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## Original Investigation

# Differentiating Reversible Cerebral Vasoconstriction Syndrome With Subarachnoid Hemorrhage From Other Causes of Subarachnoid Hemorrhage

Susanne Muehlschlegel, MD, MPH; Oguzhan Kursun, MD; Mehmet A. Topcuoglu, MD; Joshua Fok, MD; Aneesh B. Singhal, MD

**IMPORTANCE** Reversible cerebral vasoconstriction syndrome (RCVS) is a clinical-angiographic syndrome characterized by recurrent thunderclap headaches and reversible segmental multifocal cerebral artery narrowing. More than 30% of patients with RCVS develop subarachnoid hemorrhage (SAH). Patients with RCVS with SAH (RCVS-SAH) are often misdiagnosed as having potentially ominous conditions such as aneurysmal SAH (aSAH) or cryptogenic "angiogram-negative" SAH (cSAH) owing to overlapping clinical and imaging features.

**OBJECTIVE** To identify predictors that can distinguish RCVS-SAH from aSAH and cSAH at the time of clinical presentation.

**DESIGN** Retrospective analysis of 3 patient cohorts: patients with RCVS (1998-2009), patients with aSAH (1995-2003), and patients with cSAH (1995-2003).

**SETTING** Academic hospital and tertiary referral center.


**PARTICIPANTS** Consecutive patients with RCVS-SAH (n = 38), aSAH (n = 515), or cSAH (n = 93) whose conditions were diagnosed using standard criteria.

**MAIN OUTCOMES AND MEASURES** Multivariate logistic regression analysis was used to identify predictors that differentiate RCVS-SAH from aSAH and cSAH.

**RESULTS** Predictors differentiating RCVS-SAH from aSAH were younger age, chronic headache disorder, prior depression, prior chronic obstructive pulmonary disease, lower Hunt-Hess grade, lower Fisher SAH group, higher number of affected arteries, and the presence of bilateral arterial narrowing. Predictors differentiating RCVS-SAH from cSAH were younger age, female sex, prior hypertension, chronic headache disorder, lower Hunt-Hess grade, lower Fisher SAH group, and the presence of bilateral arterial narrowing.

**CONCLUSIONS AND RELEVANCE** We identified important clinical and imaging differences between RCVS-SAH, aSAH, and cSAH that may be useful for improving diagnostic accuracy, clinical management, and resource utilization.

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Recent studies have characterized the reversible cerebral vasoconstriction syndrome (RCVS) as a clinical-angiographic syndrome typically heralded by acute, severe “thunderclap” headaches (TCHs) associated with reversible segmental multifocal cerebral artery vasoconstriction.<sup>1-5</sup> Approximately one-third of patients develop ischemic stroke, lobar hemorrhage, or convexal subarachnoid hemorrhage (SAH). Patients with RCVS who develop SAH (hereafter referred to as patients with RCVS-SAH) pose a unique diagnostic dilemma. Although the TCH is a cardinal symptom of RCVS, it is also the main presenting symptom of a ruptured brain aneurysm (aneurysmal SAH [aSAH]), and both conditions can be complicated by arterial narrowing and ischemic stroke. Owing to its relatively recent characterization, RCVS remains underrecognized, and although it is a usually benign and self-limited condition, the fear of missing aSAH (which can be fatal<sup>6</sup>) makes it challenging to confidently diagnose and manage RCVS-SAH, especially at patient presentation.

