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Validation of the Ruptured Arteriovenous Malformation Grading Scale in a pediatric cohort

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OBJECTIVE Pediatric brain arteriovenous malformations (AVMs) are the leading cause of spontaneous intracranial hemorrhage (SICH) in children. Although the incidence of SICH is low in pediatric populations, such events cause substantial morbidity. The recently created Ruptured Arteriovenous Malformation Grading Scale (RAGS) is proposed as a reliable and novel grading system to specifically serve as a predictor of clinical outcomes in patients following AVM rupture, similar to the Hunt and Hess (HH) grade for ruptured aneurysms. While these data are promising, pediatric patients were notably absent from the original study validating the RAGS. Therefore, correlation of the RAGS score with clinical outcomes following AVM rupture in individuals younger than 18 years of age using the RAGS score is needed. The objective of this study was to validate the RAGS in a cohort of pediatric patients with AVMs who presented with hemorrhage, thereby demonstrating the score's generalizability, and expanding its external validity.

METHODS A cohort of children with ruptured AVMs were retrospectively reviewed. Using disability, measured by the modified Rankin Scale (mRS), as the response variable, the area under the receiver operating characteristic curve (AUROC) was calculated for patients based on their RAGS scores for three time periods. The AUROC values were then compared with those generated by two commonly used clinical grading systems, the HH classification and Glasgow Coma Scale.

RESULTS A total of 81 children who presented with ruptured AVMs were included in the study, with a mean follow-up duration of 4 years. The RAGS score outperformed other clinical grading scales in predicting mRS scores, with AUROC values of 0.81, 0.82, and 0.81 at three distinct follow-up periods.

CONCLUSIONS The RAGS score correlated well with the clinical outcome after AVM rupture in pediatric patients. Additional validation studies across multiple treatment centers are needed to further demonstrate the generalizability of the scoring system.

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KEYWORDS arteriovenous malformation; pediatric; disability; vascular disease; vascular disorders

Pediatric brain arteriovenous malformations (AVMs) are the leading cause of spontaneous intracranial hemorrhage (SICH) in children (< 18 years of age), accounting for 50% of pediatric SICH cases.[1–3] Although the incidence of SICH is low in pediatric populations (approximately 1.1–4.5 per 100,000), such events can result in devastating neurological injury.[1,2]

Clinical outcomes following AVM rupture in pediatric populations are varied, and a standardized method for predicting clinical outcomes is lacking.[4–6] The high proportion of pediatric SICH cases attributable to ruptured AVM underscores the need for a prognostication tool to predict clinical outcomes following AVM rupture.[1,5,6]

Historically, grading scales for subarachnoid hemorrhage (e.g., Hunt and Hess [HH]), ICH, and trauma (i.e., Glasgow Coma Scale [GCS]) have been used to predict clinical outcomes in patients presenting with ruptured AVM and determine the course of treatment in patients

ABBREVIATIONS AUROC = area under the receiver operating characteristic curve; AVM = arteriovenous malformation; GCS = Glasgow Coma Scale; HH = Hunt and Hess; mRS = modified Rankin Scale; RAGS = Ruptured Arteriovenous Malformation Grading Scale; SICH = spontaneous intracranial hemorrhage.

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with brain AVMs. However, there is evidence to suggest that clinical outcomes following ICH secondary to AVM rupture differ from those following ICH caused by aneurysmal rupture or hypertensive hemorrhage.[7–11]

To address the lack of a specific predictive grading scale for clinical outcomes following AVM rupture, the Ruptured Arteriovenous Malformation Grading Scale (RAGS), a 9-point grading scale derived from the HH classification for subarachnoid hemorrhage (1–5 points), patient age (0–2 points), presence of deep venous drainage (0–1 point), and eloquent cortex involvement (0–1 point), was recently developed. The RAGS score was intended to organize and normalize hemorrhaged AVM cases to form a benchmark among surgeons and centers.[12] In the first study to validate the RAGS score, Silva et al. found that it outperformed other commonly available grading scales in predicting clinical disability across multiple follow-up periods as determined by modified Rankin Scale (mRS) scores.[12] Therefore, the RAGS has been proposed as a reliable and novel grading system to specifically serve as a predictor of clinical outcomes in patients following AVM rupture, similar to the HH grade for ruptured aneurysms.[12]

