Journal of the American Heart Association

ORIGINAL RESEARCH

Noncontrast Computed Tomography Markers as Predictors of Revised Hematoma Expansion in Acute Intracerebral Hemorrhage

Wen-Song Yang, MD*; Shu-Qiang Zhang, MD*; Yi-Qing Shen, MD; Xiao Wei, MA; Li-Bo Zhao, MD, PhD; Xiong-Fei Xie, MD; Lan Deng, MD; Xin-Hui Li, MD; Xin-Ni Lv, MD; Fa-Jin Lv, MD, PhD; Dar Dowlatshahi, MD, PhD; Qi Li, MD, PhD; Peng Xie, MD

BACKGROUND: Noncontrast computed tomography (NCCT) markers are the emerging predictors of hematoma expansion in intracerebral hemorrhage. However, the relationship between NCCT markers and the dynamic change of hematoma in parenchymal tissues and the ventricular system remains unclear.

METHODS AND RESULTS: We included 314 consecutive patients with intracerebral hemorrhage admitted to our hospital from July 2011 to May 2017. The intracerebral hemorrhage volumes and intraventricular hemorrhage (IVH) volumes were measured using a semiautomated, computer-assisted technique. Revised hematoma expansion (RHE) was defined by incorporating the original definition of hematoma expansion into IVH growth. Receiver operating characteristic curve analysis was used to compare the performance of the NCCT markers in predicting the IVH growth and RHE. Of 314 patients in our study, 61 (19.4%) had IVH growth and 93 (23.9%) had RHE. After adjustment for potential confounding variables, blend sign, black hole sign, island sign, and expansion-prone hematoma could independently predict IVH growth and RHE in the multivariate logistic regression analysis. Expansion-prone hematoma had a higher predictive performance of RHE than any single marker. The diagnostic accuracy of RHE in predicting poor prognosis was significantly higher than that of hematoma expansion.

CONCLUSIONS: The NCCT markers are independently associated with IVH growth and RHE. Furthermore, the expansion-prone hematoma has a higher predictive accuracy for prediction of RHE and poor outcome than any single NCCT marker. These findings may assist in risk stratification of NCCT signs for predicting active bleeding.

Key Words: active bleeding ■ computed tomography ■ hematoma expansion ■ intracerebral hemorrhage ■ intraventricular hemorrhage

Intracerebral hemorrhage (ICH) accounts for 8% to 27% of all strokes and leads to high mortality and morbidity worldwide.[1] The mortality of patients with ICH ranges from 35% at 7 days to 59% at 1 year, and >60% of survivors are left with severe functional disability.[2] Hematoma expansion (HE) occurs in ≈30% of patients with ICH[3,4] and is considered as a potentially modifiable predictor target for antiexpansion treatment in many clinical trials.[5–8] Although several trials have curbed the growth of hematoma, the outcomes of patients have not been improved accordingly.[6–8]

Correspondence to: Qi Li, MD, PhD, Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. E-mail: qili_md@126.com and Peng Xie, MD, Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. E-mail: peng_xie@yahoo.com

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018248

For Sources of Funding and Disclosures, see page 7 and 8.

*Dr Yang and Dr Zhang contributed equally to this work.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We have investigated whether the noncontrast computed tomography markers could predict the intraventricular hemorrhage growth and revised hematoma expansion criteria, which has not been reported in previous studies.
- We tested the diagnostic performance of noncontrast computed tomography markers in predicting intraventricular hemorrhage growth and revised hematoma expansion criteria, and found that noncontrast computed tomography markers are independently associated with intraventricular hemorrhage growth and revised hematoma expansion.
- The expansion-prone hematoma has a higher predictive accuracy for predicting revised hematoma expansion and poor outcome than any single noncontrast computed tomography marker.

What Are the Clinical Implications?

- Our findings may assist in the risk stratification of active bleeding, and be helpful for providing more accurate prognostic information for clinical decision-making.
- Our results may help clinicians to select patients for antiexpansion treatment in future clinical trials.

Nonstandard Abbreviations and Acronyms

ATACH-2	Antihypertensive Treatment of Acute Cerebral Hemorrhage 2
EPH	expansion-prone hematoma
NCCT	noncontrast computed tomography
RHE	revised hematoma expansion

More recently, many investigators have shifted their focus to the dynamic changes of intraventricular hemorrhage (IVH). Delayed IVH, which accounted for 8% to 10% of ICH, is an independent predictor of poor outcome.[9,10] IVH volume of >2 mL could also independently predict the poor outcome of ICH.[11] Some investigators reported that IVH volume growth as small as 1 mL could be an optimal threshold for predicting unfavorable outcomes.[12] Li et al[13] have found that combined delayed IVH and IVH expansion of >1 mL is closely correlated with poor outcome. Therefore, the conventional definition of HE may be one part of the active bleeding of ICH. Extending the current HE definition to the dynamic changes of hematoma volume in intraparenchymal tissues and ventricular system may be necessary. Furthermore, it is important to predict the dynamic process of ICH for antiexpansion treatment.

The computed tomographic angiography spot sign is a promising indicator to stratify the risk of HE and poor outcome.[14–16] Dowlatshahi et al[17] have innovatively discussed the association of computed tomographic angiography spot sign with revised HE (RHE). However, seeing that the computed tomographic angiography spot sign is not widely available in most hospitals, the association of the noncontrast computed tomography (NCCT) markers may be the alternatives to the computed tomographic angiography spot sign to establish simple models for predicting the HE.[18–22] Meantime, whether NCCT markers could predict IVH growth and RHE remains unclear.

In this study, we aim to investigate whether the NCCT markers could predict the IVH growth and RHE criteria. We further tested this diagnostic performance of NCCT markers in predicting IVH growth and RHE criteria.

