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Bleeding risk evaluation in cerebral cavernous malformation, the role of medications, and hemorrhagic factors: a case-control study

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OBJECTIVE Cerebral cavernous malformations (CCMs) are vascular lesions with an overall risk of rupture from 2% to 6% per year, which is associated with significant morbidity and mortality. The diagnostic incidence is increasing, so it is of paramount importance to stratify patients based on their risk of rupture. Data in the literature seem to suggest that specific medications, particularly antithrombotic and cardiovascular agents, are associated with a reduced risk of bleeding. However, the effect of the patient coagulative status on the cumulative bleeding risk remains unclear. The aim of this study was to assess the impact of different radiological, clinical, and pharmacological factors on the bleeding risk of CCMs and to assess the predictive power of an already validated scale for general bleeding risk, the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly).

METHOD This was a multicenter retrospective observational study. The authors collected imaging, clinical status, and therapy data on patients with bleeding and nonbleeding CCMs. Univariate analysis and subsequent multivariate logistic regression were performed between the considered variables and bleeding or nonbleeding status to identify potential independent predictors of bleeding.

RESULTS The authors collected data on 257 patients (46.7% male, 25.3% with bleeding CCMs). Compared with patients with nonbleeding lesions, those with bleeding CCMs were younger, less frequently had hypertension, and less frequently required antiplatelet drugs and beta-blockers (all $p < 0.05$). Bleeding lesions, however, had significantly higher median volumes (1050 mm^3 vs 523 mm^3, $p < 0.001$). On multivariate analyses, after adjusting for age, history of hypertension and diabetes, and use of antiplatelet drugs or beta-blockers, lesion volume ≥ 300 mm^3 was the only significant predictor of bleeding (adjusted OR 3.11, 95% CI 1.09–8.86). When the diagnostic accuracy of different volume thresholds was explored, volume ≥ 300 mm^3 showed a limited sensitivity (36.7%, 95% CI 24.6%–50.0%), but a high specificity 78.2% (95% CI 71.3%–84.2%), with an area under the curve of 0.57 (95% CI 0.51–0.64).

CONCLUSIONS This study supports previous findings that the CCM volume is the only factor influencing the bleeding risk. Antithrombotic agents and propranolol seem to have a protective role against the bleeding events. A high HAS-BLED score was not associated with an increased bleeding risk. Further studies are needed to confirm these results.

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KEYWORDS cavernous malformation; cavernoma; cavernous angioma; bleeding risk; propranolol; cerebral hemorrhage

ABBREVIATIONS AUC = area under the curve; CCM = cerebral cavernous malformation; GOS = Glasgow Outcome Scale; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; INR = international normalized ratio; MACE = major cardiovascular events; mRS = modified Rankin Scale; RCT = randomized controlled trial.

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Cerebral cavernous malformations (CCMs) are vascular lesions composed of low-flow, cluster-organized capillaries that account for 5%–10% of total cerebral vascular pathologies.[1] Even if a precise measure is difficult, since the majority are clinically silent, the estimated annual incidence in the general population is between 0.4% and 1.0%[2]. Up to 40% are discovered incidentally with an increasing trend over time,[3] so follow-up timing and monitoring strategies have a fundamental role in the clinical and surgical management of these patients.

Although histologically benign in nature, these lesions are prone to bleeding rupture with an estimated rate of 2%–6% per year.[4] When located in eloquent areas, ruptures are associated with significant morbidity and mortality.[5,6] Factors associated with bleeding are not completely understood, but previous studies have found that a single, large infratentorial lesion is most commonly associated with a symptomatic CCM[7] and that a previous history of hemorrhages and associated developmental venous anomaly increase the risk of rupture.[8,9]

