## ON-LINE APPENDIX

### *Methodologic Considerations*

**Location of Ruptured BAVMs.** It is difficult to precisely identify the borders of BAVMs in the setting of acute hemorrhage. However, most patients in our series did not undergo intervention for BAVMs during the acute period, and >85% of patients underwent repeat MR imaging 14 days after the hemorrhage. The median time to the last pretreatment MR image was 41 days (interquartile range, 17–114 days; mean, 302 ± 661 days) after a BAVM hemorrhage. Interobserver agreement between the 2 neuroradiologists regarding the periventricular location of a ruptured BAVM led to an excellent $\kappa$ coefficient of 0.82 (95% CI, 0.67–0.97). Therefore, the location of a ruptured BAVM can be outlined more precisely on MR images after the acute phase.

### *Hemorrhage Rate Based on Follow-Up from a BAVM Diagnosis to an ICH*

Some previous studies have reported an annual hemorrhage rate based on follow-up from a diagnosis of BAVM to an ICH event, an approach that is free of assumptions. Therefore, we reanalyzed the data on the basis of follow-up after a diagnosis with a BAVM until an ICH occurred.

### *Patients Who Did Not Undergo Interventional Treatment*

Sixteen of the 108 (14.8%) children with BAVMs did not receive any treatment (On-line Table 6). The mean follow-up was 4.4 years (range, 10 months to 13 years). Complete follow-up was available for all 16 patients. During the total follow-up of 70 patient-years, 1 patient experienced a hemorrhage from a BAVM, yielding an overall annual hemorrhage rate of 1.4%.

Nine of the 42 (21.4%) patients with unruptured BAVMs did not undergo any interventional treatment for BAVMs (3 with nonperiventricular BAVMs and 6 with periventricular lesions). No hemorrhages occurred in these patients during 43.8 patient-years of follow-up.

Seven of the 66 (10.6%) patients with ruptured BAVMs underwent conservative treatment with observation (2 with nonperiventricular BAVMs and 5 with periventricular lesions). One subsequent hemorrhage occurred in 7 patients with 26.2 patient-years of follow-up, yielding an annual hemorrhage rate of 3.8%. None of the nonperiventricular BAVMs ruptured; the only hemorrhage events occurred in 5 periventricular BAVMs with 16.5 patient-years of follow-up, yielding an annual hemorrhage rate of 6%. Because all hemorrhage events occurred in periventricular BAVMs during this follow-up period, no further univariate or survival analyses were performed.

### *Patients with More Than 1 Month of Treatment-Free Follow-Up*

Although 85% of the children in this cohort underwent interventional treatment, 66 of 108 (61.1%) patients had >1 month of treatment-free follow-up (On-line Table 6). The mean follow-up was 2.1 years (range, 1.1 months to 13 years). During the total follow-up of 136.7 patient-years, 5 patients experienced a hemorrhage from a BAVM, yielding an overall annual hemorrhage rate of 3.7%.

Interventional treatment was not initiated in 31 of 42 (73.8%) patients with unruptured BAVMs within 1 month after diagnosis. No hemorrhages occurred in these patients with 76.9 patient-years of follow-up.

Thirty-five of 66 (53%) patients with ruptured BAVMs were followed for >1 month before treatment (9 with nonperiventricular BAVMs and 26 with periventricular lesions). Five hemorrhages occurred in these patients, who had 59.8 patient-years of follow-up, yielding a hemorrhage rate of 8.4% per year. No hemorrhages occurred in 9 nonperiventricular BAVMs with 12.5 patient-years of follow-up. In contrast, 5 hemorrhagic events occurred in 26 periventricular BAVMs, with 47.3 patient-years of follow-up, yielding an annual hemorrhage rate of 10.6%. The follow-up time of the periventricular group was longer than that in the nonperiventricular group. Therefore, future studies may be expected to reduce the difference in the follow-up period. Although survival analysis did not suggest that periventricular BAVMs ruptured earlier (log-rank, $P = .123$), all hemorrhage events occurred in periventricular BAVMs (On-line Table 6). These analyses indicate that a periventricular location can distinguish BAVMs at risk of subsequent hemorrhage from those without a hemorrhage risk.

