Predictors of poor outcome from aneurysmal subarachnoid hemorrhage and an exploratory analysis into the causes of delayed neurosurgical clipping at a major public hospital in the Philippines

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Abstract

Objective:

The provision of neurosurgical care for patients with aneurysmal subarachnoid hemorrhage (SAH) is beset with particular challenges in low- to middle-income countries (LMICs) like the Philippines. In this study located in a low-resource setting, we identify the factors that contribute to unfavorable outcomes of dependency and death.

Methods:

The authors retrospectively reviewed 106 patients who underwent surgery for aneurysmal subarachnoid hemorrhage in a single institution from January 2016 to September 2018. Data were obtained on exposure variables comprising patient demographics, clinical features, perioperative management, and complications and other interventions; while outcomes on discharge were investigated using the modified Rankin scale (mRS). Descriptive statistics and multivariate logistic regression analyses were done. Root cause analysis was done to identify the causes of delay.

Results:

The percentage of patients who had unfavorable outcome ($mRS \geq 3$) was 29.2%. The timing of surgery—whether early (<3 days), intermediate (3-10 days), or late (>10 days)—was not found to be significantly associated with dependency or mortality. On multiple logistic regression, the factors associated with unfavorable outcome were: intraoperative rupture (OR 23.98, 95%CI 3.56–161.33, $p=0.001$), vasospasm (OR 12.47, 95%CI 3.01–51.57, $p<0.001$), and a high Hunt & Hess grade (OR 5.96, 95%CI 1.47–24.18, $p=0.012$). Intraoperative rupture and vasospasm were further found to be independent predictors of mortality. Many causes of delay were identified in terms of patient-, provider-, and health system-levels. These constitute as barriers to timely care and also contribute to the gap in quality and efficiency of neurosurgical treatment situated in low-resource settings in LMICs.

Conclusion:

The identified predictors of poor outcomes, as well as the causes delays in neurosurgical treatment, pose as significant challenges to the care of socioeconomically-disadvantaged SAH patients. When considering the solutions to these challenges, the broader environment of practice ought to be taken into account.

Introduction:

Despite advances in diagnostics, critical care management, and neurosurgical treatment options for patients with aneurysmal subarachnoid hemorrhage (SAH), overall outcome remains unsatisfactory. Outcomes depend on several factors, including the severity of the initial hemorrhage, perioperative care, rebleeding, and the timing and technical success of aneurysm occlusion.¹ Because SAH is a resource-intensive disease to treat and manage, neurosurgical centers in low- to middle-income countries (LMICs) are presented with particular challenges. In the Philippines where there is a deficit of neurosurgical workforce and lack of infrastructure,²

socioeconomically-disadvantaged patients afflicted with the disease often need to surmount barriers to proper care and also lack the broad range of therapeutic options. These patients do not have default access to endovascular aneurysm treatment; therefore, only surgical clipping remains the deliberate and upfront treatment option. Moreover, while clinical practice guidelines^{3,4,5,6} recommend early intervention for the ruptured intracranial aneurysm, the reality is that many patients in low-resource settings are not provided for with timely neurosurgical treatment. In this study, the authors from a high-volume⁴ neurosurgical center in the Philippines aim to determine and analyze the risk factors for poor outcomes among this group of vulnerable patients. The timing of surgical treatment is also of interest. The causes of such delays are further explored.

Methods:

Study Setting and Design

The authors performed a retrospective review of cases involving patients who were transferred and admitted to the Jose R. Reyes Memorial Medical Center for surgical treatment of ruptured intracranial aneurysm during the period from January 2016 to September 2018. As a government-funded public hospital, the academic neurosurgical training center has since catered primarily to socioeconomically disadvantaged patients all over the country. This study was approved by the institutional review board.

Patient Variables and Outcome Measures

During the study period, the study population consisted of patients who had cerebral computed tomography angiography for diagnostics, were managed with the standards of care despite the limitations of the setting, and underwent surgery at the soonest possible time. Data were gathered on the characteristics of patients—specifically, factors under the categories of patient demographics, clinical features, perioperative management, and complications and other interventions—while clinical outcome was measured by the modified Rankin Scale (mRS) score. The outcomes were dichotomized into favorable (mRS 0–2) and unfavorable, i.e., dependency (mRS ≥ 3) or death (mRS 6).

Statistical Analysis

Measures of frequencies, centrality and dispersion were calculated for all descriptive variables. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval-ratio variables. Independent Sample T-test, Mann-Whitney U test, and Fisher's Exact/Chi-square test were used to determine the difference of mean, median and frequency between groups, respectively. Odds ratios and the corresponding 95% confidence interval from binary logistic regression were computed to determine the association between other clinical factors with unfavorable mRS, while exact logistic regression was used to determine association with mortality. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. The significance level adopted was $p < 0.05$. The software Stata 15.0 (StataCorp, College Station, TX, US) was used for performing the statistical tests.

Root Cause Analysis

Using the conceptual model of regional variation in the use of surgery⁷ and the Three Delays framework⁸ applied in the landmark article on global surgery,⁹ we determined the categories by which to further identify

the reasons for the delays in surgical intervention and poor outcomes in our patient population. By way of root cause analysis, the fractionation of identified problems into more manageable situations and scenarios allowed the recognition of specific causes for such delays.

