Noncontrast Computed Tomography Hypodensities Predict Poor Outcome in Intracerebral Hemorrhage Patients

Gregoire Boulouis, MD, MSc; Andrea Morotti, MD; H. Bart Brouwers, MD, PhD; Andreas Charidimou, MD, PhD; Michael J. Jessel, BS; Eitan Auriel, MD, PhD; Octavio Pontes-Neto, MD, PhD; Alison Ayres, BA; Anastasia Vashkevich, BA; Kristin M. Schwab, BA; Jonathan Rosand, MD, MSc; Anand Viswanathan, MD, PhD; Mahmut E. Gurol, MD, MSc; Steven M. Greenberg, MD, PhD; Joshua N. Goldstein, MD, PhD

Background and Purpose—Noncontrast computed tomographic (CT) hypodensities have been shown to be associated with hematoma expansion in intracerebral hemorrhage (ICH), but their impact on functional outcome is yet to be determined. We evaluated whether baseline noncontrast CT hypodensities are associated with poor clinical outcome.

Methods—We performed a retrospective review of a prospectively collected cohort of consecutive patients with primary ICH presenting to a single academic medical center between 1994 and 2016. The presence of CT hypodensities was assessed by 2 independent raters on the baseline CT. Unfavorable outcome was defined as a modified Rankin score >3 at 90 days. The associations between CT hypodensities and unfavorable outcome were investigated using uni- and multivariable logistic regression models.

Results—During the study period, 1342 patients presented with ICH and 800 met restrictive inclusion criteria (baseline CT available for review, and 90-day outcome available). Three hundred and four (38%) patients showed hypodensities on CT, and 520 (65%) patients experienced unfavorable outcome. In univariate analysis, patients with unfavorable outcome were more likely to demonstrate hypodensities (48% versus 20%; P<0.0001). After adjustment for age, admission Glasgow coma scale, warfarin use, intraventricular hemorrhage, baseline ICH volume, and location, CT hypodensities were found to be independently associated with an increase in the odds of unfavorable outcome (odds ratio 1.70, 95% confidence interval [1.10–2.65]; P=0.018).

Conclusions—The presence of noncontrast CT hypodensities at baseline independently predicts poor outcome and comes as a useful and widely available addition to our ability to predict ICH patients’ clinical evolution. (Stroke. 2016;47:2511-2516. DOI: 10.1161/STROKEAHA.116.014425.)

Key Words: computed tomography ▪ hematoma expansion ▪ intracerebral hemorrhage ▪ morbidity/mortality ▪ prognosis

Spontaneous intracerebral hemorrhage (ICH) accounts for 15% of all strokes and is associated with a poor prognosis. Several neuroimaging features are associated with worse clinical outcome, including larger baseline hematoma volumes, presence of intraventricular hemorrhage (IVH), infratentorial location, and the computed tomographic (CT) angiography (CTA) spot sign.

Among them, the CTA spot sign (and derived spot-sign score) has been shown to accurately identify those patients at highest risk of hematoma expansion, early mortality, and poor functional outcome. However, CTA is not readily available in many centers, and often noncontrast CT scan is the only available imaging tool. Therefore, a better understanding of noncontrast CT-based neuroimaging markers of outcome may help improve prognostication and stratification of patients for specific therapies.

Because prognostic scores are currently imperfect tools, several lines of evidence suggest that the noncontrast CT appearance of the hematoma on neuroimaging can potentially provide additional prognostic information. Several groups
have published overlapping sets of findings examining heterogeneity or irregularity of the hematoma itself. It seems that any type of hypodensity within the hematoma may mark those with ongoing bleeding, that is, those at risk for further expansion. However, the impact of these findings on outcome is unclear and scantily reported. Baseline noncontrast computed tomography (NCCT) hypodensities, as an easily assessable and widely available predictor of expansion, represent a promising marker for predicting clinical outcome and a reasonable candidate for helping clinical care stratification at presentation.

The current study aims to assess whether baseline CT hypodensities can be used to improve identification of ICH patients at risk of poor clinical outcome and investigate the impact of other baseline NCCT markers on outcome.