Notably, several drugs, commonly used for different pathologies, have been studied to assess their role in the clinical and radiological evolution of CCMs. Antithrombotic medications have been associated with a reduced risk of bleeding in different studies,[1,3,10,11] thought to be due to the inhibition of the inflammatory mechanism causing rupture. Beta-blockers, specifically propranolol, have been proposed to have a therapeutic effect in causing regression of the CCM and stopping recurrent bleeding.[12] A randomized controlled trial (RCT) was initiated on the use of propranolol for familial CCMs,[13] but recent studies have found conflicting results regarding a protective role of propranolol in sporadic CCMs.[1,14] Statins have well-known vessel wall stabilization effects, and a synergistic protective effect has been found when combined with antithrombotic drugs[15] but not when used alone.[1,11,14]

Indeed, the role of hemorrhagic factors in general, such as renal or liver disease, labile international normalized ratio (INR), prior major bleeding or predisposition to bleeding, is also not clear. The aim of this study was to evaluate possible predictive factors for bleeding, in particular regarding medications and already validated hemorrhagic scales such as the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly).[16]

Methods

This was a nonfunded national multicenter case-control study with retrospective data collection. The minimum follow-up time was 28 days. The study was approved by the local ethics committee. Inclusion criteria were patients older than 18 years with a previous or new diagnosis of CCM, including single, multiple, and familial CCMs, based on neuroimaging findings.

We collected data on patient demographics (sex and age), CCM characteristics (median time from diagnosis, number, Zabramski type, familial CCM mutations, anatomical lesion site, side, symptomatic lesions, and epilepsy), major cardiovascular events (MACE), alcohol or smoking use, comorbidities (diabetes, obesity and BMI, hypertension, and menopause), HAS-BLED score for hemorrhagic risk stratification (a score that estimates the risk of major bleeding for patients on anticoagulation therapy to assess risks and benefits in atrial fibrillation care), modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) scores, and surgical treatment.

For MACE, we included history of stroke, acute myocardial infarction, cardiac arrhythmias, deep vein thrombosis, and pulmonary embolism. We included current and former smokers (defined as adults who smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of the interview). We considered alcohol use disorders as defined by criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*.

Volumes were measured by tracing areas of the T2-hypointense hemosiderin ring on consecutive MRI slices. Lesion volumes were divided into the following quartiles: < 11.9 mm^3, 11.9–79 mm^3, 80–299 mm^3, and ≥ 300 mm^3.

All medications (antiplatelets, anticoagulants, beta-blockers, autonomic nervous system–acting drugs, central nervous system–acting drugs, cardiovascular agents, smooth muscle–acting agents, lipid modifying/antigout agents, antirheumatic drugs, endocrine drugs, chemotherapy drugs, and others) were collected.

Bleeding was defined as a hemorrhage in the extracapsular zone with a volumetric increase of the lesion of at least 20% on MRI. Size was measured as the maximum diameter including surrounding hemosiderin on T2-weighted 1.5T MRI.

Statistical Analysis

Potential differences in the recorded clinical characteristics among patients with bleeding versus nonbleeding CCMs were first evaluated using the chi-square test for categorical variables and the t-test and Kruskal-Wallis test for normally distributed and nonnormally distributed continuous variables, respectively, The Shapiro-Wilk test was used to assess the distribution of the continuous variables.

The potential independent predictors of bleeding CCMs were then evaluated using multivariate logistic regression. Covariates were selected for inclusion in the final model using a stepwise forward process with the following inclusion criteria: clinical relevance, $p < 0.15$ on univariate analysis, hypertension, and antiplatelet and beta-blocker use. Lesion volume was included in the analyses both in its original (continuous) form and after categorization, exploring different possible cutoffs. Quintiles and quartiles of lesion volumes were separately evaluated in two different models (with all other covariates remaining stable), with no significant differences. Given the higher R^2 of the model including quartiles, quartiles were retained in the final model, and four categories were identified (< 11.9 mm^3, 11.9–79 mm^3, 80–299 mm^3, and ≥ 300 mm^3). A minimum events-to-variable ratio of 10 was maintained in multivariate modeling to avoid overfitting. The goodness-of-fit was checked using the Hosmer-Lemeshow test, and the predictive power assessed through C-statistics (area under the receiving operating characteristic [ROC] curve [AUC]).

