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ORIGINAL ARTICLE

Long-term outcomes and prognostic predictors of 111 pediatric hemorrhagic cerebral arteriovenous malformations after microsurgical resection: a single-center experience

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Abstract

Comparison in pediatric hemorrhagic arteriovenous malformations (AVMs) to clarify the long-term neurological outcomes and prognostic predictors after surgical intervention was relatively rare, especially in the selection of surgical timing. The objective of this study was to elucidate these points. The authors retrospectively reviewed the pediatric hemorrhagic AVMs resected in their neurosurgical department between March 2010 and June 2017. The natural history was represented by rupture risk. Neurological outcome was assessed with the modified Rankin Scale (mRS) for children. Multivariate logistic regression analyses were used to assess the risk factors for disability (mRS > 2). The hemorrhagic early phase was defined as less than 30 days after bleeding. The corresponding prognosis of different surgical timing (early intervention or delayed intervention) was compared after propensity-score matching (PSM). A total of 111 pediatric hemorrhagic AVM patients were evaluated. The average patient age was 11.1 ± 4.0 years, with a mean follow-up of 4.3 ± 2.1 years. The annualized rupture risk was 9.3% for the pediatric hemorrhagic AVMs, and the annualized re-rupture risk was 9.8%. 7.2% of the patients had disabilities (mRS > 2) and 82.0% achieved neurological deficit-free (mRS < 2) at the last follow-up. Pre-treatment mRS (P = 0.042) and flow-related aneurysms (P = 0.039) were independent factors for long-term disability. In terms of short-term outcomes, early intervention was better than delayed intervention (P = 0.033), but the long-term outcomes were similar between the two groups (P = 0.367). Surgical intervention for pediatric hemorrhagic AVMs is recommended, most of the patients can achieve good neurological outcomes. Moreover, early surgical intervention is preferred after the initial hemorrhage.

Keywords Hemorrhagic arteriovenous malformation · Microsurgery · Pediatric · Timing to surgery · Long-term outcomes · Prognostic predictors

Introduction

Brain arteriovenous malformations (AVMs) are the most common cause of intracranial hemorrhage in pediatric patients, accounting for 30%–50% of pediatric spontaneous cerebral hemorrhage [4, 34]. The overall mortality rate due to AVM rupture in children is as high as 21%–25% in some series [16, 19]. In general, the natural history of hemorrhage in AVMs is 1.9%–4.61% in the general population. However, the angioarchitecture of AVMs is not static and changes over time as children grow and develop into adults [6, 14], which means the annual risk of hemorrhage in children may differ from that in adults. Current treatment strategies include microsurgical resection, embolization, radiosurgery, or a combination of therapies [4]. The majority of pediatric hemorrhagic AVMs

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should undergo microsurgical resection because of the particularly elevated cumulative risk of recurrent hemorrhage during their lifetimes and the high rate of postoperative obliteration [20]. Generally, emergent surgery was suggested in patients with acute cerebral hernia or acute deterioration, and delayed intervention was recommended to the clinically stable ruptured AVMs for the adequate preoperative evaluation [2]. However, the high risk of recurrent hemorrhage and re-destruction of the reconstructed neurofunction might be detrimental [1, 23]. In this study, we retrospectively reviewed 111 consecutive pediatric hemorrhagic AVMs to elucidate long-term neurological outcomes and corresponding prognostic predictors, and to try to confirm the advantages of early intervention.

Materials and methods

Study design and participants

We performed a retrospective review of all patients diagnosed with AVMs resected at our neurosurgical institution from March 2010 to June 2017. Pediatric cases were isolated from the database of all AVMs with a cutoff age of 18 years at diagnosis. The study was performed according to the guideline of the Helsinki Declaration and was approved by the ethics committee of Beijing Tiantan Hospital. The inclusion criteria were as follows: (1) The diagnosis of AVM was confirmed with digital subtraction angiography (DSA) and/or magnetic resonance imaging (MRI). (2) Patients underwent microsurgical resection surgery. (3) Pediatric patients with a history of hemorrhage which could be attributed to AVM rupture. Patients with multiple AVMs, hereditary hemorrhagic telangiectasia (HHT), or unobtainable data were excluded from the study.

Data collection

Baseline demographic, clinical features and neuroimaging characteristics of the pediatric hemorrhagic AVM patients were retrospectively collected. Hemorrhage presentation was defined as hemorrhage that could be attributed to AVM rupture. The natural hemorrhage observation period was defined as the interval between birth to admission, and the re-rupture observation period was defined as the interval between the first hemorrhagic event to admission. Radiological data included review for lesion size, eloquent area, venous drainage style, and other angioarchitectural/hemodynamic characteristics (location, aneurysms, deep perforating arteries, diffuse nidus, etc.). The definition of eloquent area and deep venous drainage was consistent with the evaluation criteria in Spetzler-Martin (SM) grading system [33]. Flow-related aneurysms are operational terms describing aneurysms which lie on a pathway that carries nonnutritive blood flow (contrast) supplying the AVM shunt [17]. Diffuseness was determined from preoperative angiograms with TOF images used to identify intervening brain parenchyma within the nidus. Deep perforating arteries supplying was determined from preoperative angiograms or TOF images and included lateral lenticulostriate arteries from the M1 segment of middle cerebral artery (MCA), medial lenticulostriates from the A1 segment of anterior cerebral artery (ACA), anterior and posterior choroidal arteries, thalamoperforators from the posterior communicating artery, and P1 segment of posterior cerebral artery (PCA).

