OPEN ACCESS

Original research

Re-rupture in ruptured brain arteriovenous malformations: a retrospective cohort study based on a nationwide multicenter prospective registry

Kexin Yuan ,[1] Yu Chen ,[1] Debin Yan,[1] Ruinan Li,[1] Zhipeng Li ,[1] Haibin Zhang ,[1] Ke Wang,[1] Heze Han ,[1] Yahui Zhao,[1] Li Ma,[1,2] Qiang Hao,[1] Xun Ye,[1] Hengwei Jin,[3] Xiangyu Meng ,[4] Ali Liu,[5] Dezhi Gao,[5] Shibin Sun,[5] Shuai Kang,[1] Hao Wang,[1] Youxiang Li,[6,7] Shuo Wang ,[1] Xiaolin Chen,[1] Yuanli Zhao[1,4,7]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnis-2023-020650).

For numbered affiliations see end of article.

Correspondence to
Dr Yuanli Zhao; zhaoyuanli@126.com and Dr Xiaolin Chen; cxl_bjtth@163.com

KY and YC contributed equally.

Received 31 May 2023
Accepted 3 October 2023
Published Online First 30 October 2023

ABSTRACT

Background This study aimed to investigate the natural history of re-rupture in ruptured brain arteriovenous malformations (AVMs) and to provide comprehensive insights into its associated factors and prevention.

Methods This study included 1712 eligible ruptured AVMs from a nationwide multicenter prospective collaboration registry between August 2011 and September 2021. The natural rupture risk before intervention and the annual rupture risk after intervention were both assessed. Cox proportional hazard regression models and Kaplan–Meier survival curves were used to explore independent factors associated with AVM re-rupture. The correlation between these factors and AVM re-rupture was verified in multiple independent cohorts, and the prevention effect of intervention timing and intervention strategies on AVM re-rupture was further analyzed.

Results The annual re-rupture risk in ruptured AVMs was 7.6%, and the cumulative re-rupture risk in the first 1, 3, 5, and 10 years following the initial rupture were 10%, 25%, 37.5%, and 50%, respectively. Cox proportional hazard regression analysis confirmed adult patients, ventricular system involvement, and any deep venous drainage as independent factors associated with AVM re-rupture. The intervention was found to significantly reduce the risk of AVM re-rupture (annual rupture risk 11.34% vs 1.70%, p<0.001), especially in those who underwent surgical resection (annual rupture risk 0.13%).

Conclusions The risk of re-rupture in ruptured AVMs is high. Adult patients, ventricular system involvement, and any deep venous drainage are independent risk factors for re-rupture. Applying the results universally to all ruptured AVM cases may be biased. Intervention could effectively reduce the risk of re-rupture.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several risk factors of re-rupture such as age, sex, deep location, deep vein drainage, and flow-related aneurysms have been reported.

⇒ However, ruptured AVMs usually undergo early intervention, and the small sample size and cross-sectional design of previous studies have made it difficult to conduct in-depth analysis and have weakened the reliability of their findings.

WHAT THIS STUDY ADDS

⇒ The risk of re-rupture in ruptured AVMs is high. Adult age, ventricular system involvement, and any deep venous drainage are independent risk factors for re-rupture. Intervention could effectively reduce the risk of re-rupture.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will help to enhance clinicians' understanding of the re-rupture of AVMs, identify high-risk patients with re-rupture, and promote the formulation of clinical individualized treatment decisions.

INTRODUCTION

Brain arteriovenous malformations (AVMs) are defined as congenital vascular abnormalities characterized by complex aggregations of tortuous intracranial arteries and veins, lacking intervening capillary beds, forming a high-flow, low-resistance shunt between the arterial and venous systems.[1] The most common manifestation is intracranial hemorrhage.[2 3] For unruptured AVMs the annual rupture risk is approximately 1–3%, but the risk of subsequent rupture increases to a staggering five-fold once ruptured, especially within the first year after the initial hemorrhage.[2 4–7] Therefore, accurate identification of patients at high risk of re-rupture can help to prevent the occurrence of re-rupture in ruptured AVMs.

The five-fold increased risk of re-rupture implies a fundamental difference in the mechanism by which unruptured AVMs undergo primary rupture and ruptured AVMs undergo re-rupture. However, most previous studies did not distinguish between the initial rupture and re-rupture, which makes it impossible to effectively identify AVMs at high risk of re-rupture and to take timely intervention in clinical practice.[5 6 8–11] Some small-sample studies

To cite: Yuan K, Chen Y, Yan D, *et al*. *J NeuroIntervent Surg* 2024;**16**:1145–1151.

Table 1 Baseline characteristics

	Overall n=1555	Without re-rupture n=1354	Re-rupture n=201	P value
Demographic characteristics				
Female gender, n (%)	668 (43.0)	570 (42.1)	98 (48.8)	0.089
Initial rupture age, mean (SD)	25.3 (14.9)	25.1 (14.7)	26.6 (15.9)	0.198
Clinical features				
Seizure, n (%)	191 (12.3)	163 (12.0)	28 (13.9)	0.517
Headache, n (%)	234 (15.1)	206 (15.2)	28 (13.9)	0.712
Neurological complications, n (%)	298 (19.2)	256 (18.9)	42 (20.9)	0.567
Morphologic features				
SM grade, n (%)				
1	273 (17.6)	259 (19.1)	14 (7.0)	<0.001
2	551 (35.4)	500 (36.9)	51 (25.4)	
3	497 (32.0)	420 (31.0)	77 (38.3)	
4	202 (13.0)	153 (11.3)	49 (24.4)	
5	32 (2.1)	22 (1.6)	10 (5.0)	
Ventricular system involvement, n (%)	1022 (65.7)	863 (63.7)	159 (79.1)	<0.001
Deep location, n (%)	492 (31.6)	421 (31.1)	71 (35.3)	0.262
AVM size, n (%)				
<3 cm	956 (61.5)	872 (64.4)	84 (41.8)	<0.001
3–6 cm	516 (33.2)	419 (31.0)	97 (48.3)	
>6 cm	83 (5.3)	63 (4.7)	20 (10.0)	
Eloquent region, n (%)	893 (57.4)	760 (56.1)	133 (66.2)	0.009
Angioarchitectural features				
Feeding artery dilation, n (%)	537 (34.5)	453 (33.5)	84 (41.8)	0.025
Feeding arteries number, mean (SD)	2.0 (1.2)	1.9 (1.1)	2.5 (1.3)	<0.001
Arterial borderzone, n (%)	316 (20.3)	252 (18.6)	64 (31.8)	<0.001
Associated aneurysm, n (%)	302 (19.4)	258 (19.1)	44 (21.9)	0.394
Diffuse nidus, n (%)	699 (45.0)	615 (45.4)	84 (41.8)	0.374
Any deep venous drainage, n (%)	704 (45.3)	582 (43.0)	122 (60.7)	<0.001
Exclusive deep venous drainage, n (%)	509 (32.7)	427 (31.5)	82 (40.8)	0.011
Number of arteries/venous, mean (SD)	8.9 (3.2)	8.8 (3.1)	9.6 (3.5)	0.003
Draining vein stenosis, n (%)	300 (19.3)	256 (18.9)	44 (21.9)	0.366
Venous aneurysm, n (%)	99 (6.4)	77 (5.7)	22 (11.0)	0.007

AVM, arteriovenous malformation; SM, Spetzler–Martin.

have analyzed the risk factors for re-rupture of ruptured AVMs but, due to the cross-sectional study design, the conclusions were inevitably biased by factors such as changes in the angioarchitectures after rupture.[10 12 13] These limitations lead to poor robustness and generalization of risk factors identified in previous studies in predicting re-rupture. Further studies focusing only on ruptured AVMs will help to investigate the natural history of re-rupture in ruptured AVMs and provide comprehensive insights into its associated factors.

This was a retrospective cohort study from a nationwide multicenter prospective registry which examined the natural history of re-rupture in ruptured AVMs and investigated available risk factors of re-rupture to assist in evaluating the risk of re-rupture of ruptured AVMs in clinical practice. In addition, this study further explored the impact of intervention timing and strategies on AVM re-rupture.

METHODS

Data source and study design

The registry of multimodality treatment of brain AVMs in mainland China (MATCH study) was a nationwide multicenter prospective collaboration registry (ClinicalTrials.gov, NCT NCT04572568) to explore the natural history of AVMs in Asia and the optimal management strategies for AVMs. The protocol of data quality management in the MATCH study is shown in online supplemental method 1. Several previously published studies have proved the validity of the database.[14–16]

This study was a retrospective cohort-designed analysis using AVMs from the MATCH registry of patients recruited from August 2011 to September 2021. Patients with at least one hemorrhagic stroke confirmed through CT or MRI were eligible for this study. The exclusion criteria were as follows: (1) patients missing critical baseline information; (2) patients experiencing treatment before initial rupture; and (3) patients with

Table 2 Univariable and multivariable Cox proportional hazards model for the risk of re-rupture in 1555 exploratory cohort patients

	Univariable			Multivariable		
Characteristics	HR	95% CI	P value	HR	95% CI	P value
Adult patients	1.35	1.01 to 1.8	0.043	1.46	1.09 to 1.97	0.012
SM grade	1.24	1.08 to 1.42	0.003	0.84	0.66 to 1.06	0.138
Ventricular system involvement	1.74	1.23 to 2.46	0.003	1.52	1.03 to 2.25	0.033
Deep location	1.45	1.08 to 1.94	0.002	1.23	0.87 to 1.72	0.241
Number of feeding arteries	1.18	1.06 to 1.31	0.013	1.21	0.98 to 1.51	0.079
Arterial borderzone AVM	1.47	1.09 to 1.98	0.011	1.13	0.78 to 1.62	0.515
Any deep drainage	1.77	1.33 to 2.36	<0.001	1.64	1.02 to 2.82	0.037
Exclusive deep drainage	1.53	1.15 to 2.03	0.003	1.07	0.63 to 1.84	0.792
Number of arteries/veins	1.13	1.00 to 1.27	0.045	1.14	0.9 to 1.45	0.285

No collinearity was present between the independent variables (variance inflation factor <3).
AVM, arteriovenous malformation; SM, Spetzler–Martin.

conservative management but lost to follow-up. All the analyses were carried out according to the Helsinki Declaration guideline. This study was reported in accordance with the STROBE guidelines for observational cohort studies.