**Methods**

**Study Population**

A total of 1352 consecutive primary ICH adult patients admitted to a single academic tertiary care medical center and enrolled in an prospective cohort study (as previously described) were screened for inclusion between January 1994 and January 2016. Patients were excluded from the current study because either (1) the baseline CT was performed outside the 24-hour time window from the patient’s last known well, (2) the patient had primary IVH, (3) the baseline ICH volume was <1 ml, (4) the patient was included in ICH-related clinical trials, (5) the patient had ≥2 simultaneous ICHs, or (6) there was unreliable follow-up data.

This study was performed with approval and in accordance with the guidelines of the institutional review board at the Massachusetts General Hospital, which allows us to collect data on all subjects with ICH treated at Massachusetts General Hospital.

**Clinical Characteristics**

Data collection and subjects’ recruitment have previously been described in detail. In brief, clinical data were prospectively collected through in-person interviews with the patients or their surrogates by trained study investigators. Admission variables, including Glasgow coma scale, time of symptom onset, and time of baseline CT were also acquired prospectively. A known time of onset was only recorded if it was witnessed or confirmed by the patient within a 15-minute margin of error. Otherwise, time since onset of symptoms was recorded as unknown. All patients were treated according to a standard institutional protocol during the recruitment period (current version available online at https://www2.massgeneral.org/stopstroke/treatmentProtocols.aspx).

Modality Rankin scale (mRs) was assessed at 90 days through telephone interviews by senior physicians or a phone call by trained study staff. Poor outcome was defined as (1) the inability to walk or attend to own bodily needs without assistance (mRs score =4), (2) being bedridden, incontinent, and requiring constant nursing care and attention (mRs score =5), or (3) death (mRs score =6).

**Imaging Acquisition and Interpretation**

NCCT acquisitions were performed according to standard departmental protocols on 16- or 64-section General Electric helical CT scanners (General Electric Medical Systems) using axial technique with 120 to 140 kVp, 170 mA, and 5-mm slice thickness reconstruction.

The presence of CT hypodensities was assessed by 2 independent raters (Radiologist, Dr Boulouis; Neurologist, Dr Morotti) on the baseline CT blinded to follow-up scan, as well as outcome data, using a fixed reading window of 110 HU and a level of 50 HU as described previously. Hypodensities directly connected to the outer surface of the hematoma were not considered positive.

Other noncontrast CT markers, including heterogeneity and irregularity (according to Barras et al) and presence of the Blend Sign (according to Li et al), fluid levels (according to Blacquiere et al), and the swirl sign (according to Selariu et al) were also rated independently. See Figure I in the online-only Data Supplement for visual examples of each of those signs. Disagreements were adjudicated by consensus.

The hemorrhage locations were ascertained by trained study staff and categorized into lobar (believed to be originating from the cortical–subcortical junction), deep (affecting the deep supratentorial white matter or the basal ganglia), or infratentorial (brain stem and cerebellar).

ICH and IVH volumes were calculated by study staff blinded to clinical data according to standard protocols using available software (Alice; PAREXEL International Corporation, and Analyze 10.0; Mayo Clinic). Additionally, spot signs were read in patients who received a CTA at baseline, as described previously.

**Statistical Analysis**

Continuous variables were summarized using means (SDs) or medians (interquartile ranges), where appropriate, and discrete variables were summarized using counts (percentages). Chi square tests, Fisher exact tests, t tests, and Mann–Whitney tests were used as appropriate for the univariable analysis, with a P value <0.05 as the threshold for statistical significance.

We constructed a multivariable logistic regression model to determine the correlation of the presence of hypodensities with unfavorable outcome at 90 days, adjusting for variables with a P value ≤0.1 in univariable analysis.

Sensitivity analyses were conducted with the same approach further including patients with only discharge mRs available.

All tests of significance were 2-tailed, and a P value of <0.05 was considered statistically significant. Statistical analyses were performed with JMP Pro 12 (SAS Institute Inc, Cary, NC).

This report was prepared according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

**Results**

**Study Population**

Among the 1342 patients with primary ICH presenting during the study period, 1080 met our study criteria and 800 had

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**Figure 1.** Flowchart of patients’ selection. CT indicates computed tomography; FU, follow-up; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and mRs, modified Rankin scale.
available clinical information at 90 days (see Figure 1 for patients selection details). Detailed baseline characteristics are displayed in Table 1.

