Density and Shape as CT Predictors of Intracerebral Hemorrhage Growth

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Background and Purpose—Intracerebral hemorrhage (ICH) growth predicts mortality and functional outcome. We hypothesized that irregular hematoma shape and density heterogeneity, reflecting active, multifocal bleeding or a variable bleeding time course, would predict ICH growth.

Methods—Three raters examined baseline sub-3-hour CT brain scans of 90 patients in the placebo arm of a Phase IIb trial of recombinant activated Factor VII in ICH. Each rater, blinded to growth data, independently applied novel 5-point categorical scales of density and shape to randomly presented baseline CT images of ICH. Density and shape were defined as either homogeneous/regular (Category 1 to 2) or heterogeneous/irregular (Category 3 to 5). Within- and between-rater reliability was determined for these scales. Growth was assessed as a continuous variable and using 3 binary definitions: (1) any ICH growth; (2) ≥33% or ≥12.5 mL ICH growth; and (3) radial growth >1 mm between baseline and 24-hour CT scan. Patients were divided into tertiles of baseline ICH volume: “small” (0 to 10 mL), “medium” (10 to 25 mL), and “large” (25 to 106 mL).

Results—Inter- and intrarater agreements for the novel scales exceeded 85% (±1 category). Median growth was significantly higher in the large-volume group compared with the small group (P<0.001) and in heterogeneous compared with homogeneous ICH (P=0.008). Median growth trended higher in irregular ICHs compared with regular ICHs (P=0.084). Small ICHs were more regularly shaped (43%) than medium (17%) and large (3%) ICHs (P<0.001). Small ICHs were more homogeneous (73%) compared with medium (37%) and large (17%) ICHs (P<0.001). Adjusting for baseline ICH volume and time to scan, density heterogeneity, but not shape irregularity, independently predicted ICH growth (P=0.046) on a continuous growth scale.

Conclusions—Large ICHs were significantly more irregular in shape, heterogeneous in density, and had greater growth. Density heterogeneity independently predicted ICH growth using some definitions. (Stroke. 2009;40:1325-1331.)

Key Words: density ■ growth ■ intracerebral hemorrhage ■ recombinant activated factor VII ■ predictors ■ shape

Intracerebral hemorrhage (ICH) is the most sinister stroke subtype with a high early mortality.1,2 Despite this, there is convincing evidence that aggressive care can bring about meaningful recovery, even in the worst initial prognostic groups.3,4 CT scanning remains the standard diagnostic technique for ICH. Hematoma growth occurs in >70% of patients on CT performed within 3 hours of symptom onset and independently predicts mortality and functional outcome.5 Hemostatic therapy has been demonstrated to attenuate ICH growth in 2 pivotal studies of recombinant activated Factor VII administered within 4 hours of symptom onset.6,7 In contrast, the clinical outcomes in these trials were discordant and the positive results were not replicated in the second, larger trial.6,7 Attenuated hematoma growth has also been suggested in an acute blood pressure reduction trial.8 Hence, hematoma growth is a key therapeutic target in ICH therapy. The identification of techniques to predict ICH expansion has been expressed as a research priority by the National Institute of Neurological Disorders and Stroke9 and the European Stroke Workshop.10

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Larger baseline ICH volume and earlier time to scan predict subsequent ICH expansion.\textsuperscript{11,12} The recently reported CT angiographic “spot sign”\textsuperscript{11–15} is an important predictor of ICH growth and is being prospectively verified.\textsuperscript{16} Other imaging predictors of poor outcome include early ICH expansion,\textsuperscript{17} intraventricular extension,\textsuperscript{18,19} midline shift,\textsuperscript{20,21} and hydrocephalus.\textsuperscript{22} Rating systems have been used that incorporate clinical and radiological features of ICH into a variety of prognostic scores.\textsuperscript{23,24}

