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The natural history of AVM hemorrhage in the posterior fossa: comparison of hematoma volumes and neurological outcomes in patients with ruptured infra- and supratentorial AVMs

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Abstract

Object—Patients with posterior fossa arteriovenous malformations (AVMs) are more likely to present with hemorrhage than those with supratentorial AVMs. Observed patients subject to the AVM natural history should be informed of the individualized effects of AVM characteristics on the clinical course following a new, first-time hemorrhage. The authors hypothesize that the debilitating effects of first-time bleeding from an AVM in a previously intact patient with an unruptured AVM are more pronounced when AVMs are located in the posterior fossa.

Methods—The University of California, San Francisco prospective registry of brain AVMs was searched for patients with a ruptured AVM who had a pre-hemorrhage modified Rankin Scale (mRS) score of 0 and a post-hemorrhage mRS score obtained within 2 days of the hemorrhagic event. A total of 154 patients met the inclusion criteria for this study. Immediate post-hemorrhage presentation mRS scores were dichotomized into nonsevere outcome (mRS > 3) and severe outcome (mRS > 3). There were 77 patients in each group. Univariate and multivariate logistic regression analyses using severe outcome as the binary response were run. The authors also performed a logistic regression analysis to measure the effects of hematoma volume and AVM location on severe outcome.

Results—Posterior fossa location was a significant predictor of severe outcome (OR 2.60, 95% CI 1.20–5.67, p = 0.016) and the results were strengthened in a multivariate model (OR 4.96, 95% CI 1.73–14.17, p = 0.003). Eloquent location (OR 3.47, 95% CI 1.37–8.80, p = 0.009) and associated arterial aneurysms (OR 2.58, 95% CI 1.09, 6.10; p = 0.031) were also significant predictors of poor outcome. Hematoma volume for patients with a posterior fossa AVM was 10.1

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Disclosure

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

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± 10.1 cm^3 compared with 25.6 ± 28.0 cm^3 in supratentorial locations (p = 0.003). A logistic analysis (based on imputed hemorrhage volume values) found that posterior fossa location was a significant predictor of severe outcome (OR 8.03, 95% CI 1.20–53.77, p = 0.033) and logarithmic hematoma volume showed a positive, but not statistically significant, association in the model (p = 0.079).

Conclusions—Patients with posterior fossa AVMs are more likely to have severe outcomes than those with supratentorial AVMs based on this natural history study. Age, sex, and ethnicity were not associated with an increased risk of severe outcome after AVM rupture, but posterior fossa location, associated aneurysms, and eloquent location were associated with poor post-hemorrhage mRS scores. Posterior fossa hematomas are poorly tolerated, with severe outcomes observed even with smaller hematoma volumes. These findings support an aggressive surgical posture with respect to posterior fossa AVMs, both before and after rupture.

Keywords

arteriovenous malformation; infratentorial; posterior fossa; supplementary grade; Spetzler-Martin grade; microsurgical resection

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Despite recent randomized trials suggesting unruptured arteriovenous malformations (AVMs) fare better with medical management than with intervention, very few patients in ARUBA (A Randomized Trial of Unruptured Brain AVMs) received surgical treatment, the current gold standard for a radiographic cure of brain AVMs.[7,8] The overwhelming majority of treated patients in ARUBA received embolization or radiosurgery, treatment modalities with less than 25% and 70% rates of cure, respectively.[7] In contrast to resection, in which the AVM is immediately obliterated, a radiosurgical cure radiosurgery may require up to 10 years.[5] At our center, we continue to treat patients in the following categories with surgery: a) those with ruptured AVMs, b) those with low-grade AVMs (Spetzler-Martin I or II), and c) those with radiographic evidence of old hemorrhage, even without overt clinical hemorrhage. We also seek to identify risk factors that help patients with unruptured AVMs understand the natural history of their AVM.

Patients with posterior fossa AVMs are significantly more likely to present with hemorrhage than those with supratentorial AVMs.[1] Our current investigation focuses on the effect that AVM location has on patients with previously unruptured AVMs after those AVMs rupture. Our high-volume AVM center puts us in a unique position to identify and follow the natural history of previously unruptured AVMs that rupture while they are being managed with observation. We sought to investigate whether neurologically intact patients (mRS score 0) with unruptured AVMs have worse outcomes following hemorrhage from posterior fossa AVMs and whether this effect is durable in a multivariate model. We hypothesize that the debilitating effects of bleeding are more pronounced when AVMs are located in the posterior fossa.

