Original Article

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Long-term outcomes and prognostic factors after surgery alone for brain arteriovenous malformation

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Abstract:

OBJECTIVES: There is a paucity of data regarding the long-term hemorrhage/progression outcomes of brain arteriovenous malformation (BAVM). The purpose of this study was to examine the outcomes of surgical treatment alone over a long follow-up period.

MATERIALS AND METHODS: All patients (n = 356) harboring Grade I–III BAVMs who had been surgically treated alone between January 2010 and December 2019 were included. Univariate analysis and multivariate analysis with proportional hazard models were implemented to identify the predictors of hemorrhage-free survival (HFS) (n = 356) and progression-free survival (PFS) (n = 334).

RESULTS: Of the 356 BAVM patients, 233 were male and 123 were female (male-to-female ratio of 1.89:1). Rehemorrhage was observed in 22 (6.2%) patients. The overall HFS rates at 5, 10, and 15 years in the entire cohort were 96.0%, 92.4%, and 91.1%, respectively. A 1 cm^3 increase in lesion volume (hazard ratio [HR] = 1.049, 95% confidence interval [CI] = 1.013–1.085; P = 0.007) was a significant adverse factor for HFS. The probabilities of PFS at 5, 10, and 15 years were 94.9%, 90.6%, and 85.5%, respectively. With respect to clinical predictors of PFS, only male sex (HR = 3.146, 95% CI = 1.088–9.098; P = 0.034) was a significant predictor of PFS after surgical treatment in the univariate analysis.

CONCLUSIONS: For the majority of patients, surgery remains the first-line treatment for BAVMs. Our study included a significant subset of patients who were successfully managed by surgery alone.

Keywords:

Brain arteriovenous malformation, hemorrhage-free survival, progression-free survival, surgery alone

Introduction

Brain arteriovenous malformations (BAVMs), without intervening capillary networks between feeding arteries and draining veins, commonly present with intracranial hemorrhage (ICH) due to either arterial steal or venous outflow obstruction.[1-4] While AVMs have traditionally been regarded as congenital lesions, recent evidence supports a more nuanced view, highlighting the potential role of somatic mutations and angiogenic pathways. We gradually realized that similar to other recognized lesion entities, pathological intraparenchymal vascular lesions constitute a spectrum of diseases with marked variation in vascular biology, clinical manifestations, and outcomes.[5-8]

The optimal method for BAVM is controversial, and decision-making is usually modulated by a range of clinical presentations and radiological findings. Spetzler–Martin Grade IV/V BAVMs are generally amenable for conservative treatment. Surgery has been established for the treatment of Grade I/II BAVMs, and favorable surgical outcomes for BAVMs have been extensively described. Furthermore, evidence for the effectiveness of surgery as monotherapy for most Grade III lesions

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with small- to medium-sized lesions was obtained from multiple institutional case series.[9]

However, given the paucity of data regarding long-term hemorrhage outcomes and the lack of data on the optimal surgical strategies for patients with BAVM, a deep understanding of the determination of disease progression is lacking. Patients with BAVMs have long hemorrhage/progression survival expectations, and because of this, long-term studies are required to understand their prognosis. Therefore, the purpose of this study was to examine the outcomes of surgical treatment alone over a long follow-up time, which contributed to increasing our understanding of this disease.

Materials and Methods

With institutional review board approval, we retrospectively analyzed the data of 356 patients harboring Grade I–III BAVMs who had been surgically treated alone between January 2010 and December 2019. All the clinical and radiographic data collected from the patients' electronic medical records were retrospectively reviewed according to the guidelines of the Helsinki Declaration. The inclusion criteria included patients: (1) who had BAVMs on magnetic resonance imaging (MRI), computed tomographic angiography (CTA), or digital subtraction angiography (DSA); (2) who underwent surgery alone as the primary intervention; and (3) who had Grade I–III BAVMs. We excluded the patients (1) who had a treatment history of BAVM lesions before admission or (2) who had unavailable clinical data or follow-up information.

