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ORIGINAL ARTICLE

Intracranial Hemorrhage Rate and Lesion Burden in Patients With Familial Cerebral Cavernous Malformation

Shantel Weinsheimer, PhD; Jeffrey Nelson, MS; Adib A. Abla, MD; Nerissa U. Ko, MD, MAS; Cynthia Tsang, BS; Obiora Okoye, MBBS, MPH; Joseph M. Zabramski, MD; Amy Akers, PhD; Atif Zafar, MD; Marc C. Mabray, MD; Blaine L. Hart, MD; Leslie Morrison, MD; Charles E. McCulloch, PhD; Helen Kim, PhD; The Brain Vascular Malformation Consortium Cerebral Cavernous Malformation Investigator Group*

BACKGROUND: Familial cerebral cavernous alformation (CCM) is an autosomal dominant disease caused by mutations in *KRIT1*, *CCM2*, or *PDCD10*. Cases typically present with multiple lesions, strong family history, and neurological symptoms, including seizures, headaches, or other deficits. Intracranial hemorrhage (ICH) is a severe manifestation of CCM, which can lead to death or long-term neurological deficits. Few studies have reported ICH rates and risk factors in familial CCM. We report ICH rates and assess whether CCM lesion burden, a disease severity marker, is associated with risk of symptomatic ICH during follow-up in a well-characterized cohort of familial CCM cases.

METHODS AND RESULTS: We studied 386 patients with familial CCM with follow-up data enrolled in the Brain Vascular Malformation Consortium CCM Project. We estimated symptomatic ICH rates overall and stratified by history of ICH before enrollment. CCM lesion burden (total lesion count and large lesion size) assessed at baseline enrollment was tested for association with increased risk of subsequent ICH during follow-up using Cox regression models adjusted for history of ICH before enrollment, age, sex, and family structure and stratified on recruitment site. The symptomatic ICH rate for familial CCM cases was 2.8 per 100 patient-years (95% CI, 1.9–4.1). Those with ICH before enrollment had a follow-up ICH rate of 4.5 per 100 patient-years (95% CI, 2.6–8.1) compared with 2.0 per 100 patient-years (95% CI, 1.3–3.5) in those without (P=0.042). Total lesion count was associated with increased risk of ICH during follow-up (hazard ratio [HR], 1.37 per doubling of total lesion count [95% CI, 1.10–1.71], P=0.006).

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CONCLUSIONS: Patients with familial CCM with prior history of an ICH event are at higher risk for rehemorrhage during follow-up. In addition, total CCM lesion burden is significantly associated with increased risk of subsequent symptomatic ICH; hence lesion burden may be an important predictor of patient outcome and aid patient risk stratification.

Key Words: cerebral cavernous malformation ■ familial ■ hemorrhage ■ risk factor

Familial cerebral cavernous malformation (CCM) is a rare autosomal dominant disease caused by mutations in 1 of 3 CCM genes (*CCM1/KRIT1*, *CCM2*, and *CCM3/PDCD10*), and typically characterized by strong family history and by multiple lesions on magnetic resonance imaging (MRI) that can grow both in

Correspondence to: Helen Kim, PhD, Department of Anesthesia and Perioperative Care, Center for Cerebrovascular Research, University of California, 1001 Potrero Avenue, Box 1363, San Francisco, CA 94143. Email: helen.kim2@ucsf.edu

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*Complete list of "The Brain Vascular Malformation Consortium Cerebral Cavernous Malformation Investigator Group" given in Appendix section.

For Sources of Funding and Disclosures, see page 6.

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CLINICAL PERSPECTIVE

What Is New?

- To estimate the risk of intracranial hemorrhage (ICH) in familial cerebral cavernous malformation (CCM) cases we conducted a large, multicenter cohort study of 386 familial CCM cases and found an overall ICH rate of 2.8 per 100 patient-years. The ICH rate was 2.2 times higher in those with a prior history of ICH compared with those without a prior history.
- Total number of CCM lesions at study enrollment was a significant predictor of subsequent symptomatic ICH during prospective follow-up, independent of prior ICH.

