Relative Edema Volume Is a Predictor of Outcome in Patients With Hyperacute Spontaneous Intracerebral Hemorrhage

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Background and Purpose—Little is known about the relationship between perihematomal edema in spontaneous intracerebral hemorrhage (ICH) and outcome. The purpose of this study was to determine whether absolute or relative edema volume (edema volume divided by hematoma volume) predicts mortality or functional outcome in patients with hyperacute spontaneous ICH. We hypothesized that increasing baseline relative edema volume is associated with greater probability of poor functional outcome.

Methods—This was a secondary analysis of a prospective, population-based study of hematoma growth in 142 patients with spontaneous ICH. Patients were imaged within 3 hours of onset, then 1 and 20 hours later. Our primary analysis excluded patients with anticoagulant use (n=7), underlying aneurysm/vascular malformation (n=9), trauma (n=1), incomplete data (n=20), infratentorial ICH (n=17), intraventricular extension (n=38), and no consent (n=2). We analyzed whether associations existed between baseline edema volumes or other clinical/radiological variables and either 12-week modified Rankin Scale score ≥2 or 30-day mortality. Secondary analyses used 20-hour CT scan data, all patients with supratentorial ICH, and 12-week Barthel Index score <85.

Results—By multivariable logistic regression analysis, baseline relative edema was the strongest independent predictor of functional outcome and was associated with lesser odds of poor 3-month functional outcome (odds ratio, 0.09 per 1.0-unit [100%] increase; 95% CI, 0.01 to 0.64; P=0.016) and 12-week Barthel Index score <85 (odds ratio, 0.12; 95% CI, 0.02 to 0.91; P=0.039) but did not predict mortality. Secondary analyses confirmed this result. Absolute edema volume predicted neither mortality nor functional outcome.

Conclusions—Relative edema is strongly predictive of functional outcome in patients with hyperacute supratentorial spontaneous ICH without intraventricular extension. (Stroke. 2002;33:2636-2641.)

Key Words: computed tomography ⊕ intracerebral hemorrhage ⊕ mortality

Perihematomal edema is present in most patients with spontaneous intracerebral hemorrhage (SICH) (not related to thrombolysis or anticoagulants), even when imaged within 3 hours of onset.1 Significant, delayed edema growth can occur days to weeks after SICH and may be associated with increased mass effect and clinical neurological deterioration.2 There is minimal information, however, on the early natural history of edema in hyperacute SICH and regarding whether edema in this time frame predicts mortality or functional outcome. We recently reported that absolute perihematomal edema volume doubles, on average, during the first 24 hours after intracerebral hemorrhage (ICH) in patients with SICH imaged within 3 hours of onset.3 We also reported that absolute edema volume was not independently associated with 30-day mortality in the 103 patients studied, largely because absolute edema volume was strongly correlated with hematoma volume, which, by contrast, strongly and independently predicted 30-day mortality.3

In this study we sought to define a priori a patient group in whom to most ideally study the relationship between absolute and relative edema volume and outcome. This “primary analysis” patient population (defined below) was chosen with the specific intent of eliminating variables that could confound the formation or measurement of perihematomal edema volume. We hypothesized that, within such a study population, increasing baseline CT scan relative edema volume, which quantifies perihematomal edema in the context of the associated hematoma, would be independently predictive of increased 30-day mortality and poorer 12-week functional outcome.

Subjects and Methods

Study Design

This study was a secondary analysis of data prospectively collected during a previously published 142-patient study of the natural history of hematoma growth in patients with SICH first imaged within 3

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hours of clinical onset. The patient population of this study has been described in detail elsewhere. All patients presented to emergency departments in the study area and were imaged by noncontrast brain CT within 3 hours of ICH onset. Most patients underwent a second brain CT scan 1 hour later, and many underwent a third CT scan 20 hours after the baseline scan.

