Original Article

The Factors Associated with Outcomes in Surgically Managed Ruptured Cerebral Aneurysm

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Abstract

Background: **Ruptured cerebral aneurysm is a life-threatening condition that requires urgent medical attention. In Malaysia, a prospective study by the Umum Sarawak Hospital, Neurosurgical Center, in the year 2000–2002 revealed an average of two cases of intracranial aneurysms per month with an operative mortality of 20% and management mortality of 25%. Failure to diagnose, delay in admission to a neurosurgical centre, and lack of facilities could have led to the poor surgical outcome in these patients. The purpose of this study is to identify the factors that significantly predict the outcome of patients undergoing a surgical clipping of ruptured aneurysm in the local population.**

Material and Method: **A single center retrospective study with a review of medical records was performed involving 105 patients, who were surgically treated for ruptured intracranial aneurysms in the Sultanah Aminah Hospital, in Johor Bahru, from July 2011 to January 2016. Information collected was the patient demographic data, Glasgow Coma Scale (GCS) prior to surgery, World Federation of Neurosurgical Societies Scale (WFNS), subarachnoid hemorrhage (SAH) grading system, and timing between SAH ictus and surgery. A good clinical grade was defined as WFNS grade I–III, whereas, WFNS grades IV and V were considered to be poor grades. The outcomes at discharge and six months post surgery were assessed using the modified Rankin's Scale (mRS). The mRS scores of 0 to 2 were grouped into the "favourable" category and mRS scores of 3 to 6 were grouped into the "unfavourable" category. Only cases of proven ruptured aneurysmal SAH involving anterior circulation that underwent surgical clipping were included in the study. The data collected was analysed using the Statistical Package for Social Sciences (SPSS). Univariate and multivariate analyses were performed and a *P*-value of < 0.05 was considered to be statistically significant.**

Result: **A total of 105 patients were included. The group was comprised of 42.9% male and 57.1% female patients. The mean GCS of the patients subjected to surgical clipping was 13, with the majority falling into the good clinical grade (78.1%). The mean timing of the surgery after SAH was 5.3 days and this was further categorised into early (day one to day three, 45.3%), intermediate (day four to day ten, 56.2%), and late (after day ten, 9.5%). The total favourable outcome achieved at discharge was 59.0% as compared to 41.0% of the unfavourable outcome, with an overall mortality rate of 10.5%. At the six-month post surgery review (*n* = 94), the patients with a favourable outcome constituted 71.3% as compared to 28.7% with an unfavourable outcome. The mortality, six months post surgery was 3.2%. On a univariate analysis of early surgical clipping, patients with a better GCS and good clinical grade had a significantly better outcome at**

discharge. Based on the univariate study, six months post surgery, the timing of the surgery and the clinical grade remained significant predictors of the outcome. On the basis of the multivariate analysis, male patients of younger age, with a good clinical grade, were associated with favourable outcomes, both at discharge and six months post surgery.

Conclusion: **In this study, we concluded that younger male patients with a good clinical grade were associated with a favourable outcome both at discharge and six months post surgery. We did not find the timing of the surgery, size of the aneurysm or duration of surgery to be associated with a patient's surgical outcome. Increasing age was not associated with the surgical outcome in a longer term of patient's follow up.**

Keywords: *Ruptured aneurysm, WFNS grading, mRS scoring, timing of surgery, Sultanah Aminah Hospital*

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a catastrophic condition (1, 2) affecting 30,000 individuals in the United States every year. A majority of individuals (60%) either die or suffer permanent disability; 50% of the survivors, with favourable outcomes, experience considerable neuropsychological dysfunction. In Japan, the mortality rate post clipping for ruptured aneurysms was 9.6% and for unruptured aneurysms was 0.2% (3). In Malaysia, this condition is commonly seen, however, there is not much local information published (4).

A prospective study by the Umum Sarawak Hospital, Neurosurgical Center in year 2000–2002 (4) revealed that an average of two cases of intracranial aneurysm per month presented to their centre. The centre managed to achieve an operative mortality and management mortality of 20% and 25%, respectively (4). On an average, the Sultanah Aminah Hospital, in Johor Bahru, received around two to three cases of patients with ruptured aneurysms, per month. It is the only government neurosurgical centre covering the entire southern peninsular of Malaysia, with an estimated population of three million. Multiple predicting factors of the outcome of a patient with ruptured aneurysm have been discussed in various international studies, however, there is no local data available (4).