METHODS

Study Population

All patients with ICH admitted to the First Affiliated Hospital of Chongqing Medical University were included in our ongoing prospective study. More than 1000 patients with acute stroke were treated in this tertiary referral hospital over a year period. Patients aged >18 years were enrolled from July 2011 to May 2017. Patients with an axial computed tomography (CT) scan performed within 6 hours after ICH onset and a follow-up CT scan performed within 36 hours after the initial CT scan were included. We excluded patients with anticoagulant-associated ICH, primary IVH, hemorrhagic transformation after cerebral infarction, and secondary ICH as a result of tumor or trauma.

Standard Protocol Approval and Patient Consent

All study procedures and protocols involving human participants comply with the ethical standards of the Declaration of Helsinki. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. All patients (or their legal representatives) provided written informed consent.

Clinical Data Collection and Image Analysis

The clinical and imaging data, including age, sex, medical history, prior medication use, admission

Glasgow Coma Scale score, time from ICH onset to initial CT scans, and baseline blood pressure (BP), were recorded. Modified Rankin Scale (mRS) score was assessed at 90 days through telephone by trained neurologists. All CT scans were performed without intravenous contrast injection. All CT images were saved as Digital Imaging and Communications in Medicine format and further reviewed independently by 2 experienced readers (Q.L. and W.S.Y.) who were blinded to clinical and outcome data.

Hematoma location was classified as basal ganglia, thalamus, lobar, and infratentorial. The ICH volumes and IVH volumes were measured using a semiautomated computer-assisted software (Mimics Software, version 20.0; Materialise NV, Leuven, Belgium). Briefly, predefined maximum and minimum Hounsfield units were set for building a mask. The segmentation accuracy of ICH and IVH hematomas was confirmed by a region growing algorithm with a visual inspection.[23] We manually segmented the ICH hematomas and IVH hematomas if they were connected.

HE was defined as relative intraparenchymal hematoma growth >33% or absolute hematoma growth of >6 mL of the baseline hematoma volume.[3] IVH growth was defined as either a newly occurring IVH on follow-up CT without the presence of IVH on initial CT (delayed IVH) or an absolute growth of IVH volume >1 mL from initial CT scan to follow-up CT scan, as previously described.[12,13] We defined the RHE criteria as HE or IVH growth, including 4 types, as follows: ≥6 mL or >33% or IVH expansion ≥1 mL or delayed IVH.[24] Active bleeding refers to the definition of HE, IVH growth, or RHE.

Several NCCT markers, including blend sign, black hole sign, and island sign, were defined, as previously described (Figure S1).[25–27] In brief, we defined the NCCT blend sign as follows: (1) blending of the relatively hyperattenuating area with an adjacent hypoattenuating region within a hematoma with an easily recognized border; (2) there was at least an 18–Hounsfield unit difference between the 2 density area in a hematoma, and the relatively high-density area cannot encapsulate the low-density area.[25] The NCCT black hole sign was defined as the low-density area wrapped in the high-density area with an identifiable border, and the difference between the density regions was >28 Hounsfield units.[26] The NCCT island sign was defined as >3 scattered small round or oval hematomas separated from the main hematoma or >4 small hematoma parts or all of which may link with the main hematoma.[27] Expansion-prone hematoma was defined as the presence of ≥1 of the above-mentioned NCCT markers.[28] Our primary outcome was poor outcome, defined as 90-day mRS score of 4 to 6.[7,29] The poor clinical outcome of mRS score of 3 to 6 was considered as a secondary outcome.[24]

Statistical Analysis

All statistical analyses were performed using SPSS 21.0 (SPSS, Chicago, IL) and MedCalc version 11.4.2. The performances of blend sign, black hole sign, island sign, and expansion-prone hematoma for predicting IVH growth and RHE were evaluated using the receiver operating characteristic curve analysis. The area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated to evaluate the predictive performance. All categorical variables, such as sex, alcohol consumption, smoking, diabetes mellitus, history of hypertension, presence of IVH on initial CT, NCCT markers, expansion-prone hematoma, poor outcome, and ICH location, were compared using the χ^2 test or the Fisher exact test, where appropriate. The continuous variables, including age, baseline ICH volume, baseline IVH volume, baseline Glasgow Coma Scale score, time from onset to initial CT, admission systolic BP, and admission diastolic BP, were compared using the Student *t* test or the Mann-Whitney *U* test. Interobserver agreement on categorical variables was calculated using the Cohen κ interagreement test. Multivariate logistic regression analyses were performed by including all variables with $P \leq 0.1$ in the univariate analysis. The level of significance was set to a $P<0.05$.

The data that support the findings of this study are available from the corresponding author on reasonable request.

RESULTS

We finally included 314 patients with ICH in the analysis (Figure 1). The mean age of these patients was 59.7±12.3 years. The median time from ICH onset to initial CT scans was 2 hours (interquartile range, 1–4 hours), and the interval time from symptom onset to follow-up CT scan was 20 hours (interquartile range, 14–26 hours). Hematomas on the initial CT scan were located at basal ganglia (173 [55.1%]), thalamus (78 [24.8%]), cerebral lobes (40 [12.7%]), and infratentorial area (23 [7.3%]). There were 48 (15.3%) patients with blend sign, 43 (13.7%) with black hole sign, 47 (15.0%) with island sign, and 96 (30.6%) with expansion-prone hematoma. Interobserver agreement was excellent for evaluation of the presence of blend sign (κ=0.84 [95% CI, 0.74–0.92]), black hole sign (κ=0.87 [95% CI, 0.77–0.94]), and island sign (κ=0.91 [95% CI, 0.84–0.96]).

