Noncontrast Computed Tomography Markers of Intracerebral Hemorrhage Expansion

Gregoire Boulouis, MD, MSc; Andrea Morotti, MD; Andreas Charidimou, MD, PhD; Dar Dowlatshahi, MD, PhD; Joshua N. Goldstein, MD, PhD

Spontaneous intracerebral hemorrhage (ICH) is a common and ominous consequence of cerebral small vessel disease. It is now known to be a dynamic disease, with up to one third of patients experiencing continued bleeding after initial presentation. This growth, also termed hematoma expansion, is an independent predictor of early neurological deterioration and worse long-term outcome and represents an appealing therapeutic target. Early identification of patients at high risk of ICH expansion is, therefore, crucial to target therapies to those likeliest to expand. The presence of active contrast extravasation within the hematoma, also known as the spot sign, is a validated imaging marker of hematoma expansion. However, this sign has a limited sensitivity for expansion. Furthermore, the identification of the spot sign requires computed tomography angiography (CTA), with potential drawbacks including additional radiation delivery. Several noncontrast CT (NCCT) biomarkers have been studied since the early 1980s and have recently gained attention as promising predictors of ICH expansion.

Unlike CTA, NCCT is almost universally performed to diagnose ICH in the emergency department. NCCT biomarkers have the potential to become an inexpensive and readily available tool to stratify the risk of hematoma growth in clinical practice and for clinical trials. In this review, we summarize the current evidence on spontaneous ICH expansion prediction using NCCT and aim at paving the way toward a standardization of NCCT biomarker nomenclature.

Hemorrhage Formation, Expansion, and Its NCCT Appearance

Initial Hemorrhage Formation

The imaging appearance of an acute ICH varies by many biological factors, including the patient’s hematocrit and the intrahemorrhage protein concentration. It is constantly though characterized by the presence of a spontaneously hyperattenuating area within the brain parenchyma, explained by the relative higher attenuation of fresh blood by comparison to the surrounding brain tissue. The higher attenuation of recent blood has been shown in experimental models to be disproportionately driven by the presence of intact globin within the extravasated red blood cells trapped in the hematoma. At the initial phase of hemorrhage formation, and in the absence of modifying conditions (eg, anticoagulation/severe blood disorders), the early hematoma consists of a heterogeneous mass formed by red blood cells, white blood cells, and platelet thrombi mixed with protein-rich serum with a relative higher density to the brain parenchyma. Eventually, as the hemorrhage evolves to the early subacute stage, the extrusion of the lower attenuating plasma that occurs when the clots retract results in an even higher attenuation of the hematoma, making it entirely hyperdense.

Hemorrhage Growth and Evolution

Up to 50% of ICH patients can experience secondary hematoma expansion ≤24 hours after presentation, but the biological mechanisms underlying this event are yet to be understood. The ideal timing for assessing hemorrhage expansion is unknown; however, because hematoma expansion is rare after 24 to 48 hours, this time frame is reasonable for repeat imaging to evaluate final hemorrhage volume. There have been case reports of dynamic CTA/magnetic resonance imaging showing active bleeding in progress suggesting that expansion can indeed be visually captured at the acute phase. However, the translation of the intricate mechanisms leading to hemorrhage expansion in terms of NCCT appearance remains entirely speculative. In a simplistic model where the hemorrhage arises from a single culprit small vessel and grows by continuous extravasation, the intrahematomal hematocrit and protein concentration are the sole determinants of its acute and subacute density. Its appearance may vary depending on adjacent structures, including degree of surrounding...
parenchymal injury, perihemorrhage edema, and intraventricular extension. Animal models (and human studies) have suggested conversely that the initial hemorrhage growth and its subsequent expansion may occur sequentially with the initial rupture enabling secondary mechanical shear of peripheral vessel resulting in a cascade of ruptures that maintain ongoing bleeding. Pathological evidence has shown that the final hemorrhage volume results from multiple surrounding vessel ruptures. This sequential model is also supported by the observation that hemorrhages commonly assume irregular shape and can expand in changing axial directions over time. In this avalanche model, the acute and early subacute CT appearance of the hemorrhage results from a matrix of acute and subacute blood. Fresh blood coexists with subacute clot resulting in higher hemorrhage heterogeneity, and hyperattenuating regions constitute mature areas of the bleed and lower attenuating regions more immature areas.

