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Comparison of outcomes between a ruptured and unruptured intracranial aneurysm: results from an Indonesian cohort study

Julius July[1], Patrick Putra Lukito[1*], Vanessa Angelica[1], Jeremiah Hilkiah Wijaya[1], Audrey Hamdoyo[1], Nyoman Aditya Sindunata[2], Rusli Muljadi[2]

[1]Department of Neurosurgery, Neuroscience Centre Siloam Hospital, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia;
[2]Department of Radiology, Siloam Hospital, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia;

*Corresponding author:
Patrick Putra Lukito;
Department of Neurosurgery, Neuroscience Centre Siloam Hospital, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia;
lukito_patrick@yahoo.co.id

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ABSTRACT

Purpose: A ruptured intracranial aneurysm has a high mortality rate. Moreover, many of its surviving patients have to live with severe disabilities. Therefore, surgical or endovascular treatment is recommended in some patients with a known aneurysm and a high risk of rupture. However, many patients are reluctant to undergo treatment, fearing its complications. This study aimed to evaluate the treatment outcomes and safety in patients with a ruptured and unruptured intracranial aneurysm.

Methods: We retrospectively reviewed the records of patients treated for intracranial aneurysms in our hospital between 2017 to 2021. Our primary outcome was discharge functional outcome. We also evaluated cerebral infarction, stay duration, and mortality. We used bivariate and multivariate analysis.

Results: 85 patients were included in this study. 69 (77.5%) patients were treated after rupture. Most patients were treated with clipping (78.8%). Patients with a ruptured aneurysm significantly had a higher risk of poor discharge functional outcome (OR 5.708 [1.061 – 30.712]; p 0.042). Six patients with a ruptured aneurysm died. Patients with a ruptured aneurysm also spent more time at the hospital. There was no mortality or complication in patients with an unruptured aneurysm.

Conclusion: Patients treated before their aneurysms ruptured had better outcomes with no complications. Therefore, treatment should be considered for high-risk patients.

Keywords: Aneurysmal subarachnoid hemorrhage, clipping, coiling, functional outcome.

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INTRODUCTION

Aneurysmal subarachnoid hemorrhage that results from a ruptured intracranial aneurysm is one of the most devastating neurosurgical conditions, with mortality reaching as high as 20%.[1] Although there has been a significant advance in treatment modalities[2-4], its mortality and morbidity remain high. Compared to the other types of strokes, aSAH patients are relatively younger. With its high rate of disability, aSAH hugely impacts patients while they are still productive.

The unsatisfactory treatment outcome of aSAH highlights the importance of preventing this condition in the first place. Smoking, hypertension, excessive alcohol consumption, dyslipidemia, heart disease, familial history, female sex, and older age are some risk factors for aSAH.[5,6] The other obvious risk factor is the presence of an unruptured intracranial aneurysm. Its prevalence ranged from 2.3% to 8.8% in healthy populations.[7] This high prevalence rate justifies the need for intracranial aneurysm screening in patients with the risk factors mentioned earlier.

A discovered unruptured intracranial aneurysm can be treated surgically or conservatively, according to the presence of risk factors or aneurysm growth.[8] However, based on our experience in Indonesia, many patients are reluctant to undergo screening. Even if they do and an unruptured aneurysm was found, some patients do not want surgery or endovascular procedures, especially if they are asymptomatic. Treating an aneurysm before it ruptures results in a better outcome, with ischemic complication ranging from 2.9 to 11%[8], lower than the rate of infarction that occurred in an aneurysmal subarachnoid hemorrhage that could reach as high as 25.4%.[9] Mortality also significantly increases from 2.5% to 22.1% after an aneurysm has ruptured.[10] We designed the present study to report the difference in outcomes of patients with ruptured and unruptured aneurysms, hoping to highlight the importance of treating an aneurysm before it ruptures.