The baseline demographics, clinical, radiological characteristics, and functional outcome between

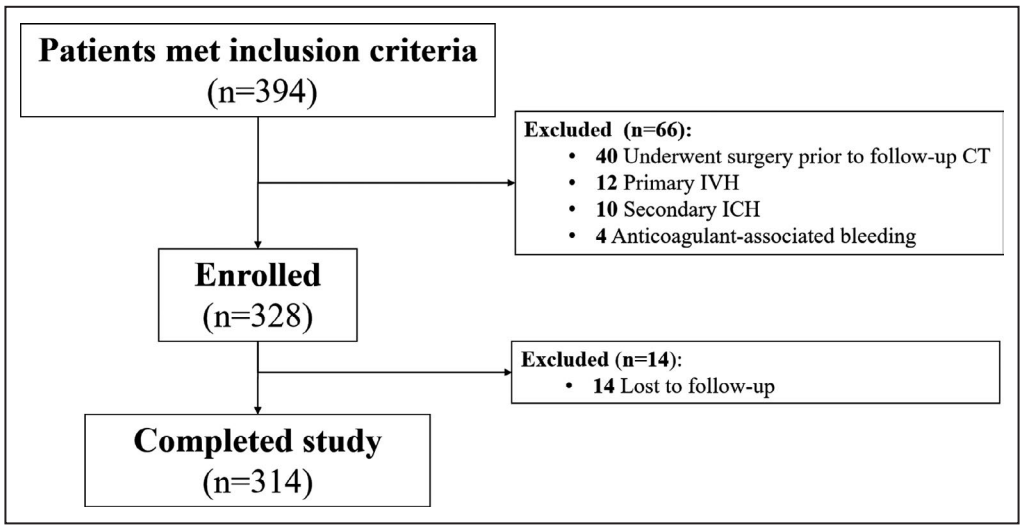

Figure 1. Cohort selection flowchart.
CT indicates computed tomography; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage.

patients with and without IVH growth or RHE were shown in Table 1. Of 314 patients, 75 (23.9%) had HE, 61 (19.4%) had IVH growth, and 93 (29.6%) had RHE. Of 61 patients with IVH growth, there were 18 (29.5%) without HE. Among these 18 patients, 14 (77.8%) had the primary outcome (mRS score 4–6) and 16 (88.9%) had the secondary outcome (mRS score 3–6). Of 93 patients with RHE, there were 29 (31.2%) with blend sign, 26 (28.0%) with black hole sign, 34 (36.6%) with island sign, and 54 (58.1%) with expansion-prone hematoma (Table 1). Different active bleeding definition, stratified by HE-defining characteristics, was shown in Table S1. Among these 25 patients with delayed IVH, 23 (92%) had HE.

After adjustment for age, baseline Glasgow Coma Scale score, time from onset to initial CT, baseline hematoma volume, baseline IVH volume, presence of IVH on initial CT, systolic BP, and ICH location, we found that blend sign, black hole sign, island sign, and expansion-prone hematoma could predict IVH growth in the multivariate logistic regression analysis, individually (Table 2). Moreover, blend sign, black hole sign, island sign, and expansion-prone hematoma could independently predict RHE in the multivariate logistic regression analysis after adjusting the potential confounding factors (Table 2).

The diagnostic performances of the NCCT markers in predicting the active bleeding of ICH were illustrated in Table 3. Briefly, the model of expansion-prone hematoma (AUC=0.70) had higher predictive performance for prediction of RHE than blend sign (AUC=0.61), black hole sign (AUC=0.60), and island sign (AUC=0.65; Table 3). Univariate predictors of primary and secondary outcome were shown in Table S2. Multivariable logistic regression models of NCCT markers and the definitions of active bleeding for primary and secondary outcome were shown in Table S3. The NCCT markers and the definitions of active bleeding for predicting primary and secondary outcome were illustrated in Figure 2. Expansion-prone hematoma had a higher predictive value than blend sign or island sign in predicting the primary outcome (P<0.05; Figure 2A). Expansion-prone hematoma had higher predictive value than any single sign in predicting secondary outcome (P<0.05; Figure 2D). The diagnostic accuracy of RHE in predicting primary and secondary outcome was significantly higher than that of HE (P<0.05; Figure 2B and 2E). In addition, the diagnostic performances between expansion-prone hematoma and RHE were not significantly different in predicting primary and secondary outcome (Figure 2C and 2F).

DISCUSSION

In this study, we found that blend sign, black hole sign, and island sign could independently predict IVH growth and RHE. Furthermore, we found that the model of expansion-prone hematoma showed higher performance for predicting RHE and poor outcome than any single NCCT maker. The predictive accuracy among expansion-prone hematoma and RHE was similar in predicting poor outcome.

In previous studies, heterogeneous or irregularly shaped hematoma in the intraparenchymal tissue may reflect the active bleeding of HE.[30,31] Many NCCT markers, such as blend sign,[25] black hole sign,[26] CT hypodensities,[32] and island sign,[27] are associated with HE and have been validated in several studies.[33,34] Recently, the standards for detecting NCCT markers of HE from the