The primary endpoint was hemorrhage, which was defined as evidence of BAVM-related hemorrhage within the residual lesion or new lesion along with symptomatic presentations of incomplete resection/total resection. The secondary endpoint, recurrence for BAVMs, in our study, was defined as evidence of the angiographic appearance of new arteriovenous shunting and/or nidus vessels on the follow-up MRI or CTA in cases of total resection with/without symptomatic presentations. Given that one of the aims was to identify the predictors of progression, patients with residual lesions after primary incomplete surgical resection alone were included in the "hemorrhage-free survival (HFS) (n = 356)" group but not in the "progression-free survival (PFS) (n = 334)" group.

Patients were recommended to receive postoperative radiological examinations (MRI or CTA) every 6 months after primary surgery alone in the first 2 years and then annually thereafter. The survival status of patients at the final follow-up was obtained from the records. Follow-up was calculated as the period between lesion surgical resection alone and last patient contact or death. The neurological status was evaluated by the modified Rankin scale (mRS) score (0–6), and the last follow-up mRS >2 was considered a poor outcome.

We described the lesion size as the equivalent (abc) $^{1/3}$ and calculated the corresponding value as abc/2, where a, b, and c represent the diameter on preoperative axial, sagittal, and coronal MRI with contrast, respectively. Based on our experience,[10] the lesion location was divided into three locations: superficial supratentorial, deep supratentorial (basal ganglia, periventricular, and thalamus), and posterior cranial fossa (brain stem and cerebellum). BAVM is considered a single lobar if it occupies the frontal, parietal, temporal, occipital, and insula lobes or a single deep area, and it is considered two or multiple lobes when it occupies more than two or more areas or lobes of the brain. In our study, complete resection was defined as the absence of residual nidus or arteriovenous shunting on postoperative imaging. Specifically, we utilized MRI, CTA, or DSA for postoperative evaluation. Among these, DSA was considered the gold standard due to its high sensitivity in detecting residual nidus and shunting. We defined the early hemorrhagic phase as occurring within 1 month after bleeding.

Statistical analysis

Univariate proportional hazard models were implemented to identify the predictors of HFS and PFS, including the following variables: sex, age, lesion size (diameter and volume), lesion location, lesion lobe, hemorrhagic presentation, and vein drainage. Factors with P = 0.1 or less in the univariate analysis were entered into the multivariate analysis to exclude possible confounding factors. Statistical analysis was performed using SPSS (IBM, Armonk, New York, USA). For all the statistical analyses, $P < 0.05$ was considered to indicate statistical significance. We used the Kaplan Meier method with a log-rank test to calculate the incidence of HFS/PFS after primary resection and compared the results with computer-generated curves.

Clinical trial registry

This work is a retrospective study. No clinical trials were involved.

Results

Patient characteristics

We included data from 356 patients with Grade I–III BAVMs in our study cohort, 294 (82.6%) of whom had Grade I–II BAVMs [Table 1]. Two hundred and thirty-three (65.4%) patients were male, and 123 (34.6%) patients were female. There were 74 (20.8%) pediatric

Table 1: Clinical and treatment characteristics for patients

Patient characteristics	*n* (%)
Overall	356
Gender	
Male	233 (65.4)
Female	123 (34.6)
Age (year)	
Range	2–71
Mean	30.1±0.8
Median	28
Preoperative mRS	
1–2	43 (12.1)
3–5	313 (87.9)
Spetzler–Martin grade	
I	136 (38.2)
II	158 (44.4)
III	62 (17.4)
Ruptured	289 (81.2)
Preoperative symptoms	
Headache	248 (69.7)
Dizzy	84 (23.6)
Epilepsy	42 (11.8)
Limbs weakness	59 (16.6)
Disturbance of consciousness	56 (15.7)
Disturbance of sensation	15 (4.2)
Visual disturbance	7 (2.0)
Duration	
Range	4h-17yrs
Location	
Superficial	301 (84.6)
Deep	20 (5.6)
Posterior	35 (9.8)
Lobe (s)	
Single	270 (75.8)
Two or more	86 (24.2)
Side	
Left	163 (45.8)
Right	185 (52.0)
Middle	8 (2.2)
Tumor diameter, cm	
Range	0.5-7.7
Mean	2.7±0.1
Median	2.6
Tumor volume, cm^3	
Range	0.1-108.5
Mean	8.0±0.7
Median	3.6
Aneurysm	45 (12.6)
Venous drainage	38 (10.7)
Rehemorrhage	22 (6.2)
Recurrence	27 (7.6)
mRS at follow-up	
1–2	314 (88.2)
3–5	32 (9.0)
Death	10 (2.8)

