Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion

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ABSTRACT

Objective: To validate various noncontrast CT (NCCT) predictors of hematoma expansion in a large international cohort of ICH patients and investigate whether intensive blood pressure (BP) treatment reduces ICH growth and improves outcome in patients with these markers.

Methods: We analyzed patients enrolled in the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) randomized controlled trial. Participants were assigned to intensive (systolic BP <140 mm Hg) vs standard (systolic BP <180 mm Hg) treatment within 4.5 hours from onset. The following NCCT markers were identified: intrahematoma hypodensities, black hole sign, swirl sign, blend sign, heterogeneous hematoma density, and irregular shape. ICH expansion was defined as hematoma growth >33% and unfavorable outcome was defined as modified Rankin Scale score >3 at 90 days. Logistic regression was used to identify predictors of ICH expansion and explore the association between NCCT signs and clinical benefit from intensive BP treatment.

Results: A total of 989 patients were included (mean age 62 years, 61.9% male), of whom 186/869 experienced hematoma expansion (21.4%) and 361/952 (37.9%) had unfavorable outcome. NCCT markers independently predicted ICH expansion (all $p < 0.01$) with overall accuracy ranging from 61% to 78% and good interrater reliability ($k > 0.6$ for all markers). There was no evidence of an interaction between NCCT markers and benefit from intensive BP reduction (all p for interaction >0.10).

Conclusions: NCCT signs reliably identify ICH patients at high risk of hematoma growth. However, we found no evidence that patients with these markers specifically benefit from intensive BP reduction.

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GLOSSARY

ATACH-II = Antihypertensive Treatment of Acute Cerebral Hemorrhage II; **BP** = blood pressure; **CTA** = CT angiography; **ICH** = intracerebral hemorrhage; **mRS** = modified Rankin Scale; **NCCT** = noncontrast CT.

Intracerebral hemorrhage (ICH) expansion occurs in up to one-third of ICH patients and is strongly associated with poor outcome.^{1,2} Accurate stratification of expansion risk is therefore crucial, in order to identify patients with the highest likelihood to benefit from antiexpansion treatment. The CT angiography (CTA) spot sign is a robust predictor of hematoma expansion,^{3,4} but this marker can only be evaluated on CTA, which is not widely available⁵ and carries the risk of iodine contrast allergy and increased radiation exposure. Several noncontrast CT (NCCT) markers associated with ICH expansion have been recently reported. These findings have many overlapping definitions and include the black hole sign,⁶ the blend sign,⁷ the morphologic appearance of the hematoma,⁸ the heterogeneity and irregularity of the

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hematoma,⁹ the swirl sign,¹⁰ and the presence of intrahematoma hypodensities.^{5,11} However, the majority of these findings were observed in single-center, retrospective studies with relatively small sample sizes.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) trial^{12,13} provides a profound opportunity. This cohort can test the predictive value of NCCT for ICH expansion in a large international multicenter cohort and also whether intensive BP reduction differentially affects outcome in those patients with high-risk radiographic markers. We investigated (1) the prevalence of different NCCT markers and their ability to predict which patients will expand and have poor neurologic outcome and (2) whether participants with NCCT biomarkers of hematoma growth derive clinical benefit from intensive blood pressure (BP) reduction.

METHODS **Standard protocol approvals, registrations, and patient consents.** All patients provided informed consent as per local institutional review board requirements. ATACH-II is registered with ClinicalTrials.gov, number NCT01176565.

Patient selection. Participants were prospectively enrolled from 2011 to 2015 as part of the multicenter randomized ATACH-II trial.¹² In ATACH-II, patients with ICH were randomly assigned to intensive (systolic BP target: 110–139 mm Hg) vs standard (systolic BP target: 140–179 mm Hg) BP treatment within 4.5 hours from stroke onset. Demographic and clinical characteristics were collected upon enrollment in the clinical trial, as previously described.¹²

Image acquisition and analysis. Axial NCCT and images were obtained at each participant's institution using standard local protocols. Baseline and follow-up hematoma volumes at 24 hours were calculated on NCCT images with semiautomated computer-assisted volumetric analysis (Analyze Direct 11.0).