Failure to recognise, delay in admission to the neurosurgical centre, and lack of facilities are the factors contributing to the outcome of the surgically clipped patients. The purpose of this study is to review the epidemiology of the surgically clipped ruptured cerebral aneurysms in this region and to identify the predicting factors that influence the prognosis and outcome of these patients.

Methodology

A single centre retrospective study with review of case notes was performed involving 105 patients, who were surgically treated for ruptured intracranial aneurysms from July 2011 until January 2016. Information collected included, the patient demographics, presenting symptoms, Glasgow Coma Scale (GCS) prior to surgery, timing between SAH ictus and surgery, duration of surgery, location of aneurysm, and maximum size of the aneurysm. A patient's pre-operative neurological condition was classified using the World Federation of Neurosurgical Societies grading system for SAH (WFNS grades I–V, Table 1) (3) and sub-classified into good clinical grade (WFNS I–III) and poor grade (WFNS IV and V) (5). The outcomes at discharge and six months post-surgery were assessed by using the modified Rankin's Scale (mRS score 0–6, Table 2). A dichotomised mRS score, based on other aneurysm studies (3, 6, 7), was used as a clinical outcome measurement for patients post clipping. The mRS scores of 0 to 2 were grouped into the "favourable" and mRS scores of 3 to 6 were grouped into the "unfavourable" categories. The data collected were analysed using SPSS and the association between the predictor factors and outcome were studied using univariate and multivariate logistic regression, where a P-value of < 0.05 was considered to be statistically significant.

Only cases of angiographically proven ruptured aneurysmal SAH, involving anterior circulation that underwent surgical clipping, were included in this study. Cases of non-aneurysmal SAH or SAH with negative computed tomography (CT), magnetic resonance (MR) angiogram, cerebral angiogram, aneurysms combined with arteriovenous malformation (AVM), mycotic aneurysms, and unruptured aneurysms, were all excluded from the study. Out of the 128 cases that met the criteria, 23 of them were excluded from the study due to incomplete information and loss of follow up. This series represents 105 cases of ruptured aneurysms from a single center, treated with surgical clipping.

Table 1. WFNS grading system for patient with ruptured aneurysm

Grade	*GCS Score	Motor Deficit
I	15	Absent
II	13 or 14	Absent
III	13 or 14	Present
IV	7 to 12	Either
V	3 to 6	Either

*GCS (Glasgow Coma Scale)

Table 2. Modified Rankin Scale (mRS)

Score	
0	No symptoms
1	Minor symptoms which do not interfere with lifestyle
2	Minor handicap which leads to some restriction in lifestyle but does not interfere with the patient's capacity to look after themselves
3	Moderate handicap which significantly restricted lifestyles and prevents a totally independent existence
4	Moderately severe handicap which clearly prevents an independent existence though not needing constant attention
5	Severe handicap requiring constant attention night and day
6	Death

In this institution, spontaneous SAH was diagnosed mainly by CT brain and rarely by analysis of cerebrospinal fluid via lumbar puncture. Cerebral aneurysms were further diagnosed via CT angiogram, MR angiogram or digital subtraction angiogram and these patients were admitted under neurosurgical care. They were started with nimodipine for 21 days and phenytoin for seizure prophylaxis. Those patients with hydrocephalus were treated with external ventricular drainage (EVD) and those who developed a huge hematoma underwent urgent decompression. In view of the absence of a neurointerventionist and limited resources, surgical clipping was selectively performed in this institution and mainly concentrated in the patient with a good WFNS grade. The surgery was scheduled mainly on weekdays during office hours when the surgeon and the staff were better prepared. Clipping was performed by the consultant neurosurgeon, using mainly a Leica OH 5 microscope or occasionally with a Carl Zeiss NC31. The surgical clips available included Aesculap standard clips, miniclips, and Mizoho Sugita clips. For post-surgical clipping, the patients were admitted to the High Dependency Unit (HDU) with triple "H" therapy (8) for at least 72 h. The patients with poor GCS recovery post clipping were subjected to tracheostomy and those that were EVD-dependent were subjected to permanent cerebral spinal fluid diversion. Clinical conditions of the patients were obtained upon discharge and six months post surgery. Data collected were analysed using SPSS, and a P-value of < 0.05 was considered to be statistically significant.

