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CLINICAL ARTICLE

Outcome of 107 conservatively managed unruptured brain arteriovenous malformations: a single center's 30-year experience

Philippe Dodier, MD, PhD, Beate Kranawetter, MD, Dorian Hirschmann, MD, Muhammet Dogan, Anna Cho, MD, Helena Untersteiner, MD, Philipp Göbl, MD, Brigitte Gatterbauer, MD, Wei-Te Wang, MD, Christian Dorfer, MD, Karl Rössler, MD, Gerhard Bavinzski, MD, and Josa M. Frischer, MD, PhD

Department of Neurosurgery, Medical University of Vienna, Austria

OBJECTIVE Since the publication of A Randomized Trial of Unruptured Brain AVMs (ARUBA), the management of unruptured brain arteriovenous malformations (bAVMs) has been controversially discussed. Long-term follow-up data on the exclusively conservative management of unruptured bAVMs are scarce. The authors evaluated the long-term outcomes of patients with unruptured untreated bAVMs in a real-life cohort.

METHODS A retrospective observational cohort of 107 patients (of 897 bAVM patients referred to the authors' institution) with a diagnosis of unruptured and conservatively managed bAVMs is presented. AVMs of all Spetzler-Martin grades were observed. The mean follow-up period was 84 months. In 44% of patients, a follow-up period of 5 years or longer was observed. A national death register comparison completed the outcome analysis.

RESULTS The median age at diagnosis, sex distribution, neurological presentation, and modified Rankin Scale score were comparable to the patients in the medical management arm of the ARUBA study. Patients were mainly young, predominantly male, and in good clinical condition. Similar to the ARUBA cohort, 77% of this study's cohort presented in an excellent clinical status at the time of last follow-up. However, 17% of patients had at least one hemorrhage, resulting in an overall annual hemorrhage risk of 2.7% in the observation period. Moreover, the cumulative 1-, 5-, and 10-year overall hemorrhage rates were 3.0%, 11.3%, and 15.3%, respectively. Consequently, the long-term follow-up AVM-related mortality rate amounted to 8%. The estimated median overall survival after AVM diagnosis was 19.3 years (95% CI 14.0–24.6 years). A multivariate Cox regression model revealed temporal and deep-seated localization as an independent risk factor for AVM hemorrhage, while the presence of seizures reached borderline significance as a risk factor.

CONCLUSIONS The authors' results represent the long-term course of unruptured untreated bAVMs. Their data support the conclusion that even in the post-ARUBA era, tailored active treatment options may be offered to patients with unruptured bAVMs. For patient counseling, individual risk factors should be weighed against the center's treatment-specific risks.

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KEYWORDS unruptured brain arteriovenous malformation; conservative management; hemorrhage risk; vascular disorders

Brain arteriovenous malformations (bAVMs) are a relatively rare disease with a detection rate of 1/100,000 person-years. However, over the past decades, the prevalence of unruptured bAVMs has greatly increased because of technical advances in neuroradiological imaging.[1–3] Following a bAVM rupture, mortality rates of 11% and permanent morbidity of up to 40% have been reported.[2] Consequently, the main treatment goal is to prevent an AVM rupture. Management options include microsurgical resection, endovascular embolization, stereotactic radiosurgery, and combinations thereof and, in case of high-grade AVMs, mainly conservative management.[1–3] Recommendations to surgically treat low-grade AVMs and to radiosurgically treat high-risk and deep-seat-

ABBREVIATIONS ARUBA = A Randomized Trial of Unruptured Brain AVMs; AVM = arteriovenous malformation; bAVM = brain AVM; KPS = Karnofsky Performance Status; mRS = modified Rankin Scale.

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ed AVMs do exist but do not represent level I evidence.[4] Since data of the prospective A Randomized Trial of Unruptured Brain AVMs (ARUBA) have been available, concluding that medical management is superior to any form of interventional treatment, the optimal management of unruptured bAVMs has been controversially discussed.[5,6] Although many studies have assessed the outcome of different treatment options in ARUBA-eligible patients with bAVMs, studies on the conservative management of exclusively unruptured ARUBA-eligible bAVMs are lacking.[2] We present the long-term outcome of a single-center real-life cohort of 107 conservatively managed and ARUBA-eligible patients with unruptured bAVMs.

Methods

Study Population and Outcome Evaluation

We reviewed our institutional records of 897 patients who were referred to our clinic between 1992 and 2020 with the diagnosis of a bAVM. After retrospective chart review, 107 patients with conservatively treated unruptured bAVMs fulfilled the inclusion criteria (Fig. 1 and Table 1). Reasons for conservative management are detailed in Table 2 and predominantly included the patient's wish. AVM angioarchitecture, size, and localization were evaluated based on retrospective chart review and available imaging such as digital subtraction angiography, CT/CTA, MRI/MRA, or a combination of these modalities. The Spetzler-Martin and Spetzler-Ponce grading systems as well as the modified Rankin Scale (mRS) and Karnofsky Performance Status (KPS) were applied.[7–10] At the last follow-up, mRS and KPS scores were rated as mRS 6/KPS 0% if the patient died of an AVM hemorrhage. If the patient's death was due to other reasons, the last available clinical follow-up was used.

A national death register comparison for all study patients was performed. The study adhered to the STROBE statement and was approved by the local ethics review committee.