Baseline NCCT scans with 5-mm slice thickness reconstruction were reviewed by 2 raters (A.M., stroke neurologist, and G.B., neuroradiologist), who were blinded to clinical data and treatment arm. The following NCCT markers were identified: intrahematoma hypodensities,⁵ swirl sign,¹⁰ black hole sign,⁶ blend sign,⁷ irregular shape and heterogeneous density,⁹ and presence of intrahematoma fluid level.⁸ Table e-1 at Neurology.org summarizes the diagnostic criteria used to identify different NCCT markers.

The interrater reliability was calculated in a subgroup of 299 patients and discrepancies were resolved with joint reading and consensus agreement. Figure e-1 provides an illustrative summary of all NCCT findings.

Randomization and masking. Eligible participants were randomized at 1:1 ratio via a centralized web-based randomization process to either the intensive or standard antihypertensive treatment group. A minimization randomization scheme proposed by Pocock and Simon (1975)¹⁴ was used to control for age, baseline Glasgow Coma Scale score, presence of intraventricular

hemorrhage, and clinical site. These baseline prognostic factors were identified a priori as those whose imbalances could potentially affect the primary outcome of the trial. Because of the nature of the treatment in this trial where the infusion of nicardipine was titrated to target systolic BP, the treatment physicians and study personnel could not be blinded to treatment assignment. However, all sites were required to designate an individual who was blinded to treatment assignment and did not participate in the randomization or treatment of patients in the trial to be the blinded assessor of the 30- and 90-day outcomes.

Outcome measures. The primary outcomes of the present analysis were the proportion of patients with NCCT markers who experienced hematoma expansion and had an unfavorable functional outcome at 90 days. ICH expansion was defined as volume increase >33% from baseline hematoma volume.¹² Functional outcome was measured using the modified Rankin Scale (mRS) and poor outcome was defined as mRS greater than 3 at 3 months.

Statistical analysis. Continuous variables with normal and non-normal distribution were expressed as mean (SD) and median (range), respectively, while categorical variables were expressed as count (%). The interrater reliability for the identification of NCCT markers was calculated with Cohen kappa statistic. We calculated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of different NCCT findings in predicting ICH expansion and unfavorable outcome (defined as 3-month mRS >3). The association between NCCT markers, hematoma expansion, and outcome was further investigated with a multivariable logistic regression analysis, adjusted for known predictors of hematoma growth and unfavorable outcome in ICH patients.^{15,16} Finally, the effect of intensive BP control on hematoma growth and outcome was studied with a logistic regression model stratified by presence or absence of different NCCT markers. *p* Values <0.05 were considered statistically significant and all the analyses were performed using the statistical software SAS 9.4.

RESULTS Baseline NCCT images were available for 989 participants enrolled in ATACH-II. We included 869 and 952 patients in the hematoma expansion and outcome analysis, respectively. The flowchart of the study population selection is shown in figure e-2. A total of 186/869 patients (21.4%) experienced hematoma expansion and 361/952 (37.9%) had unfavorable outcome at 3 months. The case fatality rate at 90 days was 6.7%. The characteristics of the study population are summarized in table e-2.

Prediction of hematoma expansion and unfavorable outcome. Table 1 shows the prevalence and diagnostic performance of different NCCT markers in predicting ICH expansion and unfavorable outcome. The interrater reliability was good to excellent for all NCCT signs. Only 9 patients (0.9%) had an intrahematoma fluid level and therefore this marker was not included in the main analyses.

Hematoma shape and density and the presence of any intrahematoma hypodensity showed higher sensitivity for prediction of ICH expansion and unfavorable functional outcome whereas black hole sign and blend sign had superior specificity.

