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Volumetric quantification of aneurysmal subarachnoid hemorrhage independently predicts hydrocephalus and seizures

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OBJECTIVE Hydrocephalus and seizures greatly impact outcomes of patients with aneurysmal subarachnoid hemorrhage (aSAH); however, reliable tools to predict these outcomes are lacking. The authors used a volumetric quantitative analysis tool to evaluate the association of total aSAH volume with the outcomes of shunt-dependent hydrocephalus and seizures.

METHODS Total hemorrhage volume following aneurysm rupture was retrospectively analyzed on presentation CT imaging using a custom semiautomated computer program developed in MATLAB that employs intensity-based k-means clustering to automatically separate blood voxels from other tissues. Volume data were added to a prospectively maintained aSAH database. The association of hemorrhage volume with shunted hydrocephalus and seizures was evaluated through logistic regression analysis and the diagnostic accuracy through analysis of the area under the receiver operating characteristic curve (AUC).

RESULTS The study population comprised 288 consecutive patients with aSAH. The mean total hemorrhage volume was 74.9 ml. Thirty-eight patients (13.2%) developed seizures. The mean hemorrhage volume in patients who developed seizures was significantly higher than that in patients with no seizures (mean difference 17.3 ml, p = 0.01). In multivariate analysis, larger hemorrhage volume on initial CT scan and hemorrhage volume > 50 ml (OR 2.81, p = 0.047, 95% CI 1.03–7.80) were predictive of seizures. Forty-eight patients (17%) developed shunt-dependent hydrocephalus. The mean hemorrhage volume in patients who developed shunt-dependent hydrocephalus was significantly higher than that in patients who did not (mean difference 17.2 ml, p = 0.006). Larger hemorrhage volume and hemorrhage volume > 50 ml (OR 2.45, p = 0.03, 95% CI 1.08–5.54) were predictive of shunt-dependent hydrocephalus. Hemorrhage volume had adequate discrimination for the development of seizures (AUC 0.635) and shunted hydrocephalus (AUC 0.629).

CONCLUSIONS Hemorrhage volume is an independent predictor of seizures and shunt-dependent hydrocephalus in patients with aSAH. Further evaluation of aSAH quantitative volumetric analysis may complement existing scales used in clinical practice and assist in patient prognostication and management.

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KEYWORDS aneurysm; volume; subarachnoid hemorrhage; hydrocephalus; seizures; vascular disorders

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with significant morbidity and mortality.[1] Besides the initial hemorrhagic event, multiple complications associated with aSAH, namely cerebral vasospasm, delayed cerebral infarction (DCI), seizures, and hydrocephalus, can arise in the following days after aneurysm rupture.[2] Given that these conditions are known to greatly impact patient outcomes, tools that can identify patients who are at a higher risk of developing such outcomes can assist with prognostication and management. There are multiple scales used today that help in evaluating the risk for cerebral vasospasm and can be calculated upon presentation, including the Hunt and Hess grade,[3] the World Federation of Neurosurgical Societies (WFNS) grade,[4] and

ABBREVIATIONS AED = antiepileptic drug; aSAH = aneurysmal SAH; AUC = area under the receiver operating characteristic curve; DCI = delayed cerebral infarction; EVD = external ventricular drain; IVH = intraventricular hemorrhage; ROI = region of interest; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

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the Fisher and modified Fisher grades.[5,6] However, commonly used tools to evaluate the risk of hydrocephalus and seizures following aSAH are lacking. Furthermore, the scales used for evaluation of the risk of cerebral vasospasm and DCI have been criticized given their qualitative nature and being open to variability in interpretation.[7,8] Hydrocephalus that follows aSAH is hypothesized to be related to one or several mechanisms, including obstruction of CSF flow by blood products or adhesions, impaired CSF absorption at the arachnoid granulations, or alterations in CSF dynamics and increases in CSF secretion.[9,10] The reported rate of hydrocephalus found on CT imaging after aSAH ranges from 15% to 87%.[11] Similarly, seizures in aSAH patients are not uncommon and occur at a rate reported to range from 3% to 26%.[12–14]

The effect of hemorrhage volume has long been thought to be associated with clinical outcomes and complications in patients with intracerebral hemorrhage and aSAH.[15–17] However, given the diffuse nature of the hemorrhage in aSAH, direct measures to evaluate blood volume have been limited. More recent studies have used semiquantitative and quantitative methods to evaluate the extent of hemorrhage and volume in aSAH but focused on the association with cerebral vasospasm and DCI.[15,18,19] However, to date, no study has directly evaluated the impact of total hemorrhage volume following aSAH on the occurrence of seizures or hydrocephalus and shunt dependency. We aimed to evaluate the association of hemorrhage volume following aneurysm rupture with the outcomes of shunt-dependent hydrocephalus and seizures, through a volumetric quantitative analysis tool of intracranial total hemorrhage volume.

