38</sup> and the disruption of normal hemodynamic behavior, which activates the renin-angiotensin pathway, changing vascular remodeling mechanisms<sup>10</sup> and instigating migration of smooth muscle cells at sites of injury, contributing to destabilization of the aneurysm structure.<sup>5,10</sup>

### Limitations

A potential bias is related to our limited sample size. The individuals included in this study were patients with an existing



**Table 4.** Primary Area Involved in Symptomatic Vasospasm

Related Artery	%	n/N
Middle cerebral artery	15	5/32
Internal carotid artery		
General	37	11/32
Ophthalmic artery	45	5/11
Superior hypophyseal artery	9	1/11
Posterior communicating artery	9	1/11
Supraclinoid portion	9	1/11
Anterior cerebral artery		
General	22	7/32
Pericallosal artery		
Anterior communicating artery	7	2/32
Basilar artery	15	5/32
Posterior cerebral artery	4	1/32
Posterior inferior cerebellar artery	4	1/32

clinical record in our institution, with no patients from private consult or public hospitals, thus limiting the sample. A probability test showed a 78% probability of finding an association in our sample. Although this is an acceptable reduction in the probability of type II error, we encourage future research with a multicentric prospective cohort, involving a larger sample size and including such variables as smoking cessation as well as morphological variables suggested by Zuan et al,<sup>39</sup> such as height–width ratio, flow angle, and aneurysm width–parent artery diameter ratio.

### CONCLUSION

Our results suggest a trend toward an increasing rate of AR in aneurysms smaller than 10 mm, with higher rates in 5–7 mm aneurysms. This trend is most prominent in women with heavy tobacco consumption. In addition, women in the 6th decade of life show a trend toward a higher incidence of ruptures, likely associated with hormonal changes related to perimenopause. Studies including European, Asian, and American women suggest that the prevalence of AR in aneurysms <10 mm is increasing. In our analysis of AR morphology and outcomes, aneurysm size represents only one aspect of a complex evaluation. Future research with multicentric prospective cohorts is needed to further evaluate risk factors and possible cofounders.

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**Table 5.** Literature Review of SAH Associated with Aneurysms of <10 mm

Study	Country/Region	Treatment	Number (%)	Size, mm	P Value	Size, mm, mean $\pm$ SD	Artery, % (n)
Molyneux et al., 2002 <sup>28</sup>	ISAT	Surgery	572 (53)	<5	<0.0001		AComA, 50.5 (1084)
			426 (40)	6–10			
		Endovascular	552 (51)	<5			
			438 (41)	6–10			
UCAS Japan Investigators, 2012 <sup>29</sup>	Japan	Surgery	554 (18.2)	7–9	<0.001	6.1 $\pm$ 3.8	MCA, 39.8 (1215)
			993 (32.6)	5–6			
			1132 (37.1)	3–4			
Forget et al., 2001 <sup>30</sup>	USA	Surgery	86 (35)	<5			AComA, 67; PComA, 42
			124 (50.6)	6–10			
Dolati et al., 2015 <sup>31</sup>	Canada		46 (37)	<5	<0.001		AComA, 86.5; MCA, 39
			52 (42)	>5–10			
Ohashi et al., 2004 <sup>32</sup>	Japan	Surgery	208 (74.3)	<10		7.6	AComA, 39.7 (29)
Orz et al., 1997 <sup>33</sup>	Japan	Surgery	475 (64.6)	<5		6.7	AComA, 70.8; PComA, 5.1
			681 (73.9)	>5–10			
Weir, 2002 <sup>34</sup>	USA		6 (20)	<3		5	AComA, 35.0; MCA, 28.8
			60 (80)	4–10			
Yasui et al., 1996 <sup>35</sup>	Japan		16 (64)	<5			MCA, 28; AComA, 20
			6 (24)	>5–10			
Inagawa, 1990 <sup>15</sup>	USA		18 (17)	<4		9.5	AComA, 30; ICA, 40
			50 (46)	5–9			

AComA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PComA, posterior communicating artery.

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