Results:

Patient Demographics and Characteristics

During the specified time period, a total of 106 patients underwent surgical treatment of their ruptured aneurysm—majority of whom had favorable outcomes and cardiovascular comorbidities (Table 1). In terms of clinical grade upon presentation, the median scores were: Hunt and Hess grade 2, WFNS grade 2, and modified Fisher grade 3. Among all those who underwent surgical clipping, 75 (71%) patients had a good outcome (mRS 0–2) upon discharge. Fifteen of the surgically-managed patients died and overall mortality rate was 14.1%. The patients with unfavorable outcomes (mRS 3–6) had significantly higher median clinical grades on admission in terms of Hunt and Hess ($p = 0.002$) and WFNS grades ($p < 0.001$). Among their subgroup, majority had significantly higher proportion of preoperative rebleeding (16.13% versus 4%, $p = 0.045$) and intraoperative rupture (29% versus 2.67%, $p < 0.001$).

Time to Admission and Timing of Surgery

The median time interval from first aneurysm rupture (day 0) to hospital admission were 5 days among those with favorable outcomes and 3 days among those with dependency or death (Table 1). Regardless of outcome, a greater proportion of the patients underwent surgical clipping at a later time of more than 10 days from first rupture, compared to those who underwent surgery within 3–10 days and those who had early clipping within 48 hours from aneurysm rupture. The median time interval from first aneurysm rupture to surgery (range 1–302 days) were 14 days for those who had good outcomes and 16 days for those who had poor outcomes. In terms of timing of surgery, data were stratified into early (0 to 2 days), intermediate (3–10 days), or late (> 10 days) as per the landmark study by Kassell and colleagues.³³ Majority of the patients in this series underwent late surgery (67.0%) followed by intermediate time interval (29.2%); while only a minority (3.7%) had early intervention. In terms of both their time interval to admission and time interval to surgery, the differences between patients with good and poor outcomes were not significant.

Interventions and Complications

Those patients with unfavorable outcomes had a significantly higher proportion of having had the need for osmotic therapy which is the use of mannitol, and triple-H therapy which is the induction of hypertension, hemodilution, and hypervolemia. Only 11 (10.38%) of surgically-managed patients were admitted to the intensive care unit (ICU). There was no significant difference between patients with favorable versus unfavorable outcomes in terms of admission to the ICU, as well as various other medical and pharmacologic treatment. For those patients with unfavorable outcomes, there were significantly higher rates of vasospasm, increased intracranial pressure requiring CSF diversion or decompressive hemicraniectomy, healthcare-associated infections, and surgical or medical complications (Table 1).

Risk Factors for Dependency and Mortality

Simple logistic regression analysis of risk factors for unfavorable outcomes revealed the following covariates to be statistically significant: female sex (OR 2.79, 95% CI 1.14–6.86, $p = 0.025$), higher WFNS grades 3 (OR 3.60, 95% CI 1.06–12.28, $p = 0.041$) and 4 (OR 18.90, 95% CI 3.69–96.69, $p < 0.001$), large aneurysm size (OR 5.76, 95% CI 1.18–27.98, $p = 0.030$), intraoperative rupture (OR 14.93, 95% CI 3.00–74.30, $p = 0.001$), having required triple-H therapy (OR 2.65, 95% CI 1.05–6.68, $p = 0.038$), having had the surgical complications of infarct (OR 11.17, 95% CI 3.08–40.47, $p < 0.001$) and hemorrhage (OR 13.40, 95% CI 2.46–73.01, $p = 0.003$), having had the medical complication of sodium and water balance disorder (OR 4.38, 95% CI 1.67–11.50, $p = 0.003$), and having had pneumonia (OR 7.88, 95% CI 2.69–23.08, $p < 0.001$).

For the outcome of mortality (mRS 6) alone, exact logistic regression was done due to the relatively small proportion of patients who died. The following risk factors were found to be statistically significant (Table 2): intraoperative rupture (OR 18.00, 95% CI 3.70–103.79, $p = 0.001$), vasospasm (OR 10.52, 95% CI 2.76–43.92, $p = 0.001$), having required external ventricular drain (OR 36.69, 95% CI 3.17–1992.07, $p = 0.002$), having required decompressive hemicraniectomy (OR 9.11, 95% CI 2.00–42.88, $p = 0.003$), disorders of sodium and water balance (OR 6.02, 95% CI 1.59–24.34, $p = 0.006$), and sepsis and septic shock (OR 38.15, 95% CI 5.27–480.90, $p = 0.001$). When the timing of surgery was analyzed in terms of dependency (mRS ≥ 3) and mortality (mRS 6), the patients with poor outcomes did not differ significantly among the three treatment times (Table 3).

When controlling for patient demographics and other covariates, stepwise multivariate logistic regression analysis revealed three independent predictors for unfavorable outcomes (Table 4): intraoperative rupture (OR 23.98, 95% CI 3.56–161.33, $p = 0.001$), vasospasm (OR 12.47, 95% CI 3.01–51.57, $p < 0.001$), and a Hunt & Hess grade of ≥ 3 (OR 5.96, 95% CI 1.47–24.18, $p = 0.012$). Two risk factors—*intraoperative rupture* and *vasospasm*—were found to be significantly associated throughout both dependency and death.

Causes of Delays

Viewed through the lens of conceptual frameworks after root cause analysis of the thematic factors identified, we determined the causes can be classified in terms of being patient-related, provider-related, or health-systems-related factors. Majority of patients who need neurosurgical intervention for this illness have geographic limitations and other barriers to surmount prior to their admission in a referral hospital with neurosurgical service. Financial barriers are present when costly diagnostics and other surgical implements require out-of-pocket expenses, or when catastrophic expenditures result in impoverishment. Misconceptions also abound from both patient and health-provider sides. These misconceptions may be sociocultural or financial in context and are often about the risks and benefits of the procedure, the care and referral pathways, or the risks and prognosis of the disease. Owing to the decentralized but disorganized nature of hospital referral systems in the country—between rural to urban / lower-level to higher-level centers—delays are magnified by lack of hospital catchment arrangements (e.g. a neurosurgical center can refuse a transfer due to current high volume) and logistical concerns (e.g. lack of adequate ambulance transport to conduct the patient). On an institutional level, the hospital often has inconsistent availability of supplies (e.g. procurement of clips and other incidentals are delayed), and the inefficiency of operating room (OR) throughput is matched also by lack of related and needed infrastructure (e.g. bottleneck in OR queue of emergency procedures such as surgical clipping because of few surgical theatres or insufficient nursing workforce). On a health-system

level, the lack of universal health insurance coverage for the whole population and the chronic underfunding of public hospitals with neurosurgical centers stand out as two important root causes of delays. All the identified causes are in turn influenced by the broader environmental considerations of workforce, infrastructure and service delivery, and financial and governance arrangements (Fig. 1).