What Are the Clinical Implications?

- Higher CCM lesion burden may be useful for counseling patients with familial CCM about future ICH risk and may warrant more intensive follow-up.

Nonstandard Abbreviations and Acronyms

BVMC	Brain Vascular Malformation Consortium
CCM	cerebral cavernous malformation
ICH	intracranial hemorrhage

size and number over time.[1,2] CCMs are leaky vascular lesions that can cause premature hemorrhagic strokes, recurrent seizures, and other disabling neurological deficits[3–5]; however, the mechanisms or events triggering clinical symptoms remain unknown.[6] Further, disease severity is highly variable even among individuals with the same gene mutation, within the same family, or of similar age, suggesting the presence of additional environmental or genetic disease modifiers.[7–9]

Preventing intracranial hemorrhage (ICH) is the primary reason to treat these lesions, but not all patients can be offered treatment. Current clinical guidelines recommend neurosurgical treatment of symptomatic lesions in easily accessible locations or that have previously ruptured.[10] Thus, treatment risks must be weighed against the risk of ICH in the natural history course. Only 4 studies have reported ICH rates in familial cases, with estimates ranging from 4.3% to 16.5% per patient-year.[1,2,11,12] In a separate systematic pooled analysis of 7 studies including both sporadic and familial CCM, the overall annual ICH rate was 2.5% per patient-year over 5081.2 patient-years of follow-up (95% CI, 1.3%–5.1%).[13] It is assumed that the ICH rate is higher in familial CCM, yet previous studies have been small, with different enrollment criteria and different populations; hence, the evaluation of a larger familial CCM cohort is needed to provide a more precise ICH rate estimate.

Several CCM-specific risk factors have been studied including CCM localization, CCM size, previous history of ICH, and presence of associated developmental venous anomaly.[13] However, familial CCM lesions are not typically associated with developmental venous anomaly[14] and individuals present with a multitude of lesions that are dynamic in nature and highly variable. There is insufficient understanding of ICH risk factors in familial CCM, which is needed for counseling patients. Hence, we hypothesized that greater lesion burden, a marker of disease severity in familial CCM, predicts risk of ICH. Thus, the purpose of this study was to report symptomatic ICH rates and assess whether lesion burden is associated with risk of symptomatic ICH during follow-up in a well-characterized cohort of familial CCM cases.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Brain Vascular Malformation Consortium (BVMC) CCM Project is a longitudinal cohort study to understand the natural history and risk factors of ICH, lesion burden, and other outcomes in familial CCM. Familial CCM cases either had to have a known genetic mutation in CCM genes or meet 2 of the 3 following clinical criteria: diagnosis of CCM, family history of CCM, or multifocal CCMs. Eligible cases were enrolled and followed prospectively in two 5-year study phases between 2010–2019 at 4 sites. In the first 5 years of the study (2009–2014), only patients with *CCM1* and the common Hispanic mutation (Q455X) were recruited from the University of New Mexico. In the second 5 years of the study (2014–2019), all familial CCM cases were enrolled with an emphasis on *CCM1* at 4 sites: University of New Mexico, University of California San Francisco, Barrow Neurological Institute, and the Alliance to Cure Cavernous Malformation. The study was approved by the local institutional review boards at the University of New Mexico, University of California San Francisco, Barrow Neurological Institute, and Quorum IRB (Alliance to Cure Cavernous Malformation) and by the National Institute of Neurological Disorders and Stroke. Written informed consent was obtained from all participants.

Study Variables

We collected data on demographics, medical characteristics, clinical and presenting symptoms, treatments, and functional outcome at baseline enrollment and at annual follow-up visits that occurred either in person during clinic visit or by phone; data were also obtained

from medical records. Baseline research MRI scans (first 5 years of study) or clinical MRI scans (second 5 years of study) with T2- and susceptibility-weighted sequences were reviewed by the study neuroradiologists (B.H., M.M.), who were blinded to clinical outcomes. CCM lesions were manually counted to obtain counts of total and large lesions (≥5 mm at maximal diameter, defined as the greatest trans axial dimension measured on the T2-weighted images, including the hypointense rim) as previously described.[15,16] Prior history of ICH and subsequent symptomatic ICH during follow-up were reported by patients and/or documented in medical records using standard definition of symptomatic hemorrhage.[17] Not all cases were able to be verified by MRI; for example, MRIs performed at outside hospitals may have not been available for review.

