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Rupture Resemblance Score (*RRS*)—Toward Risk Stratification of Unruptured Intracranial Aneurysms Using Hemodynamic-Morphological Discriminants

Jianping Xiang, PhD^{1,2,3}, Jihnhue Yu, PhD⁵, Hoon Choi, MD^{1,6}, Jennifer M. Dolan Fox, PhD^{1,3}, Kenneth V. Snyder, MD PhD^{1,3,4}, Elad I. Levy, MD^{1,3,4}, Adnan H. Siddiqui, MD PhD^{1,3,4}, and Hui Meng, PhD^{1,2,3}

¹Toshiba Stroke and Vascular Research Center, University at Buffalo, The State University of New York, Buffalo, NY, USA

²Department of Mechanical and Aerospace Engineering, University at Buffalo, The State University of New York, Buffalo, NY, USA

³Department of Neurosurgery, University at Buffalo, The State University of New York, Buffalo, NY, USA

⁴Department of Radiology, University at Buffalo, The State University of New York, Buffalo, NY, USA

⁵Department of Biostatistics, University at Buffalo, The State University of New York, Buffalo, NY, USA

⁶Department of Neurosurgery, Upstate Medical University, Syracuse, NY, USA

Abstract

Objective: We previously developed three logistic regression models for discriminating intracranial aneurysm rupture status from 119 aneurysms based on hemodynamic-morphological parameters. Now we exploit their use as a tool for “predicting” rupture risk with a defined rupture resemblance score.

Methods: We collected 3D images of 85 consecutive aneurysms, applied the 3 regression models and compared model performance at predicting rupture status against anecdotal metrics—aneurysm size and aspect ratio. Then we reinterpreted the model-predicted probability as Rupture Resemblance Score (*RRS*), where the higher the score the closer the resemblance to previously known rupture components. We applied *RRS* prospectively to 4 unruptured aneurysms with borderline treatment decision.

Results: All three models yield excellent sensitivity (0.78–0.83) and specificity (0.78–0.84) at a cutoff score of 50%, whereas aneurysm size and aspect ratio showed poor sensitivities (0.28 and 0.33, respectively). Lowering the cutoff score to 30% improved sensitivity to 0.90. *RRS* identified not only the majority of the ruptured aneurysms, but also some unruptured ones that highly

resemble ruptured aneurysms hemodynamically and/or morphologically. The prospective application of *RRS* to unruptured aneurysms shows that *RRS* could provide additional insight for treatment decision.

Conclusions: Previous regression models based on hemodynamic-morphological parameters are able to discriminate rupture in a new cohort in the same population. A higher probability of rupture is associated with larger size ratio, lower normalized wall shear stress and higher oscillatory shear index. *RRS* could potentially stratify rupture risk and assist in treatment decision for unruptured aneurysms.

Keywords

Hemodynamics; Intracranial aneurysm; Morphology; Rupture; Stratification

Introduction

Intracranial aneurysms (IAs) affect as much as 5~8% of the entire population.¹ Aneurysm rupture leads to subarachnoid hemorrhage (SAH), a devastating event with high mortality (45% within the first year) and morbidity (50% of survivors with major disability).^{2, 3} The estimated annual cost for the hospitalized patients with unruptured IAs (UIAs) in the United States is \$522,500,000 and \$1,755,600,000 for patients with SAH.³ Recent advancements in neurovascular imaging have increased the detection of asymptomatic UIAs, placing more pressure on clinicians to decide which UIAs to treat and which ones to observe, since treatments are fraught with risk of complications and high costs.

Currently, aneurysm size is the main quantitative metric in evaluating the rupture risk of UIAs.^{4, 5} However, small aneurysms still account for a large portion of ruptured cases presented clinically.⁶ Subsequently, shape-based morphological parameters have been explored and correlated with rupture.⁶⁻⁸ On the other hand, hemodynamics is widely studied for IAs and believed to play a fundamental role in the mechanisms involved in aneurysm growth and rupture.⁹⁻¹³ A practical goal of IA research is to develop objective models to identify and only treat those UIAs at high risk of rupture.