Baseline characteristics

Demographic information including age at initial rupture, sex, and clinical manifestations were recorded at admission. Hemorrhagic stroke was the clinically symptomatic event (any new focal neurological deficit, seizure, or new-onset dramatic headache) confirmed by imaging findings (intracranial hematoma or subarachnoid hemorrhage that could be attributed to AVM on CT or MRI).

The radiological information was determined by digital subtraction angiography (DSA) and MRI, and the definition of these features was consistent with the reporting terminology guidelines.[17] The definition of eloquent regions complied with the Spetzler–Martin grade. The following variables are defined in this study. Venous drainage was dichotomized into any deep drainage (deep drainage with or without superficial venous drainage), exclusively deep venous drainage, or superficial-only drainage. AVM location was dichotomized into deep (brainstem, basal ganglia, thalamus, cerebellum, insular lobe, and corpus callosum) and superficial (all other locations).[18] Ventricular system involvement was classified as the nidus (with a contrast-enhancement or flow void) contacting the ependymal lining of the ventricle on contrast-enhanced T1- and T2-weighted images. All radiological characteristics were independently evaluated by two credentialed senior neurointerventional radiologists. If inconsistency was present, the final determination was made by a senior professor of neurointerventional radiology with more than 30 years of clinical experience.

Cohort definition and follow-up

In the analysis of the natural history of AVM re-rupture, patients with re-rupture were defined as those with ruptured AVMs that occurred subsequent to re-rupture events before initial intervention (patients who underwent intervention treatment) or the last clinical follow-up (patients maintained on conservative management).

Clinical follow-up was conducted via telephone interviews or record review by well-trained clinical research coordinators at 3 months, annually (1, 2, and 3 years), and every 5 years after admission. In the analysis of the natural history, the inception point of the observation was the date of onset of the initial rupture that led to the diagnosis of AVM. The endpoint was the date of re-rupture (in patients with re-rupture) or the date of the first intervention (in patients without re-rupture who underwent intervention treatment), or the last follow-up (patients without re-rupture and maintained on conservative management). In the further subcohort validation analysis, in order to simplify the cohort we screened out a special cohort of patients who were simply waiting for treatment, which we defined as patients who had no risk factors for intervention but ultimately chose to have an intervention. The risk factors for intervention are shown in online supplemental table S1. In addition, the intervention cohort was further analyzed for the risk of AVM re-rupture after the intervention.

Statistical analysis

Categorical variables are presented as frequency (percentages) and continuous variables are presented as mean (SD) or median (IQR). A Pearson χ^2 test or Fisher exact test was used to compare categorical variables as appropriate. After testing for normality, continuous variables were analyzed using the independent Student t-test or Mann–Whitney U rank-sum test, as appropriate.

The whole cohort was divided into a single-center exploratory cohort and a multicenter validation cohort. Survival analysis was conducted in the single-center exploratory cohort to identify potential risk factors of re-rupture. The multicenter validation cohort was used to verify the robustness and generalization of the independent risk factors. In the single-center exploratory cohort, cases were judged to be censored at the time of death or intervention. Kaplan–Meier survival curves were plotted to determine the cumulative risk of re-rupture in the whole cohort. Hazard ratios (HRs) were estimated using the Cox proportional hazards regression model for the re-rupture event. The proportional hazards assumption was assessed by examining Schoenfeld's global test and was visually inspected for potential time-variant biases (online supplemental figure S1). The independent variables included in the Cox proportional hazards regression model excluded collinearity (variance inflation factor <3). In order to verify the robustness and generalization of the risk factors in the sensitivity analyses, we used three independent subcohorts for validation, including an external validation cohort (other centers in the MATCH registry except Beijing Tiantan Hospital), a conservative cohort (patients who were treated conservatively throughout the whole course with regular follow-up), and a surgical indication cohort (patients who were simply waiting for treatment).

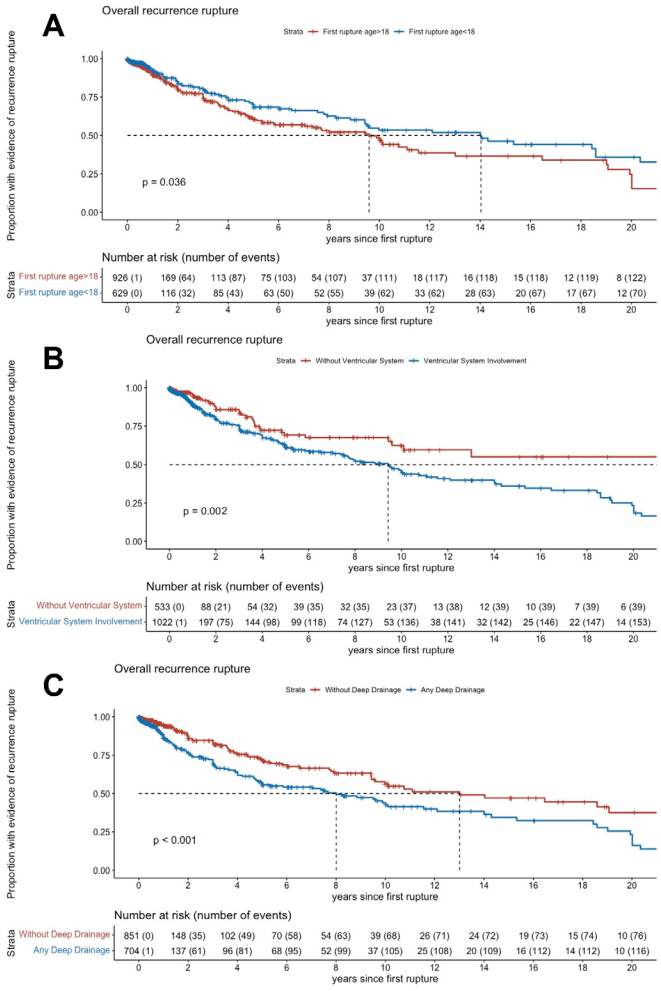

Figure 1 Kaplan–Meier survival curves of re-rupture-free survival between the risk factors shown in the multivariable Cox proportional hazards regression model of the single-center exploratory cohort. (A) Initial rupture in adults (age ≥18 years) and children (age <18 years). (B) Patients without and with ventricular system involvement. (C) Patients without and with any deep venous drainage.

All statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing). P values were two-sided and p<0.05 was considered statistically significant.

RESULTS

Patient baseline

Patinets with a total of 3923 brain AVMs were enrolled in the MATCH registry between August 2011 and September 2021. A total of 1712 eligible ruptured AVMs were included for further analysis. Of these, 1555 were from Beijing Tiantan Hospital and 157 were from nine other participating institutions. Among the 1555 patients, 138 (8.9%) maintained conservative management and long-term follow-up, 1120 (72.0%) underwent intervention treatment within the first year after the initial rupture, and 297 (19.1%) received intervention 1 year after the initial rupture. Online supplemental figure S2 shows the details of patient selection.

Demographic, clinical, and morphologic characteristics of the 1555 patients are shown in table 1. Among the 1555 patients, in 201 (12.9%) the AVMs occurred as secondary rupture events during 2638 person-years of follow-up, yielding an annual secondary rupture risk of 7.6%. The Kaplan–Meier survival curves showed middle re-ruptured time since the initial rupture was 10 years (online supplemental figure S3). The cumulative re-rupture risk in the first 1, 3, 5, and 10 years following the initial rupture was 10%, 25%, 37.5%, and 50%, respectively. In a further analysis of the risk of secondary rupture during the early phase after rupture, 1.3% of subsequent rupture events occurred within 30 days of the initial rupture, indicating a staggering monthly risk of secondary rupture of 1.3% in the first month after rupture, significantly higher than the monthly risk of secondary rupture of 0.6% 1 month later.