Discussion:

The Quality Chasm Viewed Through the Lens of Neurosurgical Treatment of Aneurysmal Subarachnoid Hemorrhage

In this series of socioeconomically disadvantaged patients who survived the initial rupture of SAH and were treated with upfront surgical clipping, we report the late timing of surgery experienced by majority of them, the factors predictive of their poor outcomes, and the causes of delay that are specific in a low-resource setting. While many of these socioeconomic factors would be beyond the scope of usual clinical and neurosurgical practice, an awareness of the context allows the realization of the magnitude of systemic problems¹⁰ that are more prevalent in LMICs.¹¹ From such knowledge, solutions could then be formulated. Although by no means exhaustive, we also proffer solutions broadly categorized into either micro-level interventions directed at clinical decision making or macro-level interventions directed at health systems.^{11,12} The example of our series of patients and the institutional and country contexts will now serve as focal points for our discussion.

Deliberate Upfront Clipping in Low-Resource Settings

Since the publication of long-term outcomes from seminal trials,^{13,14} patients with ruptured aneurysms ought to be offered the endovascular option for treatment. Emerging recommendations on standards of care, when situated in the context of financial constraints at both the provider and receiver ends of neurosurgical care, pose a negative experience of contrasts. The trend in developed countries is a rise in the use of endovascular treatment option, or at the very least an involvement of a multidisciplinary team for reaching a consensus on the initial course of treatment. This is not the case however in LMICs, where the costs of coils and modern devices are prohibitive—and there are still few specialists who could offer this treatment option.¹⁵ Providers of care regardless of specialty therefore commonly apprise the socioeconomically disadvantaged patients with the clipping option only. The socioeconomic context of our patient population does not constitute a justification to be accepted but rather becomes a reflection of the gap between current evidence and actual practice. Despite the realities, it is incumbent for decision makers, on behalf of the recipients of neurosurgical care whom they represent, to have the symmetry of information about the range of treatment options in order to provide the right informed consent. Expanding the workforce of endovascular neurosurgeons and neurointerventionalists—when coupled with systems-level public policy and use of competitive market forces¹⁶—also augurs well with increasing accessibility to this treatment option.

Late Timing of Surgical Clipping—A Symptom of Systemic Problems

Peculiar in our study setting would be the late time interval to surgery for the majority of the patients. Although the timing of surgery is not statistically significant—similar to what was found in studies with clipping as the

exclusive intervention^{17,18,19,20,21}—this remains a modifiable factor in the institutional or regional catchment setup of our center, partly because the delays are avoidable for the most part.

Variations in surgical care occur on various levels;⁸ the causes of which are mostly due to the locus of control of either the physician or the patient and relatives. Similar to the literature, several reasons for the delays were physician-related: physician diagnostic problems (37%) and delayed referral policy (23%) from the series of Kassell and colleagues,²² sending patient home or wrong diagnosis for at least one day in the diagnosis of SAH (26%) from the series of Hernesniemi and colleagues.²³ Conversely, some of the delays in their series^{22,23} were patient-related: unstable patient condition, failure of patients to recognize severity of illness, logistical reasons, and untimely decisions by patients and relatives. These reasons are also commonplace in our setting, but the added problem of scarce resources further magnify the causes of delay.

Other than the causes beyond the level of the individual patient, it becomes essential to identify which of those factors might be amenable to modification from the perspective of the provider. For example, we have taken measures to institute an open-line network communication channel²⁴ in order to improve inter-hospital coordination of transfers as well as pre-hospital management. Efforts have been made to address the timeliness of surgery by doing the surgical clipping beyond OR hours, even during the evenings, at which time the OR throughput is usually decreased. Often, when the workforce is adequate, it is the limitation of OR infrastructure that causes the bottleneck. Our data also illustrate the disparities from the expectations for timely and appropriate care of the patient with SAH in LMICs,²⁵ where reasonable timeframes are often unmet especially in our setting. Much work remains to be done in order to improve efficiency and expand the capacity of under-resourced neurosurgical centers in meeting the demands of the increasing surgical volume.

Aside from the fact that many patients from our center's catchment population live below the poverty threshold, the publicly-funded health system that is supposed to provide an enabling mechanism for them to receive proper neurosurgical care continues to be underfunded.²⁶ This twin problem at both receiving and providing ends of the spectrum remains the perennial limitation in publicly-funded neurosurgical centers such as our setting. Late timing of surgical treatment is also an outward manifestation of a structural problem—it represents the magnitude of the fragmentation of a publicly-funded healthcare system. The financing of hospital-based inpatient services in the public setting are often limited by capitation-based reimbursements from the national social health insurance because the overall scarce resources of the national government are prioritized for population-based health programs.²⁷ From our example of neurosurgical service delivery, the undersupply and depletion of relevant medical supplies such as aneurysm clips, arterial line, bone flap implants, and other surgical implements highlight the inefficiencies inherent in the procurement processes and supply chain management of government-funded centers of any health system.^{28,29,30} Improving systems-level governance³¹ and financial arrangements³² by streamlining how common neurosurgical supplies are purchased might improve access to care, and in turn health outcomes.¹¹ Given that hemorrhagic stroke, including SAH, is one of the leading causes of mortality in the country,²⁷ it becomes necessary to make essential neurosurgical care as one of the priorities for long-term capital expenditures and investments by the governing health sector.¹¹