Pediatric patients were not included in the study by Silva et al., and it is unclear if the RAGS is generalizable to patients with a ruptured AVM who are younger than 18 years.[1,4] All patients in the study who were younger than 35 years were analyzed as a single age group, despite that, in prior studies, outcomes in pediatric patients following rupture and microsurgical resection have been shown to be different from those in adults.[2,4,12] While the score lends itself to straightforward and rapid calculation, scoring systems designed for adult patients sometimes require adjustments to increase utility in pediatric patients.[4,6,12] This study aimed to determine the score's validity in predicting disability across multiple time points in a cohort of children presenting with ruptured brain AVMs.

Methods

Patient Cohort

A prospectively maintained database of patients with AVMs at the University of California, San Francisco was analyzed for the period from June 1998 to January 2017. All children (aged ≤ 18 years) were included. The initial AVM presentation was defined as the clinical event that led to initial presentation and subsequent diagnosis of the malformation. Modes of AVM presentation were stratified into hemorrhage, seizure, persistent focal neurological deficit, headache, coma, combinations of those, and incidental. Hemorrhagic AVM presentation was defined as any clinically symptomatic event (sudden-onset headache, seizure, or neurological deficit) with signs of acute, intracerebral hemorrhage on head imaging (CT or brain MRI) or based on CSF sampling at the time of the inciting event. Only patients who presented with hemorrhage were included in downstream analysis.

Data Collection

All malformations were diagnosed and further characterized based on brain MRI and cerebral DSA of the internal and external carotid arteries and the vertebrobasilar system. The radiological studies were reviewed independently by neuroradiologists based on original images and coded on predefined database forms. Morphological variables used in the present analysis included AVM size (measured as maximum nidus diameter in millimeters on pretreatment angiography or brain MRI), AVM location (classified as temporal, frontal, deep, cerebellar, brainstem, or parieto-occipital), laterality (left vs right), supra versus infratentorial, and eloquence (eloquent or noneloquent). Venous drainage patterns were categorized as angiographic drainage into the superficial veins or sinuses, exclusive drainage into the deep venous system, and combined superficial and deep venous drainage.

The HH grade, GCS score, and RAGS score were calculated for each patient by retrospectively reviewing admission documentation. The notes used to determine the scores were generated by clinical assessment of symptomatic presentation and were based on assessment by a neurologist or neurosurgeon. Patients with insufficient notation to calculate scores in a standardized fashion were subsequently excluded. Disability was assessed using the pediatric mRS at three follow-up periods following initial presentation. The mRS scores were dichotomized into favorable (0–2) and unfavorable (3–6) for downstream analysis. Treatment modalities for patients were decided based on multidisciplinary discussion between the neurology, neurosurgery, radiation oncology, and neurointerventional radiology departments and were assessed by retrospective chart review. Patients were grouped according to the initial treatment modality used. Additionally, patient demographics (age and sex) were gleaned by retrospectively analyzing patient notes.

Statistical Analysis

To assess the validity of the model in a pediatric cohort, the area under the receiver operating characteristic curve (AUROC) was calculated for mRS outcome at a total of three time periods: follow-up between initial treatment and 9 months, follow-up between 9 and 15 months, and follow-up between 15 months and the end of follow-up. These follow-up ranges were used because not all patients received follow-up at the same time points. Prior to the AUROC analysis, mRS outcome was dichotomized into favorable (mRS scores 0–2) and unfavorable (mRS scores 3–6). Standard logistic regression and AUROC calculation was performed for this binary response variable at each of the follow-up time points. The RAGS score was compared against the other grading system scores for each patient by applying the same AUROC analysis. All statistical analyses were performed in R version 3.5.1 and RStudio version 1.1463 (The R Foundation).