Statistical Analysis

We summarized key variables at enrollment by cohort and overall using mean and SD, median and interquartile range (IQR) or the range, and sample size (n) and percentage. We first tested whether ICH before enrollment was associated with total lesion count and large lesion count (separately) using logistic regression models. Lesion counts were log-transformed (log base 2) before analysis to lessen skewness and the influence of outliers. To accommodate cases with 0 lesions, a value of 1 was added to all values before log transformation.

Cross-sectional analysis of baseline data was performed using logistic regression models adjusted for age, sex, and recruitment site; robust standard errors were used to accommodate clustering on family membership. Logistic regression results are presented as odds ratios (OR) with 95% CIs.

Patients with at least 1 follow-up visit were included in a Kaplan–Meier time-to-ICH survival analysis. The survival analysis time started at date of enrollment to date of first symptomatic ICH during follow-up, censoring at date of last follow-up (12/321 died following last follow-up). We calculated the per-patient rate of follow-up ICH and jackknife-based 95% CI that accommodated clustering on family membership. This rate was calculated as the number of ICH events divided by total person-years of follow-up time in the entire cohort and stratified by ICH status before enrollment. We used a Poisson model to calculate the incident rate ratio comparing the event rate of those with prior ICH to those without; this model uses adjusts standard errors by clustering on family membership. We used Cox proportional hazards models to test whether log-transformed total and large lesion counts (separately) assessed at baseline enrollment was associated with ICH during follow-up. Cox models included adjustments for history of ICH before enrollment, age, and sex. We stratified on recruitment site to allow baseline hazard rates to vary, and we used robust standard errors to account for clustering on family membership. Cox regression results are presented as hazard ratios (HR) with 95% CI. Statistical significance was determined by $P \leq 0.05$. As a sensitivity analysis, we repeated all analyses including only patients with genetically confirmed *CCM1*.

RESULTS

A total of 386 patients were enrolled into the BVMC between June 2010 and August 2019 and contributed baseline data to the following analyses. Summary statistics are presented in Table 1. A total of 206 families were represented including 133 singletons and the remainder ranging from 2 to 12 individuals per family. The median age at enrollment was 42 (IQR=21–55, range=0–85) and 236 (61%) were female. Among those with a CCM mutation identified via genetic testing (n=309), most were *CCM1* (n=300, 97%), as by design the first BVMC cycle recruited patients with CCM1-common Hispanic mutation. A total of 127 (33%) had an ICH before enrollment. The median total lesion count was 13.5 (IQR=5–47, range=0–713). The median large lesion count was 3 (IQR=1–5, range=0–104).

Results of the logistic regression models are presented in Table 2. We found that higher total lesion count at baseline was associated with a higher odds of prior ICH (OR, 1.16 per doubling of total lesion count [95% CI, 1.01–1.34], P=0.031). Large lesion count was strongly associated with prior ICH (OR, 1.96 [95% CI, 1.53–2.50], P<0.001). Sensitivity analyses restricted to patients with confirmed *CCM1* had similar results (Table S1).

A total of 321 patients had at least 1 follow-up visit and were included in the survival analysis. The median follow-up time was 3.0 years, the mean follow-up was 3.5 years, and the longest follow-up was 8.3 years. We observed a total of 31 ICH events during 1122 patient-years of follow-up. The rate of ICH was 2.8 per 100 patient-years (95% CI, 1.9–4.1). Those with an ICH before enrollment had a follow-up ICH rate (4.5 per 100 patient-years [95% CI, 2.6–8.1]) that was 2.2 times higher (P=0.042) than those without an ICH before enrollment (2.0 per 100 patient-years [95% CI, 1.3–3.5]). Kaplan–Meier curves stratified by ICH status before baseline are shown in the Figure.

