RESEARCH ARTICLE

Demographic and anatomical comparison of ruptured and unruptured intracranial aneurysms: a case control study

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Abstract

Background: Our understanding of the pathophysiology and management of intracranial aneurysms (IAs) continuously advances. This case-control study analyzed the demographics of patients with IAs and the morphological Digital Subtraction Angiography (DSA) characteristics of ruptured and unruptured IAs.

Methods: Two patient groups with saccular ruptured and unruptured IAs eligible for coiling were prospectively analyzed during a 3-year period. Patient groups were compared regarding gender, age, arterial vasculature side, anatomical location, diameter, preoperative DSA appearance, aneurysmal and anatomical Circle of Willis variations (CWV) coexistence.

Results: One hundred and three patients with ruptured and eighty-six patients with unruptured IAs were studied. Anterior communicating and internal carotid artery IAs were the dominant locations: 42.7% and 23.3% in ruptured and 29% and 41.9% in unruptured IAs, respectively. The female-to-male ratio was 1.78 in ruptured and 2.44 in unruptured IAs (p =0.317), while the rupture was more frequent in younger patients (p =0.034). Angiographically, smaller diameter (p =0.01), abnormal morphology (p =0.0001), and co-existence of CWV (p =0.016) were reported in ruptured IAs. Location at bifurcation/trifurcation (p =0.487) and the co-existence of additional or mirror IA did not differ significantly (p =0.879).

Conclusions: On DSA, ruptured and unruptured IAs differed in size, morphology, and co-existence of CWV; findings that may favor the treatment of specific unruptured IAs. However, a higher level of evidence is needed to include all these factors in the treatment decision process, provide patient-oriented treatment and reliably identify unruptured IAs at greater risk. HIPPOKRATIA 2021, 25 (3):100-107.

Keywords: Intracranial aneurysms, aneurysm morphology, aneurysm rupture, endovascular treatment, digital subtraction angiography, circle of Willis variations

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Introduction

Ruptured intracranial aneurysms (IAs) are frequently associated with high morbidity and mortality among survivors¹⁻³. Furthermore, the incidence of IA-related subarachnoid hemorrhage (SAH) in Europe in 2010 was 6.3 per 100.000 person-years [95 % Confidence interval (CI), 4.9-8.1]⁴.

Identifying IAs prone to rupture is essential in reducing SAH-related mortality and establishing standard clinical practice guidelines^{2,5}. Literature constantly enriches our knowledge: anterior circulation, specifically anterior communicating artery (aCOM), IA sack diameter, irregular shape, smoking, and hypertension carry cumulative risk^{1,2,6}.

The present study compared the baseline characteristics of two discrete groups of patients with ruptured and unruptured IAs treated with endovascular coil embolization. Additionally, we tested the hypothesis that ruptured and unruptured IAs share similar Digital Subtraction Angiography (DSA) characteristics. Therefore, we aimed to contribute to decision-making concerning which unruptured IAs carry increased risk.

Materials and Methods

Study Population and data extraction

This prospective study included adult patients with ruptured or unruptured saccular IAs treated with endovascular coiling at the Department of Neurosurgery and Neu-

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roendovascular Surgery of the 401 Army General Hospital in Athens from 01/01/2015 until 31/12/2017. During their hospitalization, patients received the standards of care according to institutionally approved protocols, and data were prospectively and consecutively recorded in accordance with the 1964 declaration of Helsinki and its later amendments. Approval was obtained from the Institutional Research and Scientific Ethics Committee regarding data analysis and usage. The STROBE casecontrol checklist7 was applied. Patients' demographics, radiological and morphological IAs characteristics were analyzed: gender, age, aneurysmal side, aneurysmal location and diameter, preoperative angiographic image, arterial variations, mirror, and co-existence of additional IAs. We used the Rstudio's8 statistical tests and methods for each group's statistical analysis and comparison of the collected information.