Additionally, to estimate the potential of increasing lesion volumes to predict bleeding, we computed the sensi-

tivity, specificity, positive and negative predictive values, and the AUC for each quartile of lesion volume; 95% CIs were computed according to the efficient-score method (corrected for continuity) described by Newcombe.[17] Statistical significance was defined as a two-sided p value < 0.05, and all analyses were carried out using Stata version 13.1 (StataCorp).

Results

Clinical and radiological data of 257 patients were collected. Sixty-five (25.3%) patients presented with a bleeding CCM. All results are reported in Tables 1 and 2.

Demographic Characteristics of the Population

Male patients represented 46.7% of the overall population (46.2% in the bleeding group and 46.9% in the nonbleeding group). The average age was 43.4 years (range 18–68 years) in the overall population (37.4 years in the bleeding group and 45.4 years in the nonbleeding group, p = 0.004), The mean follow-up for the nonbleeding group was 1329 days (3.6 years, range 30–8136 days) and that for the bleeding group was 1442 days (3.9 years, range 28–8124 days).

Clinical Risk Factors for CCM Bleeding

CCM1 mutation was present in 5.9% of patients (1.5% in the bleeding group and in 7.3% in the nonbleeding group). Results regarding smoking history and alcohol use are reported in Table 1. Diabetes was present in 3.9% of patients (4.6% in the bleeding group and 3.7% in the nonbleeding group). Hypertension was present in 25.8% of patients (9.2% in the bleeding group and 31.4% in the nonbleeding group, p < 0.0001). Results regarding BMI, menopause status, MACE are reported in Table 1.

Pharmacological Risk Factors for CCM Bleeding

Antiplatelets were used in 16.8% of all patients (4.6% in the bleeding group and 20.9% in the nonbleeding group, p = 0.0002), while only 2.3% of patients took anticoagulants (direct acting oral anticoagulants or non–vitamin K oral anticoagulants) (1.5% in the bleeding group and 2.6% in the nonbleeding group). Beta-blockers were used in 16.8% of patients (4.6% in the bleeding group and 17.3% in the nonbleeding group, p = 0.011). Results of other pharmacological treatments are reported in Table 1.

Clinical Presentation and Outcome After CCM Bleeding

In all patients, the most common Zabramski types were I (50.3%) and II (39.5%): 68.9% and 26.2%, respectively, in the bleeding group and 26.2% and 46.5%, respectively, in the nonbleeding group (see Table 1 for further details). Multiple lesions were reported in 37.5% of patients (20.0% in the bleeding group and 43.5% in the nonbleeding group, p = 0.001). Results regarding anatomical site and side are reported in Table 1. The overall median volume was 800 mm^3. Volume quartiles are reported in Table 1.

Epilepsy was reported in 34.8% of patients (49.2% in the bleeding group and 29.8% in the nonbleeding group). The HAS-BLED score was 0 or 1 (low bleeding risk) in most patients (57.0% and 23.1%, respectively) with the same trend in patients in the bleeding and nonbleeding groups (Table 1). Most patients (70.7%) had a favorable outcome with a GOS score of 5, with the same trend in the bleeding (66.2%) and in the nonbleeding (72.3%) groups. Similar results were recorded for the mRS score (Table 1). Surgery was performed in 71.6% of patients (89.2% in the bleeding group and 65.6% in the nonbleeding group).

Potential Predictors of Bleeding

We performed a logistic regression model evaluating the potential predictors of bleeding (Table 2). Results showed that the only statistically significant predictor for bleeding was volume ≥ 300 mm^3. We also evaluated the diagnostic accuracy of each quartile of lesion volume to predict bleeding (Table 3, Fig. 1).

When translating these findings into diagnostic models, all lesion volumes had similarly limited diagnostic accuracy in predicting bleeding (AUC 0.40, 95% CI 0.35–0.45; AUC 0.50, 95% CI 0.44–0.57; AUC 0.52, 95% CI 0.46–0.59; and AUC 0.57, 95% CI 0.51–0.64) for lesions < 11.9 mm^3, 11.9–79 mm^3, 80–299 mm^3, and ≥ 300 mm^3, respectively).