Various aspects of the NCCT appearance of acute hemorrhages have drawn attention as potential indicators of the risk of hemorrhage expansion. These works are discussed below (and summarized in Table I in the online-only Data Supplement).

**NCCT Biomarkers of the Risk of Hemorrhage Expansion**

**Hemorrhage Volume**

The volume of the hemorrhage at presentation is the simplest and most established marker of the risk of subsequent hemorrhage expansion, independent from other confounders and most importantly from time since onset of symptoms. It can be easily measured in routine clinical practice using the ellipsoid approximation method ABC/2, where A, B, and C represent the 3 maximal orthogonal dimensions of the hemorrhage. Although larger hemorrhages have been shown to be at higher risk of expansion, the inverse holds true and smaller hemorrhages consistently demonstrate a lower risk for expansion and lower absolute ICH volume increase.

**Hemorrhage Margin Irregularity**

The first investigation of the relationship between hemorrhage shape and hemorrhage expansion was performed by Fuji et al in 1994. In this work, the authors classified hemorrhages into 3 categories round, with round and smooth margins; irregular, with irregular, multinodular margins; and separated, with a fluid level in the cavity eventually dichotomized into regular versus irregular. In a multivariable model including 627 patients, the authors found irregular hemorrhages to be associated with a significantly higher risk of subsequent expansion. In a later work, Barras et al introduced a novel 1 to 5 categorical scale to reflect the spectrum of appearance of ICH shape from most regular (1) to most irregular (5). This scale demonstrated a good-to-substantial between-observer agreement but failed to demonstrate an independent association with ICH expansion when dichotomized into regular (<3) and irregular (≥3) in a sample of 90 patients imaged <3 hours since onset (Figure). More recently, using the same dichotomized scale, Blacquiere et al found an independent association between margin irregularity and hemorrhage expansion with a sensitivity of 0.69 (0.59–0.78) and a specificity of 0.46 (0.40–0.53) for significant expansion in a sample of 356 patients. Similarly, in a single-center retrospective cohort of 1029 patients, irregular margins were found to be independently associated with hemorrhage expansion (adjusted odds ratio [OR], 1.72; 95% confidence interval [CI], 1.07–2.76; \( P = 0.02 \)) with sensitivity and specificity of 0.66 and 0.56, respectively. Finally, although these studies did not specifically investigate the impact on hemorrhage expansion, several additional reports showed a strong association between hemorrhage margin irregularity and poor clinical outcome, potentially mediated by hemorrhage expansion.

Overall, margin irregularity seems to be associated with hemorrhage expansion in various settings investigating hemorrhage expansion. The pathophysiological explanation of this finding could tentatively be explained by the avalanche model of secondary growth. Margin irregularity may reflect peripheral sites of secondary bleeding (occurring at the border of the hematoma), visually capturing the immaturity of the hemorrhage. A recent study also demonstrated that the only factor associated with the amplitude of hemorrhage expansion along the surface was the proximity to the initial hematoma centroid (3-dimensional center), suggesting that the physical features of the brain–hemorrhage interface might favor a final spherical/ellipsoid and regular shape, regardless of the location of initial and secondary sites of vessel rupture. Irregular hemorrhages may, therefore, be at an intermediate stage of maturity, with persisting bleeding or increased intrahemorrhage pressure favoring the bulging of the hematoma into surrounding brain structures.

**Hemorrhage Density Heterogeneity**

**Swirl Sign**

The first straight-forward evidence of a relationship between hemorrhage heterogeneity and expansion comes from Kim et al in 2008. In this work, the authors used the extra axial swirl sign known to correlate in extradural hemorrhages with perioperative active bleeding and unclotted blood and examined its value in spontaneous ICH. The criteria for establishing the positivity of a swirl sign were not well defined. The authors found a univariable association between the swirl sign and poor outcome, but no association with hemorrhage growth. Among the 56 patients included, 13 patients (23%) demonstrated a swirl sign. Selariu et al later used the swirl sign in a cohort of 203 patients with ICH to investigate its relation with clinical outcome (Figure). In this study, the swirl sign was defined as region(s) of hypodensituation or isoattenuation (compared with the attenuation of brain parenchyma) within the hyperattenuated ICH. The areas of hypodensituation or isoattenuation may vary in shape and can be rounded, streak-like, or irregular. No cutoff for the delta in Hounsfield units between swirl and hemorrhage was provided. Selariu et al found in ancillary analyses that swirls were less prevalent in smaller hemorrhages, indirectly suggesting a lower risk of hemorrhage expansion.