(%) is the percentage of the proportion in this group. mRS: Modified Rankin Scale

patients under 18 years of age, and the ages ranged from 2 to 71 years. Two hundred and eighty-nine (81.2%) patients presented with ICH as the mode of presentation, and 280 patients underwent surgical resection in the early phase. Regarding preoperative symptoms, 248 (69.7%) patients had a headache, 84 (23.6%) patients had dizziness, 42 (11.8%) patients had epilepsy, 59 (16.6%) patients had limb weakness, and 56 (15.7%) patients had a disturbance of consciousness. The duration of preoperative symptoms ranged from 4 hours to 17 years.

Of the 356 lesions, 301 (84.6%) were superficial, 20 (8.6%) were deep, and 35 (9.8%) were posterior. The lesion maximal diameter ranged from 0.5 to 7.7 cm, with a mean size of 2.7 ± 0.1 cm, and the lesion volume ranged from 0.1 to 108.5 cm^3, with a mean of 8.0 ± 0.7 cm^3. The preoperative mRSs were 1–2 and 3–5 in 12.1% and 87.9% of the patients, respectively.

Survival analysis

Complete resection was achieved in 334 (93.8%) patients. A minority of patients, 22/356 (6.2%), developed new hemorrhages after surgery alone, and the mean time to postoperative hemorrhage was 162.7 ± 2.0 months, and 10 (2.8%) patients died. Among the 22 patients with rehemorrhage, 18 were males and 4 were females, with a mean ± standard deviation age of 32.1 ± 0.5 years, and hemorrhagic stroke presented in 19 patients; the median lesion volume was 5.76 cm^3. The overall HFS rates at 5, 10, and 15 years in the entire cohort were 96.0%, 92.4%, and 91.1%, respectively [Figure 1a]. In the cohort with recurrence (n = 27, 7.6%), 19 patients presented with hemorrhagic stroke, 5 patients presented epilepsy alone, 2 patients presented headache, and 1 patient presented dizzy. The mean PFS was 159.8 ± 2.3 months. The probabilities of PFS at 5, 10, and 15 years were 94.9%, 90.6%, and 85.5%, respectively [Figure 1b]. The follow-up mRS was 1–2 and 3–5 in 88.2% and 9.0%, respectively.

Figure 2a summarizes the findings for predictors of HFS. Patients with an increased lesion volume of 1 cm^3 (hazard ratios [HRs] = 1.035, 95% confidence intervals [CIs] = 1.017–1.054; P = 0.001) presented with worse HFS than their counterparts. Although not significant, there was a trend toward a greater likelihood of postoperative hemorrhage in adult patients than in pediatric patients (HR = 5.601, 95% CI = 0.753–41.640; P = 0.092), and a larger lesion diameter with a 1 cm increase trended toward a higher risk of postoperative hemorrhage (HR = 1.288, 95% CI = 0.955–1.738; P = 0.098). Three predictors, age, lesion diameter, and lesion volume, were integrated into the Cox proportional hazard regression model. The difference in lesion volume remained statistically significant in the multivariate analysis (HR = 1.049, 95% CI = 1.013–1.085;