When we explored the diagnostic accuracy of the different volume thresholds, lesions ≥ 300 mm^3 showed a limited sensitivity (36.7%, 95% CI 24.6–50.1) but a high specificity (78.2% (95% CI 71.3%–84.2%), with an AUC of 0.57 (95% CI 0.51–0.64).

Discussion

For patients with CCMs, the knowledge of risk factors for bleeding and the possibility of positively influencing them is particularly crucial. No pharmacological treatment is at present available to inhibit the formation of new malformations, to stabilize the existing ones, and to stop their progression. To date, the standard of care is represented by treatment of CCM-associated clinical manifestations, such as headache and epilepsy, and consists of antiepileptic drugs or drugs for recurrent headache.[13,18] Neurosurgical excision is considered in patients with intractable seizures, recurrent hemorrhage, or mass effect. Risk factor assessment therefore represents an important issue in decision-making in patients with asymptomatic lesions. The 5-year risk of intracerebral hemorrhage in individuals with CCMs ranges from 3.8% to 30.8%.[13]

Results of our study demonstrated that age, diabetes, and nidus volume ≥ 300 mm^3 are possible potential predictors of bleeding, while a history of hypertension and use of antiplatelet and beta-blocker agents could have a protective effect. However, logistic regression analysis confirmed a predictive role only for lesion volume, most likely because some risk factors lose sensitivity due to the relatively small sample size examined.

These results are similar to those recently published by Rauscher et al.,[19] which found that none of the modifiable vascular risk factors showed a strong indication for influencing hemorrhage risk. Their findings may only suggest a more aggressive course in patients with active nicotine abuse or diabetes.

Beta-blockers, more specifically, propranolol, have al-

TABLE 1. Characteristics in patients with bleeding versus nonbleeding CCMs

Variable	Overall Sample	Bleeding CCM	Nonbleeding CCM	p Value*
No. of patients	257	65	192	
Male sex, %	46.7	46.2	46.9	0.9
Mean age, yrs	43.4	37.4	45.4	0.004
Median time from diagnosis to op, mos (IQR)	16.6 (52.1)	12.2 (33.3)	16.6 (70.9)	0.4
Familial CCM mutations, %				
CCM1	5.9	1.5	7.3	0.09
CCM2	0.0	0.0	0.0	
CCM3	0.0	0.0	0.0	
Smoking status, %				
Current	7.1	9.2	6.3	0.02
Former*	8.6	1.6	11.1	0.2
Never	84.3	89.2	82.6	0.4
Alcohol use, %	2.0	3.1	1.6	0.5
Diabetes, %	3.9	4.6	3.7	0.7
Hypertension, %	25.8	9.2	31.4	<0.001
Mean BMI (SD)	25.3 (3.4)	25.1 (3.5)	25.4 (3.4)	0.6
Menopause status, % (n = 137/35/102)†	24.8	14.3	28.4	0.10
History of MACE, % (n = 78/4/74)†	51.3	100	48.7	0.045
MACE type, % (n = 40/4/36)†				
Stroke	5.0	0.0	5.6	
AMI	2.5	0.0	2.8	
Arrhythmias	22.5	0.0	25.0	
DVT/PE	12.5	50.0	8.3	0.02
Other	57.5	50.0	58.3	0.8
Antiplatelet drug use, %	16.8	4.6	20.9	0.002
Anticoagulant drug use, %				
None	97.7	98.5	97.4	0.9
DOAC	1.5	0.0	2.1	0.4
NOAC	0.8	1.5	0.5	0.9
Beta-blocker use, %	14.1	4.6	17.3	0.011
Other pharmacological treatment, %				
ANS-acting drugs	0.0	0.0	0.0	
CNS-acting drugs	29.5	50.0	28.4	0.4
Cardiovascular agents	67.9	50.0	68.9	0.4
Smooth muscle–acting agents	6.4	25.0	5.4	0.12
Lipid modifying/antigout agents	11.5	25.0	10.8	0.3
Antirheumatic drugs	12.8	0.0	13.5	0.4
Endocrine drugs	20.5	50.0	18.9	0.13
Chemotherapy drugs	0.0	0.0	0.0	—
Other drug classes	25.6	50.0	24.3	0.3
Zabramski classification, % (n = 177/61/116)†				
Accidental	1.1	1.6	0.9	0.9
Type I	50.3	68.9	40.5	<0.001
Type II	39.5	26.2	46.5	0.009
Type III	2.3	1.6	2.6	0.7
Type IV	6.8	1.6	9.5	0.046
Presence of multiple lesions, %	37.5	20.0	43.5	0.001