In those patients waiting for their ruptured aneurysm to be clipped, the future risk of poor outcome needs to be understood with respect to both the impact of the cerebral insult they initially had during ictus and the arguably increased likelihood of them avoiding other complications like vasospasm, nosocomial infection, and many other time-dependent factors like rebleeding and even hospitalization costs—some of which may be curtailed or avoided had they undergone an earlier surgery.^{33,34} While early aneurysm treatment remains to be recommended and is therefore preferred even in low-resource settings, this ideal still remains a daunting task to achieve.

Vasospasm and Intraoperative Rupture—Hardly Modifiable Factors

Our data identify vasospasm as an independent predictor of mortality. Rosengart and colleagues³⁵ pointed out that while there are several studies that examined the factors associated with outcome prior to the era of widespread endovascular use, only 3 studies^{36,37,38} have sufficient study population to allow analysis of the effect of multiple independent factors. Our findings are consistent with reports from those studies, that vasospasm is an enduring predictor of unfavorable outcomes.^{35,37,38} Therefore, systems of care have to be responsive in diagnosing and treating this prophylactically and reversibly. This is not the case in our institution, where asymptomatic angiographic vasospasm may have been underdiagnosed and undertreated when compared to global state-of-the-art treatment, partly because of limitations of equipment and infrastructure,³ and the lack of endovascular treatment options.¹⁵ Notwithstanding the fact that neurointervention also grants the SAH patient with several options for the diagnosis and novel treatment of vasospasm—a risk factor predictive of mortality in this study—the increase in accessibility and availability of endovascular suites and care providers should fill a huge gap of the long unmet nationwide need for this niche of subspecialty care.

Our data also reveal intraoperative aneurysm rupture at the time of surgery as an independent predictor of mortality. Whereas other studies^{39,40,41} only identify it as significant factor for poor outcome, Batjer and colleagues⁴¹ went further to characterize it as largely dependent on specific microsurgical techniques employed by the aneurysm surgeon. The rapidity of rupture control, which reflects the dexterity of the primary surgeon, may be similarly as important as intraoperative rupture.^{39,42,43} At the time, the operating microscope for use during microneurosurgery was an old model (Fig. 2) that posed difficulties in maneuverability for quick responses during rupture. Considering that technical proficiency can be enhanced by judicious application of technology to operative imaging and visualization, equipment such as the operating microscope become invaluable tools that aid the neurosurgical procedures to become uneventful.

Regardless, our rates of unfavorable outcomes appear comparable to that of recent studies.^{44,45} The rates of unfavorable outcomes were 43.3% and 22%, while mortality rates were 18.4% and 5.9% in studies by Roquer et al.⁴⁴ and Macdonald et al.⁴⁵, respectively. Factors such as intraoperative rupture and vasospasm were similarly found to be independent predictors of poor outcomes in those studies,^{44,45,46} despite the fact that their contemporary series of patients had been given the option of treatment by both open surgical and endovascular means. Our experience, however, remains to stand in stark contrast to that of ideal well-resourced settings. The care of the patient with SAH becomes especially difficult when standards of care

cannot be offered—often due to inadequate infrastructure and even lack of supply of medicines. Suboptimal pharmacologic treatment often occurs when the supply of nimodipine runs out in the pharmacy, requiring out-of-pocket expenditures from the family of the now unemployed breadwinner-patient with SAH. Other systems-related problems that are commonplace: a postop poor-grade patient who ideally requires ICU admission is instead cared for in the wards with a 1:20 nurse-to-patient ratio; or a neurologically deteriorating post-clipping patient who would have to be transported outside the hospital because the CT scanner has not been repaired for the longest time. These situations are testament to the fact that inadequate funding reduces the quality of care—and that addressing the problem of finite resources for neurosurgery in LMICs can have major effects on improving the outcomes of vulnerable patients.¹¹

The Way Forward

Recognizing that social determinants of health⁴⁷ can affect the health of a population, a systems approach to the problem-solving of delays, can improve outcomes of interventions to a large extent. Advocacy work for public health and hospital improvement is also needed therefore, in order to lower the barriers to care can address health inequities, particularly in terms of public-private investments in infrastructure and equipment.^{3,10,11} Preparing the needed workforce entails capacity-building and aligning of payment policies to serve the goal of quality and efficiency. All these must be entrenched in public policy and regulatory frameworks for sustainability and consistency,²⁷ because after all, improvements in care processes result in better quality.

Limitations of the Study

The study excluded patients with presumptive or confirmed diagnosis of aneurysmal SAH but who died before hospital admission or aneurysm treatment. In as far as assessing outcomes of the delayed treatment group, there is also a high likelihood of survival bias. Long-term outcomes after discharge as well as surrogate end points such as post-clipping durability of treatment were not assessed due to lack of postoperative angiography. Additionally, the correlations of our study variables may have been under- or overrepresented because of the retrospective study design. All these constitute a selection bias. Other confounding factors may also be present despite our exhaustive list of variables. For example, we did not have data for potentially clinically-significant variables like duration of brain retraction and temporary occlusion time, due to limitations of data recording. Other variables that have not been found to be statistically significant in this present study, and yet are ordinarily considered to be clinically significant in majority of cases of SAH, remain potential topics for future intensive investigation.

