

# Clinical and Morphological Factors for Ruptured Anterior Communicating Artery Aneurysms

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**Introduction:** The anterior communicating artery (ACoA) aneurysm, the most frequent cerebral aneurysm to rupture, carries a significant clinical burden, yet the factors influencing its rupture are limited in Indonesia. This study aims to determine the clinical and morphological features associated with ruptured ACoA compared to non-AcoA aneurysms among Indonesians.

**Patients and Methods:** We retrospectively reviewed our center's aneurysm patient registry from January 2019 to December 2022, and compared the clinical and morphological features between ruptured ACoA aneurysms and ruptured aneurysms elsewhere with univariate and multivariate analyses.

**Results:** Of the 292 patients with 325 ruptured aneurysms, 89 were from ACoA. The mean age of patients was 54.99 years, with female preponderance in the non-ACoA group (non-ACoA: 73.31%, ACoA: 46.07%). On univariate analysis, ages  $\geq 60$  [ages 60–69: OR = 0.311 (0.111–0.869),  $p=0.026$ ; ages  $\geq 70$ : OR = 0.215 (0.056–0.819),  $p=0.024$ ], female gender [OR = 0.311 (0.182–0.533),  $p<0.001$ ], and smoking [OR=2.069 (1.036–4.057),  $p=0.022$ ] exhibited significant association with ruptured ACoA aneurysm. On multivariate analysis, only the female gender was independently associated with ruptured ACoA aneurysm (aOR 0.355 [0.436–1.961],  $p=0.001$ ).

**Conclusion:** In our study, ruptured ACoA aneurysm was inversely associated with advanced age, female gender, presence of daughter aneurysm, and directly associated with smoking. After multivariate adjustment, the female gender showed an independent association with ruptured ACoA aneurysm.

**Keywords:** ACoA aneurysm, ruptured, morphology, risk factor, Indonesian population

## Introduction

Cerebral aneurysm is a pathological bulging of the wall of blood vessels in the brain, which, when ruptured, can lead to aneurysmal subarachnoid hemorrhage (aSAH). The estimated prevalence of cerebral aneurysm is at 0.5–6% globally and although the consequent aSAH constitutes only 5% of all stroke cases, the condition carries a significant clinical burden.<sup>1–4</sup> Half of aSAH patients are under 55 years old, one-third of patients do not survive the first days to weeks post bleeding, and a majority of those who do have to endure lifelong cognitive and functional impairment.<sup>4</sup> Mortality associated with the rupture of cerebral aneurysms comprises up to 25% of all deaths from cerebrovascular diseases.<sup>5</sup>

The anterior communicating artery (ACoA) remains the most common site for intracranial aneurysms, with 30–37% of all cerebral aneurysms localized here.<sup>5,6</sup> ACoA aneurysms are also the most frequent to rupture, accounting for up to 40% of aSAH.<sup>7,8</sup> Being adjacent to a number of important blood vessels and structures, the complex management of ACoA aneurysms – ie, surgical clipping, endovascular coiling – carries notable potential iatrogenic complications and financial burden.<sup>5,7</sup> Accordingly, an understanding of factors that contribute to the rupture of ACoA aneurysms is of considerable value to physicians in treatment decision-making.

Multiple studies have identified several clinical – eg, age, gender, hypertension, family history of cerebral aneurysms, smoking – and morphological – eg, aneurysmal location, size, number – parameters related to the rupture of cerebral aneurysms, and scoring systems such as PHASES and the Unruptured Intracranial Aneurysm Treatment Score (UIATS) have been devised to predict rupture risk.<sup>2,5,8–12</sup> However, in addition to displaying geographical variation, a consensus on which of these variables are consistent descriptors of rupture risk is nonexistent and, inevitably, the applicability of scoring systems in guiding treatment plans remains questionable.<sup>8,12–15</sup>

In Indonesia, where epidemiological knowledge on cerebral aneurysms remains limited, the risk factors associated with ACoA aneurysm rupture are poorly understood. Moreover, due to inadequate screening, more patients in Indonesia are only admitted to the hospital once their aneurysm has ruptured. Therefore, this study aims to determine the clinical and morphological factors associated with ruptured ACoA aneurysms among Indonesian patients, compared to cerebral aneurysms of other origin.