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TABLE 1. Characteristics in patients with bleeding versus nonbleeding CCMs

Variable	Overall Sample	Bleeding CCM	Nonbleeding CCM	p Value*
Anatomic lesion site, % (n = 253/65/188)†				0.8
Frontal	30.0	29.2	30.3	
Parietal	11.5	10.8	11.7	
Temporal	21.3	16.9	22.9	
Insular	1.6	1.5	1.6	
Occipital	7.1	4.6	8.0	
Brainstem	12.7	16.9	11.2	
Cerebellum	12.3	16.9	10.6	
Other	3.5	3.2	3.7	
Lesion side, %				0.3
Midline	16.8	18.5	16.2	
Rt	32.8	24.6	35.6	
Lt	50.4	56.9	48.2	
Lesion vol (n = 230/60/170)†				
Median vol, mm^3 (IQR)	800 (2881)	1050 (4560)	523 (2000)	<0.001
By vol quartile, %				
<11.9 mm^3	25.2	10.0	30.6	0.002
11.9–79 mm^3	24.4	25.0	24.1	0.9
80–299 mm^3	24.8	28.3	23.5	0.5
≥300 mm^3	25.6	36.7	21.8	0.02
Symptomatic lesion, %	83.6	98.5	78.5	<0.001
Epilepsy, %	34.8	49.2	29.8	0.005
HAS-BLED score, %				0.13
0	57.0	69.2	52.9	
1	23.1	23.1	23.0	
2	11.3	3.1	14.1	
3	6.3	4.6	6.8	
4	1.5	0.0	2.1	
≥5	0.8	0.0	1.0	
GOS score, %				0.5
1	0.8	1.5	0.5	
2	0.0	0.0	0.0	
3	12.5	16.9	11.0	
4	16.0	15.4	16.2	
5	70.7	66.2	72.3	
mRS score, %				0.4
0	46.1	36.9	49.2	
1	36.7	38.5	36.1	
2	8.6	13.8	6.8	
3	6.3	6.2	6.3	
4	0.8	1.5	0.5	
5	0.8	1.5	0.5	
6	0.8	1.5	0.5	
Treated w/ surgery, %	71.6	89.2	65.6	<0.001

AMI = acute myocardial infarction; ANS = autonomic nervous system; CNS = central nervous system; DOAC = direct-acting oral anticoagulants; DVT = deep vein thrombosis; NOAC = non–vitamin K antagonist oral anticoagulants; PE = pulmonary embolism.

* Defined as an adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview.

† Values expressed as n indicate the number of overall, bleeding CCM, and nonbleeding CCM patients with data for the variable, respectively.