Results

Overall, 119 of the total cohort of 189 patients presented with spontaneous hemorrhage. Of these, 81 patients had sufficient clinical information in the electronic health record to allow retrospective clinical grading. The cohort was 56% male and had a mean age of 11.8 years. The mean AVM size for the cohort was 2.6 cm, and 35% of AVMs had associated aneurysms. There were 31 (38%)

TABLE 1. Clinical and demographic characteristics of the patient cohort

	Value (n = 81)
Mean age, yrs (SD)	11.8 (4.3)
Male sex, n (%)	45 (56%)
HH grade, n	
I	11
II	32
III	19
IV	13
V	6
GCS score, n	
13–15 (mild)	57
9–12 (moderate)	10
3–8 (severe)	14
Spetzler-Martin score, n	
1	23
2	15
3	24
4	17
5	2
Mean AVM size, cm (SD)	2.6 (1.8)
Eloquent, n (%)	43 (53%)
Deep drainage, n (%)	45 (56%)
Left-sided, n (%)	42 (52%)
AVM location, n	
Frontal	21
Parieto-occipital	16
Temporal	11
Cerebellar	9
Deep	15
Periventricular	9
Associated aneurysm, n (%)	28 (35%)
Treatment, n	
Resection	31
Stereotactic radiosurgery	24
Embolization	25
Medical management only	1
Mean FU duration, yrs	3.9

FU = follow-up.

AVMs in the cohort treated by resection, 24 (30%) treated by Gamma Knife radiosurgery, and 25 (31%) treated by embolization. The mean follow-up for the cohort was 3.9 years (Table 1).

The range of RAGS scores in the cohort was 1 to 7. The scoring distribution was 3 patients with a RAGS score of 1, 17 patients with a RAGS score of 2, 18 patients with a RAGS score of 3, 16 patients with a RAGS score of 4, 16 patients with RAGS scores of 5, 9 patients with a RAGS score of 6, and 2 patients with a RAGS score of 7 (Fig. 1).

The RAGS score outperformed the other clinical grading scales tested at all three time points, generating AUROC values of 0.81, 0.82, and 0.81 at the three follow-up periods, respectively. Comparatively, HH grades generated AUROC values of 0.79, 0.77, and 0.66, and GCS scores generated AUROC values of 0.72, 0.75, and 0.71. A summary of AUROC analysis for the prediction of disability using mRS scores at the three follow-up time points is displayed in Table 2.

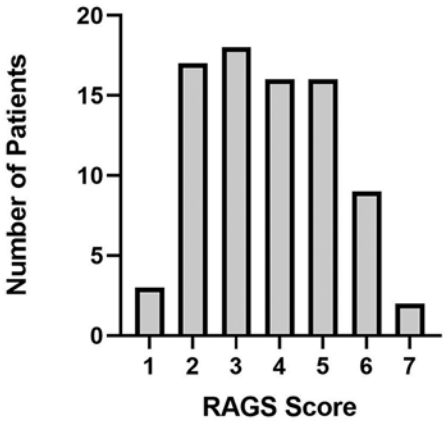

FIG. 1. Bar graph showing RAGS score distribution among the patient cohort.

To improve the predictive value of the RAGS score for pediatric patients, variables (AVM size using Spetzler-Martin scoring, diffuse vs compact nidus, seizure on presentation, presence of an associated aneurysm, and focal neurological deficit on presentation) not included in the initial analysis were added and subsequently tested at each of the three follow-up time points. While accounting for seizures on presentation and AVM size using the point system established in Spetzler-Martin grading improved AUROC values at one or more time points, no individual variables or combination of variables improved AUROC across all three follow-up time points. Additionally, the treatment modality used and subgroups of pediatric age had no impact on patient outcomes. The optimization of the RAGS using the aforementioned variables is shown in Table 3.

