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Clinical Profile of Patients with Aneurysmal Subarachnoid Hemorrhage in A Tertiary Government Hospital

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ABSTRACT

INTRODUCTION: Aneurysmal subarachnoid hemorrhage (aSAH) remains a serious disease with high morbidity and mortality. Early detection and treatment contribute to increase chance of survival and better prognosis. This study aims to determine the clinical profile of patients with aSAH who were admitted in a tertiary government hospital in Cebu, Philippines.

METHODS: A single, cross-sectional study was performed on 250 patients diagnosed with aSAH at Vicente Sotto Memorial Medical Center (VSMMC), Cebu, Philippines from January 2016 to June 2020.

RESULTS: Majority of the patients were female (68.0%) while 32.0% were male. Most of these patients were <60 years old. Hypertension was the most common comorbidity associated with aneurysm. On the other hand, history of smoking was noted in 26.0% of patients. Seventy five percent of patients had elevated BP, while other vital signs were mostly normal. The clinical presentation included severe headache (73.0%), followed by loss of consciousness (16.0%), neurologic deficit (8.0%), seizure (1.0%), and cranial nerve (CN) palsy (1.0%). Most of the patients on admission were classified as good grade at 69% while 31% were poor grade. On CT scan, most patients had Fisher grade III (33.0%). Small size aneurysms were the most common ruptured aneurysms

CONCLUSION: The identified risk factors in developing aneurysmal subarachnoid hemorrhage (aSAH) were advanced age, female gender, and hypertension. Majority of the patients complained of severe headache, loss of consciousness and neurologic deficit. Predominantly, these patients had good grade aneurysm. The most common location of aneurysms were the posterior communicating artery, anterior communicating artery, and middle cerebral artery. Small size aneurysms had the highest frequency of ruptured aneurysms.

Keywords: Aneurysmal Subarachnoid Hemorrhage, Clinical Profile, Ruptured Aneurysm, Craniotomy
Word Count: 2130

STRENGTH AND LIMITATION OF THE STUDY:

- A sample size of 250 patients within 5-year period in one of the largest tertiary government hospital in the low-middle income country.
- The study reported clinical profile of admitted patients diagnosed with aneurysmal subarachnoid hemorrhage via digital subtraction angiogram or computed tomography (CT) angiogram .
- Diagnosed cases of unruptured aneurysms were excluded as it may alter the findings of the study.
- This is a single -centered study which does not represent the general population and still lacks external validation.

BACKGROUND

A ruptured cerebral aneurysm is the most common cause of spontaneous subarachnoid hemorrhage (SAH)[1-2] and is accounted for 80% of the cases.[3-4] Several factors are attributed to the incidence of cerebral aneurysm and its subsequent rupture. The rate of rupture may be affected by factors associated with aneurysm itself or the patient.[5-6] Gender, advanced age, smoking, substance abuse, hypertension,[7-11] and diabetes[8] have been identified as predictive factors in the development and rupture of cerebral aneurysm. An increased risk of ruptured cerebral aneurysm is also noted among patients with higher incidence of cardiac arrhythmia, myocardial dysfunction, and hyponatremia.[12-13]

A non-contrast computed tomography (CT) scan is one of the most important diagnostic tools for detecting aneurysmal subarachnoid hemorrhage (aSAH), where positivity rate reached up to 98-100% within 12 hours after the ictus, then declines to 93% in the first 24 hours, with decreasing positive results with time.[14] Most of the time, CT scan is widely available in secondary hospitals in the provinces and prompt referral is made to tertiary hospital if findings is positive for SAH. CT angiography (CTA) is another tool for screening of intracranial aneurysm; sensitivity ranged from 53% (95% confidence interval (CI): 44-62%) for 2 mm aneurysms to 95% (95% CI: 92-97%) for 7 mm aneurysms, while the overall specificity was 98.9% (95% CI: 91.5- 99.99%).[15] Digital subtraction angiography (DSA) remains the gold standard imaging modality for intracranial aneurysms. Morphologic characteristics of aneurysm in terms of size, involved small branches and perforators near the aneurysm are properly assessed especially with the help of its 3D configuration.[16]

· Majority of cerebral aneurysms in Vicente Sotto Memorial Medical Center (VSMMC) were ruptured cases. Most of them came from a referring primary or secondary hospital in the province or from other neighboring provinces with identified SAH on CT scan. Because of accessible health care program, there is a trend of increasing cases due to early diagnosis with subsequent improvement of the outcome. To date, local evidences of clinical profile of patients with aSAH are yet to be established. Thus, the aim of this study is to provide a comprehensive information of such patients

METHODS

We conducted a descriptive cross sectional study among patients diagnosed with aneurysmal subarachnoid hemorrhage via DSA or CTA at Vicente Sotto Memorial Medical Center, Cebu City, Philippines, between January 2016 to June 2020. Medical records of patients included in the study were reviewed within the time frame. All patients with unruptured cerebral aneurysm were excluded.

