Significance of Hematoma Shape and Density in Intracerebral Hemorrhage

The Intensive Blood Pressure Reduction in Acute Intracerebral Hemorrhage Trial Study

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Background and Purpose—In patients with acute intracerebral hemorrhage (ICH), the shape and density of the hematoma are associated with its subsequent growth, but the impact of these parameters on clinical outcome is uncertain.

Methods—Baseline computed tomographic scans and clinical data were obtained in the Intensive Blood Pressure Reduction in Acute Intracerebral Hemorrhage Trial (INTERACT2). Three independent neurologists blind to clinical data assessed ICH for shape and density using a previously described scale. Shape was defined as irregular when the ICH had ≥2 extra lesions added to the ellipsoid-shaped ICH. Density was heterogeneous when there were ≥3 low-density lesions within the ICH. Outcome measures were death and major disability (modified Rankin scale score of 3–5), combined and separate at 90-day postrandomization. Multivariable logistic regression models were used to determine the significance of hematoma characteristics on outcome.

Results—There were 2066 patient computed tomographic scans included in the analysis, with 46% and 38% having irregular and heterogeneous ICH, respectively. Irregular shape was independently associated with death/major disability (adjusted odds ratio, 1.60; 95% confidence interval [CI], 1.29–1.98) and major disability alone (adjusted odds ratio, 1.60; 95% CI, 1.31–1.95), but not with death alone (adjusted odds ratio, 0.97; 95% CI, 0.68–1.39). Heterogeneous density was not associated with clinical outcomes (adjusted odds ratio, 1.06; 95% CI, 0.85–1.33), 1.04 (95% CI, 0.73–1.48), and 1.14 (95% CI, 0.93–1.39), respectively, for death/major disability, death alone, and disability alone).

Conclusions—Irregular shape, but not heterogeneous density, is independently associated with poor outcome after ICH.

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In patients with acute intracerebral hemorrhage (ICH), the volume of hematoma adjusted for the time from the onset of symptoms is a well-recognized predictor of hematoma growth and is a strong predictor of clinical outcome.[1] Other hematoma characteristics, such as shape and density, have also been recently highlighted as outcome predictors: degree of shape irregularity seems related to hematoma growth[2,3]; and density, described as homogeneous or heterogenous,[4] or as a blend sign,[5] has additionally been shown to be associated with hematoma growth.[6] To date, however, only 1 group has shown a relationship between irregular shape and 30-day mortality in a retrospective study of 106 patients.[7] Therefore, the relevance of these other hematoma parameters to clinical outcome remains uncertain. Using the large

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and well-characterized data set offered by the main Intensive Blood Pressure Reduction in Acute Intracerebral Hemorrhage Trial (INTERACT2) study, we assessed the association of hematoma shape (irregularity) and density (heterogeneity) on clinical outcomes at 90 days.

Methods

Patients

INTERACT2 was an international, multicenter, open, blinded end point, randomized controlled trial, as described in detail elsewhere.[8] Patients with spontaneous ICH within 6 hours of onset and elevated systolic blood pressure (150–220 mm Hg) were allocated to intensive (target systolic blood pressure<140 mm Hg within 1 hour and maintained for 7 days) or contemporaneous guideline-recommended (<180 mm Hg) blood pressure–lowering treatment. Patients were followed up for 90 days, and outcomes of separate and combined death and major disability were assessed by blinded observers according to the modified Rankin scale (mRS).

Procedures

Demographic and clinical characteristics were recorded at the time of enrollment. Computed tomographic (CT) images were analyzed centrally by 3 neurologists (C.D., S.S., and S.Z.), blinded to clinical data, using the MIStar software version 3.2 (Apollo Medical Imaging Technology, Melbourne, Australia).

Irregularity of shape and heterogeneity in density were assessed by visual inspection and rated using the scale of Barras et al[4] on the axial slice, showing the largest area of hematoma. The density and shape scale ranges from 1 (most regular shape or most homogeneous density) to 5 (most irregular shape or most heterogeneous density). Each progressive category is defined by an extra lesion edge irregularity on the shape scale, or a degree of density variation on the density scale. Shape or density was defined as irregular or heterogeneous when the total rating was 3, 4, or 5 on the visual scale, and regular or homogenous when the rating was 1 or 2 (Figure I in the online-only Data Supplement). Hematoma volume, location, and other imaging characteristics that might be associated with outcome were not remeasured in this study but derived from the previously published data set.[8,9] For descriptive purposes, baseline volumes were divided into 3 groups labeled as small (0–10 mL), medium (10–25 mL), or large (>25 mL). Hematoma location was categorized as lobar, deep (caudate nucleus, thalamus, and putamen), cerebellar, or brain stem.