Result

Patient Demographics

With reference to Table 3, a total of 105 patients' medical records were reviewed and included into this study, which consisted of 45 (42.9%) male and 60 (57.1%) female patients. The patients' ages ranged from 25.0 to 75.0 with a mean (SD) of 51.0 (11.84) years. The majority of patients (32.4%) were in the age group of 51 to 60 years. The most common presenting symptom was headache, which occurred in 73.3% of the cases. This was followed by reduced consciousness in 15% and seizure in 7%. Other symptoms of presentation included neck pain, photophobia, weakness, and cranial nerve deficits, which accounted for 6%. The mean GCS (SD) of the patients subjected to surgical clipping was 13 (2.3) with the majority falling into group WFNS grade 2 (41.0%), followed by WFNS grade 1 (21.0%), and WFNS grade 3 (16.2%). In our observation, only 15.2% of the patients of WFNS grade IV and 6.7% of grade V were subjected to surgery. Mean (SD) timing of surgery after SAH was 5.3 (3.6) days and was further categorised into early (day 1 to day 3), intermediate (day 4 to day 10), and late (after day 10), according to Ahmed Alfotih et al. (9). A majority of the surgeries were done in the intermediate group (n = 59) followed by early (n = 36) and late (n = 10). The average size of the clipped aneurysm was 6.4 mm with a range from 3 mm to 21 mm. The most common site of origin for the aneurysm was from the anterior communicating artery (31.4%), followed by middle cerebral artery (26.7%). The aneurysms that arose from the internal cerebral artery, anterior cerebral artery, and posterior communicating artery contributed 12.4%, respectively, and those that finally arose from the distal anterior cerebral artery contributed 4.8%. The documented duration of the surgical clipping ranged from 170 to 630 min, with a mean (SD) of 322.8 (88.9) min.

Outcomes of the Patients Who Underwent Surgical Clipping

A majority of the postsurgical clipping patients, upon discharge, achieved an outcome of an mRS score of 2 (32.4%), followed by an mRS score of 1 (24.8%), and mRS score of 3 (20.0%) as shown in Table 4. The mortality of the patient post clipping (mRS 6) was 10.5% at discharge. Hence, the total favourable outcome achieved at discharge was 59.0% as compared to 41.0% of unfavourable. At the sixth month of review (*n* = 94) in Table 5, the percentage of patients with favourable outcome was 71.3% as compared to 28.7% of unfavourable. There were 13.8% of patients with an mRS score of 0, 26.6% of the patients with an mRS score of 1, 30.9% of patients with an mRS score of 2, and 20.2% of patients with an mRS score of 3. Mortality (mRS score 6) of 3.2% was observed after six months.

Table 3. Characteristics of patients with surgically clipped ruptured aneurysm (*n* = 105)

		n	%
Age, Mean (SD)		51 (11.82) years	
Gender	Male	45	42.9
	Female	60	57.1
GCS, Mean (SD)		13 (2.3)	
WFNS	Grade I	22	21
	Grade II	43	41
	Grade III	17	16.2
	Grade IV	16	15.2
	Grade V	7	6.7
WFNS dichotomised	Good grade (WFNS I-III)	82	78.1
	Poor grade (WFNS IV-V)	23	21.9
Symptoms	Headache	77	73.33
	Reduced consciousness	15	14.3
	Seizure	7	6.7
	Others	6	5.7
Timing, Mean (SD)		5.3 (3.6) days	
Timing dichotomised	Early (1–3)	36	45.3
	Intermediate (4–10)	59	56.2
	Late(> 10)	10	9.5
Size of aneurysm, Mean (SD)		6.4 (3.2) millimeters	
Location of aneurysm	Ica	13	12.4
	Mca	28	26.7
	Aca	13	12.4
	Daca	5	4.8
	Pcom	13	12.4
	Acom	33	31.4
Duration		322.8 (88.9) min	