The system-level causes of delay identified in this study were not subjected to statistical analyses. Certainly they have an effect in one way or another,¹¹ but we did not demonstrate how these causes or even potential solutions may be strongly or weakly affective of outcomes. Studies that explore the link of nation-level indicators and indices to patient outcomes are recommended to fill this knowledge gap. We also hope that our experience of neurosurgical care in LMICs—particularly with regard to cerebrovascular treatment—can inform the process of guideline^{3–6} formulation, in a manner similar to how the living guidelines for the management of traumatic brain injury take into account global experiences.⁴⁸ Further studies of high-quality evidence in LMIC settings are therefore needed.

Conclusion:

In terms of neurosurgical care for survivors of SAH in low-resource settings, the quality chasm—between the ideal and the reality—is indeed wide. From our experience of care for our series of socioeconomically disadvantaged patients, we provide the reasons for delays to seeking treatment and surgical clipping as they relate to vasospasm and intraoperative rupture—two independent predictors of both dependency and death in this series. Given that a favorable outcome is often precarious and not guaranteed for all patients suffering from both SAH and a low socioeconomic status, the way forward entails a focus on modifiable causes that address both micro-level (provider-directed) and macro-level (health systems-directed) solutions. Neurosurgeons who serve in under-resourced centers have the gargantuan task of systematically addressing the noted risk factors of unfavorable outcomes, while simultaneously needing to take health systems into account. The accessibility and availability of proper neurosurgical care in LMICs can be viewed as deeply disjointed from the global sense of how the quality of neurosurgical should be, thereby calling for much work that remains to be done in the task of bridging this chasm.

References:

1. Grasso G, Alafaci C, Macdonald RL. Management of aneurysmal subarachnoid hemorrhage: State of the art and future perspectives. *Surg Neurol Int.* 2017;8.
2. Ferraris KP, Matsumura H, Wardhana DPW, et al. The state of neurosurgical training and education in East Asia: analysis and strategy development for this frontier of the world. *Neurosurg Focus.* 2020;48(3):E7.
3. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage. *Stroke.* 2012;43(6):1711–1737.
4. Committee for Guidelines for Management of Aneurysmal Subarachnoid Hemorrhage, Japanese Society on Surgery for Cerebral Stroke. Evidence-Based Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage English Edition. *Neurol Med Chir(Tokyo).* 2012;52(6):355–429.
5. Diring MN, Bleck TP, Claude Hemphill J, et al. Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care.* 2011 Oct;15(2):211–40.
6. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage. *Cerebrovasc Dis.* 2013;35(2):93–112.
7. Birkmeyer JD, Reames BN, McCulloch P, et al. Understanding of regional variation in the use of surgery. *Lancet.* 2013;382(9898):1121–1129.
8. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. *Soc Sci Med.* 1994;38(8):1091–1110.
9. Meara JG, Leather AJM, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet.* 2015;386(9993):569–624.
10. Rutter H, Savona N, Glonti K, et al. The need for a complex systems model of evidence for public health. *Lancet.* 2017;390(10112):2602–2604.
11. Bukhman G, Mocumbi AO, Atun R, et al. The Lancet NCDI Poverty Commission: bridging a gap in universal health coverage for the poorest billion. *Lancet.* 2020;S0140-6736(20)31907–3.

12. McCulloch P, Nagendran M, Campbell WB, et al. Strategies to reduce variation in the use of surgery. *Lancet*. 2013;382(9898):1130–1139.
13. Molyneux AJ, Birks J, Clarke A, et al. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet*. 2015;385(9969):691–697.
14. Spetzler RF, McDougall CG, Zabramski JM, et al. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. *J Neurosurg*. 2019;132(3):771–776.
15. Zubair Tahir M, Enam SA, Pervez Ali R, et al. Cost-effectiveness of clipping vs coiling of intracranial aneurysms after subarachnoid hemorrhage in a developing country—a prospective study. *Surg Neurol*. 2009;72(4):355–360.
16. Dossani RH, Waqas M. Letter: Challenges to Neuroendovascular Care in Developing Countries: Example of Pakistan in Global Perspective. *Neurosurgery*. 2018;82(5):E141-E142.
17. Whitfield PC, Kirkpatrick P. Timing of surgery for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2001;(2).
18. Ross N, Hutchinson P, Seeley H, Kirkpatrick P. Timing of surgery for supratentorial aneurysmal subarachnoid haemorrhage: report of a prospective study. *J Neurol Neurosurg Psychiatry*. 2002;72(4):480–484.
19. Dellaretti M, Batista DM, Almeida JC de, et al. Surgical treatment of ruptured intracranial aneurysms: Timing of treatment and outcome. *Interdiscip Neurosurg*. 2018;14:178–182.
20. Chee LC, Siregar JA, Ghani ARI, et al. The Factors Associated with Outcomes in Surgically Managed Ruptured Cerebral Aneurysm. *Malays J Med Sci*. 2018;25(1):32–41.
21. Enriquez CAG, Diestro JDB, Omar AT, et al. Safety and Clinical Outcome of Good-Grade Aneurysmal Subarachnoid Hemorrhage in Non-Intensive Care Units. *J Stroke Cerebrovasc Dis*. 2020;29(10):105123.
22. Kassell NF, Kongable GL, Torner JC, et al. Delay in referral of patients with ruptured aneurysms to neurosurgical attention. *Stroke*. 1985;16(4):587–590.
23. Hernesniemi J, Vapalahti M, Niskanen M, et al. One-year outcome in early aneurysm surgery: a 14 years experience. *Acta Neurochir (Wien)*. 1993;122(1–2):1–10.
24. Coiera E. Communication Systems in Healthcare. *Clin Biochem Rev*. 2006;27(2):89–98.
25. Mansouri A, Ku JC, Khu KJ, et al. Exploratory Analysis into Reasonable Timeframes for the Provision of Neurosurgical Care in Low- and Middle-Income Countries. *World Neurosurg*. 2018;117:e679-e691.
26. Picazo OF: Public hospital governance in the Philippines, in Huntington D, Hort K (eds): *Public Hospital Governance in Asia and the Pacific, Vol 1*. Geneva: World Health Organization Western Pacific Regional Publications, 2015, pp 186–221.
27. Wong JQ, Uy J, Haw NJL, et al. Priority Setting for Health Service Coverage Decisions Supported by Public Spending: Experience from the Philippines. *Health Syst Reform*. 2018;4(1):19–29.
28. Cameron A, Ewen M, Ross-Degnan D, et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*. 2009;373(9659):240–249.
29. Diaconu K, Chen Y-F, Cummins C, et al. Methods for medical device and equipment procurement and prioritization within low- and middle-income countries: findings of a systematic literature review. *Global*