Patient sample consisted of two independent groups: Group A included patients presenting with IA rupture, whereas Group B included patients with unruptured IAs (both symptomatic and asymptomatic). In both groups, patients were referred to our unit to undergo evaluation and optimization for coiling embolization. For maximum accuracy in diagnosis and evaluation, the target aneurysm was spotted using DSA: i) blood distribution in SAH, ii) the largest IA, and iii) abnormal IA sack in cases of unidentified SAH.

According to the institutional protocol, patients with ruptured aneurysms amenable to endovascular treatment were treated except for those in severe clinical conditions (e.g., fixed and dilated pupils, multiorgan failure, terminal stage disease, limited life expectancy, etc.). In unruptured aneurysms, optimization was applied in: i) saccular IAs, ii) anatomical location of the IA with difficult or unfeasible surgical clipping (e.g., basilar apex aneurysm), iii) life expectancy >10 years, iv) general health condition allowing subjection to endovascular treatment, v) age <80 years, vi) presenting symptoms other than mass effect (e.g., epileptic episode, thromboembolic events)². Management of unruptured aneurysms with size 7-12 mm was individualized, and the decision to treat was largely based on the individual patient and aneurysmal risk factors (family history, location in the posterior circulation, previous SAH, daughter sac, etc.)^{2,5}. Aneurysms with size <7 mm are usually followed with repeat angiographic control unless risk factors such as specific location (aCOM and posterior circulation) for rupture exist, where the cut-off size is 4 mm^{2,3,9}. Exclusion criteria for the study were: i) non-saccular IAs, ii) clipped IAs, iii) aneurysms treated with flow diverters, iv) lack of sufficient patient data, v) age <18 years, vi) past medical history of aneurysmal SAH, vii) non-aneurysmal SAH, viii) diameter <2 mm in unruptured IAs, ix) unruptured IAs which co-existed with ruptured IA, x) partially thrombosed IAs, xi) IAs of traumatic/infectious cause, xii) DSA not performed or of suboptimal quality, and xiii) unruptured IAs with mass-effect symptoms or any other IA-related symptoms.

Imaging and aneurysm characteristics

Both groups underwent computed tomography and/ or magnetic resonance angiography before DSA. The coiling procedure was performed by releasing into the aneurysmal sack platinum micro-coils until its' complete occlusion and exclusion from the circulation. During the procedure, the whole cerebral vasculature was investigated for additional findings (aneurysms and/or arterial malformations).

Aneurysm morphology was characterized as regular (spherical, ellipse) or irregular (pseudolobes/additional lobes, protrusions, blebs)¹⁰. Aneurysmal maximum diameter was measured during DSA on a one-mm scale. The risk of rupture for every one mm of IA sack growth was estimated using regression analysis. Arterial anomalies such as circle of Willis variations (CWV), hypoplasia/aplasia or previously undetected IAs were also recorded. We characterized as hypoplastic an artery where contrast could barely pass along, whereas as aplastic where no contrast could pass distally¹¹.

Statistical analysis

Statistical tests were performed using the Rstudio⁸. For qualitative variables, frequencies and percentages (%) were used. Normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. For quantitative variables, discrete numbers with percentages (%), mean, range, and standard deviation (± after mean values) were used. Two-sample t-test and Mann-Whitney U test were used for independent variables based on the normality of distribution. Chi-square and Fisher tests were used for categorical variables. In order to investigate the correlation between the risks of aneurysm rupture for every one mm growth of its sack, we used regression analysis. Specifically, a logistic regression model with a continuous explanatory variable for aneurysmal diameter was also applied to calculate the odds of rupture. The p-value (p) threshold of statistical significance was set at 0.05. CIs were calculated at a 95 % level and were rounded to two digits.

Results

Demographics

One hundred eighty-nine patients were identified; one hundred and three with ruptured and 86 with unruptured IAs (Table 1). The mean age was 55.7 ± 11.1 (range: 29-83) years (p =0.034). No association between rupture and gender was found (p =0.317). No aneurysm was ruptured during the coiling procedure, and normal and unobstructed blood flow of the parent vessel was preserved in all patients.

