ORIGINAL ARTICLE

Higher mean arterial pressure increases risk of in-hospital mortality in aneurysmal subarachnoid hemorrhage

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ABSTRACT

BACKGROUND

The majority (80%) of spontaneous subarachnoid hemorrhage (SAH) cases are caused by cerebral aneurysm rupture. The reported case fatality rate of aneurysmal SAH is still as high as 25 to 50%. Even though studies on aneurysmal SAH have been conducted, the mechanism and factors contributing to its mortality have not yet been clearly understood. The present study aimed to determine the predictors of mortality in aneurysmal SAH.

METHODS

This was an observational analytic cross-sectional study. Data of 264 patients with aneurysmal SAH was obtained retrospectively from the medical records. Age, degree of consciousness, blood pressure, absence of aneurysmal treatment and mortality were collected. The simple and multiple logistic regression were used to analyze the data.

RESULTS

The in-hospital mortality rate of aneurysmal SAH was still very high, with 140 (53.1%) patients dying during hospitalization. Simple logic regression analysis showed that patients with older age, lower Glasgow Coma Scale (GCS) score, higher mean arterial pressure (MAP) and no aneurysm treatment had higher in-hospital mortality risk. However, multivariate logistic regression showed that the strongest in-hospital mortality predictor was higher MAP (aOR 2.29; p=0.025), while younger age (aOR 0.39; p=0.006) and aneurysm treatment (aOR 0.34; p=0.006) were independent protective factors against in-hospital death.

CONCLUSION

Patients with higher mean arterial pressure on initial measurement had higher risks of mortality. More endovascular neurointervention facilities are needed to decrease the mortality rate of aneurysmal SAH.

Keywords : Cerebral aneurysm, mortality, subarachnoid hemorrhage, stroke

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INTRODUCTION

Subarachnoid hemorrhage (SAH) is a form of bleeding that occurs in the subarachnoid space between the pia mater and arachnoid mater, whereas its most frequent cause is from traumatic injury. Even so, spontaneous SAH is also commonly found as one of the forms of stroke. [1] The reported incidence rate of SAH varies from 6.2 in Finland,[2] Nigeria 6.51,[3] US 7.7 [4] per 100,000 population each year and Japan [5] 27.63 per 100,000 person-years, with women still predominating, namely 71.9% in Kenya [6] and 61.6% in China. [7]

The majority of spontaneous SAH is caused by ruptured cerebral aneurysm, which accounts for 70 to 80% of cases.[8] Cerebral aneurysm occurs in 1 to 3% of the population.[9] The detection rate of unruptured cerebral aneurysm worldwide has been growing due to advancement of CT and MR angiographies and its treatment has been widely discussed to prevent future aneurysmal SAH (aSAH).[8] Some countries have even started screening of first-degree relatives of aSAH patients.[10,11] This has not yet been carried out in Indonesia, because the use of CT scan and MRI in non-symptomatic patients is still not routinely done. Prior studies regarding predictors of mortality and poor outcome in aSAH have been done. Aneurysm re-bleeding and delayed cerebral ischemia in the course of this disease have been the strongest independent predictors of unfavorable outcome.[12,13] Higher age was found to be associated with death and worse outcomes in various studies.[14-16] Patients having in-hospital complications such as nosocomial infection and pneumonia experienced significantly worse outcomes.[17-19] Radiological findings including the characteristics of aneurysms [14,19] and other space-occupying lesions on CT-scan [14,20] and laboratory findings such as red cell distribution width (RDW) [21] and leukocyte counts [22] were also found to be associated with patients' outcome. Witsch et al.[16] and Ahn et al.[23] have even developed scores that are used to predict patient outcome.[16, 23]

An understanding of the pathophysiology of aSAH and evidence-based recommendations concerning its acute management might have important roles in decreasing aSAH mortality rates;[24,25] however, it remains unclear whether this decrease in mortality can be attributed to a specific cause. The key to further improving survival after aSAH is to identify and eliminate factors or events that predict a negative outcome. This study aimed to identify the factors associated with in-hospital mortality in aSAH patients.

METHODS

Research design

This was an observational analytic cross-sectional study conducted in Dr. Soetomo General Hospital, Surabaya, from March 2013 to July 2018.

Research subjects

The population in this study consisted of patients with SAH hemorrhage who had been admitted to Dr. Soetomo General Hospital, Surabaya. The inclusion criterion was patients with ICD-10 code for non-traumatic SAH (I60.9). Exclusion criteria were patients with known arteriovenous malformation, those with incomplete medical records and those with missing data in recorded initial clinical assessments and history-taking. A total sample of 264 subjects was used in this study. Subjects were then divided into two groups, survivors and non-survivors.