Methods

Patients and Study Design

This study was approved by our local institutional review board and performed in compliance with Health Insurance Portability and Accountability Act regulations. Patients were identified from a prospectively maintained database for the University of California, San Francisco, Brain Arteriovenous Malformation Study Project. All neurological outcomes were assessed using the modified Rankin Scale (mRS). We identified certain patients from this database that would allow us to investigate certain risk factors in their natural history. Those patients who met all of these requirements met the inclusion criteria: a) availability of pre-hemorrhage clinical data, b) a prehemorrhage mRS score of 0, c) initial pre-hemorrhage management with observation, d) recorded AVM location, and e) a mRS score recorded within 2 days of the presenting hemorrhage. Clinical data, including Spetzler-Martin and supplementary grades and the associated component scores, were collected from the prospectively maintained database, as were clinical outcomes measures. A clinician not directly involved in the care of these patients performed all mRS outcome assessments. Demographic and clinical data were analyzed for 154 patients meeting inclusion criteria. Patients were enrolled from a time period beginning in 2001 and ending in 2013. One hundred thirty-six patients (88%) had complete covariate information.

Statistical Analysis

Immediate post-presentation mRS was dichotomized into nonsevere outcomes, which included patients with mRS scores of 3 or less, and severe outcomes, which included patients with mRS scores greater than 3. There were 77 patients in each group. We analyzed patient characteristics by immediate post-presentation mRS score using t-tests for continuous variables and chi-square tests for categorical variables.

Our primary working hypothesis was that hemorrhage from posterior fossa AVMs results in worse outcomes compared with supratentorial AVMs. We tested this by using univariate and multivariate logistic regression analyses using severe outcome as the binary response, recording both odds ratios (ORs) and corresponding 95% confidence intervals (95% CI). We used a multivariate logistic model with posterior fossa location, gender, age at presentation, non-Hispanic white ethnicity, associated arterial aneurysm, AVM size, deep location, eloquence, and exclusively deep venous drainage as predictors. To assess the predictive ability of the multivariate model, we measured the area under the receiver operating characteristic (AUROC) curve based on predicted values from a 10-fold cross-validation procedure. As an ancillary analysis, we performed ordinal logistic regression using the change in mRS score as the outcome.

We analyzed hemorrhage volume to compare differences by AVM location (infratentorial vs supratentorial). We were able to ascertain hemorrhage dimensions for 59 patients in our database (10 of whom are included in our primary analysis and 49 additional patients not part of the current study cohort) and estimated volume via the following formula: $V = (1/2) \times \text{length} \times \text{width} \times \text{height}$.

Using imputed data, we performed a logistic regression analysis measuring the effects of hemorrhage volume and AVM location as predictors of severe outcome on presentation. We used a multiple imputation by chained equations (MICE) algorithm to impute hemorrhage volume data using all patients in the primary analysis data set and all available hemorrhage volume data (49 additional cases) on the basis of 25 imputations. The conditional models used for the procedure were 1) severe outcome = hemorrhage volume + AVM location and 2) hemorrhage volume = severe outcome + AVM location.

We considered p values less than 0.05 to be significant. All statistical analyses were performed using Stata/SE 12.0 (StataCorp LP).

Results

Univariate analysis of demographic and clinical characteristics of patients presenting with severe presentation (poor mRS scores) and those with nonsevere presentation after hemorrhagic events are demonstrated in Table 1. No significant difference in outcome severity was attributable to sex, age at presentation, or non-Hispanic white ethnicity. Several AVM characteristics, including posterior fossa location, associated arterial aneurysm, and eloquent AVM location, were associated with severe outcome. These results are consistent with the univariate logistic regression analysis (Table 2). Posterior fossa location was a significant predictor of severe outcome after hemorrhage on univariate analysis (OR 2.60, 95% CI 1.20–5.67, $p = 0.016$). The strength of the effect of posterior fossa location increased in the multivariate model (OR 4.96, 95% CI 1.73–14.17, $p = 0.003$). Additionally, eloquent location (OR 3.47, 95% CI 1.37–8.80, $p = 0.009$) and associated arterial aneurysms (OR 2.58, 95% CI 1.09–6.10, $p = 0.031$) were significant predictors of poor outcome in the multivariate model (Table 2). Female sex was predictive of poor outcome in the univariate but not the multivariate model.