Data Collection
Relevant demographic, clinical, laboratory, and functional outcome data were prospectively collected during the original study. Relative edema volume was calculated several years later when another study comparing hyperacutely imaged thrombolysis/anticoagulant-related ICH with hyperacutely imaged SICH was performed. All data were collected before the present study was conceived and implemented. Patients were classified as hypertensive or diabetic only if they had a known history of these disorders and not on the basis of actual blood pressure or glucose levels, the data for which were analyzed separately.

Creation of Primary Analysis Group
We first created a primary analysis patient group consisting of patients with few conceivable variables that might confound the genesis or measurement of perihematomal edema. From the original population of 142 patients, we first excluded those patients with anticoagulant use (n=7), underlying aneurysm or vascular malformation (n=9), head trauma (n=1), incomplete clinical or CT data (n=20), or no consent (n=2). This left a group of 103 patients with true SICH and adequate data, from which we further excluded those with infratentorial ICH (n=17) because of concern about petrous apex streak artifact obscuring edema borders and preventing accurate edema volume measurement. Finally, we excluded patients with initial or subsequent intraventricular extension (n=38) because of concerns about admixture of cerebrospinal fluid and edema confounding edema evolution and measurement. We included patients subsequently undergoing surgery or having hematoma growth because these represented relatively common events in the overall population, and we wished to maximize the generalizability of our results to clinical practice.

Study Hypothesis
Our primary hypothesis was that, within this 48-patient primary analysis population, increasing amounts of relative edema volume would be associated with an increased probability of poor 12-week functional outcome (modified Rankin Scale [MRS] score ≥3). We assumed that hematomas with relatively greater amounts of perihematomal edema would exert more mass effect and/or induce greater local tissue injury, thereby worsening outcome. Patients who died (regardless of cause) were assigned a MRS score of 6 and were included in this poor outcome group. All other patients with MRS score ≥2 were considered to have a good functional outcome.

Primary Analysis
The primary outcome variable was a 12-week MRS score of ≥3 (poor functional outcome). Baseline CT scan relative edema and other relevant clinical and radiological variables were first analyzed for their univariate association with the primary dependent outcome variable. Variables found to have a statistically significant association with poor functional outcome were then entered into multivariable logistic regression models to determine whether such associations would remain significant when we controlled for other variables.

Subsequent (Secondary) Analyses
All secondary analyses were implemented after the primary analysis to verify its results. First, absolute edema volume was used as the independent variable of interest instead of relative edema volume for the outcome of 12-week MRS. We then analyzed the association between baseline relative edema volume and outcomes using the 12-week Barthel Index (BI), the only other 12-week functional outcome assessment collected (once again a priori dichotomized as ≥85 [‘good’ outcome] versus ≤80 [‘bad’ outcome]), and 30-day mortality. These 2 additional analyses were not repeated for absolute edema volume. Patients who died were assigned BI scores of zero and included in the poor outcome group. Subsequent secondary analyses (relative edema volume only) used the entire supratentorial ICH patient population (n=86) and those with intraventricular extension (n=38) and analyzed 20-hour CT scan relative edema volume and radiological data instead of baseline CT scan values.

Finally, we repeated the primary analysis excluding 1 patient with a possible outlier relative edema volume value of 4.13 to ensure that this value was not the basis of any of the results.

Definition and Measurement of Relative Perihematomal Edema Volume
Relative edema volume was defined as absolute edema volume divided by hematoma volume, yielding a unitless ratio variable. Absolute edema volume was measured by a previously published computer-assisted volumetric measurement technique. Specifically, each brain CT image was scanned and preprocessed to standardize brightness levels of brain tissue and hematoma between images. For each image, K-means histogram-based clustering was used to determine standardized brightness (attenuation) values for background (noise) level, brain tissue level, and skull level. The skull was then extracted. The study neuroradiologist (T.A.T.) marked the center of each hematoma, defining the center of the region of interest for subsequent hematoma and edema volume measurement. The same K-means clustering algorithm was used to divide the region of interest into foreground (hematoma) and background (perihematomal edema and brain parenchyma).