Rupture risk prediction models should theoretically be built from longitudinal aneurysm data. However, most diagnosed UIAs are defensively treated, leaving only a small number of UIAs for conservative observation and periodical imaging. These cases tend to involve aneurysms small in size with low assumed rupture risks, or aneurysms having no clear or safe surgical options, or patients who refuse treatment. Therefore, models built from longitudinal data tend to be severely skewed and not representing all of high-risk aneurysm features.

However, it is possible to derive rupture status classification models from cross-sectional aneurysm datasets. In a retrospective study of 119 aneurysms,⁹ we identified morphology and hemodynamics that discriminate ruptured from unruptured IAs. Through multivariate logistic regression analysis, we built 3 distinct aneurysm rupture classification models based on morphological, hemodynamic, and combined metrics. Higher probability of rupture status was found to be associated with larger size ratio (*SR*) in the morphological model,

lower normalized wall shear stress (*WSS*) and higher oscillatory shear index (*OSI*) in the hemodynamic model, and all three parameters in combined model.⁹

The objectives of the current study were to validate the rupture status prediction in a new cohort of IAs by the previous built regression models and to explore the potential of these models in risk stratification of UIAs.

Methods

Study Population

We prospectively collected 85 new aneurysms (18 ruptured; 67 unruptured) in 74 consecutive patients imaged at Millard Fillmore Gates Hospital in Buffalo between 2009 and 2010 after receiving Institutional Review Board approval from the University at Buffalo. This cross-sectional dataset was consecutive with the 119 aneurysms in our previous study in which we developed regression models.⁹

Morphological and Hemodynamic Parameter Extraction

Morphological and hemodynamic parameters for each aneurysm were calculated as previously described.^{8, 9} Briefly, 3D images were segmented at the region of interest—aneurysm lumen and adjacent vessels—using the Vascular Modeling Toolkit (www.vmtk.org).¹⁴ An in-house MATLAB code was used to calculate the 3 morphological parameters used in the current study:⁸ *aneurysm size*, *SR*, and *AR*. For computational fluid dynamics (CFD) simulations, finite volume meshes of 0.5–1 million elements generated from ICEM CFD (ANSYS Inc, Canonsburg, PA) were imported into the CFD solver Star-CD (CD Adapco, Melville, NY) to calculate time-resolved 3D velocity and pressure fields. Three pulsatile cycles were simulated, with the last cycle being taken as the output to ensure that numerical stability had been reached. From the flow solutions, we calculated the two most critical hemodynamic parameters:⁹ *WSS* and *OSI*.

Performance Evaluation of the Regression Models

We applied the 3 regression models from our previous study⁹ to each aneurysm of the 85 IAs in the new cohort and calculated their probability of being ruptured. Adopting a 50% probability cutoff, the statistic models classified each aneurysm from the current study as either ruptured (>50%) or unruptured (<50%). The sensitivity (the rate of correct prediction of ruptured IAs) and specificity (the rate of correct prediction of UIAs) for classifying these 85 new aneurysms were calculated by comparing their probability with the actual rupture status at the time of imaging. Classifications were also made from clinically used metrics—aneurysm size (>7mm classified as high risk of rupture)⁵ and aspect ratio (*AR*, >1.6 as high risk of rupture)⁶. To examine if these common classifications can pick out the ruptured IAs in the cohort, we evaluated their sensitivity and specificity. Furthermore, for the three regression models we varied the probability threshold and plotted the resulting sensitivities and specificities to examine its influence on prediction performance in these 85 IAs.

Exploring the Potential of the Regression Models in Risk Stratification of UIAs

We further examined the false-positive cases in the 85 new IAs, namely UIAs classified as ruptured IAs by the regression models. We take an alternative view of the prediction by these regression models, which were originally intended to evaluate the probability of an aneurysm being a ruptured one. When applied to a given UIA, the regression models measure how much the aneurysm in question resembles the ruptured IAs in the original (training) database hemodynamically and/or morphologically. Hence, we reinterpret this probability as the *Rupture Resemblance Score (RRS)*, where the higher the score the closer the resemblance to previously known rupture components. *RRS* can identify unruptured aneurysms that highly resemble rupture aneurysms and thus may merit treatment recommendation. This allows us to explore the potential of these regression models for risk stratification in UIAs in general. In order to illustrate how *RRS* could assist in clinical treatment decision, we then prospectively applied these regression models to 4 additional UIAs encountered in our clinical practice.