**On-line Table 1: Association of potential predictors with BAVM hemorrhage**

| Characteristic | Univariate Logistic (Hemorrhage Presentation) (*n* = 108) | | | Multivariable Logistic[a] (Hemorrhage Presentation) (*n* = 108) | | | Univariate Cox Proportional Hazards (Hemorrhage after Birth) (*n* = 108) | | | Multivariable Cox Proportional Hazards[a] (Hemorrhage after Birth) (*n* = 108) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Periventricular location | 2.784 | 1.274–6.215 | .012[b] | 3.443 | 1.328–8.926 | .011[b] | 1.917 | 1.131–3.250 | .016[b] | 1.140 | 0.702–1.851 | .597 |
| Maximal AVM size (mm) | 0.972 | 0.951–0.994 | .012[b] | 0.965 | 0.941–0.989 | .005[b] | 0.983 | 0.969–0.997 | .015[b] | 0.987 | 0.974–1.001 | .063 |
| Age at diagnosis | 0.928 | 0.842–1.022 | .129 | 0.962 | 0.855–1.081 | .514 | 0.643 | 0.573–0.721 | .000[b] | 0.596 | 0.531–0.669 | <.001[b] |
| Male sex | 0.889 | 0.402–1.964 | .771 | 0.868 | 0.353–2.134 | .758 | 1.059 | 0.645–1.739 | .821 | 1.026 | 0.640–1.643 | .916 |
| Deep location | 1.524 | 0.662–3.510 | .322 | 1.304 | 0.470–3.621 | .610 | 1.182 | 0.719–1.944 | .510 | 0.587 | 0.338–1.021 | .059 |
| Posterior fossa location | 1.066 | 0.241–4.712 | .933 | 0.705 | 0.128–3.892 | .689 | 1.054 | 0.422–2.631 | .911 | 0.720 | 0.275–1.890 | .505 |
| Exclusively deep venous drainage | 2.759 | 0.556–13.68 | .214 | 1.601 | 0.257–9.978 | .614 | 1.784 | 0.847–3.756 | .128 | 1.259 | 0.578–2.742 | .562 |
| Associated aneurysm | 1.696 | 0.496–5.807 | .400 | 1.478 | 0.338–6.461 | .604 | 1.893 | 0.958–3.741 | .066 | 1.138 | 0.595–2.177 | .695 |

**Note:**—HR indicates hazard ratio.

[a] Adjusted for age at diagnosis, sex, deep location, posterior fossa location, periventricular location exclusively deep venous drainage, associated aneurysm, and maximal nidus size.

[b] Statistically significant.

**On-line Table 2: Factors associated with severe presentation after BAVM hemorrhage by univariate analysis[a]**

| Characteristic | Nonsevere Presentation (mRS ≤3) (*n* = 38) | Severe Presentation (mRS >3) (*n* = 28) | Total (*n* = 66) | *P* Value |
|---|---|---|---|---|
| Demographics | | | | |
| Sex | | | | .461 |
| Female | 17 (44.7) | 10 (35.7) | 27 (40.9) | |
| Male | 21 (55.3) | 18 (64.3) | 39 (59.1) | |
| Age at diagnosis (yr) | 10.92 ± 3.96 | 9.86 ± 4.12 | 10.47 ± 4.03 | .292 |
| Radiologic | | | | |
| Venous drainage | | | | .399[b] |
| Not exclusively deep | 35 (92.1) | 23 (82.1) | 58 (87.9) | |
| Exclusively deep | 3 (7.9) | 5 (17.9) | 8 (12.1) | |
| Deep location | | | | .219 |
| No | 26 (68.4) | 15 (53.6) | 41 (62.1) | |
| Yes | 12 (31.6) | 13 (46.4) | 25 (37.9) | |
| Periventricular location | | | | .059 |
| No | 15 (39.5) | 5 (17.9) | 20 (30.3) | |
| Yes | 23 (60.5) | 23 (82.1) | 46 (69.7) | |
| Posterior fossa location | | | | .643[c] |
| No | 36 (94.7) | 25 (89.3) | 61 (92.4) | |
| Yes | 2 (5.3) | 3 (10.7) | 5 (7.6) | |
| Associated aneurysm | | | | .858[b] |
| No | 33 (86.8) | 23 (82.1) | 56 (84.8) | |
| Yes | 5 (13.2) | 5 (17.9) | 10 (15.2) | |
| Maximal nidus size (mm) | 32.79 ± 16.83 | 39.49 ± 20.31 | 35.64 ± 18.54 | .148 |
| Deep hematoma | | | | .006[d] |
| No | 33 (86.8) | 16 (57.1) | 49 (74.2) | |
| Yes | 5 (13.2) | 12 (42.9) | 17 (25.8) | |
| Temporal hematoma | | | | .309 |
| No | 30 (78.9) | 19 (67.9) | 49 (74.2) | |
| Yes | 8 (21.1) | 9 (32.1) | 17 (25.8) | |
| Hematoma >30 mL | | | | .003[d] |
| No | 34 (89.5) | 16 (57.1) | 50 (75.8) | |
| Yes | 4 (10.5) | 12 (42.9) | 16 (24.2) | |
| Hydrocephalus | | | | .010[b,d] |
| No | 36 (94.7) | 19 (67.9) | 55 (83.3) | |
| Yes | 2 (5.3) | 9 (32.1) | 11 (16.7) | |