## Materials and Methods

### Ethics Approval

Our study protocol was reviewed and approved by the Committee of Research Ethics of the National Brain Center Hospital, Jakarta, Indonesia (approval number LB.02.01/KEP/102/2022). The ethics committee decided that informed consent was not required for this study, as no personal information of patients was included. This study was conducted in compliance with the Declaration of Helsinki.

### Patient Selection

We retrospectively reviewed the cerebral aneurysm patient registry at the National Brain Center Hospital, Jakarta, and looked at admissions from 1 January 2019 to 31 December 2022. We excluded patients with unruptured aneurysms and/or incomplete clinical or morphological data. Data obtained for analysis included clinical variables as well as morphological parameters.

### Clinical Variables

The ruptured cerebral aneurysm variable was divided into ACoA and other than ACoA. Clinical variables obtained for analysis were age and gender; personal history of hypertension, diabetes mellitus, and/or dyslipidemia; smoking; and family history of cerebrovascular disease. Hypertension was defined as systolic blood pressure of  $\geq 140$  mmHg and/or diastolic blood pressure of  $\geq 90$  mmHg preceding the onset of SAH; or regular usage of one or more antihypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of  $\geq 126$  mg/dL, random blood glucose level of  $\geq 200$  mg/dL in the presence of classic clinical manifestations (polyuria, polydipsia, polyphagia, unexplained weight loss), and/or HbA1c level of  $\geq 6.5\%$ ; or usage of antidiabetic agents and/or insulin injection. Dyslipidemia was defined as a total cholesterol level of  $\geq 200$  mg/dL, HDL levels of  $\leq 40$  mg/dL, LDL levels of  $\geq 100$  mg/dL, and/or triglyceride levels of  $\leq 150$  mg/dL; or the use of lipid-lowering agents. Family history of cerebrovascular disease was considered relevant when concerning first- or second-degree relatives. Smoking status was considered positive for patients who were active smokers, and negative for patients who have never smoked before or were past smokers.

### Morphological Parameters

The morphological parameters of interest for analysis in this study were the aneurysmal size and the presence of a daughter aneurysm. Aneurysmal size was based on the dome diameter and classified into three groups: small ( $< 5$  mm), medium (5–10 mm), and large ( $> 10$  mm). These size thresholds were based on previously established classifications seen in the IAUTS while taking into account that most aneurysms identified in the Asian population were of sizes less than 5 mm.<sup>6,16,17</sup> Readings of morphological parameters were obtained with angiography, using the DSA-3D tool: Philips Allura Xpert FD 20 X-Ray system with 258° complex rotation scan and the XIOM Artis® C-arm (Siemens Healthcare, Erlangen, Germany) with 360° complex rotation scan.

## Statistical Analysis

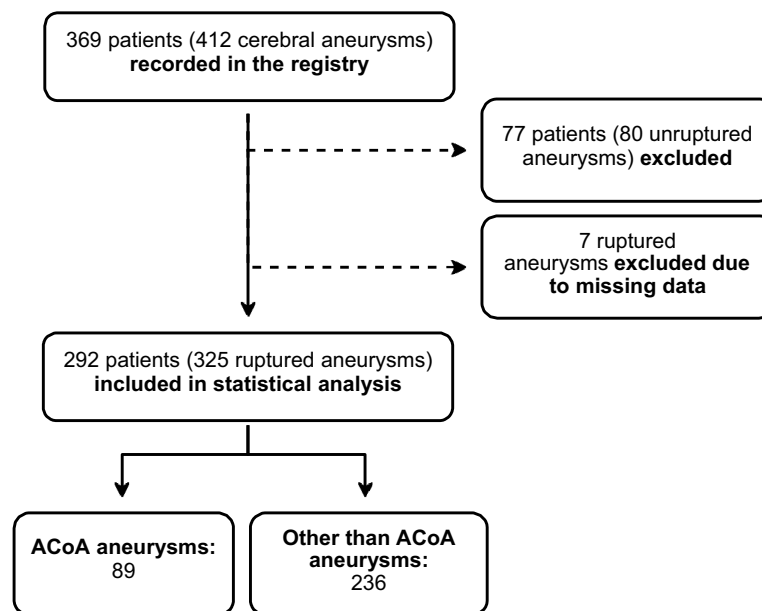
Data analysis was carried out using STATA statistical software version 17.0 (StataCorp, Texas, USA). Numerical variables were represented as mean and standard deviation if normally distributed, or as percentage (%) when appropriate. Categorical variables were represented as frequency and percentage (%). Univariate analysis with a Chi-square test was performed to determine differences in the occurrence of clinical and morphological variables between groups of ACoA aneurysms and aneurysms elsewhere. For variables with  $p < 0.1$  on univariate analysis, multivariate regression analysis was performed. Variables with  $p < 0.05$  on multivariate analysis were independently associated with ruptured ACoA aneurysm. For each variable, an odds ratio (OR) with a 95% confidence interval (CI) was also obtained.