The primary outcome was similar to that of the main study: the proportion of patients with poor outcome, defined as death or major disability (mRS score of 3–5) at 90 days after randomization. Secondary outcomes were death and major disability considered separately.

Statistical Analysis

Baseline characteristics were summarized as mean (SD) or median (interquartile range) for continuous variables, and as number (%) for categorical variables. Two neurologists (S.S. and S.Z.) independently analyzed 50% of the scans each, and an independent neurologist (C.D.) checked 20% of the scans for assessment of intraclass correlation coefficients for the Barras scale. Binary logistic regression was used to evaluate the association of hematoma shape and density on death/major disability, death, and major disability, with adjustment for age, China region, systolic blood pressure, National Institutes of Health stroke scale (NIHSS) score, prior use of antithrombotics, time from onset to CT scan, location and volume of hematoma at baseline, intraventricular extension of the ICH, randomized treatment, and decision to withdraw active treatment. Associations between shape and density and a shift of scores across all levels of the mRS were also calculated using ordinal logistic regression models as a sensitivity analysis. A standard level of significance (P<0.05) was used, and the data are reported as odds ratios (ORs) and 95% confidence intervals (CIs). Analyses were performed using SAS software (version 9.3).

Results

A total of 2066 subjects were included in the present analysis after excluding 732 patients without suitable brain CT scan images (not available in a format compatible with MiStar, magnetic resonance imaging or poor quality imaging) to allow adequate assessment of hematoma shape and density (n=701) or without mRS scoring at 90 days (n=31). Included patients were as a group, more severe than excluded patients on the Glasgow coma scale (median 14, interquartile range 13–15 versus 14, 12–15; P=0.002), and more likely to have deep (83% versus 59%) and small hematomas (median volume: 10.7 mL, interquartile range: 5.6–18.7 versus 11.9, 6.3–23.6; P=0.001; Table I in the online-only Data Supplement).

Baseline Characteristics

The baseline characteristics of the group are shown in Table 1. In summary, 946 (45.8%) patients had irregular hematomas and 781 (37.8%) had heterogeneous hematomas. In terms of inter-rater reliability for the Barras scale, the intraclass correlation coefficient for shape was good (0.71; 95% CI, 0.67–0.74) and for density was fair (0.57; 95% CI, 0.52–0.61), respectively.

When compared with those with regular hematomas, patients with irregular hematomas, were older, less likely to be in China, had a more severe neurological status, were less likely to be on antihypertensive drugs, had larger hematomas, were more likely to have a lobar hematoma, and less likely to have an infratentorial hematoma. Patients with heterogeneous hematomas, when compared with patients with homogeneous hematomas, were clinically more severe, had larger hematomas, were more likely to have lobar hematoma, and less likely to have intraventricular extension. Smaller hematomas are more likely to be regular and homogeneous, whereas larger hematomas are more likely to be irregular and heterogeneous (Table 2). Decision to withdraw active treatment was more likely to be made among patients with irregular hematoma (n=63 [7%]) than those with regular one (n=29 [3%]; P<0.0001) and among patients with heterogeneous hematoma (n=53 [7%]) than those with homogeneous one (n=39 [3%]; P<0.0001).

Association of Shape and Density With 90-Day Outcomes

Table 3 shows that irregular shape was independently associated with a higher risk of death/major disability (mRS score of ≥3; OR, 1.60; 95% CI, 1.29–1.98), and major disability at 90 days (OR, 1.60; 95% CI, 1.31–1.95). Irregular shape was not associated with an increased risk of death alone (OR, 0.97; 95% CI, 0.68–1.39). Heterogeneous density was not associated with an increased risk of death/major disability (OR, 1.06; 95% CI, 0.85–1.33), death (OR, 1.04; 95% CI, 0.73–1.48), or disability alone (OR, 1.14; 95% CI, 0.93–1.39). Irregular shape (OR, 1.46; 95% CI, 1.23–1.72) but not heterogeneous density (OR, 1.08; 95% CI, 0.91–1.28) was associated with higher grade (poorer functioning) on the ordinal logistic analysis of mRS scores (Figure).