Risk factors associated with AVM re-rupture

In univariable analysis, various parameters including demographic, morphological, and angioarchitectural factors were associated with AVM re-rupture. To facilitate the differentiation, the age of patients was divided into children and adults of ≥18 years. In the multivariable analysis, only adult patients (HR 1.46, 95% CI 1.09 to 1.97; p=0.012), ventricular system involvement (HR 1.52, 95% CI 1.03 to 2.25; p=0.033), and any deep venous drainage (HR 1.64, 95% CI 1.02 to 2.82; p=0.037) retained their significance in predicting the re-rupture events after adjusting for all significant variables in the univariable analysis after excluding collinearity (table 2). To reduce abnormal deletions due to short follow-up duration, we repeated this analysis in a cohort that excluded patients who received an intervention in the first year after the initial rupture and found consistent risk factors for AVM re-rupture to those found in the overall cohort (see online supplemental table S2). Kaplan–Meier survival curves showed the cumulative risk of re-rupture grouped according to the three independent risk factors (figure 1).

Further, we defined the combination of 0–1 risk factors as a low-risk group and 2–3 risk factors as a high-risk group after a rigorous review of each risk factor. The multivariate model in the single-center exploratory cohort confirmed the association of the high-risk group with AVM re-rupture (HR 1.78, 95% CI 1.18 to 2.69; p=0.006) (see online supplemental table S3), and the Kaplan–Meier survival curves showed that the median rupture time in the high-risk group may occur 10 years earlier than that in the low-risk group (log-rank, p<0.001) (figure 2A).

To further clarify the confounding of risk factors for re-rupture between different cohorts that may be due to selective bias, we conducted further validation across different cohorts. First, for single-center bias we conducted a validation analysis on 157 patients from nine other hospitals (online supplemental table S4) and found that the high-risk group still had a significantly higher cumulative risk of re-rupture (log-rank, p=0.040) (figure 2B), as well as in the overall cohort (log-rank, p<0.001) (online supplemental figure S4). Second, for bias in the treatment strategy we analyzed patients in the exploration cohort who had maintained conservative management throughout the whole course and were followed up regularly (online supplemental table S5), and the Kaplan–Meier survival curve also confirmed the ability of these risk factors to differentiate the risk of AVM re-rupture (log-rank, p=0.004) (online supplemental figure S5). Third, in the simplified cohort of patients who were simply waiting for treatment, 45 (8.6%) re-rupture events occurred in 526 AVMs during a follow-up period of 520.87 person-years, with an annual risk of re-rupture of 8.64%, which was similar to the previously calculated annual rupture rate (7.6%) in the overall cohort. Unfortunately, we found no independent risk factors associated with AVM re-rupture in this cohort (online supplemental table S1), but the high-risk/low-risk groupings were still valid for differentiating the risk of AVM re-rupture (online supplemental figure S6).

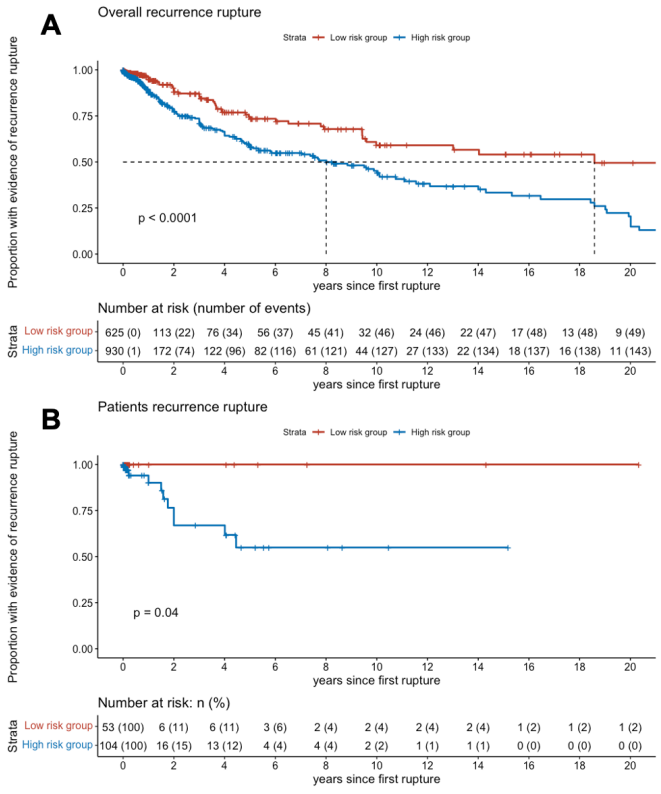

Figure 2 Kaplan–Meier survival curves of re-rupture-free survival of the low-risk group and the high-risk group in (A) the single-center exploratory cohort and (B) the multicenter external validation cohort.

Impact of intervention timing and treatment modality on AVM re-rupture

In terms of multiple re-ruptures, 335 re-rupture events occurred in the 201 patients who experienced re-rupture before the intervention or the last conservative follow-up, yielding an annual rupture risk of 12.7% after the initial rupture. Among 1417 (91.1%) patients with AVMs who received the intervention, 172 (12.1%) experienced 228 re-rupture events before the intervention and 120 (8.5%) had 138 re-rupture events after the intervention (annual rupture risk 11.34% vs 1.70%; p<0.001) (four of 445 patients who underwent surgical resection had four re-ruptures, annual rupture risk 0.13%; 17 of 157 patients who underwent embolization had 20 re-ruptures, annual rupture risk 2.26%; 13 of 236 patients undergoing radiosurgery had 16 re-ruptures, annual rupture risk 1.16%; three of 227 patients who received single-stage combined embolization + resection had three re-ruptures, annual rupture risk 0.36%; and 83 of 352 patients who experienced other multi-modality strategies had 95 re-ruptures, annual rupture risk 4.62%) (online supplemental table S6) .

The intervention timing has a significant influence on the occurrence of AVM re-rupture, and timely and effective intervention can effectively curb the occurrence of re-rupture events. We analyzed the cumulative risk of re-rupture after the initial rupture in four subgroups with different intervention timing (0–3 months, 3–6 months, 6–12 months, >12 months) and found that their monthly risk of a secondary rupture was 1.85%, 1.20%, 1.18%, and 0.87% before the initial intervention. Furthermore, it is well known that different intervention strategies have different preventive effects on long-term hemorrhagic stroke with AVMs. We conducted a more in-depth analysis of the preventive effects of different intervention strategies on AVM re-rupture events and found that the risk of subsequent rupture varies with different intervention strategies, with surgical resection having unparalleled advantages (online supplemental figure S7).

DISCUSSION

Rupture of AVMs is a life-threatening clinical presentation with much higher morbidity and mortality than other clinical symptoms.[13] Accurate identification of AVMs at high risk of re-rupture can help to avoid the recurrence of devastating hemorrhage. In this study we found the annual risk of re-rupture in ruptured AVMs was 7.6%, and three independent risk factors were found to be associated with the re-rupture event in ruptured AVMs—namely, adult patients, ventricular system involvement, and any deep venous drainage. We further divided the patients into high-risk and low-risk groups based on the above risk factors, and verified their robustness and generalizability across multiple cohorts. In addition, we confirmed the prevention effects of the intervention on AVM re-rupture. This study will help to enhance the understanding of the re-rupture of AVMs, to identify high-risk patients with re-rupture, and to promote the formulation of clinical individualized treatment decisions.

Many previous studies have reported that the risk of subsequent rupture in AVMs increases fivefold once ruptured (range 2–17.8%), especially during the first year after the initial hemorrhage.[2 4–7] In this study we found the annual risk of re-rupture after the initial rupture was 7.6%, and the overall annual risk of re-rupture was 12.7%. Consistent with previous studies, this study also found that the risk of re-rupture in the early stage after AVM rupture was significantly higher than in the late stage.[2] The monthly risk of re-rupture within the first month after rupture was 1.3%, which was significantly higher than the monthly risk of re-rupture of 0.6% 1 month later. Previous studies have not provided reliable data on the cumulative risk of AVM re-rupture, but this study found that the cumulative re-rupture risk in the first 1, 3, 5, and 10 years after the initial rupture was 10%, 25%, 37.5%, and 50%, respectively. Based on these data, we were surprised to find that half of the patients experienced re-rupture within 10 years of the natural course of the initial AVM rupture, which is much higher than the optimistic estimates of the benign course of unruptured AVMs in previous studies.[4 19] Therefore, from the perspective of natural disease course, a negative attitude similar to that of unruptured AVMs should not be adopted towards ruptured AVMs.[4] This study confirmed the sharply increased risk of AVM re-rupture through large sample data, providing a basis for the selection of intervention programs.

Several individual risk factors of AVM re-rupture have been reported in previous studies, such as age, sex, deep location, deep vein drainage, and flow-related aneurysms.[7 9 20–26] However, due to the fact that ruptured AVMs usually undergo intervention at an early stage after hemorrhage, the small sample size and the low incidence of re-rupture events make it difficult to conduct in-depth analysis of the risk factors for AVM re-rupture in previous studies. In addition, the cross-sectional design of previous studies will seriously weaken the reliability of their findings.[10] Therefore, a prospectively designed retrospective cohort study that takes into account exposure duration will help to find more reliable risk factors for AVM re-rupture. In this study we found the increasing age of the patient at the initial rupture, ventricular system involvement, and any deep venous drainage were independent risk factors for AVM re-rupture in the multivariable Cox proportional hazards model. Most of them were consistent with most previous studies. A previous patient-level meta-analysis of hemorrhage predictors also proposed that

increasing age (1.34-fold per decade, 1.17–1.53) could predict the subsequent hemorrhage in unruptured and ruptured AVMs.[2] In terms of the morphological characteristics, Ma *et al* indicated that periventricular location is an independent predictor for severe hemorrhage in pediatric untreated AVMs, and a subsequent prediction model of AVM initial rupture also confirmed this finding.[19 27] This study further recognized that ventricular system involvement also has a significant correlation with AVM re-rupture. Cerebrospinal fluid fluctuation outside the nidus, hemodynamic sustained stress inside the nidus, and unstable transmural pressure gradient are more likely to keep the nidus in an unstable state for a long time.[28] In terms of another morphological character, deep venous drainage is often one of the anatomical manifestations of venous outflow tract obstruction. However, it is worth noting that, slightly different from the findings of this study, most previous studies have recognized exclusive deep venous drainage as an important risk factor for the initial rupture.[7 23 29 30] Therefore, we speculate that the mechanisms of the initial rupture and re-rupture may be different.