The following data were collected: patients profile (age, gender, employment, geographic location), admitting vital signs, clinical presentation, comorbidities, coagulation studies, ECG, electrolytes, admitting Glasgow Coma Scale, Hunt and Hess Grade, Fisher Score on first CT scan, location of aneurysm, aneurysm size, history of on and off headache, smoking and substance abuse (methamphetamine, cocaine, marijuana).

The data gathered were recorded and tabulated in frequency distribution tables using MS Excel (2013). The mean and percentages were computed and described quantitatively using the same software. This study underwent a review and approval from the institution's research technical and ethical committee. Privacy and confidentiality were observed throughout the study by performing measures to prevent divulging patient's name and identity in any manner. Patients and the public were not involved in the design and conduct, dissemination of results and evaluation of studies.

RESULTS

There were a total of 250 patients admitted and diagnosed with aneurysmal subarachnoid hemorrhage (aSAH) in Vicente Sotto Memorial Medical Center (VSMMC) from January 2016 to June 2020 . Table 1 presents the patients' profile in terms of sex, age, and health history. It shows that most of the patients in the study were female (67.6%). Majority were less than 60 years of age (62.8%), mostly employed (58.8%), and resided in Cebu Province (43.6%). It also revealed that most patients with ruptured cerebral aneurysm had significant co-morbidity of hypertension (59.6%), however, patients predominantly had no history of on-and-off headache (96.8%), no history of smoking (74.4%), and no record of substance abuse (99.6%).

Table 1. Frequency of Cerebral Aneurysm Rupture according to Patient Profile and Health History

Profile		Frequency (f)	%	p-value
Sex	Male	81	32.4	<0.0001
	Female	169	67.6	
Age (Years)	< 60	157	62.8	<0.0001
	≥ 60	93	37.2	
Occupation	Employed	147	58.8	0.008
	Unemployed	103	41.2	
Geographic Location	Cebu City	38	15.2	0.002
	Cebu Province	109	43.6	
	Outside Cebu Province	103	41.2	
Co-morbidities	None	99	39.6	0.001
	Diabetes	2	0.8	
	Hypertension	149	59.6	
History of on-and-off headache	Positive	8	3.2	<0.0001
	Negative	242	96.8	
History of Smoking	Positive	64	25.6	

	Negative	186	74.4	<0.0001
History of Substance abuse	Positive	1	0.4	<0.0001
	Negative	249	99.6	

Table 2 shows admitting vital signs and laboratory parameters of patients admitted with aSAH. Majority of the patients had elevated blood pressure during admission (75.2 %). Other vital signs were mostly within normal limits. Bleeding and clotting parameters were normal. In 145 patients, 49 had ECG with myocardial injury while 60 had possible myocardial injury. The electrolytes were unremarkable.

Table 2 . Admitting Vital Signs and Laboratory Parameters

Parameters			
Admitting Vital Signs	**Conditions**	**Frequency (f)**	**%**
BP	Hypertensive	188	75.2
	Normal	53	21.2
	Hypotensive	9	3.6
HR	Increased	22	8.8
	Normal	219	87.6
	Decreased	9	3.6
RR	Increased	92	36.8
	Normal	153	61.2
	Decreased	5	2.0
Temp	Increased	25	10.0
	Normal	222	88.8
	Decreased	3	1.2
Admitting Coagulation Studies			
PT	Increased	24	9.6
	Normal	226	90.4
	Decreased	0	0.0
PTT	Increased	8	3.2
	Normal	226	90.4
	Decreased	16	6.4
CT	Increased	0	0.0
	Normal	250	100.0
	Decreased	0	0.0
BT	Increased	1	0.4
	Normal	248	99.2
	Decreased	1	0.4
Admitting ECG	Normal Sinus Rhythm	34	23.4
	With benign Changes	2	1.4

	With possible myocardial injury	60	41.4
	With myocardial injury	49	33.8
Electrolyte Status			
Sodium	Increased	16	6.4
	Normal	159	63.6
	Decreased	75	30.0
Potassium	Increased	2	0.8
	Normal	151	60.4
	Decreased	97	38.8

Table 3 shows that the most common clinical presentation was severe headache (73.4%), followed by loss of consciousness (16.2%), neurologic deficit (7.7%), CN palsy (1.4%) and seizure (1.4%), respectively. Majority of the admitted patients were good grade (Hunt and Hess grade's 1-3) at 69%. On CT scan, the most common findings were vertical layers of blood > 1mm thickness (Fisher 3 score).

