The factors associated with hemorrhagic presentation in children with untreated brain arteriovenous malformation: a meta-analysis

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OBJECTIVE Rupture of arteriovenous malformations (AVMs) would result in high mortality and prevalence of disability in pediatric patients. Decisions regarding the treatment of AVMs need to weigh the risk of rupture over the course of their natural history against the possibility of creating a lesion during treatment. Multiple factors have been proposed to predict hemorrhagic presentation of pediatric patients with AVMs. The aim of this meta-analysis was to evaluate the predictors of hemorrhagic presentation in pediatric patients with AVMs.

METHODS The authors searched the PubMed and EMBASE databases. Studies reporting the predictors of hemorrhagic presentation in children with untreated brain AVMs were included. The predictive ability of identified predictors was assessed by odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS A higher risk of hemorrhagic presentation was found in AVMs with smaller size (< 3 cm, OR 2.97, 95% CI 1.94–4.54, $p < 0.00001$), deep venous drainage (OR 2.28, 95% CI 1.55–3.36, $p < 0.0001$), a single draining vein (OR 2.23, 95% CI 1.27–3.92, $p = 0.005$), a single feeder (OR 3.72, 95% CI 1.31–10.62, $p = 0.01$), a deep location (OR 1.82, 95% CI 1.22–2.72, $p = 0.004$), an infratentorial location (OR 2.25, 95% CI 1.19–4.26, $p = 0.01$), and diffuse morphology (OR 8.94, 95% CI 3.01–26.55, $p < 0.0001$). In addition, the AVMs with draining vein ectasia (OR 0.35, 95% CI 0.13–0.97, $p = 0.04$) and high Spetzler-Martin (SM) grade (OR 0.53, 95% CI 0.36–0.78, $p = 0.001$) had a lower risk of hemorrhagic presentation in pediatric patients.

CONCLUSIONS Smaller AVMs, deep venous drainage, a single draining vein, a single feeder, deep/infratentorial location, diffuse morphology, and high SM grade were identified as positive predictors for hemorrhagic presentation. Particularly, patients with diffuse AVMs have a higher risk of hemorrhagic presentation than other factors and may need active treatments. However, factors such as age, sex, draining vein stenosis, and associated aneurysms were not associated with hemorrhagic presentation.

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KEYWORDS arteriovenous malformation; pediatric; hemorrhagic presentation; vascular disorders

BRAIN arteriovenous malformations (AVMs) are the most common cause of intracranial hemorrhage in pediatric patients.³⁴ AVM rupture in pediatric patients leads to a high mortality rate of 25% and permanent neurological defects in 20.2%–40.6% of patients.^{7,26,39} Decisions regarding the treatment of AVMs need to weigh the risk of hemorrhage over the course of their natural history against the possibility of creating a lesion during treatment. Despite the remarkable improvement in the treatment of AVMs, the natural history and risk factors of pediatric AVMs remain unclear.¹⁷

The angioarchitecture, clinical presentation, and outcomes of AVMs are different in pediatric and adult patients. The annual hemorrhagic rate of AVMs in the general population ranges from 2% to 4.61%,^{10,19} whereas the risk of hemorrhage in pediatric patients is not entirely understood. AVM rupture is more common in the pediatric population than in the adult population and accounts for 58%–77% of total admissions.⁸³ In addition, many studies^{29,35} reported that AVMs in children more often have exclusively deep venous drainage and are located in deep areas of the brain, both of which would increase the risk

ABBREVIATIONS AVM = arteriovenous malformation; CI = confidence interval; NOS = Newcastle-Ottawa Scale; OR = odds ratio; SM = Spetzler-Martin.

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of intracranial hemorrhage. Multiple factors have been proposed as predictors for hemorrhagic presentation among pediatric patients with AVMs,^{17,59} such as size, draining vein, location, associated aneurysm, and nidus morphology.

