



# Prognostic variables and outcome in relation to different bleeding patterns in arteriovenous malformations

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## Abstract

Subarachnoid hemorrhage as bleeding pattern occurs rarely in ruptured arteriovenous malformations (AVM). The aim of the present study is to evaluate different bleeding patterns in hemorrhages due to an AVM and their impact on outcome in terms of risk and treatment stratification. We evaluated 158 patients with ruptured AVMs who were admitted to our neurosurgical department from 2002 to 2017. We compared different bleeding patterns, such as intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), or both (ICH + SAH) and evaluated predictive variables for outcome in the last follow-up. ICH was found in 48.7% of patients, isolated SAH in 20.9% of patients, and both in 30.4% of patients. The mean parenchymal blood volume was 34.5cm<sup>3</sup>. 38.6% of the patients had AVM-associated aneurysms, mostly located pre-nidal (77%). AVMs with ruptured aneurysms often resulted in ICH with SAH component ( $p < 0.001$ ) and SAH pattern occurred more often infratentorial ( $p = 0.003$ ). In a multivariate logistic regression model, poor clinical state on admission (WFNS IV-V) ( $p < 0.01$ ), eloquence, infratentorial location ( $p = 0.05$ ), and presence of ICH with SAH component ( $p = 0.02$ ) were the most relevant predictors of a poor outcome after AVM rupture. Bleeding pattern in AVM hemorrhage depends on angioarchitectural and hemodynamic features and SAH component predicts outcome negatively. AVM-associated pre-nidal aneurysms may harbor a higher risk for rupture and SAH pattern when located infratentorial. Treatment decisions and risk stratifications should be considered in view of these findings.

**Keywords** Arteriovenous malformation · Subarachnoid hemorrhage · Hemorrhage pattern

## Introduction

Outcome in hemorrhage due to an arteriovenous malformation (AVM) is infrequently devastating and depends on bleeding pattern. While recent studies suggest that AVM hemorrhage is not as devastating as previously presumed compared to aneurysmal subarachnoid hemorrhage (SAH), which is more often lethal, AVM rupture tends to result in more neurological deficits [1]. In addition to several negative prognostic factors such as older age [2], poor initial admission state [3], hematoma volume [4], and infratentorial location [5, 6], a subarachnoid component seems to impact outcome significantly. Intraparenchymal hematoma is the most common

pattern in AVM-associated hemorrhage [7]. SAH due to an AVM is described to amount 9% and literature therefore is rare. The objective of our single-center study is to assess how far subarachnoid component in AVM-associated hemorrhage impacts the final outcome negatively.

## Materials and methods

### Study design

The study was performed in accordance with our institutional ethical review board. A retrospective review of patients with ruptured brain arteriovenous malformation (AVM) who were registered and evaluated at our neurosurgical department from 2002 to 2017 and entered into our prospectively maintained database was carried out. The onset of hemorrhage was considered as the day at which the patient was admitted to our emergency service. The diagnosis AVM was confirmed with magnetic resonance imaging (MRI) or digital subtraction angiography (DSA). Different bleeding patterns such as

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intracerebral hemorrhage (ICH), SAH, and intraventricular hemorrhage (IVH) were compared. All patients were treated in accordance with our institutional vascular board and national guidelines for the treatment of brain AVMs.

### Data collection

Patients gender, age, and admission grade based on the World Federation of Neurosurgical Societies (WFNS) [8] were recorded. Outcome was assessed at discharge and within 6 months, using the modified Rankin Scale (mRS) [9] and outcome was classified as favorable (mRS 0–2) and unfavorable (mRS 3–6).