Statistical Analysis

IBM SPSS Statistics for Windows (version 26.0, IBM Corp.) was used for statistical analysis. Categorical data were presented as counts and percentages and continuous parameters as median and range. To compare patient groups, the chi-square, Fisher's exact, Mann-Whitney U-, and Wilcoxon signed-rank tests were performed as appropriate. Annual hemorrhage rates were calculated as the number of AVM hemorrhages during the observation period from the time of documented bAVM diagnosis divided by patient-years at risk. The median time to rupture and cumulative hemorrhage rates were estimated by the Kaplan-Meier method and lifetable analysis. Log-rank and Breslow tests were used to evaluate group differences as appropriate. Univariate Cox proportional hazards regression analyses were applied to identify risk factors for AVM rupture. Univariate Cox regression analyses were performed including AVM localization groups (temporal, brainstem, basal ganglia, thalamus, and corpus callosum vs other lobes and cerebellum), Spetzler-Martin grade, Spetzler-Ponce class, sex, age groups (≤ 60 vs > 60 years), venous drainage (superficial vs deep), AVM size groups (< 6 vs ≥ 6 cm),[10] presence or absence of seizures at diagnosis, treatment era (premodern [1992–2022] vs modern as defined previously[12]), and antihypertensive medication in the patient history (medication prescribed vs no medication/not known). In a next step, multivariate Cox regression models with an automated stepwise backward selection and a threshold p value of 5% were performed. A two-sided p value < 0.05 was considered statistically significant.

Results

Patient Characteristics, Overall Clinical Follow-Up, and Survival

Table 1 gives an overview of patient and AVM characteristics. In the overall sample, the median age at diagnosis was 44 years, and the median mRS score was 1. The sample included patients in all Spetzler-Martin grades and Spetzler-Ponce classes.

The median follow-up was 4.4 years (range 0.1–37.0 years). The total observation period amounted to 751 patient-years (697 years in the observation period until change of treatment plan or first hemorrhage; Fig. 1). Of note, in almost half of our patients (44%, 47/107) a follow-up period of 5 years or longer was observed. Most patients (76%, 81/107) stayed with their medical management without complications. In 8 patients (7%), the treatment strategy changed over time from medical to surgical or radiosurgical treatment, mainly because of the patient's wish. However, the remaining 18 patients (17%), representing all Spetzler-Martin grades and Spetzler-Ponce classes, had at least one hemorrhage in the observation period (Table 1). Among these 18 patients with a ruptured bAVM, conservative management at AVM diagnosis had been decided according to the patient's wish (n = 8, 44%) or the neurosurgeon's recommendation (n = 9, 50%, predominantly Spetzler-Martin grades IV and V). The remaining patient who experienced hemorrhage (6%) was not cleared for anesthesia. Consequently, in 10 (56%) of these 18 patients, microsurgery, embolization, or radiosurgery or combinations thereof were used to treat the ruptured AVM. The remaining 8 patients (44%) who had experienced an AVM rupture underwent no further specific AVM treatment and had an almost immediately fatal hemorrhage.

At the time of the study's conclusion, 78% of patients (83/107) were alive and 14% (15/107) had died of other causes. Of note, the remaining 9 patients had died as a consequence of an AVM rupture, resulting in a mortality rate of 8% (Table 1). Among patients who died of an AVM hemorrhage, the AVMs were diagnosed as Spetzler-Martin grade II in 38% of patients and grade IV or V in the remaining 62% of patients (p = 0.032). The estimated median overall survival after AVM diagnosis was 19.3 years (95% CI 14.0–24.6 years; Fig. 2A). At the last follow-up, the median mRS score was 1 (range 0–6) and the median KPS was 90% (range 0%–100%). Thus, the vast majority of patients (n = 82, 77%) had an excellent clinical status at last follow-up (mRS score 0 or 1; Table 1).