Results

Validation of the Regression Models

At a 50% probability cutoff, the 3 hemodynamic-morphological classification models predicted aneurysm rupture status in the new cohort with high sensitivity (0.78, 0.83, and 0.79 for morphological, hemodynamic and combined models, respectively) and specificity (0.81, 0.84, and 0.78 for the 3 models) (Figure 1). In contrast, if used to discriminate ruptured from unruptured IAs, Size and AR showed poor sensitivities (0.28 and 0.33, respectively) and high specificities (both 0.81) (Figure 1).

Exploration of the Models in Risk Stratification of UIAs

Figure 2 demonstrated how the sensitivity and specificity of the 3 classification models varied with the probability cutoff. Lowering the cutoff threshold increased the sensitivity of rupture classification but reduced the specificity. 50% gave sensitivity and specificity values of around 0.8, but the catastrophic nature of SAH necessitated a high sensitivity for identifying ruptured IAs. From Figure 3, a lower threshold of 30% delivered higher sensitivity values (0.89, 0.89, and 0.94 for morphological, hemodynamic and combined predictive models respectively) and acceptable specificity values (0.67, 0.67, and 0.72). At 30% probability cutoff, the combined model produced higher sensitivity and specificity than the hemodynamic and the morphological models.

At 30% probability cutoff, we encountered 22, 22, and 19 cases of false-positive prediction out of the 67 unruptured cases using the morphological, hemodynamic and combined models, respectively. As shown in Figure 3, these UIAs bore high resemblance to ruptured IAs in morphology (complex geometry, high SR) and hemodynamics (complex flow pattern, low WSS, high OSI). Clinical records showed that all these aneurysms were treated immediately. This suggests that *RRS* could be valuable at identifying those potentially dangerous UIAs that highly resemble ruptured IAs hemodynamically and/or morphologically.

Illustrative Cases

The 4 additional prospective UIA cases anecdotally support that *RRS* could assist treatment decision-making for various types of aneurysms, especially those with borderline treatment decision. The angiographic images, flow field, WSS and OSI of these aneurysms are shown in Figure 4. We used a conservative criterion that if one or more of the 3 regression models gave an *RRS* greater than 30%, the aneurysm probably should be treated. The final treatment decisions of these aneurysms were made based on our surgeon's clinical judgment.

Case 1: *RRS* could confirm decision to treat.—Patient 1 was admitted with symptoms of dizziness and nausea for a few months. Digital subtraction angiography (DSA) revealed an 8mm right posterior inferior cerebellar artery (PICA) aneurysm, located immediately adjacent to the takeoff of the right PICA (Figure 4). Our clinical team intended to treat this aneurysm based on its high 2D SR measured from the angiogram,^{15, 16} despite its size being slightly larger than the conventional threshold of 7mm. We calculated its 3D morphological and hemodynamic parameters. Its high SR (9.6), low normalized WSS (0.1), and high OSI (0.0179) (Figure 4) gave rather high *RRS*: 100%, 93.7% and 100% from morphological, hemodynamic and combined models, respectively. Our models could confirm the decision to treat. In reality this patient was treated by clipping without any complication.