In addition to the common angioarchitecture characteristics, factors leading to re-rupture may be more complex, including but not limited to the impact of the hematoma produced by the first rupture such as compression, and the response of hemosiderin, macrophages, endothelial cells, and even the structure of AVM may also change. Inflammation causes the wall of the blood vessels to weaken, which leads to vascular instability and makes AVMs more prone to rupture. The levels of inflammatory cells were higher in ruptured cerebral AVMs than in unruptured ones.[31–33] However, these unknown changes still need to be studied, and this is one of the directions we will study in the future. The identification of re-rupture risk factors contributes to the in-depth understanding of the mechanism and the early warning of patients at high risk of re-rupture in clinical practice.

Treatment strategy options for ruptured AVMs often need to be balanced against post-intervention injury and natural history re-rupture risk. In general, intervention for most ruptured AVMs can result in satisfactory prevention of re-rupture and acceptable neurological impairment, except for Spetzler–Martin grade V AVMs.[34] In this study we found that the annual rupture risk decreased significantly after intervention (from 12.7% to 1.70%). However, the effect of different intervention strategies on preventing the re-rupture events varies significantly. This study shows that surgical resection should undoubtedly remain the first-line treatment strategy for ruptured AVMs (annual rupture risk 0.13%). Endovascular embolization, as previously reported, did not show an advantage in preventing the re-rupture of ruptured AVMs,[16] and neither did radiosurgery. In addition, this study found an abnormal re-rupture risk in patients receiving other multimodal strategies. This may be due to the bias of the observational study design—that is, patients with re-rupture tend to receive more complex unplanned treatment strategies and this orientation of treatment intentions may lead to significant selective bias.

Study limitations

Several limitations of our study need to be discussed. First, the biggest limitation of this study—the inherent bias of observational study design selective bias—may lead to the masking of potential AVM re-rupture factors, especially in terms of surgical indications and timing. Specifically, the factors that lead patients to undergo intervention may be the same factors that lead to AVM re-rupture, and early intervention may result in high-risk patients ending observation before the onset of re-rupture. In this study, baseline characteristics were compared between the intervention and conservative groups, and no significant association between surgical indications and re-rupture was found (online supplemental table S7), and no other potentially hidden risk factors were found after excluding potential confounding factors (online supplemental table S1 and S8). Second, the characteristic parameters of the initial hemorrhage were lacking in this study, such as hemosiderin deposition, peripheral gliosis, and inflammatory stimulation, so the impact of previous hematomas could not be analyzed. However, the fact that two successive hemorrhages from AVMs often occurred at different sites suggests that the impact of previous hematomas on the occurrence of re-rupture may be limited. Third, the majority of patients received intervention within 1 year after the initial hemorrhage, making it unclear whether the risk factors would remain robust long after the initial rupture. However, the validation cohort that maintained long-term conservative management confirms to a certain extent that these risk factors can still effectively identify high-risk groups for re-rupture in the long term. Finally, it should be noted that early intervention reduces the natural history observation time of re-rupture, which may lead us to underestimate the risk of AVM re-rupture. Therefore, the annual re-rupture rate may be lower than the true incidence.

CONCLUSION

In this retrospective cohort study based on a nationwide multicenter prospective registry, the annual risk of re-rupture of ruptured AVMs was 7.6%. Adult patients, ventricular system involvement, and any deep venous drainage were independent risk factors of re-rupture. However, it is essential to exercise caution when generalizing our findings to all cases of ruptured AVMs, given the potential for bias inherent in our study design. Nevertheless, our results highlight the potential effectiveness of intervention in reducing the risk of re-rupture, offering valuable insights for clinical decision-making in this complex patient population.

Author affiliations
[1]Department of Neurosurgery, Beijing Tiantan Hospital, Beijing, China
[2]Center for Cerebrovascular Research, University of California San Francisco, San Francisco, California, USA
[3]Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Beijing, China
[4]Beijing Neurosurgical Institute, Beijing, China
[5]Department of Gamma-Knife center, Beijing Tiantan Hospital, Beijing, China
[6]Department of Interventional Neuroradiology, Capital Medical University, Beijing, Fengtai District, China
[7]Beijing Engineering Research Center, Beijing, Fengtai District, China

Acknowledgements We thank the Organizing Committee of the MATCH study and the Multidisciplinary Team at Beijing Tiantan Hospital for their efforts in this study.

Contributors KY: Conceptualization, methodology, formal analysis, investigation, writing – original draft. YC: Methodology, investigation, writing – original draft, funding acquisition. DY: Resources. RL: Resources. ZL: Resources. HZ: Resources. KW: Resources. HH: Resources. YZ: Investigation. LM: Investigation. QH: Methodology. HW: Methodology. XY: Methodology. HJ: Resources. XM: Resources. AL: Investigation. DG: Investigation. SS: Investigation. SK: Investigation. HW: Investigation. YL: Conceptualization, supervision. SW: Conceptualization, supervision. XC: Conceptualization, supervision, funding acquisition. YZ: Conceptualization, supervision, funding acquisition. All authors confirm that they contributed to manuscript reviews and critical revision for important intellectual content, and read and approved the final draft for submission. All authors agree to be accountable for the content of this study. YZ serves as the guarantor for this article.

Funding This work was supported by the National Key Research and Development Program of China (Grant No. 2022YFB4702800 to YZ, and No. 2021YFC2501101 and 2020YFC2004701 to XC), Natural Science Foundation of China (grant no. 81771234 and 82071302 to YZ, and 82202244 to YC), Beijing Municipal Administration of Hospitals Incubating Program (pX2020023 to QH), Natural Science

Foundation of Beijing (7204253 to QH).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The Institutional Review Board of Beijing Tiantan Hospital approved this study (KY 2020-003-01). Written informed consent for collecting clinical information was obtained from each patient at admission.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data that support the findings of this study are available from the corresponding author on reasonable request. No data are available.

ORCID iDs
Kexin Yuan http://orcid.org/0000-0002-0937-2711
Yu Chen http://orcid.org/0000-0003-2491-3974
Zhipeng Li http://orcid.org/0000-0001-9122-092X
Haibin Zhang http://orcid.org/0000-0003-0366-4040
Heze Han http://orcid.org/0000-0001-9155-038X
Xiangyu Meng http://orcid.org/0000-0002-7703-1177
Shuo Wang http://orcid.org/0000-0003-4919-5390