METHODS

Study Population

We retrospectively collected the data for all intracranial aneurysm patients treated with a surgical or endovascular procedure in our hospital between 2017 to 2021. We excluded patients with non-aneurysmal subarachnoid hemorrhage, those aged < 18 years old, and those not diagnosed using a head CT scan or MRI and CT angiographic study. We also excluded patients without complete medical records and radiographic studies. Informed consent was not required because of the retrospective and observational design. Moreover, no patients' identifiers were presented in this study.

Data Collection

We collected patients' baseline characteristics from their medical records. These included age, sex, comorbidities, presenting signs and symptoms, Glasgow Coma Scale (GCS), and blood pressure. Increased blood pressure was defined as systolic blood pressure (SBP) > 120mmHg or diastolic blood pressure (DBP) > 90 mmHg. We collected radiographical data from our radiology archive. In patients with a ruptured aneurysm, severity was classified using the World Federation of Neurosurgical Societies (WFNS) scale and the modified Fisher (mFisher) scale. Treatment and patients' discharge data were also collected from the medical records.

Imaging

The diagnosis of an intracranial aneurysm was made using either head computed tomography (CT) scan or magnetic resonance imaging (MRI) and supplemented by CT angiography (CTA). CT scan and CTA were performed using Siemens SOMATOM drive dual source 128-slice CT scanner. Scan was done caudocranially from cranial base to vertex with 0.75 mm slice thickness. CTA was performed using 50-70 ml of 370 mg I/ml iodinated contrast with 4.0-4.5 ml/second flow rate followed by 30-50 ml of saline chaser. Scan was started when the region of interest (ROI) in carotid artery reached 100 Hounsfield Unit (HU) during bolus tracking. MRI was performed using Phillips Achieva 1.5T or 3T, with the following scan sequences and planes: axial DWI, axial T1 SE, axial FLAIR, axial T2 TSE & FFE, coronal T2 TSE, and sagital T1 FFE.

To find and exclude iatrogenic infarcts, we performed radiological imaging 48 hours after each procedure and identified infarct that occurred during that time period as iatrogenic and differentiated it from infarcts that occurred afterward. A final radiographical evaluation was performed before the patient's discharge, although the treating clinician could order another radiographical evaluation during the patient's hospital stay. In the data collection process of the present study, a blinded radiologist performed another reading of the radiographic image to confirm the presence of intracranial aneurysm and identify any intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), or cerebral infarction. We defined cerebral infarction as the presence of cerebral infarction on a CT scan or MRI of the brain during the hospital stay until a maximum of 6 weeks or on the latest CT scan or MRI study obtained before death within six weeks, and not attributable to other causes such as surgical clipping or endovascular treatment. For patients with a ruptured aneurysm, the radiologist also graded them using the mFisher grade.

Outcome Evaluation

The primary outcome of this study was discharge functional outcome. We used the modified Rankin Scale (mRS) for this purpose and classified poor functional outcome as mRS 3 – 6. We also reported cerebral infarction, mortality, intensive care unit (ICU) length of stay (LOS), total hospital LOS, and complications.

Statistical Analysis

Patients' characteristics were compared between those with a ruptured and an unruptured aneurysm. Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were analyzed for their distribution and were compared using Student's t-test or Mann-Whitney U test according to their distribution. We also planned a multivariate logistic regression to determine the effect of a ruptured aneurysm to discharge functional outcome. Variables that showed statistical significance in the bivariate analysis were included in the regression model. Statistical significance was set at $p < 0.05$.