Predictions produced by a 10-fold cross-validation technique for the multivariate model generated an AUROC curve of 0.64 (95% CI 0.55–0.74, Fig. 1), suggesting a modest ability to predict poor outcome based on included variables. Results from the ordinal logistic regression were concordant with the other analyses, as posterior fossa location was a significant predictor of mRS in both the univariate case (OR 2.44, 95% CI 1.23–4.84, $p = 0.010$) and the multivariate case (OR 3.75, 95% CI 1.59–8.82, $p = 0.003$, data not shown). Overall, there were 37 patients with infratentorial AVMs and 117 patients with AVMs in supratentorial locations; their presenting mRS scores following hemorrhage are shown in Table 3; the differences between the categorical mRS presentation of patients with and without posterior fossa AVMs showed a nearly significant difference ($p = 0.056$, chi square, Table 3).

Of the 59 persons studied with recorded hemorrhage (hematoma) dimensions, 12 (20%) had an AVM located in the posterior fossa region. Mean hemorrhage volume (± SD) for the 12 patients with posterior fossa AVMs was 10.1 ± 10.1 cm^3, while for those with AVMs in other locations, the mean hematoma volume was 25.6 ± 28.0 cm^3 ($p = 0.003$, Fig. 2). The logistic analysis based on imputed hemorrhage volume values found that posterior fossa location was a significant predictor of severe outcome (OR 8.03, 95% CI 1.20–53.77, p =

0.033) and logarithmic hemorrhage volume showed a positive, but not statistically significant, association in the model ($p = 0.079$).

Discussion

Treatment of unruptured AVMs with any form of procedural intervention is being questioned after the ARUBA trial. At this critical juncture, it is important to individualize management recommendations and identify risk factors for poor outcomes with observation. Posterior fossa AVM location may be one such risk factor. Posterior fossa AVMs are more likely to rupture, and patients with these lesions are more likely to present with symptomatic hemorrhage.[3] Based on our findings, these infratentorial hemorrhages are more likely to cause severe outcomes.

It is known that larger hematoma volumes in patients with ruptured AVMs correlate with poor mRS scores.[14] For patients with posterior fossa AVMs, our data make it clear that AVM hemorrhage results in worse outcomes despite smaller hematoma volumes. This is not surprising given the proximity of infratentorial AVMs to vital deep structures, including the brainstem. Hemorrhage can cause direct brainstem compression leading to upward herniation through the tentorial incisura or downward tonsillar herniation through the foramen magnum. Compression of the fourth ventricle can cause obstructive hydrocephalus. Although we found larger hematoma volumes in the supratentorial compartment, supratentorial AVMs were less likely to result in severe outcomes than infratentorial ones.

We found that the presence of associated arterial aneurysms is associated with worse outcomes. Previous observational studies have also shown that AVM-associated aneurysms in the posterior fossa portend a worse outcome.[3,9] This finding may be due to bleeding in the form of subarachnoid hemorrhage rather than intraparenchymal hemorrhage, which is generally better tolerated. Posterior fossa AVM treatment should focus primarily on complete resection of the nidus and secondarily on occlusion of any associated aneurysms to eliminate the risk of future hemorrhage.[10]

Published Surgical and Natural History Risks for Posterior Fossa AVMs

Patients with posterior fossa AVMs present with hemorrhage in the majority of cases, and these lesions have annual rates of hemorrhage ranging from 4.4% to as high as 11.6%,[1] much higher than the often-quoted 2%–4% rate for all AVMs. Furthermore, re-hemorrhage rates for ruptured AVMs that are managed conservatively are as high as 34.4% annually, when considering ruptured AVMs in the posterior fossa that have deep locations and deep venous drainage.[12] This current study adds to our understanding of the natural history of posterior fossa AVMs by characterizing the effects of hemorrhage in patients with previously unruptured and untreated AVMs. These previously intact patients are impacted more severely if their AVM is located in the posterior fossa than if their AVM is supratentorial as evidenced by significant differences in AVM location between severe and nonsevere presentation (Table 1) and evidenced by absolute differences in posthemorrhage presentation mRS scores when comparing infratentorial AVMs to supratentorial AVMs ($p = 0.056$, Table 3). All of these grim natural history data support a more aggressive management posture with posterior fossa AVMs, but only if the risks of surgical intervention are relatively lower.