The decision-making process with regard to patients presenting with TCHs or SAH is complex. In addition to RCVS and aSAH, TCHs can be a symptom of cerebral venous sinus thrombosis, cerebral artery dissection, and intracerebral hemorrhage.<sup>7</sup> Neuroimaging is urgently needed for all patients with TCHs, to exclude potentially life-threatening conditions. If brain imaging reveals SAH, it becomes imperative to pursue vascular imaging to exclude a ruptured brain aneurysm. However, ruptured aneurysms can be missed on initial angiography owing to factors such as vascular thrombosis or obliteration by an adjacent hematoma,<sup>6,8</sup> and approximately 3% to 8% of individuals harbor incidental unruptured brain aneurysms,<sup>9</sup> making it difficult to determine the source of the SAH. For approximately 15% of patients, the source of the SAH remains undetermined despite repeatedly undergoing angiography (cryptogenic SAH [cSAH]); this group of patients has variable outcomes depending on whether the patients have nonperimesencephalic SAH, perimesencephalic SAH (blood localized to the basal cisterns), or evidence for recent SAH only on cerebrospinal fluid examinations (negative for SAH on a computed tomographic [CT] scan).<sup>10</sup> Patients with aSAH or nonperimesencephalic SAH have a high risk for death and disability; hence, all patients with SAH are typically admitted to the intensive care unit and repeatedly undergo angiography, which rarely reveals the source of the SAH.<sup>8</sup>

These challenges suggest that patients with SAH who truly have RCVS (ie, RCVS-SAH) may be subjected to the unnecessary risks of repeated imaging procedures (contrast reactions, radiation exposure, and vessel dissections) and prolonged intensive care unit stays. Our recent experience suggests that widely used SAH therapies such as induced hypertension, glucocorticoids, and intra-arterial vasodilator treatment may pose risks for patients with RCVS-SAH.<sup>11,12</sup> These issues emphasize the importance of distinguishing RCVS-SAH from aSAH and cSAH. In the present 2-center study, we compared the clinical and imaging features of RCVS-SAH, aSAH, and cSAH in order to identify clinical and radiological variables that can distinguish these conditions promptly after presentation.

## Methods

### Patient Cohorts

The present study was approved by the institutional review boards at Massachusetts General Hospital and University of Massachusetts Memorial Medical Center. The patients were derived from 3 previously published cohorts for RCVS-SAH,<sup>12</sup> aSAH,<sup>13,14</sup> and cSAH.<sup>8</sup>

The RCVS-SAH group comprised 38 patients, including 35 patients with RCVS-SAH from a total of 84 consecutive RCVS cases encountered by one of the authors (A.B.S.) at Massachusetts General Hospital between 1998 and 2009 and 3 additional consecutive patients encountered by one of the authors (S.M.) at University of Massachusetts Memorial Medical Center from 2008 to 2009. All 38 patients had SAH detected on CT scans of the head or magnetic resonance imaging scans of the brain and typical clinical-imaging features of RCVS as published in the literature.<sup>1-5</sup>

The aSAH and cSAH cohorts were derived from a database of 918 consecutive patients from 1995 to 2003 retrieved from the Massachusetts General Hospital electronic medical record system using the *International Classification of Diseases, Ninth Revision*, code 430 for SAH. The medical charts of all patients were reviewed. The aSAH cohort comprised 515 patients with evidence of SAH detected on CT scans of the head or by examination of cerebrospinal fluid samples and with evidence of at least 1 intracranial aneurysm following initial digital subtraction cerebral angiography (DSA), CT angiography (CTA) of the head, or magnetic resonance angiography (MRA) of the head or a ruptured aneurysm identified during neurosurgery. The cSAH cohort comprised 93 patients for whom initial laboratory and vascular imaging failed to reveal the underlying cause (eg, aneurysm, vascular malformation, arterial dissection, RCVS, or vasculitis). At our hospital, all patients with SAH undergo 2 to 4 repeated vascular studies, including DSA and CTA,<sup>8</sup> before they receive the diagnosis of cSAH. Of these 93 patients, 48 had nonperimesencephalic cSAH, 36 had perimesencephalic cSAH, and 9 had CT-negative SAH. Four patients, all with nonperimesencephalic SAH, proved to have cerebral aneurysms after repeatedly undergoing DSA. These patients were also included in the aSAH cohort; we justified their inclusion in both cohorts because they were clinically treated as having cSAH prior to the discovery of their aneurysms. The remaining patients (n = 314) were excluded owing to SAH resulting from other causes (eg, arteriovenous malformation or trauma), late admission after day 14 of SAH (after the typical vasospasm window), early death on days 0 to 4 of SAH (death before the typical vasospasm window), moribund clinical status (repeated vessel imaging or treatment of SAH was not attempted), or incorrect coding for SAH.