Among the 800 included patients with restrictive criteria, 304 (38%) demonstrated hypodensities on the baseline noncontrast CT ( Interrater agreement 0.87; 95% confidence interval [CI] 0.77–0.97). Patients with hypodensities were more likely to be younger ($P=0.08$), to be on warfarin ($P<0.0001$), to have an elevated international normalized ratio ($P<0.0001$), to have lobar or deep ICH ($P=0.006$), to have a lower Glasgow coma scale ($P<0.0001$), as well as to have a larger ICH volume ($P<0.0001$). Please see Table I in the online-only Data Supplement for the baseline characteristics of the full cohort.

### Outcome

A total of 521/800 patients (65%) experienced unfavorable outcome, including death in 373 (47%) at 90 days. Univariable analyses (see Table 2) showed that patients with unfavorable outcome were twice as likely to have baseline CT hypodensities when compared with those with favorable outcome (48% versus 20%; $P<0.0001$). Figure 2 details mRs scores in patients with and without CT hypodensities.

After adjustment for age, admission Glasgow coma scale, warfarin use, IVH presence, baseline hemorrhage volume, and location, the presence of hypodensities remained independently associated with unfavorable outcome (adjusted odds ratio =1.70, 95% CI 1.10–2.65; $P=0.018$; see Table 3 for detail).

The association remained significant when using IVH volume in the multivariable model instead of IVH presence versus absence (hypodensities adjusted odds ratio for poor outcome =1.64, 95% CI 1.05–2.56; $P=0.0289$) and when further adjusting our model for time from onset to CT (data not shown).

### Sensitivity Analyses

A sensitivity analysis was conducted among all 1080 patients, carrying forward the discharge mRs for those patients (280; 26%) without 90-day assessment, and that did not change the magnitude and significance of the results in the same multivariable model (CT hypodensities adjusted odds ratio for poor outcome =1.78, 95% CI 1.23–2.6; $P=0.0027$).

### Other NCCT Predictors of Expansion

Similar approaches were used, entering previously reported NCCT predictors of expansion in the same logistic regression model to test associations between these markers and mRs score ≥3 at 90 days. In these models, we found that an irregular shape (score ≥3 according to Barras et al)$^{12}$ was independently associated with poor outcome (please see Tables II and III in the online-only Data Supplement), but other predictors did not achieve significance.

### Discussion

In this study, we demonstrated that the newly described baseline noncontrast CT hypodensities predict poor outcome in primary ICH patients.

Although numerous groups have examined the value of other NCCT markers in predicting hemorrhage expansion,$^{3,8,19,20}$ the data regarding their impact on clinical outcome remain meager.$^{13}$ We found that of these other NCCT markers, only hemorrhage irregularity is independently associated with worse functional outcomes.

The pathophysiology of CT hypodensities remains, to date, elusive. Hypodensities are related to shorter time to CT, larger hemorrhage volumes, and anticoagulation (all being associated with more severe presentations and worse outcomes), as well as the CTA spot sign$^1$ and, therefore, present an easily assessed acute-phase prognostic sign. From a pathophysiological standpoint, CT hypodensities seem to mark those hemorrhages captured at an earlier evolution stage (ie, less mature ICH)$^{14,21}$ independent of time since onset, with perhaps higher risk of subsequent expansion. It has been shown that relative hypodensities in acute hemorrhages represent unclotted (eg, more recent) blood.$^{21}$ However, the question of whether the presence of hypodensities marks sites of active bleeding or conversely corresponds to impaired local coagulation processes remains unanswered.$^5$

In a previous work, we have shown that the presence of hypodensities was associated with hemorrhage expansion,
independent of the presence of the CTA spot sign. We also showed that although being partially overlapping spatially with spot sign in patients with available CTAs, hypodensities were not seen in all patients with spot sign, and conversely, some patients with hypodensities showed no spot sign. Therefore, NCCT hypodensities may represent a subtly different neuroimaging feature.

Overall, our findings support the inference that hypodensities capture immature hematomas, with higher risk of subsequent expansion independent of time since onset, which likely explains their association with poor clinical outcome.