SD = standard deviation

Predicting Factors for Favourable Outcomes

Univariate logistic regression was done for each of the predicting factors that may be associated with the outcomes of patients with a surgically clipped aneurysm at discharge as shown in Table 6. Early surgery (P = 0.015) and better GCS (P < 0.001) had significantly higher odds to a favourable outcome of the patient with surgically clipped aneurysm, at discharge. Patients with WFNS grade I (P = 0.004) and WFNS grade II (P = 0.014) had a significant favourable outcome compared to WFNS grade V, at discharge. A good clinical grade patient had 11.4 times higher odds for having a favourable outcome as compared to a poor grade (95% CI: 3.5–37.3, P < 0.001) patient. Age, gender, size of aneurysm, and the duration of surgery had no statistical significance on the outcome of the patient at discharge. GCS, WFNS grading, and timing of surgery remained significant predicting factors (P < 0.05) for the outcome of the patients six months post surgery as shown in Table 7.

Table 4. Outcome of patient with surgically clipped ruptured aneurysms upon discharge (n = 105)

	n	%
mRS at discharged		
0	2	1.9
1	26	24.8
2	34	32.4
3	21	20
4	9	8.6
5	2	1.9
6	11	10.5
Outcome at discharge		
Favourable (mRS 0–2)	62	59
Unfavourable (mRS 3–6)	43	41

Table 5. Outcome of patients with surgically clipped ruptured aneurysms at post-surgery 6-month (n = 94)

	n	%
mRS at 6th month		
0	13	13.8
1	25	26.6
2	29	30.9
3	19	20.1
4	3	3.2
5	2	2.1
6	3	3.2
Outcome at 6th months (n = 94)		
Favourable	67	71.3
Unfavourable	27	28.7

On multivariate analysis, tabulated in Table 8, increase in age of one year for surgical clipping had 0.95 times lower odds of having a favourable outcome at discharge (95% CI :0.92–1.00, P = 0.028) when adjusted for gender, clinical grade, and timing of surgery. Male gender had 2.9 times higher odds of having a favourable outcome at discharge (95% CI: 1.09–7.72, P = 0.033) and good clinical grade had 11.67 times higher odds of having a favourable outcome (95% CI: 3.010–44.02, P < 0.001) when other factors were adjusted. In Table 9, multivariate analysis done for similar factors for the outcome at the sixth month, showed that only male patients (P = 0.039; OR = 3.19) and a good clinical grade (P = 0.005, OR = 6.45) were associated with a favourable outcome when other factors were adjusted.

Discussion

Patient Demographics

Ruptured cerebral aneurysm is a life-threatening condition that requires urgent medical attention (1, 2). On an average, almost two patients per month were subjected to surgical clipping for ruptured aneurysm in this centre. A majority of the patients were female ranging, from the age of 51 to 60 years. This is correlated to the drop in estrogen level during the post-menopausal period among the women, as suggested by Ghods et al. (10). Estrogen has been shown to promote normal physiologic vascular endothelial function and reduction in the estrogen level leads to compromised arterial integrity, and hence, the development of an aneurysm (10). Female patients tend to have a poorer outcome probably due to multiple comorbid and late presentation to the hospital. In this center, a majority of surgeries are done at the interval of day 4 to day 10 post-ictal due to time taken for proper investigation and imaging as well as limited operating theater time.

Outcomes of Surgical Clipping

Our centre managed to achieve a 59% favourable outcome at discharge and 71.3% at

Table 6. Univariate logistic regression analysis of the factors affecting clinical outcome at discharge

