Comparative Analysis and Quantitative Rupture Risk Assessment of Intracranial Aneurysms

OUWB School of MEDICINE
OAKLAND UNIVERSITY WILLIAM BEAUMONT

Jeremy F. Santamaria[1], Madan Krishnamurthy, Ph.D.[2], Fakhare Alam, PhD[2], Khalid M. Malik, Ph.D. [2], Hesham Zakaria, M.D.[3], Ghaus M. Malik, M.D.[3]

[1]Class of 2022 M.D. Candidate, Oakland University William Beaumont School of Medicine
[2]Department of Computer Science and Engineering, Oakland University
[3]Department of Neurosurgery, Henry Ford Hospital

Introduction

Six million people in the United States, or 1 in 50 people, are afflicted with an unruptured intracranial aneurysm (IA). It has also been estimated that a brain aneurysm ruptures every 18 minutes, with as many as 30,000 people in the United States suffering from ruptured intracranial aneurysms annually[1]. An aneurysm is a weak bulging on the wall of a blood vessel when hemodynamic pressures are too great to resist. Ruptured IA's may present with sudden severe headaches, focal neurological deficits, or even ischemic stroke due to vasospasms caused from ruptured blood contents[12].

Treatment plans for intracranial aneurysms must be weighed critically[2,3], since the risks of these invasive treatment plans may present with permanent neurological disabilities for the patient. Moreover, traditional risk scores for aneurysm rupture like PHASES or UIATS have poor performances in some clinical institutions[13 - 15]. Existing statistical and traditional approaches neither provide accurate rupture prediction nor offer quantitative comparison among a group of risk factors (RF). This study proposes a novel risk assessment methodology, Rupture Criticality Index (RCI), that would fill this knowledge gap.

Aims and Objectives

Aim I: To determine rupture risk assessment for a saccular aneurysm using a hybrid statistical and knowledge-based techniques on different vessels.

Aim II: To incorporate several anterior and posterior circulation locations and different sizes of IA's in determining rupture risk.

Aim III: To evaluate how a combination of intracranial aneurysm risk factors compare to other contributory combinations.

Objectives:

A) Use multivariable analysis and RCI to identify risk factor combinations (or cohorts) that are at highest risk for aneurysm rupture.

B) Compare RCI to Relative Risk (RR) in predicting aneurysm rupture.

C) Compare PHASES and UIATS performance on dataset.

Methods

- Retrospectively analyzed 915 patient records involving treatment for IA in the last 30 years in the Henry Ford Hospital System. We outline 50 risk factors (RF) from 14 variables out of the dataset (Table 1)[4-11].
- Individual RF or RF cohort that has 5 or more ruptured records were included for multivariable analysis (equations 1 – 3). RF cohorts are defined by the combination of aneurysm size, location, and a third RF. Screening for RCI evaluation is illustrated in Figure 1.
- RCI was then obtained by taking the average (equation 4) of the three equations. Relative Risk (RR) was compared against RCI with four RF cohorts[16,17].
- Lastly, PHASES score was applied to 895 patients while UIATS was applied to 215 patients that matched their respective criteria on our dataset. Both traditional score's performances were then evaluated against actual status of aneurysm.

Equations for RCI Calculation:

$$(1)\quad \alpha = \frac{\#\, ruptured\ aneurysms\ with\ RF\ cohort}{Total\ Population\ of\ a\ Subset}$$

$$(2)\quad \beta = \frac{\#\, ruptured\ aneurysms\ with\ RF\ cohort}{Total\ Ruptured\ Population\ of\ a\ Subset}$$

$$(3)\quad \gamma = \frac{\#\, ruptured\ aneurysms\ with\ RF\ cohort}{Total\ Population\ of\ Aneurysms\ with\ RF\ cohort}$$

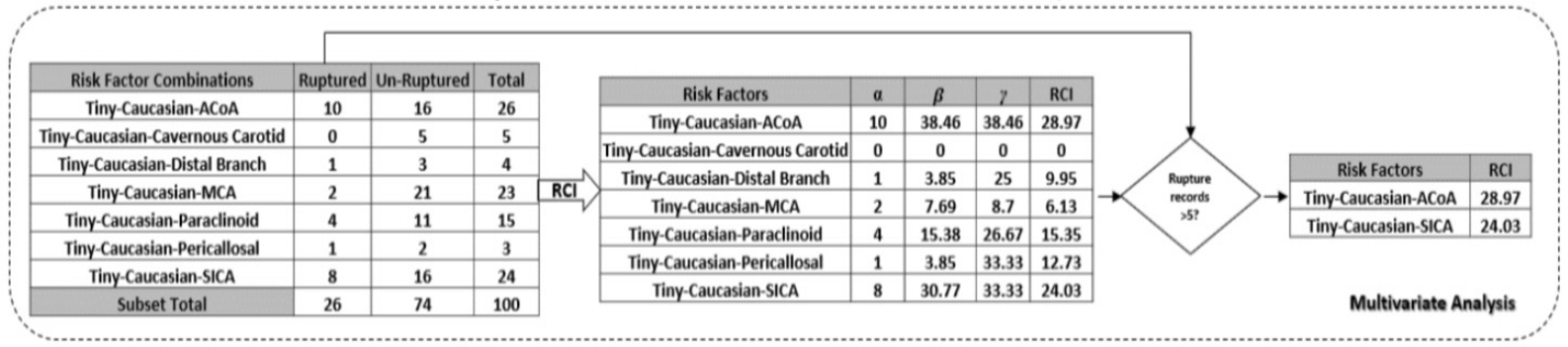
$$(4)\quad RCI = \frac{\alpha + \beta + \gamma}{3}$$