Health. 2017;13.

30. Seidman G, Atun R. Do changes to supply chains and procurement processes yield cost savings and improve availability of pharmaceuticals, vaccines or health products? A systematic review of evidence from low-income and middle-income countries. *BMJ Glob Health*. 2017;2(2):e000243.
31. Herrera CA, Lewin S, Paulsen E, et al. Governance arrangements for health systems in low-income countries: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2017;2017(9).
32. Wiysonge CS, Paulsen E, Lewin S, et al. Financial arrangements for health systems in low-income countries: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2017;2017(9).
33. Kassell NF, Torner JC, Jane JA, et al. The International Cooperative Study on the Timing of Aneurysm Surgery: Part 2: Surgical results. *J Neurosurg*. 1990;73(1):37–47.
34. Öhman J, Heiskanen O. Timing of operation for ruptured supratentorial aneurysms: a prospective randomized study. *J Neurosurg*. 1989;70(1):55–60.
35. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic Factors for Outcome in Patients With Aneurysmal Subarachnoid Hemorrhage. *Stroke*. 2007;38(8):2315–2321.
36. Torner JC, Kassell NF, Wallace RB, Adams HPJ. Preoperative prognostic factors for rebleeding and survival in aneurysm patients receiving antifibrinolytic therapy: report of the cooperative aneurysm study. *Neurosurgery*. 1981; 9: 506–513.
37. Kassell NF, Torner JC, Haley EC Jr, et al. The international cooperative study on the timing of aneurysm surgery. part 1: overall management results. *J Neurosurg*. 1990; 73: 18–36.
38. Niskanen MM, Hernesniemi JA, Vapalahti MP, Kari A. One-year outcome in early aneurysm surgery: prediction of outcome. *Acta Neurochir (Wien)*. 1993; 123: 25–32.
39. Hsu C-E, Lin T-K, Lee M-H, et al. The Impact of Surgical Experience on Major Intraoperative Aneurysm Rupture and Their Consequences on Outcome: A Multivariate Analysis of 538 Microsurgical Clipping Cases. *PLoS ONE*. 2016;11(3):e0151805.
40. Darkwah Oppong M, Pierscianek D, Ahmadipour Y, et al. Intraoperative Aneurysm Rupture During Microsurgical Clipping: Risk Re-evaluation in the Post–International Subarachnoid Aneurysm Trial Era. *World Neurosurg*. 2018;119:e349-e356.
41. Batjer H, Samson D. Intraoperative Aneurysmal Rupture: Incidence, Outcome, and Suggestions for Surgical Management. *Neurosurgery*. 1986;18(6):701–707.
42. van Lindert EJ, Böcher–Schwarz H-G, Perneczky A. The influence of surgical experience on the rate of intraoperative aneurysm rupture and its impact on aneurysm treatment outcome. *Surg Neurol*. 2001;56(3):151–156.
43. Wong JM, Ziewacz JE, Ho AL, et al. Patterns in neurosurgical adverse events: open cerebrovascular neurosurgery. *Neurosurg Focus*. 2012;33(5):E15.
44. Roquer J, Cuadrado-Godia E, Guimaraens L, et al. Short- and long-term outcome of patients with aneurysmal subarachnoid hemorrhage. *Neurology*. 2020;95(13):e1819-e1829.
45. Macdonald RL, Kassell NF, Mayer S, et al. Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1). *Stroke*. 2008;39(11):3015–3021.

46. Eagles ME, Tso MK, Ayling OGS, et al. Unfavorable Outcome After Good Grade Aneurysmal Subarachnoid Hemorrhage: Exploratory Analysis. *World Neurosurg.* 2020;144:e842-e848.

47. Carey G, Crammond B. Systems change for the social determinants of health. *BMC Public Health.* 2015;15(1):662.

48. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6–15.

