Correlation between arteriovenous malformation nidus size and intraparenchymal hematoma volume in the event of rupture

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1. Introduction

Brain arteriovenous malformations (BAVMs) are high-flow cerebrovascular lesions consisting of a tangle of abnormal blood vessels. The high-pressure arterial blood shunts through the nidus without an intervening capillary bed, which normally acts as a pressure resistor, leading to venous-side pressure load. Chronic hemodynamic stress and abnormal angiogenesis lead to histopathological changes in AVMs. AVM rupture is believed to be a consequence of high-pressure load on the venous side concurrently with abnormal and fragile vessels.

Rupture is still the most common reason why AVMs come to clinical attention (42%–72% of cases), although the hemorrhage rate has been declining along with the increasing availability of cranial MRIs, due to which more AVMs are diagnosed as unruptured (Gross and Du, 2013; Hernesniemi et al., 2008; Ondra et al., 1990; da Costa et al., 2009; van Beijnum et al., 2009). Although AVM rupture is not considered as dangerous as spontaneous ICH, it is still associated with 4–13% mortality and 25–40% morbidity, affecting mostly young, otherwise healthy, adults in their 20–40s (Oulasvirta et al., 2019; Kim et al., 2019; da Costa et al., 2009; van Beijnum et al., 2009). Consequently, the primary purpose of the treatment is to eliminate rupture risk. However, not all AVMs rupture, and some of them can be asymptomatic throughout a patient’s lifetime. As the treatment itself involves risks, especially in AVMs, which can be highly complex, it is not surprising that a vast amount of research has focused on analyzing the rupture risk. It is estimated that the overall risk of hemorrhage is 2–4% per year, but the risk varies considerably, depending on various factors (Gross and Du, 2013; Hernesniemi et al., 2008; Ondra et al., 1990; da Costa et al., 2009). The most consistently reported risk for subsequent hemorrhage is a previous rupture (Gross and Du, 2013; Hernesniemi et al., 2008; Crawford et al., 1986; Stapf et al., 2006; Forster et al., 1972; Yamada et al., 2007; Mast et al., 1997; Halim et al., 2004; Yang et al., 2016). Among other factors for rupture risk, the most frequently reported are deep location and exclusively deep venous drainage (Gross and Du, 2013; Hernesniemi et al., 2008; Stapf et al., 2006; Yamada et al., 2007).

One factor causing confusion from time to time is the size of the AVM’s nidus and its relationship to hemorrhage risk. Small nidus size is consistently associated with hemorrhagic presentation (Hernesniemi et al., 2008; Oulasvirta et al., 2019; Ding et al., 2016; Spetzler et al., 1992; Laakso and Hernesniemi, 2012). However, small AVM size has not been a risk factor for subsequent hemorrhage in any longitudinal studies using multivariate models. Most small AVMs do not appear to become symptomatic unless they rupture. However, back in 1992, Spetzler et al. studied the relationship between feeding artery pressure (FMAP), nidus size, and hematoma volume (Spetzler et al., 1992). Feeding artery pressures were measured intraoperatively with a No. 27 needle attached to a strain gauge inserted into the main feeding artery simultaneously with measurements of the systemic mean arterial blood pressure (MABP). The authors observed an inverse relationship between nidus size and feeding artery pressures together with hematoma volumes, as smaller
AVMs tended to have higher FMAP and larger hematoma volumes. It is not surprising that intraoperative FMAP measurements have not been replicated. Three decades later, there are still very few studies on the relationship between AVM size and hematoma volume and severity of the bleeding. Research has focused on risk factors for rupture, which is to be expected, as the primary goal is to avoid hemorrhage. However, when contemplating the overall risk of the lesion, it is also important to understand the magnitude of the consequences in the event of rupture. While the consequences of rupture can be appreciated by evaluating the clinical outcome, hematoma volume is a more quantitative parameter, and its causal relationship to the AVM and its properties is much more direct. The clinical consequences are apparent; if smaller AVMS cause larger and more severe hemorrhage in the event of a rupture, this should be considered when contemplating the treatment. The primary purpose of our study was to observe the relationship of AVM nidus size to hematoma volume and to clinical severity of the hemorrhage. Our hypothesis was that small nidus size leads to an increased pressure gradient across the vasculature of the nidus, and, in the event of rupture, to a larger hematoma volume and more severe bleeding. Our secondary goals were to determine the association of nidus size, ICH volume, and clinical rupture severity to the patient's outcome and to validate the arteriovenous malformation related intracerebral hemorrhage (AVICH) (Neidert et al., 2016) score in our cohort.