RESULTS

Patients Characteristics

We identified 85 patients with intracranial aneurysms that underwent surgical or endovascular procedures. The majority of them had a ruptured aneurysm (77.5%). The baseline characteristics can be seen in Table 1. Patients with a ruptured aneurysm had a higher rate of decreased consciousness (26/69 [37.7%] vs. 0/16) and seizure (7/69 [10.1%] vs. 0/16) as the presenting symptoms, but only decreased consciousness reached statistical significance (p 0.002). We also combined the presence of other neurological deficits with decreased consciousness and found no difference between the two groups (36/69 [52.2%] vs. 8/16 [50.0%]). Patients with a ruptured aneurysm had a similar rate of hypertension (33/69 [47.8%] vs. 9/16 [56.3%]) but a higher diabetes mellitus (5/69 [7.2%] vs. 0/16), coronary artery disease (3/69 [4.3%] vs. 0/16), and congestive heart failure (2/16 [2.9%] vs. 0/16), but none reached statistical significance. Increased blood pressure on presentation was significantly higher in those with a ruptured aneurysm (42/69 [60.9%] vs. 5/16 [31.3%]; p 0.032). GCS score was lower in patients with a ruptured aneurysm (12 [9 – 15] vs. 15). None of the patients with an unruptured aneurysm experienced a decrease in GCS score; therefore, statistical comparison for the difference in the median was not possible. Among the patients with a ruptured aneurysm, the majority had poor WFNS grade (grade 1: 22 [31.9%]; grade 2: 3 [4.3%]; grade 3: 8 [11.6%]; grade 4: 32 [46.4%]; grade 5: 4 [5.8%]).

Radiological Data

ICH (14/69 [20.3%] vs. 0/16], hydrocephalus (34/69 [49.3%] vs. 2/16 [12.5%]), and IVH (38/69 [55.1%] vs. 0/16) occurred more frequently in patients with a ruptured aneurysm, but only hydrocephalus and IVH reached statistical significance (p 0.007 and $p < 0.001$). The rate of thick (mFisher grade ≥ 3) and thin hemorrhage (mFisher grade ≤ 2) were similar among patients with a ruptured aneurysm (36/69 [52.2%] vs. 33/69 [47.8%]).

Treatment Data

The majority of patients received clipping (67/85 [78.8%] vs. 18/85 [20.2%]). The rate of clipping (54/69 [78.3%] vs. 13/16 [81.3%]) and ventilator use (55/69 [79.7%] vs. 12/16 [75.0%] did not differ among

Table 1. Patients baseline characteristics and outcomes.

Variables	Ruptured aneurysm (n = 69)	Unruptured aneurysm (n=16)	p value
Demographic			
Age	53.4 ± 12.8	53.3 ± 14.4	0.985
Male	30 (43.5)	6 (37.5)	0.663
Symptoms on admission			
Cephalgia	49 (72.1)	12 (75.0)	1.000
Decreased consciousness	26 (37.7)	0 (0.0)	**0.002**
Seizure	7 (10.1)	0 (0.0)	0.338
Any neurological deficit + decreased consciousness	36 (52.2)	8 (50.0)	1.000
Comorbidities			
Hypertension	33 (47.8)	9 (56.3)	0.544
Diabetes mellitus	5 (7.2)	0 (0.0)	0.578
Coronary artery disease	3 (4.3)	0 (0.0)	1.000
Congestive heart failure	2 (2.9)	0 (0.0)	1.000
Admission status			
Increased blood pressure	42 (60.9)	5 (31.3)	**0.032**
GCS	12 (9 – 15)	15	N/A
WFNS		N/A	N/A
• 1	22 (31.9)		
• 2	3 (4.3)		
• 3	8 (11.6)		
• 4	32 (46.4)		
• 5	4 (5.8)		
Radiographical data			
ICH	14 (20.3)	0 (0.0)	0.062
Hydrocephalus	34 (49.3)	2 (12.5)	**0.007**
IVH	38 (55.1)	0 (0.0)	**0.000**
mFisher scale		N/A	N/A
• 1	14 (20.3)		
• 2	22 (31.9)		
• 3	17 (24.6)		
• 4	16 (32.2)		
Treatment			
Coiling	15 (21.7)	3 (18.8)	1.000
Clipping	54 (78.3)	13 (81.3)	1.000
Ventilator	55 (79.7)	12 (75.0)	0.737
Shunt	22 (31.9)	2 (12.5)	0.216
Outcome			
Poor discharge functional outcome	44 (63.8)	2 (12.5)	**< 0.001**
Cerebral infarction	22 (31.9)	1 (6.3)	0.058
Mortality	6 (8.7)	0 (0.0)	0.589
ICU LOS	7.7 ± 5.9	2.7 ± 3.4	**< 0.001**
Hospital LOS	15.2 ± 9.1	8.9 ± 4.6	**0.003**
Complication			
Pneumonia	5 (7.2)	0 (0.0)	0.578
AKI	2 (2.9)	0 (0.0)	1.000
Cerebral edema	2 (2.9)	0 (0.0)	1.000
Rebleeding	1 (1.4)	0 (0.0)	1.000
ALO	1 (1.4)	0 (0.0)	1.000

Notes: Bold type indicates statistical significance.
Abbreviations: GCS, Glasgow Coma Scale; WFNS, World Federation of Neurosurgical Societies; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mFisher, modified Fisher; AKI, acute kidney injury; ALO, acute lung oedema.