Time to Rupture, Hemorrhage Rates, and Risk Factors for AVM Rupture

Eighteen patients (17%) had a total of 19 hemorrhages

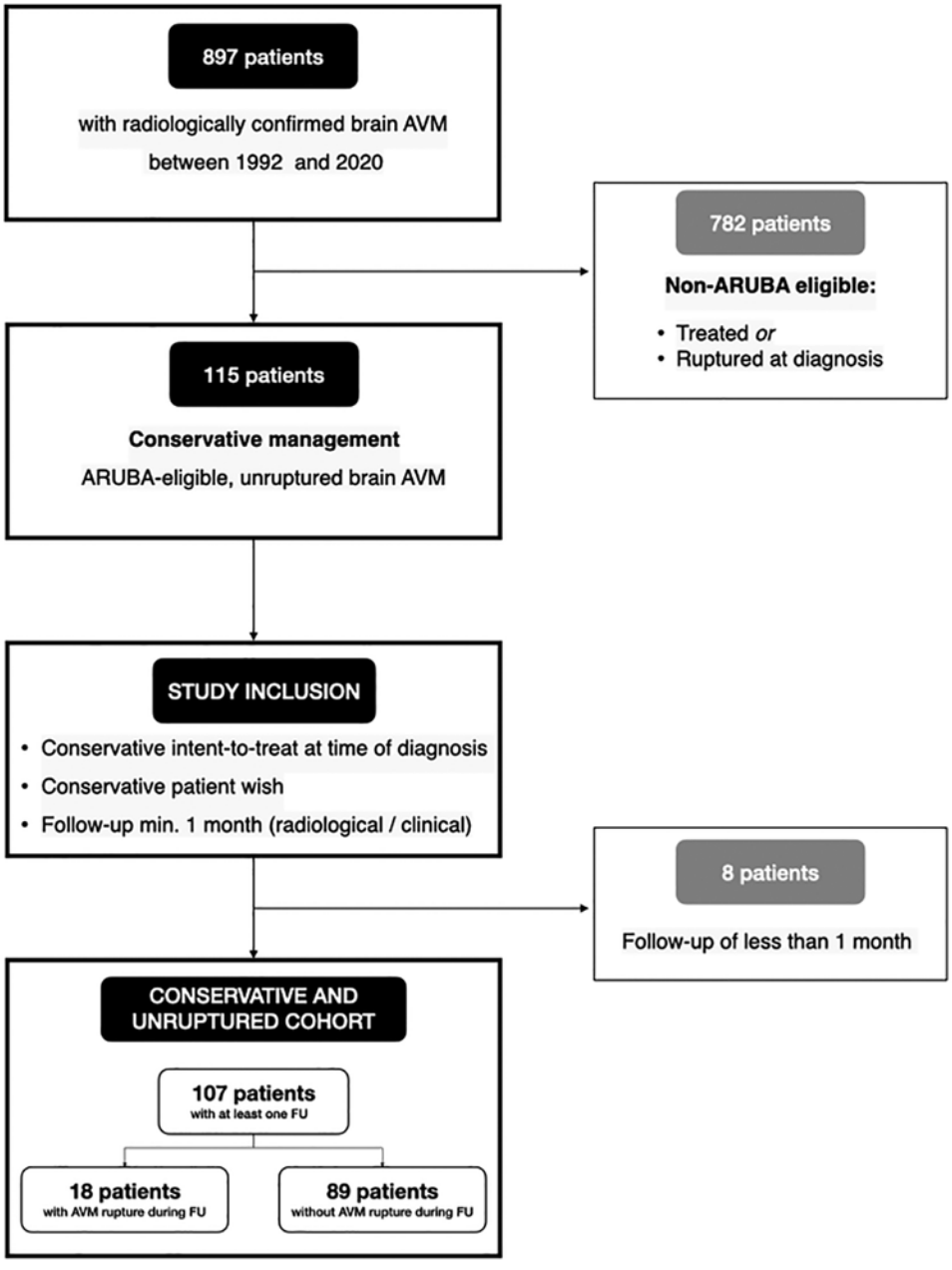

FIG. 1. Flowchart of study identification and inclusion. Between 1992 and 2020, 897 patients were referred to our clinic with the diagnosis of a bAVM. For the present study, only patients (115/897, 13%) with unruptured bAVMs at diagnosis that were managed conservatively were included. The remaining patients (782/897, 87%) were treated for their bAVM or already presented with an AVM hemorrhage at diagnosis. Patients with a follow-up of less than 1 month (only one documented visit at our clinic, no further data in the death register comparison) were further excluded from our study. Thus, 107 unruptured and conservatively treated bAVM patients fulfilled the inclusion criteria. FU = follow-up.

in the observation period until last follow-up or change in treatment plan, resulting in an overall annual hemorrhage risk of 2.7%. The Kaplan-Meier estimated median time to AVM rupture was 19.9 years (95% CI 11.5–28.3 years; Fig. 2B). The cumulative 1-, 5-, and 10-year hemorrhage rates in the total cohort were 3.0%, 11.3%, and 15.3%, respectively (Table 3 and Fig. 2B).

Table 1 shows patient and AVM characteristics with and without rupture during the observation period. Comparing these two groups, the localization of AVMs within the brain was the only apparent statistically significant difference ($p = 0.024$) in AVM characteristics. Ruptured AVMs were more often localized in the temporal lobe or in the thalamus/basal ganglia/brainstem/corpus callosum, but less often in other lobes or cerebellum. Consequently, the calculated annual hemorrhage risk was highest among temporal AVMs and thalamus/basal ganglia/brainstem/corpus callosum AVMs (Table 4). The estimated time to