TABLE 2. Logistic regression model evaluating the potential predictors of bleeding CCMs

	Bleeding, %	Adjusted OR (95% CI)	p Value
Age, 10-yr increase		0.91 (0.74–1.11)	0.3
Hypertension			
No	31.1	1 (ref)	
Yes	9.1	0.42 (0.11–1.54)	0.2
Diabetes			
No	25.2	1 (ref)	
Yes	30.0	1.38 (0.23–8.50)	0.7
Antiplatelet drug use			
No	29.1	1 (ref)	
Yes	7.0	0.39 (0.07–2.12)	0.3
Beta-blocker drug use			
No	28.2	1 (ref)	
Yes	8.3	1.24 (0.60–2.57)	0.6
Lesion vol*			
Model A: by quartile			
<11.9 mm^3	10.3	1 (ref)	
11.9–79 mm^3	26.8	2.82 (0.95–8.37)	0.06
80–299 mm^3	29.8	2.09 (0.71–6.17)	0.2
≥300 mm^3	37.3	3.11 (1.09–8.86)	0.034
Model B: 10-mm^3 increase		1.00 (0.99–1.00)	0.4

The raw percentages refer to the proportion of patients with bleeding lesions in each category of exposed and unexposed subjects (e.g., the percentage of bleeding lesions among those with and without hypertension). The final model is based on 230 observations, with 60 successes.

* Two separate models were fit. Model A included lesion volume categorized into quartiles. Model B included the same variable in its original (continuous) form, with all other covariates remaining stable. Model A: AUC 0.70; Hosmer-Lemeshow test for goodness-of-fit, p = 0.99. Model B: AUC 0.66; Hosmer-Lemeshow test for goodness-of-fit, p = 0.99.

TABLE 3. Diagnostic accuracy of each quartile of lesion volume to predict bleeding

Vol Quartile	AUC (95% CI)
<11.9 mm^3	0.40 (0.35–0.45)
11.9–79 mm^3	0.50 (0.44–0.57)
80–299 mm^3	0.52 (0.46–0.59)
≥300 mm^3	0.57 (0.51–0.64)

Lesion volume ≥ 300 mm^3: sensitivity: 36.7% (95% CI 24.6%–50.0%); specificity: 78.2% (95% CI 71.3%–84.2%); positive predictive value: 37.3% (95% CI 25.0%–50.9%); negative predictive value: 77.8% (95% CI 70.8%–83.8%).

ready been studied as a potential medical treatment for CCMs.[12] Propranolol use in fact has been shown in RCTs to have a positive effect for the treatment of infantile hemangiomas, another common vascular lesion affecting the skin.[20–23]

Common precursor cells for propranolol-sensitive vascular tumors are CD15-positive cells that are usually found in the placental vessels.[24] The assumption of beta-blockers might then stabilize the vascular lesions, although there might be some other factors and drugs implied in the underlying mechanism. A recent randomized, open-label, blinded-endpoint, phase 2 pilot trial on symptomatic familial CCMs demonstrated that propranolol was safe and well tolerated in this population.[25] Propranolol might be beneficial for reducing the incidence of clinical events in individuals with symptomatic familial CCMs and might also reduce the number of new CCMs over 2 years, although the trial was not designed to be adequately powered to investigate efficacy.[13] However, the mechanism of action of propranolol for CCMs remains poorly understood.

This molecule has a pleiotropic effect on vascular permeability and angiogenesis and was found to rescue the function of the endothelium and to reduce de novo CCM formation in preclinical models, although propranolol did not significantly reduce the incidence of intracerebral hemorrhage in murine models.[13,26]

Our study also showed a potential protective effect of antiplatelet agents in the univariate analysis. This is in agreement with the report of Schneble et al., which found that long-term antithrombotic treatment with antiplatelet drugs or warfarin did not increase the frequency of CCM-related hemorrhage in their prospective cohort study of 87 patients.[27] Moreover, in their systematic review and meta-analysis of 1342 patients from 6 cohort studies, Zuurbier et al. reported that antithrombotic therapy (including both anticoagulant and antiplatelet drugs) is associated with a lower risk of intracranial hemorrhage or focal neurological deficit from CCMs compared with the avoidance of antithrombotic therapy (incidence rate ratio 0.25, 95% CI 0.13–0.51; $p < 0.0001$).[10]

Another study by Marques et al. showed that antiplatelet medication alone and in combination with statins was associated with a lower risk of hemorrhage at CCM diagnosis.[15] The underlying proposed pathophysiological mechanism is that the bleeding event might be triggered by thrombus formation in the dilated caverns of CCMs, where the blood flow is slow, and by the associated inflammatory response. The mechanism of thrombus formation can be divided into four steps: platelet tethering, activation and firm adhesion, aggregation and platelet recruitment, and thrombus stabilization;[28] platelets then play a key role in thrombus formation but also in the inflammatory response due to the cocktail of molecules in their granules, which are inhibited by the same antiplatelet agents.