REFERENCES

1 Lawton MT, Rutledge WC, Kim H, *et al*. Brain arteriovenous malformations. *Nat Rev Dis Primers* 2015;1:15008.
2 Kim H, Al-Shahi Salman R, McCulloch CE, *et al*. Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology* 2014;83:590–7.
3 Brown RD Jr, Wiebers DO, Forbes G, *et al*. The natural history of unruptured intracranial arteriovenous malformations. *J Neurosurg* 1988;68:352–7.
4 Mohr JP, Parides MK, Stapf C, *et al*. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet* 2014;383:614–21.
5 Halim AX, Johnston SC, Singh V, *et al*. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. *Stroke* 2004;35:1697–702.
6 Hernesniemi JA, Dashti R, Juvela S, *et al*. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. *Neurosurgery* 2008;63:823–9;
7 Mast H, Young WL, Koennecke HC, *et al*. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. *Lancet* 1997;350:1065–8.
8 Guo Y, Saunders T, Su H, *et al*. Silent intralesional microhemorrhage as a risk factor for brain arteriovenous malformation rupture. *Stroke* 2012;43:1240–6.
9 Stapf C, Mast H, Sciacca RR, *et al*. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology* 2006;66:1350–5.
10 Yamada S, Takagi Y, Nozaki K, *et al*. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. *J Neurosurg* 2007;107:965–72.
11 da Costa L, Wallace MC, Ter Brugge KG, *et al*. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke* 2009;40:100–5.
12 Blauwblomme T, Bourgeois M, Meyer P, *et al*. Long-term outcome of 106 consecutive pediatric ruptured brain arteriovenous malformations after combined treatment. *Stroke* 2014;45:1664–71.
13 Choi JH, Mast H, Sciacca RR, *et al*. Clinical outcome after first and recurrent hemorrhage in patients with untreated brain arteriovenous malformation. *Stroke* 2006;37:1243–7.
14 Chen Y, Han H, Ma L, *et al*. Multimodality treatment for brain arteriovenous malformation in mainland China: design, rationale, and baseline patient characteristics of a nationwide multicenter prospective registry. *Chin Neurosurg J* 2022;8:33.
15 Chen Y, Li R, Ma L, *et al*. Long-term outcomes of brainstem arteriovenous malformations after different management modalities: a single-centre experience. *Stroke Vasc Neurol* 2021;6:65–73.
16 Chen Y, Han H, Jin H, *et al*. Association of embolization with long-term outcomes in brain arteriovenous malformations: a propensity score-matched analysis using nationwide multicenter prospective registry data. *Int J Surg* 2023;109:1900–9.
17 Atkinson RP, Awad IA, *et al*. Reporting terminology for brain arteriovenous malformation clinical and radiographic features for use in clinical trials. *Stroke* 2001;32:1430–42.
18 Stefani MA, Porter PJ, terBrugge KG, *et al*. Large and deep brain arteriovenous malformations are associated with risk of future hemorrhage. *Stroke* 2002;33:1220–4.
19 Chen Y, Han H, Meng X, *et al*. Development and validation of a scoring system for hemorrhage risk in brain arteriovenous malformations. *JAMA Netw Open* 2023;6:e231070.
20 Crawford PM, West CR, Chadwick DW, *et al*. Arteriovenous malformations of the brain: natural history in unoperated patients. *J Neurol Neurosurg Psychiatry* 1986;49:1–10.
21 Fullerton HJ, Achrol AS, Johnston SC, *et al*. Long-term hemorrhage risk in children versus adults with brain arteriovenous malformations. *Stroke* 2005;36:2099–104.
22 Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg* 1983;58:331–7.
23 Kader A, Young WL, Pile-Spellman J, *et al*. The influence of hemodynamic and anatomic factors on hemorrhage from cerebral arteriovenous malformations. *Neurosurgery* 1994;34:801–7;
24 Stapf C, Mohr JP, Pile-Spellman J, *et al*. Concurrent arterial aneurysms in brain arteriovenous malformations with haemorrhagic presentation. *J Neurol Neurosurg Psychiatry* 2002;73:294–8.
25 Stefani MA, Porter PJ, terBrugge KG, *et al*. Angioarchitectural factors present in brain arteriovenous malformations associated with hemorrhagic presentation. *Stroke* 2002;33:920–4.
26 Yang W, Porras JL, Xu R, *et al*. Comparison of hemorrhagic risk in intracranial arteriovenous malformations between conservative management and embolization as the single treatment modality. *Neurosurgery* 2018;82:481–90.
27 Ma L, Huang Z, Chen X-L, *et al*. Periventricular location as a risk factor for hemorrhage and severe clinical presentation in pediatric patients with untreated brain arteriovenous malformations. *AJNR Am J Neuroradiol* 2015;36:1550–7.
28 Marks MP, Lane B, Steinberg GK, *et al*. Hemorrhage in intracerebral arteriovenous malformations: angiographic determinants. *Radiology* 1990;176:807–13.
29 Mansmann U, Meisel J, Brock M, *et al*. Factors associated with intracranial hemorrhage in cases of cerebral arteriovenous malformation. *Neurosurgery* 2000;46:272–9;
30 Dashe JF. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology* 2007;68:535; author reply 535.
31 Wright R, Järvelin P, Pekonen H, *et al*. Histopathology of brain AVMs part II: Inflammation in arteriovenous malformation of the brain. *Acta Neurochir (Wien)* 2020;162:1741–7.
32 Chen Y, Zhu W, Bollen AW, *et al*. Evidence of inflammatory cell involvement in brain arteriovenous malformations. *Neurosurgery* 2008;62:1340–9;
33 Neyazi B, Herz A, Stein K-P, *et al*. Brain arteriovenous malformations: implications of CEACAM1-positive inflammatory cells and sex on hemorrhage. *Neurosurg Rev* 2017;40:129–34.
34 Derdeyn CP, Zipfel GJ, Albuquerque FC, *et al*. Management of brain arteriovenous malformations: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017;48:e200–24.

Context

Supplemental Methods. Protocol for Data Quality Management in the *BLINDED* study

1. Definition of variables was discussed and unified according to the terminology reporting standards or published papers before the initiation of data collection. Clinical research coordinators (CRCs) and neurosurgery residents were then trained by a cerebrovascular neurosurgeon with more than 15 years' working experience. CRCs were responsible for demographic information and follow-up data, and neurosurgery residents for angiographic features. The two parts were blinded to each other to ensure the data collected were not biased by imaging characteristics or clinical outcomes.
2. A standard training dataset with 50 cases was used to check the consistency of data collectors. For those variables or cases with significant interobserver variation, the consensus was reached by either modifying the confusing definitions or retraining the data collectors. Only when the consistency reached 90% can the CRC or the resident be allowed to extract information independently.
3. While recording data, one could ask for help about unsure cases in a discussion group with cerebrovascular neurosurgeons in it or mark these cases and discuss them in weekly meetings.
4. The group leader with more than five years' working experience randomly spot-checks these data biweekly. Investigators would receive training again if their data were of low quality, and these data would be recollected by other investigators.

Yuan K, *et al. J NeuroIntervent Surg* 2023;0:1–7. doi: 10.1136/jnis-2023-020650

Table S1. Univariable and Multivariable Cox proportional hazards model for risk of re-rupture in 526-low risk treatment cohort patients. (patients who had no risk factors for intervention treatment and in the end chose intervention therapy)

Characteristics	Univariable			Multivariable		
	HR	95%CI	P	HR	95%CI	P
Ventricular System Involvement	1.95	1.04 – 3.65	0.037	1.70	0.85 - 3.40	0.132
Number of Feeding Arteries	1.37	1.01-1.85	0.041	1.39	0.97 - 1.98	0.072
Any Deep Drainage	1.96	1.08 – 3.54	0.027	1.81	0.97 - 3.38	0.063
Arterial borderzone AVM	2.08	1.08 – 3.99	0.028	1.26	0.58 - 2.73	0.563

Risk factors for intervention treatment were defined as: the diameter of the nidus>6cm, located in Eloquent region, deep location, SM grade 4-5.

Figure S1. Schoenfeld's global test before the Cox proportional hazards regression.

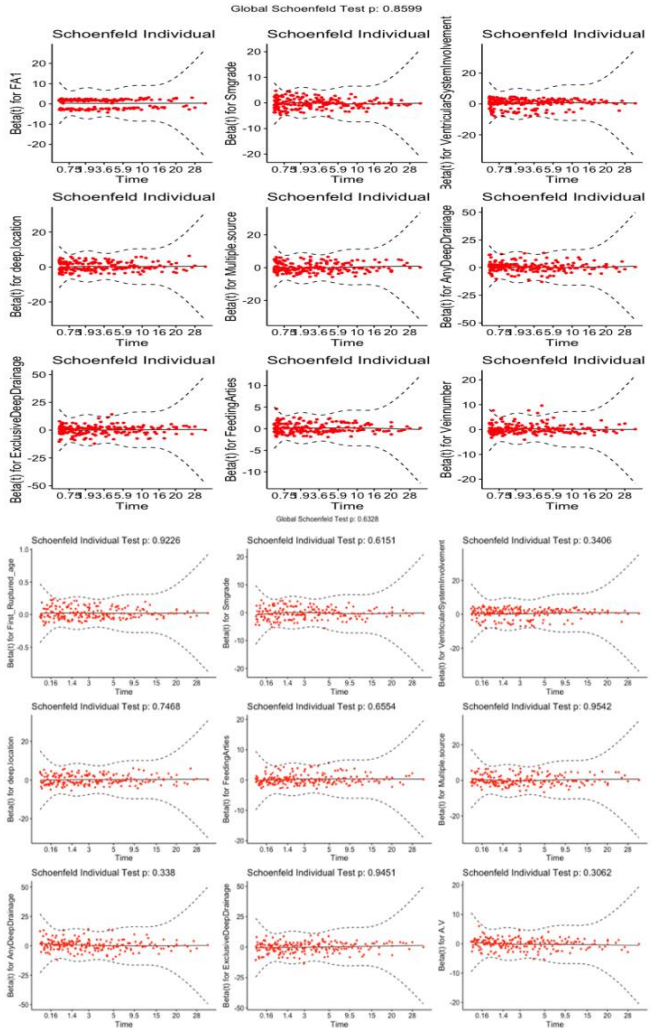

Figure S2. Patient selection flowchart.