Methods

Patient Selection

Consecutive patients admitted and managed for aSAH at a tertiary care center from January 2014 to May 2019 were included in the study. Patients < 18 years of age, those with nonaneurysmal subarachnoid hemorrhage (SAH; n = 101, traumatic, angiogram-negative, and perimesencephalic SAH), and patients with noncontrast CT imaging not available on presentation (n = 87) or poor-quality CT scans (n = 6) were excluded. All patients had clinical signs, symptoms, and imaging findings of SAH with vascular imaging (CT angiography or digital subtraction angiography) demonstrating an aneurysmal etiology. Total hemorrhage volume analysis was carried out retrospectively through analysis of noncontrast CT imaging and data were added to the existing database. The study protocol was approved by the Institutional Review Board.

Outcomes

Two primary outcomes were evaluated in this study, seizures and shunt-dependent hydrocephalus. The first goal was to evaluate the association of hemorrhage volume with the occurrence of seizures. Both clinically apparent focal and generalized seizures with or without loss of consciousness, as well as nonconvulsive seizures detected only on EEG, were included when determining the outcome of seizures. Patients with seizures diagnosed at any time during the follow-up period were accounted for. Continuous EEG monitoring was readily available on nights and weekends and was obtained at the discretion of the treating physician when there was a clinical indication, typically for any unexplained decline in the level of consciousness or new neurological deficits. The second goal was to evaluate the impact of hemorrhage volume on the development of shunt-dependent hydrocephalus. Shunt-dependent hydrocephalus was defined as hydrocephalus evident radiographically on CT imaging and associated with clinical symptoms during patient hospitalization, where external ventricular drain (EVD) placement was deemed insufficient and a permanent shunt (typically a ventriculoperitoneal shunt) was considered necessary by the treating physician for the management of hydrocephalus.

Hemorrhage Volume Analysis

The total hemorrhage volume, including subarachnoid blood and associated intraparenchymal and intraventricular blood, was calculated using a custom semiautomated computer program developed in MATLAB (MATLAB and Image Processing Toolbox, release 2018b; MathWorks, Inc.). Noncontrast CT scans were evaluated by two of the authors who were blinded to outcomes. CT scans were retrieved from our hospital's digital archive system in DICOM format. The CT scan performed on initial presentation was used for volume analysis in all patients (standard CT with 5-mm slice thickness). Prior to volume calculation, a 3D region of interest (ROI) about 1 cm from the inner table of the skull was manually drawn on a single thin-cut CT to serve as an atlas. An affine transformation matrix that comprised translation, rotation, scale, and shear was automatically calculated to transform the atlas CT and ROI onto each new CT. Hemorrhage volume calculations were limited to those pixels within the ROI in order to minimize the effect of streak artifact on the volume analysis and to exclude signal from the extracranial compartment. The program then employed intensity-based k-means clustering to automatically separate blood voxels from other tissues (Fig. 1).[20] The user then identified the cluster corresponding to blood, and the number of voxels within the blood cluster were automatically counted. The number of blood voxels was then multiplied by the length-per-pixel conversion factor in each of the 3 dimensions, specified within the DICOM metadata, in order to yield total hemorrhage volume in milliliters.[21] In some patients, if some small amount of cortical aSAH was excluded, it was reincluded within the ROI. Careful slice-by-slice review was carried out and hemorrhage volume calculation was then recorded. The hemorrhage volumes recorded by the two authors were then averaged to obtain the final volume.

Statistical Analysis

The data are presented as mean and range or standard deviation for continuous variables and as frequency for categorical variables. Statistical analysis was performed using Stata (StataCorp). Univariate analysis was used to test the association of total hemorrhage volume with the following dependent outcomes: seizures and shunt-dependent hydrocephalus. Odds ratios and 95% confidence intervals were calculated. Statistically significant covariates and those of