Table 1. Dataset

Variable	Risk Factor	No. Records
Location	ACoA	229
	Basilar SCA	12
	Basilar Tip	63
	Basilar Trunk	14
	Cavernous Carotid	39
	Distal Branch	15
	MCA	160
	Paraclinoid	107
	Pericallosal	26
	PICA	18
	SICA	232
Size	Giant (22.6 mm)	14
	Large (14.6 – 22.5 mm)	67
	Medium (8.3 – 14.5 mm	179
	Small (4.8 – 8.2 mm)	417
	Tiny (≤ 4.7mm)	238
Side	Midline	184
	Bilateral	12
	Left	289
	Right	326
	Unknown	104
Age	≤ 37 years (Gen Y)	61
	38 – 55 years (Gen X)	390
	56 - 73 years (Baby Boomer)	373
	≥ 74 years (Silent Gen)	91

Variable	Risk Factor	No. Records
Gender	Female	695
	Male	220
Ethnicity	Asian/Oriental	18
	Black/African American	371
	Native American	2
	Other	24
	White/Caucasian	500
Multiple Aneurysms	Yes	268
	No	647
HTN	Yes	521
	No	394
Diabetes	Yes	96
	No	819
CVD	Yes	39
	No	876
COPD	Yes	75
	No	840
PKD	Yes	7
	No	908
Family Hx of IA	Yes	22
	No	893
Smoking Status	Current Smoker	372
	Former Smoker	167
	Never Smoked	183
	Unknown	193

Figure 1. Illustration of RCI Calculation with Sample Subsets



Results

- Based on RCI rankings, 75 RF combinations for anterior circulation and 10 for posterior circulation were identified.
- RCI values were normalized on a 1-10 scale and were categorized based on degree of criticality using Jenk's natural breaks method (Table 2).

Table 2. Degree of Criticality

Minor	Mild	Moderate	Severe	Critical
3.46 – 4.83	4.84 – 5.87	5.88 - 6.95	6.96 – 8.28	8.29 - 10

- To compare the utility of RCI to RR, Table 3 demonstrates how RCI notes different degrees of rupture risk while RR stays consistent with the same RF combinations.

Table 3. Comparison between Relative Risk and RCI

RF Cohort (size-location-3rd RF)	Ruptured	Unruptured	Total	Gamma	RR	RCI
Medium – SICA – Right Side	10	9	19	52.63	1.39	8.11
Tiny – ACoA – Baby Boomer	10	9	19	52.63	1.39	6.34
Small – ACoA – Multiple Aneurysms	10	9	19	52.63	1.39	5.58
Tiny – MCA – African American	7	13	20	35	Ref	3.48

- Notable RF cohorts with the greatest risk for rupture based on RCI were identified in Table 4.

Table 4. Critical Risk Factor Cohorts

RF Cohort	Region	Size	Location	3rd RF	RCI
1	Posterior	Medium	Basilar Tip	Male	10
2	Anterior	Small	ACoA	Male	10
3	Anterior	Medium	ACoA	Male	9.87
4	Anterior	Small	SICA	Right Side	9.42
5	Posterior	Large	Basilar Tip	38 – 55 Years	9.35
6	Posterior	Large	Basilar Tip	Caucasian	9.25
7	Anterior	Small	ACoA	≤ 37	8.99
8	Anterior	Small	ACoA	38 – 55 Years	8.67
9	Posterior	Tiny	PICA	56 – 73 Years	8.51

- PHASES and UIATS performances against actual rupture status demonstrates poor clinical performance when applied to our dataset.