Results of the Cox regression models are presented in Table 3. Total lesion count was associated with an increased risk of ICH during follow-up (HR, 1.37 per doubling of total lesion count [95% CI, 1.10–1.71], P=0.006), and ICH before study enrollment increased risk during follow-up (HR, 1.97 [95% CI, 0.96–4.06], P=0.066), but this result was not statistically significant. When

Table 1. Demographic and Clinical Characteristics of Familial Cerebral Cavernous Malformation Subjects Enrolled in the Brain Vascular Malformation Consortium Study

Characteristic	ACCM	BNI	UCSF	UNM	Overall
Count	20	23	49	294	386
Mutation					
CCM1	7/13 (54%)	1/1 (100%)	9/12 (75%)	283/283 (100%)	300/309 (97%)
CCM2	2/13 (15%)	0	3/12 (25%)	0	5/309 (2%)
CCM3	4/13 (31%)	0	0	0	4/309 (1%)
Age at enrollment, y	35 (17–52)	56 (41–67)	44 (34–58)	41 (19–54)	42 (21–55)
Female sex	14 (70%)	16 (70%)	30 (61%)	176 (60%)	236 (61%)
Hispanic ethnicity	1/16 (6%)	13/22 (59%)	16/48 (33%)	290/293 (99%)	320/379 (84%)
White	20/20 (100%)	23/23 (100%)	38/45 (84%)	275/276 (99%)	356/364 (98%)
Hemorrhage(s) before enrollment	6 (30%)	14 (61%)	19 (39%)	88 (30%)	127 (33%)
Seizure(s) before enrollment	10 (50%)	8 (35%)	21 (43%)	102 (35%)	141 (37%)
Headache(s) before enrollment	15 (75%)	16 (70%)	30 (61%)	169 (57%)	230 (60%)
Total lesion count	28 (9–87.5)	16 (8–61)	10 (2–28)	13 (5–47)	13.5 (5–47)
Large lesion count	3 (2–4)	5 (2–10)	2 (1–4)	3 (1–5)	3 (1–5)

Values are n (%), n/total (%), or median (interquartile range). ACCM indicates Alliance to Cure Cavernous Malformation; BNI, Barrow Neurological Institute; CCM, cerebral cavernous malformation; UCSF, University of California San Francisco; and UNM, University of New Mexico.

analyzing large lesion count, we observed a similar, albeit nonsignificant, effect size (HR, 1.37 per doubling of total lesion count [95% CI, 0.95–1.97], P=0.090); the prior ICH effect size was slightly attenuated when analyzed simultaneously with large lesion count (HR, 1.71 [95% CI, 0.80–3.65], P=0.168). Sensitivity analyses restricted to patients with confirmed *CCM1* yielded similar results (Table S2).

DISCUSSION

In this large cohort study of 386 familial CCM cases with prospective follow-up, we found an ICH rate of 2.8 per 100 patient-years. The rate was 2.2 times higher in those with a prior history of ICH versus those without a prior history of ICH. Both total and large lesion burden at baseline enrollment were associated with an increased risk of subsequent ICH during follow-up (HR, 1.37 for every doubling of count), although only total lesion count was statistically significant.