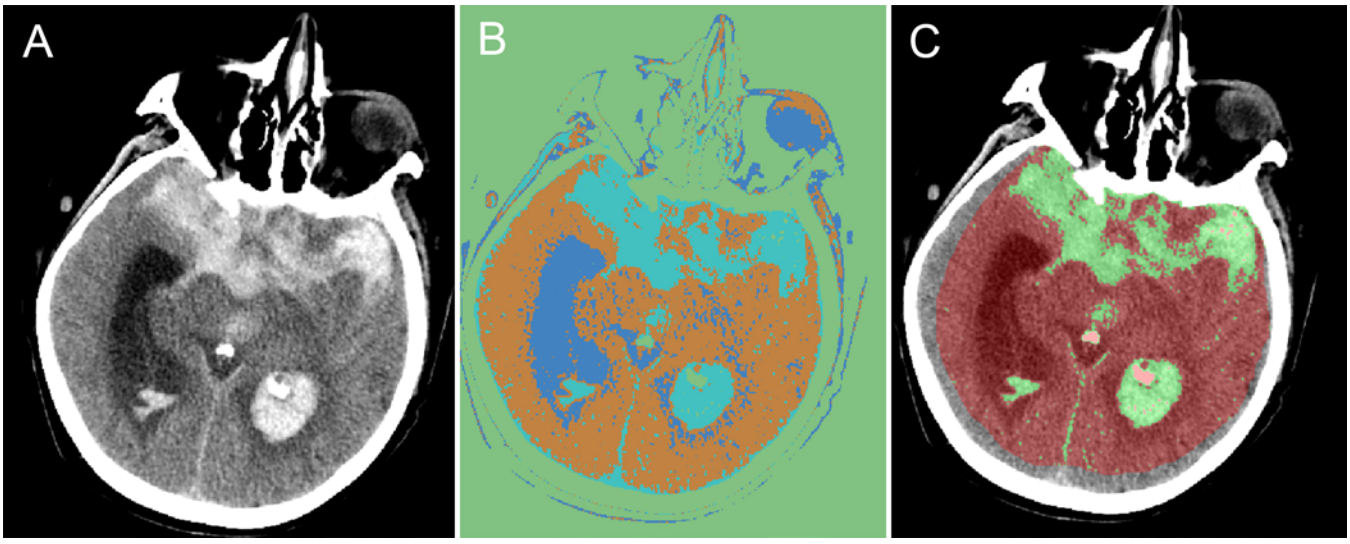

FIG. 1. A: Noncontrast CT scan on presentation demonstrating aSAH and associated IVH. **B:** The computer program employed intensity-based k-means clustering to automatically separate blood voxels from other tissue. The user then identified the cluster corresponding to blood, and the number of voxels within the blood cluster (*light blue*) was automatically counted. **C:** Hemorrhage volume (blood is *green*) calculations were limited to those pixels within the ROI in order to minimize the effect of streak artifact on the volume analysis, and to exclude signal from the extracranial compartment. Figure is available in color online only.

clinical relevance were entered in the multivariate logistic regression analysis. Statistics of means were carried out using paired Student t-tests. The diagnostic accuracy of hemorrhage volume analysis and other tested variables was obtained by calculating the area under the receiver operating characteristic curve (AUC), with graphical and standard nonparametric receiver operating characteristic measurements. Sensitivity and specificity analyses were conducted for various hemorrhage volume cutoffs, and p values ≤ 0.05 were considered statistically significant.

Results

Baseline Characteristics

The study population consisted of 288 patients with aSAH who had a mean hemorrhage volume of 74.9 ± 39.7 ml (range 5.05–180.74 ml). At baseline, the median modified Rankin Scale (mRS) score was 0, the median WFNS grade was II, and the median Hunt and Hess grade was III. The mean Hijdra score was 21 ± 10, and the median modified Fisher scale grade was 3. Seventy-six patients (26.4%) had intraparenchymal hemorrhage and 81 patients (28.1%) had intraventricular hemorrhage (IVH). Additional patient characteristics are shown in Table 1.

Seizures

Thirty-eight patients (13.2%) developed seizures. The mean hemorrhage volume in these patients was 90 ml (range 22.4–146.1 ml) versus 72.7 ml for patients who did not have seizures (mean difference 17.3 ml, p = 0.01).

In univariate analysis, a larger hemorrhage volume on initial CT scan (OR 1.01, p = 0.014, 95% CI 1.002–1.02) was associated with the onset of seizures. More specifically, hemorrhage volume > 50 ml (OR 2.90, p = 0.022, 95% CI 1.17–7.19; sensitivity 84.21%, specificity 35.20%) and hemorrhage volume > 75 ml (OR 3.07, p = 0.003, 95% CI 1.46–6.47; sensitivity 68.42%, specificity 56.40%) were predictive of seizures. Additionally, younger patient age (OR 1.04, p = 0.003, 95% CI 1.01–1.06), Hunt and Hess grade ≥ IV (OR 3.46, p = 0.001, 95% CI 1.68–7.09), WFNS grade ≥ 4 (OR 2.96, p = 0.003, 95% CI 1.45–6.07), associated intraparenchymal hemorrhage (OR 2.87, p = 0.003, 95% CI 1.42–5.79), and rebleeding (OR 4.58, p = 0.011, 95% CI 1.41–14.8) were associated with the occurrence of seizures.