In addition to volume and location, appearances of ICH on CT vary widely. Two major imaging characteristics that have received little attention are lesion shape (irregular versus regular) and clot density variation (homogeneous versus heterogeneous). Conceptually, a hematoma arising from a solitary focus will tend to present a more regular expanding lesion edge, growing from one epicenter, with more homogeneous density of blood. A hemorrhage arising from multiple foci is more likely to present an irregular lesion edge at its expanding interface with the brain. A heterogeneous CT density might reflect active hemorrhage, more variable hemorrhagic time course, and multifocality. Heterogeneous bleeds are potentially fed by multiple bleeding vessels resulting in patches of hypoattenuating liquid blood from very recent bleeding alongside hyperattenuating thrombus. We therefore hypothesized that irregular shape and density heterogeneity on baseline CT ICH appearance would predict ICH growth. To measure these characteristics, we created 2 novel categorical scales aimed at developing a simple imaging-based prognostic instrument. We evaluated this hypothesis on the placebo data set from the proof-of-concept trial of recombinant activated Factor VII.\textsuperscript{6}

**Methods**

The data set comprised the baseline CT brain scans of the placebo group of the randomized, double-blind, placebo-controlled Phase IIb trial of recombinant activated Factor VII for ICH, reported previously, in which CT scans were obtained within 3 hours of ictus.\textsuperscript{6} Of the 96 patients in this group, 90 baseline CT scans were transferred for analysis from Bioimaging Technologies, Newtown, Pa. Six patients’ scans could not be analyzed at our center because of file compatibility reasons. Baseline volume, volume change at 24 hours, and time-to-scan data did not vary significantly from the complete data set. Baseline volume and volume change at 24 hours for each included patient were derived from the previously published data set using the planimetric ICH volume calculations of one neuroradiologist.\textsuperscript{25} Volume data were not recalculated for this study. Intraventricular blood, when present, was not included in the volume calculations. The dependent variable, ICH growth between baseline and 24-hour CT scan, was prespecified to be examined continuously and using 3 binary growth definitions: (1) any ICH growth; (2) \( \geq 33\% \) or \( \geq 12.5 \text{ mL} \) ICH growth; and (3) radial growth \( > 1 \text{ mm} \) (the median radial expansion for the data set).

Blinded to growth and clinical data, 2 novel 5-point categorical scales were created, reflecting the spectrum of appearance of ICH shape and Hounsfield unit density variation (Figure 1A), to provide an agreed visual representation of the terms “regular/irregular” and “homogeneous/heterogeneous.” The 2 scales ranged from Category 1 (most regular shape and most homogeneous density) to Category 5 (most irregular shape and most heterogeneous density). Each progressive category added an extra lesion edge irregularity on the shape scale or degree of density variation on the density scale. In cases of “satellite” bleed(s), progressive irregularity and heterogeneity features could be joined or separate from the principal hemorrhage. If a hematoma had more numerous lesion edge irregularities or more heterogeneous density than represented on the scale, they were assigned a Category 5 (maximum) rating. Intraventricular blood, when present, was not included in these ratings.

Three raters independently reviewed the scans: a neuroradiologist (B.T.), a stroke imaging fellow (C.B.), and a brain imaging scientist (S.C.). An initial training session was conducted to facilitate consensus application of the scales using images external to the trial data set. Each observer, blinded to growth and clinical data, then independently applied these 2 scales to randomly presented axial CT scan slices allocating the most representative category. Each rater received the same randomization generated using MATLAB Version 7.4.0 (The MathWorks Inc). In addition, a randomly selected set of 10% of images was represented to the raters to allow within-rater reliability studies. Shape and density scores were analyzed using the largest ICH slice (usually the central axial slice in the vertical dimension) as determined by an automated calculation of slice-by-slice pixel count for each ICH. For this calculation, slice dimensions were those derived from the regions of interest created using Analyze (Mayo Clinic) imaging analysis software by the trial neuroradiologist for planimetric volume calculation.

For descriptive purposes, baseline volumes were divided into tertiles labeled “small” (0 to 10 mL), “medium” (10 to 25 mL), and “large” (25 to 106 mL). Shape Categories 1 and 2 were labeled “regular” and Categories 3 to 5 “irregular.” Density Categories 1 and 2 were labeled “homogeneous” and Categories 3 to 5 “heterogeneous” (Figure 1B).

To enable analysis of any interactions between shape, density, and time and their effect on ICH growth, times to scan were dichotomized into 2 periods, \( \leq 90 \) minutes and \( > 90 \) minutes.