2. Methods

Every patient with a ruptured AVM admitted to the Department of Neurosurgery of Helsinki University Hospital in 2000–2018 was retrospectively reviewed. Data were collected from patient medical records, radiology archives, and the Helsinki AVM database. Age, sex, AVM location and size, the Spetzler-Martin grading scale (SMG) (Spetzler and Martin, 1986) and the supplementary grading scale (Lawton-Young) (Lawton et al., 2010), the Hunt and Hess score (HHS) (Hunt and Hess, 1968) on admission, the World Federation of Neurological Surgeons (WFNS) (Report of World Federation of, 1988) score on admission, the arteriovenous malformation related intracerebral hemorrhage (AVICH) score, and the Glasgow Outcome Score (GOS) (Jennett and Bond, 1975) at first follow-up (2–4 months) were analyzed for each patient. One patient from abroad did not have a 2–4 month GOS score available because he was treated as an emergency while visiting Finland and was later transferred to his own country.

The AVM diagnosis was based on digital subtraction angiography (DSA). Size, location, angioarchitecture, and associated aneurysms of the AVM were evaluated from angiography, computed tomography (CT), and/or magnetic resonance images (MRI). The maximum diameter of the nidus (in any direction in lateral or AP view), measured from DSA was used as the measure of nidus size in statistical analyses. The AVM was considered deep if it was in paracallosal, basal ganglia, intraventricular, trigonal, temporomesial, pontomesencephalic, or deep cerebellar locations; all other locations were considered superficial. The AVM was regarded as ruptured before admission if there were signs of bleeding in CT or MRI.

Patients with substantial intraventricular hemorrhage (IVH) were excluded since bleeding into a CSF-filled ventricular space is a very different biomechanical phenomenon (less resistance against hematoma expansion) than formation of intraparenchymal hematoma. Infratentorial AVMS were also excluded, again, because confined infratentorial compartment likely inflicts higher resistance against hematoma expansion than supratentorial space, yet smaller hematomas infratentorially cause more severe clinical consequences, making direct comparison to supratentorial hemorrhages questionable.

Hematoma volume was evaluated from CT scans with 4-mm slice thickness. The scans were transferred to Brainlab Elements software (1990–2018, copyright Brainlab AG, Germany), which was used to calculate the hematoma volumes. The margins of the hematoma were outlined manually in each slice, and the program then calculated the volume of the hematoma. The calculations were verified by two of the authors independently. To ensure good comparability of the measured hematoma volumes, patients without CT scans prior to the treatment of the AVM were excluded from the study.

The clinical severity of AVM rupture was assessed on two scales for each patient:

1. Hunt and Hess
2. World Federation of Neurological Surgeons (WFNS)

The association between the clinical severity of rupture and AVM size and hematoma volume was tested. An association to hematoma volume was tested as a validation of the cohort.

The AVICH score, a novel grading system to predict the outcome of AVM-related ICH, was assessed for each patient along with the Spetzler-Martin grading system and the Lawton-Young (supplementary SMG) scale.

The outcome was measured with the Glasgow Outcome Score (GOS) at the first follow-up in the outpatient clinic (2–4 months post-operatively). The association of hematoma volume and the HH and WFNS scales with the 2–4-month GOS score was assessed for every patient. Finally, the ability of the AVICH score, along with the SMG and the Lawton-Young scales, to predict the 2–4-month GOS score was tested. An outcome analysis was conducted for hematoma volume, HH, and WFNS scales to validate that these variables really did measure the clinical severity of AVM bleeding.

The HH, WFNS, SMG, Lawton-Young, and AVICH scales are presented in detail in the supplementary material.

3. Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 24.0, IBM Corp.). Quantitative variables were handled as continuous or ordinal. The associations between the variables were assessed with two-tailed Spearman's correlation test. P-value <0.05 was considered as statistically significant.

4. Data availability

Owing to Finnish legislation, pseudonymized raw data are personal data that are not to be shared outside Helsinki University Hospital. The study was approved by the ethics committee of Helsinki University Hospital. Under Finnish law, informed consent is not required for a retrospective study based on hospital records.

5. Results

A total of 115 patients with ruptured AVMs were admitted to the Department of Neurosurgery in Helsinki University Hospital during 2000–2018. After exclusion of 27 patients with infratentorial AVMS and 24 patients with substantial IVH, the final study cohort analyzed comprised 64 patients.