Measurements

Data were all obtained from subjects' medical records. We defined SAH as patients with symptoms of acute onset of thunderclap headache, seizures, focal neurologic signs, or decrease of consciousness that showed subarachnoid high attenuation on CT-scan. Patients' ages were taken from their national

ID card. Degree of consciousness in Glasgow Coma Scale (GCS) and blood pressure were measured in the emergency department during admission to our hospital. History of hypertension, diabetes mellitus, cerebrovascular diseases and smoking were taken by asking the patients and their families. Aneurysm treatment data was obtained from the procedure report in the medical record.

The independent variables were all dichotomous, patients' age was categorized into ≥45 years and < 45 years. We used 135mmHg as the cutoff point for the mean arterial pressure (MAP). Patients' degree of consciousness that was scored in the Glasgow Coma Scale (GCS) was divided into ≥13 and <13. The other variables were categorized into present (yes) and absent (no) according to history-taking and medical records.

Statistical analysis

Simple logistic regression analysis was used to analyze the relationship between dependent and independent variables. The results of the analysis were expressed as Odds Ratio (OR), 95% Confidence Interval (CI) and p-value. Significant results are the ones with a p-value of less than 0.05.

The independent variables that had p<0.25 in the bivariate analysis were included in the multivariate logistic regression analysis. The results were expressed as Adjusted Odds Ratio (aOR), 95% Confidence Interval (CI) and p-value, which was considered significant if p-value<0.05.

Ethical clearance

The ethical committee of Dr. Soetomo General Hospital issued ethical clearance no. 1573/KEPK/X/2019 on October 9th, 2019.

RESULTS

Subjects in this study were divided into two groups, those who survived and those who died during hospitalization. Hundred and forty patients (53.1%) did not survive hospital treatment. The median age of the subjects was 55 years (interquartile range [IQR] 47–63), with initial mean arterial pressure of 116.45±22.69 mmHg. Degree of consciousness was measured with GCS Score, with median of 11 (IQR 9 -15). More than half (57.2%) of the subjects had a history of hypertension, and most of the subjects did not have a history of diabetes mellitus (88.3%), cerebrovascular diseases (89.4%), and smoking (90.9%). During hospitalization, aneurysm treatment was only administered to 39 patients (14.8%), in which 36 of them underwent endovascular coiling, two patients underwent surgical clipping and one patient underwent both procedures (data not shown).

Simple logistic regression analysis showed that the risk of mortality was lower in younger patients than in the older ones (OR= 0.36; 95% CI= 0.19-0.69; p=0.002). Similar finding was found in patients with higher GCS score during admission (OR= 0.42; 95% CI = 0.25-0.71; p=0.001). Patients with higher initial MAP had 2.82 times higher risk of death (OR= 2.82; CI 95% 1.44-5.52; p=0.002). As expected, aneurysm treatment was found to be a protective factor against mortality (OR= 0.27; 95% CI = 0.13-0.58; p<0.001). History of hypertension, diabetes mellitus, smoking and cerebrovascular disease were not found to be associated with mortality in aSAH (Table 1).

Multivariate analysis found that age, MAP, and aneurysm treatment were the factors associated with mortality in aSAH. Younger subjects had a smaller risk of death (aOR 0.39; CI95% 0.20-0.76; p=0.006), those with higher mean arterial pressure had a higher risk of death (aOR 2.29; CI 95% 1.10-4.39; p=0.025) and the ones who underwent aneurysm treatment were more likely to survive (aOR 0.34; CI 955 0.16-0.74; p=0.006) (Table 2). Despite its significance, this logistic regression model had area under ROC of 0.63 (CI 95% 0.57-0.68) (Figure 1).

Table 1. Relationship between clinical predictors and in-hospital mortality,
estimated using simple logistic regression analysis

	Non-survivors (n=140)		Survivors (n=124)		OR	95% CI	p-value
	n	%	n	%			
Age					0.36	0.19-0.69	0.002
<45 years	17	12.2	34	117.5			
≥45 years	123	87.8	90	72.5			
GCS					0.42	0.25-0.71	0.001
13-15	45	35.1	64	54.7			
≤ 12	87	64.9	53	45.3			
MAP					2.82	1.44-5.52	0.002
≥135mmHg	37	26.4	14	11.3			
< 135mmHg	103	73.6	110	88.7			
Hypertension					1.12	0.69-1.83	0.631
Yes	82	58.6	69	55.7			
No	58	41.4	55	44.3			
Diabetes mellitus					1.08	0.51-2.31	0.830
Yes	17	12.1	14	11.3			
No	123	87.9	110	88.7			
Cerebrovascular diseases					1.42	0.63-3.21	0.388
Yes	17	12.1	11	8.9			
No	123	87.9	113	91.1			
Smoking					0.73	0.31-1.71	0.459
Yes	11	7.8	13	10.5			
No	129	92.2	111	89.5			
Aneurysm treatment					0.27	0.13-0.58	<0.001
Yes	11	17.9	28	12.8			
No	129	92.1	90	77.1			