Some important points deserve mention. First, the baseline hemorrhage volumes in patients with hypodensities were over 3-fold higher than those without (Median 43 mL versus 12 mL). It is known that larger presenting hematoma volume is associated with significant hemorrhage expansion, as well as poor clinical outcome. Although hypodensities were independently associated with poor outcome in our sample, it may still be that abnormal CT findings are more frequent (by chance) in larger hematomas, simply because of greater opportunity to capture them.

Second, we note that hypodensities have low sensitivity for poor outcome in our sample. However, both specificity and positive predictive value were conversely high (81%, 95% CI 79%–90% and 82%, 95% CI 80%–91.7%). Operationally, this means that CT hypodensities might better serve as an ominous prognostic sign when present but, perhaps, may not be as reassuring when absent.

The strengths of this study are its large sample size, the prospectively acquired clinical data, and the small number of
excluded patients because of a lack of available follow-up data. There are limitations to the current analysis, first being its retrospective design and the fact that it was performed at a single academic center. It is likely that the referral patterns concentrated the more severe patients to our center, thus, limiting the external validity of our findings to similar settings. Our findings will, therefore, require replication in an independent cohort. In addition, over the study period, clinical practice may have significantly varied, as well as the imaging protocols. Finally, we were unable to adjust for early withdrawal of care, known to be an important confounder in studies investigating outcome.23

Conclusions
The presence of noncontrast CT hypodensities at baseline is associated with poor outcome, independently of other variables, and comes as a useful addition to our ability to predict ICH prognosis.

Sources of Funding
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Disclosures
Dr Goldstein has received consulting and research from CSL Behring and Boehringer Ingelheim. The other authors report no conflicts.

References

Table 3. Multivariable Nominal Regression for Poor Outcome

<table>
<thead>
<tr>
<th>90-Day mRs &gt;3</th>
<th>90-Days Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aOR</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Age*</td>
<td>1.07</td>
</tr>
<tr>
<td>Admission GCS*</td>
<td>0.88</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>1.13</td>
</tr>
<tr>
<td>IVH at baseline</td>
<td>1.66</td>
</tr>
<tr>
<td>CT hypodensities</td>
<td>1.70</td>
</tr>
<tr>
<td>ICH baseline volume, ml†</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Lobar [reference] 1 … … 1 … …
Deep 3.10 2.0–4.9 <0.0001 2.16 1.40–3.39 0.005
Infratentorial 5.17 2.52–8.98 <0.0001 2.57 1.29–5.15 0.007

Eight hundred patients in the last step of both models. aOR indicates adjusted odds ratio; CT, computed tomography; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage.

*Per unit change in regressor.
†Per 10 ml increase in ICH baseline volume.


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Phone +1 617 991 0816 - Fax +1 617 643 3939
Email: gregoireboulouis@gmail.com
Supplemental Tables

**Supplemental Table I:** Baseline characteristics of patients with and without CT hypodensities.

<table>
<thead>
<tr>
<th>Variable *</th>
<th>Hypodensities (n=370, 34%)</th>
<th>No Hypodensities (n=710, 66%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.7 ± 12.8</td>
<td>72.1 ± 12.8</td>
<td>0.0802</td>
</tr>
<tr>
<td>Male Gender</td>
<td>217 (58.6%)</td>
<td>381 (53.7%)</td>
<td>0.1172</td>
</tr>
<tr>
<td>Diabetes</td>
<td>75 (20.4%)</td>
<td>148 (21%)</td>
<td>0.8222</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>145 (39.9%)</td>
<td>281 (40.1%)</td>
<td>0.9502</td>
</tr>
<tr>
<td>Hypertension</td>
<td>287 (78.2%)</td>
<td>566 (80.3%)</td>
<td>0.4241</td>
</tr>
<tr>
<td>Statin use</td>
<td>126 (35%)</td>
<td>236 (33.9%)</td>
<td>0.7233</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>78 (21.8%)</td>
<td>260 (36.9%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>102 (27.9%)</td>
<td>112 (15.8%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline INR a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>224 (73.4%)</td>
<td>555 (84.9%)</td>
<td></td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>36 (11.8%)</td>
<td>46 (7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>45 (14.8%)</td>
<td>53 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>150.6 ± 62</td>
<td>149.4 ± 82.7</td>
<td>0.7926</td>
</tr>
<tr>
<td>Onset to CT (hours) a</td>
<td>2.7 [1.2-5.4]</td>
<td>5.2 [2.8-8.4]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≤6h</td>
<td>231 (62.4%)</td>
<td>318 (44.8%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>&gt; 6h</td>
<td>55 (14.9%)</td>
<td>204 (28.7%)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>ICH Volume (cc)</td>
<td>43 [21-70]</td>
<td>12 [5-27]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICH Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>188 (50.8%)</td>
<td>289 (40.7%)</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>160 (43.2%)</td>
<td>346 (48.7%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>22 (5.9%)</td>
<td>75 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>IVH at baseline</td>
<td>188 (50.0%)</td>
<td>278 (39.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Spot Sign</td>
<td>107/233 (46%)</td>
<td>67/518 (13%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90-days Unfavourable outcome</td>
<td>256 (82%)</td>
<td>273 (45%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Variables are expressed as Mean ± Standard Deviation or Absolute number (Percentage of column total) or Median [IQR] as appropriate.