In multivariate analysis, hemorrhage volume > 50 ml (OR 2.81, p = 0.047, 95% CI 1.03–7.80), hemorrhage volume > 75 ml (OR 2.92, p = 0.013, 95% CI 1.25–6.80), younger age (OR 1.04, p = 0.002, 95% CI 1.01–1.07), intraparenchymal hemorrhage (OR 2.41, p = 0.03, 95% CI 1.06–5.47), rebleeding (OR 6.10, p = 0.015, 95% CI 1.43–26.04), WFNS grade ≥ IV (OR 3.02, p = 0.008, 95% CI 1.34–6.82), and Hunt and Hess grade ≥ IV (OR 3.47, p = 0.003, 95% CI 1.53–7.88) were associated with the outcome of seizures.

Hemorrhage volume had adequate discrimination for the development of seizures, with an AUC of 0.635 (95% CI 0.55–0.72) (Fig. 2).

Shunt-Dependent Hydrocephalus

In total, 126 patients (43.8%) had radiographic evidence of hydrocephalus in the acute period and 218 patients (75.7%) were managed with an EVD. Forty-eight patients (17%) developed shunt-dependent hydrocephalus, which represented the outcome of interest. The mean hemorrhage volume in these patients was 89.3 ml (range 28.5–176.7 ml) versus 72.1 ml for patients who did not have shunt-dependent hydrocephalus (mean difference 17.2 ml, p = 0.006).

TABLE 1. Baseline characteristics of the study patients

	Value
Age, yrs	57.7 ± 14.6
Sex	
Male	88 (30.6%)
Female	200 (69.4%)
Comorbidities	
Hypertension	140 (48.6%)
Dyslipidemia	44 (15.3%)
Diabetes mellitus	24 (8.3%)
Stroke	10 (3.5%)
Coronary artery disease	28 (9.7%)
Smoking	148 (51.4%)
Alcohol abuse	21 (7.3%)
Aneurysm location	
Anterior circulation	261 (90.6%)
Posterior circulation	27 (9.4%)
Aneurysm size, mm	7.06 ± 5.06
Presence of multiple aneurysms	44 (15.3%)
Treatment modality	
Clipping	101 (35.1%)
Coiling	140 (48.6%)
Combination of coiling and clipping	8 (2.8%)
No treatment	39 (13.5%)

Values are presented as number (%) of patients or mean ± SD.

In univariate analysis, a larger hemorrhage volume on initial CT scan (OR 1.01, p = 0.007, 95% CI 1.002–1.02), hemorrhage volume > 50 ml (OR 2.79, p = 0.012, 95% CI 1.25–6.24; sensitivity 83.33%, specificity 35.83%), hemorrhage volume > 75 ml (OR 2.27, p = 0.013, 95% CI 1.19–4.32; sensitivity 62.50%, specificity 56.25%), Hijdra score (OR 1.05, p = 0.008, 95% CI 1.01–1.08), and associated IVH (OR 2.25, p = 0.013, 95% CI 1.19–4.25) were the only factors associated with shunt-dependent hydrocephalus. In multivariate analysis accounting for IVH, hemorrhage volume was the only factor predictive of shunt-dependent hydrocephalus (OR 1.01, p = 0.032, 95% CI 1.001–1.002), with hemorrhage volume > 50 ml (OR 2.45, p = 0.03, 95% CI 1.08–5.54) and hemorrhage volume > 75 ml (OR 1.99, p = 0.04, 95% CI 1.03–3.85) being the cutoffs associated with shunt-dependent hydrocephalus (Table 2).

Hemorrhage volume had adequate discrimination for the development of shunted hydrocephalus, with an AUC of 0.629 (95% CI 0.54–0.71) (Fig. 3).

Discussion

Seizures and hydrocephalus greatly impact outcomes of patients with aSAH.[22–26] Multiple studies have demonstrated that seizures, hydrocephalus, and shunt dependency are associated with increased hospital stays, medical costs, morbidity, and mortality.[23,25,27,28] Yet, reliable tools to predict shunt-dependent hydrocephalus and seizures following aSAH are lacking. The amount of cisternal, intraventricular, or intraparenchymal blood following aSAH has been thought to be associated with these sequelae,[12,17,29–31] but given the diffuse and multicompartmental nature of the hemorrhage in aSAH cases, tools for accurate volume