Ruptured vs unruptured aneurysms

The group of ruptured IAs included 103 patients. The characteristics of the aneurysms' parent artery and specific location are presented in Table 1 and Figure 1. The female-to-male ratio was 1.78. Internal carotid artery (ICA) aneurysms had a larger mean diameter (6.92 ± 4.17)

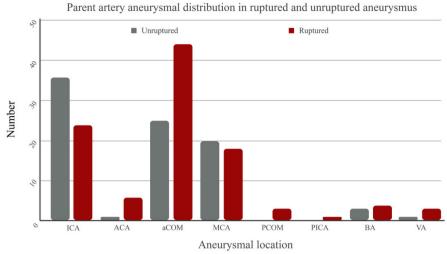


Figure 1: Bar plot of aneurysmal parent artery location. The X-axis presents the number of aneurysms at each parent artery location. The Y-axis shows the discrete number of parent arteries at each aneurysmal location. Ruptured aneurysms are represented in red color, whereas unruptured in gray.

ICA: internal carotid artery, ACA: anterior carotid artery, aCOM: anterior communicating artery, MCA: middle cerebral artery, PCOM: posterior communicating artery, PICA: posterior inferior cerebellar artery, BA: basilar artery, VA: vertebral artery

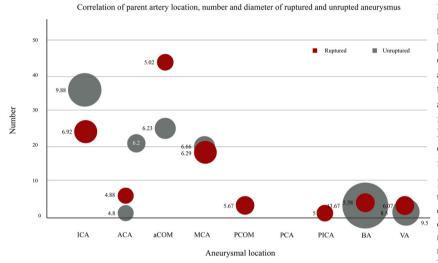


Figure 2: Chart showing the correlation of parent artery location, number of aneurysms at the specific parent artery location, and the mean diameter. The size of the circle is analogous to the mean diameter of the aneurysms at the specific parent artery location. The mean diameter is shown on the left of each circle. Ruptured aneurysms are represented in red color, whereas unruptured in gray.

ICA: internal carotid artery, ACA: anterior carotid artery, aCOM: anterior communicating artery, MCA: middle cerebral artery, PCOM: posterior communicating artery, PICA: posterior inferior cerebellar artery, BA: basilar artery, VA: vertebral artery.

mm), while aCOM aneurysms had the smallest diameter $(5.02\pm2.55\text{ mm})$ (Figure 2). The smallest diameter was 2.4 mm (supraclinoid segment of ICA), while the largest was 21 mm (ICA bifurcation). In multivariate regression analysis, only size predisposed to rupture. Specifically, the odds of aneurysmal rupture increased by 18.8 % per one mm of aneurysmal diameter increase (p =0.0006, 95 % CI: 1.08, 1.32).

The unruptured IAs group included 86 patients (Table 1 and Table 2). The female-to-male ratio was 2.44, and ICA location prevailed (36, 41.9 %), with the majority located at the supraclinoid segment of ICA (28, 32.6 %) (Figure 1 and Figure 2). The largest IA had a 38 mm diameter and was located at the supraclinoid segment of ICA, whereas the smallest aneurysm was 3 mm in diameter and was located at the ICA bifurcation.

Aneurysm anatomical location and additional aneurysms
Information extracted during DSA was categorized
(Table 1, Table 2, Table 3, and Table 4)3.12.13. Anterior

circulation prevailed (89.3 % in ruptured and 95.3 % in

unruptured IAs), with ruptured IAs associated more frequently with the anterior circulation (p =0.013, Table 2). aCOM was the commonest location (42.7 %) in ruptured IAs (Figure 1), while ICA was the most common site (41.8 %) in unruptured IAs. Eleven out of 14 aneurysms (78.6 %) found in the posterior circulation were ruptured (Table 2, Figure 1). The right and left sides of the cerebral vasculature were equally presented. Seventy-one (37.5 %) IAs were found at arterial bifurcation/trifurcation; 41 ruptured and 30 unruptured (p =0.487).