### Image analysis

All patients received at least a computed tomography (CT), and to confirm an AVM and for follow-up, we performed a MRI and DSA. Imaging was performed and interpreted by an experienced neuroradiologist. The bleeding patterns were categorized, and in cases of SAH, the primary Fisher score was recorded. For computer-assisted volumetric measurements of intracerebral hemorrhage, the BrainLab® elements software (BrainLab Germany Headquarters, Munich, Germany) was used. AVMS were classified according to the Spetzler Martin grading system. The location of the AVM was categorized as supratentorial and infratentorial. AVM features such as size, the existence of AVM-associated aneurysms (AAA), and deep venous drains were recorded. AAAs were divided into pre-nidal arterial and intra-/post-nidal venous aneurysms.

### Statistical analysis

Statistical analysis was performed using the statistical software package SPSS (IBM SPSS Statistics for Windows, Version 22; Armonk, New York, USA. IBM Corp.) and the statistical software package BIAS (Version 11.08). Categorical variables were analyzed in contingency tables using the Fisher exact test, and an unpaired *t* test was used for parametric statistics. For univariate analysis, statistical significance was set at  $p < 0.05$ . Variables with a possible association with a vascular malformation ( $p < 0.1$ ) were entered into a forward stepwise multiple logistic regression analysis.

## Results

### Demographic characteristics and AVM features

Demographic data, radiologic findings, and AVM features are listed in Table 1.

**Table 1** Demographic characteristics of 158 patients with AVM-associated hemorrhage

No. of patients	158 (%)
Clinical features	
Female	80 (50.6)
Mean age years, (range)	43 (2–82)
WFNS admission—good (I–III)	104 (65.8)
mRS—favorable (0–2)	119 (75.3)
AVM features	
Spetzler Martin 1	27 (17.1)
Spetzler Martin 2	52 (32.9)
Spetzler Martin 3	62 (39.2)
Spetzler Martin 4	14 (8.9)
Spetzler Martin 5	3 (1.9)
Aneurysm	
Arterial	47 (77)
Venous	14 (23)
Deep drainage	93 (58.9)
AVM location	
Supratentorial	109 (69)
Infratentorial	49 (31)
Hemorrhage characteristics	
Mean hemorrhage volume cm <sup>3</sup>	34.5
IVH component	
Isolated SAH	33 (20.9)
SAH + ICH	48 (30.4)
Isolated ICH	77 (48.7)
Fisher 1–2	29 (36.7)
Fisher 3–4	50 (63.3)
DCI*	10 (6.3)

\*Delayed cerebral infarction

A total of 158 patients with ruptured brain AVMs were included and reviewed. Patients mean age was 43 years and ranged from 2 to 82 years. Gender distribution was similar, and 66% of the patients presented in a good clinical condition (WFNS I–III).

Spetzler Martin grade 1 to 3 AVMs were found in 89.2% of patients, and angiography showed AAAs in 38.6%. Most of them were arterial pre-nidal aneurysms (77%). Venous aneurysms were mostly located supratentorial (85.7% vs 14.3%; [95%CI 6.26 (1.3; 31.1)];  $p = 0.03$ ). The rate of ruptured infratentorial aneurysms was higher than unruptured infratentorial aneurysms (88.5% vs. 11.5%;  $p = 0.02$ ) and resulted in SAH bleeding pattern (isolated or with ICH) significantly (95%CI 2.99 [1.46; 6.12];  $p = 0.003$ ). The posterior inferior cerebellar artery (PICA) was more prone to develop AAA and caused hemorrhage frequently (47.4%). In general, pre-nidal aneurysms tended to rupture more often compared to post-nidal aneurysms (90.9% vs 9.1%; [95%CI 14.3 (3.5; 58.5)];  $p < 0.0001$ ).

The majority of the AVMs (93; 58.9%) had a deep draining system and was located supratentorial (109; 69%).