There have been only 5 studies to our knowledge that have reported ICH rates in familial CCM (sample size >20 familial CCM cases) (Table S3 and Figure S1). Zabramski et al prospectively followed 21 patients from 6 unrelated families, primarily of Hispanic descent.[2] They reported 3 ICH events during 46 patient-years of follow-up, yielding a ICH rate of 6.5%. Labauge et al conducted a retrospective study of 40 patients with familial CCM from 29 unrelated French families.[11] They observed 21 acute ICHs in 14 patients over 127 patient-years of follow-up for a rate of 16.5%. However, most of the ICHs (14/21) were clinically silent and revealed only on routine MRI. Additionally, a prospective follow-up of 33 asymptomatic patients with familial CCM reported 3 ICHs in 3 patients during a mean period of 2.1 years (range 0.5–4.5 years) including 1 symptomatic ICH case, which yielded an ICH rate of 4.3%.[1] In Carrión-Penagos et al, 22 ICH events were observed over 212.3 patient-years for an ICH rate of 10.4%.[18] More recently, Santos et al reported the cumulative 5-year risk for ICH and recurrent ICH in 238 patients with multiple CCM.[12] Ninety individuals in that study had confirmed familial CCM, with an annual ICH rate of 5.6%. In a study of 129 pediatric patients with CCM, 35 familial cases were observed to have an annual ICH risk of 6.2%.[19] Patients with brain-stem CCM and family history of CCM had a higher risk of ICH as the initial mode of presentation and had similar risk of rehemorrhage during untreated 5-year follow-up compared with adult patients.[19] Lanfranconi et al evaluated 30 patients with multiple CCMs from 20 independent families, including 10 sporadic and 10 familial CCM.[20] During the 4-year period of follow up, only 3 subjects had an ICH.

There are some key differences between these studies that make direct comparison a challenge, including the mean period of follow-up, the inclusion of individuals with multiple lesions but no genetic testing, and different patient populations (eg, racial or ethnic groups, different CCM gene mutations, pediatric

Table 2. Total and Large Lesion Count Associated With Prior Hemorrhage

Characteristic*	OR	95% CI	*P* value
Total lesion count (log base 2)	1.16	(1.01–1.34)	0.031
Large lesion count (log base 2)	1.96	(1.53–2.50)	<0.001

*Total and large lesion counts were tested separately. OR indicates odds ratio.

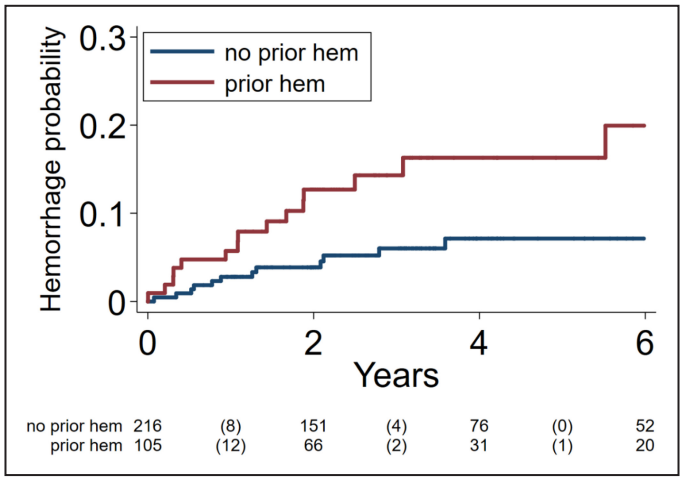

Figure. Kaplan–Meier survival curves of hemorrhage during follow-up in a cohort of patients with familial cerebral cavernous malformation enrolled between 2010 and 2019.
Number in parentheses is number of events that occur within each interval. Numbers at 2, 4, and 6 years indicate individuals still at risk for intracranial hemorrhage (ie, not lost to follow-up). Figure is truncated at 6 years (includes most data). Hem indicates hemorrhage.

cases), and the lack of CCM lesion burden data across studies to assess whether these characteristics predict ICH. In the BVMC familial CCM cohort, the annual ICH rate of 2.8% was lower than previous reports in smaller familial cohorts (4.3%–16.5%).[1,2] One potential reason that we observe a lower familial CCM ICH rate is that many cases in the first cycle of our study were recruited based on genotype and not phenotype, so there are many more asymptomatic, younger individuals included. Our study also focused on symptomatic ICH; hence we expect a lower ICH rate than studies that include both acute and clinically silent ICH. To our knowledge, this is the first study to examine lesion burden in familial CCM as a risk factor for ICH.