Table 2. Logistic regression model for poor discharge functional outcome.

Variables	OR (95% CI)	p value
Ruptured aneurysm	5.708 (1.061 – 30.712)	**0.042**
Decreased consciousness	8.139 (1.823 – 36.345)	**0.006**
Increased blood pressure	2.056 (0.719 – 5.881)	0.179
Hydrocephalus	1.167 (0.356 – 3.826)	0.798
IVH	0.916 (0.269 – 3.118)	0.888

Notes: Bold type indicates statistical significance.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; IVH, intraventricular hemorrhage.

the groups. More patients with a ruptured aneurysm required a shunt placement (22/69 [31.9%] vs. 2/16 [12.5%]), although it did not reach statistical significance.

Outcome

Patients with a ruptured aneurysm significantly had a higher rate of poor discharge functional outcome (44/69 [63.8%] vs. 2/16 [12.5%]; p < 0.001) (Table 1). They also had significantly longer ICU LOS (7.7 ± 5.9 vs. 2.7 ± 3.4; p < 0.001) and hospital LOS (15.2 ± 9.1 vs. 8.9 ± 4.6; p 0.003). Cerebral infarction occurred more frequently in patients with a ruptured aneurysm (22/69 [31.9%] vs. 1/16 [6.3%]). Six patients (8.7%) died from a ruptured aneurysm, while none had died from an unruptured aneurysm. However, the difference in cerebral infarction and mortality did not reach statistical significance. Complications were also higher in the ruptured aneurysm group, although the difference was insignificant.

Multivariable Analysis

We included decreased consciousness, increased blood pressure, hydrocephalus, and IVH as confounders in our regression model (Table 2). We found that a ruptured aneurysm increased the rate of poor discharge functional outcome (OR 5.708 [1.061 – 30.712]; p 0.042). Decreased consciousness on presentation remained significant in the regression model (OR 8.139 [1.823 – 36.345]; p 0.006).

DISCUSSION

This paper showed that patients with a ruptured aneurysm had a worse functional outcome (OR 5.708 [1.061–30.712]; p 0.042). The major cause of neurological deficits and disabilities is cerebral infarction[9,10], which reflects the ultimate end-point for an ischemic event. Cerebral vasospasm was thought to be the only mechanism behind it, but recent studies have shed some light on other possible causes. The current paradigm states that cerebral infarction results from a complex interplay between various biological processes, such as microthromboembolism, microvascular constriction, blood-brain barrier disruption, neuroinflammation, cortical spreading ischemia, and impaired cerebral autoregulation.[11] The lysis of hemoglobin and the presence of platelet are thought to incite these mechanisms.[11] Therefore, aneurysm rupture and the release of blood into the subarachnoid space pose the patient with a very high risk of cerebral injury.

We also found a higher rate of cerebral infarction in patients with a ruptured aneurysm, but the difference was marginally insignificant (22/69 [31.9%] vs. 1/16 [6.3%]; p 0.058). We also found no mortality and complications in patients treated before their aneurysm had ruptured. These results supported the safety and benefit of treating an intracranial aneurysm before it ruptures. We admitted that treating an unruptured aneurysm is not without complications. However, the rate is much lower. The ischemic complication in patients with unruptured aneurysms ranged from 2.9 to 11% for clipping and 2.9 to 5% for coiling.[8] This is much lower compared to the rate of cerebral infarction in patients with a ruptured aneurysm which could reach as high as 25.4%.[12] Mortality after a clipping or coiling procedure in patients with an unruptured aneurysm ranged from 0.5 to 2.5%[8], lower than the mortality rate of aSAH, which reached 22.1%.[13] The risk of rupture itself varied between 0.6 to 1.5% per year.[14] Size is one of the most important predictors. Intracranial aneurysms with a size of 5 to 6 mm had a low 0.5% risk of rupture per year, but this figure shot out to 33.4% for aneurysms larger than 25mm.[14] Other important predictors are age, prior history of aSAH, familial history, and aneurysm location.[8] Seeing that the risk of complications was much higher in a ruptured aneurysm, a patient with a known risk factor is recommended to consider treatment before a rupture occurs.[8] We also suggested future studies to study the rate of rupture in the Indonesian population.