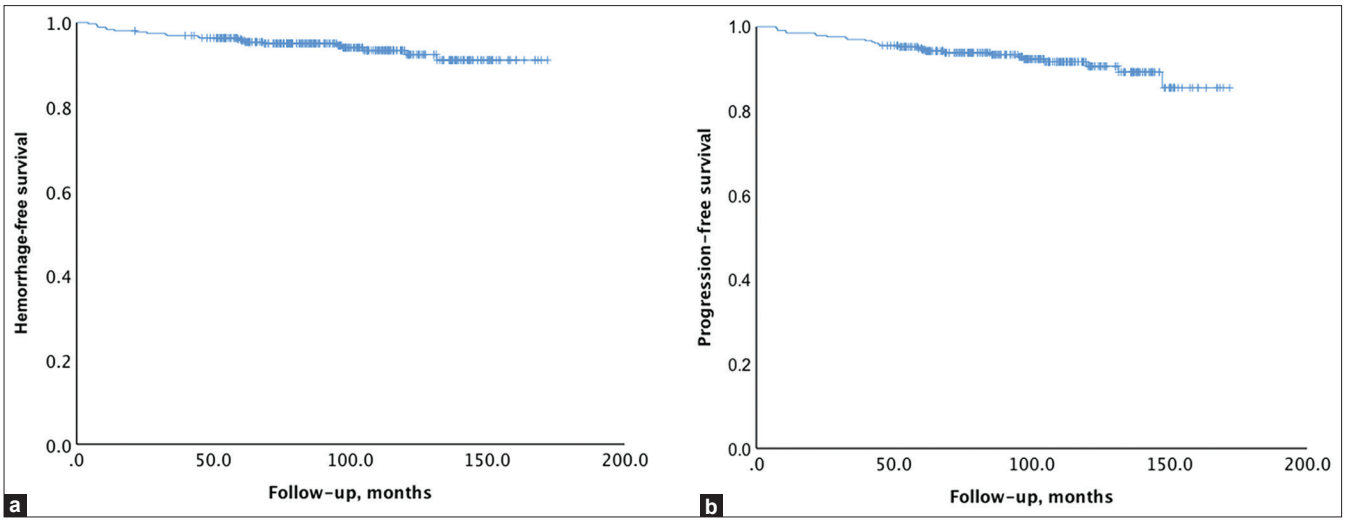

Figure 1: (a) Image showing hemorrhage-free survival and (b) progression-free survival

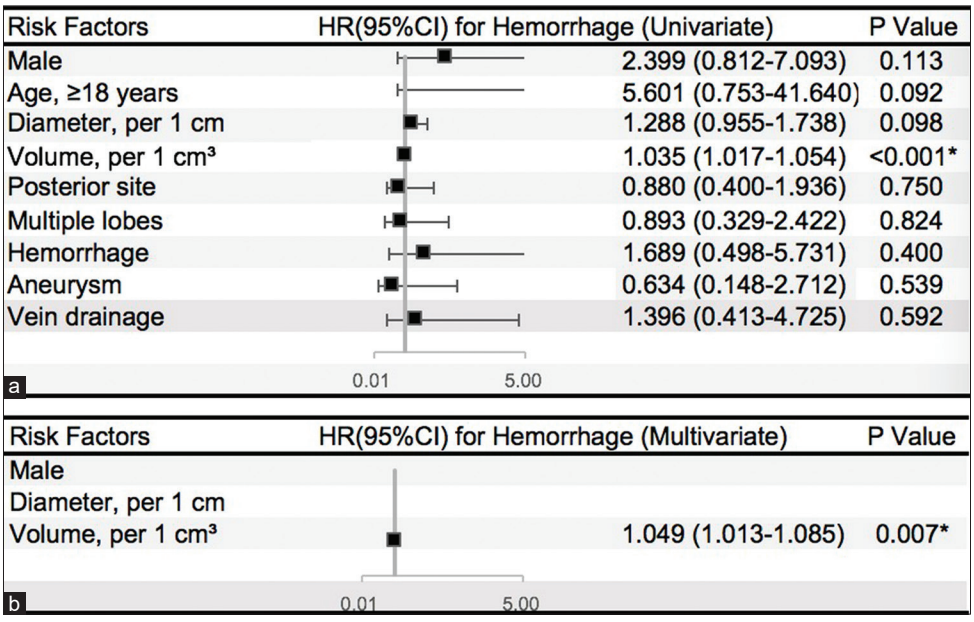

Figure 2: Univariate (a) and multivariate Cox regression analyses (b) were used to estimate the adverse factors for hemorrhage stroke after surgery alone. Black squares indicate the odds ratio, error bars represent the 95% confidence intervals, and *P < 0.05. HR: Hazard ratio, CI: Confidence interval

