SUPPLEMENTAL DATA

Table e-1 Codebook for variables extracted from each MARS cohort

Description	Method	Range	Units	Notes
Unique patient identifier	Assigned after merging			
Unique patient ID	Assigned by each site			
Cohort identifier	Assigned	UCSF, COL, KPNC, SIVMS		
Patient age at diagnostic event	History	0–99	Decades	
Sex	Physical Exam	M / F		
Race/ethnicity	History			per NIH reporting style
Hemorrhage at initial presentation	CT/MRI evidence of fresh bleeding into parenchyma or CSF spaces	Yes/No		Hierarchical according to Joint Writing Group. Aneurysmal SAH not differentiated from AVM hemorrhage
Seizure at initial presentation	History	Yes/No		
Headache at initial presentation	History	Yes/No		
Focal deficit at initial presentation	History/ Physical Exam	Yes/No		
Asymptomatic at initial presentation	History	Yes/No		
AVM surgical resection	History	Yes/No		
AVM endovascular therapy	History	Yes/No		
AVM radiosurgery	History	Yes/No		
Non–interventional management	History	Yes/No		
Maximum AVM size	Angiogram or MRI	>0	centimeters	
Venous Drainage pattern	Angiogram	Superficial; Deep; Both		
Any lobar location	Angiogram or MRI	Yes/No		
Any infratentorial location	Angiogram or MRI	Yes/No		
AVM side	Angiogram or MRI	Yes/No		
Any arterial AVM–related aneurysm	Angiogram or MRI	Yes/No		Includes proximal and distal flow–related aneurysm and intranidal aneurysms
Spetzler–Martin surgical risk grade	Derived	I, II, III, IV, V		Sum of AVM size (small =1(<3cm), medium=2 (>= 3 and <= 6 cm), large=3 (>6 cm)), + eloquence (no=0, yes=1), + venous drainage (superficial only=0, any deep=1).
Event time	Derived	>0	days	Time to event for Kaplan Meier analysis; numbers of days between diagnosis and event or censoring; in days because some patients will have very short follow up time

New hemorrhage after diagnosis K–M Survival Analysis Censor Variable	Derived	Yes/No		K–M Survival Analysis Censor Variable. Censor date is (a) any AVM treatment; (b) last follow–up; c) death; Hem on same date as tx is censored and NOT treated as new event.
Death after diagnosis K–M Survival Analysis Censor Variable		Yes/No		Time to event for Kaplan Meier analysis; numbers of days between diagnosis and death

Table e-2. Annual hemorrhage rates per 100 patient-years based on different truncated survival times for all AVMs and by rupture status at presentation

	Overall			Ruptured			Unruptured		
Survival time	ICH Events	Rate per year	95% CI	ICH Events	Rate per year	95% CI	ICH Events	Rate per year	95% CI
10 years	141	2.32	(1.97, 2.74)	85	4.80	(3.88, 5.94)	56	1.30	(1.00, 1.69)
5 years	109	2.73	(2.27, 3.30)	68	5.85	(4.61, 7.42)	41	1.45	(1.07, 1.97)
2 years	72	5.25	(4.17, 6.62)	47	10.73	(8.06, 14.29)	25	2.68	(1.81, 3.97)
1 year	57	4.40	(3.39, 5.71)	40	9.76	(7.16, 13.31)	17	1.92	(1.19, 3.09)