Discussion

Arteriovenous malformation rupture often carries devastating consequences.[1,7,13] Clinical tools with long-term prognostic value are needed and may influence diagnostic and treatment algorithms for patients with brain AVMs.[1,12] This is especially true for children, for whom ruptured AVMs account for a much higher proportion of SICHs (30% to 50%) than in adults (1.4% to 2%).[1,3] Additionally, due to their younger age, children experience the associated posthemorrhage disabilities over a greater number of years. With untreated AVMs, the annual risk of rupture in children is 2% to 4%, and that risk is significantly reduced after treatment.[1,4] The current shortage of reliable outcome predictors in this population warrants further investigation.

The RAGS score was designed to organize and nor-

TABLE 2. AUROC for prediction of dichotomized mRS scores at three follow-up points among the clinical grading systems assessed

Predictor	AUROC 1st FU	AUROC 2nd FU	AUROC 3rd FU
RAGS	0.81	0.82	0.81
HH	0.79	0.77	0.66
GCS	0.72	0.75	0.71

malize hemorrhagic AVM cases to form a benchmark among physicians and treatment centers. The score was intended to further characterize patients with ruptured AVMs at presentation, regardless of the treatment modality, and provide clinically meaningful results.[12] The RAGS score utilizes components of the neurological examination, combined with data on several morphological AVM characteristics, to gain insight into patient prognosis.[12] The score can be calculated quickly and efficiently and can be readily used by treating clinicians of different specialties. The scoring system can potentially help providers benchmark their results against anticipated outcomes, and may be used to better explain otherwise unexpected patient outcomes following ruptured AVM treatment.[12]

The RAGS score showed promise in its initial validation for its ability to predict morbidity over time in patients with ruptured AVMs; however, a notable shortcoming of the initial study was that all patients younger than 35 years were grouped in the same outcome cohort. This is problematic, as there are many demographic and clinical characteristics of AVMs in children that warrant their study as a unique population, rather than be included with adults.[6,12,13] Our goal with the current study was to examine the validity of the score in a population of children with ruptured AVMs to see if the score's strong ability to predict outcomes (AUROC > 0.8 across adult cohorts) remained consistent in this important population.

We found excellent concordance between RAGS scores and disability on follow-up using serial dichotomized mRS scores. An AUROC of 0.5 indicates no discrimination whereas an AUROC of 1 indicates perfect discrimination. Generally, an AUROC of 0.8 is considered clinically useful, and the RAGS met or exceeded this threshold at all time points tested.[14] Although all predictive systems measured reliably predicted outcomes, the RAGS score consistently outperformed other scoring systems. Additionally, the RAGS score did not drop off in predictability over time, whereas others did (Fig. 2). Both high predictability and long-term validity of scores should be considered when contemplating their use in clinical settings. In this small retrospective study, the RAGS score performed well in both regards. These results are the first to demonstrate the external validity of the RAGS performance using outside data.

TABLE 3. AUROC for prediction of dichotomized mRS scores at three follow-up points using the RAGS score plus additional variables to optimize the score for pediatric patients

Variable Added to RAGS	AUROC 1st FU	AUROC 2nd FU	AUROC 3rd FU
Aneurysm	0.80	0.79	0.80
AVM size*	0.78	0.82	0.87
Seizure	0.82	0.82	0.80
Diffuse nidus	0.79	0.81	0.85
Focal deficit	0.80	0.81	0.83

* Using the Spetzler-Martin grading system.