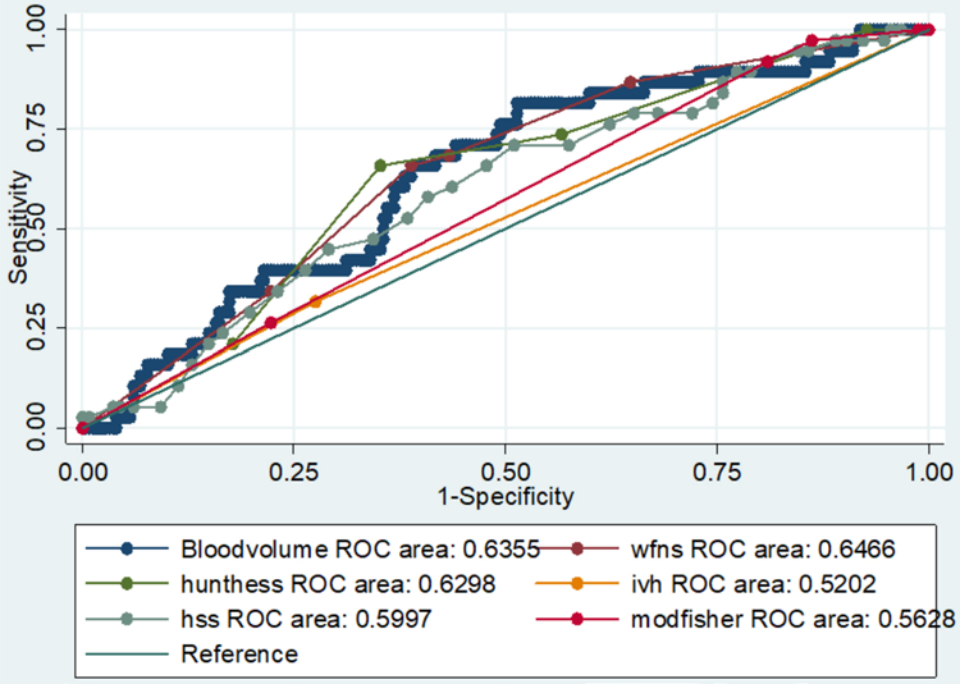

FIG. 2. ROC curves for the outcome of seizures. Hss = Hijdra sum score; modfisher = modified Fisher. Figure is available in color online only.

TABLE 2. Univariate and multivariate analyses for shunt-dependent hydrocephalus and seizures

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Seizures						
Increasing hemorrhage volume	1.01	1.002–1.02	0.014	1.01	1.002–1.02	0.014
Blood volume >30 ml	1.84	0.53–6.30	0.33	1.54	0.41–5.8	0.52
Blood volume >50 ml	2.90	1.17–7.20	0.022	2.81	1.03–7.80	0.047
Blood volume >75 ml	3.07	1.46–6.47	0.003	2.92	1.25–6.80	0.013
Increasing Hijdra score	1.04	0.99–1.07	0.057	1.04	0.99–1.08	0.06
Hijdra score ≥23	1.95	0.97–3.93	0.059	1.91	0.90–4.07	0.09
WFNS grade ≥IV	2.96	1.45–6.06	0.003	3.02	1.34–6.82	0.008
Hunt and Hess grade ≥IV	3.45	1.68–7.09	0.001	3.47	1.53–7.88	0.003
Modified Fisher grade ≥3	2.79	0.82–9.44	0.1	2.34	0.64–8.53	0.2
Intracerebral hemorrhage	2.87	1.42–5.79	0.003	2.41	1.06–5.47	0.03
Use of AED	3.94	0.51–30.06	0.18	2.26	0.28–18.39	0.45
Rebleeding	4.58	1.41–14.84	0.01	6.1	1.43–26.04	0.015
Delayed cerebral ischemia	1.38	0.58–3.24	0.46	—	—	—
Hyponatremia	0.95	0.45–2.01	0.895	—	—	—
Age	0.96	0.94–0.99	0.003	0.96	0.93–0.98	0.002
Sex	0.91	0.43–1.93	0.80	—	—	—
Hypertension	0.73	0.37–1.47	0.39	—	—	—
Hyperlipidemia	0.62	0.20–1.83	0.39	—	—	—
Diabetes	0.27	0.03–2.03	0.2	—	—	—
Coronary artery disease	0.22	0.03–1.69	0.15	—	—	—
Smoking	1.35	0.69–2.69	0.39	—	—	—
Alcohol use	2.21	0.76–6.4	0.14	—	—	—
Statin treatment	0.37	0.05–2.87	0.34	—	—	—
Aneurysm location (value range for the 18 locations)	0.28–6.14	—	0.14–0.86	—	—	—
Aneurysm size	0.9	0.82–1.008	0.07	0.89	0.79–1.001	0.053
Multiple aneurysms	0.64	0.21–1.90	0.42	—	—	—
Aneurysm treatment modality (open or endovascular)	1.01	0.71–1.43	0.9	—	—	—
Shunt-dependent hydrocephalus						
Increasing hemorrhage volume	1.01	1.003–1.02	0.007	1.01	1.001–1.002	0.032
Blood volume >30 ml	8.29	1.11–62.03	0.039	7.11	0.94–53.60	0.057
Blood volume >50 ml	2.79	1.25–6.23	0.012	2.45	1.08–5.54	0.03
Blood volume >75 ml	2.27	1.19–4.31	0.013	1.99	1.03–3.85	0.04
Increasing Hijdra score	1.04	1.01–1.08	0.008	1.03	0.99–1.07	0.053
Hijdra score ≥23	2.00	1.06–3.77	0.032			
WFNS grade ≥4	1.41	0.76–2.6	0.27	—	—	—
Hunt and Hess grade ≥IV	1.83	0.98–3.42	0.057	—	—	—
Modified Fisher grade ≥3	2.69	0.92–7.87	0.07	—	—	—
Intracerebral hemorrhage	0.91	0.44–1.86	0.8	—	—	—
IVH	2.25	1.19–4.25	0.013	1.94	0.99–377	0.051
Rebleeding	2.33	0.69–7.91	0.17	—	—	—
Delayed cerebral ischemia	0.885	0.39–2.03	0.77	—	—	—
Age	1.002	0.98–1.02	0.83	—	—	—
Sex	0.62	0.30–1.29	0.20	—	—	—
Hypertension	0.64	0.34–1.21	0.17	—	—	—
Hyperlipidemia	0.45	0.15–1.33	0.15	—	—	—
Diabetes	0.43	0.097–1.90	0.26	—	—	—
History of stroke	1.26	0.26–6.13	0.77	—	—	—