Table 1. Univariate Analysis for IVH Growth or RHE

	IVH Growth (n=61; 19.4%)	No IVH Growth (n=253; 80.6%)	*P* Value	RHE (n=93; 29.6%)	No RHE (n=221; 70.4%)	*P* Value
Demographic						
Age, mean (SD), y	63.3 (10.9)	58.8 (12.5)	0.009*	62.0 (11.6)	58.7 (12.5)	0.029*
Sex, male, n (%)	39 (63.9)	167 (66.0)	0.760	64 (68.8)	142 (64.3)	0.437
Clinical characteristics						
Alcohol consumption, n (%)	25 (41.0)	108 (42.7)	0.809	41 (44.1)	92 (41.6)	0.687
Smoking, n (%)	26 (42.6)	119 (47.0)	0.535	45 (48.4)	100 (45.2)	0.611
Diabetes mellitus, n (%)	7 (11.5)	29 (11.5)	0.998	13 (14.0)	23 (10.4)	0.364
History of hypertension, n (%)	45 (73.8)	177 (70.0)	0.557	67 (72.0)	155 (70.1)	0.735
Admission SBP, mean (SD), mm Hg	178.8 (32.8)	169.1 (26.8)	0.016*	177.6 (30.4)	168.1 (27.0)	0.007*
Admission DBP, mean (SD), mm Hg	102.3 (19.1)	98.3 (17.7)	0.124	101.8 (18.6)	98.0 (17.7)	0.082*
Admission GCS score, median (IQR)	10 (6–14)	14 (12–15)	<0.001*	12 (7.5–14)	14 (12–15)	<0.001*
Imaging features						
Time from onset to CT, median (IQR), h	1 (1–2)	2 (1–4)	<0.001*	1.5 (1–2.75)	2 (1–4)	0.001*
Presence of IVH on initial CT, n (%)	36 (59.0)	63 (24.9)	<0.001*	38 (40.9)	61 (27.6)	0.021*
Baseline ICH volume, median (IQR), mL	15.9 (9.7–28.9)	11.7 (7.1–20.9)	0.001*	16.8 (9.2–30.1)	11.4 (6.7–19.3)	<0.001*
Baseline IVH volume, median (IQR), mL	1.1 (0–7.8)	0 (0–0.12)	<0.001*	0 (0–4.2)	0 (0–1.1)	0.046*
Blend sign, n (%)	17 (27.9)	31 (12.3)	0.002*	29 (31.2)	19 (8.6)	<0.001*
Black hole sign, n (%)	19 (31.1)	24 (9.5)	<0.001*	26 (28.0)	17 (7.7)	<0.001*
Island sign, n (%)	25 (41.0)	22 (8.7)	<0.001*	34 (36.6)	13 (5.9)	<0.001*
Expansion-prone hematoma, n (%)	35 (57.4)	61 (24.1)	<0.001*	54 (58.1)	42 (19.0)	<0.001*
ICH locations, n (%)						
Basal ganglia hemorrhage	26 (42.6)	147 (58.1)	0.029*	46 (49.5)	127 (57.5)	0.193
Thalamic hemorrhage	23 (37.7)	55 (21.7)	0.010*	24 (25.8)	54 (24.4)	0.797
Lobar hemorrhage	8 (13.1)	32 (12.6)	0.922	17 (18.3)	23 (10.4)	0.056*
Infratentorial hemorrhage	4 (6.6)	19 (7.5)	1.000	6 (6.5)	17 (7.7)	0.700
Outcome						
90-d mRS score of 4–6, n (%)	51 (83.6)	69 (27.3)	<0.001*	65 (69.9)	55 (24.9)	<0.001*
90-d mRS score of 3–6, n (%)	56 (91.8)	103 (40.7)	<0.001*	74 (79.6)	85 (38.5)	<0.001*
90-d mRS score, median (IQR)	6 (4–6)	2 (1–4)	<0.001*	5 (3–6)	2 (1–3.5)	<0.001*

CT indicates computed tomography; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; RHE, revised hematoma expansion; and SBP, systolic blood pressure.

*$P \leq 0.1$.

International NCCT ICH Study Group have summarized practical standards for detecting NCCT markers and encourage that future clinical investigators may include the NCCT markers in the studies on HE.[31]

It is generally known that HE is strongly related to unfavorable outcome.[4] What is more, the dynamic changes of IVH volume increase >1 mL or delayed IVH also could predict poor outcomes.[9,10,12] In our study, of 61 patients with IVH growth, 18 (29.5%) patients had not undergone HE. Among these patients, 14 (77.8%) had poor outcomes, which were traditionally defined as nonexpanders. Moreover, we found that IVH growth possessed a higher AUC value and odds ratio for prediction of poor outcome than HE. Thus, in clinical practice, it is important to predict the dynamic process of IVH growth together with conventional definitions of HE in the short-term stage of ICH. In this study, the NCCT markers, including blend sign, black hole sign, and island sign, were considered as the independent factors for predicting IVH growth, which would be expected to improve the ability to predict clinical functional outcomes.

Recently, Yogendrakumar et al[24] have pointed out that the inclusion of IVH expansion into the current definition of HE could provide superior diagnostic accuracy for predicting poor outcome compared with the conventional definition of HE, which is confirmed in our results. Moreover, blend sign, black hole sign, and island sign could independently predict the revised definition of HE by incorporating IVH growth and the current definition of HE. From a clinical standpoint, although the specificity of the single sign in predicting RHE is high, its sensitivity still needs to be improved. A prediction model composed

Table 2. Multivariable Logistic Regression Models of NCCT Markers for Predicting IVH Growth and RHE

Variables	Adjusted Odds Ratio	95% CI	*P* Value
IVH growth*			
Blend sign	5.08	2.00–12.91	0.001
Black hole sign	2.81	1.13–6.98	0.026
Island sign	6.94	2.78–17.33	<0.001
Expansion-prone hematoma	7.38	3.03–17.99	<0.001
RHE‡			
Blend sign	5.58	2.56–12.18	<0.001
Black hole sign	2.57	1.14–5.83	0.023
Island sign	6.55	2.88–14.87	<0.001
Expansion-prone hematoma	6.11	3.13–11.93	<0.001

IVH indicates intraventricular hemorrhage; NCCT, noncontrast computed tomography; and RHE, revised hematoma expansion.

*Adjusted for age, baseline Glasgow Coma Scale score, time from onset to initial computed tomography, baseline hematoma volume, baseline IVH volume, presence of IVH on initial computed tomography, admission systolic blood pressure, and intracerebral hemorrhage location.

‡Adjusted for age, baseline Glasgow Coma Scale score, time from onset to initial computed tomography, baseline hematoma volume, baseline IVH volume, presence of IVH on initial computed tomography, admission systolic blood pressure, admission diastolic blood pressure, and intracerebral hemorrhage location.

of NCCT markers is expected to improve the risk prognostication.