### Clinical Variables

Data definitions have been published<sup>8,12-14</sup> and were consistent across cohorts, allowing for comparison and analysis. Medical history variables were obtained by reviewing the patients' medical records; the variable was considered absent if not listed as positive or not documented as a prior medical con-

dition. The term *chronic headache disorder* was used for patients reporting migraines or other chronic headaches in their medical history; the onset of headaches (eg, TCHs or sentinel headaches) was not considered the onset of chronic headaches but rather a component of the acute presentation. Because the original RCVS data set did not include SAH Hunt-Hess grades<sup>15</sup> or Fisher groups,<sup>16</sup> these variables were retrospectively added by A.B.S. and S.M. The modified Rankin Scale score at hospital discharge was derived from physical and occupational therapists' notes.

### Radiological Variables

Every patient underwent DSA or CTA at admission. Most patients also had follow-up CTA, MRA, or serial transcranial Doppler ultrasonographic studies. At Massachusetts General Hospital, transcranial Doppler ultrasonographic studies are performed for patients with SAH at least once daily and whenever there is a change in the neurological examination. All patients with RCVS-SAH underwent 2 angiographic studies (79% underwent DSA, 84% underwent CTA, and 63% underwent MRA), except for 1 patient who only underwent DSA. The presence of arterial narrowing was assessed, in order of preference, by DSA, CTA, MRA, or transcranial Doppler ultrasonographic study. The degree of arterial narrowing was graded as 0 (none), 1 (<50% narrowing), or 2 (≥50% narrowing) based on visual inspection of angiographic studies (consensus by 2 reviewers, J.F. and A.B.S.) or using standard transcranial Doppler ultrasonographic study criteria.<sup>17</sup> If multiple arteries were affected, the most severe grade of arterial narrowing was selected. The laterality and number of vessels involved were recorded. The time to vasoconstriction was measured in days after onset of first TCH. All admission and follow-up brain imaging studies were reviewed for the presence of infarction or edema.

### Statistical Analysis

Data were analyzed using the *t* test, the  $\chi^2$  test, or the Fisher exact test, as appropriate. To avoid overfitting due to the small number of patients with RCVS-SAH, we created 2 separate multivariable logistic regression models for baseline epidemiological and acute clinical-radiological predictors. For the development of the latter model, the presence of CT hypodensity was omitted because hypodensities were considered present if they developed at any time during hospitalization and not solely on the CT scan at admission. We omitted the variable "time to vasoconstriction" in the multivariable analysis owing to a large amount of missing data in the aSAH (343 of 515 patients [67%]) and cSAH (66 of 93 patients [71%]) cohorts. Odds ratios (ORs) and 95% CIs were computed. *P* values of less than .05 were considered to be statistically significant. Variables with *P* < .05 in the univariate analysis were entered in a forward stepwise logistic regression model. Goodness of fit was assessed by negative log likelihoods. The final model performance was reported using the C statistic. The preplanned logistic regression model size was limited to 4 predictors, each due to the small sample size of patients with RCVS-SAH. Owing to the baseline inequalities of the groups for prior antidepressant use, we adjusted for this variable in the epidemiological model, thereby

allowing 5 variables in this model. Careful analysis of ORs and 95% CIs confirmed that the model was not overfitted. Firth's bias correction was used to handle the quasi-complete separation of data points of the Fisher group variable.<sup>18</sup> Analyses were performed using SAS version 9.3 (SAS Institute).