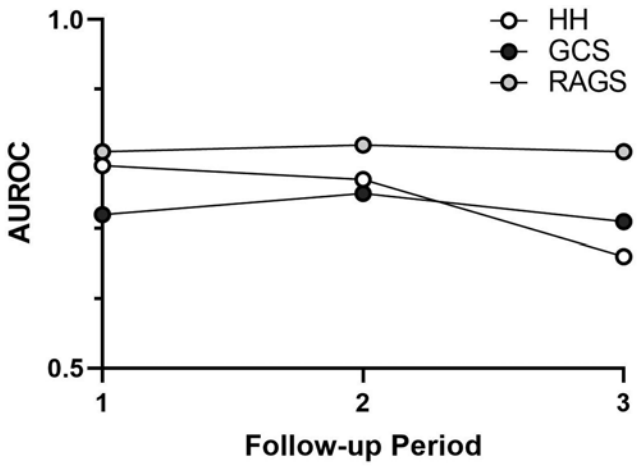

FIG. 2. Line graph showing AUROC values at the three follow-up time points for the clinical grading systems tested (HH, GCS, and RAGS).

There are several ways in which this score may be useful in pediatric patients with ruptured brain AVMs.[15,16] The first is in the hospital setting where prognosis may influence diagnostic and treatment algorithms for patients. Additionally, the score can be used to help counsel caregivers of pediatric patients on expected outcomes and the potential for recovery following AVM rupture. While recovery times between children and adults may differ due to anatomical and physiological differences, the RAGS score offers a standardized method to approximate a reasonable prediction of outcomes in both groups. As it is calculated based on examination findings and morphological AVM characteristics, the score is easily calculated and can be used by trainees and experienced staff alike. The RAGS score can also be used as a communication tool between healthcare providers and as a prognostic indicator across patients of different age groups.

Study Limitations

The results of this study should be interpreted in the context of several limitations. This was a retrospective evaluation of a prospectively enrolled cohort and may be subject to recall bias. Additionally, the cohort represents patients from a single institution, and, thus, sampling bias may have occurred, and more nuanced associations seen in larger multicenter studies may have gone undetected. Both the initial clinical assessment (HH) and clinical outcome (mRS), although based on standardized scales that are used universally, are subjective. Validation from other centers will improve the generalizability of these

findings. While the RAGS score holds prognostic value for pediatric patients with ruptured brain AVMs, clinicians and parents may prioritize the preservation of life at all costs in the initial decision-making process for these patients, and, therefore, the score may hold less clinical utility in a practical sense. Furthermore, several variables not accounted for in the RAGS would be expected to influence outcomes in children with ruptured AVMs (e.g., AVM location). The study was somewhat limited by the lack of usable clinical notes in several children who presented prior to electronic health record conversion, reducing the number of patients included in the final analysis. A mean follow-up time of 3.9 years, while similar to that in the original RAGS paper (4 years), may not be representative of outcomes over longer follow-up periods for children, especially younger ones. Finally, this study is unable to directly determine if applying the RAGS prospectively will enhance diagnostic accuracy or influence treatment algorithms. However, the value of this score is based on its ability to combine information from standardized clinical assessments with morphological characteristics available via standard imaging techniques, to potentially provide clinicians with more precise estimates of the probability outcomes for children with ruptured AVMs. Continued validation based on external data will improve the generalizability of these findings.

Conclusions

In clinical practice, the ability to reliably predict long-term patient disability is crucial to normalize ruptured AVM cases between providers across treatment centers. The RAGS score has the potential to become a much-needed tool for clinicians in the evaluation of patients, including children, presenting with hemorrhagic brain AVMs. The development and validation of this scoring system have established a strong correlation between RAGS scores and neurological deficits over time. While the results of this study are promising, additional validation studies across multiple treatment centers are needed to further demonstrate generalizability of the RAGS.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Abla, Garcia, Rutledge. Acquisition of data: Garcia, Rutledge, Winkler, Carrete, Morshed, Lu, Saggi. Analysis and interpretation of data: Garcia, Rutledge. Drafting the article: Garcia, Carrete. Critically revising the article: Abla, Garcia, Rutledge, Winkler, Morshed, Lu. Reviewed submitted version of manuscript: Abla, Winkler, Carrete, Morshed, Lu, Saggi, Fox, Fullerton, Kim, Cooke, Hetts, Lawton, Gupta. Statistical analysis: Garcia. Administrative/technical/material support: Abla.

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