a Symptoms onset unknown for 84 (23%) /188 (26%) patients

Abbreviations. GCS: Glasgow Coma Scale – IVH: Intraventricular Hemorrhage – CT: Computed Tomography – ICH: Intracerebral Hemorrhage
**Supplemental Table II: Diagnostic test evaluation for predicting 90 day mRs > 3 and interrater agreement of NCCT signs**

<table>
<thead>
<tr>
<th></th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>Cohen-Kappa [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypodensities</td>
<td>0.48</td>
<td>0.8</td>
<td>0.81</td>
<td>0.45</td>
<td>0.59</td>
<td>0.87 [0.77-0.97]</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>0.42</td>
<td>0.84</td>
<td>0.82</td>
<td>0.45</td>
<td>0.57</td>
<td>0.77 [0.66-0.89]</td>
</tr>
<tr>
<td>Irregular</td>
<td>0.66</td>
<td>0.71</td>
<td>0.8</td>
<td>0.54</td>
<td>0.68</td>
<td>0.71 [0.57-0.85]</td>
</tr>
<tr>
<td>Blend Sign</td>
<td>0.14</td>
<td>0.83</td>
<td>0.6</td>
<td>0.35</td>
<td>0.39</td>
<td>0.67 [0.44-0.89]</td>
</tr>
<tr>
<td>Fluid Level</td>
<td>0.07</td>
<td>0.98</td>
<td>0.85</td>
<td>0.37</td>
<td>0.4</td>
<td>/</td>
</tr>
<tr>
<td>Swirl sign</td>
<td>0.26</td>
<td>0.83</td>
<td>0.82</td>
<td>0.41</td>
<td>0.46</td>
<td>0.8 [0.63-0.97]</td>
</tr>
</tbody>
</table>
Supplemental Table III: Nominal logistic multivariable models for unfavorable outcome at 3 months. Other non contrast CT markers.

<table>
<thead>
<tr>
<th>Source</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneous ICH</td>
<td>1.11</td>
<td>0.63-1.97</td>
<td>0.71</td>
</tr>
<tr>
<td>Irregular ICH</td>
<td>1.68</td>
<td>1.02-2.77</td>
<td>0.043</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blend sign</td>
<td>0.79</td>
<td>0.44-1.42</td>
<td>0.42</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid level</td>
<td>1.74</td>
<td>0.55-6.39</td>
<td>0.36</td>
</tr>
</tbody>
</table>

All models are adjusted for Age, Admission Glasgow Coma Scale, Intraventricular Hemorrhage presence, time to initial CT and baseline hemorrhage volume.

- Irregular / Heterogenous ICH as defined by a score ≥3 on the scale by Barras and colleagues. 1
- Blend sign as defined by Li and colleagues. 2
- Fluid level as defined by Blacquiere and colleagues. 3
Axial sections of brain non-contrast CTs. Top row (1A-C) shows different examples of hypodensities – black arrowheads – as well as an heterogeneous hemorrhage (1C).  
1 Middle row (2A-C), shows an example of irregular hemorrhage (2A) 1, a blend sign (2B) 2 and a fluid level (2C). 3 Bottom row (3A, 3B) shows two examples of non-contrast CT hypodensities that are connected to the outer surface of the hemorrhage, either on the same slice (3A) or on the immediately adjacent slice (3B) thus not qualifying as true hypodensities.
Supplemental References