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TABLE 2. Univariate and multivariate analyses for shunt-dependent hydrocephalus and seizures

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Shunt-dependent hydrocephalus (*continued*)						
Smoking	0.56	0.3–1.06	0.075	—	—	—
Alcohol use	0.82	0.23–2.9	0.76	—	—	—
Statin treatment	0.28	0.036–2.14	0.22	—	—	—
Aneurysm location (value range for the 18 locations)	0.57–5.67	—	0.17–0.87	—	—	—
Aneurysm size	1.02	0.97–1.08	0.40	—	—	—
Multiple aneurysms	1.34	0.59–3.01	0.47	—	—	—
Aneurysm treatment modality (open or endovascular)	1.1	0.57–2.13	0.77	—	—	—

calculation have been lacking. In addition, most scoring systems used in clinical practice today for aSAH patients are employed to assess the risk of cerebral vasospasm and DCI but do not account for the risk of seizures and hydrocephalus. We describe a quantitative hemorrhage volume analysis method and report hemorrhage volume in aSAH to be an independent predictor of seizures and shunt-dependent hydrocephalus.

A wide range of descriptions of the incidence of hydrocephalus following aSAH have been reported, likely related to the various definitions used.[9,17,27,32–34] Regardless, hydrocephalus development in patients with aSAH may worsen neurological function and outcomes and may commit patients to further surgical procedures, including shunt placement and associated complications.[35,36] We intended to evaluate shunt-dependent hydrocephalus and identified this outcome in 17% of patients. Several factors have been linked to the development of shunted hydrocephalus following aSAH, including a high Hunt and Hess grade (≥ IV), a higher modified Fisher grade, rebleeding, hypertension, posterior circulation aneurysm location, female sex, and older age (≥ 60 years).[9,23,27,33,34,36,37] Some studies also found correlations with the location of the ruptured aneurysm and treatment modality (clipping vs coiling).[27] However, the literature has been mixed on many of these variables.[38] The most prominent factor, however, remains the presence of IVH, which has been identified as an independent predictor of shunt-dependent hydrocephalus, mortality, and functional outcome in aSAH.[39] Besides IVH, many of these factors were not reproduced in our study, and we found no significant association between shunt dependency and the modified Fisher, Hunt and Hess, and WFNS grades. Based on the existing literature, certain scores have been formulated in an attempt to predict shunt-dependent hydrocephalus, including the Barrow Neurological Institute (BNI) score, which evaluates the thickness of the subarachnoid blood clot measured perpendicular to a cistern or fissure;[40] the shunt dependency in aSAH (SDASH) score, which combines the BNI score, the Hunt and Hess grade, and the presence of acute hydrocephalus;[29] the CHESS (Chronic Hydrocephalus Ensuing from SAH Score), which takes into account the Hunt and Hess grade, aneurysm location, presence of acute hydrocephalus, presence of IVH, and early cerebral infarction;[41] and the Graeb and LeRoux scores, which qualitatively evaluate the amount and location of intraventricular blood.[30,42] To date, these scores have not gained wide clinical use and are limited by their qualitative nature. So far, none of these prognostic models considered the influence of the quantified hemorrhage volume on the development of shunt-dependent hydrocephalus. Our results show that hemorrhage volume estimated through quantitative volumetric analysis is significantly associated with shunt-dependent hydrocephalus. The utilization of similar quantitative tools in practice may be beneficial in stratifying the risk for shunt-dependent hydrocephalus and thus have an impact on patient management. Knowledge of hemorrhage volume, when combined with clinical data, can possibly help guide decisions regarding shunt placement and early patient counseling. Furthermore, hemorrhage volume may be used to assist with decisions regarding EVD placement and management. In patients with hydrocephalus on presentation, the decision for EVD placement is more obvious, but in cases with low/moderate-grade SAH with no hydrocephalus on presentation, insight into total hemorrhage volume can assist with decision-making for EVD. Furthermore, early identification of patients in need of shunt placement can help to reduce the duration of EVD and hence catheter-associated infections, ICU and hospital stays, and possibly hospitalization costs.