The microsurgical procedures were performed with intraoperative neuronavigation, ultrasonography, indocyanine fluorescence angiography (ICG), continuous monitoring of electroencephalogram, and somatosensory evoked potential. Circumferential dissection was carried along the borders of AVM within the perinidal gliotic tissue. The short-term neurological outcomes were evaluated 1 week after the surgery, and the long-term neurological outcomes were assessed at the last follow-up. The neurological status were assessed by modified Rankin Scale (mRS) system for children with age-specific modification as described previously [22]. The presence of new or persisting neurological deficits, or repeat hemorrhage were collected during the follow-up. A final mRS > 2 was considered disabled.

Follow-up was conducted at the first 3–6 months and annually after discharge by clinical visit and telephone interview. A brain MRI at 6 months, angiogram at 1 year, and yearly brain MRI up to 5 years after surgery were routinely performed. Researchers who performed follow-up assessments were blinded to treatment modalities.

Statistical analysis and propensity-score matching

The categorical variables were presented as counts (with percentages); the continuous variables were presented as the means ± standard deviations. Two-tailed *t* tests were used otherwise for continuous variable with Gaussian distribution. The Mann-Whitney U (Wilcoxon) test was used to compare non-normal distribution continuous variables. For categorical variables, either the Fisher exact test or the Pearson chi-square test was used.

Propensity-score analysis methodology (PSM) was used to compare the postoperative neurological outcomes of different surgical timing before the surgery by reducing the imbalance in the baseline patient characteristics. The hemorrhagic early phase was defined as less than 30 days after bleeding. On the basis of the covariates from the logistic model, the propensity score for each patient with respect to the baseline characteristics was generated. Nearest matching algorithm with a 1:1 ratio was applied. Absolute standardized difference analysis was performed to verify the representativeness of matching

results. The outcome of interest was mRS score during follow-up. Annualized rupture rate was calculated and a Poisson rate test was used to compare the differences between the annualized rupture risk and re-rupture risk (Stata 15.0, StataCorp, College Station, TX). The follow-up time of the annualized rupture risk was calculated from the time of birth. The multilogistic regression test was used to determine prognostic predictive factors. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SPSS (Version 25.0, IBM).

Results

Baseline characteristics

A total of 111 pediatric hemorrhagic AVM patients (63.1%, 60 males and 51 females) were included from our institutional microsurgical database of 176 pediatric AVMs from March 2010 to June 2017 (Fig. 1). The patients' mean age was 11.1 ± 4.0 years (range 1.0–18.0 years). The mean hematoma volume of preoperative hemorrhagic event was 31.1 ± 12.2 ml (range 5–50 ml). The mean pre-treatment mRS scores were 1.7 ± 0.9. Most of the lesions (101 cases, 91.0%) were located in supratentorial area. The average size was 3.4 ± 1.4 cm (range 1.1–9.1 cm), and the SM grade of all AVMs were as follows: 72 grade I–II lesions (64.9%), 25 grade III lesions (22.5%), and 14 grade IV–V lesions (12.6%). Forty-one patients (36.9%) involved eloquent areas, and 28 patients (25.2%) had deep venous drainage. Twelve patients (10.8%) were accompanied with flow-related aneurysms. Twenty-five patients (22.5%) had a diffuse nidus and 19 patients (17.1%) had deep perforating arteries (Table 1).

The annualized rupture rate for the whole pediatric AVM cohort ($n = 176$) was 5.5% per patient per year. For the pediatric hemorrhagic AVM cohort, the annualized rupture rate was 9.3% per patient per year, and the annualized re-rupture rate was 9.8% per patient per year. No significant difference was found between the rupture rate and the re-rupture rate in the pediatric hemorrhagic AVM cohort ($P = 0.844$) (Table 2).

Clinical outcomes

All of the 111 pediatric hemorrhagic AVM patients maintained continuous clinical or angiographic follow-up during an average 4.3 ± 2.1 years (range 1.2–8.7 years) follow-up period. All patients (100.0%) were confirmed obliteration of the AVMs after microsurgical resection by perioperative DSA or MRI. AVM recurrence was found in one patient 9 months after the resection surgery due to recurrent hemorrhage. The mean short-term mRS score was 2.0 ± 0.9, and the mean long-term mRS score was 1.1 ± 0.9. Eight patients (7.2%) of the