Table 5. PHASES and UIATS Scores Performance

Traditional Scores	Recall	Precision	F1-Score	Accuracy
PHASES	0.54	0.51	0.51	0.54
UIATS	0.59	0.59	0.56	0.59

Conclusions

This study presents a novel Rupture Criticality Index that is built from stratifying clinical, morphological, and anatomical features of ruptured and unruptured saccular aneurysms. Prior studies only consider 6-7 vessel locations, while ours follow 11 locations and includes different sizes including aneurysm sizes less than 5 mm. Overall, RCI potentially can be used to help understanding how a group of risk factors contribute towards lifetime aneurysm rupture risk. RCI could be used to make better informed decisions regarding treatment and follow-up managements compared to traditional methods like RR, PHASES, or UIATS.

Our study is limited by the nature of being a retrospective cohort study from a single-institution. Multi-center data may provide a more robust data to improve RCI accuracy and potentially extending our analysis to more than three risk factors, which may even reveal more unique combinations. Our results did not provide every possible patient presentation, but only the most common observed ones from our dataset. Comparing PHASES/UIATS with our proposed grouped based risk identification may be elaborated in the future. Future works involve discovering more combinations using association rule mining with combination of probabilistic models and machine learning techniques

References

1. *Brain Aneurysm Foundation*. [online] Available at: https://www.bafound.org/ [Accessed 25 March 2019].
2. Thompson BG, Brown Jr RD, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly Jr ES, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015 Aug;46(8):2368-400.
3. Bijlenga P, Gondar R, Schilling S, Morel S, Hirsch S, Cuony J, et al. PHASES score for the management of intracranial aneurysm: a cross-sectional population-based retrospective study. Stroke. 2017 Aug;48(8):2105-12.
4. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007 Apr 1;38(4):1404-10.
5. Greving JP, Wermer MJ, Brown RD, Morita A, Juvela S, Yonekura M, et al.. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies.**Lancet Neurol**. 2014; 13:59–66. doi: 10.1016/S1474-4422(13)70263-1
6. Tominari S, Morita A, Ishibashi T, Yamazaki T, Takao H, Murayama Y, et al.; Unruptured Cerebral Aneurysm Study Japan Investigators. Prediction model for 3-year rupture risk of unruptured cerebral aneurysms in Japanese patients.**Ann Neurol**. 2015; 77:1050–1059. doi: 10.1002/ana.24400
7. Kashiwazaki D, Kuroda S; Sapporo SAH Study Group. Size ratio can highly predict rupture risk in intracranial small (<5 mm) aneurysms.**Stroke**. 2013; 44:2169–2173. doi: 10.1161/STROKEAHA.113.001138
8. Sonobe M, Yamazaki T, Yonekura M, Kikuchi H. Small unruptured intracranial aneurysm verification study: SUAVe study, Japan.**Stroke**. 2010; 41:1969–1977. doi: 10.1161/STROKEAHA.110.585059
9. Feigin V, Parag V, Lawes CM, Rodgers A, Suh I, Woodward M, et al.; Asia Pacific Cohort Studies Collaboration. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants.**Stroke**. 2005; 36:1360–1365. doi: 10.1161/01.STR.0000170710.
10. Juvela S, Korja M. Intracranial aneurysm parameters for predicting a future subarachnoid hemorrhage: a long-term follow-up study.**Neurosurgery**. 2017; 81:432–440. doi: 10.1093/neuros/nyw049
11. Broderick JP, Brown RD, Sauerbeck L, Hornung R, Huston J, Woo D, et al.; FIA Study Investigators. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms.**Stroke**. 2009; 40:1952–1957. doi: 10.1161/STROKEAHA.108.542571
12. Frosen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A, Niemela M, Hernesniemi J. Saccular intracranial aneurysm: Pathology and mechanisms. Acta Neuropathologica. 212 vol: 123 (6) pp: 773-786. doi:10.1007/s00401-011-0939-3.
13. Molenberg R, Aalbers MW, Mazuri A, et al. The Unruptured Intracranial Aneurysm Treatment Score as a predictor of aneurysm growth or rupture. *Eur J Neurol*. 2021;28(3):837-843. doi:10.1111/ene.14636
14. Feghali J, Gami A, Xu R, et al. Application of unruptured aneurysm scoring systems to a cohort of ruptured aneurysms: are we underestimating rupture risk?. *Neurosurg Rev*. 2021;44(6):3487-3498. doi:10.1007/s10143-021-01523-3
15. Pagiola I, Mihalea C, Caroff J, et al. The PHASES score: To treat or not to treat? Retrospective evaluation of the risk of rupture of intracranial aneurysms in patients with aneurysmal subarachnoid hemorrhage. *J Neuroradiol*. 2020;47(5):349-352. doi:10.1016/j.neurad.2019.06.003
16. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. Apr 2007;38(4):1404-1410.
17. Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends onrisk factors: a prospective Finnish cohort study. Stroke. Jul 2014;45(7):1958-1963.

Acknowledgements

This study is based upon work supported by the Brain Aneurysm Foundation, Oakland University, and Department of Neurosurgery at Henry Ford Hospital.