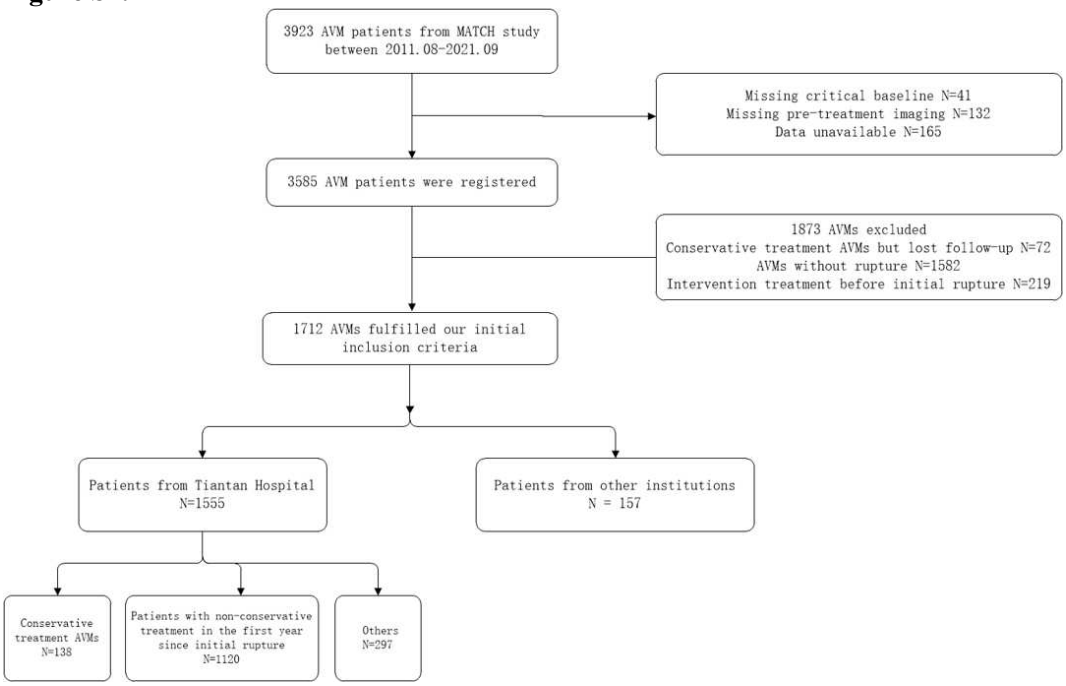

Figure S3. The Kaplan-Meier survival curve of the 1555 patients cohort.

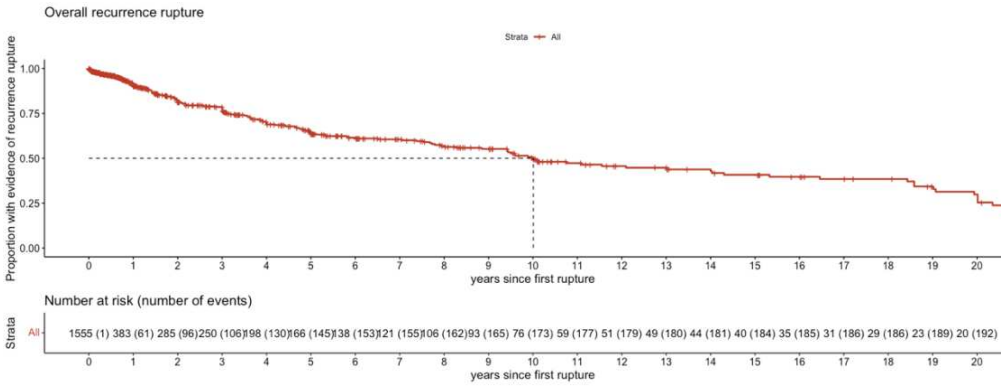

Table S2. Univariable and Multivariable Cox proportional hazards model for risk of re-rupture in sensitivity analyses cohort excluding patients who received intervention in the first year since the initial rupture

	HR	CI95	P	HR	CI95	P
First rupture age	1.02	1.01-1.03	0.001	1.02	1.01 - 1.03	<0.001
SM grade	1.19	1.04-1.37	0.014	0.79	0.63 - 1.01	0.057
Ventricular System Involvement	1.69	1.19-2.39	0.003	1.59	1.08 - 2.35	0.020
Deep location	1.45	1.08-1.95	0.013	1.16	0.82 - 1.63	0.394
Number of Feeding Arties	1.16	1.04-1.28	0.006	1.24	0.99 - 1.54	0.057
Arterial borderzone AVM	1.42	1.05-1.91	0.021	1.17	0.81 - 1.69	0.416
Any Deep Drainage	1.76	1.32-2.34	<0.001	1.97	1.12 - 3.45	0.018
Exclusive Deep Drainage	1.55	1.17-2.06	0.002	0.97	0.56 - 1.67	0.917
Number of Arteries / Venous	1.11	0.99-1.25	0.076	0.97	0.77 - 1.21	0.770

No collinearity was present between the independent variables (variance inflation factor <3).

HR: hazard ratio; CI: confidence interval;

AVM: arteriovenous malformation

Table S3. Univariable and Multivariable Cox proportional hazards model analysis of influencing factors (Cox regression).

	Univariable					Multivariable				
Characteristic	N	Event N	HR1	95% CI1	p-value	N	Event N	HR1	95% CI1	p-value
SM Grade										
1	273	14	—	—		273	14	—	—	
2	551	51	1.47	0.81, 2.66	0.21	551	51	1.08	0.59, 1.99	0.80
3	497	77	1.86	1.05, 3.30	0.033	497	77	0.98	0.51, 1.87	0.95
4	202	49	2.07	1.14, 3.77	0.017	202	49	0.78	0.37, 1.63	0.51
5	32	10	2.68	1.18, 6.05	0.018	32	10	0.88	0.33, 2.33	0.80
Deep location										
0	1,063	130	—	—		1,063	130	—	—	
1	492	71	1.45	1.08, 1.94	0.013	492	71	1.24	0.88, 1.74	0.22
Number of feeding arteries	1,555	201	1.18	1.07, 1.31	0.002	1,555	201	1.24	1.01, 1.53	0.044
Arterial borderzone AVM										
0	1,239	137	—	—		1,239	137	—	—	
1	316	64	1.47	1.09, 1.98	0.011	316	64	1.14	0.79, 1.65	0.47
Exclusive deep venous drainage										
0	1,046	119	—	—		1,046	119	—	—	
1	509	82	1.53	1.15, 2.03	0.003	509	82	1.20	0.78, 1.83	0.41
Number of arteries/venous	1,555	201	1.13	1.00, 1.27	0.045	1,555	201	0.92	0.75, 1.14	0.46
Risk groups										
Low risk	**625**	**52**	—	—		**625**	**52**	—	—	
High risk	**930**	**149**	**2.03**	**1.48, 2.80**	**<0.001**	**930**	**149**	**1.78**	**1.18, 2.69**	**0.006**

1HR = Hazard Ratio, CI = Confidence Interval

Number in dataframe = 1555, Number in model = 1555, Missing = 0, Number of events = 201, Concordance = 0.608 (SE = 0.027), R-squared = 0.020(Max possible = 0.754), Likelihood ratio test = 32.053 (df = 10, p = 0.000)

Table S4. Baseline characteristics and group comparisons between the re-rupture and non-re-rupture AVM groups in multi-center validation cohort data.

	level	Overall N=157	Non- recurrence Rupture AVM N=146	Recurrence Rupture AVM N=11	p-value
Demographic characteristics					
Female gender, n (%)		63 (40.13)	59 (40.41)	4 (36.36)	1.000
Initial rupture age (mean (SD))		26.688 (15.952)	26.500 (15.806)	29.182 (18.433)	0.592
Clinical features					
Seizure, n (%)		9 (5.73)	9 (6.16)	0 (0.00)	0.861
Headache, n (%)		138 (87.90)	129 (88.36)	9 (81.82)	0.872
Neurological Complications, n (%)		42 (26.75)	39 (26.71)	3 (27.27)	1.000
Morphologic features					
SM Grade, n (%)	1	18 (11.46)	17 (11.64)	1 (9.09)	0.440
	2	47 (29.94)	45 (30.82)	2 (18.18)	
	3	56 (35.67)	53 (36.30)	3 (27.27)	
	4	35 (22.29)	30 (20.55)	5 (45.45)	
	5	1 (0.64)	1 (0.68)	0 (0.00)	
Ventricular System Involvement, n (%)		106 (67.52)	95 (65.07)	11 (100.00)	0.040
Deep location, n (%)		72 (45.86)	65 (44.52)	7 (63.64)	0.361
AVM Size, n (%)	< 3cm	88 (56.05)	82 (56.16)	6 (54.55)	0.915
	3-6cm	67 (42.68)	62 (42.47)	5 (45.45)	
	>6cm	2 (1.27)	2 (1.37)	0 (0.00)	
Eloquent region, n (%)		111 (70.70)	102 (69.86)	9 (81.82)	0.620
Feeding artery dilation, n (%)		81 (51.59)	73 (50.00)	8 (72.73)	0.254
Feeding arteries number (mean (SD))		2.242 (1.242)	2.267 (1.261)	1.909 (0.944)	0.358
Arterial borderzone, n (%)		35 (22.29)	32 (21.92)	3 (27.27)	0.971
Associated aneurysm, n (%)		41 (26.11)	37 (25.34)	4 (36.36)	0.655
Diffuse nidus, n (%)		70 (44.59)	67 (45.89)	3 (27.27)	0.377
Any Deep venous drainage, n (%)		86 (54.78)	77 (52.74)	9 (81.82)	0.120
Exclusive deep venous drainage, n (%)		67 (42.68)	60 (41.10)	7 (63.64)	0.254
Number of Arteries/Venous (mean (SD))		1.798 (1.083)	1.841 (1.096)	1.218 (0.695)	0.066
Draining vein stenosis, n (%)		54 (34.39)	47 (32.19)	7 (63.64)	0.074
Risk Group (%)	**High risk**	104 (66.24)	93 (63.70)	11 (100.00)	**0.034**
	Low risk	53 (33.76)	53 (36.30)	0 (0.00)	

Figure S4. The high-low risk groupings were still valid for differentiating AVM re-rupture risk.