**Black Hole Sign**

This was further elaborated by Li et al in a recent work investigating the predictive ability of the black hole sign, defined as a swirl sign that needed to be encapsulated within the
hemorrhage, present a clear border, and demonstrate a delta of ≥28 Hounsfield units by comparison to the adjacent hemorrhage (Figure). In this study, the authors found that the presence of a black hole was independently associated with an increased risk of hemorrhage expansion (adjusted OR, 4.12; 95% CI, 1.44–11.77; P=0.008) with notably an excellent specificity (0.94).

**Density Heterogeneity Scale**

Barras et al. defined a 1 to 5 heterogeneity scale in a pioneering article, in which 1 represents homogeneous hemorrhages and 5 heterogeneous hemorrhages. In this work, heterogeneous hemorrhages at baseline (defined as a score of ≥3) demonstrated an independent association with increased expansion risk (defined as a continuous variable of increase in ICH volume; P=0.046). This result was not found consistent when treating hemorrhage expansion as a categorical variable (eg, volume increase of ≥33% or 12.5 mL). The association between hemorrhage expansion and global heterogeneity of the hemorrhage, however, was replicated in at least 2 different settings.26,33–35

**Hypodensities**

The above-mentioned signs have in common the ability to capture the presence of hypodense structures within the hemorrhage, but it remains unclear to what extent the swirl sign, black hole sign, and density heterogeneity scale capture the same phenomenon. There is most likely an important degree of overlap, especially because the black hole represents a subcategory of the swirl sign and because an important degree of heterogeneity should capture the presence of all swirls, hence black holes (Figure).

More recently, using retrospective data from 1029 patients from our center, we aimed at defining categories of hypodensities to investigate their associations with hemorrhage expansion.7 We empirically defined 4 types of hypodensities based on their density relative to the adjacent parenchyma and the aspect of their separation from the hematoma (clear, blur). We carefully aimed at excluding hypodensities with any connection with the surface of the hemorrhage, to avoid partial volume effect with surrounding brain parenchyma. We found that the specific pattern of hypodensities did not influence the association with hemorrhage expansion. In this work, we also examined the predictive ability of the previously reported NCCT markers and found that the simplest approach, for example, presence of any hypodensity encapsulated inside the hemorrhage, demonstrated the highest nominal OR for hemorrhage expansion risk assessment (OR, 4.37; 95% CI, 2.05–9.62; P<0.001).7 These results have not yet been externally validated.

**Blend Sign and Fluid Levels**

Additional peculiar patterns of hemorrhage density heterogeneity have been described, including the blend sign by Li et al. This sign was defined as blending of relatively hyperattenuating area with adjacent hyperattenuating region within the hematoma […] with a well-defined margin between these regions and a delta of at least 18 Hounsfield units between the 2 regions.11 This sign, seen in 17% of patients, demonstrated a good capacity to predict hemorrhage expansion in a single-center retrospective cohort (with sensitivity and specificity of 40% and 96%, respectively), but this predictive value could not be replicated in a different setting while the prevalence of a blend sign was of similar magnitude (13.7%).7

Similarly, the presence of intrahematoma fluid levels (or early sedimentation) has been shown recently to be associated with both expansion26 and worse clinical outcome.28 This sign has been correlated to anticoagulation treatments and lobar location of the bleed and may reflect anomalies in the intrahemorrhage coagulation process (coagulation state), leading to early sedimentation of higher density proteins. Of note, this sign is only rarely found in ICH patients, with a reported prevalence of 1% to 7%.7,26,36

**Computational Approaches**

Finally, various promising postprocessing approaches using histogram-based analyses of hemorrhage heterogeneity (eg, textural patterns using intrahemorrhage density repartition kurtosis, skewness, etc) have been investigated.9,38 In these works, a higher density heterogeneity was again linked to a higher likelihood of hemorrhage expansion. However, these approaches require a certain amount of time and image processing, as well as specialized software that may not be available for rapid use in the emergency setting.
To summarize, the heterogeneity of hemorrhage density seems to represent an appealing marker for assessing the risk of hemorrhage expansion. However, the profusion of reports reveals a lack of standardization of rating methods and of simplicity to pave the way toward clinical use. Lumping all these signs into any hypodensity category might be a step toward simplification but would require external validation and general consensus on the rating methods.