On the basis of the algorithm-generated threshold value to differentiate hematoma from edema, the number of contiguous 3-dimensional voxels within the foreground (hematoma) is summed to yield hematoma volume. Analogously, perihematomal edema measurement is accomplished by “growing” thin layers (rings) sequentially outward from the edge of the hematoma. Each such ring of pixels is examined with the use of several computer-generated K-means clustering algorithm-based threshold values for edema, the most optimal of which is selected by the operator. For each layer, the number of pixels falling within the selected range of pixel attenuation is summed and added to the previous layer’s number of edema pixels. This iterative process is continued until no new pixels are selected in the current (final) layer. The sum total of pixels is the absolute edema volume.

The reproducibility and accuracy of this method were verified by its correlation with conventional volumetric measurement of hematoma and edema volumes, with an overall Spearman correlation coefficient of 0.9744. When very small, unmeasurable amounts of edema were present, values of zero were assigned for both absolute and relative edema volume. An example of 2 patients with different amounts of relative edema volume is shown in the Figure.

Statistical Methods
We used SAS software (SAS Institute) for data management and analysis. Baseline demographic and risk factor variables are descriptively summarized as mean (SD) for continuous variables and as percentages for categorical variables. Hematoma volumes, edema volumes, and other non-normally distributed variables were summarized as median and range. Correlations between relative edema volume and other continuous variables were performed with the use of the Spearman correlation coefficient. Multiple logistic regression was used to analyze the relationship of candidate predictor variables, including relative edema volume, to categorical functional outcome. Sample size constraints limited analyses to 3 variables per multiple logistic regression analysis. Effect values are summarized as odds ratios per 1.0 unit of each respective independent variable with 95% CIs. Probability values ≤0.05 were considered statistically significant.
Example of 2 patients with different relative perihematomal edema volumes. Patient on the left has a relative perihematomal edema volume of 0.10 compared with a relative perihematomal edema volume of 1.30 for patient on the right.

Results

Baseline Data

Selected baseline demographic, risk factor, and laboratory data for the primary study population are shown in Table 1. No significant differences existed between these values for the primary analysis group and the entire supratentorial SICH population. Median baseline CT scan hematoma volume for the primary patient population was 12.2 cm³ (range, 0.4 to 124.5 cm³); 75% of the hematomas were in deep anatomic locations, whereas 25% were lobar. Seventy percent of hematomas exerted at least some mass effect (ventricular and/or cisternal effacement), and 37% were associated with measurable horizontal midline shift at the level of the pineal gland. Median absolute edema volume was 7.4 cm³, with a range of 0 to 94.7 cm³. Median relative edema volume was 0.524 (52.4%), with a range of 0 to 4.13.

Primary Analysis

Our initial bivariate analysis assessed clinical and radiological variables for their association with an increased probability of poor functional outcome. Notably, of major clinical variables, only time from ICH symptom onset to baseline CT scan was associated with an increased probability of poor 12-week functional outcome (2-tailed \( P = 0.050 \), Wilcoxon rank sum test). Neither baseline Glasgow Coma Scale (GCS) score (\( P = 0.145 \)), nor age (\( P = 0.186 \), 2-tailed \( t \) test) was significantly associated with 12-week functional outcome. By contrast, of major radiological variables, hematoma volume (odds ratio, 1.6 per cm³; 95% CI, 1.1 to 2.3; \( P = 0.015 \)), presence of mass effect (\( P = 0.024 \), Fisher exact test), and presence of midline shift (\( P = 0.0114 \), Fisher exact test) were significantly associated with an increased probability of poor 12-week functional outcome, whereas anatomic location (deep versus lobar) was not.