Table 3. Clinical Presentation and Grading

	Frequency (f)	%
Clinical Presentation		
Seizure	3	1.4
Severe Headache	163	73.4
Cranial Nerve (CN) Palsy	3	1.4
Neurologic deficit	17	7.7
Loss of Consciousness	36	16.2
Hunt and Hess Grade on Admission		
I	17	6.8
II	71	28.6
III	83	33.5
IV	67	27.0
V	10	4.0
Fisher Score		
1	39	15.8
2	65	26.3
3	75	30.4

4	68	27.5

Table 4 shows that small size aneurysms were the most common ruptured aneurysms (87.37%), followed by large size aneurysms (11.63%). There were 3 cases of giant aneurysm which were all addressed with surgery. The posterior communicating artery (29.9%) was the most common location of the aneurysm, followed closely by the anterior communicating artery (29.6%), then the middle cerebral artery (19.4%).

Table 4. Size and location of aneurysm

Aneurysm Size	Frequency	%
≤10mm	263	87.4
11-25mm	35	11.6
>25mm	3	0.1
Aneurysm Location		
Internal Carotid Artery	10	3.3
Anterior Communicating Artery	90	29.6
Anterior Cerebral Artery	16	5.3
Middle Cerebral Artery	59	19.4
Vertebral Artery	2	0.7
Posterior Communicating Artery	91	29.9
Posterior Cerebral Artery	3	1.0
Anterior Choroidal Artery	8	2.6
Superior Hypophyseal Artery	12	4.0
Posterior Inferior Cerebellar Artery	4	1.3
Anterior Inferior Cerebellar Artery	2	0.7
Basilar Artery	7	2.3

DISCUSSION

Most patients with aneurysmal subarachnoid hemorrhage (aSAH) were less than 60 years old and majority were female (ratio 2:1). Female sex is significantly associated with subarachnoid hemorrhage (SAH), doubling the risk in the postmenopausal age group.[17] In addition, females are found to be significantly associated with the development of multiple cerebral aneurysms.[18] In a parallel study conducted in the same institution, 27 out of 36 patients who had multiple aneurysms were female.[19] Women had a significantly higher risk for aneurysm formation than men in a long-term follow-up study, and being female was a significant independent risk factor for aneurysm growth.[20]

Majority of patients were from the province of Cebu since the institution is the only capable tertiary government hospital in the province. However, 41% were from outside the province, catering nearby provinces of Bohol, Negros, Zamboanga Peninsula, Surigao and Misamis. This stresses the significant

role of the institution in the management of vascular cases in the area of northern, northwestern Mindanao and Central Visayas. Moreover, the institution also catered 15% of the cases from Cebu City.

Among patients with aSAH, 60% were hypertensive. Hypertension is an independent risk factor for aSAH,[21-23] and Asian descents are more prone to hypertension compared with Caucasians.[24-26] In the Philippines, it is the leading cardiovascular disease at 38%.[27] In a study by Tada, et.al (2013) hypertension has long been considered a risk factor of aneurysmal rupture. It may weaken the aneurysmal wall by directly increasing mechanical stresses.[28] In addition, the activation of the local renin–angiotensin system by systemic hypertension can cause vascular inflammation and remodeling and may contribute to aneurysmal rupture.[28] The control of blood pressure during aSAH is vital to prevent re-rupture.

Diabetes, on the other hand, had 1% prevalence in this study. The low prevalence of diabetes in SAH patients was supported by the study conducted by Kim et al., and concluded that diabetes and elevated fasting blood glucose were inversely associated with the risk of SAH. It also did not affect the risk of cerebral aneurysm formation.[30] However, in patients with aSAH, hyperglycemia is associated with worse outcomes.[31-36]

Cigarette smoking is one of the independent risk factors for cerebral aneurysm development and rupture,[37-38] yet the exact mechanism remains unknown.[38-41] There is a dose-response relationship in intensity and duration of smoking consumption and increased risk of cerebral aneurysm rupture.[42-43] Hypertensive individuals who smoked had a risk of SAH that is 15 times higher when compared with normotensive nonsmokers.[44] However in this study, only 25% had smoking history. Likewise, 99% of patients reported no history of substance abuse.