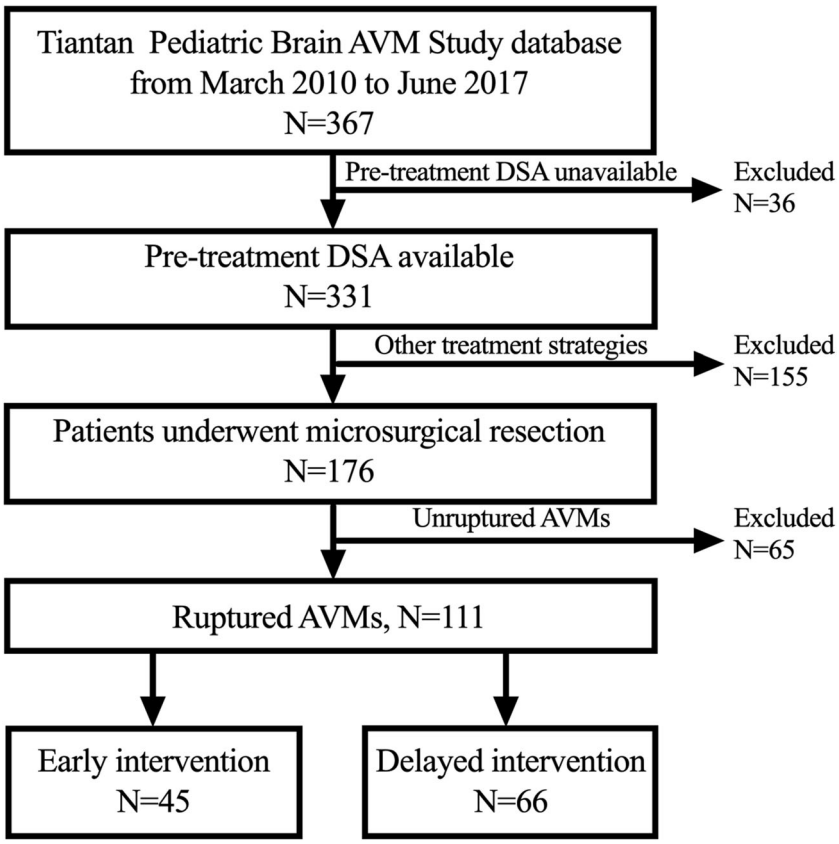

Fig. 1. The flow diagram of patient screening.

Table 1 Demographic and angiographic characteristics of the pediatric hemorrhagic AVM patients

Characteristics	Pediatric hemorrhagic AVMs (n = 111)
Age (years)	11.1 ± 4.0
Sex (male)	60 (54.1%)
Hematoma volume (ml)[a]	31.1 ± 12.2
Pre-treatment mRS	
Mean ± SD	1.7 ± 0.9
Side (left)	56 (50.5%)
Location (supratentorial)	101 (91.0%)
AVM size (cm)	
Mean ± SD	3.4 ± 1.4
Eloquence	41 (36.9%)
Deep venous drainage	28 (25.2%)
Long venous drainage	33 (29.7%)
Venous ectasia	16 (14.4%)
Venous stenosis	9 (8.1%)
Spetzler-Martin Grade	
I–II	72 (64.9%)
III	25 (22.5%)
IV–V	14 (12.6%)
Aneurysms	
Flow-related	12 (10.8%)
Non-flow-related	0 (0.0%)
Diffuse nidus	25 (22.5%)
Deep perforating arteries	19 (17.1%)
Follow-up time (years)	4.3 ± 2.1

AVM arteriovenous malformation, *mRS* modified Rankin Scale, SD standard deviation

Values are numbers of cases (%) unless otherwise indicated. Mean values are presented with SDs

[a] The total number of preoperative hemorrhagic event was 117

patients had disabilities (mRS > 2) and 91 patients (82.0%) achieved neurological deficit-free (mRS < 2) at the last follow-up. No patient died during follow-up.

During the perioperative period, 38 patients (34.2%) appeared improved mRS than pre-operation, 48 patients (43.3%) were unchanged, and 25 patients (22.5%) were worsened. Postoperative ICH occurred in three patients (2.7%) and hematoma evacuation was necessary in two patients (1.8%). In terms of long-term neurological outcomes, most of the patients (75 patients, 67.6%) were improved, whereas 22.5% (n = 25) unchanged and 9.9% (n = 11) worsened (Fig. 2).

Predictors of long-term disability (mRS > 2)

In the univariable logistic regression analyses, hematoma volume (25.0 ± 16.7 vs 17.2 ± 10.2 ml, P = 0.050) and pre-treatment mRS (2.6 ± 1.1 vs 1.6 ± 0.9, P = 0.002) had an unadjusted association with long-term disabilities (n = 8). Accompanied flow-related aneurysms showed a trend toward significance (37.5% vs 8.7%, P = 0.053). The multivariable logistic regression analyses demonstrated that pre-treatment mRS (OR 2.393, 95%CI 1.031–5.555, P = 0.042) accompanied with flow-related aneurysms (OR 6.174, 95%CI 1.100–34.649, P = 0.039) were independent risk factors for long-term disabilities (Table 3).

We further explored the relationship between surgical timing and clinical prognosis. To reduce the selectivity error caused by inconsistent baseline characteristics, we matched 27 hemorrhagic early phase cases to 27 hemorrhagic non-early phase cases according to propensity score. The two groups were compared with each other to verify that no significant differences were present between these two groups after the propensity-score matching (PSM). Finally, the short-term mRS of the early intervention group was found better than the delayed intervention group (P = 0.033). However, the long-term neurological outcomes were similar between these two groups (P = 0.367, follow-up period: average 4.4 ± 2.1 years). Interestingly, one patient in the early intervention

Table 2 The annualized rupture risk of pediatric AVM patients

	Patients with rupture	Total rupture frequency	Observation time (years)	Annual rate
Pediatric AVMs (n = 176)				
Annualized rupture risk	111	117	2122.9	5.5%
Pediatric hemorrhagic AVMs (n = 111)				
Annualized rupture risk	111	117	1265.0	9.3%
Annualized re-rupture risk	6	6	61.2	9.8%

Poisson rate test of the annualized rupture rate and the re-rupture rate in the pediatric hemorrhagic AVM cohort showed no significant difference (P = 0.844)