6. Patient and disease characteristics

The median admission age was 48 (SD 20) years. There was a slight predominance of males (55% males vs 45% females). The mean AVM size was 21 mm (SD 12) and the mean hematoma volume was 31 ml (SD 26). Most of the patients had a small AVM: in 83% (n = 53) nidus size was <30 mm, in 14% (n = 9) 30–60 mm, and in 3% (n = 2) >60 mm. The majority of patients (90%) were surgically treated, either with surgery alone or in combination with endovascular embolization. In one patient treated initially with embolization and subsequently with radiotherapy, the remaining AVM was finally surgically operated on after it ruptured. Patient and AVM characteristics, along with the results of the SMG, Lawton-Young, HH, and WFNS scores, are presented in more detail in
7. Hematoma volume, nidus size, HHS, and WFNS correlation

The two-tailed Spearman's test showed no correlation between the volume of the hematoma and the size of the AVM nidus (correlation coefficient $-0.072$, p $= 0.570$, confidence interval 95%) (Fig. 1 presents the results as a scatter plot). Neither did the WFNS score and HHS at admission correlate with AVM size (WFNS: correlation coefficient $-0.130$, p $= 0.307$, confidence interval 95%, HHS: correlation coefficient $-0.112$, p $= 0.376$, confidence interval 95%) (Figs. 2 and 3). However, larger hematoma volume was associated with higher HH (correlation coefficient 0.572, p $< 0.001$, confidence interval 95%) and WFNS scores (correlation coefficient 0.657, p $< 0.001$, confidence interval 95%) (Figs. 4 and 5).

8. Outcome

The GOS was assessed at the outpatient clinic 2–4 months after the AVM rupture. One patient was lost to follow-up as subsequent treatment was outside Finland. Half of the patients (50%) made a good recovery, 31% had a moderate disability, 16% had a severe disability, and one patient (2%) had died (Table 3). The two-tailed Spearman’s correlation test was used to assess the relationship between ranked variables. Larger hematoma volumes were associated with lower GOS scores at first follow-up (correlation coefficient .541, p $< 0.001$, confidence interval 95%) (Fig. 6). Nidus size did not correlate with the 2–4-month GOS score (correlation coefficient 0.112, p $= 0.382$, confidence interval 95%) (Fig. 7). Higher HH and WFNS scores were also associated with a lower GOS score at the first follow-up (HHS: correlation coefficient 0.464, p $< 0.001$, confidence interval 95%, WFNS: correlation coefficient 0.438, p $< 0.001$, confidence interval 95%) (Figs. 8 and 9).

The AVICH score demonstrated a clear correlation with the 2–4-month GOS score (correlation coefficient 0.570, p $< 0.001$, confidence interval 95%) (Fig. 1). AVICH scores at admission correlate with the 2–4-month GOS score (correlation coefficient 0.570, p $< 0.001$, confidence interval 95%). However, the supplementary SMG did not correlate with the 2–4-month GOS score (correlation coefficient 0.167, p $= 0.191$, confidence interval 95%).

9. Discussion

Our study of 64 ruptured supratentorial AVM patients did not support the hypothesis that small AVMs cause larger hematomas or clinically more severe bleedings in the event of a rupture. Hematoma volumes, along with HH and WFNS scores, were evenly distributed across the nidal

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**Table 1** Patient and disease characteristics.

| Sex                  |        |        |
|----------------------|--------|--------|
| Male                 | 35     | 55%    |
| Female               | 29     | 45%    |
| Total                | 64     | 100%   |

**Location of the AVM**

| Location             |        |        |
|----------------------|--------|--------|
| Frontal              | 26     | 41%    |
| Parietal             | 13     | 20%    |
| Temporal             | 19     | 30%    |
| Occipital            | 5      | 8%     |
| Multiple             | 1      | 2%     |
| Total                | 64     | 100%   |

**AVM size**

| Size                  |        |        |
|-----------------------|--------|--------|
| Small (<30 mm)        | 53     | 83%    |
| Medium (30–60 mm)     | 9      | 14%    |
| Large (>60 mm)        | 2      | 3%     |
| Total                 | 64     | 100%   |

**Treatment modality**

| Treatment             |        |        |
|-----------------------|--------|--------|
| Surgery               | 44     | 69%    |
| Embolization + surgery| 13     | 20%    |
| Embolization + surgery + radiotherapy | 1 | 2% |
| Embolization          | 4      | 6%     |
| Embolization + radiotherapy | 1 | 2% |
| Conservative          | 1      | 2%     |
| Total                 | 64     | 100%   |

**Spetzler-Martin Grade**

| Grade |        |        |
|-------|--------|--------|
| 1     | 15     | 23%    |
| 2     | 31     | 31%    |
| 3     | 14     | 14%    |
| 4     | 3      | 3%     |
| 5     | 1      | 2%     |
| Total | 64     | 100%   |