## Results

Between January 2019 and December 2022, our cerebral aneurysm registry recorded 369 patients with 412 cerebral aneurysms. From these, 77 patients with 80 unruptured aneurysms were excluded. From the remaining 292 patients, 7 out of 332 ruptured aneurysms had incomplete morphological data and were excluded. The final 292 patients with 325 ruptured cerebral aneurysms (322 saccular) were included in the analysis (Figure 1). The anterior communicating artery was the most common site of ruptured cerebral aneurysms (89; 27%), followed by the posterior communicating artery (82; 25%), internal carotid artery (60; 18%), middle cerebral artery (50; 15%), and anterior cerebral artery (23; 6%). Other aneurysmal sites identified among our patients were the basilar, vertebral, ophthalmic, and superior cerebellar arteries.

Clinical and morphological features of the subjects can be seen in Table 1. More than half of patients with ruptured aneurysms were female (65%), and the majority of them developed aneurysms in other cerebral arteries (73% of non-ACoA aneurysms). On univariate analysis, the female gender was inversely associated with ruptured ACoA aneurysms, with a significant difference between groups (OR 0.31, 95% CI [0.18–0.53],  $p < 0.001$ ).

Most patients were less than 60 years old (mean age  $\pm$  SD:  $54.99 \pm 11.26$  years), comprising the majority of those with ruptured ACoA aneurysms (81%) and ruptured aneurysms elsewhere (60%). The preponderance of younger patients was also seen on univariate analysis; there was a significant inverse association between ages 60 or older and ruptured ACoA aneurysms (age group 60–69: OR 0.31, 95% CI [0.11–0.87],  $p = 0.026$ ; age group  $\geq 70$ : OR 0.22, 95% CI [0.06–0.82],  $p = 0.024$ ).



**Figure 1** Subject selection flow chart.

**Table I** Clinical and Morphological Features of Subjects

Variables	ACoA Aneurysms (N=89)		Aneurysms Elsewhere (N=236)*		OR (95% CI)	p-value
	Frequency	%	Frequency	%		
Clinical Features						
Age (years)						
<40	9	10	14	6	Reference	
40–49	32	36	53	23	0.939 (0.365–2.417)	0.897
50–59	31	35	75	32	0.643 (0.252–1.639)	0.355
60–69	13	15	65	27	0.311 (0.111–0.869)	<b>0.026</b>
≥70	4	4	29	12	0.215 (0.056–0.819)	<b>0.024</b>
Gender						
Male	48	54	63	27	0.311 (0.182–0.533)	<b>&lt;0.001</b>
Female	41	46	173	73		
Hypertension						
Yes	70	79	192	81	0.844 (0.447–1.641)	0.582
No	19	21	44	19		
Diabetes Mellitus						
Yes	16	18	51	22	0.795 (0.397–1.528)	0.470
No	73	82	185	78		
Dyslipidemia						
Yes	36	41	79	33	1.349 (0.789–2.294)	0.241
No	53	59	157	67		
Smoking						
Yes	20	22	29	12	2.069 (1.036–4.057)	<b>0.022</b>
No	69	78	207	88		
Family History of Cerebrovascular Disease						
Yes	5	6	7	3	1.947 (0.473–7.333)	0.258
No	84	94	229	97		
Morphological Features						
Aneurysmal Size (n=322)**						
<5 mm	57	65	137	59	Reference	
5–10 mm	23	26	78	33	0.709 (0.406–1.239)	0.227
>10 mm	8	9	19	8	1.012 (0.419–2.445)	0.979
Daughter Aneurysm						
Yes	4	4	27	11	0.364 (0.091–1.094)	<b>0.057</b>
No	85	96	209	89		

**Notes:**  $p < 0.1$  (in bold) is of statistical significance in univariate analysis. \*Aneurysmal sites other than the anterior communicating artery include the internal carotid, anterior cerebral, middle cerebral, posterior communicating, basilar, vertebral, ophthalmic, and superior cerebellar arteries. \*\*Only applicable to saccular aneurysms.