TABLE 1. Overview of patient and AVM characteristics

	Total Sample of ubAVMs (n = 107)	No Hemorrhage After AVM Diagnosis (n = 89)	Hemorrhage After AVM Diagnosis (n = 18)	p Value
Median age at diagnosis, yrs (range)	44 (17–86)	44 (17–86)	35 (19–71)	0.159
Female/male ratio	50:57	41:48	9:9	0.760
Median KPS at diagnosis (range)	90 (40–100)	90 (40–100)	90 (80–100)	0.547
Median mRS score at diagnosis (range)	1 (0–4)	1 (0–4)	1 (0–2)	0.547
Localization of AVM				**0.024**
Occipital	23 (21)	22 (25)	1 (6)	
Frontal	14 (13)	14 (16)	0	
Central region	21 (20)	18 (20)	3 (17)	
Temporal	15 (14)	10 (11)	5 (27)	
Parietal	12 (11)	9 (10)	3 (17)	
Brainstem, thalamus, & basal ganglia	10 (9)	6 (7)	4 (22)	
Corpus callosum	7 (7)	5 (6)	2 (11)	
Cerebellar	5 (5)	5 (6)	0	
Max diameter, cm				0.404*
<3.0	41 (38)	35 (39)	6 (33)	
3.1–6.0	49 (46)	42 (47)	7 (39)	
>6.1	14 (13)	10 (11)	4 (22)	
Not known	3 (3)	2 (2)	1 (6)	
Venous drainage				0.596*
Superficial only	57 (53)	49 (55)	8 (44)	
Any deep	47 (44)	38 (43)	9 (50)	
Not known	3 (3)	2 (2)	1 (6)	
Eloquence				0.758
Yes	84 (79)	69 (78)	15 (83)	
No	23 (21)	20 (22)	3 (17)	
Flow-related aneurysms				0.155*
Yes	9 (8)	6 (7)	3 (17)	
No	97 (91)	83 (93)	14 (78)	
Not known	1 (1)	0	1 (6)	
SM grade				0.052*
I	9 (8)	8 (9)	1 (6)	
II	30 (28)	25 (28)	5 (27)	
III	30 (28)	28 (31)	2 (11)	
IV	25 (23)	21 (24)	4 (22)	
V	10 (9)	5 (6)	5 (27)	
Not known	3 (3)	2 (2)	1 (6)	
SP class				0.121*
A	39 (36)	33 (37)	6 (33)	
B	30 (28)	28 (31)	2 (11)	
C	35 (33)	26 (29)	9 (50)	
Not known	3 (3)	2 (2)	1 (6)	
Symptoms at time of diagnosis				0.242
Seizures	39 (36)	29 (33)	10 (56)	
Headache	30 (28)	28 (31)	2 (11)	
Hemiparesis/focal deficit	20 (19)	17 (19)	3 (17)	
Other	10 (9)	9 (10)	1 (6)	
None	8 (7)	6 (7)	2 (11)	
Seizures at time of diagnosis				0.065
Yes	39 (36)	29 (33)	10 (56)	
No	68 (64)	60 (67)	8 (44)	
Group era†				**<0.001**
Premodern	29 (27)	17 (19)	12 (67)	
Modern	78 (73)	72 (81)	6 (33)	

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TABLE 1. Overview of patient and AVM characteristics

	Total Sample of ubAVMs (n = 107)	No Hemorrhage After AVM Diagnosis (n = 89)	Hemorrhage After AVM Diagnosis (n = 18)	p Value
Median follow-up, yrs (range)	4.4 (0.1–37.0)	4.0 (0.1–24.4)	5.4 (0.2–37.0)	0.180
mRS score at last follow-up				**<0.001**
0	13 (12)	12 (14)	1 (6)	
1	69 (64)	66 (74)	3 (17)	
2	7 (7)	6 (7)	1 (6)	
3	1 (1)	1 (1)	0	
4	4 (4)	2 (2)	2 (11)	
5	4 (4)	2 (2)	2 (11)	
6‡	9 (8)	0	9 (50)	

SM = Spetzler-Martin; SP = Spetzler-Ponce; ubAVM = unruptured bAVM.
Values represent the number of patients (%) unless stated otherwise. Boldface type indicates statistical significance.
* Statistical tests were performed without unknown values.
† As defined in our previous publication (Hirschmann et al.[12]).
‡ Only includes patients with AVM-related death.

AVM rupture was significantly shorter among temporal AVMs and thalamus/basal ganglia/brainstem/corpus callosum AVMs compared with AVMs localized in the remaining cerebral lobes or the cerebellum (p = 0.004; Fig. 2C). Thus, 1-, 5-, and 10-year cumulative hemorrhage rates were highest among temporal and thalamus/basal ganglia/brainstem/corpus callosum AVMs (Table 3). Of note, 1-, 5-, and 10-year cumulative hemorrhage rates were also higher among patients with seizures than among patients without seizures (Table 3). Consequently, a trend was observed that patients with seizures experienced an AVM hemorrhage earlier (median 15.3 years, 95% CI 12.3–18.3 years) than patients without seizures (p = 0.099; Fig. 2D).

The difference in the distribution of Spetzler-Martin grades between patients with and without hemorrhage almost reached statistical significance (p = 0.052). Fifty percent of patients with hemorrhage were diagnosed as having a Spetzler-Martin grade IV or V AVM (Table 1). There was no significant difference in the distribution of Spetzler-Ponce classes comparing these groups. However, the calculated annual hemorrhage risk was rather equal among AVMs classified as Spetzler-Ponce class A and C (Table 4).

There was also no significant difference in the estimated median time to AVM rupture when comparing Spetzler-Martin grades or Spetzler-Ponce classes (Fig. 2E and F). Calculated annual hemorrhage rates separated for sex, age group, superficial or deep venous drainage, AVM size groups, and neurological symptoms are summarized in Table 4.

As a next step, we performed univariate followed by multivariate Cox regression analyses to identify risk factors for AVM rupture. Univariate Cox regression analyses revealed that AVM localization predominantly in the temporal lobe, brainstem, thalamus, basal ganglia, and corpus callosum was significantly associated with an increased risk of death (HR 4.113, 95% CI 1.555–10.879; p = 0.004).