[a] Data entries are No. (%) or mean ± SD.
[b] *P* values are from the $\chi^2$ test (correction for continuity).
[c] *P* values are from the Fisher exact test.
[d] Statistically significant.

**On-line Table 3: Demographic data and risk factors for hemorrhage across pediatric untreated BAVM studies**

| Study (yr) | No. of Subjects | Mean Age (yr) | Hemorrhage Presentation | Risk Factor | Primary Outcome | OR/HR | 95% CI | *P* Value |
|---|---|---|---|---|---|---|---|---|
| Kellner et al (2011)[26] | 77 | – | 62.0% | Small nidus size | Hemorrhage presentation | – | – | .005 |
| | | | | Eloquent location | | | | .02 |
| | | | | Deep venous drainage | | | | .009 |
| Anderson et al (2012)[24] | 77 | 13.4 | 62.3% | Associated aneurysm | Hemorrhage presentation | – | – | .37 |
| | | | | Deep venous drainage[a] | | | | .393 |
| Ellis et al (2013)[25] | 135 | 10.1 | 63.7% | AVM size | Hemorrhage presentation | 0.57 | 0.43–0.77 | <.01 |
| | | | | Exclusive deep venous drainage | | 4.94 | 1.30–18.8 | .02 |
| | | | | Infratentorial location | | 9.94 | 1.71–51.76 | .01 |
| Zheng et al (2014) [27b] | 127 | 13.2 | 70.9% | AVM size | Hemorrhage presentation | – | – | .000 |
| | | | | Deep venous drainage | | | | .03 |
| | | | | Infratentorial location | | | | >.05 |
| Kellner et al (2014)[28] | 81 | 13.3 ± 5.4 | 63.0% | Single draining vein | Hemorrhage presentation | 5.16 | 1.05–25.5 | .04 |
| | | | | Deep venous drainage | | 8.22 | 1.32–51.1 | .02 |
| Present study | 108 | 10.95 ± 4.13 | 61.1% | Periventricular location | Hemorrhage presentation | 3.443 | 1.328–8.926 | .011 |
| | | | | Maximal AVM size | | 0.965 | 0.941–0.989 | .005 |

**Note:**—HR indicates hazard ratio; –, none.
[a] Univariate analysis and not incorporated in the multivariable logistic regression model.
[b] Multivariable analysis results were reported without description of methods.

**On-line Table 4: Demographic data across studies with periventricular location as a risk factor for BAVM prognosis**

| Study (yr) | No. of Subjects | Mean Age (yr) | Survival Analysis | Periventricular Location Evaluation | Primary Outcome | OR | *P* Value |
|---|---|---|---|---|---|---|---|
| Marks et al (1990)[14] | 65 | 33 | Multivariate linear discriminant analysis | CT/MRI | Hemorrhage | 0.746[a] | <.05 |
| Friedman et al (1996)[21] | 201 | 39 | Descriptive | MRI | Hemorrhage after radiosurgery | – | – |
| Meder et al (1997)[22] | 102 | 33 ± 14.7 | Univariate | MRI and angiogram | Obliteration at 2 yr after radiosurgery | – | – |
| Zipfel et al (2004)[15] | 268 | 40 | Logistic regression | CT | Pretreatment hemorrhage | 6.358 | .000 |
| Kasliwal et al (2009)[29] | 14 | 26 | Descriptive | Angiography | Hemorrhage after GKS | – | – |
| Present study | 108 | 10.95 ± 4.13 | Logistic regression | MRI | Hemorrhage presentation | 3.443 | .011 |

**Note:**—GKS indicates gamma knife surgery; –, none.

[a] Positively associated with hemorrhage presentation.