Absolute edema volume was not associated with 12-week functional outcome (\( P = 0.820 \), Wilcoxon rank sum test). By contrast, relative edema volume was significantly associated with 12-week functional outcome. However, the nature of this association was inverse, with an odds ratio of 0.89 per 1.0-unit (100%) increase (95% CI, 0.12 to 6.4; \( P = 0.016 \)).

Thus, increasing amounts of relative edema volume were associated with a decreased probability of poor 12-week functional outcome (MRS >2), a result diametrically opposite to our a priori hypothesis. Neither baseline absolute edema volume nor relative edema volume (odds ratio, 0.68; \( P = 0.677 \)) was significantly associated with 30-day mortality. Finally, no significant association between baseline absolute or relative edema volume and subsequent hematoma growth was observed.

When relative edema volume was entered into multiple logistic regression models with 1 other dependent variable to control for the effects of other previously reported ICH outcome predictor variables (Table 2), the observed association between relative edema volume and good functional outcome remained significant. However, the associations observed between other clinical and radiological variables and 12-week functional outcome became nonsignificant, except for hematoma volume and mass effect, whose associations with 12-week functional outcome remained marginally statistically significant (Table 2). An insufficient number of observations were available for a valid logistic regression model incorporating midline (horizontal pineal) shift. Two additional analyses were performed. The first incorporated relative edema volume, baseline GCS score, and baseline hematoma volume. In this analysis, the observed association between relative edema volume and lesser probability of poor functional outcome once again remained significant (\( P = 0.014 \); odds ratio, 0.035; 95% CI, 0.002 to 0.51), whereas no significant association persisted between hematoma volume (\( P = 0.0984 \); odds ratio, 1.15 per 1 cm³ volume; 95% CI, 0.98 to 1.35) or GCS score (\( P = 0.241 \); odds ratio, 0.60; 95% CI, 0.25 to 1.41) and functional outcome. Similar results were observed in a second 3-variable multiple logistic regression model incorporating hematoma volume, mass effect, and relative edema volume.

Secondary Analyses

When categorical 12-week BI score (see above) was used as the dependent outcome variable in the primary analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage or Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS score</td>
<td>12.8 (2.52)</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.4 (11.6)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>66.7%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.3%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.8%</td>
</tr>
<tr>
<td>Arterial blood pressure, mm Hg</td>
<td>125.1 (17.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>174.0 (25.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>100.8 (16.9)</td>
</tr>
<tr>
<td>Blood glucose level, mg/dL</td>
<td>130 (56)</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>12.1 (0.80)</td>
</tr>
<tr>
<td>Partial thromboplastin time, s</td>
<td>25.2 (2.5)</td>
</tr>
<tr>
<td>Fibrinogen level, mg/dL</td>
<td>325 (84)</td>
</tr>
<tr>
<td>Platelet count, ( \times 10^9/\mu L )</td>
<td>273 (80)</td>
</tr>
</tbody>
</table>

Categorical variables are reported as percent prevalence. Continuous variables are reported as mean (SD).
group, the association between baseline relative edema volume and decreased probability of poor functional outcome was statistically significant by both bivariate analysis ($P=0.0314$) and multivariable analysis (multiple logistic regression, controlling for hematoma volume, $P=0.039$; odds ratio, 0.12 per 1.0 unit; 95% CI, 0.016 to 0.91). Similarly, when relative edema volume values recorded 20 hours after baseline CT scan were substituted for baseline relative edema volume values in the primary analysis population, the observed association between (20-hour) relative edema volume and decreased probability of poor functional outcome was again, no significant differences were observed.

Finally, we analyzed whether relative edema volume was independently predictive of outcome in only those patients with intraventricular extension of their hematomas. Of these 38 patients, 37 had poor functional outcomes or death at 12 weeks. Thus, in this subgroup we could not assess whether other variables (including relative and absolute edema volume) were independently predictive of functional outcome in multivariable logistic regression analyses, since intraventricular extension was almost perfectly predictive of poor outcome.