A previous meta-analysis³⁷ had focused on AVM rupture risk in adult patients, and only adult patients were included in the cohort of the Scottish Intracranial Vascular Malformation Study (SIVMS) and Multicenter AVM Research Study (MARS). In addition, the mean age of the included patients was about 37 years, which may not reflect the clinical characteristic of pediatric patients. However, pediatric patients with AVMs differ from adult patients in terms of the clinical characteristics of the AVMs,^{3,17} clinical presentations, and outcomes.⁸³ Thus, for hemorrhagic presentation, we assessed the rate of hemorrhage and risk factors in pediatric patients using a meta-analysis to identify better treatment for pediatric patients with AVMs.

Methods

Literature Review

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). We searched the literature from the beginning of indexing until April 3, 2018, using the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases. The following words were used: (“cerebral arteriovenous malformations” OR “brain arteriovenous malformations”) AND (“children” OR “pediatric”). The detailed search strategy was as follows: (“child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields]) OR (“pediatrics”[MeSH Terms] OR “pediatrics”[All Fields] OR “pediatric”[All Fields]) AND (“intracranial arteriovenous malformations”[MeSH Terms] OR “intracranial”[All Fields] AND “arteriovenous”[All Fields] AND “malformations”[All Fields]) OR “intracranial arteriovenous malformations”[All Fields] OR (“cerebral”[All Fields] AND “arteriovenous”[All Fields] AND “malformations”[All Fields]) OR “cerebral arteriovenous malformations”[All Fields] OR (“brain”[MeSH Terms] OR “brain”[All Fields]) AND (“arteriovenous malformations”[MeSH Terms] OR (“arteriovenous”[All Fields] AND “malformations”[All Fields]) OR “arteriovenous malformations”[All Fields])). The additional related studies were found by checking the references of retrieved articles.

Inclusion and Exclusion Criteria

After filtering duplicates, the titles and abstracts of all available articles were screened to find the relevant articles. The full texts of these articles were independently reviewed by two reviewers, following the inclusion and exclusion criteria. The inclusion criteria were as follows: 1) articles reporting pediatric patients (age < 18 years) diagnosed with cerebral AVMs; 2) articles reporting the odds ratio (OR) and 95% confidence interval (CI) of variables for hemorrhagic presentation; and 3) randomized controlled studies, and cohort, case-control, or case reports (> 20 cases). If the OR was > 1, the factors were considered

as increasing the risk of hemorrhage of untreated AVMs, and the factors with ORs < 1 were considered as having protective effects. The original data could be used to calculate the ORs and 95% CIs as follows: $OR = ad/bc$, in which “a” = number of patients with hemorrhage and the factor, “b” = number of patients with the factor but without hemorrhage, “c” = number of patients with hemorrhage but without the factor, and “d” = number of patients without hemorrhage and the factor. The exclusion criteria were as follows: 1) articles not in English, 2) systematic reviews or animal articles, and 3) patients who had previously undergone treatment for an AVM.

Data Extraction

The data from included articles were extracted independently by two reviewers, and the disagreement was resolved by the third reviewer. With a standard data form, the following data were extracted: author, year of publication, country, study design, number of patients, sex, mean age of patients on admission, hemorrhage rate, mean score of Spetzler-Martin (SM) grade, study period, Newcastle-Ottawa Scale (NOS),⁷³ and the ORs and 95% CIs of variables for hemorrhagic presentation. AVM was diagnosed by digital subtraction angiography, magnetic resonance angiography, or CT angiography. Hemorrhagic presentation was the initial presentation at diagnosis that was confirmed with CT or MRI. The results of multivariate regression analysis were pooled for analysis when they were available; if not, the results of univariate regression analysis were pooled.

Quality Assessment of the Included Articles

Two reviewers evaluated the quality of each included study independently using the NOS,⁷³ which ranged from 0 to 9. A high-quality study was defined as one with an NOS score ≥ 6 , and a low-quality study as one with an NOS score < 6.