### Differences and predicting variables in bleeding patterns

48.7% of the patients had an isolated ICH; isolated SAH was found in 20.9% of the patients and ICH with SAH component was present in 30.4% of cases. Of those, 63.3% suffered a Fisher score 3 to 4 hemorrhage. Patients with isolated ICH or SAH were less affected than patients with combined ICH and SAH component on admission (95%CI 3.03 [1.5; 6.2];  $p = 0.002$ ). A ruptured aneurysm was found more often in isolated SAH as the underlying bleeding source (95%CI 2.42 [1.17; 5.02];  $p = 0.02$ ). Intraventricular hemorrhage occurred in 49.4% of patients, mostly in patients with SAH and ICH (95%CI 2.78 [1.37; 5.66];  $p = 0.005$ ), and a decompressive craniectomy was more often necessary in patients with ICH and SAH (95%CI 6.10 [1.50; 24.79];  $p = 0.009$ ). Bleeding patterns did not predict cerebral infarction. The relationship of different variables to bleeding patterns is demonstrated in Fig. 1.

### Outcome

Data of predictive variables for outcome in univariate and multivariate analysis are summarized in Table 2. No correlation between outcome and age or gender was detected. The

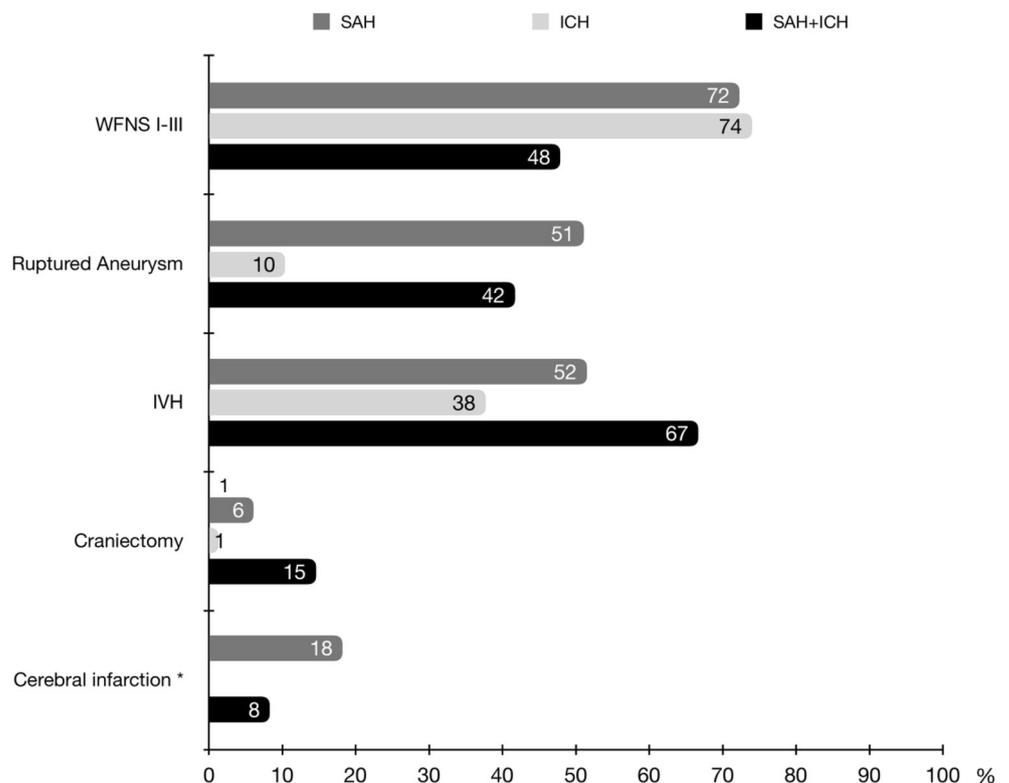
mean hemorrhage volume was 34.50 cm<sup>3</sup> with a calculated cutoff value up to 47.5cm<sup>3</sup> for favorable outcome (AUC 0.82; 95%CI [0.74; 0.90]). AAA, aneurysm rupture, and a high Fisher score (3 and 4) were significantly associated with unfavorable outcome only in univariate analysis. When studied in a multivariate logistic regression model, poor clinical grade on admission (WFNS IV-V), the eloquent and infratentorial location, and ICH with SAH component bleeding pattern were the most related predicting factors for an unfavorable outcome. A clear increase in the proportion of patients with poor outcome for ICH with SAH component is presented in Fig. 2.