		B (SE)	Univariate Analysis Crude OR (95% CI)	*P*-value
Age		−0.033 (0.018)	0.97 (0.93–1.00)	0.058
Gender	Male	−0.728 (0.413)	0.48 (0.92–4.65)	0.078
	Female		1	
GCS		0.611 (0.165)	1.84 (1.33–2.54)	< 0.001
WFNS	Grade I	3.219 (1.118)	25.0 (2.79–223.67)	0.004
	Grade II	2.245 (0.917)	9.44 (1.57–56.96)	0.014
	Grade III	−0.262 (1.013)	0.77 (0.11–5.61)	0.796
	Grade IV	−1.030 (1.128)	0.36 (0.04–3.26)	0.361
	Grade V		1	
WFNS dichotomised (Clinical grade)	Good grade (WFNS I-III)	2.441 (0.601)	11.46 (3.53–37.30)	< 0.001
	Poor grade (WFNS IV-V)		1	
Size of aneurysm		−0.034 (0.062)	(0.97) 0.86–1.09	0.062
Timing (days)		−0.068 (5.876)	(0.85) 0.74–0.97	0.015
Timing	day 1–3	1.957 (0.863)	(7.08) 1.30–38.44	0.023
	day 4–10	1.906 (0.835)	(6.73) 1.31–34.57	0.022
	> day 10		1	
Duration (mins)		0.000 (0.002)	1.00 (1.00–1.01)	0.897

SE = Standard error, OR = Odd ratio, CI = Confidence interval, B = Logistic regression coefficient

Table 7. Univariate logistic regression analysis of the factors affecting clinical outcome at 6th month

		B (SE)	Univariate Analysis Crude OR (95% CI)	*P*-value
Age (years)		−0.036 (0.021)	0.097 (0.93–1.00)	0.083
Gender	Male	0.895 (0.487)	2.45 (0.94-6.36)	0.066
	Female		1	
Clinical grade	Good	1.944 (0.580)	7.00 (2.24–21.79)	0.001
	Poor		1	
Timing (days)		−0.0164 (0.070)	0.85 (0.74–0.97)	0.019

SE = Standard error, OR = Odd ratio, CI = Confidence interval, B = Logistic regression coefficient

the sixth month post surgery. We observed a 10% increase in favourable outcomes on comparing both the time frames. This is possibly due to good post-operative care by the multidisciplinary team namely the Rehabilitation Medicine Department, Physiotherapy, and Occupational Therapy as well as Medical Department. Functional recovery for all stroke patients is estimated to be completed within 12.5 weeks after proper acute treatment and all stages of rehabilitation (11), hence, the increment of favourable outcomes is explained at the sixth month.

Predicting Factors for Favourable Outcomes

Multiple studies have been conducted to determine the outcome of patients post surgical clipping, however, different centers yield different results. A few predicting factors associated with unfavourable outcome have been proven by Rosengart et al. (12), which include worse WFNS grades of the patient on admission, larger aneurysm size, and increased age. Study by Lantigua et al. (1) showed that re-bleeding (13) and intracerebral hematoma are common causes that lead to death or

Table 8. Multivariate logistic regression analysis of the factors affecting the outcome at discharge after purposeful variable selection

		B (SE)	Multivariate analysis adjusted OR (95%CI)	*P*-value
Age		−0.047 (0.021)	0.95 (0.92–1.00)	0.028
Gender	Male	−1.066 (0.499)	2.9 (1.09–7.72)	0.033
	Female		1	
Clinical Grade	Good	−2.458 (0.677)	11.67 (3.10–44.02)	< 0.001
	Poor		1	
Timing		−0.085 (0.075)	0.92 (0.79–1.06)	0.256

SE = Standard error, OR = Odd ratio, CI = Confidence interval, B = Logistic regression coefficient, R^2 = 36%

Table 9. Multivariate logistic regression analysis of the factors affecting the outcome at 6 months after purposeful variable selection

		B (SE)	Multivariate analysis adjusted OR (95%CI)	*P*-value
Age		−0.039 (0.023)	0.96 (0.92–1.01)	0.086
Gender	Male	1.159 (0.560)	3.19 (1.06–9.56)	0.039
	Female		1	
Clinical Grade	Good	−1.864 (0.666)	6.45 (1.75–23.78)	0.005
	Poor		1	
Timing		−0.100 (0.080)	0.905 (0.77–1.05)	0.211

SE = Standard error, OR = Odd ratio, CI = Confidence interval, B = Logistic regression coefficient, R^2:29%

devastating neurology. Ahmed Alfotih et al. (9) concluded that timing of surgery does not affect the outcome of patients, however, a study by Dorhout Mees et al. (14) supports early aneurysm treatment, with both coiling and clipping, in SAH patients.