P = 0.007) [Figure 2b]. Only male sex (HR = 3.146, 95% CI = 1.088–9.098; P = 0.034) was a significant adverse predictor of PFS after surgical treatment [Figure 3].

There was no significant difference in HFS (167.5 months vs. 160.9 months, the mean time; P = 0.056, log-rank) or PFS (165.5 months vs. 157.7 months, the mean time; P = 0.071, log-rank) between pediatric patients and adult patients.

Discussion

The natural history of BAVM is characterized by a significant risk of ICH, which can lead to substantial morbidity and mortality. The annual rupture risk varies based on factors such as AVM size,[11,12] location, venous drainage pattern,[6,7,12] and the presence of associated aneurysms,[6,12] with rates ranging from 2% to 4% per year.[13] Intervention, particularly surgical resection, aims to alter this natural course by eliminating the nidus, thereby reducing the risk of future hemorrhage. However, the decision to intervene is influenced by considerations of lesion grade, patient age, and neurological status. Our study focuses on the long-term outcomes of surgical treatment, highlighting its role in modifying the disease trajectory and improving patient prognosis over time.

Surgery is widely used for the treatment of BAVMs[8,14,15] and aims at an improvement in the natural history

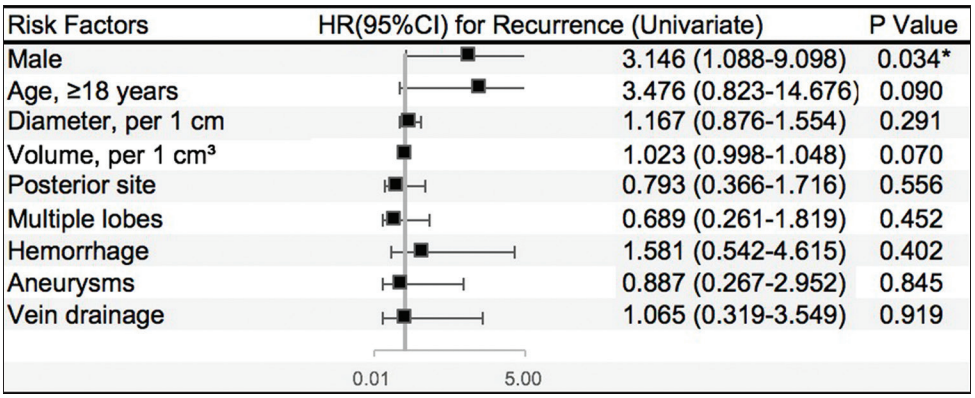

Figure 3: Univariate Cox regression analysis was used to estimate the adverse factors for progression. Black squares indicate the odds ratio, error bars represent the 95% confidence intervals, and **P* < 0.05. HR: Hazard ratio, CI: Confidence interval

through the complete obliteration of the nidus; however, the application of surgery alone has not been fully elucidated. To date, data examining the predictors of outcomes have been derived from small cases with a short follow-up. The focus of this study was mainly on ruptured and superficial lesions that underwent surgery alone stratified by grade. In line with the published studies,[16,17] Grade II was the most common in the surgical resection cohort. The majority of patients (93.8%) underwent complete resection of the BAVM, and a reduction in the volume of a large lesion might be related to a favorable outcome.