## Results

### Univariate Analysis

Baseline clinical characteristics are shown in **Table 1**. Patients with RCVS-SAH were predominantly women and, on average, 12 years younger than the patients with aSAH and 11 years younger than the patients with cSAH. Compared with both aSAH and cSAH cohorts, more patients with RCVS-SAH had a history of chronic headache disorder, depression/anxiety, chronic obstructive pulmonary disease (COPD), and illicit drug and alcohol use. No collinearity was found between chronic headache and depression. A larger proportion of patients with RCVS-SAH used antidepressants. Patients with RCVS-SAH had less severe neurological presentations and lower Hunt-Hess grades at presentation than did patients with aSAH or cSAH (**Table 1**). Patients with RCVS-SAH had shorter lengths of stay and better clinical outcomes at hospital discharge than patients with aSAH or cSAH.

Baseline radiological features are listed in **Table 2**. Patients with RCVS-SAH had a higher incidence of CT hypodensities (infarct or edema observed at admission or on early follow-up scan) than did patients with aSAH or cSAH. All patients with RCVS-SAH had subarachnoid blood located in the hemispheric convexities (Fisher SAH group 2), as opposed to blood in the sylvian fissure or basal cisterns commonly observed in patients with aSAH or cSAH.

By definition, all patients with RCVS-SAH developed cerebral arterial narrowing. In comparison, cerebral vasospasm developed in 62% of patients with aSAH and in 29% of patients with cSAH at the median time points of day 6 and day 7 after SAH, respectively. The RCVS-SAH group showed more severe cerebral artery narrowing and more commonly had multiple-artery involvement and bilateral abnormalities compared with the aSAH and cSAH groups.

### Multivariable Analysis

#### Predictors of RCVS-SAH vs aSAH

Multivariable logistic regression modeling of baseline epidemiological variables, adjusting for prior antidepressant use, showed that younger age, chronic headache disorder, history of depression/anxiety, and COPD were independent predictors of RCVS-SAH (model 1 in **Table 3**). The adjusted clinical-radiological model (model 2 in **Table 3**) showed that a lower Hunt-Hess grade, a lower Fisher SAH group, a higher number of vessels affected, and the presence of bilateral vasoconstriction (compared with unilateral or no vasoconstriction) independently predicted RCVS-SAH.

#### Predictors of RCVS-SAH vs cSAH

The multivariable logistic regression model of baseline epidemiological variables, adjusted for prior antidepressant use

Table 1. Clinical Features

Clinical Variable	No. (%)			P Value	
	RCVS-SAH (n = 38)	aSAH (n = 515)	cSAH (n = 93)	RCVS-SAH vs aSAH	RCVS-SAH vs cSAH
Age, mean (SD), y	43 (12)	55 (14)	54 (14)	<.001	<.001
Female sex	33 (87)	365 (71)	38 (41)	.04	<.001
Medical history					
Hypertension	17 (45)	176 (35)	23 (25)	.21	.02
Diabetes mellitus	4 (11)	16 (3)	6 (7)	.045	.47
Coronary artery disease	2 (5)	35 (7)	7 (8)	.99	.99
Hypercholesterolemia	6 (16)	45 (9)	14 (15)	.16	.99
Chronic headache disorder	18 (47)	39 (8)	5 (5)	<.001	<.001
Depression/anxiety	17 (45)	41 (8)	7 (8)	<.001	<.001
Drug abuse	8 (21)	24 (5)	2 (2)	.001	<.001
Smoking	14 (37)	184 (36)	15 (16)	.95	.01
Alcohol abuse	13 (34)	45 (9)	4 (4)	<.001	<.001
COPD	12 (32)	43 (9)	5 (5)	<.001	<.001
Prior antidepressant use	15 (39)	46 (9)	7 (8)	<.001	<.001
Hunt-Hess grade					
1	3 (8)	154 (30)	65 (70)	<.001	<.001
2	34 (89)	76 (15)	14 (15)		
3	1 (3)	167 (33)	6 (7)		
4	0 (0)	98 (19)	7 (8)		
5	0 (0)	17 (3)	1 (1)		
Median Hunt-Hess grade (IQR)	2 (2-2)	3 (1-3)	1 (1-2)		
LOS, median (IQR), d	7 (3-9)	19 (12-26)	11 (8-17)	<.001	<.001
mRS score, median (IQR)	0 (0-1)	2 (0-5)	1 (0-3)	<.001	.02

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; COPD, chronic obstructive pulmonary disease; cSAH, cryptogenic SAH; IQR, interquartile range; LOS, length of stay; mRS, modified Rankin Scale; RCVS-SAH, reversible cerebral vasoconstriction syndrome with SAH.