**Statistical Analysis**

Standard tests for normality were applied. Given that many of the outcomes were not consistent with a normal distribution, nonparametric methods were used for 2-group (Mann–Whitney U test) and multiple-group (Kruskal–Wallis test) comparisons citing median
values with interquartile ranges (IQRs). Crosstabulations were analyzed using Fisher exact test. Within- and between-rater reliability tests were analyzed using measures of raw agreement as well as kappa statistics. Growth was examined as a continuous variable in an analysis of covariance using a general linear model, after cube-root transformation of the dependent variable, to fulfill normality assumptions applied to residuals. Binary logistic regression was used to model the relationships between the independent variables (shape category and density category) and 3 binary growth definitions adjusting for known growth predictors, baseline ICH volume, and time to scan. Interactions between shape, density, and time and their effect on growth as a continuous variable were also performed using the general linear model. Analyses were performed using SPSS Version 15.0 software (SPSS Inc, Chicago, Ill) A probability value <0.05 was considered statistically significant.

Results

Between-observer raw agreement across over 750 CT images (approximately 8 axial CT slices per patient) exceeded 85% (±1 category) for both shape and density scales. Average raw within-observer agreement (±1 category) exceeded 90% for both scales. Shape and density category distributions show a predominance of high shape (median score 5) and density (median score 3) ratings (Figure 2A–B). Weighted kappa values (0.61) express “moderate” to “substantial” agree-
Baseline median ICH volume was 14 mL (IQR, 28 mL). Median volume change was 2.5 mL (IQR, 11.5 mL). Median time to baseline scan was 1.75 hours (IQR, 0.63 hours) from ictus.

Median growth was significantly higher in the large baseline volume group (7.39 mL; IQR, 17.8) compared with the small group (1.10 mL; IQR, 2.08; \( P < 0.001 \); Figure 3A). Median growth was higher in the heterogeneous than the homogeneous group (5.07 mL; IQR, 18.01 versus 1.21 mL; IQR 3.77; \( P = 0.008 \); Figure 3B). There was a trend to higher median growth in irregular ICHs (2.69 mL; IQR, 13.14) compared with regular ICHs (1.32 mL; IQR, 4.51; \( P = 0.084 \); Figure 3C). Large ICHs were more irregularly shaped (97%) than medium (83%) and small (57%) ICHs (\( P < 0.001 \); Figure 4A). Similarly, large ICHs were more heterogeneous (83%) compared with medium (63%) and small ICHs (17%; \( P < 0.001 \); Figure 4B).

In multivariate analysis, heterogeneous lesions underwent significantly greater mean growth, with growth defined as a continuous variable, and after adjustment for baseline ICH volume and time to scan (\( P = 0.046 \)). With a binary radial growth definition, heterogeneous bleeds showed a trend toward greater growth (\( P = 0.07 \)). Other binary growth definitions showed no such association. Irregular shape showed no significant independent relationship to growth (\( P = 0.159 \), growth as a continuous variable) regardless of growth model after adjustment for baseline ICH volume and time to scan (Table).

There was a strong relationship between shape irregularity and density heterogeneity. Irregularly shaped ICHs were more likely to be rated as heterogeneous in density (\( P < 0.001 \)). After dichotomizing times to scan into \( \leq 90 \) minutes (n=28) and >90 minutes (n=62) subgroups, there was no significant interaction with either shape or density in their effect on volume change using a continuous scale of growth. The association between density heterogeneity and growth was consistent and significant at both time points. Although the effect of density heterogeneity on growth appeared to diminish with time, there was no significant difference in this effect between the 2 time categories.

**Discussion**

In this novel study, we have explored the prediction of acute ICH growth by the assessment of hematoma shape and density heterogeneity. Irregularly shaped ICHs were more likely to be rated as heterogeneous in density (\( P < 0.001 \)). After dichotomizing times to scan into \( \leq 90 \) minutes (n=28) and >90 minutes (n=62) subgroups, there was no significant interaction with either shape or density in their effect on volume change using a continuous scale of growth. The association between density heterogeneity and growth was consistent and significant at both time points. Although the effect of density heterogeneity on growth appeared to diminish with time, there was no significant difference in this effect between the 2 time categories.