The cohort study by Marques et al.[15] reported robust data regarding bleeding risk of CCMs, but they are limited to the role of antiplatelets and statins. However, our study also collected data not only about anticoagulants, but also regarding other kinds of drugs, such as anti-inflammatory drugs, antirheumatics, and beta-blockers as well as other systemic conditions that can be considered as hemorrhagic risk factors.

This is the first study evaluating the possible correlation of the HAS-BLED score to a higher risk of bleeding. This score estimates the risk of major bleeding for patients on anticoagulation therapy to assess the risks and benefits in atrial fibrillation care. It includes the presence of sys-

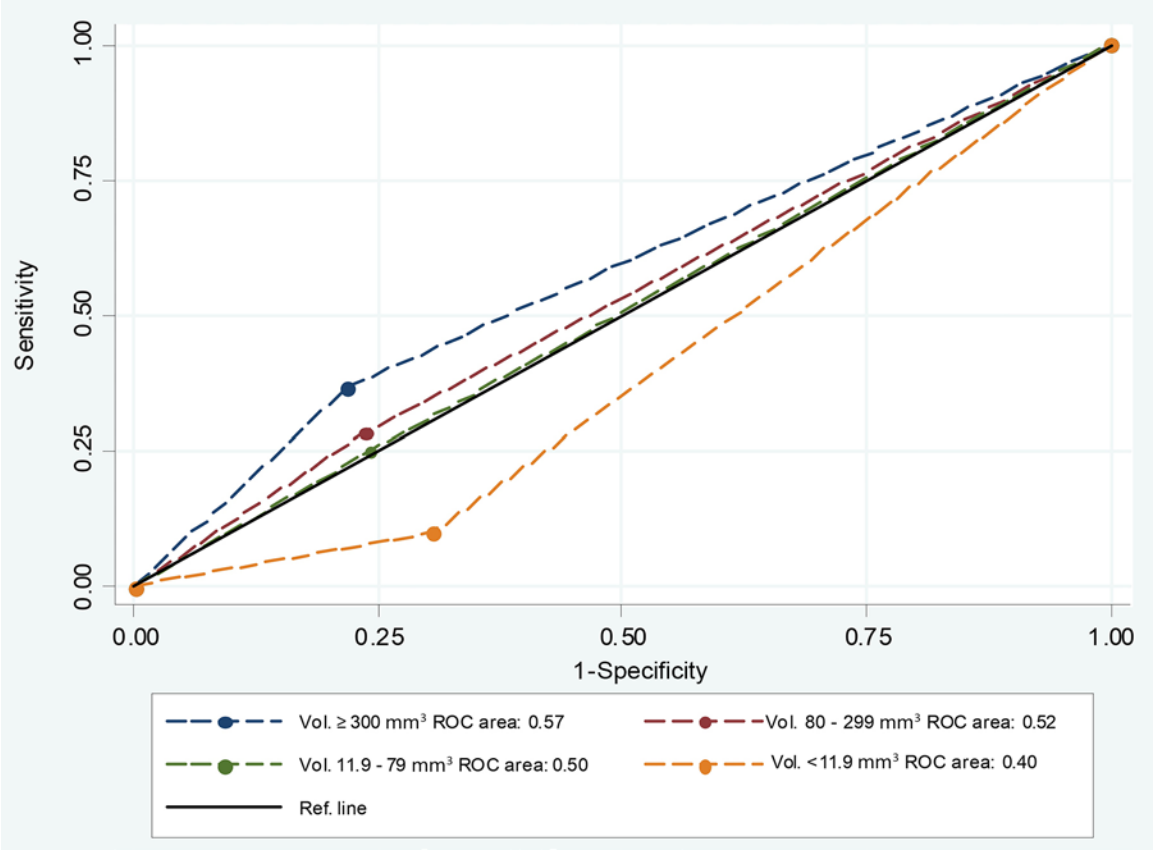

FIG. 1. ROC curves showing the diagnostic performance of each lesion volume in predicting lesion bleeding. Ref. = reference.