Tables

Table 1. Univariate and logistic regression analysis of factors related to unfavorable outcomes in patients with SAH

Factor		Number of Patients (%)			Univariate Analysis	Simple Logistic Regression Analysis	
		Total (n = 106)	Unfavorable outcome/ mRS 3-6 (n = 31)	Favorable outcome/ mRS 0-2 (n = 75)		Correlation	p Value
Patient Demographics	Age	49.91± 11.38	52.39 ± 11.29	48.89 ± 11.33	0.150*	1.03 (0.99 - 1.07)	0.151
	Gender						
	Male	49 (46.23)	9 (29.03)	40 (53.33)		Ref	-
	Female	57 (53.77)	22 (70.97)	35 (46.67)		2.79 (1.14 - 6.86)	0.025
	Smoking history	29 (27.36)	7 (22.58)	22 (29.33)	0.478†	0.70 (0.26 - 1.87)	0.479
	Hypertension and pre-existing cardiac comorbidity	78 (73.58)	23 (74.19)	55 (73.33)	0.927†	1.04 (0.40 - 2.71)	0.927
Clinical Features	Hunt & Hess grade	2 (1 - 4)	3 (1 - 4)	1 (1 - 3)	0.002[‡]		
	Grade 1	50 (47.17)	11 (35.48)	39 (52)	<0.001[§]	Ref	-
	Grade 2	29 (27.36)	4 (12.90)	25 (33.33)		0.57 (0.16 - 1.98)	0.374
	Grade 3	18 (16.98)	7 (22.58)	11 (14.67)		2.26 (0.71 - 7.20)	0.169
	Grade 4	9 (8.49)	9 (29.03)	0		Omitted	-
	WFNS grade	1 (1 - 4)	2 (1 - 4)	1 (1 - 4)	<0.001[‡]		
	Grade 1	78 (73.58)	15 (48.39)	63 (84)	<0.001[§]	Ref	-
	Grade 2	4 (3.77)	1 (3.23)	3 (4)		1.40 (0.14 - 14.42)	0.777
	Grade 3	13 (12.26)	6 (19.35)	7 (9.33)		3.60 (1.06 - 12.28)	0.041
	Grade 4	11 (10.38)	9 (29.03)	2 (2.67)		18.90 (3.69- 96.69)	<0.001
	Grade 5	0	0	0			
	Modified Fisher grade	3 (1 - 4)	3 (1 - 4)	3 (1 - 4)	0.082 [‡]		
	Grade 1	34 (32.08)	7 (22.58)	27 (36)	0.269 [§]	Ref	-
	Grade 2	6 (5.66)	2 (6.45)	4 (5.33)		1.93 (0.29 - 12.77)	0.496
	Grade 3	49 (46.23)	14 (45.16)	35 (46.67)		1.54 (0.55 - 4.35)	0.412
	Grade 4	17 (16.04)	8 (25.81)	9 (12)		3.43 (0.97 - 12.14)	0.056
	Aneurysm size (mm)				0.075 [§]		
	<5mm	49 (46.23)	11 (35.48)	38 (50.67)		Ref	-
	6 - 15	49 (46.23)	15 (48.39)	34 (45.33)		1.52 (0.62 - 3.77)	0.362
	16 - 25	8	5 (16.13)	3 (4)		5.76 (1.18	0.030

		(7.55)			- 27.98)	
	>25	0	0	0		
	Aneurysm type				0.333 [§]	
	Saccular	94 (88.68)	26 (83.87)	68 (90.67)		Ref -
	Fusiform	4 (3.77)	1 (3.23)	3 (4)		0.87 (0.09 - 8.76) 0.907
	Multiple	8 (7.55)	4 (12.90)	4 (5.33)		2.61 (0.61 - 11.24) 0.196
	Aneurysm location				0.036 [§]	0.34 (0.12 - 1.02) 0.054**
	Anterior communicating	36 (33.96)	5 (16.13)	31 (41.33)		
	Posterior communicating	4 (3.77)	3 (9.68)	1 (1.33)		
	Middle cerebral	32 (30.19)	11 (35.48)	21 (28)		
	Internal carotid	8 (7.55)	1 (3.23)	7 (9.33)		
	Paraclinoid	1 (0.94)	0	1 (1.33)		
	Vertebral	5 (4.72)	1 (3.23)	4 (5.33)		
	Basilar	7 (6.60)	4 (12.90)	3 (4)		
	Distal	5 (4.72)	2 (6.45)	3 (4)		
	Multiple	8 (7.55)	4 (12.90)	4 (5.33)		
	Preoperative rebleeding	8 (7.55)	5 (16.13)	3 (4)	0.045 [§]	3.41 (0.85 - 13.70) 0.083
	Intraoperative rupture	11 (10.38)	9 (29.03)	2 (2.67)	<0.001 [§]	14.93 (3.00- 74.30) 0.001
Perioperative Management	Time to admission (days)	5 (0 - 156)	3 (1 - 20)	5 (0 - 156)	0.132 [‡]	
	Time interval to surgery***	15 (1 - 302)	14 (2 - 70)	16 (1 - 302)	0.578 [‡]	
	Early (0-2d)	4 (3.77)	1 (3.23)	3 (4)	0.921 [§]	Ref -
	Intermediate (3-10d)	31 (29.25)	10 (32.26)	21 (28)		1.43 (0.13 - 15.52) 0.769
	Late (>10d)	71 (66.98)	20 (64.52)	51 (68)		1.18 (0.12 - 11.99) 0.891
	ICU admission	11 (10.38)	6 (19.35)	5 (6.67)	0.077 [§]	3.36 (0.94 - 11.98) 0.062
	Lumbar CSF drainage	85 (80.19)	25 (80.65)	60 (80)	0.940 [†]	1.04 (0.36 - 2.99) 0.940
	Skull base approach	15 (14.15)	6 (19.35)	9 (12)	0.364 [§]	1.76 (0.57 - 5.45) 0.327
	Postoperative nimodipine	94 (88.68)	28 (90.32)	66 (88)	1.000 [§]	1.27 (0.32 - 5.06) 0.732
	HHH therapy	62 (58.49)	23 (74.19)	39 (52)	0.035 [†]	2.65 (1.05 - 6.68) 0.038
	Osmotic therapy	73 (68.87)	26 (83.87)	47 (62.67)	0.032 [†]	3.10 (1.07 - 8.99) 0.038
	Prophylactic antiepileptic drug	75 (70.75)	23 (74.19)	52 (69.33)	0.617 [†]	1.27 (0.50 - 3.26) 0.617