Aside from admitting BP, vital signs of most patients were within normal limits. Elevated BP were observed in 75% of all patients during admission. This is consistent with literatures and it is an anticipated finding in a majority of hypertensive patients. Bleeding, clotting parameters and electrolytes were within normal limits.

Cardiac manifestations in aSAH have been well documented in literatures. Greenhoot et al., and Melville et al., demonstrated that direct electrical stimulation of the hypothalamus results in ECG abnormalities resembling those seen in aSAH patients. Changes include mild electrocardiogram variability, reversible left ventricular dysfunction (Takotsubo), non-ST elevation myocardial infarction, ST-elevation myocardial infarction and cardiac arrest. In this study, of the 145 patients with ECG tracings, 49 had myocardial infarction, 60 had possible myocardial infarction, 2 had benign changes and 34 had normal findings. In a parallel study, mortality rate of patients who underwent clipping and coiling of ruptured aneurysm in the same institution was 8.45% and the most common complications were vasospasm (25%), pneumonia (24%) and hydrocephalus, respectively.[19] Complications related to cardiovascular disease was only 5%.[19]

The most common clinical presentations were severe headache (73.2%), loss of consciousness (16.22%), neurologic deficit (7.66%), CN palsy (1.35%) and seizure (1.35%). Some patients presented with history of recent but less severe headache days to weeks prior to the onset of aneurysmal rupture which was due to minor leaking of blood into the subarachnoid space. However in this study, only 3% reported with such history.

The most common location of aneurysm was in the posterior communicating artery which accounted for 91 patients, followed by anterior communicating artery aneurysm with 90 patients, and middle cerebral artery with 59 patients. The former demonstrated significantly higher annual increases in dimensional growth, volume and surface area when compared to other internal carotid artery aneurysms.[47]

There were 3 cases of giant aneurysm which were addressed with surgeries. Small size aneurysms were the most common ruptured aneurysms (87.37%) .

Patients who have a poor clinical grade, those who came with stupor or coma, with moderate to severe hemiparesis or with posturing (Hunt and Hess grades 4 and 5), generally have a poor prognosis. They usually compose about 20–30% of those admitted to the hospital with aSAH.[48] Published studies emphasized that patients with poor grades (Grade 4-5) are treated by delaying surgery until they showed clinical improvement (grade 1-3). Comparatively, most of the patients admitted were good grade at 69%. Thus, those who consented underwent surgery.

The study is only limited to the clinical profile of patients diagnosed with ruptured cerebral aneurysm in a single institution regardless if patient is operated or not. A parallel study conducted at the same institution was cited to complement the data needed. For further study, the author recommends a multicenter study regarding the clinical profile and outcome of patients with ruptured cerebral aneurysm.

CONCLUSION

The identified risk factors in developing aneurysmal subarachnoid hemorrhage (aSAH) were advanced age, female gender, and hypertension. Majority of the patients complained of severe headache, loss of consciousness and neurologic deficit. Predominantly, these patients had good grade aneurysm. The most common location of aneurysms were the posterior communicating artery, anterior communicating artery, and middle cerebral artery. Small size aneurysms had the highest frequency of ruptured aneurysms.

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REFERENCES

1. Suarez JI, Tarr RW, and Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354:387–396. doi: 10.1056/NEJMra052732
2. Sweeney K, Silver N, and Javadpour M. Subarachnoid haemorrhage (spontaneous aneurysmal). BMJ Clin Evid. 2016;2016:1213. Published 2016 Mar 17.
3. Pierot L, Cognard C, Anxionnat R, and Ricolfi F. Ruptured intracranial aneurysms: factors affecting the rate and outcome of endovascular treatment complications in a series of 782 patients (CLARITY study). Radiology. 2010;256(3):916-923. doi:10.1148/radiol.10092209
4. Maher M, Schweizer TA, and Macdonald RL. Treatment of Subarachnoid Hemorrhage. Stroke. 2020;51:1326–1332https://doi.org/10.1161/STROKEAHA.119.025997
5. Schneiders JJ, Marquering HA, van den Berg R, et al. Rupture-associated changes of cerebral aneurysm geometry: high-resolution 3D imaging before and after rupture. AJNR Am J Neuroradiol. 2014;35(7):1358-1362. doi:10.3174/ajnr.A3866
6. Britz G, Winn HR. The Natural History of Cerebral aneurysms. In: Winn HR, ed. Youmans Neurological Surgery. 6th ed. Philadelphia, PA: Elsevier Saunders; 2011
7. National Institute of Neurological Disorders and Stroke. Cerebral Aneurysms Fact Sheet. Methesda, MD 2013.