Table 1. Baseline Characteristics of Patients Included in This Study

	Shape			Density		
	Regular (n=1120)	Irregular (n=946)	*P* Value	Homogeneous (n=1285)	Heterogeneous (n=781)	*P* Value
Demographics						
Age, y, mean	63.0 (12.8)	64.4 (13.2)	0.028	63.4 (12.8)	64 (13.3)	0.376
Sex, male, %	406 (36%)	365 (39%)	0.275	483 (38%)	288 (37%)	0.746
China region	785 (70%)	596 (63%)	0.001	871 (68%)	510 (65%)	0.245
Clinical characteristics						
SBP, mm Hg (mean, SD)	179 (17)	180 (17)	0.196	179 (17)	179 (17)	0.487
DBP, mm Hg (mean, SD)	101 (15)	100 (15)	0.369	101 (15)	100 (15)	0.372
NIHSS, median, IQR	9 (4–13)	13 (8–18)	<0.0001	9 (5–14)	13 (8–18)	<0.0001
GCS, median, IQR	15 (13–15)	14 (12–15)	<0.0001	15 (13–15)	14 (12–15)	<0.0001
Medical history						
Hypertension	807 (72%)	682 (72%)	0.953	933 (73%)	556 (71%)	0.469
Diabetes mellitus	128 (11%)	101 (11%)	0.593	143 (11%)	86 (11%)	0.930
Previous ICH	99 (8%)	72 (8%)	0.840	100 (8%)	60 (8%)	0.931
Previous ischemic stroke	114 (10%)	97 (10%)	0.949	137 (11%)	74 (9%)	0.385
Current medications						
Antihypertensive drugs	541 (48%)	412 (44%)	0.033	598 (47%)	355 (45%)	0.621
Anticoagulant drugs	31 (3%)	31 (3%)	0.497	32 (2%)	30 (4%)	0.082
Aspirin	107 (10%)	93 (10%)	0.826	123 (10%)	77 (10%)	0.835
Statins	80 (7%)	71 (8%)	0.747	87 (7%)	64 (8%)	0.230
Imaging characteristics						
CT time from ICH onset, h (median, IQR)	1.8 (1.2–2.7)	1.7 (1.2–2.6)	0.309	1.9 (1.3–2.8)	1.6 (1.1–2.5)	<0.0001
Median hematoma volume, mL	8.1 (3.8–14.1)	14.4 (8.4–25.4)	<0.0001	8.5 (4.2–14.4)	15.3 (8.9–25.9)	<0.0001
Hematoma location						
Lobar	80 (7%)	121 (13%)	<0.0001	110 (9%)	91 (12%)	0.006
Deep	933 (83%)	785 (83%)		1066 (83%)	652 (83%)	
Cerebellum	57 (5%)	19 (2%)		56 (4%)	20 (3%)	
Brain stem	43 (4%)	20 (2%)		46 (4%)	17 (2%)	
Intraventricular extension	317 (28%)	277 (29%)	0.625	407 (32%)	187 (24%)	0.0002
Intensive BP lowering	557 (50%)	475 (50%)	0.828	627 (49%)	405 (52%)	0.177
Decision to withdraw active treatment	29 (3%)	63 (7%)	<0.0001	39 (3%)	53 (7%)	<0.0001

Data are n (%), mean (SD), or median (IQR). *P* values are based on χ^2 or Kruskal–Wallis test. BP indicates blood pressure; CT, computed tomography; DBP, diastolic blood pressure; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

Discussion

We have shown the importance of hematoma shape in predicting poor clinical outcome in ICH. Hematomas with an irregular shape were associated with both combined death and disability, and disability alone, at 90 days. Conversely, hematoma density was not associated with either of these outcomes.