In our study among the local population, we demonstrated that patients with good clinical grade (WFNS I-III) are associated with favourable outcome at discharge and also six months post surgery. Hutchinson et al. (15) reported that as high as 60% patients with poor clinical grade will become dependent or die, while Zhang et al. (16) reported that many neurosurgeons are reluctant to treat patients with poor clinical grade due to higher mortality and disability as well as medical cost. Poor clinical grades are associated with poorer GCS, and hence, patients will have a poorer surgical outcome. An observational study by Helbok et al. (17) suggest that patients with poor clinical grade are associated with global cerebral edema after initial SAH, resulting in metabolic distress. The initial bleeding is associated with a rapid increase in intracranial pressure and thus a reduction in cerebral blood flow (18) leading to decreased substrate delivery to the brain during a time of increased demand.

In our study, male patients are associated with a favourable outcome both at discharge and six months post surgery. Poorer outcome in females is possibly explained by the significantly higher vasospasm that leads to cerebral infarction, which is demonstrated in the study of Rosenlrn et al. (19). However, a recent study by Duijghuisen et al. (20) documented no difference in outcome between males and females.

In multivariate regression, we did not find the timing of surgery to be significantly associated with the outcome in post clipping patients, both at discharge and six months post surgery, when other factors were adjusted. Recent studies by Zhao et al. (7) and Ross et al. (5) also concluded that timing of surgery is not significantly associated with the clinical outcome of the patient post surgery. Early surgery may increase the periprocedural complication due to a swollen, hyperemic, and poorly auto-regulated brain, which is more prone to laceration, contusion, and infarction due to retraction (21). Despite that, it is proven that early surgery prevents the risk of re-bleeding that usually occurs in the first 6 h after initial

SAH (22), thus allowing aggressive medical management via triple 'H', which is to be started promptly to prevent vasospasm and delayed ischemic neurological deficits. The study by Phillips TJ et al. (13) showed that treatment of a ruptured aneurysm within 24 h is associated with an improved clinical outcome compared to treatment > 24 h.

Our study found that advancing age is a predictor factor for poor outcome at discharge, which is also reported by Sharma et al. (23) and Ross et al. (5). Younger age patient have a better outcome because of the fact that they have better regenerative capacity and neural plasticity as compared to the elderly (24). However, at the longer term of follow up, at six months post surgery, increasing age does not show a significant association with the patient's outcome. This might be contributed by the other confounding factors such as extensive physiotherapy and rehabilitation by the multidisciplinary team throughout the discharge period, which was not studied.

Limitation and Further Recommendation

Limitation of this study includes a single center study with a small sample size and the study design of a retrospective review which is associated with missing data, selection bias, and information bias. A prospective model is proposed for a future study, which includes a bigger sample size and more predictor factors such as imaging findings, presence of vasospasm, and temporary clip placement. Considering the high annual incidence of ruptured cerebral aneurysm and its devastating complications, we recommend the need of developing a national cerebral aneurysm registry, to collect all the necessary data in Malaysia. A multicentric collaborative effort is needed to understand the fallacies in the management of aneurysms and develop strategies to improve them. A multicentre data registry via online software also allows the institutions to share their best practices and ultimately develop a standardised approach to management. On a long-term basis, the national registry can yield important information regarding the natural history, the factors and outcomes of cerebral aneurysms managed in Malaysia.

Conclusion

In our study of factors associated with the outcomes of patients with surgically clipped ruptured aneurysms, we conclude that younger male patients with good clinical grade are associated with favourable outcomes at discharge and six months post surgery. We did not find the timing of surgery, size of aneurysm, and duration of surgery to be associated with the surgical outcome. Despite the age being significant at discharge, increasing age is not associated with the surgical outcome in the long term of the patient's follow up.

Authors' Contributions

Conception and design: LCC
Analysis and interpretation of the data: LCC
Drafting of the article: ZI
Critical revision of the article for important intellectual content: ARIG
Final approval of the article: JAS, ARIG
Provision of study materials: JAS, NAAR@M
Statistical expertise: ZI
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