Table 2. Baseline Radiological Variables

Imaging Variable	No. (%)			P Value	
	RCVS-SAH (n = 38)	aSAH (n = 515)	cSAH (n = 93)	RCVS-SAH vs aSAH	RCVS-SAH vs cSAH
CT hypodensity	24 (63)	180 (35)	12 (13)	<.001	<.001
Fisher SAH group					
1	0 (0)	20 (4)	8 (9)	<.001	<.001
2	38 (100)	191 (38)	64 (69)		
3	0 (0)	295 (58)	21 (23)		
Median Fisher SAH group (IQR)	2 (2-2)	3 (2-3)	2 (2-2)		
Occurrence of vasospasm	38 (100)	319 (62)	27 (29)	<.001	<.001
Duration of vasospasm, median (IQR), d	1 (1-1)	6 (5-8)	7 (5-9)	<.001	<.001
Narrowed arteries, median (IQR), No.	6 (6-9)	2 (0-4)	0 (0-1)	<.001	<.001
Narrowing in ≥2 arteries	36 (95)	273 (53)	22 (24)	<.001	<.001
Laterality of vessels affected					
Unilateral	4 (11)	124 (24)	11 (12)	<.001	<.001
Bilateral	34 (89)	187 (36)	17 (18)		
Degree of narrowing, <sup>a</sup> median (IQR)	2 (2-2)	2 (1-2)	1 (1-1)	.05	<.001

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; cSAH, cryptogenic SAH; CT, computerized tomographic; CTA, CT angiogram; IQR, interquartile range; RCVS, reversible cerebral vasoconstriction syndrome.  
<sup>a</sup> Severity of arterial narrowing: 0, no arterial narrowing; 1, <50% narrowing; and 2, ≥50% narrowing.

(model 1 in Table 4), showed that younger age, female sex, history of hypertension, prior antidepressant use, and chronic headache disorder were independent predictors of RCVS-SAH. The adjusted acute clinical-radiological model (model 2 in Table 4) revealed that a lower Hunt-Hess grade, a lower Fisher group, and the presence of bilateral vasoconstriction (compared with unilateral or no vasoconstriction) independently predicted RCVS-SAH.

**Predictors of RCVS-SAH vs "Nonperimesencephalic" cSAH**

Because all patients with RCVS-SAH had convexity SAH, we performed an exploratory analysis restricted to the 48 patients with nonperimesencephalic cSAH. After adjusting for prior antidepressant use, we found that the multivariable logistic regression model of baseline epidemiological variables identified similar predictors as in the nonrestricted cSAH model: younger age (OR, 0.88 [95% CI, 0.83-0.94]), female sex

**Table 3. Multivariate Logistic Regression Models Differentiating RCVS-SAH From aSAH**

Variable	OR (95% CI)	C Statistic
Model 1 <sup>a</sup>		
Age	0.93 (0.90-0.96)	
Chronic headache disorder	9.4 (3.9-22.5)	
History of depression	5.9 (1.9-18.0)	0.90
COPD	7.6 (2.9-20.1)	
Prior antidepressant use	2.4 (0.8-7.4)	
Model 2 <sup>b</sup>		
Hunt-Hess grade	0.4 (0.2-0.7)	
Fisher group	0.1 (0.05-0.3)	0.94
No. of affected arteries	1.4 (1.2-1.6)	
Laterality of affected arteries	5.7 (2.1-15.0)	

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; COPD, chronic obstructive pulmonary disease; OR, odds ratio; RCVS, reversible cerebral vasoconstriction syndrome.

<sup>a</sup> Baseline epidemiological variables, adjusted for prior antidepressant use.