**Supplementary Spetzler-Martin grade**

| Grade |        |        |
|-------|--------|--------|
| 2     | 3      | 5%     |
| 3     | 17     | 27%    |
| 4     | 22     | 34%    |
| 5     | 17     | 27%    |
| 6     | 2      | 3%     |
| 7     | 2      | 3%     |
| 8     | 1      | 2%     |
| Total | 64     | 100%   |

**Hunt & Hess at admission**

| Grade |        |        |
|-------|--------|--------|
| 1     | 6      | 9%     |
| 2     | 11     | 17%    |
| 3     | 25     | 39%    |
| 4     | 16     | 25%    |
| 5     | 6      | 9%     |
| Total | 64     | 100%   |

**WFNS at admission**

| Grade |        |        |
|-------|--------|--------|
| 1     | 13     | 20%    |
| 2     | 6      | 9%     |
| 3     | 32     | 50%    |
| 4     | 6      | 9%     |
| 5     | 7      | 11%    |
| Total | 64     | 100%   |

**Table 2** AVICH.

| Score at admission |        |        |
|--------------------|--------|--------|
| 3                  | 5      | 8%     |
| 4                  | 18     | 28%    |
| 5                  | 17     | 27%    |
| 6                  | 15     | 23%    |
| 7                  | 4      | 6%     |
| 8                  | 4      | 6%     |
| 9                  | 1      | 2%     |
| Total              | 64     | 100%   |

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![Fig. 1. Hematoma volume did not correlate with AVM size. The volume was calculated from 4-mm slice thick CT scans using Brainlab Elements software. Nidus maximum diameter was measured from digital subtraction angiography (DSA). Two-tailed Spearman's test was used to assess the correlation between variables: correlation coefficient $-0.072$, p $= 0.570$, confidence interval 95%.](image-url)
size range. To validate these results, we analyzed the correlation between hematoma volumes and HH and WFNS scores on admission. As expected, patients with larger hematomas had higher HH and WFNS scores.

Yu et al. had similar results in their study of 169 ruptured AVMs: no correlation between AVM size and hematoma volumes was observed (Yu et al., 2018). However, they did not exclude IVH patients, which could have affected the ICH volumes observed. In contrast, Miyasaka et al. observed significantly larger hematoma volumes of small (<3 cm) AVMs than of medium and large AVMs (>3 cm) in their study of 55 patients (30.0 ± 3.7 cm³ vs 7.0 ± 2.7 cm³) (Miyasaka et al., 1999). The discrepancies between the former study and ours can be attributed to different statistical methods, as we analyzed hematoma volumes and AVM diameters as continuous variables, while they dichotomized between <3 cm and larger AVMs, which together with a relatively small sample size makes their results more susceptible to the random effect. Finally, Alén et al. reported that micro-AVMs (<1 cm) are associated with large ICH volumes (mean volume 25 ml) (Alén et al., 2013), but they did not include a comparison group, and their reported mean hematoma volume

![Fig. 2. The World Federation of Neurological Surgeons (WFNS) scale did not correlate with AVM size. The WFNS score was assessed at admission. Nidus maximum diameter was measured from digital subtraction angiography (DSA). Two-tailed Spearman's test was used to assess the correlation between variables: correlation coefficient –0.130, p = 0.307, confidence interval 95%.](image)

![Fig. 3. The Hunt & Hess scale did not correlate with AVM size. The Hunt & Hess score was assessed at admission. Nidus maximum diameter was measured from digital subtraction angiography (DSA). Two-tailed Spearman's test was used to assess the correlation between variables: correlation coefficient –0.112, p = 0.376, confidence interval 95%.](image)

![Fig. 4. Larger hematoma volume was associated with higher Hunt & Hess grade. The volume was calculated from 4-mm slice thick CT scans using Brainlab Elements software. The Hunt & Hess score was assessed at admission. Two-tailed Spearman's test was used to assess the correlation between the variables: correlation coefficient 0.572, p < 0.001, confidence interval 95%.](image)

![Fig. 5. Larger hematoma volume was associated with higher World Federation of Neurological Surgeons (WFNS) grade. The volume was calculated from 4-mm slice thick CT scans using Brainlab Elements software. The WFNS score was assessed at admission. Two-tailed Spearman's test was used to assess the correlation between the variables: correlation coefficient 0.657, p < 0.001, confidence interval 95%.](image)

![Fig. 6. Larger hematoma volume was associated with lower Glasgow Outcome Score (GOS). The volume was calculated from 4-mm slice thick CT scans using Brainlab Elements software. The GOS was assessed at the outpatient clinic at 2–4 months. Two-tailed Spearman's test was used to assess the correlation between the variables: correlation coefficient 0.541, p < 0.001, confidence interval 95%.](image)

**Table 3**

| Outcome         | Count | Percentage |
|-----------------|-------|------------|
| Good recovery   | 32    | 50%        |
| Moderate disability | 20  | 31%        |
| Severe disability | 10  | 16%        |
| Dead            | 1     | 2%         |
| Total           | 63    | 100%       |
| Missing         | 1     |            |
should be interpreted in relation to the mean hematoma volume of 31 ml in our study.