Data Analysis

The risk of variables for hemorrhagic presentation was evaluated by the pooled ORs and 95% CIs. The risk of variables for hemorrhagic presentation was pooled by Review Manager (version 5.3, Cochrane Collaboration). By the generic inverse variance method, the pooled results of discontinuous variables were presented as ORs with 95% CIs. The pooled results of continuous variables were presented as mean differences with 95% CIs. The factors were categorized as having minimal evidence (OR 1.0–1.5 or 0.9–1.0), moderate evidence (OR 1.5–2.0 or 0.8–0.9), and strong evidence (OR > 2.0 or < 0.8). According to the Cochrane review guidelines,³¹ the heterogeneity of the pooled outcomes was assessed by the I^2 statistic. If I^2 was < 50%, the heterogeneity was not significant and the fixed-effects model was used. If I^2 was > 50%, heterogeneity was significant and the random-effects model was used.³² The sensitivity analysis was used to confirm the robustness of pooled results.⁵⁶ If the number of articles referring to the same risk factor was more than 5, the publication bias of included articles was assessed by a funnel plot with Begg’s rank correlation, using Stata (version

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FIG. 1. The PRISMA flow diagram of procedures to search the included studies.

13.0, StataCorp.). The statistical significance was defined as $p < 0.05$.

Results

Literature Search

Initial research identified 70 eligible articles and included 15 articles^{1,2,11,16,17,20,35,46,47,51,53,59,62,66,76} that described any factors associated with hemorrhagic presentation, after excluding 55 articles for the following reasons: no data for calculating the risk of variables for hemorrhagic presentation,^{22,44,58,63,64,75,79,83} inclusion of the same cohort as another report,^{48,69} patients with AVMs treated before hemorrhage,^{14,49,51,55,74} inclusion of only specific cases (such as patients with hereditary hemorrhagic telangiectasia,⁷⁸ cerebellar AVM,²⁵ Gamma Knife surgery,^{4,6–8,13,15,24,27,34,38,40,54,57,60,70,80–82} embolization,^{12,67} or microsurgery^{18,23,26,43} treatment), impossibility of separating pediatric patients from adult patients,^{10,28,33,41,45,77} less than 20 cases included,⁶⁵ reviews,^{5,21,40,52,61} or full text unavailable.⁵⁰

Characteristics of Included Studies

A total of 15 articles with 1155 pediatric patients were included in this meta-analysis, including 2 prospective articles^{11,46} and 13 retrospective articles^{1,2,16,17,20,35,47,51,53,59,62,66,76} (Table 1). All the included studies were conducted from 2006 to 2018. The mean age of the patients ranged from 10.1 to 13.4 years and the percentage of patients with first presentation with hemorrhage ranged from 41% to 78%. The median SM grade ranged from 2 to 3. All included studies were high quality, with scores ≥ 6 on the NOS. Among the 15 included articles, the ORs of 14 risk factors were extracted for analysis, including age, sex, size of AVM, deep venous drainage, single draining vein, draining vein ectasia/stenosis, single feeder, eloquent location, deep location, infratentorial location, associated aneurysm, nidus morphology (diffuse AVMs: presence of significant intervening brain within the AVM nidus; compact AVMs: presence of little or no intervening brain within the AVM nidus),¹⁷ and high SM grade (4–5).