However, for the multivariate Cox regression model we included all variables that reached statistical significance or borderline significance in the descriptive analysis (Table 1) or in the Kaplan-Meier estimations (Fig. 2C and D). Thus, a multivariate backward stepwise Cox regression analysis including the presence or absence of seizures at diagnosis, Spetzler-Martin grade, AVM localization groups, and treatment era was performed. The multivari-

TABLE 2. Overview of reasons for conservative management

	Total Sample of ubAVMs (n = 107)	No Hemorrhage After AVM Diagnosis (n = 89)	Hemorrhage After AVM Diagnosis (n = 18)	p Value
Reason for conservative management				0.064
Pt wish	66 (62)	58 (65)	8 (44)	
Surgeon recommendation, SM grade I or II	6 (6)	4 (4)	2 (11)	
Surgeon recommendation, SM grade III	4 (4)	4 (4)	0	
Surgeon recommendation, SM grade IV or V	18 (17)	11 (12)	7 (39)	
Age or multimorbidity	6 (6)	5 (6)	1 (6)	
Technical or administrative reasons	7 (7)	7 (8)	0	
Reason for conservative management (pooled)				0.116
Pt wish	66 (62)	58 (65)	8 (44)	
Surgeon recommendation, all SM grades, medical/technical reasons	41 (38)	31 (35)	10 (56)	

Pt = patient.

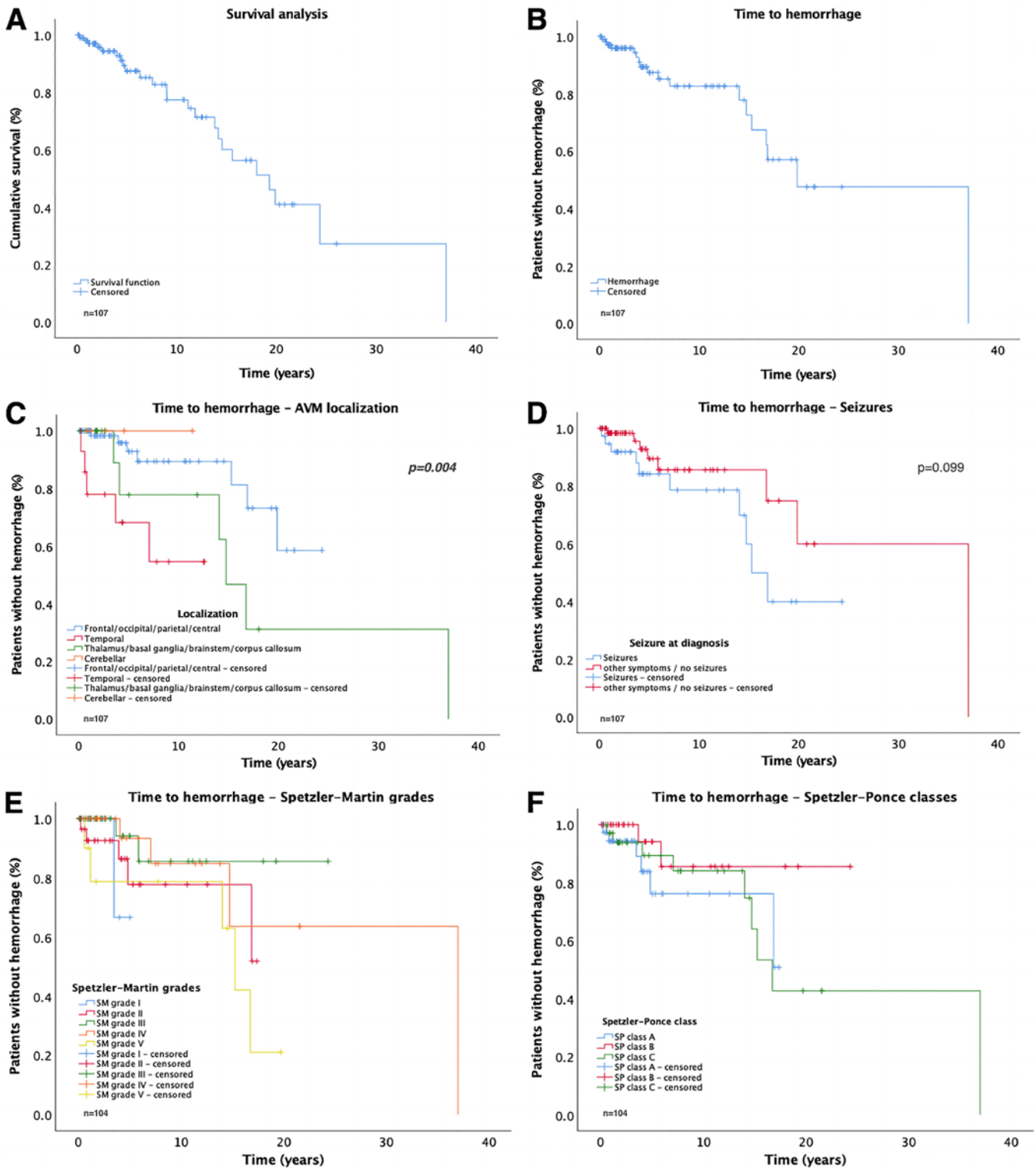

FIG. 2. Kaplan-Meier survival and time to hemorrhage estimates. **A:** Survival analysis depicting the cumulative survival of the entire cohort (n = 107). **B:** Time to first hemorrhage for the total cohort of 107 patients in the observation period until the last follow-up or change in treatment plan. **C:** Time to hemorrhage according to bAVM localization. The estimated median time to AVM rupture was significantly shorter among temporal AVMs or thalamus/basal ganglia/brainstem/corpus callosum AVMs compared with AVMs localized in the remaining cerebral lobes or the cerebellum (p = 0.004). **D:** Time to hemorrhage separated for clinical presentation at diagnosis: with or without seizure. A trend was observed that patients with seizures experienced an AVM hemorrhage earlier than patients without seizures (p = 0.099). **E and F:** Kaplan-Meier estimates were assessed for 104 patients; 3 patients with insufficient radiological data were excluded. Time to hemorrhage after diagnosis and conservative AVM management for Spetzler-Martin (SM) grades I–V (E) and Spetzler-Ponce (SP) classes (F). No significant differences among Spetzler-Martin grades or Spetzler-Ponce classes were observed.