<sup>b</sup> Acute clinical and radiological variables.

(OR, 9.9 [95% CI, 2.0-47.8]), history of hypertension (OR, 10.3 [95% CI, 1.9-55.4]), and history of chronic headache disorder (OR, 5.5 [95% CI, 1.2-24.6]). The adjusted acute clinical-radiological model showed that bilateral arterial narrowing (compared with unilateral or no arterial narrowing; OR, 9.1 [95% CI, 3.5-23.8]) was the only predictor of RCVS-SAH.

## Discussion

In the present study, we identified epidemiological and clinical-radiological predictors, obtained at the time of admission and before disease evolution, which can distinguish RCVS-SAH from 2 important mimics. Our results are clinically significant in that enhanced bedside diagnostic accuracy may effect the length of stay in the neurological intensive care unit or hospital, may reduce the number of diagnostic tests, and may improve the management of patients presenting with SAH, although we did not examine this in our study. Clinicians may use these data to distinguish RCVS-SAH, a usually benign entity, from aSAH, which is a common and often life-threatening cause of stroke in young adults. Furthermore, when the initial angiographic studies do not reveal a ruptured brain aneurysm or other sources of SAH, these predictors can be used to distinguish RCVS-SAH from cSAH, which is often a major diagnostic dilemma. Most of the RCVS-SAH predictors identified in our study are not surprising and match the typical RCVS profile<sup>1-5</sup>; indeed, the experienced clinician may find the results all too obvious. However, to date, diagnosis has been based on empirical grounds, and for the first time, we provide data showing that RCVS is a distinct entity and that RCVS-SAH is very different from aSAH and cSAH.

Some authors have questioned whether RCVS (particularly RCVS-SAH) is different from aSAH or cSAH (ie, whether minor, often undetectable amounts of subarachnoid blood can trigger the vasoconstriction observed in RCVS). We have

**Table 4. Multivariate Logistic Regression Models Differentiating RCVS-SAH From cSAH**

Variable	OR (95% CI)	C Statistic
Model 1 <sup>a</sup>		
Age	0.87 (0.82-0.93)	
Female sex	19.1 (3.8-94.9)	
History of hypertension	17.2 (3.3-88.9)	0.91
Chronic headache disorder	8.7 (2.1-36.9)	
Prior antidepressant use	6.8 (1.3-36.5)	
Model 2 <sup>b</sup>		
Hunt-Hess grade	3.1 (1.1-8.8)	
Fisher group	0.01 (<0.001-0.11)	0.97
Laterality of affected arteries	31.3 (8.9-110.0)	

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; OR, odds ratio; RCVS, reversible cerebral vasoconstriction syndrome.

<sup>a</sup> Baseline epidemiological variables, adjusted for prior antidepressant use.

<sup>b</sup> Acute clinical and radiological variables; Firth's bias-correction<sup>18</sup> was used to handle the quasi-complete separation of data points of the Fisher group variable.

previously highlighted several differences between these conditions<sup>19</sup>; in this present study, we provide evidence that RCVS-SAH differs from aSAH and cSAH in many respects, including mean age of patients, risk factors identified from the medical history and medications, clinical presentation, brain imaging, and cerebral angiographic findings. Our results suggest that the diffuse, multifocal, prolonged vasoconstriction in RCVS is unrelated to the presence or location of subarachnoid blood. We believe that RCVS-associated SAH, which is usually restricted to 1 to 2 sulcal spaces, is unlikely to cause diffuse, multifocal vasoconstriction but, instead, likely results from dynamic caliber changes affecting cortical surface vessels. The vasoconstriction in RCVS may be dependent on the activity and sensitivity of vascular receptors, which can lead to a more systemic effect on all brain vessels,<sup>1</sup> as opposed to being dependent on the vasospasm induced by local clot lysis, as has been suggested in aSAH.<sup>20</sup> Further studies are warranted to understand the pathophysiology of vasoconstriction and the cause of the convexity of SAH in RCVS.