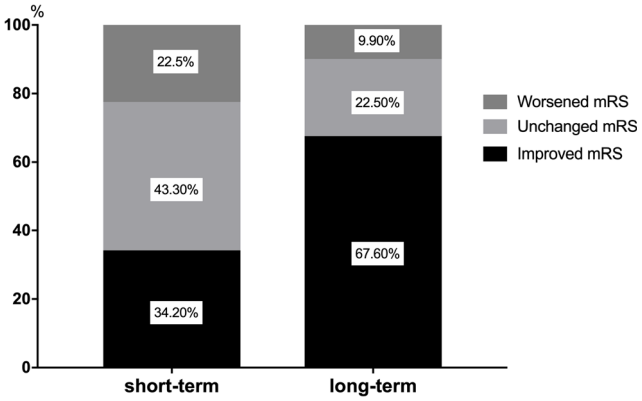

Fig. 2. The change of short-term and long-term neurological outcomes in the whole pediatric hemorrhagic AVM cohort.

group experienced a repeat hemorrhage from a recurrent AVM 9 months after the lesion resection+hematoma evacuation (perioperative DSA confirmed occlusion). The recurrent lesion was close to the original surgical cavity, and then the patient underwent reoperation (perioperative DSA and follow-up DSA 1 year after the surgery confirmed occlusion) (Table 4).

Discussion

Studies aimed at identifying clinical features, neurofunctional outcomes, and predictors of poor outcomes in pediatric hemorrhagic AVMs were relatively rare [7, 29], especially in the selection of surgical timing [2, 12]. Previous studies have propagated that hemorrhage in pediatric AVM is associated with 25% mortality rate whereas it is 6–10% in adults [9]. Given the long life expectancy of pediatric patients and high mortality and morbidity associated with AVM-related hemorrhage, the surgical outcomes and related risk factors should be identified and the pediatric hemorrhagic AVM patients should undergo definitive treatment for obliteration of the lesion to reduce the risk of recurrent hemorrhage. In this study, we found that the annualized rupture risk for the whole pediatric cohort was 5.5%. For the pediatric hemorrhagic cohort, the annualized rupture risk was 9.3%, and the annualized re-rupture risk was 9.8%. After long-term follow-up, 7.2% of the patients had disabilities (mRS > 2) and 82.0% achieved neurological deficit-free (mRS < 2). Pre-treatment mRS score accompanied with flow-related aneurysms was independent risk factors for long-term disability. In terms of surgical timing, the short-term outcomes of the early intervention

Table 3 Risk factor analysis of long-term postoperative disability in the pediatric hemorrhagic AVMs

Characteristics	All patients	Univariable		*P* value	Multivariable		*P* value
	(*n* = 111)	Present (*n* = 8)	Absent (*n* = 103)		OR	95% CI	
Age (years)	11.1 ± 4.0	11.3 ± 3.7	11.0 ± 4.1	0.887			
Sex (male)	60 (54.1%)	2 (25.0%)	58 (56.3%)	0.498			
Hematoma volume (ml)[a]	31.1 ± 12.2	25.0 ± 16.7	17.2 ± 10.2	0.050	1.033	0.962–1.109	0.370
Rupture frequency	1.1 ± 0.3	1.0 ± 0.0	1.1 ± 0.3	0.509			
Pre-treatment mRS	1.7 ± 0.9	2.6 ± 1.1	1.6 ± 0.9	0.002*	2.393	1.031–5.555	0.042*
Side (left)	56 (50.5%)	2 (25.0%)	54 (52.4%)	0.624			
Location (supratentorial)	101 (91.0%)	7 (87.5%)	94 (91.3%)	1.000			
AVM size (cm)	3.4 ± 1.4	2.6 ± 1.4	3.5 ± 1.4	0.085			
Eloquence	41 (36.9%)	4 (50.0%)	37 (35.9%)	0.679			
Deep venous drainage	28 (25.2%)	2 (25.0%)	26 (25.2%)	1.000			
Long venous drainage	33 (29.7%)	2 (25.0%)	31 (30.1%)	1.000			
Venous ectasia	16 (14.4%)	0 (0.0%)	16 (15.5%)	0.495			
Venous stenosis	9 (8.1%)	1 (12.5%)	8 (7.8%)	1.000			
Spetzler-Martin grade (I–III)	97 (87.4%)	7 (87.5%)	90 (87.4%)	1.000			
Aneurysms (flow-related)	12 (10.8%)	3 (37.5%)	9 (8.7%)	0.053	6.174	1.100–34.649	0.039*
Diffuse nidus	25 (22.5%)	3 (37.5%)	22 (21.4%)	0.540			
Deep perforating arteries	19 (17.1%)	3 (37.5%)	16 (15.5%)	0.271			
Follow-up time (years)	4.3 ± 2.1	4.7 ± 2.4	4.2 ± 2.1	0.541			

AVM arteriovenous malformation, *CI* confidence interval, *mRS* modified Rankin Scale, *OR* odd ratio, *SD* standard deviation

Values are numbers of cases (%) unless otherwise indicated. Mean values are presented with SDs

[a] For patients with multiple bleeding, the mean hematoma volume was included

* Statistical significance ($P < 0.05$)

Table 4 Comparison of the neurological outcomes between different surgical timing (early intervention vs delayed intervention) in the pediatric hemorrhagic AVMs after propensity-score matching (PSM)