TABLE 3. Cumulative hemorrhage rates

	1-yr	5-yr	10-yr
Total cohort	3.0%	11.3%	15.3%
Localization			
Temporal	22.2%	33.3%	45.5%
Thalamus, basal ganglia, brainstem, corpus callosum	0.0%	15.4%	16.0%
Frontal, occipital, parietal, central	0.0%	5.8%	8.8%
Cerebellar	0.0%	0.0%	0.0%
Seizures			
Seizures at time of diagnosis	5.3%	16.4%	20.7%
No seizures at time of diagnosis	1.6%	8.1%	11.6%
SM grade*			
I	0.0%	18.2%	—
II	7.4%	18.6%	20.5%
III	0.0%	4.5%	10.3%
IV	0.0%	5.3%	11.8%
V	10.5%	22.2%	23.5%
SP class*			
A	5.6%	18.5%	20.4%
B	0.0%	4.5%	10.3%
C	3.0%	10.7%	15.7%

Cumulative hemorrhage rates estimated by the Kaplan-Meier method and lifetable analysis are shown. Hemorrhage rates are presented for the total cohort of conservatively managed bAVMs and bAVM characteristics as illustrated in Fig. 2B–F.
* Spetzler-Martin and Spetzler-Ponce classifications included 104 patients for whom sufficient radiological data were available. The 10-year hemorrhage risk could not be estimated for Spetzler-Martin grade I cases (see also Fig. 2E).

ate Cox regression revealed a temporal, brainstem, thalamus, basal ganglia, or corpus callosum localization (HR 4.662, 95% CI 1.708–12.720; p = 0.003) as an independent risk factor for AVM hemorrhage. Of note, the presence of seizures reached borderline significance as an independent risk factor for AVM hemorrhage (HR 2.643, 95% CI 0.964–7.525; p = 0.059). The Spetzler-Martin grade was not shown as a significant risk factor for bAVM rupture.

Discussion

Long-Term Outcome of Conservatively Managed Unruptured bAVMs in Comparison With ARUBA's Medical Management Arm

The aim of bAVM treatment is the prevention of possibly life-threatening hemorrhagic events by occlusion or resection of the lesion, but also to treat refractory seizures or neurological symptoms. Although ARUBA represents the only level I evidence to date, concluding that an observational strategy might be favorable, it received severe criticism from the scientific community because of its rather short follow-up period, the lack of subgroup analyses, and the high percentage of only partially treated cases.[11] Moreover, the outcomes of the different but aggregated management options do not align with either the results of many previous retrospective studies or the experience reported by vascular specialists who regularly treat unruptured bAVMs.[2,11–15] Many studies have since then assessed the outcomes of different treatment options of ARUBA-eligible bAVM patients.[16–27] However, studies on the conservative management of exclusively unruptured ARUBA-eligible bAVMs are lacking.[2] At our tertiary referral center, we offer all available multimodal treatment options for cerebral vascular malformations. Thus, the vast majority of the 897 referred AVM patients (87%) were treated by microsurgery, radiosurgery, embolization, or a combination thereof. Only 13% of all patients who were referred to our department were managed conservatively. The predominant reason for conservative management was the patient's wish (Table 2). A surgeon's recommendation for conservative management was either limited to high-risk cases, especially in the premodern Gamma Knife era in our center, or less frequently influenced by the ARUBA results.[12] Therefore, we are able to present a retrospective, single-center follow-up study on a real-life series of 107 patients with initially unruptured and conservatively managed bAVMs.

The ARUBA study included 109 patients in its medical management arm from multiple centers worldwide. Similar to ARUBA, our study cohort mostly consisted of young and otherwise healthy patients at the time of AVM diagnosis; the median age at diagnosis (44 years) and sex distribution (46% female) in our retrospective cohort were almost identical to the prospective ARUBA cohort (44 years, 40% female). Additionally, the neurological presentation (36% vs 41% seizures) and the mRS score at diagnosis were very similar to the patients in ARUBA (94% vs 100% mRS score 0 or 1). Consequently, our long-term follow-up data allow a direct comparison to the outcome presented in the ARUBA study.[5,6]

In contrast to the ARUBA study, our cohort included patients with Spetzler-Martin grade V AVMs. Still, those patients only comprised 9% of the total cohort. However, our cohort also included a higher number of patients with AVMs localized in eloquent brain regions because of our