We also found that patients with a ruptured aneurysm spent more time in the hospital. The difference was statistically and clinically significant, as ICU LOS approximately differed by five days and hospital LOS by six days. A longer ICU stay duration in patients with acute brain dysfunction is one of the risk factors for post-intensive care syndrome (PICS).[15] PICS has now been recognized as a health burden due to its risk of causing cognitive and psychiatric problems.[15] Moreover, aside from the clinical impact, a more extended stay at the hospital also increases healthcare costs. We suggested conducting a cost-benefit analysis for future studies to gain insight into the financial benefits of treating an unruptured intracranial aneurysm.

Before the widespread use of CT or magnetic resonance (MR) angiography, diagnosis for intracranial aneurysm has been made using digital subtraction angiography (DSA). The availability of noninvasive diagnostic procedure, such as CT or MR angiography, has increased the detection rate. The availability of noninvasive procedure also prompted the American Heart Association/American Stroke Association (AHA/ASA) to recommend screening for those with a high risk of intracranial aneurysm, such as those with two or more family members with intracranial aneurysm or aSAH and those with polycystic kidney disease, coarctation of aorta, or microcephalic osteodysplastic primordial dwarfism.[8] In Korea, the incidence of unruptured intracranial aneurysm increased from 29.6 per 100,000 person-years in 2008 to 90.0 per 100,000 person-years in 2016. This was believed to result from an increase in detection rate, rather than an increase in the development of intracranial aneurysm.[7] A large study from the United States of America over a period of 10 years also found an increase in the number of intervention for unruptured intracranial aneurysm, which likely resulted from a higher detection rate. They also found that the number of interventions for aneurysmal subarachnoid hemorrhage decreased accordingly over the years. Although direct causality cannot be ascertained, they suggested that this decrease was the result of pre-emptive treatment of high-risk unruptured intracranial aneurysms.[16] This data showed the benefit of performing screening in selected individuals with a high risk for intracranial aneurysm. Regarding treatment modalities, since the publication of the International Subarachnoid Aneurysm Trial (ISAT), there has been an increase in the number of coiling procedures. Studies from the United States of America and Korea reported that the number of coiling performed for either unruptured or ruptured intracranial aneurysm has increased substantially, overtaking clipping as the most performed procedure for treating aneurysm.[16,17]

Our study has several limitations. The retrospective and single-center designs have an inherent risk of confounding bias. To deal with this, we used a multivariate regression model to reduce the effect of bias. Another limitation is the small number of samples. The lack of statistical power prevented our study from finding an independent association between aneurysm rupture and several of our outcomes. As the Indonesian and Southeast populations have been heavily underrepresented in the medical literature, we hope our initial result could spark an interest in conducting larger, prospective studies in the future.

CONCLUSION

Patients with a ruptured aneurysm had a significantly higher rate of poor discharge functional outcome. They also spent a longer time at the hospital. Our results also showed that an unruptured aneurysm could be treated successfully in Indonesia with a very low rate of complications. Therefore, as the potential benefit outweighs the risk, patients with risk factors for aneurysm rupture should not be afraid of having their unruptured aneurysms treated.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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None.

ETHICAL STATEMENT

This study was approved by the local ethics committee of Universitas Pelita Harapan with the ethical clearance number 183/K-LKJ/ETIK/XII/2021.

AUTHOR CONTRIBUTION

All author contributed equally in this study.

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