Table 1 Accuracy of different noncontrast CT markers in predicting intracerebral hemorrhage (ICH) expansion and poor outcome

	Hypodensities	Swirl sign	Black hole sign	Blend sign	Irregular shape	Heterogeneous density
Frequency, n (%)	264 (26.7)	203 (20.5)	70 (7.1)	86 (8.7)	390 (39.4)	310 (31.3)
Interrater reliability, κ	0.83 (0.76–0.90)	0.76 (0.67–0.85)	0.63 (0.48–0.80)	0.71 (0.57–0.85)	0.70 (0.61–0.78)	0.62 (0.53–0.72)
ICH expansion						
Sensitivity	0.40 (0.33–0.47)	0.33 (0.26–0.40)	0.15 (0.09–0.20)	0.13 (0.08–0.18)	0.49 (0.42–0.56)	0.44 (0.37–0.51)
Specificity	0.78 (0.75–0.81)	0.83 (0.80–0.86)	0.95 (0.94–0.97)	0.93 (0.91–0.95)	0.64 (0.61–0.68)	0.72 (0.69–0.76)
PPV	0.33 (0.27–0.39)	0.34 (0.27–0.42)	0.45 (0.32–0.58)	0.33 (0.22–0.44)	0.27 (0.22–0.32)	0.30 (0.25–0.36)
NPV	0.83 (0.80–0.86)	0.82 (0.79–0.85)	0.80 (0.78–0.83)	0.80 (0.77–0.82)	0.82 (0.79–0.85)	0.83 (0.80–0.86)
Accuracy	0.70	0.72	0.78	0.76	0.61	0.66
mRS >3 at 90 days						
Sensitivity	0.37 (0.32–0.42)	0.29 (0.25–0.34)	0.11 (0.07–0.14)	0.08 (0.05–0.11)	0.58 (0.53–0.64)	0.46 (0.41–0.51)
Specificity	0.81 (0.77–0.84)	0.85 (0.83–0.88)	0.95 (0.94–0.97)	0.90 (0.88–0.93)	0.72 (0.69–0.76)	0.78 (0.75–0.81)
PPV	0.53 (0.47–0.60)	0.55 (0.48–0.62)	0.58 (0.46–0.70)	0.33 (0.23–0.42)	0.56 (0.51–0.61)	0.56 (0.50–0.62)
NPV	0.68 (0.64–0.71)	0.66 (0.63–0.70)	0.64 (0.60–0.67)	0.62 (0.58–0.65)	0.74 (0.70–0.78)	0.70 (0.67–0.74)
Accuracy	0.64	0.62	0.63	0.59	0.67	0.66

Abbreviations: mRS = modified Rankin Scale; NPV = negative predictive value; PPV = positive predictive value.

Interrater reliability was calculated with Cohen κ statistic. Numbers in parentheses represent 95% confidence intervals.

All possible combinations of different NCCT signs did not improve sensitivity for ICH expansion compared to any single marker (not shown).

There is substantial overlap in the diagnostic criteria for different NCCT markers. In particular, all patients with evidence of a black hole sign or a swirl sign also qualify for the presence of intrahematoma hypodensities. Furthermore, the more inclusive definition of any hypodensity showed higher sensitivity for hematoma expansion compared with black hole sign and swirl sign. Therefore we decided to build the multivariable regression model including black hole sign and swirl sign in the any hypodensity definition.

Tables 2 and 3 show the results of the univariate and multivariable analyses for predictors of ICH expansion and poor outcome. NCCT hypodensities, blend sign, irregular hematoma shape, and heterogeneous densities predicted significant hematoma growth after adjustment for potential confounders. ICH shape and density were also independent predictors of poor

functional outcome at 90 days. Surprisingly, the presence of blend sign predicted good outcome, despite its association with increased risk of hematoma expansion. To further explore this unexpected finding, we performed an additional analysis comparing blend sign positive vs blend sign negative patients. The results of this analysis are shown in table e-3.

All results remained unchanged when treatment assignment was included as a covariate in the multivariable analyses.

Association between NCCT markers and benefit from intensive BP treatment. The effect of BP treatment on hematoma expansion stratified by NCCT markers status is summarized in figure 1. Intensive BP reduction was associated with reduced risk of ICH expansion in hemorrhages with irregular shape. However, there was no evidence of a significant interactive effect between any of the NCCT predictors of expansion and BP treatment (all p values for interaction >0.10).

