Radiodensity of intraventricular hemorrhage associated with aneurysmal subarachnoid hemorrhage may be a negative predictor of outcome

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OBJECTIVE The presence, extent, and distribution of intraventricular hemorrhage (IVH) have been associated with negative outcomes in aneurysmal subarachnoid hemorrhage (SAH). Several qualitative scores (Fisher grade, LeRoux score, and Graeb score) have been established for evaluating SAH and IVH. However, no study has assessed the radiodensity within the ventricular system in aneurysmal SAH patients with IVH. Prior studies have suggested that hemorrhage with a higher radiodensity, as measured by CT Hounsfield units, can cause more irritation to brain parenchyma. Therefore, the authors set out to investigate the relationship between the overall radiodensity of the ventricular system in aneurysmal SAH patients with IVH and their clinical outcome scores.

METHODS The authors reviewed the records of 101 patients who were admitted to their institution with aneurysmal SAH and IVH between January 2011 and July 2015. The following data were collected: age, sex, Glasgow Coma Scale (GCS) score, Hunt and Hess grade, extent of SAH (none, thin, or thick/localized), aneurysm location, and Glasgow Outcome Scale (GOS) score. To evaluate the ventricular radiodensity, the initial head CT scan was loaded into OsiriX MD. The ventricular system was manually selected as the region of interest (ROI) through all pertinent axial slices. After this, an averaged ventricular radiodensity was calculated from the ROI by the software. GOS scores were dichotomized as 1–3 and 4–5 subgroups for analysis.

RESULTS On univariate analysis, younger age, higher GCS score, lower Hunt and Hess grade, and lower ventricular radiodensity significantly correlated with better GOS scores (all $p < 0.05$). Subsequent multivariate analysis yielded age (OR 0.936, 95% CI 0.895–0.979), GCS score (OR 3.422, 95% CI 1.9–6.164), and ventricular density (OR 0.937, 95% CI 0.878–0.999) as significant independent predictors ($p < 0.05$). A receiver operating characteristic curve yielded 12.7 HU (area under the curve 0.625, $p = 0.032$, sensitivity = 0.591, specificity = 0.596) as threshold between GOS scores of 1–3 and 4–5.

CONCLUSIONS This study suggests that the ventricular radiodensity in aneurysmal SAH patients with IVH, along with GCS score and age, may serve as a predictor of clinical outcome.

<https://thejns.org/doi/abs/10.3171/2016.11.JNS152839>

KEY WORDS aneurysmal subarachnoid hemorrhage; radiodensity; CT Hounsfield units; vascular disorders

UP to 30%–70% of patients with aneurysmal subarachnoid hemorrhage (SAH) also exhibit intraventricular hemorrhage (IVH).^{13,19} Several qualitative scores (Fisher grade, LeRoux score, and Graeb score) have been established for evaluating SAH and IVH. However, to our knowledge, no studies have assessed the

radiodensity within the ventricular system in aneurysmal SAH patients with IVH. Radiodensity, as measured using CT Hounsfield units, has a positive correlation with the age of the hemorrhage. Prior studies have suggested that a hemorrhage with higher radiodensity can cause more irritation to brain parenchyma.^{31,32} Therefore, we investigated

ABBREVIATIONS AUC = area under the curve; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; IVH = intraventricular hemorrhage; ROC = receiver operating characteristic; ROI = region of interest; SAH = subarachnoid hemorrhage.

SUBMITTED December 4, 2015. **ACCEPTED** November 21, 2016.

INCLUDE WHEN CITING Published online May 5, 2017; DOI: 10.3171/2016.11.JNS152839.

FIG. 1. **A:** Manual selection of ventricular system as an ROI. **B and C:** Modeling using OsiriX MD, where an average radiodensity is provided. Coronal (B) and sagittal (C) projections.

the relationship between the overall radiodensity of the ventricular system in aneurysmal SAH patients with IVH and their clinical outcome scores.