Characteristics	All patients (n = 54)	Early phase (n = 27)	Non-early phase (n = 27)	P value
Age (years)	10.8 ± 4.0	10.9 ± 3.8	10.8 ± 4.2	0.946
Sex (male)	32 (59.3%)	16 (59.3%)	16 (59.3%)	1.000
Hematoma volume (ml)[a]	17.7 ± 10.3	16.7 ± 9.1	18.7 ± 11.4	0.471
Pre-treatment mRS	1.7 ± 0.7	1.7 ± 0.7	1.8 ± 0.7	0.703
Side (left)	30 (55.6%)	15 (55.6%)	15 (55.6%)	1.000
Location (supratentorial)	47 (87.0%)	24 (88.9%)	23 (85.2%)	1.000
AVM size (cm)	3.3 ± 1.3	3.2 ± 1.1	3.4 ± 1.4	0.607
Eloquence	16 (29.6%)	8 (29.6%)	8 (29.6%)	1.000
Deep venous drainage	8 (14.8%)	4 (14.8%)	4 (14.8%)	1.000
Long venous drainage	17 (31.5%)	8 (29.6%)	9 (33.3%)	0.770
Venous ectasia	7 (13.0%)	3 (11.1%)	4 (14.8%)	1.000
Venous stenosis	3 (5.6%)	1 (3.7%)	2 (7.4%)	1.000
Spetzler-Martin grade (I–III)	50 (92.6%)	25 (92.6%)	25 (92.6%)	1.000
Aneurysms (flow-related)	9 (16.7%)	5 (18.5%)	4 (14.8%)	1.000
Diffuse nidus	9 (16.7%)	5 (18.5%)	4 (14.8%)	1.000
Deep perforating arteries	8 (14.8%)	4 (14.8%)	4 (14.8%)	1.000
Follow-up time (years)	4.4 ± 2.1	4.2 ± 2.0	4.5 ± 2.3	0.693
Short-term outcomes				
Obliterated	53 (98.1%)	26 (96.3%)	27 (100.0%)	1.000
Short-term mRS	1.9 ± 0.7	1.7 ± 0.7	2.1 ± 0.7	0.033*
Disability (mRS > 2)	9 (16.7%)	3 (11.1%)	6 (22.2%)	0.465
Hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Long-term outcomes				
Obliterated	54 (100.0%)	27 (100.0%)	27 (100.0%)	1.000
Follow-up mRS	0.8 ± 0.7	0.7 ± 0.6	0.9 ± 0.9	0.367
Disability (mRS > 2)	2 (3.7%)	0 (0.0%)	2 (7.4%)	0.471
Hemorrhage	1 (1.9%)	1 (3.7%)	0 (0.0%)	1.000

AVM arteriovenous malformation, *mRS* modified Rankin Scale, *SD* standard deviation

The hemorrhagic early phase after the rupture event was defined as less than 30 days after bleeding

Values are numbers of cases (%) unless otherwise indicated. Mean values are presented with SDs.

[a] For patients with multiple bleeding, the mean hematoma volume was included

* Statistical significance ($P < 0.05$)

group might be better than the delayed intervention group, the long-term outcomes were similar between the two groups.

Annualized rupture risk in pediatric hemorrhagic AVMs

Previous studies have established the natural history of hemorrhage in AVMs is 0.9%-4.61% in the general population [3, 8, 35]. However, the natural history of AVMs in pediatric patients is not entirely understood in the existing literature. Although hemorrhagic AVMs are more common in children than adults, it does not imply that children's AVMs are more prone to rupture [28]. In fact, pediatric AVMs do not come to clinical attention so often unless they bleed. Current natural-history studies of AVMs report unruptured AVMs have an annual hemorrhage rate of 2.2% while ruptured lesions have an annual hemorrhage rate of 4.5% [3]. Yang et al. reported a 0.9% annual risk of hemorrhage in a cohort of 90 pediatric patients with AVMs after excluding the treatment selective bias [35]. However, the risk was generated using the time interval from presentation to initial treatment. A recent study has identified activating KRAS mutations in the majority of tissue samples of AVMs, providing evidence that the brain AVM is a congenital disorder [24]. In this study, the observative interval of natural hemorrhage was defined as from birth to admission, the annualized rupture risk for the whole pediatric cohort was 5.5%, which was similar to previous studies. For pediatric hemorrhagic AVMs, the annualized

hemorrhagic risk was 9.3%. To the best of our knowledge, this is the first study attempting to calculate the annualized hemorrhagic rate in a single cohort of pediatric hemorrhagic AVMs. For hemorrhagic AVMs, the hemorrhage rate could change over time, with the recurrent hemorrhage rate ranging from 2 to 18% in the first year after rupture across several studies [5, 27]. The present study suggested that the annualized re-rupture risk in pediatric hemorrhagic AVMs was 9.8%.

Outcomes of pediatric hemorrhagic AVMs

The interventional strategies for cerebral AVMs include microsurgical resection, embolization, radiosurgery, or a combination of these. Microsurgical resection has the advantages of immediate therapeutic cure and high obliteration rates [11], but the high incidence of postoperative complications hinders the choice of this strategy in clinical practice. Embolization as a primary and sole mode of therapy still remains questionable due to its low cure rate [25]. Radiosurgery is more favorable for deep lesions and lesions less than 3 cm in diameter [26]. However, long-term obliteration rate and control of recurrent hemorrhage during observation period remains unsatisfactory [32]. Recently, single-stage combined embolization and resection strategy using hybrid angio-surgical suite was proposed to solve complex cerebrovascular disease [30], but the applicable population, intraoperative embolization strategy, and long-term outcomes were still unclear.