TABLE 1. Characteristics of included articles

Authors & Year	Country	Study Design	No. of Pts	Sex (M/F)	Mean Age (yrs)	Hemorrhage Rate (%)	Median SM Grade (IQR)	Study Period	NOS Score
Oulasvirta et al., 2018	Finland	Retro	127	68:59	12.0	95 (75)	3 (2)	1942–2014	7
Ma et al., 2017 ⁴⁸	China	Prospective	110	72:38	10.9	52 (47)	2 (2)	2009–2015	8
Yang et al., 2016 ⁷⁶	US	Retro	90	39:51	13.3	37 (41)	3 (2)	1990–2013	7
Reitz et al., 2016	Germany	Retro	46	24:22	12.4	31 (67)	2 (2)	1992–2015	8
Nerva et al., 2016	US	Retro	40	26:14	11.5	27 (68)	3 (2)	2005–2012	7
Abecassis et al., 2016	US	Retro	26	19:7	12.5	17 (65)	3 (2)	2005–2012	6
Ma et al., 2015	China	Retro	108	43:65	10.9	66 (61)	—	2009–2014	7
Fok et al., 2015	China	Retro	67	28:39	12.0	52 (78)	—	2005–2013	8
Kellner et al., 2014	US	Retro	81	43:38	13.3	54 (63)	2 (2)	1991–2012	7
Ellis et al., 2013	US	Retro	135	70:65	10.1	86 (64)	—	2000–2011	7
Anderson et al., 2012	US	Retro	77	38:39	13.4	48 (63)	2 (2)	1991–2010	6
Skjøth-Rasmussen et al., 2012	Denmark	Retro	40	23:17	11.3	28 (68)	3 (2)	2000–2008	7
Darsaut et al., 2011	US	Prospective	120	61:59	11.7	58 (69)	3 (2)	1985–2009	8
Dorfer et al., 2010	Austria	Retro	56	26:30	10.9	36 (64)	2 (2)	1998–2008	7
Sanchez-Mejia et al., 2006	US	Retro	32	21:11	11.9	19 (59)	2 (2)	1997–2003	7

IQR = interquartile range; pts = patients; retro = retrospective.

Risk Factors for Hemorrhagic Presentation

Hemorrhagic Rate

All 15 articles reported the hemorrhage rate of AVMs, and the probability of hemorrhagic presentation accounted for 63% (95% CI 58%–69%, $I^2 = 72.2\%$) of pediatric AVMs.

Age on Admission

Among the included articles, seven^{1,2,47,51,62,66,76} provided the mean age of patients with ruptured and unruptured AVMs, and five^{1,11,59,62,66} provided data to calculate the risk of age < 12 years for hemorrhagic presentation. The pooled results showed that the age of patients in the ruptured AVM group (242 cases) was significantly lower than that in the unruptured AVM group (171 cases), with a weighted mean difference of -1.53 (95% CI -2.34 to -0.72 , $p = 0.0002$, $I^2 = 49\%$; Fig. 2A). However, the pooled results of patients < 12 years old for hemorrhagic presentation suggested age was not associated with hemorrhagic presentation (OR 1.38, 95% CI 0.47–5.05, $p = 0.55$; Fig. 2B), with a random-effects model for the significant heterogeneity of 5 articles ($p = 0.03$ and $I^2 = 62\%$). Based on sensitivity analysis, the heterogeneity was attributed to the article by Skjøth-Rasmussen et al.⁶⁶ After excluding this article, there was no significant heterogeneity ($p = 0.37$ and $I^2 = 4\%$) and no association between age and hemorrhagic presentation was found (OR 0.81, 95% CI 0.42–1.56, $p = 0.53$).

Sex

In 11 articles with 826 cases, two^{11,46} showed that there was no relationship between sex and hemorrhagic presentation with multivariate regression, and 10 articles^{1,2,11,16,47,51,53,62,66,76} analyzed the association between sex and hemorrhage using univariate regression. There was no heterogeneity among the results of these articles ($p = 0.60$ and I^2

$= 0\%$) and the fixed-effects model was used. The pooled results suggested that sex had no association with hemorrhagic presentation, with an OR of 0.95 (95% CI 0.76–1.19, $p = 0.68$; Fig. 2C).

Deep Venous Drainage

Among the 11 articles that reported the relationship between deep venous drainage and hemorrhagic presentation, four^{17,35,53,59} analyzed the association using multivariate regression and seven^{2,11,20,46,51,62,76} used univariate regression. There was no significant heterogeneity among these articles ($p = 0.08$ and $I^2 = 40\%$) and the fixed-effects model was used. The pooling results suggested that deep venous drainage was associated with the hemorrhagic presentation of AVMs (OR 2.28, 95% CI 1.55–3.36, $p < 0.0001$; Fig. 3A).