Methods

The approval of the institutional review board at our hospital was obtained prior to the study. To be considered for the study, the records of patients who were admitted for aneurysmal SAH between January 2011 and July 2015 were reviewed. Inclusion criteria were age greater than 18 years old, an available head CT scan demonstrating SAH prior to intervention (an external ventricular drain, clipping, or embolization), confirmed ruptured aneurysm on subsequent digital subtraction angiography, treatment with embolization, and presence of IVH. Exclusion criteria were the presence of vascular malformations, presence of intracranial artifacts (prior embolization or aneurysm clipping), and treatment with surgical clipping or open craniotomy. In total, 101 patients fulfilled the criteria for retrospective analysis. The medical records were reviewed, and the following data were extracted: age, sex, Glasgow Coma Scale (GCS) score at admission, Hunt and Hess grade, extent of SAH (none, thin [< 1 mm], and thick [> 1 mm/localized]), location of the ruptured aneurysm (anterior or posterior circulation), and Glasgow Outcome Scale (GOS) score.

To evaluate the ventricular radiodensity, the initial head CT scan was loaded into OsiriX MD (Pixmeo). The ventricular system was manually selected as the region of interest (ROI) through all pertinent axial slices. Afterward, an averaged CT Hounsfield unit value was calculated from the ROI using the software (Fig. 1).

Statistical analysis was performed using IBM SPSS (version 22, IBM). Since the protocol required selection of the ventricular system, interobserver and intraobserver reliability calculations were performed with the use of the interclass correlation coefficient (where 0 represents no agreement and 1 represents perfect agreement). A value > 0.8 was considered an indication of excellent agreement.

For univariate analysis, continuous variables (age and ventricular radiodensity) and categorical variables (sex, GCS score, Hunt and Hess grade, extent of SAH, and an-

eurysm location) were evaluated using ANOVA and Pearson's chi-square test, respectively. The main outcome variable was GOS score, which was dichotomized between GOS scores of 1–3 and 4–5. Subsequently, all variables with $p < 0.1$ from univariate analysis were used in a backward multivariate logistic regression, where the final variables in the model exhibited $p < 0.05$. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate a threshold ventricular density for correlation with GOS score. A p value < 0.05 was considered to be statistically significant.

Results

Interobserver and intraobserver correlation coefficients were 0.925 (95% CI 0.887–0.951) and 0.997 (95% CI 0.989–0.999), respectively, for the calculation of ventricular radiodensity.

Table 1 summarizes the univariate analysis. Younger age, higher GCS score, lower Hunt and Hess grade, and lower ventricular radiodensity significantly correlated with a better GOS score (all $p < 0.05$). Table 2 summarizes the multivariate logistics regression, where all of these variables were included initially. Age (OR 0.936, 95% CI 0.895–0.979), GCS score (OR 3.422, 95% CI 1.9–6.164), and ventricular density (OR 0.937, 95% CI 0.878–0.999) were significant independent predictors ($p < 0.05$). ROC curve, which optimized both sensitivity and specificity, yielded 12.7 HU (area under the curve [AUC] 0.625, $p = 0.032$, sensitivity = 0.591, specificity = 0.596) as a threshold between GOS scores of 1–3 and 4–5 (Fig. 2).

Discussion

The incidence of aneurysmal SAH is approximately 7 per 100,000.² Overall outcome remains poor; the 30-day mortality rate can be as high as one-third of patients in prior studies, while survivors may continue to demonstrate significant long-term morbidity.² Established factors associated with negative clinical outcomes and/or the need for long-term shunting, include presenting clinical demographics (age), neurological status (World Federation of Neurosurgical Societies [WFNS] and Hunt and Hess grades), ra-

TABLE 1. Parameters for evaluation of GOS score

Parameter	GOS Scores 1–3 (n = 44)	GOS Scores 4 & 5 (n = 57)	p Value
Mean age (yrs)	63.2 ± 13.8	56.5 ± 10.1	<0.01
Sex			0.881
Male	11	15	
Female	33	42	
GCS score			<0.01
≤7	23	7	
8–14	11	9	
15	10	41	
SAH			0.171
None	3	1	
Thin	12	24	
Thick/localized	29	32	
Hunt & Hess grade			<0.01
I–III	17	50	
IV & V	27	7	
Location of aneurysm (circulation)			0.32
Anterior	29	32	
Posterior	15	25	
Mean ventricular radiodensity (HU)	18.7 ± 12.5	13.4 ± 6.6	<0.01