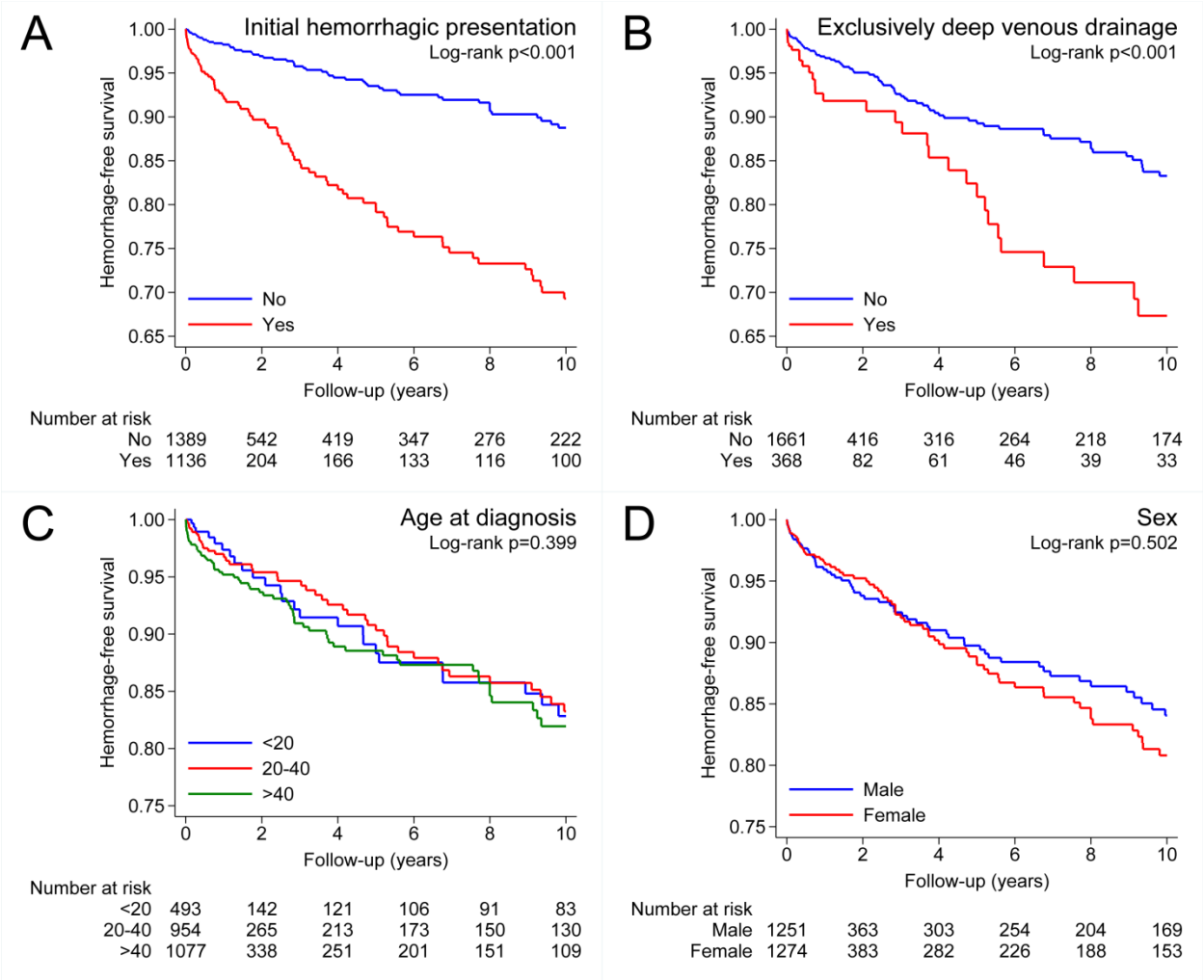
Our data suggest that hemorrhage events are more likely to occur in a short window after presentation rather than at a later time, reflected by the higher hemorrhage rates in the 1 and 2 year analyses and lower rates in the 5 and 10 year analyses.

Table e-3 Risk of hemorrhage in the natural history course by age category

Age category	No. (%) in age category	No. (%) of ICH events	No. (%) Treated	Follow-up (yrs)	Adjusted HR	95% CI	p-value
0-20 years	538 (21%)	25 (5%)	385 (72%)	2.53	Reference		
21-40 years	953 (38%)	48 (5%)	651 (68%)	2.32	1.97	0.98 – 3.98	0.058
41-60 years	777 (31%)	44 (6%)	500 (64%)	2.22	3.93	1.89 – 8.19	<0.001
61+ years	256 (10%)	23 (9%)	100 (39%)	3.05	6.17	2.61 – 14.61	<0.001