Considering the long potential life span and good neurological plasticity of children [31], the goal of treatment in the pediatric hemorrhagic AVMs must be complete obliteration. Kiri et al. reported an obliteration rate of 89% in pediatric patients with low-grade AVMs after microsurgical resection [18]. Nair et al. demonstrated that 86.1% of 36 pediatric patients with SM grade I–III AVMs achieve a good functional outcome after microsurgical resection [25]. Darsaut et al. and Yang et al. included all major modalities, and the overall proportion of patients achieving good functional outcomes was 74.2% and 68%, respectively [4, 35]. In this study, all patients (100.0%) were confirmed obliteration by perioperative DSA or MRI. After long-term follow-up (mean 4.3 ± 2.1 years), 7.2% patients had disabilities (mRS > 2) and 82% of the patients achieve good neurological deficit-free. Interestingly, one patient was found to have relapsed AVM 9 months after the surgery due to recurrent hemorrhage. The underlying mechanism might be the pseudo-occlusion of residual lesions due to the hematoma mass compression or vasospasm [29].

Risk factors for long-term outcomes

High grade, large AVM size, poor baseline mRS score [13], seizure presentation [35], unruptured lesions [11], high-grade lesions, and located in eloquent cortex were considered as significant predictors of postoperative neurofunctional deficit (NFD) in pediatric AVM patients [29]. The correlation between preoperative hemorrhage and long-term postoperative outcomes was still controversial. Several studies suggested that microsurgical resection of hemorrhagic AVMs was associated with significantly lower postoperative neurological complication rates and lower intraoperative blood loss [10, 11, 21]. There was a new published AVM grading scale that includes an older patient age, non-hemorrhagic presentation, and diffuse nidus morphology as prediction model for surgical outcomes [21]. However, some studies disagreed with this view, their data showed that the prior AVM hemorrhage showing no significant association with better functional outcomes [7, 13]. In this study, 92.8% of the pediatric hemorrhagic AVMs had an mRS score < = 2 during long-term follow-up, which was consistent with previous studies [11, 29]. We found poor pre-treatment mRS scores and accompanied with flow-related aneurysms were significantly associated with long-term disability. The presence of flow-related aneurysms might make the resection surgery more challenging, especially in the ruptured AVMs. The disorganized anatomy structure and glial cell proliferation might lead to difficulty in separating lesions and accidental rupture of aneurysms. 10.8% of the pediatric hemorrhagic AVMs were accompanied with flow-related aneurysms in the present study. Many previous studies have reported adults having more flow-related aneurysms than children [14, 15], and the differences might be attributed to chronic hemodynamic stress caused by blood shunting through the AVM [7].

Timing of surgery in pediatric hemorrhagic AVMs

Microsurgical resection was considered a preferred strategy for the treatment of ruptured cerebral AVM, especially in emergency patients [2]. However, there is still no consensus on the timing of surgery. Ahmad et al. retrospectively investigated 59 patients for surgical treatment of ruptured supratentorial AVMs, and they found the time interval between AVM bleeding and surgery did not influence early or late outcomes [23]. Martinez et al. and Beecher et al. recommended a delayed intervention for at least 4 weeks after the initial hemorrhage might benefit the clinical outcomes [1, 23]. And emergency hematoma evacuation with delayed AVM excision was considered as a safe strategy in certain situations [23]. However, Bir et al. suggested that surgical intervention after 48 h resulted in poor outcomes for ruptured AVMs [2]. In the present cohort, we compared these two intervention strategies in 54 patients according to propensity score. Finally, we found that the short-term outcomes of the early intervention group (< = 30 days) were better than the delayed intervention group (> 30 days), but the long-term outcomes were similar. The causes of better short-term outcomes in the early intervention group might be the rapid release of hematoma compression effect and avoiding the occurrence of recurrent

hemorrhage. And the early surgical intervention was indicated that may decrease the likelihood of focal neurological deficit deterioration upon surgery, as the delayed intervention might lead to re-destruction of the reconstructed neurofunction [12]. However, early surgery was prone to residual lesions due to incomplete preoperative examination and poor intraoperative visual field exposure, the intraoperative DSA in the Hybrid Angio-Surgical suite was recommended to verify complete eradication of the lesion [30]. In addition, the long-term outcomes between these two groups were similar, a contributing factor was probably children's better neural plasticity [31]. Thus, early surgical intervention was recommended for pediatric hemorrhagic AVMs after the initial hemorrhage in this cohort. And further multi-center randomized controlled trials with larger sample size are needed for pediatric hemorrhagic AVMs.

Limitation

Several potential limitations of this study need to be clarified to avoid misinterpretation of our data. Firstly, this is a single-center retrospective study and selection bias existed. The operative indication and intraoperative strategies may vary according to institutional philosophy and experience. However, to our knowledge, this study cohort remains one of the largest studies in the existing literature concerning a pediatric hemorrhagic population with AVMs. Secondly, the national policy of graded diagnosis and treatment might lead to selection bias of patients by promoting more complex pediatric AVM patients to our tertiary neurosurgical center, which will lead us to underestimate the outcomes of the pediatric hemorrhagic AVM patients.

Conclusions

The surgical intervention treatment for pediatric hemorrhagic AVMs is recommended in that the cumulative lifetime hemorrhage risk is substantial. In this patient series, the annualized rupture risk for the whole pediatric AVM cohort was 5.5%. For the pediatric hemorrhagic AVM cohort, the annualized rupture risk was 9.3%, and the annualized re-rupture risk was 9.8%. Based on the better neurological plasticity, most pediatric hemorrhagic AVM patients can achieve neurological deficit-free after surgical resection. Pre-treatment mRS score and accompanied with flow-related aneurysms were independent predictors for long-term disability (mRS > 2). In addition, early surgical intervention is recommended for pediatric hemorrhagic AVMs after the initial hemorrhage.