Recently, a predictive model with ≥1 of the blend sign, black hole sign, or island sign was considered as expansion-prone hematoma, which has higher performance for predicting HE than any single sign.[28] In this study, when we extend the conventional definition of HE by incorporating the IVH growth, expansion-prone hematoma could be a better model for predicting RHE than any single NCCT maker. In our former study, we have defined a subgroup of small hematomas without NCCT markers as benign ICH.[35] Patients with benign ICH are at low risk of HE and unfavorable outcome. It indicates that the 3 NCCT signs could represent patients with ICH with a high risk of active bleeding and poor outcome. In addition, expansion-prone hematoma could be a better predictor of poor outcome when compared with any single NCCT sign, which is similar to a prior study.[28]

In several retrospective studies, patients with NCCT markers did not benefit from tranexamic acid and intensive BP reduction.[33,34] However, a recent subsequent analysis of the ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage 2) trial found that intensive BP reduction in the ultraearly phase of ICH could reduce the rate of HE and further improved the patients' outcome.[36] In this study, our results support that NCCT markers could predict the IVH growth and RHE, and help researchers identify patients with a high risk of the extending definition of HE. Concurrently, we found that the model of expansion-prone hematoma has better accuracy for predicting the RHE and unfavorable functional outcome of ICH than any single sign, which may be beneficial to the antiexpansion treatment, such as BP reduction in the ultraearly stage.

Our findings have several clinical implications. First, NCCT markers are closely associated with IVH growth and RHE. This finding has not been reported in previous studies. Second, combining blend sign, black hole sign, and island sign into a prediction model can better predict RHE, which is conducive to the risk stratification of active bleeding. Furthermore, the model of expansion-prone hematoma may be helpful for risk prognostication and selecting patients for antiexpansion treatment in clinical trials and provide more accurate prognostic information for clinical decision-making in clinical practice.

Our research has some limitations. First, this study was a single-center study, which may limit the generalizability to other populations. Second, the sample size in this research is relatively small, which has limited the accuracy of our subgroup analysis to some degree.

Table 3. NCCT Markers Associated With IVH Growth and RHE

Outcome Points	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95% CI)
IVH growth					
Blend sign	27.9	87.7	35.0	83.0	0.58 (0.50–0.66)
Black hole sign	31.1	90.5	44.0	85.0	0.61 (0.52–0.69)
Island sign	41.0	91.3	53.0	87.0	0.66 (0.58–0.75)
Expansion-prone hematoma	57.4	75.9	36.0	88.0	0.67 (0.59–0.75)
RHE					
Blend sign	31.2	91.4	60.0	76.0	0.61 (0.54–0.69)
Black hole sign	28.0	92.3	60.0	75.0	0.60 (0.53–0.67)
Island sign	36.6	94.1	72.0	78.0	0.65 (0.58–0.73)
Expansion-prone hematoma	58.1	81.0	56.0	82.0	0.70 (0.63–0.76)

AUC indicates area under the curve; IVH, intraventricular hemorrhage; NCCT, noncontrast computed tomography; NPV, negative predictive value; PPV, positive predictive value; and RHE, revised hematoma expansion.