Although the differences are striking, we emphasize, based on our clinical experience, that the most important diagnostic feature for RCVS is the presence of recurrent TCHs, which is a feature that was not captured in this retrospective study. The presence of TCHs is the clinical hallmark of aSAH; however, more than 80% of patients with aSAH develop only a single TCH,<sup>6</sup> and less than 20% of patients with cSAH develop sentinel headaches,<sup>21</sup> whereas 82% to 100% of patients with RCVS develop 3 to 4 recurrent TCHs in the first few days.<sup>22</sup> Indeed, although TCH has a broad differential diagnosis, recurrent TCHs are the sine qua non of RCVS; including this feature with the other predictors identified in our study would easily distinguish RCVS-SAH from aSAH or cSAH.

Reversible cerebral vasoconstriction syndrome is a common cause of nontraumatic convexal SAH. In our experience, 50% of patients with RCVS develop convexal SAH,<sup>12</sup>

and a prospective study<sup>2</sup> of RCVS found a 30% incidence of convexal SAH. In a recent study<sup>23</sup> of 29 patients with convexal SAH, it was found that 16 of those patients who were 60 years of age or younger had RCVS. Clinically, it is important to distinguish RCVS from other causes of convexal hemorrhage. Hence, we performed an exploratory analysis comparing the group of patients with RCVS-SAH with the subgroup of patients with cSAH who had nonperimesencephalic SAH. Despite the small number of patients in each group, we identified independent predictors that can distinguish these conditions. We anticipate that these results may enhance the clinical decision-making process with regard to patients presenting with convexal SAH.

The association between COPD and RCVS-SAH was unanticipated and requires confirmation. It is conceivable that patients with COPD have underlying risk factors for RCVS, such as cerebrospinal fluid leakage with hypotension resulting from chronic cough, chronic exposure to decongestant (vasoconstrictive) medications, or exposure to glucocorticoids, which have been associated with worse outcomes in RCVS.<sup>12</sup> Smoking is an unlikely contributing factor because we found no difference in the proportion of smokers among the cohorts, and no colinearity between smoking and COPD. Because chronic headaches and depression often occur concurrently in clinical practice, we tested for and ruled out colinearity, confirming that they are independent predictors. We found that prior antidepressant use distinguished RCVS-SAH from cSAH and tended to distinguish it from cSAH. Antidepressants induce vasoconstriction from serotonergic and sympathomimetic effects, and have previously been associated with RCVS,<sup>1,12,24</sup> as well as symptomatic vasospasms after aSAH.<sup>14</sup> We emphasize that the CIs for

most predictors were fairly wide, likely owing to small patient numbers, and suggest that these predictors should be used in combination rather than in isolation. Future studies should seek to develop and validate a diagnostic scoring system using these variables.

Although we analyzed one of the largest cohorts of patients with RCVS-SAH and a substantial number of patients with aSAH or cSAH, we acknowledge that the sample sizes are still small and that biases may exist owing to the retrospective nature of the study and data collection spanning several years. Our aSAH data set did not contain patients with SAH from arteriovenous malformations, dural arteriovenous fistulas, or other vascular lesions. The strengths of our study lie in the use of uniform data definitions, the level of certainty in grading vasoconstriction (because all patients in all 3 cohorts underwent CTA or DSA, both of which are superior to MRA or TCD for assessing vasoconstriction),<sup>25</sup> and the management of patients with aSAH or cSAH consistent with published management guidelines.<sup>26</sup>

In summary, we envision that the epidemiological and clinical-imaging predictors identified in our study may enable a prompt and accurate diagnosis, and have an effect on patient management. Future studies should evaluate whether the use of these predictors, combined with the growing recognition of RCVS and accumulating clinical experience, will ultimately improve bedside diagnosis, reduce the number of unnecessary tests, and decrease the length of hospitalization. Diagnostic biomarker studies are unlikely to add value to these results; however, future biomarker and molecular studies may still be helpful for understanding the mechanisms of cerebral vasoconstriction or vasospasm and for developing novel treatments.

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