Our center previously reported results of surgery for 60 patients with cerebellar AVMs, of whom 44 (73%) had ruptured AVMs.[11] At presentation, only 32% of our patients with cerebellar AVMs had mRS scores of 0–2, whereas 65% of our 401 patients with supratentorial AVMs had mRS scores in that range ($p < 0.0001$). Overall, 74% of our cerebellar AVM patients had good outcomes (mRS score 0–2), and 77% were improved or unchanged in condition compared with presurgical baseline examination findings. Of the 13 patients (23%) whose condition was worse postoperatively than at baseline, 7 had good outcomes (mRS score 1 or 2). There were 6 deaths (11%), but 2 involved patients who presented with coma and did not improve with aggressive surgical management. Only 1 additional death occurred in the perioperative setting, while 3 deaths were remote from surgery and 2 of these were unrelated to surgery.[11] When comparing long-term surgical outcomes following resection of 60 cerebellar AVMs and 401 supratentorial AVMs, our center's previous experience demonstrated that the outcomes were significantly different in the supratentorial group, with 64% of patients with supratentorial AVMs with an mRS score of 0 or 1 compared with 44% in the cerebellar AVM group ($p = 0.01$).[11] However, such differences were already present prior to surgery, as mentioned above, and there was no significant between-groups difference in the proportion of patients whose long-term postsurgical scores were improved or unchanged relative to their presurgical scores (as opposed to being worse) ($p = 0.76$).[11]

Similar results can be found in other large posterior fossa AVM surgical series (excluding brainstem AVMs).[1,2,4,6,13] Reported treatment morbidity rates range between 10.4% and 25%, while mortality rates are between 7% and 15%, with one of the series including morbidity and mortality for multimodality therapy.[6]

The preponderance of ruptured AVMs in surgical series makes it difficult to compare the results with natural history studies. Such natural history studies comprise mostly unruptured AVMs with a more benign course; ruptured AVMs with a more malignant course are not managed conservatively and therefore are excluded from these studies. Therefore, side-by-side comparisons of published surgical and natural history risks are difficult. However, the generally favorable outcomes reported in surgical series with a more compromised patient population support a proactive management posture. Although some of the neurological improvement observed in surgical series reflects the natural recovery from hemorrhage, cerebral swelling, hydrocephalus, and other transient medical complications, the devastations of hemorrhage still exceed those of elective surgery in patients with unruptured AVMs and leave patients worse off than when they are only recovering from surgery. Surgically treated patients with ruptured AVMs typically improve beyond their presurgical baseline (relative mRS outcome), but they do not improve to prerupture baseline (absolute mRS outcome).

In their review of posterior fossa AVMs, Arnaout et al. reported that 84% of 246 patients with infratentorial AVMs in 6 of the largest published surgical series presented with rupture and suggested that up to 66.7% of patients die of an initial posterior fossa AVM rupture.[1]

The mortality associated with ruptured posterior fossa AVMs is probably even higher because some of it may occur prior to hospitalization or neurosurgical consultation. Additionally, surgical therapy may not be offered to ruptured AVM patients presenting in poor neurological condition. Therefore, some of the devastation of posterior fossa AVM hemorrhage eludes our accounting, and we are left underestimating the bleak consequences of conservative management. Therefore, serious consideration should be given to treating unruptured posterior fossa AVMs. The indications for treating ruptured posterior fossa AVMs surgically remain strong.

Limitations

One limitation of this analysis is that patients with infratentorial AVMs and large hematoma volumes are subject to selection bias. Large hemorrhage (hematoma) volume in the posterior fossa may not be survivable.

Conclusions

Patients with posterior fossa AVMs are more likely to present with hemorrhage[1] and more likely to have worse outcomes than those with supratentorial AVMs. Age, sex, and ethnicity were not associated with an increased risk of severe outcome after AVM rupture, while posterior fossa location, associated aneurysms, and eloquent location were strong predictors of severe outcome. Posterior fossa hematomas are poorly tolerated, with severe outcomes observed more frequently, despite the observation that infratentorial AVMs produce smaller hematoma volumes than ruptured AVMs in supratentorial locations. These findings support an aggressive surgical posture with respect to posterior fossa AVMs, both before and after they rupture.