Cases 2&3: *RRS* could inform which aneurysms to treat among multiple aneurysms.—Patient 2 presented with right hand and foot numbness. Diagnostic DSA revealed 3 aneurysms located at: left internal carotid artery (ICA, 10mm), left middle cerebral artery (MCA, 3mm), and basilar tip (7mm). The left ICA and MCA aneurysms are shown as Case 2 and basilar tip aneurysm is shown as Case 3 in Figure 4. Our clinical team initially decided to treat the left ICA aneurysm due to the symptoms. We calculated the SR, WSS and OSI for all 3 aneurysms and plugged the values into the hemodynamic-morphological models to evaluate their *RRS*. The *RRS* of the left ICA aneurysm are 52.7% (morphological), 27.5% (hemodynamic), and 38.6% (combined). *RRS* of the left MCA aneurysm was less than 20% from all three models. The basilar tip aneurysm had *RRS* of 82.1%, 55%, and 79.5%, despite its smaller size (7mm compared to 10mm of the ICA aneurysm). This additional information provided by *RRS* could help us to decide to treat basilar tip aneurysm in addition to the left ICA aneurysm. In reality both left ICA and basilar tip aneurysms were treated by coiling without recurrence.

Case 4: *RRS* could guide decision to treat.—Patient 3 with a family history of IAs was found to harbor an unruptured 5mm right MCA aneurysm during screening. Based on the traditional metrics of size, this small aneurysm should possess low risk and could be left to monitor. We calculated the morphological (SR=2.15) and hemodynamic metrics (WSS=0.18, OSI=0.0115). Despite its small size, *RRS* was calculated to be 30.8%, 78.5% and 63.3% from morphological, hemodynamic and combined models. This rupture resemble is considered high (>30%). Based on this information, we could decide to treat the aneurysm. In reality, this MCA aneurysm was treated by stent-assisted coiling without recurrence.

Discussion

While large trials like ISUIA^{4, 5} and the Japanese studies^{17, 18} have looked at rather simplistic predictors of rupture such as size, more comprehensive models involving both hemodynamic and morphological features are required for predicting rupture risk. The recently released new American Heart and Stroke Association guidelines for IA management¹⁹ recommends to consider morphological and hemodynamic characteristics of the aneurysm in determining rupture risk assessment and optimal treatment, in addition to the size, location, and patient demographics. Towards this end, we previously built three hemodynamic-morphological discrimination models from 119 cross-sectional aneurysm samples (the training set) to classify rupture status.⁹ This current study demonstrates that these regression models are able to predict aneurysm rupture status with high sensitivity and specificity in a testing set of a new IA cohort. This successful validation further supports our original conclusion that morphology and hemodynamics can be used to discriminate ruptured from unruptured aneurysms.⁹

Our current study not only validates the previously developed 3 rupture classification models in predicting aneurysm rupture status in a new cohort from the same center, but more importantly, it proposes and demonstrates the potential clinical utility of *RRS* in risk stratification for UIAs. Using *RRS* to stratify risk in UIAs incorporates an implicit hypothesis: the more similar an aneurysm in question is to ruptured IAs (hemodynamically and/or morphologically), the more likely this aneurysm is to experience rupture in the future. This hypothesis is difficult to test because longitudinal data of UIA (including those going on and rupture) is rare and not easy to obtain. The available longitudinal samples are small and tend to be skewed, but they may become increasingly available. For example, routine screening for IAs has recently been introduced into clinical practice in Japan, and could make longitudinal validation possible.^{20, 21}

In this study, we demonstrated the trend of sensitivity and specificity by varying the *RRS* cutoff. We favor an *RRS* cutoff of 30% over 50% for clinical use, since it gives higher sensitivities (around 0.9) and acceptable specificities (around 0.7), and high sensitivity is required for a metrics that aims at identifying dangerous IAs given the high morbidity and mortality of aneurysmal SAH. However, treatment decisions are complicated and multifactorial. Choosing a *RRS* cutoff value for informing treatment decision in reality depends on the preferences and judgments of different surgeons and should be considered with other factors such as the patient's medical conditions, age, and surgical risks. After all, *RRS* only provides an additional piece of information, which is quantitative and related to IA pathophysiology,²² to consider, and in some difficult borderline cases may provide the needed insight and direction. The 3 predictive models do not compete with each other, since the morphological and hemodynamic models calculate *RRS* from different perspectives, while the combined model consolidates the two.