## Discussion

This study first newly identifies relative edema as the most statistically significant independent predictor of (improved) 12-week functional outcome in patients with hyperacute SICH without intraventricular extension. The observed association between relative edema volume and functional outcome remained statistically and clinically significant regardless of which 12-week functional outcome scale was chosen as the dependent outcome variable, with maximum likelihood point estimate odds ratios for poor 12-week functional outcome ranging from 0.055 to 0.094. Translated into clinically meaningful terms, a patient has an 11- to 18-fold better odds of surviving and making a good long-term functional recovery for each 1.0-unit (100%) increase in hyperacute to acute relative edema volume, when one controls for other common previously reported predictors of outcome in ICH, such as hematoma volume, GCS score, hematoma location, age, mass...
effect, hydrocephalus, and time from ICH onset to CT scan (Table 2). Furthermore, when 20-hour postbaseline CT scan relative edema volume values were substituted for baseline values (which excluded patients dying or undergoing surgery after their 1-hour postbaseline CT scan), the association remained highly significant, with a maximum likelihood point estimate odds ratio of 0.02 (50-fold greater odds of good functional outcome) when we controlled for hematoma volume. Whether perihematomal edema formation beyond 24 hours after ICH bears an association (positive or negative) with functional outcome cannot be ascertained by our data.

In addition to being a strong predictor of functional outcome, relative edema volume appears to predict such outcome in a manner entirely distinct from that of other common predictors of outcome such as hematoma volume, GCS score, age, mass effect, and hydrocephalus.5–17 This is manifest by the retention of statistically significant associations of relative edema volume with functional outcome in the respective multivariable models, when one controls for these other variables. Notably, all these other variables lost or nearly lost their statistically significant associations with functional outcome in these models. GCS score did not independently predict functional outcome in any of our analyses. We did, however, previously report its association with 30-day mortality in the total patient population in our original hematoma growth study report.5 This surprising result may be explained by the fact that intraventricular extension was nearly uniformly predictive of poor functional outcome in our hyperacute patient population and by the strong correlation between GCS score and intraventricular extension.

Interestingly, neither absolute nor relative edema volume predicted 30-day mortality despite relative edema volume being the strongest and most consistent predictor of 12-week functional outcome in multivariable analyses. Conversely, many variables strongly predictive of mortality in our original study did not predict functional outcome when entered into these multivariable models. We interpret this loss or reduction of statistically significant association with functional outcome of these variables (hematoma volume, mass effect, and time from ICH symptom onset to baseline CT) to indicate that they predict functional outcome in a similar (highly correlated) manner rather than that they do not predict functional outcome. This suggests a common underlying construct between most previously reported variables predictive of SICH, such as increased intracranial pressure and/or herniation due to mass effect–related displacement of brain tissue surrounding the hematoma. While such anatomic factors may be the most important determinants of death, their relative inability to differentiate those survivors who ultimately will versus those who will not achieve meaningful functional recovery suggests that alternative, physiological variables may more accurately predict functional outcome. Relative edema volume appears to be one such variable. The recent reports of Castillo and colleagues18 analyzing the relationships between excitotoxic and inflammatory cytokine substances and outcome and the recent report of Becker and colleagues19 establishing a relationship between contrast extravasation on CT angiography and increased hematoma volume and poor outcome represent other noteworthy recent examples.

We considered a number of biologically plausible explanations for the seemingly paradoxical association between increasing relative edema volume and increased probability of a good functional outcome. One explanation was that decreased relative edema volume resulted from an actively bleeding and expanding hematoma obliterating the rim of perihematomal edema, which might otherwise be more readily visible. However, we observed no association between relative edema volume and subsequent hematoma growth. We also excluded the possibilities of any association between relative edema volume and hematoma location or volume as the explanation of our observations. Similarly, we controlled for treatment effects due to osmotic diuretic use with no change in our results. Finally, we excluded outlier relative edema volume values as another possible explanation for our findings. Given our prior observations that hyperacute thrombolysis/anticoagulant-related ICH lacks perihematomal edema compared with hyperacute SICH, hyperacute edema may reflect successful hematoma clotting. This would be a biologically plausible explanation for the paradoxical association between very early perihematomal edema and improved functional outcome. Our a priori hypothesis was based on the assumption that perihematomal edema is injurious. While such injury has been reported with delayed perihematomal edema, our results strongly suggest that such delayed edema is biochemically and physiologically distinct from hyperacute perihematomal edema. A comparable systematic study of perihematomal edema evolution in this more delayed time frame is needed.