**On-line Table 5: Demographic data across BAVM studies with follow-up from birth to primary outcome**

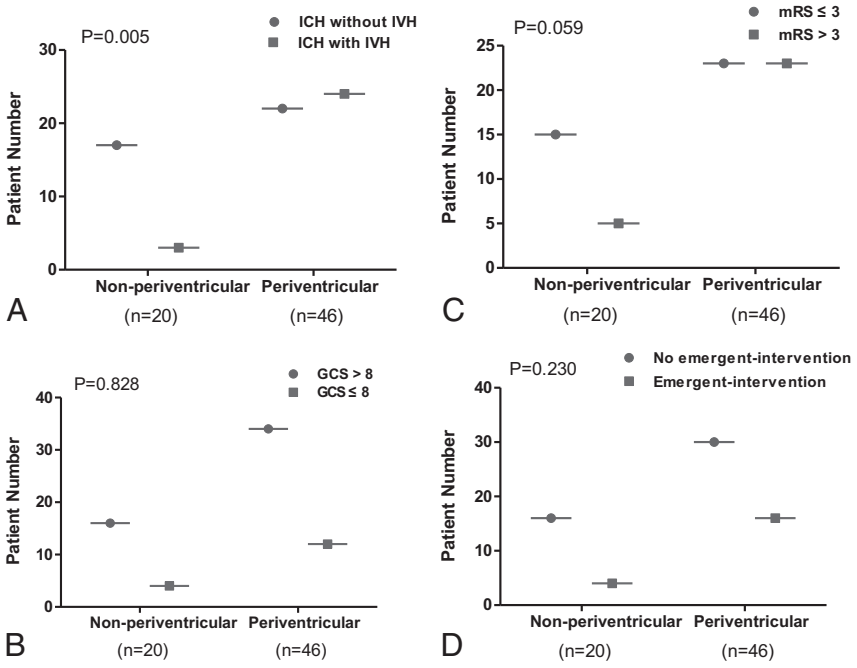
| Study (yr) | No. of Subjects | Mean Age (yr) | Survival Analysis | Reviewed Variable | Time-Dependent Covariable | Primary Outcome | Total Patient-Years |
|---|---|---|---|---|---|---|---|
| Horton et al (1990)[31] | 451 | 27.5 ± 12.9 | Descriptive and univariable | Pregnancy | – | Any hemorrhage | 14,235 |
| Pollock et al (1996)[32] | 315 | 35.0 ± 15.2 | Cox proportional hazards model | Age<br>Sex<br>Hemorrhage presentation<br>Nidus compactness<br>No. of draining veins<br>Nidus volume<br>Proximity to pial/ependymal surface<br>Related aneurysm<br>Varix | Patient age | Initial hemorrhage | 10,348 |
| Han et al (2003)[33] | 73 | 35.4 | Descriptive | Spetzler-Martin Grade | – | Initial hemorrhage | 2581 |
| Gross and Du (2012)[34] | 58 | – | Descriptive and Cox proportional hazards model | Pregnancy | Pregnancy | Any hemorrhage | 2704.9 |
| Liu et al (2014)[16] | 979 | 26.16 ± 12.4 | Descriptive and univariable (case crossover) | Pregnancy | – | Any hemorrhage | 25,578 |
| Present study | 108 | 210.95 ± 4.13 | Descriptive and univariable and Cox proportional hazards model | Age<br>Sex<br>BAVM location<br>Venous drainage<br>Associated aneurysm<br>Maximal AVM size | Patient age | Any hemorrhage | 1279 |