**Abbreviations:** ACom, anterior communicating artery; CI, confidence interval; OR, odds ratio.

**Table 2** Multivariate Analysis of Factors Associated with Ruptured ACoA Aneurysm

Variables	OR (95% CI)	p value*	aOR (95% CI)	p value**
<b>Age (years)</b>				
<40	Reference		Reference	
40–49	0.939 (0.365–2.417)	0.897	0.975 (0.363–2.618)	0.960
50–59	0.643 (0.252–1.639)	0.355	0.789 (0.299–2.079)	0.631
60–69	0.311 (0.111–0.869)	<b>0.026</b>	0.462 (0.158–1.345)	0.156
≥70	0.215 (0.056–0.819)	<b>0.024</b>	0.303 (0.076–1.197)	0.089
<b>Female</b>	0.311 (0.182–0.533)	<b>&lt;0.001</b>	0.355 (0.198–0.636)	<b>0.001</b>
<b>Smoking</b>	2.069 (1.036–4.057)	<b>0.022</b>	0.925 (0.436–1.961)	0.838
<b>Daughter Aneurysm</b>	0.364 (0.901–1.094)	<b>0.057</b>	0.355 (0.116–1.091)	0.071

**Notes:** \*On univariate analysis,  $p < 0.1$  (in bold) is of statistical significance. \*\*On multivariate analysis,  $p < 0.05$  (in bold) is of statistical significance.

**Abbreviations:** ACom, anterior communicating artery; CI, confidence interval; OR, odds ratio.

Hypertension was the most prevalent risk factor among patients across both groups of ruptured aneurysms, yet it showed no statistical significance on univariate analysis. In fact, of all clinical risk factors, smoking was the only one to exhibit a significant association with ruptured ACoA aneurysms on univariate analysis (OR 2.07, 95% CI [1.04–4.06],  $p=0.022$ ).

Most of the aneurysms in our patients were smaller than 5 mm, making up 65% of ruptured ACoA aneurysms (mean size  $\pm$  SD = 5.25  $\pm$  3.53) and 59% of ruptured aneurysms elsewhere (mean size  $\pm$  SD = 5.37  $\pm$  2.88). Nevertheless, on univariate analysis, aneurysmal size was statistically insignificant. The presence of a daughter aneurysm, however, showed a significant inverse association (OR 0.36, 95% CI [0.90–1.09],  $p=0.057$ ).

On multivariate analysis (Table 2), after adjustment, the female gender was independently associated with ruptured ACoA aneurysms (aOR 0.355, 95% CI [0.436–1.961],  $p=0.001$ ). Other variables showed no significant difference in multivariate analysis.

## Discussion

We found that ACoA aneurysms accounted for the majority of ruptured cerebral aneurysms among our patients, confirming previous reports that they were the most frequent to rupture.<sup>5–8</sup> Studies have shown that patients with ACoA aneurysms are more likely to present with worse neurological deficits, have a higher likelihood of vasospasm, and have poorer outcomes, all of which are tied to ACoA aneurysms' greater rupture risk.<sup>10</sup> This is to be expected from ACoA's proximity to important structures like the frontal cortex and optic chiasm.<sup>18</sup> Thus, an understanding of factors that influence the rupture of ACoA aneurysms is of considerable clinical value.