Twenty-seven additional sole IAs were reported in 27 patients, with 25 (92.6 %) located in the anterior circulation (Table 3). Both groups had about the same number of mirror aneurysms; 23 (22.3 %) in ruptured and 20 (23.3 %) in unruptured, p =0.879, mainly located at the supraclinoid segment of ICA (7; 43.6 %) and the medial cerebral artery (MCA) bifurcation/trifurcation (4; 25 %).

Aneurysm diameter and shape

The mean IA diameter was 6.78 ± 4.2 (range: 1.8-38) mm but differed between the two groups. In ruptured IAs,

Table 1: Baseline characteristics of the 189 patients included in the study and features of the ruptured and unruptured aneurysms.

Variable	Total	Ruptured	Unruptured	p-value
Number of patients	189	103	86	0.318
Female/Male	127 / 62	66 / 37	61/25	0.317
		64.1 % / 35.9 %	70.9 % / 29.1 %	
Age	55.7 ± 11.1	54.1 ± 10.8	57.6 ± 11.3	0.034
Diameter (mm)	6.78 ± 4.2	5.76 ± 2.9	8.06 ± 5.2	0.001
≤ 7mm diameter subgroup	129 (68.3 %)	80 (77.7 %)	49 (56.9 %)	0.002
Multiple aneurysms	43 (22.8 %)	23 (22.3 %)	20 (23.3 %)	0.879
Abnormal shape ^a	65 (34.4 %)	55 (53.4 %)	10 (11.6 %)	0.0001
Bifurcation/trifurcation	71 (37.6 %)	41 (39.8 %)	30 (34.9 %)	0.487
Circle of Willis variations b	76 (100 %)	50 (65.8 %)	26 (34.2 %)	0.010

Values are presented as discrete numbers, mean and standard deviation. ^a: Abnormal shape refers to the angiographical image of non-saccular aneurysmal shape: additional lobes, pseudolobes, protrusions, signs of rupture or imminent rupture, ^b: includes dysplastic, aplastic or hypoplastic arteries at the Circle of Willis.

the mean diameter was 5.76 ± 2.9 mm and 8.06 ± 5.2 mm in unruptured (p =0.001, Table 1). We specifically analyzed IAs with <7mm diameter^{2,3}. In ruptured and unruptured IAs, 77.7 % and 56.9 % were <7 mm, respectively (p =0.002). In total, 65 (34.4 %) IAs were found with a non-saccular/abnormal shape, with the vast majority (55; 86.4 %) in ruptured IAs (p =0.0001).

Circle of Willis variations

In total, 40.1 % of patients harbored CWV (Table 4). There were various anatomical variations of the cerebral vasculature; A1 (first part of the anterior cerebral artery) and P1 (first part of the posterior cerebral artery) anomalies prevailed. Both anterior (42.1 %) and posterior circulation (54 %) aneurysms co-existed with CWV, but no association between ruptured IAs and the presence of CWV was found. Specifically, P1 was the commonest site (35; 46.1 %). Concerning aCOM IAs, 36.2 % co-existed with A1 variations: 36.7 % in ruptured and 36 % in unruptured (p =0.975). More CWVs co-existed with ruptured aneurysms: ruptured IAs had almost double CWV (50; 65.8 %) than unruptured IAs (26; 34.2 %) (p =0.01).

Discussion

In the present study, we prospectively compared two discrete patient groups with ruptured and unruptured IAs to identify differences and factors connected to IA rupture. Furthermore, we investigated whether our results can add valuable information towards the decision of treating unruptured IAs^{2,3}. Age, gender, IA location, diameter, preoperative angiographic image, CWV were analyzed individually.