**Note:**— – indicates none.

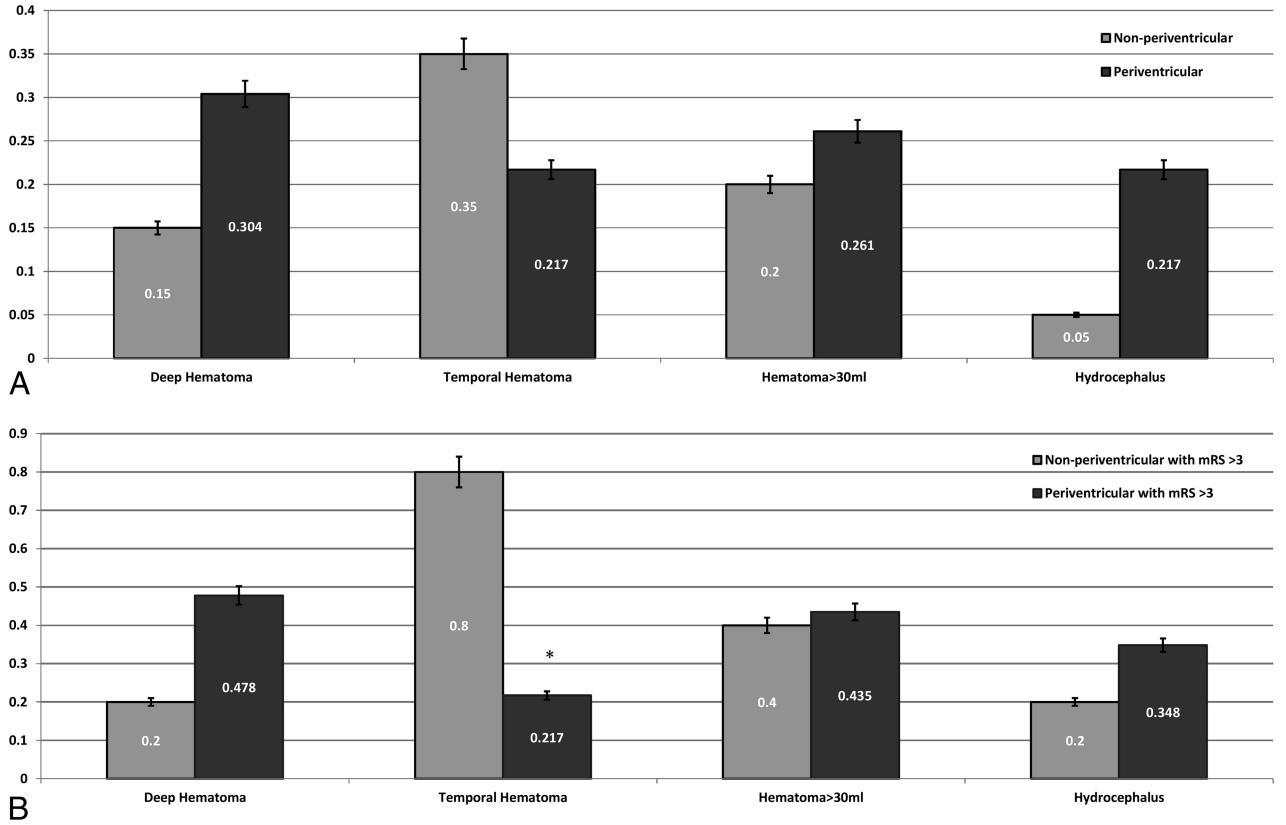
**On-line Table 6: Follow-up of BAVMs with conservative observation after diagnosis**

| Characteristic | Unruptured BAVM without Interventional Treatment | | | Ruptured BAVM without Interventional Treatment | | | Unruptured BAVM with Treatment-Free Follow-Up >1 Mo | | | Ruptured BAVM with Treatment-Free Follow-Up >1 Mo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NPV (*n* = 3) | PV (*n* = 6) | Total (*n* = 9) | NPV (*n* = 2) | PV (*n* = 5) | Total (*n* = 7) | NPV (*n* = 16) | PV (*n* = 15) | Total (*n* = 31) | NPV (*n* = 9) | PV (*n* = 26) | Total (*n* = 35) |
| Follow-up (patient-yr) | 19 | 24.8 | 43.8 | 9.7 | 16.5 | 26.2 | 35.1 | 41.8 | 76.9 | 12.5 | 47.3 | 59.8 |
| Bleeding during follow-up | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 5 | 5 |
| Annual hemorrhage rate (%) | 0 | 0 | 0 | 0 | 6 | 3.8 | 0 | 0 | 0 | 0 | 10.6 | 8.4 |

**Note:**—NPV indicates nonperiventricular; PV, periventricular.




**ON-LINE FIG 1.** Comparison of hemorrhage location (*A*), immediate posthemorrhage-presentation Glasgow Coma Scale score (*B*), modified Rankin Scale score (*C*), and emergent intervention (*D*) in children with and without periventricular BAVMs.




**ON-LINE FIG 2.** Hemorrhagic features of ruptured periventricular BAVMs versus nonperiventricular BAVMs (*A*) and ruptured BAVMs with an mRS of >3 (*B*).