**Figure 3.** Box plots of ICH growth between baseline and 24-hour CT scan depict greater growth in (A) large versus small baseline volume bleeds (\( P < 0.001 \)); (B) heterogeneous versus homogeneous density bleeds (\( P = 0.008 \)); and (C) irregular versus regular shaped bleeds (\( P = 0.084 \)).

**Figure 4.** Proportions (%) of (A) regular/irregular and (B) homogeneous/heterogeneous hemorrhages for each tertile of baseline volume. Between-group differences are statistically significant (\( P < 0.001 \)).
density using new, reliable measurement scales and statistical adjustment for known growth predictors, baseline volume, and time to scan. We have demonstrated that large hematomas are more irregular in shape, more heterogeneous in density, and significantly more likely to expand when considered in isolation. These CT characteristics are consistent features of larger hemorrhages and reflect the natural history of the enlarging ICH. In a multivariate model, adjusting for baseline volume and time to scan, we have shown that density heterogeneity independently predicts ICH growth with growth on a continuous scale.

Of the known ICH growth predictors, baseline volume is easily calculated using the established ABC/2 technique with modification in the anticoagulated. However, precise stroke onset time is frequently unknown, particularly in wake-up strokes. This study suggests that without knowledge of symptom onset time, ICH density heterogeneity, as measured by density Categories 3 to 5 on our novel visual scale, may be the next best known growth predictor from baseline noncontrast CT brain. Although our results indicate that density heterogeneity on acute CT predicts ICH growth, this association was not demonstrated across all growth definitions and requires further validation. Irregular shape was not identified as an independent predictor of ICH growth regardless of the growth model used.

The identification of baseline CT predictors of ICH expansion is an important goal with the potential to aid in selection of patients for future hemostatic therapy, particularly when other data may be limited or unavailable. In recent years, CT angiographic contrast enhancement and contrast extravasation, termed the “spot sign,” have also been shown to predict ICH expansion. These studies were based on poor prognosis associations and require further validation. Irregular shape was not identified as an independent predictor of ICH growth regardless of the growth model used.

In contrast, we used a scale that was validated by testing within- and between-observer agreement, studied patients at relatively homogeneous times after onset of symptoms, and used standardized growth definitions. These scales are the first attempt to visually categorize the spectrum of shape and density variation in ICH morphology. Raw agreement values in excess of 85% (±1 category) for within- and between-rater reliability demonstrated the applicability of the scales. Strengths of our study included the validation of these simple visually based shape and density categorical scales. Moreover, multiple growth definitions have been used exploring growth as a continuous variable and then as a range of binary variables. We added radial growth, which can be conceptualized as the growth of a sphere of equivalent volume to the ICH in question. This measure overcomes some of the descriptive limitations of percentage and absolute growth. For a given radial growth, a small baseline volume ICH will have undergone large percentage but small absolute growth. In contrast, a large baseline volume hematoma undergoing the same extent of radial expansion would have small percentage but large absolute growth. Although shape is independent of size, in this study, limited to the axial plane, no attempt was

<table>
<thead>
<tr>
<th>Growth Definition</th>
<th>Continuous Scale</th>
<th>Any Growth</th>
<th>≥33% or ≥12.5 mL</th>
<th>&gt;1-mm Radial Growth</th>
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<tr>
<td><strong>ICH Characteristic</strong></td>
<td><strong>Density</strong></td>
<td><strong>Heterogeneous</strong></td>
<td>43/52 (82.7)</td>
<td>21/52 (40.4)</td>
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<td><strong>Homogeneous</strong></td>
<td>30/38 (78.9)</td>
<td>11/38 (28.9)</td>
<td>11/38 (28.9)</td>
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<tr>
<td></td>
<td><strong>P value</strong></td>
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<td>0.614</td>
<td>0.273</td>
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<td><strong>Shape</strong></td>
<td><strong>Irregular</strong></td>
<td>60/71 (84.5)</td>
<td>25/71 (35.2)</td>
<td>30/71 (42.3)</td>
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<tr>
<td></td>
<td><strong>Regular</strong></td>
<td>13/19 (68.4)</td>
<td>7/19 (36.8)</td>
<td>8/19 (42.1)</td>
</tr>
<tr>
<td></td>
<td><strong>P value</strong></td>
<td>0.159</td>
<td>0.354</td>
<td>0.796</td>
</tr>
</tbody>
</table>

*P values are from multivariate analysis after adjustment for baseline ICH volume and time to scan.
made to standardize shape sizes so as not to separate the methodological from routine clinical application.