A male predominance was identified in our study, and univariate analysis revealed that male sex was an independent adverse factor for progression. According to a review of published studies, sex influences obliteration after stereotactic radiosurgery.[18] Male sex was identified as a statistically significant predictor of PFS following surgical treatment of BAVMs. This finding is indeed intriguing and challenges conventional understandings of gender differences in BAVM outcomes. However, it is important to note the following: our clinical data, while extensive, are limited in their ability to fully elucidate the underlying mechanisms or biological basis for this gender disparity. A more comprehensive understanding would require larger, multicenter studies, or randomized controlled trials that can account for potential confounding factors such as hormonal influences, vascular biology, or treatment responses. Children are more susceptible to recurrence after surgery.[19] In contrast, our study indicated that a trend toward reduced recurrence was observed in the younger generation, while a statistically significant difference was not observed.

Among the 289 (81.2%) patients who presented with ICH, 280 (96.9%) patients underwent surgical resection during this early phase. We recognize that acute hematoma can compress the nidus, potentially altering its measurements and influencing postoperative residuals. While our study did not specifically analyze this aspect, we agree that it is a relevant consideration that may impact surgical planning and outcomes. Previously, a meta-analysis on surgery alone for BAVMs reported by Park *et al*., who described the the complete resection rate was 93.5%.[20] Similarly, in our study, the complete resection rate was 93.8%. On the other hand, preoperative embolization for BAVMs is more apparent for patients with larger or ruptured BAVMs because of limitations related to the primary treatment strategy of surgical resection alone. However, an increasing number of studies have evaluated the use of preoperative embolization as an adjuvant to surgery, and they have suggested no improvement in clinical outcomes compared with surgery alone.[21-23]

In addition, total resection within the constraints of acceptable safety and favorable outcomes is not always achievable. Determining the lesion size or site with limited surgical access can pose a paramount threat to surgeons;[24] hence, we need clinically significant subgroups (rupture vs. unrupture and youth vs. adult) to determine whether resection alone can improve hemorrhage/progression control.

In our study, which included prolonged hemorrhage evaluations, higher-than-expected hemorrhage rates were identified.[25] Among the patients who suffered postoperative hemorrhage, we observed that postoperative imaging confirmed complete resection was achieved in most cases before the event. However, the regrowth or reappearance of BAVM was not definitively demonstrated in our data. The etiology of postoperative hemorrhage in such cases remains unclear but may involve residual micronidus undetectable by initial imaging; angiogenic processes leading to *de novo* shunting; and hemodynamic changes following resection, such as venous outflow obstruction or reperfusion injury. Based on a literature review, the

reported survival rates vary due to the rare incidence of BAVM treated by surgery alone and/or the short follow-up time.[19]

Limitations

In this retrospective study, the selection of optimal patients and the timing of surgery alone were the major questions, especially in patients with Grade I–III BAVMs. Moreover, the typical pattern of rupture/unrupture and the availability of management options prohibited the implementation of uniformly applied guidelines. In addition, we failed to provide an answer to the question of how many BAVMs were sporadic versus related to a condition such as hereditary hemorrhagic telangiectasia, which might be a key point in future for BAVM patients. Given these limitations, an increasing amount of largely retrospective evidence permits inferences.

Conclusions

For the majority of patients, surgery remains the first-line treatment for BAVM. Our study included a special group of patients who were successfully treated by surgery alone. Prospectively randomized controlled trials comparing surgery with other therapies for BAVMs, which provide evidence-based algorithms for managing BAVMs, are imperative.

Author contributions

Conception and experimental design: all authors; Acquisition of data: Li-Chuan Gao and Gui-Jun Zhang; Analysis and interpretation of data: all authors; Drafting the article: Zhao-Ying Zhu, Wei Zhang, and Li-Chuan Gao; Critically revising the article: all authors; Study supervision: all authors.

Ethical policy and institutional review board statement

The West China Hospital Institutional Review Board approved this study (NO. 2020-208, dated on March 5th, 2020), and data collection was performed according to the World Medical Association Declaration of Helsinki. Written informed consent for publication was obtained from the patient, and the ethics committee approved this procedure.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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