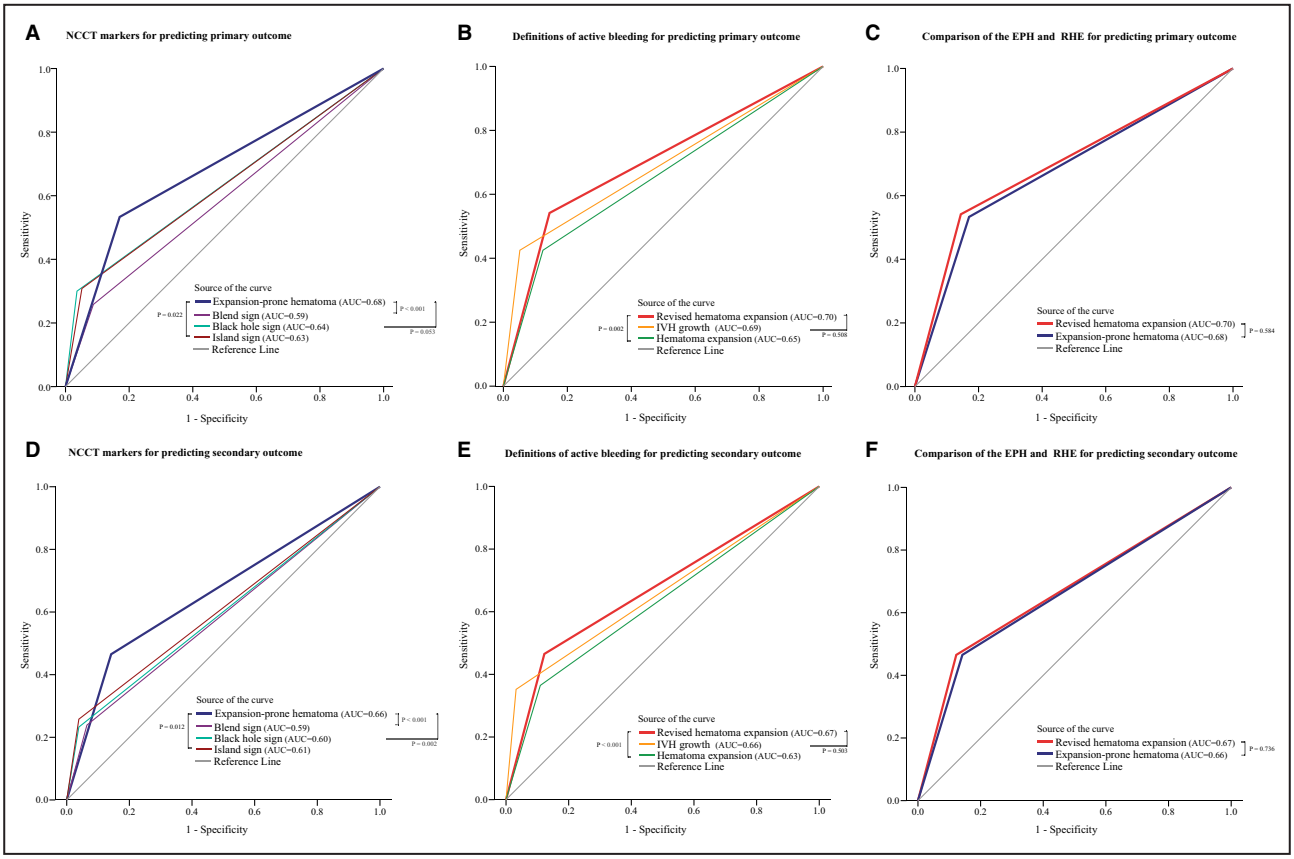

Figure 2. The receiver operating characteristic curves of noncontrast computed tomography (NCCT) markers and active bleeding for predicting primary outcome (modified Rankin Scale [mRS] score 4–6) and secondary outcome (mRS score 3–6). **A**, The NCCT markers for predicting primary outcome. **B**, Definitions of active bleeding for predicting primary outcome. **C**, Comparison of the expansion-prone hematoma (EPH) and revised hematoma expansion (RHE) for predicting primary outcome. **D**, The NCCT markers for predicting secondary outcome. **E**, Definitions of active bleeding for predicting secondary outcome. **F**, Comparison of the EPH and RHE for predicting secondary outcome. AUC indicates area under the curve; and IVH, intraventricular hemorrhage.

Therefore, further replication of our findings in a large-scale multicenter cohort is warranted.

CONCLUSIONS

We reported that NCCT markers are closely associated with IVH growth and RHE. Moreover, expansion-prone hematoma showed higher predictive accuracy for the prediction of RHE and poor outcome than any single NCCT marker. These findings may assist in risk stratification of active bleeding and clinical decision-making in patients with acute ICH.

ARTICLE INFORMATION

Received June 29, 2020; accepted December 16, 2020.

Affiliations

From the Department of Neurology (W.-S.Y., S.-Q.Z., Y.-Q.S., L.D., X.-H.L., X.-N.L., Q.L., P.X.) and NHC Key Laboratory of Diagnosis and Treatment on Brain Functional Diseases (W.-S.Y., S.-Q.Z., Y.-Q.S., X.-H.L., Q.L., P.X.), The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Department of Traditional Chinese Medicine, Chongqing Medical and Pharmaceutical College, Chongqing, China (X.W.); Department of Neurology (L.-B.Z.) and Chongqing Key Laboratory of Cerebrovascular Disease Research (L.-B.Z., Q.L., P.X.), Yongchuan Hospital of Chongqing Medical University, Chongqing, China; Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China (X.-F.X., F.-J.L.); and Department of Medicine (Neurology), Department of Medicine (Neurology), Ottawa Hospital Research Institute, University of Ottawa, Ontario, Canada (D.D.).

Acknowledgments

We thank all the individuals who participated in the study. All written permission was obtained from patients (or their legal representatives).

Author contributions: Drs W.-S. Yang, Q. Li, and P. Xie were responsible for the study concept and design and had full access to all of the data in the study. Drs W.-S. Yang, S.-Q. Zhang, Y.-Q. Shen, L.-B. Zhao, X.-F. Xie, L. Deng, X.-H. Li, X.-N. Lv, F.-J. Lv, Q. Li, and P. Xie and X. Wei did acquisition, analysis, or interpretation of data. Dr W.-S. Yang drafted the manuscript. Drs D. Dowlatshahi, Q. Li, and P. Xie did critical revision of the manuscript. Drs W.-S. Yang and S.-Q. Zhang did statistical analysis. Dr Q. Li obtained funding. Drs Q. Li and P. Xie were responsible for the administrative, technical, or material support.

Sources of Funding

This study was supported by grants from the National Key Research and Development Program of China (Nos. 2018YFC1312200 and 2018YFC1312203), the China Association of Science and Technology Young Talent Project (No. 2017QNRC001), and Chongqing High-End Young Investigator Project (No. 2019GDRC005).

Disclosures

Dr Dowlatshahi has received consulting and research contracts from Ottawa Hospital Research Institute. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S3
Figure S1