No association between gender and aneurysm rupture was found (p = 0.317). In conjunction with the literature,

there was a clear female dominance; the gender ratio can reach 3:1 and, in the present study, was approximately 2:1 $(p = 0.317)^{1.5,6,13-15}$. Neither PHASES nor UIATS trials included gender as a factor favoring treatment^{2,3,14}. Accepting the theory that aneurysms probably grow with aging, the finding that ruptured IAs were found in younger patients (p =0.034) suggests that specific factors act synergically towards rupture earlier in some occasions^{6,12-17}. Similarly to the earlier published series, aCOM was the commonest aneurysm location, with ICA being the second most common. Additionally, aCOM was associated with rupture with almost double frequency compared to unruptured aneurysms. On the contrary, unruptured ICA aneurysms represented the most frequent location in this cohort of patients. Moreover, although less frequent, almost all posterior circulation IAs were ruptured, implying that these aneurysms are also of increased risk, which is also in concurrence with both UIATS and PHASES scores 1-3,6,18,19. Additional or mirror IAs, although found in a considerable portion of patients, were not associated with rupture (p $=0.879)^{1,12,14}$.

According to the current cohort, aneurysms with smaller diameters constituted the majority of the ruptured IAs, which differs from the UIATS and PHASES classification^{2,3}. We support the notion that some aneurysms will rupture early, so they need to be identified^{9,13,20}. In our study, the mean diameter differed between the two groups, with ruptured IAs having a smaller mean diameter (p =0.001)^{1,3,6,13,19}. Furthermore, correlating rupture with the diameter revealed that the odds increased by 18.8 % per one mm of saccular growth. According to the literature, unruptured IAs even <7 mm may warrant treatment^{1,9,12,13,15,20,21}. In our cohort, aneurysms <7 mm represented 68.3 % of the total and nearly 80 % of the

Table 2: Characteristics and distribution of ruptured and unruptured aneurysms in the study's cohort.

		Ruptured Aneurysms			Unruptured Aneurysms		
Location		Number	Relative frequency	Diameter (mm)	Number	Relative frequency	Diameter (mm)
	ICA	24	23.3 %	6.92 ± 4.17	36	41.9 %	9.88 ± 6.50
	Cavernous	-			5	5.8 %	
	Supraclinoid	22	21.4 %		28	32.6 %	
	Bifurcation	2	1.9 %		3	3.5 %	
	ACA	6	5.8 %	4.88 ± 1.63	1	1.2 %	4.8
	A1	2	1.9 %			0 %	
Anterior	Pericallosal	4	3.9 %		1	1.2 %	
circulation	aCOM	44	42.7 %	5.02 ± 2.55	25	29 %	6.23 ± 2.56
	A1 – aCOM	22	21.4 %		10	11.6 %	
	body	22	21.3 %		15	17.5 %	
	MCA	18	17.4 %	6.29 ± 2.22	20	23.3 %	6.66 ± 2.87
	M1	5	4.9 %		5	5.8 %	
	Bifurcation- Trifurcation	13	12.6 %		15	17.5 %	
Posterior circulation	PCOM	3	2.9 %	5.67 ± 2.08	-	0 %	-
	PCOM body	2	1.9 %			0 %	
	P1 – PCOM connection	1	0.9 %			0 %	
	PCA	-				0 %	-
	PICA	1	0.9 %	5		0 %	-
	BA	4	3.9 %	5.58 ± 2.1	3	3.5 %	13.67 ± 9.63
	bifurcation	3	2.9 %		2	2.3 %	
	body	1	0.9 %		1	1.2 %	
	VA	3	2.9 %	6.07 ± 3.01	1	1.2 %	
Total		103	100 %	5.76 ± 2.95	86	100 %	8.06 ± 5.16

Values are presented as mean and standard deviation. ACA: Anterior cerebral artery, A1: the first part of ACA, aCOM: Anterior communicating artery, AICA: Anterior inferior cerebellar artery, BA: Basilar artery, CCA: Common carotid artery, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCA: Posterior cerebral artery, P1: the first part of the posterior cerebral artery, PCOM: Posterior communicating artery, PICA: Posterior inferior cerebellar artery, VA: Vertebral artery.

Table 3: Site of additional and mirror aneurysms in the study's cohort.