The relationship between irregularity in shape of the hematoma and poor outcome has previously been shown to be associated with higher 30-day mortality in a study of 106 patients (*P*=0.006).[7] The proposed mechanism was that irregular-shaped hematomas had a higher risk of hematoma growth, which is known to be associated with poor outcome in patients with ICH.[10,11] Although growth seems to be the logical link between irregularity and poor outcome, there might be other factors involved. It is well recognized that ICH is a dynamic phenomenon[3] and new bleeding occurring at the border of the hematoma could produce irregularity of shape. Irregular-shaped hematomas might also lead to more persisting inflammation around the lesion. The eruption of blood into the brain tissue produces an injury with

Table 2. Proportion of Hematoma by Size, Shape, and Density

	Shape			Density		
	Regular (n=1120)	Irregular (n=946)	*P* Value	Homogeneous (n=1285)	Heterogeneous (n=781)	*P* Value
ICH size						<0.0001
Small (<10 mL)	676 (60%)	294 (31%)	<0.0001	745 (58%)	225 (29%)	
Medium (10–25 mL)	355 (32%)	412 (44%)		418 (33%)	349 (45%)	
Large (>25 mL)	89 (8%)	240 (25%)		122 (9%)	207 (27%)	

Data are n (%). *P* values are based on χ^2 (categorical variable) or Kruskal–Wallis test (continuous variable). ICH indicates intracerebral hemorrhage.

an inflammatory response involving blood components and leading to enzyme activation, mediator release, inflammatory cell migration, glial cell activation, brain tissue breakdown, and repair processes.[12,13] New bleeding areas at the periphery of the hematoma could sustain this inflammation for a longer period of time and lead to worsening outcome in patients with irregular hematoma. Another possible mechanism is that irregularity could contribute to worsening perihematomal edema, a known predictor of poorer outcome.[14] It is also possible that irregular shape is a marker for the pressure within the hematoma. Lower intrahematoma pressures might be better constrained by white matter bundles producing ellipsoid hematomas, whereas higher intrahematoma pressures might produce more aggressive dissection of brain tissue, leading to both more disability and an irregular outline. This would also account for the association between irregularity and hematoma growth.

We found no relationship between heterogeneity in hematoma density and poor outcome. Variability in density relates to clot formation and sedimentation of cellular components in the plasma. This translates into the higher density of more recent ICH on brain CT scans, which attenuates while the ICH is evolving.[15] Logically, a heterogeneous pattern might be associated with continued or recurrent bleeding with a mixture of fresh blood and old hematoma in the ICH cavity. This could be associated with clinical progression after the initial presentation. Our inability to demonstrate an increase in disability might be because this assumption is valid but the grading of heterogeneity is much more subjective than that of irregularity and this is reflected in the poor values for interrater agreement on this parameter. It is possible that there is an outcome effect of variation of density but this was lost in the noise of our assessment technique. In the emergency department setting, the identification of highly irregular-shaped hematoma as predictors of poor outcome might be a useful addition to risk stratification in the acute assessment of patients with ICH.

The strength of our analysis lies in the ability to derive innovative data from a large randomized control trial of participants from multiple cultural and ethnic origins, the rigorous collection of baseline and outcome data, and the centrally coordinated and performed CT analysis with the exclusion of poor quality imaging. There are limitations to the study that should be noted. First, the present analysis was

Table 3. Association Between Hematoma Shape/Density and 90-Day Outcome

	Shape			Density		
	Regular (n=1120)	Irregular (n=946)	*P* Value	Homogeneous (n=1258)	Heterogeneous (n=781)	*P* Value
Death or major disability						
No. of events, %	485 (43%)	619 (65%)		626 (49%)	478 (61%)	
Crude OR (95% CI)	1 (reference)	2.48 (2.07–2.96)	<0.0001	1 (reference)	1.66 (1.39–1.99)	<0.0001
Adjusted OR (95% CI)*	1 (reference)	1.60 (1.29–1.98)	<0.0001	1 (reference)	1.06 (0.85–1.33)	0.609
Death						
No. of events, %	93 (8%)	158 (17%)		123 (10%)	128 (16%)	
Crude OR (95% CI)	1 (reference)	2.21 (1.69–2.91)	<0.0001	1 (reference)	1.85 (1.42–2.41)	<0.0001
Adjusted OR (95% CI)*	1 (reference)	0.97 (0.69–1.39)	0.872	1 (reference)	1.04 (0.73–1.48)	0.836
Major disability						
No. of events, %	392 (35%)	461 (49%)		503 (39%)	350 (45%)	
Crude OR (95% CI)	1 (reference)	1.77 (1.48–2.11)	<0.0001	1 (reference)	1.26 (1.05–1.51)	0.011
Adjusted OR (95% CI)*	1 (reference)	1.60 (1.31–1.95)	<0.0001	1 (reference)	1.14 (0.93–1.39)	0.207

CI indicates confidence interval; CT, computed tomography; ICH, intracerebral hemorrhage; and OR, odds ratio.