Table 2 Univariate and multivariate analysis of intracerebral hemorrhage expansion

	Univariate		Multivariate ^a	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Hypodensities	2.36 (1.67–3.33)	<0.0001	2.84 (1.90–4.25)	<0.0001
Blend sign	1.92 (1.14–3.22)	0.02	2.34 (1.35–4.05)	0.002
Irregular shape	1.74 (1.25–2.41)	0.001	1.98 (1.36–2.87)	0.0003
Heterogeneous density	2.06 (1.48–2.88)	<0.0001	2.47 (1.65–3.68)	<0.0001

Abbreviations: CI = confidence interval; OR = odds ratio.

^aAdjusted for baseline intracerebral hemorrhage volume and time from onset to baseline noncontrast CT. Hematoma expansion was defined as an increase of 33% or more in the hematoma volume from baseline to 24 hours.

Table 3 Univariate and multivariate analysis of unfavorable outcome

	Univariate		Multivariate ^a	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Hypodensities	2.39 (1.78-3.21)	<0.0001	1.33 (0.92-1.93)	0.14
Blend sign	0.77 (0.48-1.24)	0.28	0.49 (0.27-0.90)	0.02
Irregular shape	3.66 (2.78-4.83)	<0.0001	2.17 (1.54-3.05)	<0.0001
Heterogeneous density	2.99 (2.25-3.97)	<0.0001	1.54 (1.08-2.20)	0.02

Abbreviations: CI = confidence interval; OR = odds ratio.

^aAdjusted for age, baseline intracerebral hemorrhage volume, admission Glasgow Coma Scale score, and presence of intraventricular hemorrhage.

Likewise, there was no evidence of improved functional outcome in patients with NCCT markers of expansion randomized to intensive BP lowering (all *p* values for interaction >0.10), as shown in figure 2.

DISCUSSION In this prospective, multicenter, international study, we report the prevalence and clinical significance of several NCCT markers of hematoma expansion and investigated whether these imaging signs identify ICH patients more likely to benefit from intensive BP treatment. We found that NCCT markers are common and independently predicted significant hematoma growth in this cohort. However, we found no evidence that intensive BP lowering specifically improves clinical outcome in patients with these imaging markers.

Several NCCT imaging predictors of ICH expansion have been described recently.^{5-7,9,17} In the present study,

we validated these markers, showing their ability to independently predict hematoma expansion across a wide range of institutions. The overall prevalence of NCCT signs and their sensitivity for ICH expansion prediction was lower in our cohort compared to previous single-center studies.⁵⁻⁷ These discrepancies may be explained by some important differences in the ATACH-II study population compared to real-world studies. NCCT hypodensities, blend sign, black hole sign, and hematoma density and shape are directly associated with ICH size and anticoagulation, and the ATACH-II trial disproportionately included patients without anticoagulation and with smaller baseline hematoma volumes. There is also great heterogeneity in the definition of hematoma growth, which may account for some of the observed findings as well.¹

Despite the association between NCCT findings and hematoma expansion, patients with these markers

Figure 1 Effect of treatment assignment on intracerebral hemorrhage expansion, stratified by noncontrast CT markers status

Adjusted for baseline intracerebral hemorrhage volume and time from onset to baseline noncontrast CT. Hematoma expansion was defined as an increase of 33% or more in the hematoma volume from baseline to 24 hours. CI = confidence interval; OR = odds ratio.

Figure 2 Effect of treatment assignment on primary outcome, stratified by noncontrast CT markers status

Adjusted for age, baseline intracerebral hemorrhage volume, admission Glasgow Coma Scale score, and presence of intraventricular hemorrhage. CI = confidence interval; OR = odds ratio.

did not benefit from intensive BP treatment in terms of reduced hematoma growth or improved outcome. One possible explanation of our findings is that intensive BP reduction does not truly influence the risk of hematoma growth. In line with this, several randomized control trials failed to demonstrate a consistent association between intensive BP treatment and reduced risk of ICH expansion.^{12,18–20} Another possibility is that our analysis was underpowered to detect a significant association between BP treatment and hematoma growth in the subgroup of patients with NCCT hallmarks of hematoma growth. All the NCCT signs showed sensitivity below 50% for hematoma expansion, meaning that more than half of the expanders did not have evidence of these markers.