Abbreviations used in this paper

ARUBA	A Randomized Trial of Unruptured Brain AVMs
AUROC	area under the receiver operating characteristic
AVM	arteriovenous malformation
MICE	multiple imputation by chained equations
mRS	modified Rankin Scale

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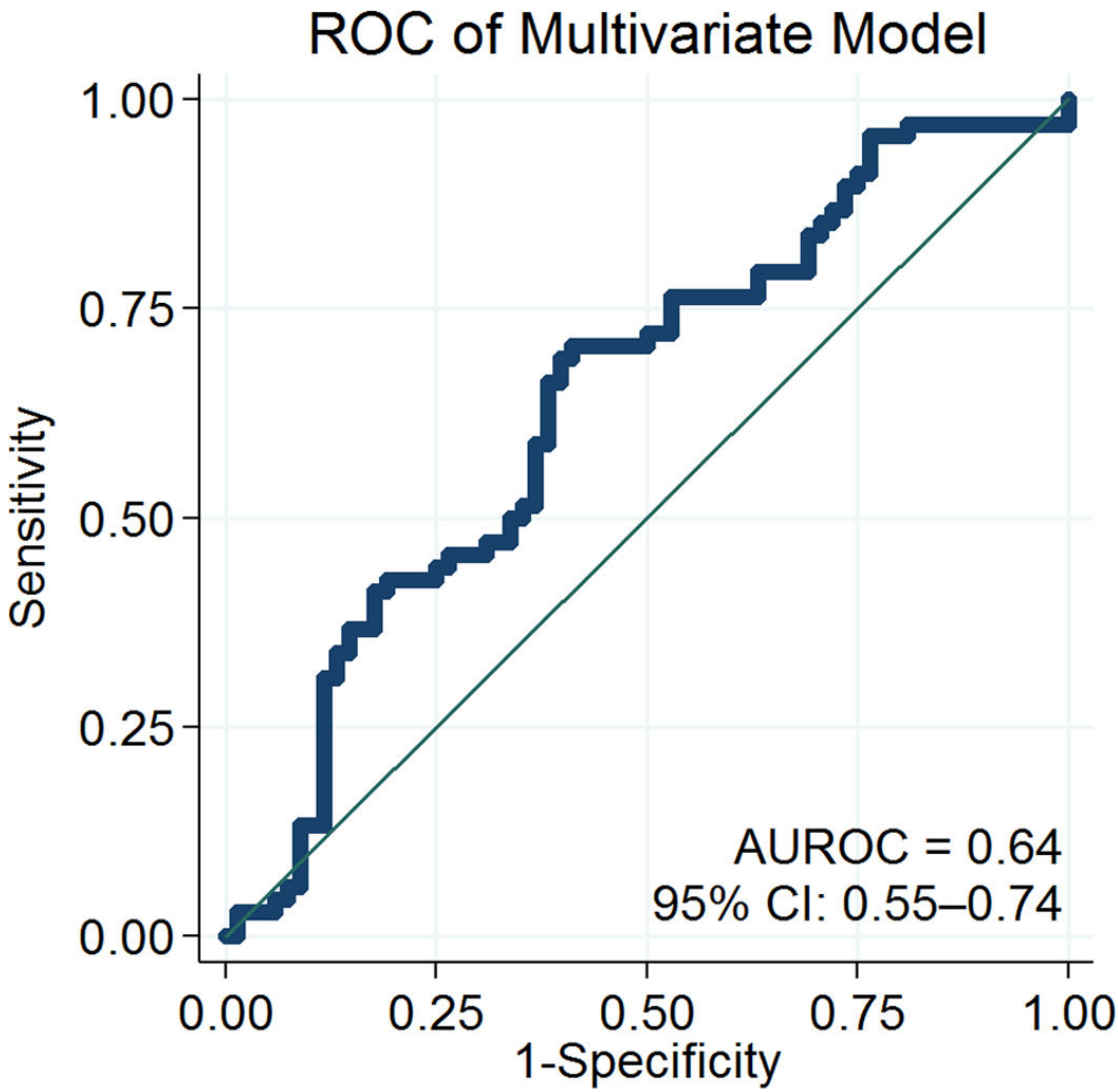

Fig. 1.