GCS: Glasgow Coma Scale; MAP: mean arterial pressure

DISCUSSION

In this study, we found that the case fatality rate of aSAH was 53.1%. This result is considered very high compared to developed countries such as Australia and New Zealand (27.2%),[26] the Netherlands (30.0%),[25] England (24.3%),[24] and Canada (21.5%) [27] and still higher compared to other studies in developing countries such as India (38.5%) [28] and Iran (44.2%).[29]

Our study shows that subjects with older age were less likely to survive. Similar results have been found in other studies, in which higher age also correlates with higher risk of death.[30,31] A recently conducted study by Kanamaru et al.[32] showed that older patients had more comorbidities, presented with poor World

Table 2. Multivariate logistic regression model

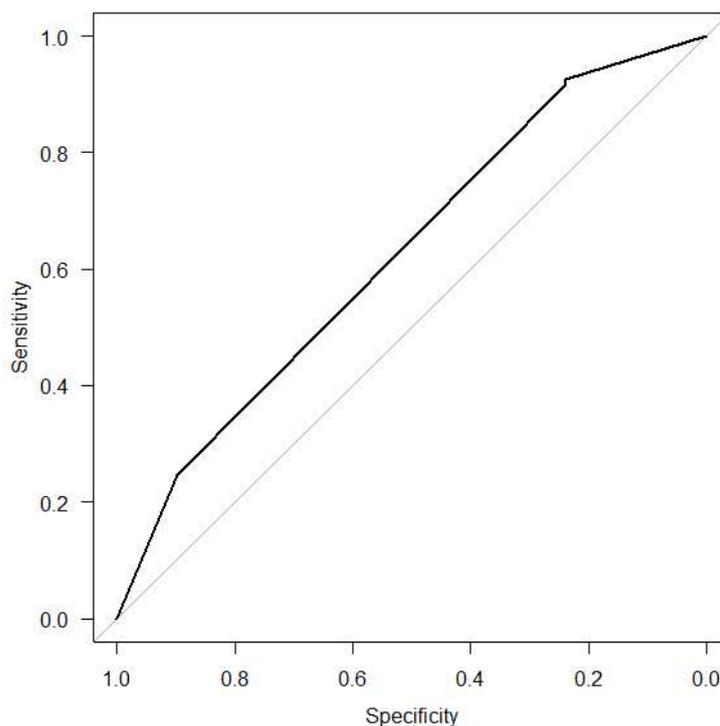|	aOR	95% CI	p-value
Age <45 years	0.39	0.20-0.76	0.006
MAP ≥ 135mmHg	2.29	1.10-4.39	0.025
Aneurysm treatment	0.34	0.16-0.74	0.006

aOR: adjusted odds ratio

Figure 1. Receiver operating characteristics graph of the final prediction mode

Federation of Neurological Societies (WFNS) grades, that resulted in poor outcomes. An interesting study in the Netherlands showed that from 1997 to 2006 there was a decline of 1.6% in the yearly mortality rate of aneurysmal SAH due to improvements in health facilities, but not in the older age group, in which the mortality rate remained constant.[33] Even in a group of patients that underwent aneurysm clipping, older patients still had worse outcomes compared to younger ones.[34] However, not all studies had similar results. A study by Yue et al.[35] showed that age was not associated with prognosis in aSAH patients who underwent endovascular coiling.

A low initial degree of consciousness measured using the GCS score on admission was found to be associated with a higher risk of mortality. This result is in line with a study in Uruguay where patients with the lowest GCS score of 3 had the highest mortality rate (82%) that was significantly different with the higher GCS scores.[36] A study in the USA also showed that 77.5% of deaths occurred in the group of patients with a GCS of 3 to 8.[37] Loss of consciousness at onset was found to be one of the risk factors of poor outcome in aSAH.[38] The degree of consciousness that is measured with the GCS score is commonly used as a predictor of outcomes in patients with both traumatic and non-traumatic brain injuries.[39]

In the present study, the higher mean arterial pressure (MAP) that was measured was found to be associated with higher risk of death. There were not many studies that we could find which used MAP as a prognostic factor. Zafar et al.[40] stated that maximum MAP measured within the first three admission days predicted outcome. Other studies used the systolic blood pressure (SBP) as a prognostic factor. A study in Finland showed that an increase of 21.4 mmHg in systolic blood pressure could contribute to a higher risk of sudden death caused by SAH (RH 1.34; CI 95% 1.09-1.65).[41] Rodriguez et al.[42] also showed that patients who had a maximum systolic blood pressure of more than 160mmHg within the first four hours of admission had worse outcomes.