**Correlation With Spot Sign**

Two studies have explored the relationship between NCCT markers and the CTA spot sign at the acute phase of ICH.7,39 Connor et al retrospectively assessed the presence of density heterogeneity and spot sign in 71 patients. The authors found that the presence of hypodensities was independently associated with hemorrhage expansion but did not investigate the spatial correlation between spots and hypodense regions on NCCT. In a subanalysis of a work investigating hypodensities as a marker of hemorrhage growth, we randomly selected 40 patients with both spot sign(s) and hypodensities.3 We found that only 35% of spots spatially matched hypodensities, suggesting that while both indicate a higher risk of hemorrhage expansion, these 2 findings may mark different processes. It may be that combining NCCT markers with CTA markers such as the spot sign could lead to even further discriminative ability for hemorrhage expansion. Such analyses would be complex as the relationship between CTA spot sign and varied NCCT markers is not yet clear. Further studies using combined CT and CTA approaches may help further improve the ability to predict expansion in the acute phase.

**Correlation With Time Since Onset**

Hypodensities and density heterogeneity were shown to be more prevalent in early scans,7,10,26 but this was not the case for hemorrhage expansion in the acute phase. Therefore, the relevance of these NCCT hematoma parameters to clinical outcome remains largely unexplored. Recently, the association between ICH shape (irregularity, defined as ICH with ≥2 extra lesions added to the ellipsoid-shaped ICH) and density (heterogeneity, defined by the presence of ≥3 low-density lesions within the ICH) on clinical outcomes at 90 days were assessed in the INTERACT2 study (Intensive Blood Pressure Reduction in Acute Intracerebral Hemorrhage Trial).27 In this analysis of 2066 ICH patients with CT scans, the prevalence of irregular and heterogeneous ICH were 46% and 38%, respectively. There was an independent relationship between ICH irregularity and poor outcome at 90 days, with irregularity linked to both major disability and death as a composite outcome (OR, 1.60; 95% CI, 1.29–1.98) and death alone (OR, 1.60; 95% CI, 1.31–1.95). ICH heterogeneity, however, was not associated with any clinical outcomes. Limitations of this analysis included that it was based on a clinical trial population in which those with normal blood pressure and a high likelihood of death were excluded, whereas those with disproportionately small hematoma volumes were included. In addition, the scale used to assess NCCT hypodensities had only fair reproducibility with low interclass correlation coefficient between the raters (OR, 0.57; 95% CI, 0.52–0.61).

More recently, a retrospective single-center cohort of 800 spontaneous ICH patients evaluated whether baseline NCCT hypodensities are associated with poor clinical outcome.41 ICH patients with unfavorable outcome were more likely to demonstrate hypodensities (48% versus 20%; P=0.0001) in univariable analysis. After adjusting for age, admission Glasgow coma scale, warfarin use, intraventricular hemorrhage, baseline ICH volume, and location, NCCT hypodensities were found to be independently associated with increased risk for unfavorable outcome (OR, 1.70; 95% CI, 1.10–2.65; P=0.018). In similar sensitivity analyses including previously reported NCCT predictors of expansion in the same logistic regression model, only irregular ICH shape (score ≥3 according to Barras et al39) was independently associated with poor outcome.

These results reinforce the notion that specific NCCT ICH characteristics may serve as widely available predictors of expansion and clinical outcome, as well as possibly to stratify therapeutic interventions. It is likely that NCCT characteristics capture hematomas with higher risk of subsequent growth, which at least partly explains the reported association with poor clinical outcome. Further studies should provide more direct evidence for this link. If substantiated, NCCT findings may mark which patients need the closest neurological monitoring and guide therapies aimed at reducing the risk of expansion. For example, elevated blood pressure in the acute ICH setting is a risk factor for hematoma expansion, and intensive blood pressure reduction may reduce this risk.42–44 In addition, there are effective but expensive agents available for anticoagulation reversal, and it may be that these can be targeted to the highest risk patients. However, the translation of these results in acute ICH clinical practice and decision making continues to be challenging, partly because of different opinions and controversies on the magnitude of benefit and the selection of the acute ICH population that is

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**Clinical Implications of NCCT Biomarkers**

The current American Heart Association/American Stroke Association guidelines for spontaneous ICH endorse the use CTA and contrast-enhanced CT to help identify patients at risk for hematoma expansion (Class IIb; Level of Evidence B).40 In this setting, NCCT biomarkers may be an alternative method in the acute clinical setting for prediction of hematoma growth, especially in centers where immediate CTA is not available. However, for clinical translation of these markers into clinical practice, further validation in large unselected ICH cohorts is urgently needed, including standardization of definitions and rating methods.