Complication and Other Intervention	Statin	67 (63.21)	19 (61.29)	48 (64)	0.792 [†]	0.89 (0.38 – 2.11)	0.792
	Short-term antifibrinolytic drug	11 (10.38)	6 (19.35)	5 (6.67)	0.077 [§]	3.36 (0.94 – 11.98)	0.062
	Dexamethasone	4 (3.77)	1 (3.23)	3 (4)	1.000 [§]	0.80 (0.08 – 8.00)	0.849
	Cilostazol	18 (16.98)	5 (16.13)	13 (17.33)	0.881 [§]	0.92 (0.30 – 2.83)	0.881
	Hydrocephalus	20 (18.87)	9 (29.03)	11 (14.67)	0.086 [†]	2.38 (0.87 – 6.50)	0.091
	Vasospasm	20 (18.87)	14 (45.16)	6 (8)	<0.001[†]	9.47 (3.17 – 28.27)	<0.001
	CSF diversion				0.001[§]		
	None	88 (83.02)	21 (67.74)	67 (89.33)		Ref	-
	Ventriculoperitoneal shunt	13 (12.26)	5 (16.13)	8 (10.67)		1.99 (0.59 – 6.76)	0.268
	External ventricular drain	5 (4.72)	5 (16.13)	0		Omitted	-
	Decompressive hemicraniectomy	12 (11.32)	12 (38.71)	0	<0.001[§]	Omitted	-
	Surgical complication				<0.001[§]		
	None	82 (77.36)	15 (48.39)	67 (89.33)		Ref	-
	Infarct	14 (13.21)	10 (32.26)	4 (5.33)		11.17 (3.08–40.47)	<0.001
	Hemorrhage/hematoma	8 (7.55)	6 (19.35)	2 (2.67)		13.40 (2.46–73.01)	0.003
	Hypovolemic shock	0	0	0			-
	Others	2 (1.89)	0	0 (2.67)		Omitted	
	Medical complication				0.004[§]		
	None	80 (75.47)	17 (54.84)	63 (84)		Ref	-
	Disorders of sodium & water balance	24 (22.64)	13 (41.94)	11 (14.67)		4.38 (1.67 – 11.50)	0.003
	Neurogenic pulmonary edema	0	0	0			
	Neurogenic stunned myocardium & cardiac events	2 (1.89)	1 (1.33)	1 (1.33)		3.706 (0.22 – 62.37)	0.363
	Healthcare-associated infection				<0.001[§]		
	None	76 (71.70)	11 (35.48)	65 (86.67)		Ref	-
	Pneumonia	21 (19.81)	12 (38.71)	9 (12)		7.879 (2.69 – 23.08)	<0.001
	Urinary tract infection	1 (0.94)	0	1 (1.33)		Omitted	-
	Sepsis & septic shock	8 (7.55)	8 (25.81)	0		Omitted	-

	Presumed endocarditis	0	0	0			
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Boldface type indicates statistical significance.

Statistical tests used: * - Independent t-test; † - Chi - square Goodness of Fit test; ‡ - Mann Whitney U-test § - Fisher's Exact test

**Logistic regression dichotomized Aneurysm location into anterior circulation and posterior circulation.

***Timing of surgery is stratified accordingly into: Early (within 0-2 days from ictus), Intermediate (3-10 days), and Late (>10 days).

Table 2. Risk factors for mortality after exact logistic regression

Factor	Exact logistic regression for mRS 6		
	Correlation	95% CI	p Value
Cooperative rupture	18.00	3.70 - 103.79	0.001
Seizure	10.52	2.76 - 43.92	0.001
External ventricular drain	36.69	3.17 - 1992.07	0.002
Compressive hemicraniectomy	9.11	2.00 - 42.88	0.003
Disorders of sodium and water balance	6.02	1.59 - 24.34	0.006
Sepsis and septic shock	38.15	5.27 - 480.90	0.001

Boldface type indicates statistical significance.

Table 3. Unfavorable outcomes stratified by timing of surgery

Factor	Timing of surgery								
	Early (0-2 days)			Intermediate (3-10 days)			Late (>10 days)		
	n/N (%)	OR (95% CI)	p Value	n/N (%)	OR (95% CI)	p Value	n/N (%)	OR (95% CI)	p Value
Dependency (mRS ≥ 3)	1/4 (25)	Ref	-	10/31 (32.3)	1.43 (0.13 - 15.52)	0.769	20/71 (28.2)	1.18 (0.12 - 11.99)	0.891
Mortality (mRS 0-5)	0/4 (0)	Ref	-	5/31 (16.1)	0.92 (0.10 - Inf)	1.000	10/71 (14.1)	0.83 (0.10 - Inf)	1.000

Boldface type indicates statistical significance.

Table 4. Independent predictors of dependency and death after multivariate logistic regression

Factor	Multivariate logistic regression for mRS 3-6		
	Correlation	95% CI	p Value
Cooperative rupture	23.98	3.56 - 161.33	0.001
Seizure	12.47	3.01 - 51.57	<0.001
Disorders of sodium and Hess grade ≥ 3	5.96	1.47 - 24.18	0.012

Boldface type indicates statistical significance.

Figures

Figure 1

Root cause analysis of the factors influencing the timeliness or delay in seeking surgical care for aneurysmal subarachnoid hemorrhage in a low-income setting. *Adapted from Birkmeyer JD, Reames BN, McCulloch P, et al. Understanding of regional variation in the use of surgery. Lancet. 2013;382(9898):1121-1129.

Figure 2

At the time, the workhorse operating microscope for surgical clipping of ruptured aneurysm at the study center in the Philippines.