8. Backes D, Rinkel GJE, Laban KG, et al. Patient and Aneurysm Specific Risk Factors for Intracranial Aneurysm Growth. Stroke. 2016;47:951–957. https://doi.org/10.1161/STROKEAHA.115.012162
9. Feigin VL , Rinkel GJE , Lawes CMM , et al Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 2005;36:2773–80.doi:10.1161/01.STR.0000190838.02954.e8
10. Inagawa T. Risk factors for aneurysmal subarachnoid hemorrhage in patients in IZUMO City, Japan. J Neurosurg2005;102:60 .doi:10.3171/jns.2005.102.1.0060
11. Sandvei MS , Romundstad PR , Müller TB , *et al* . Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. Stroke 2009;40:1958 62.
12. Couldwell W. General Neurosurgery. Youmans Neurological Surgery. Philadelphia, swPA: Elsevier Saunders; 2011.
13. Ganaw, A. E. A. , Tharayil, A. M. , Khair, A. O. M. , Tahseen, S., Hassan, J., Abdullah Malmstrom, M. F. , & Ahmed, S. M. G. (2017). Aneurysmal Subarachnoid Hemorrhage. In (Ed.), Intensive Care. IntechOpen. https://doi.org/10.5772/intechopen.68630
14. Sayer D, Bloom B, Fernando K, et al. An observational studyc of 2,248 patients presenting with headache, suggestive of subarachnoid hemorrhage, who received lumbar punctures following normal computed tomography of the head. Acad Emerg Med 2015; 22: 1267–1273
15. Van Gelder JM. Computed tomographic angiography for detecting cerebral aneurysms: Implications of aneurysm size distribution for the sensitivity, specificity, and likelihood ratios. Neurosurgery 2003; 53: 597–605; discussion 605–606.
16. Van Rooij WJ, Sprengers ME, de Gast AN, et al. 3D rotational angiography: The new gold standard in the detection of additional intracranial aneurysms. AJNR Am J Neuroradiol 2008; 29: 976–979.
17. Kumar A, McCullough L. Cerebrovascular disease in women. Therapeutic Advances in Neurological Disorders. 2021;14. doi:10.1177/1756286420985237
18. Koo K and Hwang SK. Relationship between Estrogen Hormone and Rupture of Cerebral Aneurysm in Premenopausal Women. *Nerve.* 2019;5 (2): 72-77. doi:https://doi.org/10.21129/nerve.2019.5.2.72
19. Albano, EE Jr. and Villamor RB Jr. Patients Outcome and Subarachnoid Hemorrhage Grading Scores Among those Diagnosed with Ruptured Aneurysm: A Cross-sectional, Single-Center Study. Unpublished.2021
20. Fréneau M, Baron-Menguy C, Vion AC, Loirand G. Why Are Women Predisposed to Intracranial Aneurysm? Front Cardiovasc Med. 2022 Feb 10;9:815668. PMID: 35224050; PMCID: PMC8866977doi: 10.3389/fcvm.2022.815668..
21. Jimenez-Yepes CM and Londono-Fernandez. Risk of Aneurysmal Subarachnoid Hemorrhage https://doi.org/10.1161/STROKEAHA.107.504019
22. Lindgren AE, Kurki MI, Riihinen A et al. Hypertension predisposes to the formation of saccular intracranial aneurysms in 467 unruptured and 1053 ruptured patients in Eastern Finland, Annals of Medicine, 46:3, 169-176, DOI: 10.3109/07853890.2014.883168
23. Kim T, Lee H, Ahn S, et al. Incidence and risk factors of intracranial aneurysm: A national cohort study in Korea. International Journal of Stroke. 2016;11(8):917-927. doi:10.1177/1747493016660096
24. Carson AP, Howard G, Burke GL, et al. Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension. 2011; doi:10.1161/HYPERTENSIONAHA.110.168005