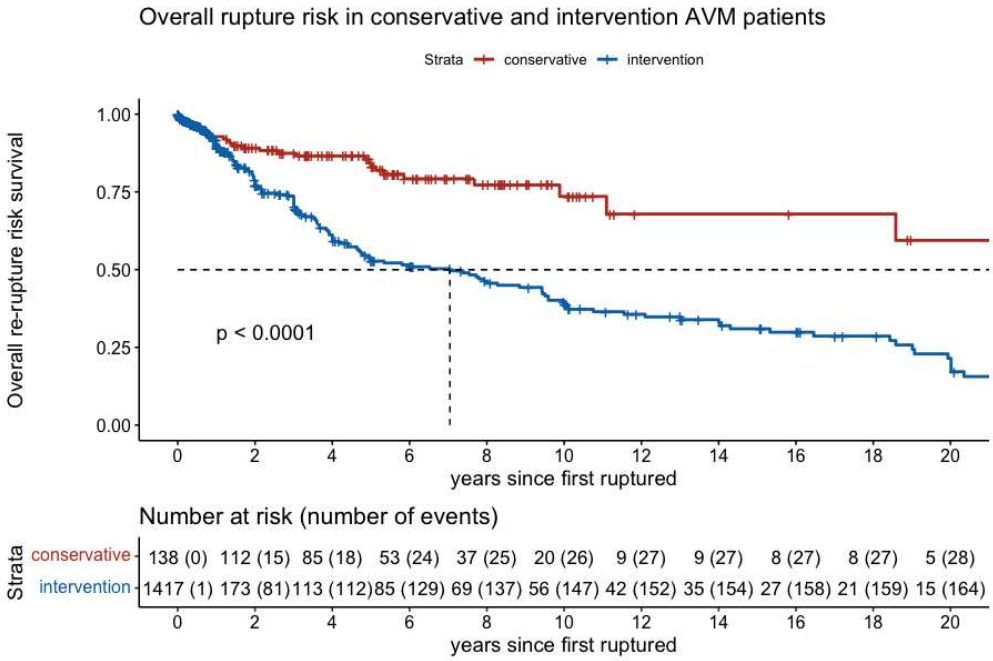

Table S5. Baseline characteristics and group comparisons between the re-rupture and non-re-rupture AVM groups in conservative group.

	level	Overall N=138	Non- recurrence Rupture AVM N=109	Recurrence Rupture AVM N=29	p-value
Demographic characteristics					
Female gender, n (%)		58 (42.03)	44 (40.37)	14 (48.28)	0.579
First rupture age (mean (SD))		28.667 (15.713)	28.018 (15.273)	31.103 (17.336)	0.349
Clinical features					
Seizure, n (%)		16 (11.59)	13 (11.93)	3 (10.34)	1.000
Headache, n (%)		24 (17.39)	18 (16.51)	6 (20.69)	0.801
Neurological Complications, n (%)		32 (23.19)	25 (22.94)	7 (24.14)	1.000
Morphologic features					
SM Grade, n (%)	1	20 (14.49)	18 (16.51)	2 (6.90)	0.001
	2	38 (27.54)	33 (30.28)	5 (17.24)	
	3	46 (33.33)	40 (36.70)	6 (20.69)	
	4	30 (21.74)	16 (14.68)	14 (48.28)	
	5	4 (2.90)	2 (1.83)	2 (6.90)	
Ventricular System Involvement, n (%)		99 (71.74)	74 (67.89)	25 (86.21)	0.086
Deep location, n (%)		57 (41.30)	47 (43.12)	10 (34.48)	0.531
AVM Size, n (%)	< 3cm	72 (52.17)	64 (58.72)	8 (27.59)	0.011
	3-6cm	52 (37.68)	36 (33.03)	16 (55.17)	
	>6cm	14 (10.14)	9 (8.26)	5 (17.24)	
Eloquent region, n (%)		87 (63.04)	65 (59.63)	22 (75.86)	0.164
Feeding artery dilation, n (%)		55 (39.86)	41 (37.61)	14 (48.28)	0.407
Feeding arteries number (mean (SD))		2.188 (1.370)	1.917 (1.195)	3.207 (1.521)	<0.001
Arterial borderzone, n (%)		37 (26.81)	21 (19.27)	16 (55.17)	<0.001
Associated aneurysm, n (%)		33 (23.91)	24 (22.02)	9 (31.03)	0.443
Diffuse nidus, n (%)		70 (50.72)	52 (47.71)	18 (62.07)	0.244
Any Deep venous drainage, n (%)		69 (50.00)	50 (45.87)	19 (65.52)	0.095
Exclusive deep venous drainage, n (%)		51 (36.96)	39 (35.78)	12 (41.38)	0.735
Number of Arteries/Venous (mean (SD))		6.181 (2.756)	5.872 (2.524)	7.345 (3.287)	0.010
Draining vein stenosis, n (%)		34 (24.64)	26 (23.85)	8 (27.59)	0.863
Venous aneurysm, n (%)		12 (8.70)	10 (9.17)	2 (6.90)	0.987

AVM: arteriovenous malformation

Figure S5. Kaplan-Meier survival curve of the exploration cohort who had maintained conservative management throughout the whole course and followed up regularly.

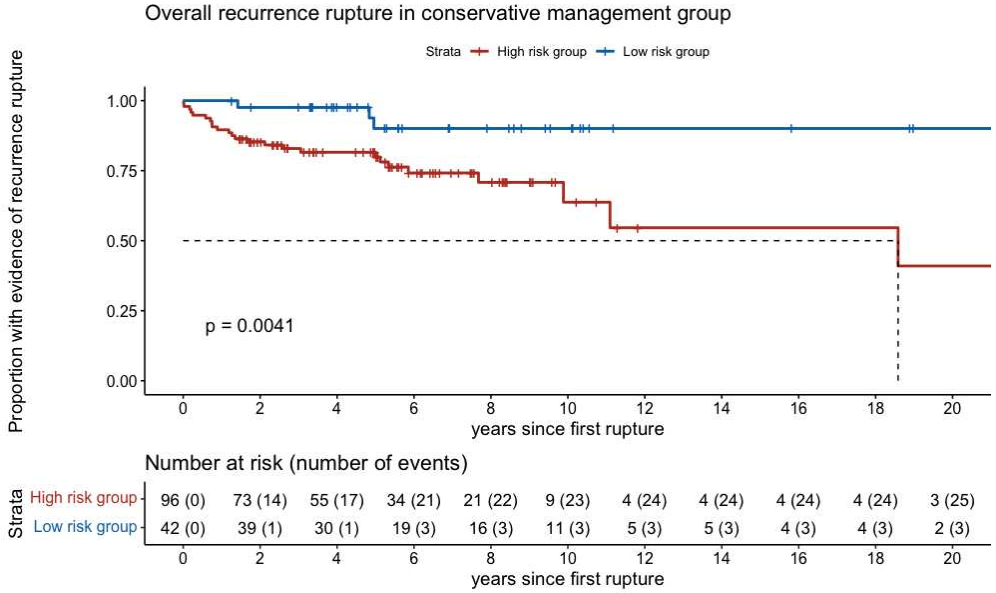

Figure S6 The high-low risk groupings in patients who were simply waiting for treatment cohort.

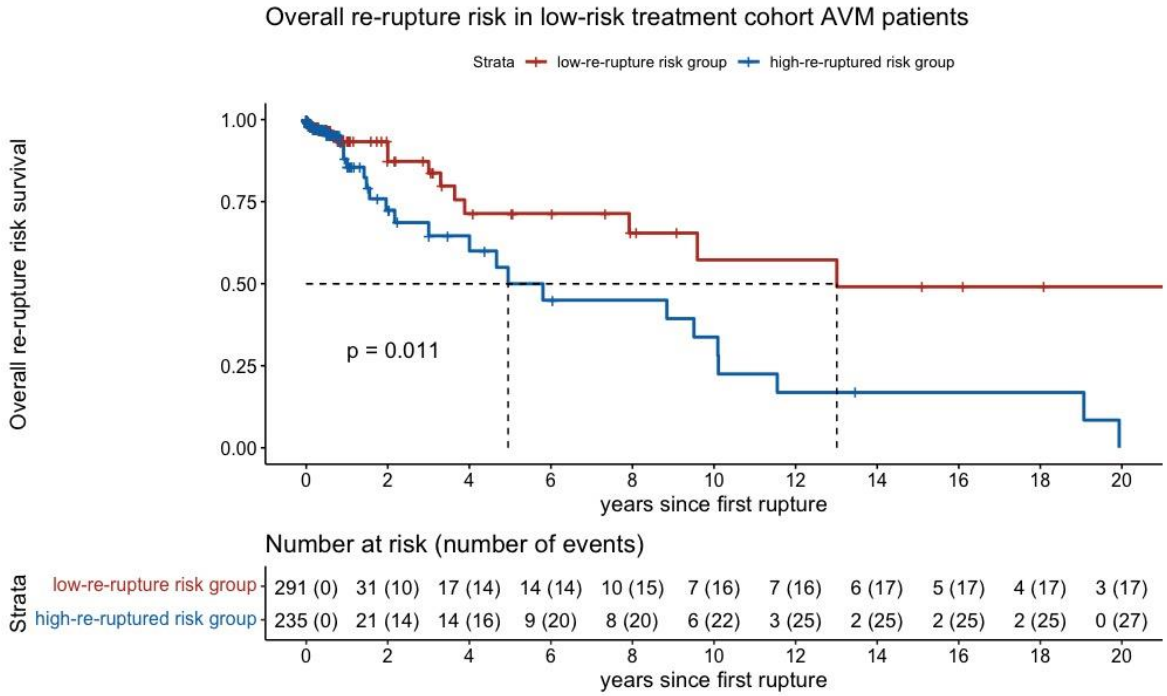

Table S6. Treatment data

Treatment type	No. of patients	No. of patients with re-rupture before treatment	The frequency of re-ruptures before treatment	No. of patients with re-rupture after treatment	The frequency of re-ruptures after treatment	Follow-up duration (years)	Annual rupture risk
Total patients	1417	172 (12.1%)	228	120 (8.5%)	138	8139.9	1.70%
Surgical resection	445	46 (10.3%)	57	4 (0.9%)	4	2975.7	0.13%
Embolization	157	23 (14.6%)	38	17 (10.8%)	20	885.3	2.26%
Radiosurgery	236	34 (14.4%)	41	13 (5.5%)	16	1381.8	1.16%
Single-stage combined embolization + resection	227	20 (8.8%)	23	3 (1.3%)	3	841.4	0.36%
Other multi-modality strategy	352	49 (13.9%)	69	83 (23.6%)	95	2055.6	4.62%