The current study has several key strengths as it includes the largest cohort of patients with familial CCM to date and includes detailed characterization of CCM lesion burden (count and size), which provided the unique data set to test for association between CCM lesion burden and ICH. As previously reported, there was high interobserver agreement in lesion counts (pairwise correlation >0.95) between the 2 neuroradiologists.[16] However, there are several limitations including (1) the majority of patients have the *CCM1* genetic mutation, thus we are unable to assess and compare the ICH rate in those who harbor *CCM2* or *CCM3* genetic risk factors; (2) the small number of ICH events prohibited us from assessing additional ICH risk factors such as imaging characteristics; (3) MRI technical heterogeneity across recruitment sites may limit the assessment of accurate lesion burden particularly with respect to smaller lesions; and (4) our results may be subject to selection bias, which may affect ICH rates.

Table 3. Predictors of Hemorrhage During Follow-Up

Characteristic*	Hazard ratio	95% CI	*P* value
Total lesion count (log base 2)	1.37	(1.10–1.71)	0.006
Hemorrhage before enrollment	1.97	(0.96–4.06)	0.066
Large lesion count (log base 2)	1.37	(0.95–1.97)	0.090
Hemorrhage before enrollment	1.71	(0.80–3.65)	0.168

*Total and large lesion counts were tested in separate Cox regression models, adjusting for prior history of intracranial hemorrhage, age, and sex and stratifying on recruitment site.

CONCLUSIONS

The annual symptomatic ICH rate of 2.8 per 100 patient-years in the BVMC familial CCM cohort is comparable yet lower than previously reported rates for familial CCM. Prior history of ICH is a strong predictor of subsequent ICH. In addition, total CCM lesion burden (count) is a significant predictor of subsequent ICH, which suggests that lesion burden may be an important predictor of patient outcome and warrants further investigation and replication in additional familial CCM cohorts.

APPENDIX

Brain Vascular Malformation Consortium Cerebral Cavernous Malformation Investigator Group

Adib A. Abla, MD; Amy Akers, PhD; Issam A. Awad, MD; Blaine L. Hart, MD; Helen Kim, PhD; Nerissa U. Ko,

MD, MAS; Michael T. Lawton, MD; Cornelia Lee, PsyD; Marc C. Mabray, MD; Charles E. McCulloch, PhD; Leslie Morrison, MD; Ludmila Pawlikowska, PhD; Edward R. Smith, MD; Michel Torbey, MD; Sudhakar Vadivelu, DO; Shantel Weinsheimer, PhD; Joseph M. Zabramski, MD; and Atif Zafar, MD.

ARTICLE INFORMATION

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Affiliations

Department of Anesthesia and Perioperative Care, Center for Cerebrovascular Research (S.W., J.N., C.T., O.O., H.K.), Institute for Human Genetics (S.W., H.K.), Department of Neurological Surgery (A.A.A.), Department of Neurology (N.U.K.), Global Brain Health Institute (O.O.), and Department of Epidemiology and Biostatistics (C.E.M., H.K.), University of California San Francisco, CA; Department of Neurosurgery, Barrow Neurological Institute, Phoenix, AZ (J.M.Z.); Alliance to Cure Cavernous Malformation, Charlottesville, VA (A.A.); Department of Neurology (A.Z., L.M.) and Department of Radiology (M.C.M., B.L.H.), University of New Mexico, Albuquerque, NM.

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Supplemental Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Logistic regression results (*CCM1*-only)

Characteristic*	OR	95% CI	p-value
Total lesion count (log base 2)	1.24	(1.04, 1.48)	0.015
Large lesion count (log base 2)	2.11	(1.60, 2.79)	<0.001

*Total and large lesion counts were tested separately and the models adjusted for age, sex, and family membership. CCM indicates Cerebral Cavernous Malformation; OR, odds ratio; CI, confidence interval.