25. UCAS Japan Investigators. The natural course of unruptured cerebral aneurysms in a Japanese cohort. New England Journal of Medicine. 2012; 366(26):2474-82
26. Agyemang C, Kunst AE, Bhopal R, et al. Hypertension in Dutch and English ethnic minorities. Blood pressure better controlled in English groups than in Dutch groups. Ned Tijdschr Geneeskd. 2011;155:A3318.
27. Sison J, Divinagracia R, Nailes J. Asian management of hypertension: Current status, home blood pressure, and specific concerns in Philippines (a country report). *J Clin Hypertens (Greenwich)*. 2020;22(3):504-507. doi:10.1111/jch.13802
28. Tada Y, Wada K, Shimada K et al. Roles of Hypertension in the Rupture of Intracranial Aneurysms. *Stroke*. 2014;45:579-586 *579* DOI: 10.1161/STROKEAHA.113.003072
29. Kim JH, Jeon J, Kim J. Lower risk of subarachnoid hemorrhage in diabetes: a nationwide population-based cohort study. *Stroke and Vascular. Neurology* 2021;6e: e000601. Doi:10.1136/svn-2020-000601
30. Choi HS, Yoon JW, Seo, H, Kang K and Kim JT. Diabetes is not protective against the formationof unruptured cerebral aneurysm. *Clinical Neurology and Neurosurgery*. 2021.
31. Badjatia N, Topcuoglu MA, Buonanno FS, et al. Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. *Crit Care Med.* 2005;33:1603–1609.
32. Harpentier C, Audibert G, Guillemin F, et al. Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. *Stroke.* 1999;30:1402–1408.
33. Dorhout Mees SM, van Dijk GW, Algra A, Kempink DR, Rinkel GJ. Glucose levels and outcome after subarachnoid hemorrhage. *Neurology.* 2003;61:1132–1133.
34. Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. *Stroke.* 2006;37:199–203.
35. Kruyt ND, Roos YW, Dorhout Mees SM, et al. High mean fasting glucose levels independently predict poor outcome and delayed cerebral ischemia after aneurysmal subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry.* 2008;79:1382–1385.
36. Lanzino G, Kassell NF, Germanson T, Truskowski L, Alves W. Plasma glucose levels and outcome after aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 1993;79:885–891.
37. Isaksen J, Egge A, Waterloo K, *et al* Risk factors for aneurysmal subarachnoid haemorrhage: the Tromsø study *Journal of Neurology, Neurosurgery & Psychiatry* 2002;73:185-187.
38. Woo D, Khoury J, Haverbusch MM, et al. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. *Neurology*. 2009;72(1):69-72. doi:10.1212/01.wnl.0000338567.90260.46
39. Chalouhi N, Ali MS, Starke RM, et al.: Cigarette smoke and inflammation: role in cerebral aneurysm formation and rupture. *Mediators Inflamm* 2012:271582, 2012
40. Ho AL, Lin N, Frerichs KU, Du R: Smoking and intracranial aneurysm morphology. *Neurosurgery*77:59–66, 2015
41. Frederick P. Mariajoseph, Leon T. Lai, Cumulative Time of Cigarette Smoking Is Associated with a Greater Risk of Aneurysmal Subarachnoid Hemorrhage and Younger Age at Presentation: A Nationwide Observation Study, World Neurosurgery, Volume 164,2022, Pages e915-e921, ISSN 1878-8750,https://doi.org/10.1016/j.wneu.2022.05.068.
42. Can A, Castro VM, Ozdemir YH, et al. Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation. *Neurology*. 2017;89(13):1408-1415. doi:10.1212/WNL.0000000000004419

43. Feng X, Qian Z , Zhang B et al. Number of Cigarettes Smoked Per Day, Smoking Index, and Intracranial Aneurysm Rupture: A Case–Control Study. Front. Neurol., 31 May 2018 Sec. Endovascular and Interventional Neurology https://doi.org/10.3389/fneur.2018.00380
44. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. Stroke. 1986;17(5):831-5. https://doi.org/10.1161/01. str.17.5.831
45. Greenhoot JH, Reichenbach DD. Cardiac injury and subarachnoid hemorrhage. A clinical, pathological and physiological correlation. J Neurosurg. 1969;30 (5):521-531
46. Melville KI, Blum B, Shister HE et al. Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation. Am J Cardiol. 1963; 12: 781-791.
47. Chien A, Lau V, Yi Q, Chang W. Posterior communicating artery aneurysms demonstrate faster interval growth than other growing aneurysms. *Neuroradiol J*. 2018;31(3):288-291. doi:10.1177/1971400917709621
48. Ban VS, El Ahmadieh TY, Aoun SG, et al. Prediction of Outcomes for Ruptured Aneurysm Surgery. Stroke. 2019 Mar;50(3):595-601. doi: 10.1161/STROKEAHA.118.023771. PMID: 30776998