Location		Ruptured	Unruptured	Total		
Additional aneurysms						
ICA	Cavernous	2	1	3		
	Supraclinoid	5	4	9		
	Bifurcation	2	2	4		
ACA	A1	2	0	2		
	A1-A2	0	1	1		
	Bifurcation-Trifurcation	2	2	4		
	Pericallosal	1	1	2		
BA	top	1	1	2		
Total		15 (55.6 %)	12 (44.4 %)	27 (100 %)		
		Mirror aneurysi	ms			
	Cavernous	1	1	2		
ICA	Supraclinoid	3	4	7		
	Bifurcation	0	1	1		
MCA	M1	0	1	1		
	M2	1	0	1		
	Bifurcation-Trifurcation	3	1	4		
Total		8 (50 %)	8 (50 %)	16 (100 %)		

ICA: Internal carotid artery, ACA: Anterior cerebral artery, A1: the first part of ACA, A2: the second part of ACA (distally to the anterior communicating artery), BA: Basilar artery, MCA: Middle cerebral artery, M1 and M2: the first and second part of MCA.

ruptured IAs. More IAs ruptured (62 %) and had significantly smaller diameters (p =0.002). As smaller ruptured IAs constituted the majority of our sample, it is supported that specific unruptured IAs with smaller diameters may necessitate treatment¹³. Juvela et al set a 7 mm threshold stating that IAs can rupture regardless of their size21. However, both PHASES score and UIATS assess IAs <7 mm in diameter as lower risk^{2,3}. Specifically, the PHASES trial also provides points for location, including aCOM artery and posterior circulation, as carrying a high risk for rupture. This compensates for the lack of a lower limit in aneurysm sac diameter in these anatomical locations, which is otherwise reduced to 4 mm. These findings suggest that although patient age and IA diameter are significant, a combined estimation of multiple risk factors (including location) may be needed to identify these high-risk aneurysms.

Morphological measurements describing an abnormal/non-spherical dome (additional lobes, pseudolobes, abnormal shape) seem to take a major place in the treatment of unruptured IAs^{1,2,13,15,17,19,21,22}. Evidence support that abnormal shape was the only factor independently associated with rupture as in our study (p =0.0001)^{1,10}. A non-smooth wall was over five times more frequent in ruptured IAs, indicating that focal wall distension and

weakening lead to rupture. Additionally, non-saccular IAs have been associated with higher growth rates⁶. Our findings are in total agreement with the aforementioned and with Abboud et al, who stated that compared to the PHASES score, the UIATS offers a more comprehensive approach for rupture risk assessment, where treatment of irregular shape IAs is favored^{2,3,22}. Thus, IAs found to have abnormal sacks may have a direct indication for treatment regardless of the patient's past medical history or aneurysmal size and location^{9,17,20}.

Despite the consistency in these known risk factors, limited research exists on CWVs. There is evidence that CWVs likely play a role in the formation and progress of IAs. Hemodynamic alterations leading to IAs formation can be implicated 11,16,23. The existence of a variation, e.g., A1 aplasia or hypoplasia implies asymmetrical inflow to the rest of brain vasculature: blood volume redistribution through arteries with specific diameter leads to hemodynamic stress 1,11,16. In the current study, 40.2 % of patients harbored CWV, with the majority in ruptured IAs group 11,16,23,24. No specific CWV was associated with IAs rupture. 36.2 % of aCOM IAs co-existed with A1 variations, and 36.7 % of ruptured aCOM IAs co-existed with A1 variations. Rinaldo et al suggested that A1 hypoplasia can affect the IA formation, size, shape, and rupture ir-

Table 4: Characteristics of Circle of Willis variations in ruptured and unruptured aneurysms in the study's cohort.