Single Draining Vein

Three articles^{17,20,59} compared the risk of hemorrhage with a single draining vein and multiple draining veins (≥ 2). No heterogeneity was found among these articles, and a fixed-effects model was used ($p = 0.36$ and $I^2 = 3\%$). After pooling the results, we found that a single draining vein was associated with a higher risk of hemorrhagic presentation (OR 2.23, 95% CI 1.27–3.92, $p = 0.005$; Fig. 3B).

Draining Vein Ectasia

Four articles^{17,20,47,59} reported the association between draining vein ectasia and hemorrhagic presentation. All articles provided the data to calculate the risk by univariate regression. There was no significant heterogeneity among these articles ($p = 0.27$ and $I^2 = 23\%$). By the fixed-effects model, the pooled results suggested that draining vein ectasia was associated with a lower risk of hemorrhage (OR 0.35, 95% CI 0.13–0.97, $p = 0.04$; Fig. 3C).

FIG. 2. Forest plots for comparison of epidemiology, including mean age (A), age > 12 years (B), and sex (C), in the hemorrhage and nonhemorrhage groups. IV = inverse variance methods.

Draining Vein Stenosis

Three articles^{17,20,59} provided the number of patients with draining vein stenosis. One article⁵⁹ reported that hemorrhage presented in all 3 patients with draining vein stenosis, and the risk could not be calculated. Thus, we analyzed the risk of draining vein stenosis with the number of patients and found that draining vein stenosis had no effect on the rate of hemorrhagic presentation (OR 1.27, 95% CI 0.56–2.85, $p = 0.57$; Fig. 3D). No significant heterogeneity was found among these articles ($p = 0.24$ and $I^2 = 31\%$).

Single Feeder

Only 2 studies^{20,59} compared the risk of hemorrhagic presentation in AVMs with a single feeder and multiple

feeders (≥ 2). There was no heterogeneity between the 2 articles ($p = 0.39$ and $I^2 = 0\%$), and the fixed-effects model was used. The pooled results suggested that the single feeder increased the rate of hemorrhage compared with multiple feeders (OR 3.72, 95% CI 1.31–10.62, $p = 0.01$; Fig. 3E).

AVM Size

Ten articles^{2,11,17,20,46,51,53,59,66,76} reported the association between the AVM size and hemorrhagic presentation. Among these articles, seven^{2,11,17,20,53,59,66} compared the risk of hemorrhage in larger (≥ 3 cm) and smaller (< 3 cm) AVMs. Three articles^{46,51,76} reported the risk of AVM size for hemorrhage, but did not define the cutoff values for AVM size. After pooling the results of 7 articles, we

FIG. 3. Forest plots for association of hemorrhagic presentation and draining vein of AVMs, including deep venous drainage (A), single draining vein (B), draining vein ectasia (C), draining vein stenosis (D), and single feeder (E). M-H = Mantel-Haenszel.

FIG. 4. Forest plots for association of hemorrhagic presentation and other characteristics of AVMs, including AVM size (A), eloquent location (B), deep location (C), infratentorial location (D), associated aneurysm (E), morphology (F), and high SM grade⁶⁸ (G).

found that the smaller AVMs had 3 times the risk of larger AVMs (OR 2.97, 95% CI 1.94–4.54, $p < 0.00001$; Fig. 4A); there was no significant heterogeneity ($p = 0.14$ and $I^2 = 38\%$), and the fixed-effects model was used.

Eloquent AVM Location

With univariate regression, 4 articles^{2,11,51,76} explored the relationship between eloquent AVM location and hemorrhagic presentation. Because there was no heterogeneity among these articles ($p = 0.88$ and $I^2 = 0\%$), the fixed-effects model was chosen. We found that there was no association between eloquent location and hemorrhagic presentation (OR 1.33, 95% CI 0.74–2.40, $p = 0.35$; Fig. 4B).