TABLE 4. Calculated annual hemorrhage rates

	No. of Pts	Pt-yrs*	Hemorrhagic Events	Annual Hemorrhage Risk
Total	107	697	19	2.7%
Age, yrs				
≤60	85	604	15	2.5%
>60	22	93	4	4.3%
Sex				
Female	50	298	10	3.4%
Male	57	399	9	2.3%
Localization				
Temporal	15	68	5	7.4%
Thalamus, basal ganglia, brainstem, corpus callosum	17	138	7	5.1%
Frontal, occipital, parietal, central	70	470	7	1.5%
Cerebellar	5	21	0	0.0%
Max diameter, cm				
<6	90	542	14	2.6%
≥6	14	105	4	3.8%
Not known	3	50	1	2.0%
Venous drainage				
Deep	47	345	10	2.9%
Superficial	57	302	8	2.6%
Not known	3	50	1	2.0%
SM grade				
I	9	23	1	4.3%
II	30	146	5	3.4%
III	30	183	2	1.1%
IV	25	202	5	2.5%
V	10	93	5	5.4%
Not known	3	50	1	2.0%
SP class				
A	39	169	6	3.6%
B	30	183	2	1.1%
C	35	295	10	3.4%
Not known	3	50	1	2.0%
Seizures at diagnosis				
Yes	39	285	10	3.5%
No	68	412	9	2.2%
Group era†				
Premodern	29	383	12	3.1%
Modern	78	314	7	2.2%

There were 19 hemorrhagic events documented in 18 patients. The annual hemorrhage rate was calculated as the number of AVM hemorrhages during the observation period from the time of documented bAVM diagnosis divided by the observed patient-years at risk.

* Total observation period until hemorrhage, last follow-up, or death.

† As defined in our previous publication (Hirschmann et al.[12]).

real-life cohort of conservatively managed unruptured bAVMs.

At the time of last follow-up, 77% of our study cohort and 82% in the medical management arm of the ARUBA cohort presented in an excellent clinical status (mRS grade 0 or 1). So far, the clinical outcome was almost equal. However, in the medical management arm of the ARUBA study, an AVM-related mortality of 0% was described after a mean follow-up of 52 months. In our cohort, the AVM-related mortality rate amounted to 8% after a mean follow-up time of 84 months. This difference in the reported mortality rates might be attributed to several facts. The majority of patients (62%) who had died of an AVM hemorrhage in our study had AVMs classified as Spetzler-Martin grade IV or V. However, the remaining 38% of patients harbored Spetzler-Martin grade II AVMs. More importantly, our observation period was longer than that in the final ARUBA follow-up study and included 44% of patients with an observation period of more than 5 years. Moreover, a national death register comparison was performed. Other previously published studies on the natural history or best medical management of unruptured bAVMs reported mortality rates ranging from 0.7% to 5.4%.[2,28,29]

Our results of significant mortality in conservatively treated AVMs are further supported by an epidemiological study comparing the mortality of AVM patients with AVMs of all Spetzler-Martin grades with a matched cohort of the general population. The authors found an association of bAVMs with a high long-term excess mortality in the conservatively treated group and thus concluded that this excess mortality may be reduced by active treatment especially among lower-grade AVMs.[28]

Hemorrhage Rates and Risk Factors for Rupture in Untreated bAVMs

In our cohort of unruptured bAVMs, the calculated overall annual hemorrhage rate amounted to 2.7%. In ARUBA's medical management arm, a comparable annual hemorrhage rate of 2.3% was given with 11 events in 110 patients after a mean follow-up of 50 months.[6] However, in our cohort of unruptured bAVMs, the cumulative 5-year hemorrhage risk rose to 11.3% while the cumulative 10-year hemorrhage risk already reached 15.3%.

In the literature, reported calculated yearly AVM hemorrhage rates vary widely and are assumed to be 1%–3% for unruptured and untreated bAVMs.[1–3] Various and even contradictory factors associated with an increased risk of hemorrhage have been reported.[1–3,30] In our cohort of previously unruptured bAVMs, univariate followed by multivariate Cox regression analyses revealed a temporal and deep-seated localization as an independent risk factor for AVM hemorrhage, while the presence of seizures almost reached statistical significance. Despite a low rate of flow-related aneurysms in our cohort, one-third of those patients experienced a hemorrhage in the observation period. Still, this low number of patients with flow-related aneurysms in our study represents a selection bias, most likely due to our department's treatment recommendations.

In a previous study, Laakso et al. concluded that previously ruptured, large, and infratentorially and deeply localized AVMs are at the highest risk for AVM hemorrhage.[28] In contrast, another study on a large group of bAVMs concluded that age, sex, seizure presentation, size, and deep location were not associated with any increased risk of hemorrhage. In the same study, prior hemorrhage, deep venous drainage, and associated aneurysms were significant predictors of future hemorrhage.[31] Several other studies identified prior hemorrhage, deep or infratentorial localization, exclusively deep venous drainage, associated aneurysms, and large AVM size as potential risk factors for hemorrhage.[2,18,24,28,31–33] However, most of these studies reported on a heterogeneous group of patients and included ruptured and unruptured bAVM cases. In contrast, our cohort consisted of only unruptured bAVMs at the time of diagnosis.

Moreover, in our cohort, Spetzler-Martin grade and Spetzler-Ponce class did not significantly influence hemorrhage rates. In contrast, high hemorrhage rates were diagnosed among low-grade and highest-grade AVMs alike. In our cohort, the high hemorrhage rates among low-grade Spetzler-Ponce class A AVMs may have been due to a high percentage of temporal lesions, while among high-grade Spetzler-Ponce class C lesions, a high number of deep-seated AVMs was found. Our findings are in line with previous publications stating that the Spetzler-Martin and Spetzler-Ponce classifications were designed to identify AVMs eligible for microsurgery but are unsuitable to predict hemorrhage rates or the outcome after other treatment modalities.[2,34]

Clinical Implications of the Long-Term Outcome of Conservatively Managed Unruptured bAVMs in Comparison With the Outcome After Treatment

To adequately counsel patients in the post-ARUBA era, it is necessary to weigh the natural course of unruptured bAVMs against specific treatment-associated complication rates. Still, the ARUBA study represents the only level I evidence so far suggesting a conservative strategy. However, long-term follow-up data on the medical management of ARUBA-eligible unruptured bAVMs are lacking.