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Author contributions ZD, YC, and LM contributed conception and design of the study; ZD and LM organized the database; YC, LM, and RL performed the statistical analysis; YC wrote the first draft of the manuscript; SW, DZ, YZ, and JZ wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review boards at both institutions and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Beecher JS, Lyon K, Ban VS, Vance A, McDougall CM, Whitworth LA, White JA, Samson D, Batjer HH, Welch BG (2018) Delayed treatment of ruptured brain AVMs: is it ok to wait? J Neurosurg 128:999–1005. https://doi.org/10.3171/2017.1.JNS16745
2. Bir SC, Maiti TK, Konar S, Nanda A (2016) Overall outcomes following early interventions for intracranial arteriovenous malformations with hematomas. J Clin Neurosci 23:95–100. https://doi.org/10.1016/j.jocn.2015.05.041
3. Can A, Gross BA, Du R (2017) The natural history of cerebral arteriovenous malformations. Handb Clin Neurol 143:15–24. https://doi.org/10.1016/B978-0-444-63640-9.00002-3
4. Darsaut TE, Guzman R, Marcellus ML, Edwards MS, Tian L, Do HM, Chang SD, Levy RP, Adler JR, Marks MP, Steinberg GK (2011) Management of pediatric intracranial arteriovenous malformations: experience with multimodality therapy. Neurosurgery 69:540–556; discussion 556. https://doi.org/10.1227/NEU.0b013e3182181c00
5. Di Rocco C, Tamburrini G, Rollo M (2000) Cerebral arteriovenous malformations in children. Acta Neurochir 142:145–156 discussion 156-148
6. Ding D, Starke RM, Liu KC, Crowley RW (2015) Cortical plasticity in patients with cerebral arteriovenous malformations. J Clin Neurosci 22:1857–1861. https://doi.org/10.1016/j.jocn.2015.06.014
7. Ellis MJ, Armstrong D, Vachhrajani S, Kulkarni AV, Dirks PB, Drake JM, Smith ER, Scott RM, Orbach DB (2013) Angioarchitectural features associated with hemorrhagic presentation in pediatric cerebral arteriovenous malformations. J Neurointerv Surg 5:191–195. https://doi.org/10.1136/neurintsurg-2011-010198