AVM Location

The AVM location was divided into deep/superficial location in 7 articles^{11,16,17,20,46,47,53} and supratentorial/infratentorial location in 8 articles.^{1,2,17,46,47,53,66,76} Before pooling the results, we found that there was no significant heterogeneity in the 2 groups ($p = 0.20$ and $I^2 = 30\%$, and $p = 0.55$ and $I^2 = 0\%$, respectively). The pooled results suggested that AVMs located in deep and infratentorial locations had a higher risk of hemorrhage: OR 1.82 (95% CI 1.22–2.72, $p = 0.004$; Fig. 4C) and OR 2.25 (95% CI 1.19–4.26, $p = 0.01$; Fig. 4D), respectively.

Associated Aneurysm

Eight articles^{2,11,17,20,46,47,59,76} discussed the risk of an associated aneurysm with hemorrhagic presentation. No heterogeneity was found among these articles ($p = 0.55$ and $I^2 = 0\%$). Using the fixed-effects model, we found that the associated aneurysm could not increase the risk of hemorrhage in pediatric patients with AVMs (OR 1.46, 95% CI 0.88–2.42, $p = 0.14$; Fig. 4E).

Morphology

Morphology of AVMs included diffuse and compact in 2 articles.^{17,20} The fixed-effects model was used for no heterogeneity ($p = 0.78$ and $I^2 = 0\%$), and the pooled results suggested that diffuse AVMs had a higher risk of hemorrhage than compact AVMs (OR 8.94, 95% CI 3.01–26.55, $p < 0.0001$; Fig. 4F).

High SM Grade

A high SM grade was defined as grade 4 or 5, and 7 articles^{1,11,16,51,62,66,76} provided the data to calculate the risk of high SM grade with hemorrhagic presentation. The fixed-effects model was used for no heterogeneity ($p = 0.60$ and $I^2 = 0\%$). The pooled results showed that high SM grade was associated with a lower risk of hemorrhage (OR 0.53, 95% CI 0.36–0.78, $p = 0.001$; Fig. 4G).

Publication Bias

There were 8 factors reported by more than 5 articles. With funnel plots and Begg's test, we found that there was no evidence of publication bias for these factors (Supplemental Fig. 1), including age ($p = 0.064$), sex ($p = 0.208$), AVM size ($p = 0.343$), deep venous drainage ($p = 0.078$), deep location ($p = 0.823$), infratentorial location ($p = 0.426$), associated aneurysm ($p = 0.274$), and high SM grade ($p = 0.160$).

Discussion

Implications of the Study

As pediatric and adult patients have different angioarchitecture, clinical presentation, and outcomes of AVMs, they usually present with different hemorrhagic features.¹⁷ Oulasvirta et al.⁵³ reported that pediatric patients with AVMs had a higher tendency to present with hemorrhage than adult patients with AVMs. Hemorrhage increases mortality and causes substantial neurological defects^{39,42} in pediatric patients compared with adult patients. In addition, pediatric patients should be treated more carefully, as the time-dependent features developed gradually and pediatric patients thus have a greater lifetime risk of brain AVM-associated morbidity.⁴² Therefore, identification of factors associated with hemorrhage in pediatric patients could help in the definitive treatment of pediatric AVM. To our knowledge, this is the first meta-analysis assessing the predictors for hemorrhagic presentation in pediatric AVM patients. The probability of hemorrhagic presentation was 63% (95% CI 58%–69%, $I^2 = 72.2\%$) in pediatric AVM patients. After pooling the results of 15 articles with 1155 patients, we found that the risk of first presentation with hemorrhage was higher in the patients with smaller AVMs, deep venous drainage, a single draining vein, deep cerebral locations, an infratentorial cerebral location, and diffuse AVMs.