## Discussion

### AVM features and influence on hemorrhage pattern

We found a significant association between the bleeding pattern and outcome. This study shows that the subarachnoid component in parenchymal AVM hemorrhage is correlated with poor outcome. AVMs show differences in hemorrhage pattern and clinical course in relation to their location and angioarchitecture. Information about size, feeding arteries, venous system, the occurrence of flow-related aneurysms, and AVM location is necessary for treatment-risk and outcome stratification [10–13]. In their study of patients with severe AVM-associated hemorrhage, Rahme et al. conclude that cisternal aneurysmal-like SAH and early seizures were

**Fig. 1** Relationship between different variables and bleeding pattern. Distribution of impact and association of different variables in relation to bleeding pattern. Initial admission state (95%CI 3.03 [1.49; 6.16];  $p = 0.002$ ), ruptured aneurysms (95%CI 2.42 [1.17; 5.02];  $p = 0.02$ ), intraventricular hemorrhage (95%CI 2.78 [1.37; 5.66];  $p = 0.005$ ), and decompressive craniectomy (6.10%1.50; 24.79];  $p = 0.009$ ) were significantly associated with the bleeding pattern. The occurrence of cerebral infarction did not correlate significantly with the bleeding pattern



**Table 2** Predictive variables for outcome in univariate and multivariate analysis

Variables	Univariate analysis		Multivariate analysis	
	OR, 95%CI	<i>p</i> value	OR, 95%CI	<i>p</i> value
WFNS	33.67 (11.72; 96.63)	< 0.001	221.43 (13.19; 3717.12)	< 0.001
Eloquent region	0.12 (0.07; 0.49)	< 0.001	0.08 (0.01; 0.67)	0.02
Infratentorial location	3.27 (1.53; 6.95)	0.003	6.93 (0.99; 48.25)	0.05
AAA	4.12 (1.92; 8.82)	< 0.001	NS	NS
Arterial aneurysm	NS	NS	NS	NS
Aneurysm rupture	3.4 (1.58; 7.29)	0.002	NS	NS
Fisher score	10.61 (2.27; 49.53)	< 0.001	NS	NS
Bleeding pattern: ICH + SAH	2.95 (1.39; 6.27)	0.005	19.31 (1.63; 228.30)	0.02

OR odds ratio, CI confidence interval, NS not significant

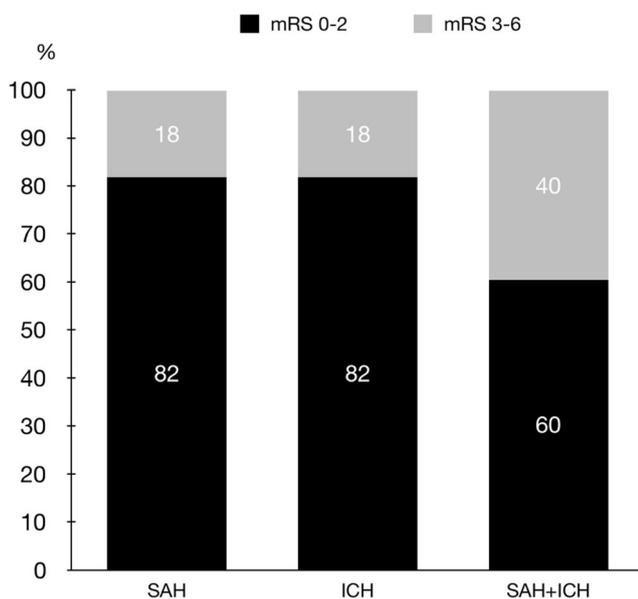
associated with a high rate of mortality [3]. Poor condition on admission [2] and infratentorial location [5, 6, 14–16] are common variables predicting an unfavorable outcome in AVM-associated hemorrhage. Hemorrhage is the initial presenting symptom of AVMs in 69.6%, as described in a population-based study in Sweden [1]. Even though subarachnoid hemorrhage in AVMs is a less common bleeding pattern [17–19], wherefore referring data in the pertaining literature are rare, special considerations regarding this are required. The most frequent cause of SAH is a ruptured aneurysm on or near the circle of Willis [19]. AVM-associated aneurysms are described to be a risk factor for hemorrhage [20–22]. The prevalence with AVM-associated aneurysms amounts 10 to 20% [23, 24] and the hemorrhage risk with associated aneurysms is described to be 63.6% compared to 50% without an associated aneurysm [25, 26]. Furthermore, the presence of