Of key clinical relevance is the demonstration of an independent association between NCCT biomarkers and functional outcome, including mortality and disability. Only one observational study has shown a relationship between irregular shape and 30-day mortality in a retrospective study of 106 patients (P=0.006).28 Therefore, the relevance of these NCCT hematoma parameters to clinical outcome
more likely to benefit. In this landscape, NCCT biomarkers can provide a useful strategy for refining risk stratification and patient selection.

Research Perspectives in Hemorrhage Expansion and Imaging

Hematoma expansion provides a compelling target for acute ICH therapy trials. However, hemostatic and hemodynamic trials have been unable to offer a definitive therapy that significantly and substantially alters outcome.44,46 This first generation of ICH trials used an all-comers approach, in which the intervention was applied without specifically targeting those at highest risk of hematoma expansion. Although this approach increases the generalizability of the intervention and improves feasibility of trial enrollment, reductions in hematoma expansion in the target population are diluted over the entire sample, which may in part explain the lack of clear therapeutic benefit. Furthermore, the full study sample is exposed to potential harms from the intervention, including those patients who will not expand and have no opportunity to benefit.

Conversely, ongoing or recently halted hematoma expansion trials (STOP-AUST, ClinicalTrials.gov NCT01702636; STOP-IT, NCT00810888; and SPOTLIGHT, NCT01359202) using spot sign as a selection tool to target a high-risk population have faced difficulty with enrollment because of a lower-than-expected sensitivity rate. These studies may face further challenges because emerging evidence suggests that the spot sign has a lower-than-expected sensitivity to predict patients at risk of hematoma expansion.5 To inform the next generation of ICH clinical trials, we need a selection tool that can identify patients at high risk of hematoma expansion, without substantially limiting the population eligible for enrollment.

Novel hematoma expansion scores were recently published; these incorporate imaging and clinical features to help better risk stratify patients.47 However, these scores are limited in their overall discriminative ability (C statistics in all 3 are below 0.8) and have a low proportion of patients in their highest risk strata.

After consensus on rating methods and external validation in a large independent and ideally real-life sample, research priorities should include building on these existing scores by incorporating NCCT markers to derive a largely applicable hematoma expansion predictive model. This model should bear a higher discriminative ability for hemorrhage expansion while still being able to capture a reasonable proportion of ICH patients to ensure trial feasibility. The ultimate goal would then be to evaluate the effect on clinical outcome of hemorrhage expansion–targeted treatments in patients at high versus low risk of hemorrhage expansion.

To conclude, NCCT markers have the potential to increase our ability to better select patients at risk for hemorrhage expansion. Hemorrhage heterogeneity (ie, the presence of encapsulated hypodense regions) and margin irregularity seem to be promising candidates to be integrated in predictive scores.

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References


Noncontrast CT and Hemorrhage Expansion

Boulouis et al


KEY WORDS: angiography ■ attention ■ cerebral hemorrhage ■ prognosis ■ stroke
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Acute non-contrast CT markers of intracerebral hemorrhage expansion

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Cover Title: Non contrast CT and hemorrhage expansion
# Supplemental Table I: Main NCCT and Expansion reports

Abbrevations: NCCT, Non Contrast Computed Tomography. RCT, Randomized controlled trial.

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Hypodensities</th>
<th>Black Hole Sign</th>
<th>Blend Sign</th>
<th>Irregular Shape</th>
<th>Heterogeneous Density</th>
<th>Irregular Margins</th>
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<td>Definition of hematoma expansion</td>
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<td>&gt;33% or &gt;12.5 mL</td>
<td>&gt;33% or &gt;12.5 mL</td>
<td>a) Continuous scale</td>
<td>a) Continuous scale</td>
<td>&gt;50% and &gt;2 mL or &gt;20 mL</td>
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<td>4.12 (1.44 – 11.77)</td>
<td>20.23 (5.13 – 79.77)</td>
<td>a) OR n/a, p = 0.159</td>
<td>a) OR n/a, p = 0.046</td>
<td>1.40 (1.11–1.78) p = 0.006</td>
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<td>* Shape analyzed as binary variable round vs irregular</td>
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**Notes:**
- * = Development plus replication cohort
- ** = Shape rated on categorical scale ranging 1 to 5
- ** Density rated on categorical scale ranging 1 to 5