In this meta-analysis, the probability of hemorrhagic presentation was higher in pediatric patients with AVMs (63%) than in studies of adult patients (30%–50%), which is consistent with the findings of many previous studies.^{22,30} Hetts et al.³⁰ found that there were significant differences in angioarchitecture of AVMs between pediatric and adult patients. Frontal and temporal AVMs accounted for 40%–50% of AVMs and were more common in adults than in children. AVMs in pediatric patients were more likely located in the basal ganglia, cerebellum, and posterior paracallosal areas,^{30,71} which were associated with higher hemorrhagic presentation of AVMs.^{14,72} In addition, deep venous drainage was more common in pediatric patients than in adult patients and it was also an independent factor for hemorrhage.^{29,35} However, Yang et al.⁷⁶ reported that pediatric patients with AVMs had a lower hemorrhage risk than adult AVM patients. They explained that children tend to not receive clinical attention until their AVMs rupture. One study²⁹ reported approximately the same annual hemorrhage risk of 2%–4% in pediatric and adult patients with AVMs. Therefore, more studies are needed to evaluate the annual hemorrhage rates for unruptured AVMs and to assess whether there are differences between pediatric and adult AVM patients.

Pooling the results of patients aged < 12 years and > 12 years for hemorrhagic presentation suggested that age was not associated with hemorrhagic presentation in pediatric AVMs. Skjøth-Rasmussen et al.⁶⁶ showed that the older patients had a significantly higher hemorrhage risk. The inconsistencies might be attributed to the limited number of patients included in this study. However, the mean age of patients in the ruptured AVM group was significantly lower than that in the unruptured AVM group, with a weighted mean difference of -1.53 . This difference suggested that a new threshold of age should be chosen to evaluate this relationship.

Small nidus size was associated with hemorrhagic presentation, which was consistent with the findings of previous studies.¹⁴ Spetzler et al.⁶⁸ reported that small AVMs presented with hemorrhage more often than large ones (82% vs 21%, $p < 0.001$). Although the pathophysiological mechanisms underlying this association remain unclear, they found that smaller AVMs were associated with higher feeding artery pressures upon surgery, as well as larger hematoma sizes; therefore, the most likely reason is that higher feeding artery pressures will increase hemorrhage risk. Despite the high rates of hemorrhagic presentation observed among small AVMs, several prospective studies^{2,11,53} have failed to find an association between AVM size and future hemorrhage. Although Fok et al.²⁰ reported that diffuse AVM nidus morphology was associated with higher hemorrhagic presentation, the definition of diffuse AVM was not clear in previous studies. Generally, diffuse AVM was defined as the presence of significant intervening brain tissue within the AVM nidus.^{17,20} Our analysis found that hemorrhagic presentation of diffuse AVMs was 8 times higher than that of compact AVMs.

The presence of deep venous drainage is an important feature associated with hemorrhage in adult AVMs. Hetts et al.³⁰ reported a significantly higher incidence of hemorrhage in pediatric patients with exclusively deep venous drainage compared with adult AVMs. Kellner et al.³⁵ identified deep venous drainage, rather than exclusively deep venous drainage, as a predictor for hemorrhagic presentation. Another report¹⁷ on 135 children with brain AVMs indicated that exclusively deep venous drainage was associated with hemorrhagic presentation, and identified exclusively deep venous drainage to be an independent predictor of hemorrhagic presentation using multivariate analysis. As pediatric AVM angioarchitecture changes over time, the association of deep venous drainage and exclusively deep venous drainage with hemorrhagic presentation becomes complex and remains controversial in children. In our meta-analysis, deep venous drainage ($p < 0.0001$) and a single draining vein ($p = 0.005$) increased the rate of hemorrhagic presentation. Deep draining veins typically have a smaller diameter than superficial draining veins, as well as a high frequency of stenosis.³⁵ Therefore, compared with superficial draining veins, nidi with deep draining veins would have higher pressure, which increases the hemorrhage risk. In addition, the single draining vein has been known as the baseline status of early-stage AVMs, with subsequent veins developing later.¹⁷ Compared with AVMs with several perinidal vessels, the single draining vein had elevated intranidal stress caused by the increased impedance to blood drainage, which may predispose the AVM to rupture. Thus, deep venous drainage and single venous drainage increased the rate of first presentation with hemorrhage.