Similarly, several markers have been linked to the development of seizures following aSAH, many of which were also identified in our study.[12,43–45] Unlike the many scoring systems used for hydrocephalus, we identified only one article that describes a predictive score for seizure occurrence after aSAH, the SAFARI score,[46] in which the authors report utilizing strictly qualitative criteria, including age ≥ 60 years, seizure occurrence prior to hospitalization, anterior circulation aneurysm location, and hydrocephalus. However, the hemorrhage volume was not included in this score. Increased subarachnoid hemorrhage thickness, larger cisternal clot burden, and increased volume of intraparenchymal hemorrhage have been reported as independent predictors of seizures in aSAH.[12,31,43] However, prior studies relied on qualitative criteria and did not evaluate the direct effect of hemorrhage volume on seizure occurrence.

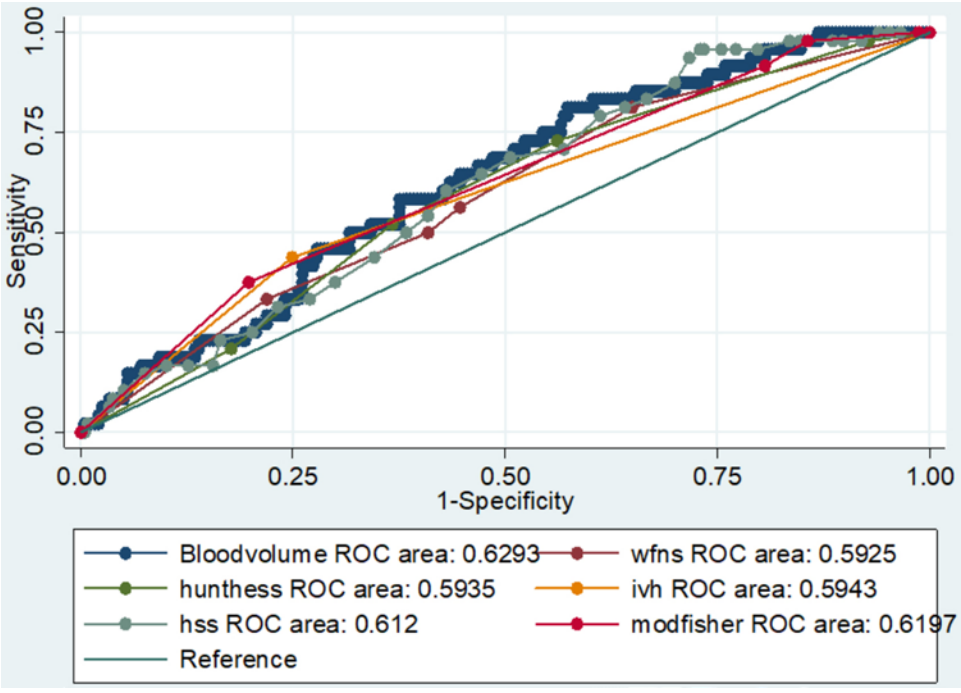

FIG. 3. ROC curves for the outcome of shunt-dependent hydrocephalus. Figure is available in color online only.

These prior descriptive associations can introduce significant interobserver variability and bias. Given that seizures are associated with increased morbidity and mortality in patients with aSAH,[47] more accurate and reliable predictive tools are needed to improve clinical management. Quantification of the hemorrhage volume can provide a supplementary tool for identification of the at-risk population. Prophylactic administration of antiepileptic drugs (AEDs) after aSAH is common at many centers.[11] AEDs are routinely used despite lack of level I evidence supporting their use and are not without adverse effects. In fact, some studies have identified worse cognitive and functional outcomes in patients who receive AEDs.[48] Having improved objective predictive models can assist with AED management, especially since current treatment guidelines do not specify choice of AED, dosage, and duration, e.g., having a lower threshold to use and maintain certain patients with high CT hemorrhage volume on AEDs or hold these agents with more confidence in patients who develop side effects and have low total hemorrhage volumes.