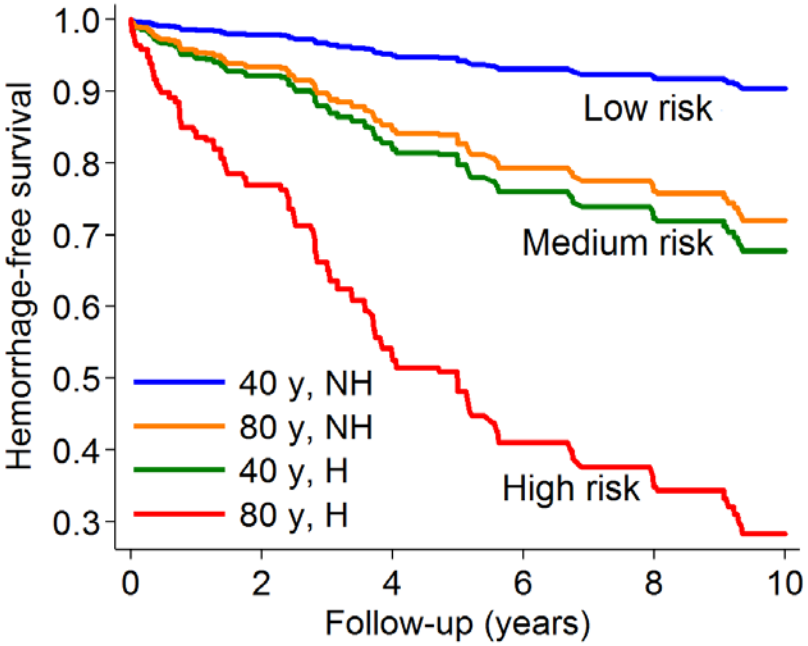
We assessed hemorrhage risk in the natural history course by age category, grouping patients into children (0-20 years), young adults (21-40 years), middle-aged adults (41-60 years) and older adults (61+ years). Children make up a large proportion of the cohort (21%) and their average follow-up time, while less than that of older adults, is not profoundly so. Compared to children, the effect of age is monotonically increasing across all successive age categories. Thus, these results provide additional justification for modeling age as a continuous variable in our paper.

Figure e-1 Kaplan-Meier survival curves for new hemorrhage in untreated brain AVM patients, by clinical characteristics



(A) Initial hemorrhagic presentation; (B) Exclusively deep venous drainage; (C) Age at diagnosis; (D) Sex. The y-axis shows the proportion of subjects who remain hemorrhage-free. The x-axis shows follow-up time after AVM diagnosis in years. The table below shows the number at risk at each follow-up time interval.

Figure e-2 Hemorrhage-free survival curves stratifying predicted probabilities of hemorrhage risk into low, intermediate and high



y = years old at diagnosis; NH = no hemorrhage at presentation; H = hemorrhage at presentation

Once a risk prediction model has been validated in external cohorts, the clinical utility of the model can be assessed. A good prediction model will be able to stratify patients into low, intermediate, and high risk.

Using our Model A estimates, we calculated the predicted probability of hemorrhage in the natural untreated course of AVM patients for various scenarios. The predicted probabilities of hemorrhage are calculated using the following formula:

$$1 - \hat{S}_i(t) = 1 - \hat{S}_0(t)^{\exp(x_i'\hat{\beta})},$$

where $\hat{S}_0(t)$ is the baseline survivor function at time *t* and $x_i'\hat{\beta}$ is the vector of covariates multiplied by the corresponding model coefficients (i.e., the log of the hazard ratios). For our model A, this equates to:

$$\text{predicted probability of event} = 1 - (\text{baseline survival at time t})^{\exp\{0.294\times A + 0.395\times G + 1.349\times P + 0.468\times V + 0.018\times S\}},$$

where A is the age at diagnosis in decades, G is gender (1=female, 0=male), P is presentation (1=hemorrhagic, 0=other), V is venous drainage pattern (1=exclusively deep, 0=other), and S is AVM size in cm. The baseline survival estimates are derived by a weighted average of the baseline estimates from the four MARS cohorts, which are given below in the Table.

Time since Diagnosis	Weighted Average of Baseline Survival
1 year	0.99584
5 years	0.98301
10 years	0.97087

For example, we compared the predicted risk for an 80-year-old male to a 40-year-old male with the following AVM characteristics: unruptured at presentation, 3 cm AVM nidus, and not exclusively deep venous drainage. This corresponds to probability of hemorrhage of 4.5% at 1 year, 17.3% at 5 years, and 27.9% at 10 years for the 80-year-old male. On the other hand, the predicted probability of hemorrhage for a 40-year-old male with similar AVM characteristics is much lower: 1.4% at 1 year, 5.6% at 5 years, and 9.6% at 10 years. This can be better seen in the Figure, showing good separation of survival curves into low, intermediate and high risk for risk stratification purposes. Thus, in this example, the 80-year-old male who has an unruptured AVM has a similar hemorrhage risk to a 40-year-old male who presents with a ruptured AVM, keeping all else constant.