temic hypertension, renal or hepatic disease, history of stroke or other major bleeding, labile INR, age > 65 years, medication predisposing to bleeding, and alcohol use. Most of the patients with moderate- and high-risk scores (scores of 2–4) were in the nonbleeding group (Table 1). Although the differences were not statistically significant ($p = 0.13$), anticoagulation in general seems not to influence the bleeding risk. HAS-BLED scores have previously been applied and validated for estimating the risk of major bleeding in patients with several pathologies or those undergoing surgical procedures.[29–31]

Moreover, the HAS-BLED scale has good predictive value for intracranial bleeding, while other scales (e.g., ATRIA [anticoagulation and risk factors in atrial fibrillation]) are not predictive.[32] In a Swedish study on atrial fibrillation cohort, the rates of major bleeding (and intracranial bleeding) increased with increasing HAS-BLED scores.[33] Indeed, a high HAS-BLED score allows the clinician to flag patients at risk of serious bleeding in an informed manner rather than relying on guesswork. The HAS-BLED score also makes clinicians think about the potentially reversible risk factors for bleeding (e.g., uncontrolled blood pressure, labile INRs if on warfarin, and concomitant use of aspirin/nonsteroidal anti-inflammatory drugs). Moreover, medical personnel in other specialties (such as cardiologists) are asking neurosurgeons if patients who require anticoagulants and have unruptured cerebral vascular lesions (such as cavernomas, arteriovenous malformations, or aneurysms) can safely take these medications.

For these reasons, we decided to also evaluate the HAS-BLED score as a summary of several factors that could influence a general risk of intracranial bleeding. Of course, a formal validation for neurosurgical diseases, with a specific prospective study and a higher number of patients, should be performed. Volume ≥ 300 mm^3 seems to be the only factor that influences bleeding risk. However, although statistically significant, the AUC representing the diagnostic accuracy remains moderate (0.57, 95% CI 0.51–0.64).

Limitations

Our data were in part obtained retrospectively, which can lead to known information and selection biases. The number of patients in the bleeding group was much smaller than in the nonbleeding group. This could constitute a bias in the final interpretation of the data, and some variables did not reach statistical significance potentially because of the small number of patients in the bleeding group.

Conclusions

Our study seems to confirm several previous findings of a bleeding risk in proportion to the size of the CCM. Al-

though with less sensitivity, cardiovascular risk factors in general and antithrombotic agents and beta-blockers could have a protective role against bleeding events. We did not find that a higher HAS-BLED score is associated with increased bleeding risk. However, to confirm these findings, larger studies of the natural history of these lesions in larger populations and pharmacological RCTs with prolonged follow-up also including patients with sporadic CCMs are needed.

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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: Scerrati, Travaglini, Bradaschia, De Bonis, Albanese, Sturiale. Acquisition of data: Travaglini, Bradaschia, Dones, Auricchio, Benato, Sturiale. Analysis and interpretation of data: Scerrati, Flacco. Drafting the article: Travaglini, Bradaschia, Flacco, Sturiale. Critically revising the article: Scerrati, Mantovani, Travaglini, De Bonis, Farneti, Flacco, Albanese, Sturiale. Reviewed submitted version of manuscript: Cavallo, Flacco, Albanese, Sturiale. Approved the final version of the manuscript on behalf of all authors: Scerrati. Statistical analysis: Flacco. Administrative/technical/material support: Auricchio. Study supervision: Scerrati, De Bonis, Cavallo.

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