A survey of members of the Neurocritical Care Society (NCS) showed that more neurointensivists (neurology and non-neurology) preferred to use SBP as a target of aneurysm treatment in aSAH compared to MAP.[43] However, the ability of the human auto-regulation system to increase MAP in response to increased intracranial pressure (ICP) to maintain cerebral perfusion should be taken into account, therefore MAP can also be used to monitor the patient's condition. Patients with effective auto-regulation had a higher chance of good outcome.[44] The pressure reactivity index (PRx) is sometimes used to monitor patients' auto-regulation. This measurement calculates the correlation of MAP fluctuation with changes in ICP, which might be more important in the initial phase of aSAH. A study in a neurological intensive care unit (NICU) in Austria showed that a higher PRx value was associated with the occurrence of delayed cerebral ischemia.[45] Treatment of high blood pressure in patients with SAH has to be done carefully to prevent secondary ischemia.[46,47]

Aneurysm treatment was found to be a protective factor against mortality in aneurysmal SAH. The number of aneurysm treatment procedures done in our hospital was as low as 14.8% of all aneurysmal SAH patients, with most of the procedures (92.3%) being endovascular coiling. Re-bleeding is one of the contributors of death in aneurysmal SAH, which can be prevented by aneurysm treatment. A study in the Netherlands showed that the decrease in deaths caused by re-bleeding (aRR 0.68; CI 95% 0.52-0.90) paralleled the shift of earlier aneurysm treatment from day-4 after SAH to day-1 after SAH.[25] The 1-year mortality rate of untreated ruptured aneurysms in Helsinki (Finland) was as high as 65%, varying with admission delay and clinical status.[48] Aneurysm treatment does not only decrease patients' mortality, since a US study showed that early aneurysm treatment also reduced hospitalization cost.[49] These studies showed that endovascular neurointervention facilities are essential to decrease mortality rate in aneurysmal SAH. Treatment in high-volume centers have been proved to increase functional outcome and decrease mortality, whereas delayed transport to neurosurgical facilities was also associated with increased mortality.[50,51] This data can be used as reference to encourage the families of patients that are to be referred to endovascular neurointervention facilities.

We did multivariate analysis on 3 variables, namely age, mean arterial pressure and aneurysm treatment, and this model proved to be statistically significant. However, its area under ROC was 0.63, signifying that the combination of these three variables was incapable of predicting mortality in aneurysmal SAH patients. One way to make a better model for predicting mortality in aneurysmal SAH patients would be the addition of the other variables used in previous studies, such as aneurysm characteristics including aneurysm location, size and type; patients' clinical scores such as the WFNS score or the Hunt-Hess score on admission; and occurrence of re-bleeding, delayed cerebral ischemia and cerebral vasospasm.

There are a number of limitations of our study. This study was a retrospective analysis of archived data. During data collection, we could not find all medical records that were listed as subarachnoid hemorrhage in the register. Moreover, the severity of aneurysmal SAH in individual cases was not recorded. Better medical record management is suggested for the medical records center in Dr. Soetomo General Hospital.

The findings in this study have clinical implications in terms of predicting patients' outcome at the time of admission and of supporting clinical decisions of physicians whether or not to administer maximum treatment. This information is also needed by the families to know the possible outcomes of patients' current conditions. The results showing aneurysm treatment to be a strong independent protective factor could be used to encourage

stable patients with a good prognosis to be referred to a higher neurosurgical unit for aneurysm treatment despite Indonesia's geographical challenges.

This study raised the question on how MAP as a blood pressure parameter could affect patients' outcome. Further studies on this matter should be done to evaluate the prognostic values of various blood pressure parameters. However, as stated before, the final logistic regression model in this study was not as accurate as expected in predicting outcome. Therefore, further research on other possible predictors should be done to develop a more accurate predictive model for aSAH mortality.

CONCLUSIONS

Patients with higher mean arterial pressure on initial measurement had higher risks of mortality. But younger age and any form of aneurysm treatment had lower risks of mortality. More endovascular neurointervention facilities are needed to decrease the mortality rate of aneurysmal SAH.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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CONTRIBUTORS

NNR and AFD built the database and did the data collection. NNR did all the analysis. AFS supervised the study and revised the article. All authors have read and approved the final manuscript.

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