Our analysis suggested that the associated aneurysm was not associated with hemorrhagic presentation in pediatric patients with AVMs. Anderson et al.² found no significant difference in the rate of hemorrhage ($p = 0.91$) between isolated AVMs (64%) and AVM-associated aneurysms (59%) in pediatric patients. However, they also found that AVM-associated aneurysms in an arterial location (91%) had a higher rate of hemorrhagic presentation compared with isolated AVMs ($p = 0.023$). In addition, a

previous study⁹ found that AVM-associated aneurysms in venous and intranidal locations did not appear to be associated with hemorrhage. The probable explanation is that the flow rate and pressure were higher on the arterial side of the AVM than that in the intranidal location or venous side, which could increase the risk of hemorrhage for arterially based aneurysms. Meanwhile, the arterially based aneurysm would affect the transmural pressure and led to an increased risk of rupture.

The location of AVMs was divided into superficial and deep locations. Some studies^{46,53} found that the deep AVM location was associated with hemorrhagic presentation; the deep AVM location in these studies included the thalamus, brainstem, or basal ganglia. Ding et al.¹⁴ reported that a significantly higher proportion of ruptured AVMs were at a deep location (41% vs 29%, $p = 0.022$). In our meta-analysis, the deep location was associated with higher hemorrhage risk. Pediatric AVMs are more likely located in the basal ganglia, cerebellar, and posterior paracallosal areas, and AVMs located in a deep location are more likely to have a high frequency of perforating artery supply and deep venous drainage.²⁹ Our meta-analysis also indicated that AVMs located in an infratentorial location had a higher risk of hemorrhage, with an OR of 2.25. Khaw et al.³⁶ suggested the infratentorial location as an independent predictor of initial and future AVM hemorrhage, and pediatric AVMs in infratentorial locations that often presented with epilepsy could not be found until rupture.

Limitations

Some limitations exist in this meta-analysis. First, although this meta-analysis only included pediatric AVMs without treatment, more prospective studies that provide the annual hemorrhage rate and factors for initial hemorrhage or recurrent hemorrhage after a long-term follow-up are needed. Second, the number of articles referring to some factors was limited, such as single feeder and morphology, and these results need more studies to confirm our findings in the future. Moreover, the results of studies referring to age (> 12 years) showed a great heterogeneity, and this pooled result needs to be discussed in future high-quality studies. Finally, the definitions of diffuse AVM and compact AVM were not quantitative, and therefore the morphology determined by the researchers might be confounded.

Conclusions

The hemorrhagic presentation of AVMs was higher in pediatric patients (63%) than in adult patients (30%–50%). The results of this meta-analysis suggested that pediatric AVMs with smaller size (< 3 cm), deep venous drainage, a single feeder, a single draining vein, deep location, infratentorial location, diffuse morphology, and high SM grade (4 or 5) were associated with higher hemorrhagic presentation. Particularly, patients with diffuse AVM have a higher risk of hemorrhagic presentation than other factors and may need active treatment. However, factors including age, sex, draining vein stenosis, and associated aneurysm were not predictors of hemorrhage in pediatric patients with AVMs.

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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: Jiang, Ai, Ye. Acquisition of data: Ai, Ye. Analysis and interpretation of data: Jiang, Ai, Ye. Drafting the article: Ai. Critically revising the article: Xu, You. Reviewed submitted version of manuscript: Xu, You. Approved the final version of the manuscript on behalf of all authors: Jiang. Statistical analysis: Jiang, Ai, Ye.

Supplemental Information

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