Hemorrhage volume was significantly associated with both seizures and shunted hydrocephalus, whereas the other scales lacked consistent predictive ability for both outcomes. However, blood volume quantification had overall comparable accuracies in predicting both seizures and hydrocephalus compared to common scores used in clinical practice, including the Hunt and Hess, modified Fisher, and WFNS grading systems. Most of these qualitative scales, including the modified Fisher scale and the Hunt and Hess scale, have been extrapolated from the vasospasm literature, with some positive data showing association with shunt-dependent hydrocephalus and seizures. Furthermore, these scales are subject to a certain degree of subjectivity. Quantitative volumetry could be less subject to interobserver variability and be a supplementary tool used in association with other scales. With an AUC of 0.635 for the outcome of seizures and an AUC of 0.629 for shunted hydrocephalus, prediction accuracy can probably be increased by identifying models or scores that incorporate hemorrhage volume and other clinical and radiographic factors to improve prognostic capabilities. Hydrocephalus and seizures are multifactorial in origin, so it is unlikely that one factor alone will have high accuracy and reliability. However, we do believe that prior work was lacking a quantitative component that can possibly improve the predictive power of existing scores. Introducing quantitative blood volume assessment to factors that are already routinely assessed in practice may complement other clinical scores and improve the prediction of shunt-dependent hydrocephalus. A combination of models, including radiographic volumetric data and clinical scores, should be further investigated to improve the accuracy of predicting seizures and shunted hydrocephalus.

Prior studies have estimated that an aSAH hemorrhage volume > 20 ml is associated with adverse outcomes and complications, including vasospasm and DCI.[18,49] The best predictive model for both seizures and shunted hydrocephalus was obtained with a volume cutoff ≥ 50 ml in our study. Notably, our study population had a relatively high average total hemorrhage volume likely attributable to the population's high radiographic SAH admission grade, where the average volume was 74.9 ml, the mean modified Fisher grade was 3, and the mean Hijdra score was 21. Furthermore, in the majority of prior volumetric studies that have looked into SAH, cisternal hemorrhage volume or a combination of cisternal and ventricular hemorrhage volume were measured, but total intracranial hemorrhage volume following aneurysm rupture was not accounted for.[15,18,19,50]

Further work into establishing optimal test cutoff values for quantified hemorrhage volume would be beneficial.

Study Limitations

This study has several limitations. The studied cohort reflects the experience of a single center managing patients with aSAH, and thus practices pertaining to antiepileptic prophylaxis, EVD placement and management, ICU management, and shunting may not be uniform across centers. We recognize that this impacts the generalizability of the study. The accuracy of our volume analysis tool was not compared to a radiological standard, as one does not currently exist, which further limits the generalizability of the results. Further studies are required to externally validate our quantitative volumetric method with imaging captured at other institutions. Additional prospective studies will be needed to assess the accuracy and impact of employing this quantitative tool on patient management and with counseling of patients and families regarding seizure likelihood, AEDs, and shunt dependency. Furthermore, even though we used a prospectively maintained comprehensive institutional aSAH database, volumetric analysis was conducted retrospectively by authors who were blinded to the outcomes. Due to the retrospective nature of the study, there is a lack of standardization regarding the indications for continuous EEG monitoring or shunt placement. Additionally, the process of hemorrhage calculation was semiautomated, whereas a fully automated method would mitigate the effects of interobserver variability. Although hemorrhage volume was predictive of seizures and shunt dependency, it had diagnostic accuracy comparable to that of the other scales and should not replace these tools. Such quantitative radiological measures could have a supplementary role if incorporated with clinical data, but this needs further validation. In addition, the widespread adoption of hemorrhage volume calculations in the clinical setting would require user-friendly integration with existing radiology viewing software.

Conclusions

Hemorrhage volume is an independent predictor of seizures and shunt-dependent hydrocephalus in patients with aSAH. The utilization of quantitative volumetric measurement software can estimate total hemorrhage volume in aSAH. The diagnostic accuracy of our quantitative analysis tool was overall comparable to those of clinical scales used in practice. It is feasible that future technological advancements will allow for more accurate calculation of hemorrhage volume and thus the potential for better ability to prognosticate for seizure and hydrocephalus. The advent of such technologies could be considered for adaptation to CT software, allowing for immediate calculation of blood volume with each head CT and thus enhancing clinical application. Similar tools may supplement existing scales, and their role warrants further evaluation in patient prognostication and decision-making regarding the use of AEDs and the need for CSF shunt implantation. Future prospective studies are needed to establish the accuracy and reliability of utilizing hemorrhage volume calculations for clinical decision-making and to validate our findings.

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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: Pandey, Daou, Khalsa, Anand, Williamson. Acquisition of data: Daou, Khalsa, Anand, Williamson, Cutler, Aaron, Srinivasan, Rajajee, Sheehan. Analysis and interpretation of data: Pandey, Daou, Khalsa, Anand, Williamson, Cutler, Aaron, Srinivasan, Rajajee. Drafting the article: Pandey, Daou, Khalsa. Critically revising the article: Pandey, Daou, Khalsa, Anand, Williamson. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Pandey. Statistical analysis: Daou, Khalsa. Administrative/technical/material support: Williamson, Rajajee, Sheehan. Study supervision: Pandey, Daou, Williamson, Rajajee.

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