Location and variation type	Total	Ruptured	Unruptured
Anterior circulation anomalies	32 (42.1%)	20	12
Hypoplasia	12	8	4
R A1	8	5	3
LA1	2	1	1
Dysplastic ACA	1	1	-
Aneurysmal dilation at distal ICA	1	1	-
Aplasia	20	12	8
RA1	12	8	4
LA1	8	4	4
P1 segment anomalies	35 (46.1%)	22	13
Hypoplasia	7	6	1
Bilateral P1	1	1	-
R P1	5	4	1
L P1	1	1	-
Aplasia	28	16	12
Bilateral	7	5	2
R P1	15	9	6
L P1	6	2	4
Vertebrobasilar system anomalies	6 (7.9%)	5	1
R VA Hypoplasia	2	2	-
L VA Hypoplasia	1	1	-
PICA Hypoplasia	1	1	-
SCA aplasia	1	-	1
BA tip	1	1	-
Total Whole circle of Willis anomalies	4 (5.3 %)	3	1
Diffuse angiopathy	2	1	1
PCOM Infundibulum	2	2	
Total	76 (100 %)	50 (65.8 %)	26 (34.2 %)

ACA: Anterior cerebral artery, R: right. L: left, A1: the first part of ACA, ICA: Internal carotid artery, P1: the first segment of Posterior cerebral artery, VA: Vertebral artery, PICA: Posterior inferior cerebellar artery, SCA: Superior cerebellar artery, BA: Basilar artery, PCOM: Posterior communication artery. Numbers in the table are presented as crude numbers and percentages.

respective of co-existing known risk factors¹⁶. However, neither the PHASES score nor UIATS include CWV in the treatment decision-making process, which may need reassessment given the supporting evidence connecting them with IAs rupture^{2,12}.

Due to underlying difficulties, literature is limited on the direct comparison between ruptured and unruptured IAs. Despite our relatively small sample, the current findings parallel the literature. The study methodology followed a two-step concept: safe conclusions were drawn once our results concurred with the literature. The current study highlights valuable information which may be directly connected with aneurysmal rupture (abnormal morphology and CWV).

Bearing in mind that our study is a single-center study,

some limitations exist. Included patients come from a large region, but eligible cases may have been missed. We used DSA, which can harbor a standard error, and analyzed specific morphological measurements. Presenting symptoms, medical history, medication, and risk factors such as smoking or hypertension were not included^{2,3}. Patients treated with flow diverters and clipped aneurysms were not included in the study, depriving these data of our analysis. Moreover, given the sample size, there were no matched groups on location and IA characteristics. In our department, patients referred from >15 hospitals from a large surrounding region are screened and treated. Our unit is one of the three National Public Hospitals located in the region where there is availability for endovascular treatment of IAs. Therefore, most patients with clipped

aneurysms do not reach our unit. Valuable information can be extracted on the long-term effectiveness of surgically clipped IAs matched with coiled IAs, but this analysis was beyond the scope of the present study.

Conclusion

Neurosurgeons and neurointeventionists have to make important decisions on managing incidentally-found unruptured IAs. Given the high morbidity and mortality of SAH, identifying unruptured IAs needing treatment is crucial. Certain morphological characteristics were observed in DSA, mainly in ruptured IAs. Thus, a more comprehensive individualized approach and assessment of the DSA findings, such as the presence of CWV, may contribute to identifying high-risk IAs and guide treatment optimization of unruptured aneurysms. This finding that smaller aneurysms constituted most of the ruptured IAs needs further validation in the Greek population.

Conflict of interest

Authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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References

- Murayama Y, Takao H, Ishibashi T, Saguchi T, Ebara M, Yuki I, et al. Risk Analysis of Unruptured Intracranial Aneurysms: Prospective 10-Year Cohort Study. Stroke. 2016; 47: 365-371.
- Étminan N, Brown RD Jr, Beseoglu K, Juvela S, Raymond J, Morita A, et al. The unruptured intracranial aneurysm treatment score: a multidisciplinary consensus. Neurology. 2015; 85: 881-889
- Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014; 13: 59-66.
- Etminan N, Chang HS, Hackenberg K, de Rooij NK, Vergouwen MDI, Rinkel GJE, et al. Worldwide Incidence of Aneurysmal Subarachnoid Hemorrhage According to Region, Time Period, Blood Pressure, and Smoking Prevalence in the Population: A Systematic Review and Meta-analysis. JAMA Neurol. 2019; 76: 588-597.
- Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American