AAA increases the risk of subarachnoid hemorrhage in AVMs [27]. We found a higher rate of AVMs without aneurysms (61.4%) than with aneurysms. The rate of aneurysm rupture was high (72.1%), mainly caused by arterial aneurysms (90.9%) and led to SAH in 45.7% of the cases. Infratentorial aneurysms were more often arterial (92.3% vs. 65.7%), and the risk of rupture was higher compared to supratentorial aneurysms (88.5% vs. 59.5%).

## Outcome and risk stratification

Outcome in AVM-associated hemorrhage is discussed controversial. While previous data suggested that AVM–ICH may be less devastating as previously thought [4, 7, 28], recent literature evinced a more unfavorable outcome in patients with intraparenchymal AVM hemorrhage [29]. Our data show that there is a subgroup of AVM patients that are more affected at ictus and are prone to have an unfavorable outcome when ICH occurs in combination with SAH. In our study, SAH occurred in 51.3% cases and the presence of SAH in ICH was strongly associated with poor admission state and poor outcome. In addition to the mass effect of parenchymal hemorrhage, SAH may cause significant brain injury, reduction in cerebral blood flow, disturbance of autoregulation, and may lead to acute cerebral ischemia and, thus, poor prognosis [3, 30].

Other predicting variables were neurologic condition on admission, eloquent location, and infratentorial locations. AAA negatively correlated with outcome only in univariate analysis. Nevertheless, AVM-associated aneurysm, especially arterial aneurysms, harbor a higher risk for rupture, as shown in our study. In particular, arterial aneurysms are more prone to arise infratentorial and are more likely to be the source of hemorrhage. PICA aneurysms as bleeding source were detected frequently. Small vessels such as PICA or SCA are described to be more prone in developing increased wall shear stress in AVMs and evolving consequently aneurysms [31–33].



**Fig. 2** Distribution of favorable and unfavorable outcome in relation to bleeding patterns. Outcome distribution in association to the different bleeding patterns. SAH with ICH bleeding pattern is negatively correlated with the outcome (95%CI 2.95 [1.39; 6.27];  $p = 0.005$ )

Outcome in AVMs is infrequently devastating and treatment regime has been discussed controversially after the ARUBA trial [34]. Nevertheless, determination of prognostic factors is necessary for risk stratification and to provide the best treatment option. The SAH component in AVM hemorrhage is associated with poor outcome, and risk factors such as arterial pre-nidal aneurysms should be taken into consideration in treatment decisions in unruptured AVMs.

## Limitations

The retrospective study design is one limitation of our study. Nevertheless, the high number of our study patients evaluated with appropriate diagnostic methods and follow-up data strengthens the evidence of our results.

## Conclusion

Patients with AVM-associated hemorrhage and subarachnoid component are more affected and more often have a poor outcome. Therefore, special attention is needed for this subgroup of patients and pre-nidal aneurysms that lead more often to SAH bleeding pattern are meant to present a high-risk factor.

## Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee (University Hospital Frankfurt) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** For this type of study, formal consent is not required.

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