Our data show that the majority of conservatively managed ARUBA-eligible patients (77%) remained in an excellent clinical status at last follow-up. These data are similar to the ARUBA results. However, a significant percentage of patients (17%) had an AVM rupture that was fatal in 50% of the cases of rupture after an observation period of 84 months. Thus, in contrast to ARUBA's 0% mortality in their medical management arm, this resulted in an AVM-associated long-term mortality rate of 8% in our series of conservatively treated patients. In the aggregated interventional therapy arm of the ARUBA study, the reported treatment-related mortality was 1.7%. This treatment-related mortality rate was most likely caused by the high number of incomplete treatments but is still significantly lower than the long-term mortality rate among our untreated cohort.[6] Moreover, in our published series of 472 bAVM patients treated by radiosurgery alone or with a combined endovascular-radiosurgical approach, the overall mortality rate was 1.5%, which dropped to 0.7% among patients treated after 2002. This series included previously ruptured and unruptured bAVMs.[12] In the same series, the calculated yearly hemorrhage risk in the observation period after first radiosurgical treatment was 1.3%, thus also significantly lower compared with the noninterventional arm of the ARUBA study or with our conservatively managed cohort.[12]

Furthermore, the advent of new technical aids and multimodal treatment strategies have considerably improved management options for unruptured bAVMs and have reduced the potential treatment-associated risks if performed in specialized high-volume centers.[2,11] It has been shown that for low-grade AVMs, the crossover point of serious neurological complications due to microsurgical treatment versus conservative management is shorter than 5 years.[30] Similarly, a crossover point 2–3 years after radiosurgery in comparison with conservative management has been reported. After that, the longer the follow-up, the greater the benefit for the patient following radiosurgery for low-grade AVMs.[14]

Moreover, several groups, including our own, reported excellent obliteration and low complication rates after stand-alone radiosurgery for Spetzler-Ponce class A and B AVMs.[12,13,35–38] Good results have also been achieved for selected Spetzler-Ponce class C AVMs after targeted embolization followed by radiosurgery.[12] In addition, staged radiosurgery enables the treatment of even larger AVMs.[12,35,39]

Overall, these results may suggest a more aggressive treatment strategy in patients with unruptured bAVMs but emphasize the importance of identifying predictors for AVM rupture to facilitate patient selection for active treatment.

Limitations

Limitations of our study include its retrospective design and its center-biased nature. Thus, patient inclusion was not randomized but mainly according to the patient's wish at the time of diagnosis. Moreover, we report a comparatively low rate of flow-related aneurysms in our cohort. This selection bias was most likely due to our department's treatment recommendations. Still, we included a consecutive real-life series of almost 30 years of only unruptured and untreated ARUBA-eligible bAVMs. In addition, we performed a national death register comparison to optimize follow-up data.

Conclusions

Our results represent the long-term course of unruptured untreated bAVMs. Our data support the conclusion that even in the post-ARUBA era, tailored active treatment options may be offered to patients with unruptured bAVMs. For patient counseling, individual risk factors should be weighed against the center's treatment-specific risks.

Key Points

- **What is already known on this topic**

  The ARUBA study concluded that medical management is superior to any form of interventional treatment among unruptured bAVMs. Still, long-term follow-up data on the exclusively conservative management of unruptured bAVMs are scarce.

- **What this study adds**

  Our results represent the long-term follow-up of unruptured untreated bAVMs in a real-life cohort. In contrast to ARUBA's 0% mortality in the medical management arm, the long-term follow-up AVM-related mortality rate amounted to unacceptable (8%) among conservatively managed AVMs in our cohort.

- **How this study might affect research, practice, or policy**

  Even in the post-ARUBA era, active treatment options should be offered to patients with unruptured bAVMs. Tailored patient counseling should weigh the natural course of unruptured bAVMs, including lesion-specific risk factors, against specific treatment-associated complication rates.

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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: Frischer, Kranawetter, Göbl. Acquisition of data: Frischer, Dodier, Kranawetter, Hirschmann, Dogan, Untersteiner, Göbl, Gatterbauer, Wang. Analysis and interpretation of data: Frischer, Dodier, Kranawetter, Cho, Untersteiner, Göbl. Drafting the article: Frischer, Dodier, Kranawetter, Bavinzski. Critically revising the article: Frischer, Dodier, Hirschmann, Dogan, Kranawetter, Cho, Göbl, Gatterbauer, Wang, Dorfer, Rössler, Bavinzski. Reviewed submitted version of manuscript: Frischer, Dodier, Kranawetter, Dogan, Cho, Untersteiner, Göbl, Gatterbauer, Wang, Dorfer, Rössler, Bavinzski. Approved the final version of the manuscript on behalf of all authors: Frischer. Statistical analysis: Frischer, Dodier, Cho. Administrative/technical/material support: Dodier, Hirschmann. Study supervision: Frischer.

Correspondence

Josa M. Frischer: Medical University of Vienna, Austria. josa.frischer@meduniwien.ac.at.