Values are presented as the number of patients (%) unless stated otherwise. Mean values are presented with SD.

diographic findings (Fisher score), and clinical course (early hydrocephalus requiring an external ventricular drain, vasospasm, and aneurysmal rehemorrhage).^{8,14,30,34,37} The presence, extent, and distribution of IVH have been associated with a poor prognosis.^{2,6,25,34} Furthermore, the clearance of IVH with tissue plasminogen activator has been the target of ongoing studies.^{11,12} Although qualitative scores (original and modified Fisher grade,³ LeRoux score,¹⁵ and original and modified Graeb scores^{1,6,21}) have been established for evaluating SAH and IVH, assessment of hemorrhage qualitatively can be inconsistent and imprecise.²⁷

A recent study positively correlated the radiodensity of intracerebral hemorrhage to perihemorrhagic edema, suggesting that radiodensity may play a role in evaluating brain irritation/injury and predict clinical outcome.³² Brain irritation may be related to a secondary cascade mediated by components of coagulation and products of clot breakdown. No studies have assessed the radiodensity of IVH in aneurysmal SAH patients as a quantitative marker. This study suggests that the ventricular radiodensity, along with

TABLE 2. Multivariate logistics regression

Variable	OR	95% CI	p Value
Age	0.936	0.895–0.979	<0.01
Ventricular radiodensity	0.937	0.878–0.999	0.046
GCS score	3.422	1.9–6.164	<0.01

FIG. 2. ROC curve for ventricular radiodensity to determine GOS scores of 1–3 versus 4–5 (AUC 0.625, $p = 0.032$, value at 12.7 HU with sensitivity = 0.591 and specificity = 0.596).

age and GCS score, may also serve as a predictor for clinical outcome in aneurysmal SAH with IVH.

Degraded blood products may explain the relationship among radiodensity, hemorrhage, and clinical outcome.³⁵ Prior studies have indicated that hemoglobin, thrombin, and iron may contribute to perihemorrhagic edema, while the extent of edema has been correlated with poorer patient outcomes.^{7,32,35,36} In studies in rats, iron depletion via deferoxamine tempers edema and enhances functional outcome after intracerebral hemorrhage is inflicted.^{23,32} In the clinical setting, a higher serum ferritin level has been associated with additional perihemorrhagic edema and poorer outcomes in patients who have sustained a spontaneous intracerebral hemorrhage.^{20,32} Wagner et al.³² noted that a higher radiodensity of hemorrhage, associated with higher in vivo iron content, correlated with increased perihemorrhagic edema. Consequently, the authors believed that radiodensity might be an indirect measure of in vivo iron content within hemorrhage. Nevertheless, iron content is unlikely to explain all variations in radiodensity.³² The level of CSF proteins has also been positively correlated with the radiodensity of IVH. Moreover, elevated levels of several CSF proteins have been linked with poorer prognosis in aneurysmal SAH patients.^{4,5,9–11,16–18,22,24,26,28,29,33,38,39}

This study had several limitations, including the small sample size and its retrospective nature. Moreover, the proposed method to calculate ventricular density involves manual selection of the ventricular system. This process requires some time with the potential to introduce ambiguities; however, the interobserver and intraobserver coefficients suggest a consistent and reliable protocol. In addition, the choroid plexus was also included in the ROI for the ventricular radiodensity, which may misleadingly elevate ventricular density.

Conclusions

This study suggests that the ventricular radiodensity in aneurysmal SAH patients with IVH, along with GCS score and age, may also serve as a predictor for clinical outcome.

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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: Nguyen. Acquisition of data: Nguyen, Li, Patel. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nguyen. Statistical analysis: Nguyen. Administrative/technical/material support: Nguyen, Kurpad, Mueller. Study supervision: Nguyen, Kurpad, Mueller.

Supplemental Information

Previous Presentations

This paper was presented at the 2016 Cerebrovascular Section Annual Meeting in Los Angeles, California, February 15–16, 2016.

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