Table S2. Cox regression results (*CCM1*-only)

Characteristic*	HR	95% CI	p-value
Total lesion count (log base 2)	1.33	(1.01, 1.75)	0.042
Hemorrhage prior to enrollment	1.89	(0.77, 4.66)	0.165
Large lesion count (log base 2)	1.30	(0.83, 2.04)	0.247
Hemorrhage prior to enrollment	1.71	(0.67, 4.37)	0.260

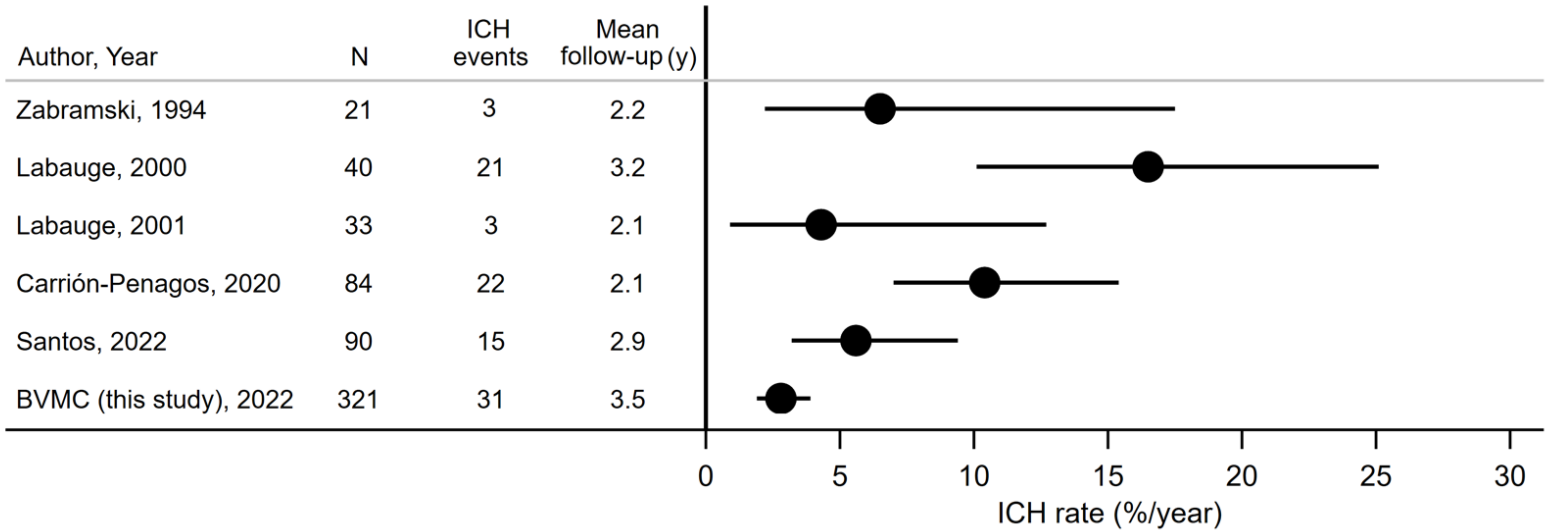
*Total and large lesion counts were tested in separate Cox regression models, adjusting for prior history of intracranial hemorrhage, age, and sex, and stratifying on recruitment site. CCM indicates Cerebral Cavernous Malformation; HR, hazard ratio; CI, confidence interval.

Table S3. Annual ICH rates in Familial CCM

Author, Year	n	Mean f/u (years)	ICH Events	ICH Rate	95% CI
Zabramski 1994	21	2.2	3	6.5%	2.2 – 17.5
Labauge 2000	40	3.2	21	16.5%	10.1 – 25.1
Labauge 2001	33	2.1	3	4.3%	0.9 – 12.7
Carrión-Penagos 2020	84	2.1	22	10.4%	7.0 – 15.4
Santos 2022	90	2.9	15	5.6%	3.2 – 9.4
BVMC Current Study	321	3.5	31	2.8%	1.9 – 4.1

ICH indicates intracranial hemorrhage; CCM, Cerebral Cavernous Malformation; CI, confidence interval.

Figure S1. Forest plot for annual ICH rates in Familial CCM



When 95% confidence intervals were not provided, we calculated them using the Poisson exact method.
Labauge, 2000: Included mostly clinically silent hemorrhages. ICH indicates intracranial hemorrhage; CCM, Cerebral Cavernous Malformation.