- Heart Association/American Stroke Association. Stroke. 2015; 46: 2368-2400.
- Brinjikji W, Zhu YQ, Lanzino G, Cloft HJ, Murad MH, Wang Z, et al. Risk f Factors for Growth of Intracranial Aneurysms: A Systematic Review and Meta-Analysis. AJNR Am J Neuroradiol. 2016; 37: 615-620.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61: 344-349.
- RStudio Team. RStudio: Integrated Development Environment for R. RStudio, Boston, MA. 2020. Available at: http://www. rstudio.com/, date accessed: 30/5/2021.
- 9. Zanaty M, Daou B, Chalouhi N, Starke RM, Jabbour P, Hasan D. Evidence That a Subset of Aneurysms Less Than 7 mm Warrant Treatment. J Am Heart Assoc. 2016; 5: e003936.
- 10. Lindgren AE, Koivisto T, Björkman J, von Und Zu Fraunberg M, Helin K, Jääskeläinen JE, et al. Irregular Shape of Intracranial Aneurysm Indicates Rupture Risk Irrespective of Size in a Population-Based Cohort. Stroke. 2016; 47: 1219-1226.
- Cornelissen BMW, Schneiders JJ, Sprengers ME, van den Berg R, van Ooij P, Nederveen AJ, et al. Aneurysmal Parent Artery-Specific Inflow Conditions for Complete and Incomplete Circle of Willis Configurations. AJNR Am J Neuroradiol. 2018; 39: 910-915
- Bijlenga P, Gondar R, Schilling S, Morel S, Hirsch S, Cuony J, et al. PHASES Score for the Management of Intracranial Aneurysm: A Cross-Sectional Population-Based Retrospective Study. Stroke. 2017; 48: 2105-2112.
- Kashiwazaki D, Kuroda S. Size ratio can highly predict rupture risk in intracranial small (<5 mm) aneurysms. Stroke. 2013; 44: 2169-2173.
- Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors. Stroke. 2014; 45: 1958-1963.
- Zheng Y, Xu F, Ren J, Xu Q, Liu Y, Tian Y, et al. Assessment of intracranial aneurysm rupture based on morphology parameters and anatomical locations. J Neurointerv Surg. 2016; 8: 1240-1246
- 16. Rinaldo L, McCutcheon BA, Murphy ME, Bydon M, Rabinstein AA, Lanzino G. Relationship of A₁ segment hypoplasia to anterior communicating artery aneurysm morphology and risk factors for aneurysm formation. J Neurosurg. 2016; 127: 89-95.
- Mocco J, Brown RD Jr, Torner JC, Capuano AW, Fargen KM, Raghavan ML, et al. Aneurysm Morphology and Prediction of Rupture: An International Study of Unruptured Intracranial Aneurysms Analysis. Neurosurgery. 2018: 82: 491-416.
- Ishibashi T, Murayama Y, Urashima M, Saguchi T, Ebara M, Arakawa H, et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. Stroke. 2009; 40: 313-316.
- Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009; 26: E2.
- 20. Chmayssani M, Rebeiz JG, Rebeiz TJ, Batjer HH, Bendok BR. Relationship of growth to aneurysm rupture in asymptomatic aneurysms ≤ 7 mm: a systematic analysis of the literature. Neurosurgery. 2011; 68: 1164-1171.
- Juvela S, Korja M. Intracranial Aneurysm Parameters for Predicting a Future Subarachnoid Hemorrhage: A Long-Term Follow-up Study. Neurosurgery. 2017; 81: 432-440.
- Abboud T, Rustom J, Bester M, Czorlich P, Vittorazzi E, Pinnschmidt HO, et al. Morphology of Ruptured and Unruptured Intracranial Aneurysms. World Neurosurg. 2017; 99: 610-617.
- Krasny A, Nensa F, Sandaleioglu IE, Göricke SL, Wanke I, Gramsch C, et al. Association of aneurysms and variation of the A1 segment. J Neurointerv Surg. 2014; 6: 178-183.
- Lazzaro MA, Ouyang B, Chen M. The role of circle of Willis anomalies in cerebral aneurysm rupture. J Neurointerv Surg. 2012; 4: 22-26.