Density of blood on CT in ICH is related to the age of the blood, the time course and number of foci of the hemorrhage as well as to hematocrit.38–41 One early CT study used basic qualitative density assessments of hematomas in various body regions, including some intracranial hematomas, to assess the influence of density variation on bleeding evolution.42 The authors concluded that density reflected the time course of bleeding. Liquid blood from active hemorrhage hypoattenuates on CT scans relative to surrounding brain or associated organized hyperattenuating thrombus.38 As clots retract, hypoattenuating serum is released.43 Later, as thrombi progressively liquefy into breakdown products, sites of hemorrhage are less dense on CT. To a varying extent, hypoattenuating edematous changes in the perihematoma region evolve due at least in part to red blood cell hemolysate products such as thrombin and iron with associated blood–brain barrier disruption.44

The heterogeneous hematoma appearances of some actively bleeding extradural hematomas, first described in the 1960s,45 correspond with operative findings46 and have been termed the “swirl sign.”43,47 In these haemorrhage, a “swirl” of hypoattenuating liquid blood could sometimes be seen to emanate from a bleeding dural vessel. Presumably inspired by this extra-axial finding, this sign was retrospectively examined in ICH as one of many characteristics of an ICH data set with a late median time to scan of 13 hours.15 This “swirl sign” was not found to be independently predictive of hematoma growth or mortality.15 In our 90 patient sub-3-hour data set, we found that density heterogeneity independently predicted ICH growth on a continuous scale. Heterogeneous ICHs are also significantly more likely to be large and irregularly shaped (P<0.001), Large and irregularly shaped hematomas probably reflect multifocal bleeding in many cases. Large hematomas are also more likely to exhibit the contrast enhancement and extravasation phenomena by other investigators.13,14

Our finding that median growth was significantly greater in lesions of heterogeneous density supports current hypotheses regarding the pathophysiology of ICH growth. In particular, our findings are consistent with the CT angiographic “spot sign” that independently predicts ICH growth and that showed significantly greater growth in ICHs with multifocal contrast enhancement.13 Multifocal bleeding, occasionally visualized as separate “satellite” hemorhages and potentially as prominent bulges at the edge of a hemorrhage may rapidly evolve from secondary bleeding in congested, progressively edematous, hypoperfused, perilesional tissue.58–51 “Satellite” hemorhages were accommodated in our shape scale and were deemed to represent another hemorrhagic focus on the density scale. Hence, hematoma growth might be predicted by an irregular hemorrhage shape or lesional density heterogeneity, indicative of an active and progressively multifocal bleeding process.

This study has several limitations. The sample size of 90 patients is small, although this data set is homogeneous with regard to time to scan and study protocol. Our findings cannot be extrapolated to ICH patient populations scanned beyond 3 hours. Analyses were limited to the axial plane. The shape and density scales created, although inspired by the spectrum of variation in ICH morphology, are arbitrary, and our conclusions are restricted to the definitions we used. The fact that at least 50% of patients received the maximal (Category V) shape rating suggests that the shape scale may benefit from adjustment to reflect a wider range of irregularity, and this may provide a different result.

In conclusion, this study has demonstrated that irregular shape and density heterogeneity may be considered part of the natural history or “signatures” of the expanding ICH. Two novel categorical scales have been developed and reliably applied to a high-quality CT data set acquired within 3 hours of ICH onset. Irregular shape was not identified as an independent ICH growth predictor. However, density heterogeneity, according to some growth definitions, was independently predictive of ICH growth beyond known determinants and awaits further validation in larger sub-3-hour CT data sets and specific examination of its relationship to the “spot sign”, functional status and mortality.

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References


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