As we noted, intraventricular extension was a nearly perfect predictor of poor functional outcome when present. Thus, we could not determine whether other variables independently predict functional outcome in patients with intraventricular extension or whether intraventricular extension confounded measurement of perihematomal edema or its ability to independently predict functional outcome. While not the focus of this report, the fact that only 1 of 38 patients with intraventricular extension had a good 12-week functional outcome indicates that intraventricular extension in a supratentorial SICH patient who presents to the emergency department within 3 hours of symptom onset virtually ensures death or a poor long-term functional outcome. We observed a significant association between increasing relative edema volume and improved functional outcome in the entire supratentorial patient population. However, we do not conclude that relative edema is a significant independent predictor of functional outcome for all such patients given that the observed association in the overall population can be statistically explained by the association in the subgroup without intraventricular extension (primary analysis) and given our aforementioned findings in the patients with intraventricular extension.

This study has a number of acknowledged and largely unavoidable limitations. First, we were restricted to available previously collected data. Because we were limited to radiological data collected in a 24-hour period, our results are not applicable to more delayed perihematomal edema formation.
We also could not systematically identify or control for differences in individual patient management by the various treating physicians in the study. Thus, the extent to which such variation or withdrawal-of-care decisions by patients’ families influenced outcome or the relationship between relative edema volume and functional outcome is unknown.

The possibility of any bias in the measurements of perihematoma edema volumes with regard to knowledge of the study hypothesis is minimal because all such measurements (and all other data) were performed before this study was conceived. Similarly, our good and bad functional outcome definitions and primary analysis were defined before any data analysis and cutoff values were chosen on the basis of their common use in clinical trials of stroke treatment. We acknowledge, however, that the MRS cutoff value of 0 to 2 to represent good outcome rather than 0 to 1 was chosen because we anticipated that the number of excellent or complete functional recoveries in any SICH population would be low. We believe that our analyses that substituted categorical BI from our study, such patients may be encountered more frequently in clinical practice, which may limit the generalizability of our results in this context.

Since this was a study of perihematoma edema and its relationship to outcome in patients with SICH (not related to thrombolysis or anticoagulants), its results are not applicable to patients with underlying structural lesions, anticoagulant-related ICH, or traumatic ICH. Although these types of patients represented a minority of patients that were excluded from our study, such patients may be encountered more frequently in clinical practice, which may limit the generalizability of our results in this context.

Finally, another important potential source of bias or error is the perihematoma edema measurement technique itself. Although the method used was semiautomated and hypothetically more objective and accurate than conventional planimetric edema volume measurement, subjective input on the part of the study neuroradiologist is still required, specifically in selecting the most appropriate of the computer-generated threshold values differentiating perihematoma edema from adjacent brain tissue. The results of this study must be interpreted within this context. Furthermore, this technique is not widely available, and its bedside utility has not been established.

In conclusion, we report that in patients with supratentorial SICH without intraventricular extension presenting within 3 hours of onset, relative edema volume during the first 24 hours after ICH is the strongest independent predictor of (paradoxically improved) 12-week functional outcome. Independent confirmation of our results is needed, as are efforts to establish the bedside utility of relative edema volume as an outcome measure. Further research is needed to examine the relationship between more delayed edema and outcome in a comparably systematic manner and to better understand the biochemical and physiological bases of brain injury associated with human ICH.

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