*Adjusted for age, region, systolic blood pressure, National Institutes of Health Stroke Scale score, current use of antithrombotic drugs, onset to CT time, ICH location, intraventricular extension, ICH volume, randomized treatment, and decision to withdraw active treatment.

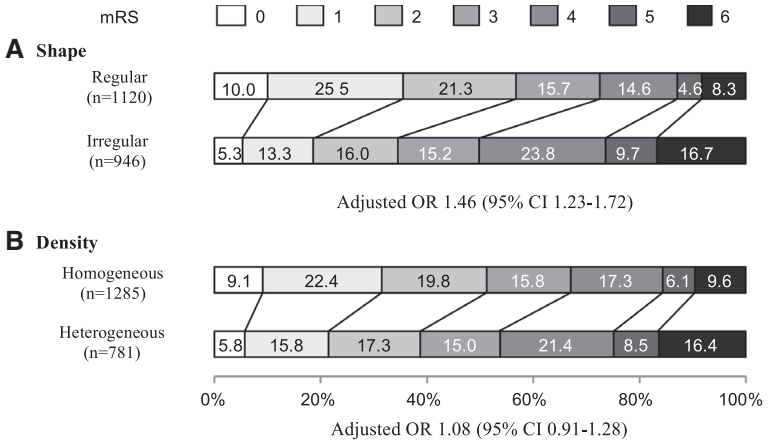

Figure. Distribution of modified Rankin scale (mRS) score at 90 days among patients with (**A**) regular or irregular shape and (**B**) homogeneous or heterogeneous density. mRS ranges from 0 (no symptoms) to 6 (death). Ordinal analysis showed unfavorable shift on mRS scores with irregular shape (crude odds ratio [OR], 2.45; 95% confidence interval [CI], 2.10–2.87; and adjusted OR, 1.46; 95% CI, 1.23–1.72), and heterogeneous density (crude OR, 1.72; 95% CI, 1.47–2.01; and adjusted OR, 1.08; 95% CI, 0.91–1.28). OR were adjusted for age, region, systolic blood pressure, National Institutes of Health Stroke Scale score, current use of antithrombotic drugs, onset to computed tomography time, intracerebral hemorrhage location, intraventricular extension, volume of intracerebral hemorrhage, randomized treatment, and decision to withdraw active treatment.

not prespecified, it is open to chance or biased associations. Second, the clinical trial population is subject to selection bias—patients with normal presenting blood pressure and a high likelihood of death in the first 24 hours where excluded. Although the association findings for shape are strong, they might require external validation in a nonclinical trial population. Third, we do not have information on hematoma growth, which would be the logical link between irregularity and poor outcome. The hematoma growth substudy in INTERACT2 only included a limited number of patients, and none had an irregular hemorrhage: it may be that investigators were reluctant to repeat CT scanning in patients with indicators of poor prognosis. Thus, although suspected, hematoma growth could not be proven as a key link in the interaction between hematoma shape and outcome. Finally, as noted above, the scale used to assess density was prone to subjectivity and had only fair reproducibility as shown by the low interclass correlation coefficient between the raters. Density assessment should not be used alone in clinical practice and further investigations are required regarding the best method of rating density and as a prognostic marker in ICH. In summary, we have shown an independent relationship between hematoma shape and poor outcome at 90 days after the onset of ICH, with irregularity being linked to both disability and death as a composite, and disability alone. These results reinforce the importance of assessing hematoma characteristics in the context of clinical features for assessing prognosis in the planning therapeutic interventions in patients with acute ICH.

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Drs Delcourt, Zhang, Sato, Arima, Heeley, and Anderson contributed to the concept and rationale for the study. Drs Delcourt, Zhang, and Sato undertook the computed tomographic scan analysis. Dr Arima contributed to statistical analysis. All the authors have contributed to the interpretation of the results. Drs Delcourt, Zhang, and Sato were responsible for the first draft, and Drs Anderson and Chalmers for the first revision. All authors participated in drafting and approval of the final manuscript and take responsibility for the content and interpretation of this article.

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