8. Fleetwood IG, Steinberg GK (2002) Arteriovenous malformations. Lancet 359:863–873. https://doi.org/10.1016/S0140-6736(02)07946-1
9. Gerszten PC, Adelson PD, Kondziolka D, Flickinger JC, Lunsford LD (1996) Seizure outcome in children treated for arteriovenous malformations using gamma knife radiosurgery. Pediatr Neurosurg 24:139–144. https://doi.org/10.1159/000121030
10. Gross BA, Duckworth EA, Getch CC, Bendok BR, Batjer HH (2008) Challenging traditional beliefs: microsurgery for arteriovenous malformations of the basal ganglia and thalamus. Neurosurgery 63:393–410; discussion 410-391. https://doi.org/10.1227/01.NEU.0000316424.47673.03
11. Gross BA, Storey A, Orbach DB, Scott RM, Smith ER (2015) Microsurgical treatment of arteriovenous malformations in pediatric patients: the Boston Children's Hospital experience. J Neurosurg Pediatr 15:71–77. https://doi.org/10.3171/2014.9.PEDS146
12. Hafez A, Oulasvirta E, Koroknay-Pal P, Niemela M, Hernesniemi J, Laakso A (2017) Timing of surgery for ruptured supratentorial arteriovenous malformations. Acta Neurochir 159:2103–2112. https://doi.org/10.1007/s00701-017-3315-9
13. Hanakita S, Koga T, Shin M, Igaki H, Saito N (2015) The long-term outcomes of radiosurgery for arteriovenous malformations in pediatric and adolescent populations. J Neurosurg Pediatr 16:222–231. https://doi.org/10.3171/2015.1.PEDS14407
14. Hetts SW, Cooke DL, Nelson J, Gupta N, Fullerton H, Amans MR, Narvid JA, Moftakhar P, McSwain H, Dowd CF, Higashida RT, Halbach VV, Lawton MT, Kim H (2014) Influence of patient age on angioarchitecture of brain arteriovenous malformations. AJNR Am J Neuroradiol 35:1376–1380. https://doi.org/10.3174/ajnr.A3886
15. Hoffman C, Riina HA, Stieg P, Allen B, Gobin YP, Santillan A, Souweidane M (2011) Associated aneurysms in pediatric arteriovenous malformations and the implications for treatment. Neurosurgery 69:315–322. https://doi.org/10.1227/NEU.0b013e31821524a1
16. Humphreys RP, Hoffman HJ, Drake JM, Rutka JT (1996) Choices in the 1990s for the management of pediatric cerebral arteriovenous malformations. Pediatr Neurosurg 25:277–285. https://doi.org/10.1159/000121140
17. Joint Writing Group of the Technology Assessment Committee American Society of I, Therapeutic N, Joint Section on Cerebrovascular Neurosurgery a Section of the American Association of Neurological S, Congress of Neurological S, Section of S, the Section of Interventional Neurology of the American Academy of N, Atkinson RP, Awad IA, Batjer HH, Dowd CF, Furlan A, Giannotta SL, Gomez CR, Gress D, Hademenos G, Halbach V, Hemphill JC, Higashida RT, Hopkins LN, Horowitz MB, Johnston SC, Lawton MW, MW MD, Malek AM, Mohr JP, Qureshi AI, Riina H, Smith WS, Pile-Spellman J, Spetzler RF, Tomsick TA, Young WL (2001) Reporting terminology for brain arteriovenous malformation clinical and radiographic features for use in clinical trials. Stroke 32:1430–1442
18. Kiris T, Sencer A, Sahinbas M, Sencer S, Imer M, Izgi N (2005) Surgical results in pediatric Spetzler-Martin grades I-III intracranial arteriovenous malformations. Childs Nerv Syst 21:69–74; discussion 75-66. https://doi.org/10.1007/s00381-004-1025-0
19. Kondziolka D, Humphreys RP, Hoffman HJ, Hendrick EB, Drake JM (1992) Arteriovenous malformations of the brain in children: a forty year experience. Can J Neurol Sci 19:40–45
20. Kondziolka D, McLaughlin MR, Kestle JR (1995) Simple risk predictions for arteriovenous malformation hemorrhage. Neurosurgery 37:851–855. https://doi.org/10.1227/00006123-199511000-00001
21. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL (2010) A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery 66:702–713; discussion 713. https://doi.org/10.1227/01.NEU.0000367555.16733.E1
22. Ma L, Kim H, Chen XL, Wu CX, Ma J, Su H, Zhao Y (2017) Morbidity after hemorrhage in children with untreated brain arteriovenous malformation. Cerebrovasc Dis 43:231–241. https://doi.org/10.1159/000458731
23. Martinez JL, Macdonald RL (2015) Surgical strategies for acutely ruptured arteriovenous malformations. Front Neurol Neurosci 37:166–181. https://doi.org/10.1159/000437121
24. Morita H, Komuro I (2018) Somatic activating KRAS mutations in arteriovenous malformations of the brain. N Engl J Med 378:1561. https://doi.org/10.1056/NEJMc1802190
25. Nair AP, Kumar R, Mehrotra A, Srivastava AK, Sahu RN, Nair P (2012) Clinical, radiological profile and outcome in pediatric Spetzler-Martin grades I-III arteriovenous malformations. Childs Nerv Syst 28:593–598. https://doi.org/10.1007/s00381-011-1668-6
26. Nicolato A, Lupidi F, Sandri MF, Foroni R, Zampieri P, Mazza C, Maluta S, Beltramello A, Gerosa M (2006) Gamma knife radiosurgery for cerebral arteriovenous malformations in children/adolescents and adults. Part I: differences in epidemiologic, morphologic, and clinical characteristics, permanent complications, and bleeding in the latency period. Int J Radiat Oncol Biol Phys 64:904–913. https://doi.org/10.1016/j.ijrobp.2005.07.983
27. Ondra SL, Troupp H, George ED, Schwab K (1990) The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg 73:387–391. https://doi.org/10.3171/jns.1990.73.3.0387
28. Oulasvirta E, Koroknay-Pal P, Hafez A, Elseoud AA, Lehto H, Laakso A (2019) Characteristics and long-term outcome of 127 children with cerebral arteriovenous malformations. Neurosurgery 84:151–159. https://doi.org/10.1093/neuros/nyy008
29. Ravindra VM, Bollo RJ, Eli IM, Griauzde J, Lanpher A, Klein J, Zhu H, Brockmeyer DL, Kestle JRW, Couldwell WT, Scott RM, Smith E (2019) A study of pediatric cerebral arteriovenous malformations: clinical presentation, radiological features, and long-term functional and educational outcomes with predictors of sustained neurological deficits. J Neurosurg Pediatr 1–8. https://doi.org/10.3171/2019.2.PEDS18731
30. Ren Z, Wang S, Xu K, Mokin M, Zhao Y, Cao Y, Wang J, Qiu H, Agazzi S, van Loveren H, Zhao J (2018) The working road map in a neurosurgical Hybrid Angio-Surgical suite - development and practice of a neurosurgical Hybrid Angio-Surgical suite. Chin Neurosurg J 4. https://doi.org/10.1186/s41016-017-0108-1
31. Singhal A, Adirim T, Cochrane D, Steinbok P (2011) Pediatric patients with poor neurological status and arteriovenous malformation hemorrhage: an outcome analysis. J Neurosurg Pediatr 7:462–467. https://doi.org/10.3171/2011.2.PEDS10355
32. Smyth MD, Sneed PK, Ciricillo SF, Edwards MS, Wara WM, Larson DA, Lawton MT, Gutin PH, McDermott MW (2002) Stereotactic radiosurgery for pediatric intracranial arteriovenous malformations: the University of California at San Francisco experience. J Neurosurg 97:48–55. https://doi.org/10.3171/jns.2002.97.1.0048
33. Spetzler RF, Martin NA (1986) A proposed grading system for arteriovenous malformations. J Neurosurg 65:476–483. https://doi.org/10.3171/jns.1986.65.4.0476
34. Yang SY, Kim DG, Chung HT, Paek SH (2012) Radiosurgery for unruptured cerebral arteriovenous malformations: long-term seizure outcome. Neurology 78:1292–1298. https://doi.org/10.1212/WNL.0b013e31825182c5
35. Yang W, Anderson-Keightly H, Westbroek EM, Caplan JM, Rong X, Hung AL, Colby GP, Coon AL, Tamargo RJ, Huang J, Ahn ES (2016) Long-term hemorrhagic risk in pediatric patients with arteriovenous malformations. J Neurosurg Pediatr 18:329–338. https://doi.org/10.3171/2016.3.PEDS15715