Correlation of hematoma volume, HH, and WFNS scores on admission with GOS at the first follow-up.

Larger hematoma volume and higher HH and WFNS scores were associated with lower GOS scores at the first follow-up 2-4 months postoperatively. Larger hematoma volumes have been associated with poorer outcomes also by other authors (Shotar et al., 2018). In addition to destructive edema and raised intracranial pressure, larger hematomas cause more damaging irritation to the surrounding brain parenchyma than do smaller hematomas. As larger hematoma volumes were associated with higher HH and WFNS scores, these scores were also associated with lower GOS scores, validating use of these scales in measuring bleeding severity.

Correlation of nidus size and SMG, Lawton-Young, and AVICH grades with GOS at the first follow-up.

Somewhat surprisingly, nidus size did not correlate with the GOS at 2-4 months either, even though most of the patients were surgically treated. Still, nidus size is one of the surgical risk factors included in most risk-assessing scales. However, these risk scales were developed to assess the surgical risk in elective patients and so do not consider the acute consequences of the ICH. Consequently, the SMG did not correlate with the 2-4-month GOS score in our series, whereas the Lawton-Young scale demonstrated a modest correlation (rupture status being included in the scale). For this reason, the AVICH score was developed to predict the outcome in the event of rupture. Indeed, our study confirmed the excellent correlation between the AVICH score and the GOS at the first follow-up.

10. Other potential factors affecting hematoma volume

The hypothesis that small AVMs lead to larger hematomas is logical in the context of fluid mechanics, which theoretically should lead to higher nidal pressure. However, our results show that small AVMs may cause hematomas ranging in volume from very small to large. Nidal pressure is probably affected by various other variables such as the number and caliber of draining veins and feeding arteries, overall pressure in the venous system, and the ability of draining veins to adapt to altered pressure (e.g., venous ectasia vs venous stenosis), which is why nidus diameter alone cannot predict nidus pressure and the consequent hematoma volume in the event of rupture.

It is also possible that the properties of the vessel wall of AVMs and the biological processes involved play a more important role in the rupture and the subsequent hematoma. A recent landmark study identified somatic activating KRAS mutations in the endothelial AVM cells (Nikolaev et al., 2018). The mutant KRAS was shown to increase endothelial cell migratory behavior as well as disassembly of adherens junctions in vitro. Consequently, the rupture risk and severity of the rupture are probably also related to the biological processes affecting AVM integrity. Furthermore, we recently published a study on the higher prevalence of smoking in AVM patients than in the matched general population (Pohjola et al., 2020). In brain aneurysms, smoking is a well-established risk factor for aneurysm formation, rupture risk, and severity of the rupture (Rautalin et al., 2020). It is possible that smoking plays a similar role in AVMs, but further studies are needed to confirm this.

11. Limitations

The largest hematomas in the poorest clinical condition may not be included in the study, as the Helsinki AVM database consists only of patients admitted to the neurosurgery department. Most AVM patients are, however, fairly young and therefore treated aggressively in the event of a rupture. The majority of the AVMs in our study were small, which may increase the likelihood of random-effect in the hematoma volumes observed in large AVMs, an effect that was, nevertheless, diminished by analyzing AVM size as a continuous variable. Assessment of the clinical severity of the bleed with different scales is always somewhat subjective: to counter this, the hematoma volume and the 2-4-month GOS were analyzed for these variables.
12. Conclusions

Our results did not support the hypothesis that small AVMs lead to larger hematoma volumes in the event of a rupture. Consequently, AVM size did not correlate with the clinical severity of the bleeding as measured with HH and WFNS scores. Conversely, WFNS and HH scores showed a strong correlation with hematoma volume and the outcome. The AVICH score was also associated with outcome.

Hematoma volume is most likely affected by numerous other variables and characteristics of the AVM that were beyond the scope of this study. Expectedly, our study confirmed that larger supratentorial hematomas are associated with a more severe clinical manifestation and a poorer outcome.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbas.2022.101663.

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