Our results indicate low WSS and high OSI as hemodynamic discriminators of rupture status. This is in contrast to studies by Cebal et al,¹⁰ which find that high WSS associates with ruptured aneurysms. WSS can drive vascular remodeling and, as we have recently proposed, both low WSS and high WSS may independently facilitate IA growth and rupture,

albeit via different biological mechanisms.^{22, 23} It seems that our studies (current and Xiang et al⁹) and the study by Cebral et al¹⁰ deal with different patient populations that might be skewed towards different types of IAs; i.e. those dominated by low WSS vs. high WSS. Our rupture discrimination models are accurate for our single-center patient population, but not necessarily for other populations, although many recent publications have also identified low WSS as the rupture indicator.^{11, 12, 24, 25} Thus, these classification models and the derived *RRS* may be useful at centers where low WSS has been associated with ruptured aneurysms in their patient populations.

RRS would be of great interest to the neurosurgical community, as many of them struggle to select unruptured aneurysms for treatment. However, we should not overstate the clinical utility of this score, and currently the clinical application of *RRS* is limited. First of all, further investigation is needed to elucidate the role of low and high WSS in aneurysm rupture mechanisms. Secondly, we should perform true prospective evaluation of the predictive ability of *RRS* in large scale of followed aneurysms in multi-centers. This study could potentially be used as foundation for conducting a prospective trial. Third, current *RRS* does not take into account patient demography, medical condition and surgical risks, which may dominate the ultimate treatment decision. The rupture risk of an aneurysm from morphology and hemodynamics is one of many factors to consider in the treatment of a given aneurysm. Thus, currently the surgeon's clinical judgment must ultimately prevail the decision-making.

There are several limitations in this study. First, the number of new cases is small and they come from the same hospital as our previous study.⁹ Even with the increased sample size in the current study, there may still be a selection bias, and our conclusion may not be valid for different patient populations. In the future, multicenter studies with larger multi-population are needed to validate these models or even build new models.²⁶ Second, aneurysm geometries may have been affected by the rupture event, although increasing evidence indicates that aneurysms do not shrink when they rupture.^{8, 27} Third, *RRS* cannot be used to predict the time span in which a given aneurysm may rupture. *RRS* is different from rupture rates from prospective aneurysm patients like ISUIA data.^{4, 5} However, *RRS* measures how much an UIA hemodynamically and morphologically resembles the ruptured IAs in our database, which is helpful for UIA treatment decision making.

Conclusions

The previously developed statistical rupture classification models based on morphometrics and hemodynamics have been validated by a new cohort of aneurysms. *RRS* calculated from these models has the potential for risk assessment of UIAs in the clinical practice. The clinical application of *RRS* needs further investigations.

Abbreviations

AR	aspect ratio
CFD	computational fluid dynamics

DSA	digital subtraction angiography
IA	intracranial aneurysm
ICA	internal carotid artery
MCA	middle cerebral artery
OSI	oscillatory shear index
PICA	posterior inferior cerebellar artery
RRS	Rupture Resemblance Score
SAH	subarachnoid hemorrhage
SR	size ratio
WSS	wall shear stress
WSSG	wall shear stress gradient
UIA	unruptured intracranial aneurysm

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Figure 1.

Sensitivity and specificity of predictions by the three regression models (M1: Morphological model, M2: Hemodynamic model, M3: Combined model; 50% probability cutoff) and by clinical metrics–Size and AR (threshold at 7mm and 1.6, respectively) for 85 aneurysms.

Figure 2.

Sensitivity and specificity of predictions vs. probability cutoffs for the three regression models. 30% cutoff delivers a higher sensitivity than 50%, and the combined model gives the best performance at this cutoff.

Figure 3.

Examples of false-positive prediction cases, where UIAs were classified as ruptured IAs. These aneurysms highly resembled ruptured IAs. In reality, they were treated right away (unrelated to the calculation).

Figure 4.

Four prospective unruptured aneurysm cases to demonstrate how the 3 models could help the treatment decision-making. The first case was a PICA aneurysm with large SR and *RRS* confirmed decision to treat. The second and third cases were from a patient with 3 aneurysms; large *RRS* favored treatment of the basilar tip aneurysm in addition to the symptomatic ICA aneurysm. The fourth case was a 5mm MCA aneurysm, and large *RRS* favored decision to treat.