Figure S7. Preventive effects of different intervention strategies on AVM re-rupture events.

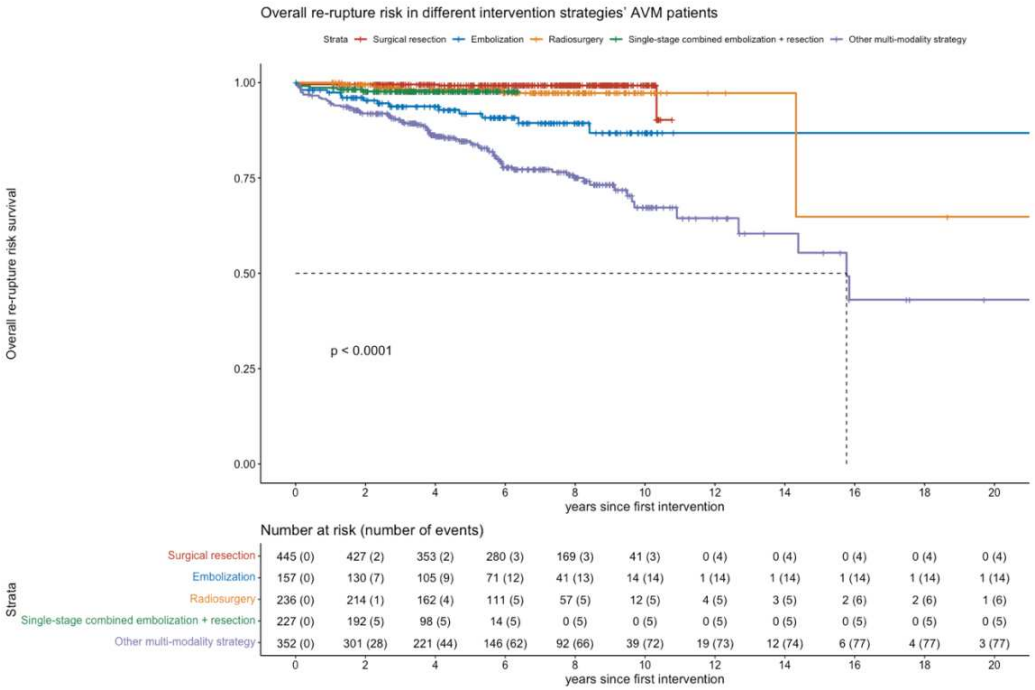

Table S7. Baseline characteristics and group comparisons between the conservative treatment and non-conservative treatment AVM groups.

	level	Overall N=1555	Conservative management AVMs N=138	Non-conservative management after re-rupture AVMs N=1417	p-value
Demographic characteristics					
Female gender, n (%)		668 (42.96)	58 (42.03)	610 (43.05)	0.089
Age>18, n (%)		898 (57.75)	79 (57.25)	819 (57.80)	0.198
Clinical features					
Seizure, n (%)		191 (12.28)	16 (11.59)	175 (12.35)	0.903
Headache, n (%)		234 (15.05)	24 (17.39)	210 (14.82)	0.495
Neurological Complications, n (%)		298 (19.16)	32 (23.19)	266 (18.77)	0.252
Morphologic features					
SM Grade, n (%)	1	273 (17.56)	20 (14.49)	253 (17.85)	**0.011**
	2	551 (35.43)	38 (27.54)	513 (36.20)	
	3	497 (31.96)	46 (33.33)	451 (31.83)	
	4	202 (12.99)	30 (21.74)	172 (12.14)	
	5	32 (2.06)	4 (2.90)	28 (1.98)	
Ventricular System Involvement, n (%)		1022 (65.72)	99 (71.74)	923 (65.14)	0.143
Deep location, n (%)		492 (31.64)	57 (41.30)	435 (30.70)	**0.014**
AVM Size, n (%)	< 3cm	956 (61.48)	72 (52.17)	884 (62.39)	0.008
	3-6cm	516 (33.18)	52 (37.68)	464 (32.75)	
	>6cm	83 (5.34)	14 (10.14)	69 (4.87)	
Eloquent region, n (%)		893 (57.43)	87 (63.04)	806 (56.88)	0.191
Feeding artery dilation, n (%)		537 (34.53)	55 (39.86)	482 (34.02)	0.199
Feeding arteries number (median (IQR))		2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.443
Arterial borderzone, n (%)		316 (20.32)	37 (26.81)	279 (19.69)	0.061
Associated aneurysm, n (%)		302 (19.42)	33 (23.91)	269 (18.98)	0.199
Diffuse nidus, n (%)		699 (44.95)	70 (50.72)	629 (44.39)	0.181
Any Deep venous drainage, n (%)		704 (45.27)	69 (50.00)	635 (44.81)	0.281
Exclusive deep venous drainage, n (%)		509 (32.73)	51 (36.96)	458 (32.32)	0.311
Number of Venous (median (IQR))		1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	0.803
Draining vein stenosis, n (%)		300 (19.29)	34 (24.64)	266 (18.77)	0.120
Venous aneurysm, n (%)		99 (6.37)	12 (8.70)	87 (6.14)	0.322

Table S8. Baseline characteristics and group comparisons between the un-re-ruptured and re-ruptured AVM groups (excluding Ventricular System Involvement and Any Deep venous drainage patients).

	level	Overall N=410	Un-re-ruptured AVMs N=386	Re-rupture AVMs N=24	p-value
Demographic characteristics					
Female gender, n (%)		163 (39.76)	150 (38.86)	13 (54.17)	0.204
First Ruptured Age (median [IQR])		24.06 [14.54, 37.12]	24.00 [14.33, 37.12]	28.00 [20.00, 35.75]	0.551
Clinical features					
Seizure, n (%)		62 (15.12)	58 (15.03)	4 (16.67)	>0.999
Headache, n (%)		51 (12.44)	51 (13.21)	0 (0.00)	0.113
Neurological Complications, n (%)		59 (14.39)	53 (13.73)	6 (25.00)	0.220
Morphologic features					
SM Grade, n (%)	1	161 (39.27)	152 (39.38)	9 (37.50)	0.971
	2	195 (47.56)	183 (47.41)	12 (50.00)	
	3	51 (12.44)	48 (12.44)	3 (12.50)	
	4	3 (0.73)	3 (0.78)	0 (0.00)	
Ventricular System Involvement, n (%)		410 (100.00)	386 (100.00)	24 (100.00)	NA
Deep location, n (%)		62 (15.12)	58 (15.03)	4 (16.67)	>0.999
AVM Size, n (%)	< 3cm	292 (71.22)	275 (71.24)	17 (70.83)	0.714
	3-6cm	110 (26.83)	104 (26.94)	6 (25.00)	
	>6cm	8 (1.95)	7 (1.81)	1 (4.17)	
Eloquent region, n (%)		180 (43.90)	170 (44.04)	10 (41.67)	0.988
Feeding artery dilation, n (%)		155 (37.80)	148 (38.34)	7 (29.17)	0.495
Feeding arteries number (median (IQR))		1 [1, 2]	1 [1, 2]	2 [1, 2]	0.177
Arterial borderzone, n (%)		50 (12.20)	48 (12.44)	2 (8.33)	0.784
Associated aneurysm, n (%)		68 (16.59)	62 (16.06)	6 (25.00)	0.390
Diffuse nidus, n (%)		173 (42.20)	161 (41.71)	12 (50.00)	0.559
Any Deep venous drainage, n (%)		410 (100.00)	386 (100.00)	24 (100.00)	NA
Exclusive deep venous drainage, n (%)		410 (100.00)	386 (100.00)	24 (100.00)	NA
Number of Venous (median (IQR))		1 [1, 1]	1 [1, 1]	1 [1, 2]	0.278
Draining vein stenosis, n (%)		87 (21.22)	82 (21.24)	5 (20.83)	1
Venous aneurysm, n (%)		26 (6.34)	22 (5.70)	4 (16.67)	0.088