Our findings may represent a paradigm shift in clinical practice and future clinical trials targeting ICH expansion. The CTA spot sign is a robust and validated predictor of hematoma expansion³ but CTA is not widely available and carries some potential drawbacks like increased radiation delivery.²¹ Furthermore, there is great heterogeneity in the CTA acquisition protocol across institutions, with lack of agreement on the optimal setting for spot sign detection.^{22,23} Unlike CTA, NCCT is an inexpensive and widely available tool that represents the gold standard technique for ICH diagnosis worldwide.²⁴ We showed that ICH appearance on NCCT can reliably stratify the risk of hematoma expansion and may allow rapid identification of patients more likely to develop ICH expansion in clinical practice or in the setting of clinical trials. NCCT markers with higher

sensitivity for expansion like hypodensities and hematoma shape and density may be preferred in clinical trials selecting patients for antiexpansion therapies with a favorable safety profile, in order to capture as many patients as possible at high risk of hematoma growth. On the other hand, blend sign and black hole sign showed excellent specificity for ICH expansion. These markers may therefore be preferred in studies targeting hematoma growth with hemostatic drugs that may carry thromboembolic risks, in order to reduce the risk of potential harm in patients with a low likelihood of ICH expansion.

Accurate prognosis prediction is still an unmet need in ICH clinical care.²⁵ We showed that hematoma shape and density are independently associated with unfavorable outcome. These markers may therefore provide additional value in identifying those patients at high risk of poor outcome after ICH. The presence of blend sign was associated with increased risk of hematoma growth but also with more favorable functional outcome at 90 days. This counterintuitive result may be a random finding arising from the very small number of patients having a blend sign (less than 10% of the entire study population).²⁶ This possibility is indirectly supported by recent evidence showing that patients with a blend sign are at high risk of clinical deterioration.²⁷ In addition, ICH expansion is a major determinant of early clinical deterioration and mortality, but other unmeasured confounders such as secondary complications²⁸ may influence 90-day outcome and explain this unexpected observation.

Some limitations of the present study should be considered when interpreting our findings. First, patients enrolled in ATACH-II were overall less severely affected compared to real-world ICH populations.^{29,30} This may have reduced our power to detect an association between NCCT signs, BP lowering, and outcome (ceiling effect). Second, anticoagulant treatment is a strong predictor of hematoma growth and poor outcome,³¹ and we were not able to account for this important confounder. Third, a subgroup of patients did not receive a follow-up NCCT scan and therefore could not be included in the hematoma expansion analysis. Finally, medical complications and in particular infections are strongly associated with poor outcome after ICH²⁸ and we were not able to fully account for these factors in our analyses.

We prospectively validated that NCCT imaging markers can reliably identify ICH patients at high risk of ICH expansion across a wide range of scanners and centers. NCCT is a widely available tool that may identify those patients more likely to experience ICH expansion in future clinical trials targeting hematoma growth. Despite the association between NCCT markers and risk of hematoma expansion, patients with these markers may not specifically benefit from intensive BP treatment in terms of improved functional outcome.

AUTHOR CONTRIBUTIONS

Study concept and design: Drs. Morotti, Rosand, and Goldstein. Acquisition of data: all authors. Imaging analysis: Drs. Morotti and Boulouis. Statistical analysis: C. Cassarly and Dr. Martin. Analysis and interpretation of data: all authors. Drafting of the manuscript: Drs. Morotti, Rosand, and Goldstein. Critical revision of the manuscript for important intellectual content: all authors. Obtained funding: Drs. Rosand and Goldstein. Study supervision: Drs. Rosand and Goldstein.

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