Predictions produced by a 10-fold cross-validation technique for the multivariate model generated an area under the receiver operating characteristic (AUROC) curve of 0.64 (95% CI 0.55–0.74).

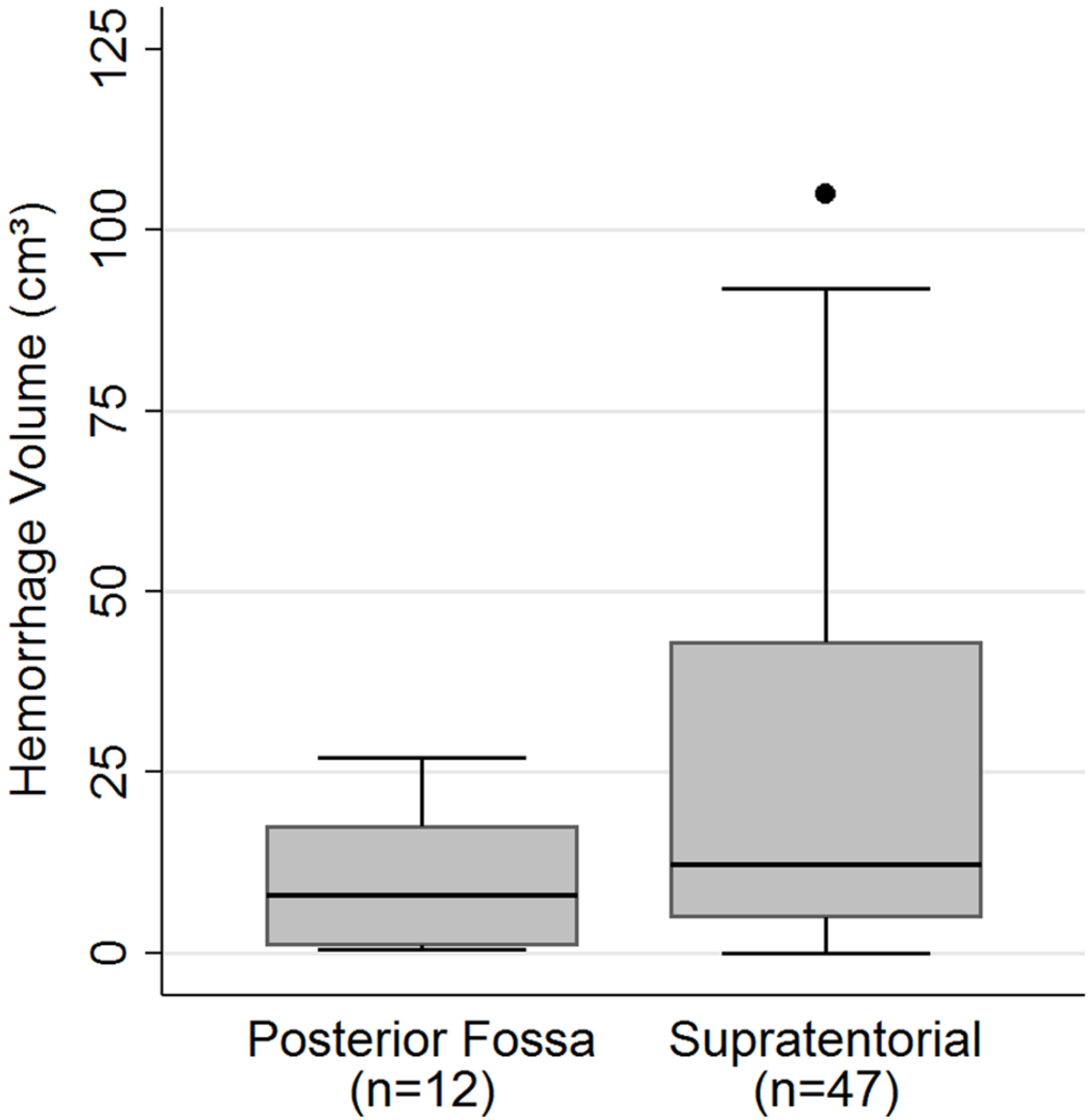

Fig. 2.
Comparison of hematoma volume in patients with posterior fossa and supratentorial AVMs. The box and whiskers plots show the median values with interquartile range and minimum and maximum values (*whiskers*). The corresponding mean volumes (± SD) were 10.1 ± 10.1 cm^3, and 25.6 ± 28.0 cm^3. The difference was statistically significant (•) for supratentorial locations (p = 0.0033). Hem Vol = hematoma volume