In our study, the female displayed a significantly inverse association with ruptured ACoA aneurysms. With respect to gender—the only independent factor after multivariate adjustment—our finding agrees with previous investigations by Park et al in South Korea, Lindner et al in the Netherlands, Krzyżewski et al in Poland, and Zhang et al in the US, female was found to be a risk factor for the growth of unruptured especially in older patients and localizes preferentially in the internal carotid artery, whereas men had ruptured aneurysms at the ACoA and anterior cerebral artery more frequently.<sup>19–22</sup> Many factors related to growth aneurysms and the risk of rupture are slightly different between males and females. In males, most of the risk factors include hypertension, atherosclerosis, and smoking, while the postmenopausal state is found as a risk factor for females.<sup>23</sup>

Older age was associated with ruptured ACoA aneurysms, results from previous studies were inconsistent; Matsukawa et al also reported that Japanese patients with ruptured ACoA aneurysms were significantly younger and the majority of them were less than 60, yet Kim et al and Zhang et al found no significant difference in age.<sup>6,10,21</sup> Conversely, Lindner et al found that when compared to ACoA, aneurysms that ruptured in other sites were more likely to occur in younger patients.<sup>20</sup>

Based on vascular risk factors, hypertension was the most frequently encountered risk factor in both groups. However, on univariate analysis, most clinical risk factors failed to exhibit significant association with ruptured ACoA aneurysms apart from smoking. Hypertension and smoking have long been known to promote the formation as well as

rupture of cerebral aneurysms, by inducing endothelial dysfunction and vascular inflammation, thus compromising vascular wall integrity.<sup>9,24,25</sup> Thus, confirming prior studies, our findings demonstrated that no single vascular risk factor is independently associated with ruptured ACoA aneurysms.

In both ACoA and non-ACoA aneurysm groups, most aneurysms were less than 5 mm. We also found that aneurysmal size was not significantly associated with the location of aneurysm rupture. A previous Indonesian study by Swatan et al found that most ruptured aneurysms were less than 5 mm in size, with ACoA as the most frequent location.<sup>16</sup> Similarly, Kim et al found that in South Korea, 55% of ruptured aneurysms were <4 mm in size, and Lai et al reported that most ruptured aneurysms in the Hong Kong Chinese population were 5 mm or smaller.<sup>6,17</sup> In contrast, studies on the Japanese and Finnish populations reported bigger aneurysmal size, averaging at 7 mm.<sup>17,25</sup> Additionally, Matsukawa et al in Japan demonstrated that a larger aneurysmal size of  $\geq 5$  mm was significantly associated with ACoA aneurysm rupture.<sup>10</sup> It appears that among Asian populations other than Japan, aneurysms rupture at smaller sizes more frequently.

We found that the presence of a daughter aneurysm was inversely associated with ruptured ACoA aneurysms. In contrast, Chen et al found that the presence of a daughter dome was a risk factor for ACoA aneurysm rupture.<sup>26</sup> Liu et al also found that aneurysm lobulations, including daughter sac, were significantly more frequent in ruptured than unruptured ACoA aneurysms.<sup>25</sup> Our result shows that the presence of a daughter aneurysm may affect the rupture of aneurysms in other sites more than ACoA.

Several limitations of this study exist. This retrospective study utilized patients from a single center. Many morphological parameters of aneurysms could be potentially analyzed, like dome-neck ratio and size ratio, presence of aplastic or hypoplasia, and hemodynamics of aneurysms. Further investigations with prospective, multi-center data accrual and analysis of more morphological measurements are still needed.

## Conclusion

We found that ruptured ACoA aneurysm among our patients was associated with advanced age, female, smoking, and the presence of a daughter aneurysm. Of these, only the female exhibited an independent inverse association with ruptured ACoA aneurysms. The relationship between the rupture of cerebral aneurysm and its risk factors remains complex, as evident by the variance between populations. Nevertheless, our investigation may help elucidate the clinical profile of ruptured ACoA aneurysms in Indonesia.

## Data Sharing Statement

The data sets supporting the conclusions of this article are available upon reasonable request to the corresponding author.

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## Author Contributions

BR, BTP, RGK, AA, and MK contributed to the conception and design of the study. BR, BTP, and RGK collected the data utilized in the study. BR, KTG, and PRW conducted the data analysis and wrote the manuscript. All authors contributed to the manuscript revision, approved the final draft of the manuscript as well as the journal for publication, and agreed to be accountable for all aspects of the study.

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## Disclosure

The authors have no conflicts of interest to declare in this work.

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