TABLE 1

Sample characteristics by post-hemorrhage presentation mRS*

Characteristic	Nonsevere Outcome (mRS ≤3) (n = 77)	Severe Outcome (mRS >3) (n = 77)	All (n = 154)	p Value
demographic				
female sex	30 (39%)	41 (53%)	71 (46%)	0.075
mean age at presentation	33.9 ± 20.1	30.6 ± 18.1	32.3 ± 19.1	0.281
non-Hispanic white	37 (48%)	34 (44%)	71 (46%)	0.628
clinical				
posterior fossa location	12 (16%)	25 (32%)	37 (24%)	**0.014**
associated aneurysm†	18 (25%)	31 (44%)	49 (35%)	**0.016**
mean AVM size (cm)‡	2.32 ± 1.67	2.50 ± 1.37	2.41 ± 1.52	0.488
deep location†	15 (19%)	19 (25%)	34 (22%)	0.412
eloquence†	41 (56%)	54 (72%)	95 (64%)	**0.045**
exclusively deep venous drainage†	19 (25%)	21 (28%)	40 (26%)	0.677

*Values represent number of patients (%) unless otherwise indicated. Means are presented with SDs. Complete clinical information for all variables was available for 136 patients. Variables with incomplete data are indicated by the dagger symbol. Boldface indicates statistical significance.

†Incomplete data.

‡Mean maximum diameter.

TABLE 2

Results of univariate and multivariate logistic analysis: predictors of severe presentation after rupture (outcome mRS score >3)*

	Univariate (n=154)			Univariate (n = 136)†			Multivariate (n = 136)		
Characteristic	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
posterior fossa location	2.60	(1.20–5.67)	**0.016**	2.47	(1.09–5.63)	**0.030**	4.96	(1.73–14.17)	**0.003**
female sex	1.78	(0.94–3.39)	0.076	2.04	(1.03–4.04)	**0.041**	1.57	(0.74–3.36)	0.241
age at presentation (decade)	0.91	(0.77–1.08)	0.279	0.92	(0.77–1.10)	0.353	0.87	(0.70–1.07)	0.195
non-Hispanic white	0.85	(0.45–1.61)	0.628	0.94	(0.48–1.85)	0.863	1.24	(0.57–2.69)	0.580
associated aneurysm	2.39	(1.17–4.86)	**0.017**	2.33	(1.13–4.78)	**0.021**	2.58	(1.09–6.10)	**0.031**
AVM size (cm)	1.08	(0.87–1.33)	0.486	1.03	(0.83–1.28)	0.779	0.90	(0.69–1.16)	0.416
deep location	1.38	(0.64–2.97)	0.413	1.64	(0.73–3.66)	0.227	1.60	(0.54–4.70)	0.396
eloquent location	2.00	(1.01–3.98)	**0.046**	1.89	(0.93–3.85)	0.077	3.47	(1.37–8.80)	**0.009**
exclusively deep venous drainage	1.17	(0.57–2.40)	0.677	1.16	(0.55–2.45)	0.702	0.80	(0.29–2.15)	0.653

*Boldface indicates statistical significance.

†Sensitivity analysis restricted to patients also included in the multivariate analysis.

TABLE 3

Post-hemorrhage presentation mRS scores stratified by AVM location*

mRS Score & Description	PF AVM (n = 37)	non-PF AVM (n = 117)	All (n = 154)
0, no symptoms	0 (0%)	0 (0%)	0 (0%)
1, no significant disability	0 (0%)	8 (7%)	8 (5%)
2, slight disability	4 (11%)	11 (9%)	15 (10%)
3, moderate disability	8 (22%)	46 (39%)	54 (35%)
4, moderately severe disability	11 (30%)	29 (25%)	40 (26%)
5, severe disability	14 (39%)	23 (20%)	37 (24%)
6, dead	0 (0%)	0 (0%)	0 (0%)

*Chi-square test comparing posterior fossa AVMs to supratentorial AVMs, p = 0.056. PF = posterior fossa.