REFERENCES

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. 2009;8:355–369. DOI: 10.1016/S1474-4422(09)70025-0.
2. de Oliveira Manoel AL, Goffi A, Zampieri FG, Turkel-Parrella D, Duggal A, Marotta TR, Macdonald RL, Abrahamson S. The critical care management of spontaneous intracranial hemorrhage: a contemporary review. *Crit Care*. 2016;20:272. DOI: 10.1186/s13054-016-1432-0.
3. Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology*. 2011;76:1238–1244. DOI: 10.1212/WNL.0b013e3182143317.
4. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175–1181. DOI: 10.1212/01.wnl.0000208408.98482.99.
5. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355–2365. DOI: 10.1056/NEJMoa1214609.
6. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127–2137. DOI: 10.1056/NEJMoa0707534.
7. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. DOI: 10.1056/NEJMoa1603460.
8. Sprigg N, Flaherty K, Appleton JP, Salman R-S, Bereczki D, Beridze M, Christensen H, Ciccone A, Collins R, Czlonkowska A, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet*. 2018;391:2107–2115. DOI: 10.1016/S0140-6736(18)31033-X.
9. Maas MB, Nemeth AJ, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Delayed intraventricular hemorrhage is common and worsens outcomes in intracerebral hemorrhage. *Neurology*. 2013;80:1295–1299. DOI: 10.1212/WNL.0b013e31828ab2a7.
10. Moullaali TJ, Sato S, Wang X, Rabinstein AA, Arima H, Carcel C, Chen G, Robinson T, Heeley E, Chan E, et al. Prognostic significance of delayed intraventricular haemorrhage in the INTERACT studies. *J Neurol Neurosurg Psychiatry*. 2017;88:19–24. DOI: 10.1136/jnnp-2015-311562.
11. Steiner T, Diringer MN, Schneider D, Mayer SA, Begtrup K, Broderick J, Skolnick BE, Davis SM. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. *Neurosurgery*. 2006;59:767–774; discussion 773–774. DOI: 10.1227/01.NEU.0000232837.34992.32.
12. Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Silva Y, Dzialowski I, Kobayashi A, et al. New and expanding ventricular hemorrhage predicts poor long-term outcome in acute intracerebral hemorrhage. *Neurology*. 2019;93:e879–e888.
13. Li Q, Li R, Zhao LB, Yang XM, Yang WS, Deng L, Lv XN, Wu GF, Tang ZP, Wei M, et al. Intraventricular hemorrhage growth: definition, prevalence and association with hematoma expansion and prognosis. *Neurocrit Care*. 2020;33:732–739. DOI: 10.1007/s12028-020-00958-8.
14. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, Symons SP. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. 2007;38:1257–1262. DOI: 10.1161/01.STR.0000259633.59404.f3.
15. Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, Levnull MH, Rosand J. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology*. 2007;68:889–894. DOI: 10.1212/01.wnl.0000257087.22852.21.
16. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, Kobayashi A, Boulanger J-M, Lum C, Gubitz G, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol*. 2012;11:307–314. DOI: 10.1016/S1474-4422(12)70038-8.
17. Dowlatshahi D, Deshpande A, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, Kobayashi A, Boulanger J-M, Lum C, et al. Do intracerebral hemorrhage nonexpanders actually expand into the ventricular space? *Stroke*. 2018;49:201–203. DOI: 10.1161/STROKEAHA.117.018716.
18. Sporns PB, Schwake M, Schmidt R, Kemmling A, Minnerup J, Schwindt W, Cnyrim C, Zoubi T, Heindel W, Niederstadt T, et al. Computed tomographic blend sign is associated with computed tomographic angiography spot sign and predicts secondary neurological deterioration after intracerebral hemorrhage. *Stroke*. 2017;48:131–135. DOI: 10.1161/STROKEAHA.116.014068.
19. Yu Z, Zheng J, Ma L, Guo R, Li M, Wang X, Lin S, Li H, You C. The predictive accuracy of the black hole sign and the spot sign for hematoma expansion in patients with spontaneous intracerebral hemorrhage. *Neurol Sci*. 2017;38:1591–1597. DOI: 10.1007/s10072-017-3006-6.
20. Zhang F, Zhang S, Tao C, Yang Z, You C, Yang M. The comparative study of island sign and the spot sign in predicting short-term prognosis of patients with intracerebral hemorrhage. *J Neurol Sci*. 2019;396:133–139. DOI: 10.1016/j.jns.2018.11.022.
21. Sporns PB, Kemmling A, Schwake M, Minnerup J, Nawabi J, Broocks G, Wildgruber M, Fiehler J, Heindel W, Hanning U. Triage of 5 noncontrast computed tomography markers and spot sign for outcome prediction after intracerebral hemorrhage. *Stroke*. 2018;49:2317–2322. DOI: 10.1161/STROKEAHA.118.021625.
22. Sporns PB, Schwake M, Kemmling A, Minnerup J, Schwindt W, Niederstadt T, Schmidt R, Hanning U. Comparison of spot sign, blend sign and black hole sign for outcome prediction in patients with intracerebral hemorrhage. *J Stroke*. 2017;19:333–339. DOI: 10.5853/jos.2016.02061.
23. Della Bona A, Borba M, Benetti P, Duan Y, Griggs JA. Three-dimensional finite element modelling of all-ceramic restorations based on micro-CT. *J Dent*. 2013;41:412–419. DOI: 10.1016/j.jdent.2013.02.014.
24. Yogendrakumar V, Ramsay T, Fergusson DA, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Silva Y, Dzialowski I, Kobayashi A, et al. Redefining hematoma expansion with the inclusion of intraventricular hemorrhage growth. *Stroke*. 2020;51:1120–1127. DOI: 10.1161/STROKEAHA.119.027451.
25. Li Q, Zhang G, Huang YJ, Dong MX, Lv FJ, Wei X, Chen JJ, Zhang LJ, Qin XY, Xie P. Blend sign on computed tomography: novel and reliable predictor for early hematoma growth in patients with intracerebral hemorrhage. *Stroke*. 2015;46:2119–2123. DOI: 10.1161/STROKEAHA.115.009185.
26. Li Q, Zhang G, Xiong X, Wang XC, Yang WS, Li KW, Wei X, Xie P. Black hole sign: novel imaging marker that predicts hematoma growth in patients with intracerebral hemorrhage. *Stroke*. 2016;47:1777–1781. DOI: 10.1161/STROKEAHA.116.013186.
27. Li Q, Liu QJ, Yang WS, Wang XC, Zhao LB, Xiong X, Li R, Cao D, Zhu D, Wei X, et al. Island sign: an imaging predictor for early hematoma expansion and poor outcome in patients with intracerebral hemorrhage. *Stroke*. 2017;48:3019–3025. DOI: 10.1161/STROKEAHA.117.017985.
28. Li Q, Shen YQ, Xie XF, Xue MZ, Cao D, Yang WS, Li R, Deng L, Wei M, Lv FJ, et al. Expansion-prone hematoma: defining a population at high risk of hematoma growth and poor outcome. *Neurocrit Care*. 2019;30:601–608. DOI: 10.1007/s12028-018-0644-3.
29. Boulouis G, Morotti A, Brouwers HB, Charidimou A, Jessel MJ, Auriel E, Pontes-Neto O, Ayres A, Vashkevich A, Schwab KM, et al. Noncontrast computed tomography hypodensities predict poor outcome in intracerebral hemorrhage patients. *Stroke*. 2016;47:2511–2516. DOI: 10.1161/STROKEAHA.116.014425.

30. Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast computed tomography markers of intracerebral hemorrhage expansion. *Stroke*. 2017;48:1120–1125. DOI: 10.1161/STROKEAHA.116.015062.
31. Morotti A, Boulouis G, Dowlatshahi D, Li Q, Barras CD, Delcourt C, Yu Z, Zheng J, Zhou Z, Aviv RI, et al. Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. *Ann Neurol*. 2019;86:480–492. DOI: 10.1002/ana.25563.
32. Boulouis G, Morotti A, Brouwers HB, Charidimou A, Jessel MJ, Auriel E, Pontes-Neto O, Ayres A, Vashkevich A, Schwab KM, et al. Association between hypodensities detected by computed tomography and hematoma expansion in patients with intracerebral hemorrhage. *JAMA Neurol*. 2016;73:961–968. DOI: 10.1001/jamaneurol.2016.1218.
33. Morotti A, Boulouis G, Romero JM, Brouwers HB, Jessel MJ, Vashkevich A, Schwab K, Afzal MR, Cassarly C, Greenberg SM, et al. Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion. *Neurology*. 2017;89:548–554. DOI: 10.1212/WNL.0000000000004210.
34. Law ZK, Ali A, Krishnan K, Bischoff A, Appleton JP, Scutt P, Woodhouse L, Pszczolkowski S, Cala LA, Dineen RA, et al. Noncontrast computed tomography signs as predictors of hematoma expansion, clinical outcome, and response to tranexamic acid in acute intracerebral hemorrhage. *Stroke*. 2020;51:121–128. DOI: 10.1161/STROKEAHA.119.026128.
35. Li Q, Yang WS, Shen YQ, Xie XF, Li R, Deng L, Yang TT, Lv FJ, Lv FR, Wu GF, et al. Benign intracerebral hemorrhage: a population at low risk for hematoma growth and poor outcome. *J Am Heart Assoc*. 2019;8:e011892. DOI: 10.1161/JAHA.118.011892.
36. Li Q, Warren AD, Qureshi AI, Morotti A, Falcone GJ, Sheth KN, Shoamanesh A, Dowlatshahi D, Viswanathan A, Goldstein JN. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. *Ann Neurol*. 2020;88:388–395. DOI: 10.1002/ana.25793.

SUPPLEMENTAL MATERIAL

Table S1. Different Active Bleeding Definition Stratified by Hematoma Expansion Defining Characteristics.

	≥33% (n = 66)	≥6 mL (n =60)	delayed IVH (n =25)	IVH expansion ≥1 mL (n = 56)
Hematoma expansion (n=75)	66 (100%)	60 (100%)	23 (92%)	40 (71.4%)
IVH growth (n=61)	43 (65.2%)	40 (66%)	25 100%)	56 (100%)
RHE (n=93)	66 (100%)	60 (100%)	25 100%)	56 (100%)

IVH indicates intraventricular hemorrhage; RHE, revised hematoma expansion.

Table S2. Univariate Predictors of Primary Outcome (mRS 4-6) and Secondary Outcome (mRS 3-6).

Variables	mRS 4-6 (n=120, 38.2%)	mRS 0-3 (n=194, 61.8%)	*p* Value	mRS 3-6 (n=159, 50.6%)	mRS 0-2 (n=155, 49.4%)	*p* Value
Demographic						
Mean age, y(SD)	62.7(12.9)	57.7(11.6)	**<0.001**	62.2(12.6)	57.1(11.5)	**<0.001**
Sex, male, n(%)	86(71.7)	120(61.9)	**0.075**	112(70.4)	94(60.6)	**0.068**
Clinical characteristics						
Alcohol consumption, n (%)	50(41.7)	83(42.8)	0.846	65(40.9)	68(43.9)	0.592
Smoking, n (%)	62(51.7)	83(42.8)	0.125	77(48.4)	68(43.9)	0.418
Diabetes mellitus, n (%)	16(13.3)	20(10.3)	0.414	20(12.6)	16(10.3)	0.530
History of hypertension, n(%)	90(75.0)	132(68.0)	0.188	114(71.7)	108(69.7)	0.694
Admission SBP, mmHg (SD)	174.0(32.5)	169.1(25.3)	0.155	173.4(30.9)	168.5(25.2)	0.128
Admission DBP, mmHg (SD)	99.9(22.1)	98.6(15.0)	0.562	99.5(20.5)	98.7(15.1)	0.710
Admission GCS score, median (IQR)	11[6.25-14]	14[13-15]	**<0.001**	12[8-14]	14[13-15]	**<0.001**
Imaging features						
Time from onset to CT, h(IQR)	2[1-3]	2[1-4]	0.164	2[1-3]	2[1-4]	**0.065**
Presence of IVH on initial CT , n(%)	59(49.2)	40(20.6)	**<0.001**	72(45.3)	27(17.4)	**<0.001**
Baseline ICH volume, mL (IQR)	19.2[10.8-31.0]	10.5[6.0-16.7]	**<0.001**	15.0[9.6-28.5]	10.5[6.2-17.1]	**<0.001**
HE, n(%)	51(42.5)	24(12.4)	**<0.001**	58(36.5)	17(11.0)	**<0.001**
Baseline IVH volume, mL (IQR)	0[0-7.6]	0[0-0]	**<0.001**	0[0-7.2]	0[0-0]	**<0.001**
Baseline IVH volume ⩾1 mL, n(%)	55(45.8)	35(18.0)	**<0.001**	67(42.1)	23(14.8)	**<0.001**
IVH growth, n(%)	51(42.5)	10(5.2)	**<0.001**	56(35.2)	5(3.2)	**<0.001**
RHE, n(%)	65(54.2)	28(14.4)	**<0.001**	74(46.5)	19(12.3)	**<0.001**
Blend sign, n (%)	31(25.8)	17(8.8)	**<0.001**	38(23.9)	10(6.5)	**<0.001**
Black hole sign, n (%)	36(30.0)	7(3.6)	**<0.001**	37(23.3)	6(3.9)	**<0.001**
Island sign, n (%)	37(30.8)	10(5.2)	**<0.001**	41(25.8)	6(3.9)	**<0.001**
Expansion-prone hematoma, n (%)	63(52.3)	33(17.0)	**<0.001**	74(46.5)	22(14.2)	**<0.001**

ICH Location						
Basal ganglia hemorrhage, n (%)	55(45.8)	118(60.8)	**0.009**	75(47.2)	98(63.2)	**0.004**
Thalamic hemorrhage, n (%)	39(32.5)	39(20.1)	**0.013**	53(33.3)	25(16.1)	**<0.001**
Lobar hemorrhage	16(13.3)	24(12.4)	0.804	19(11.9)	21(13.5)	0.671
Infratentorial hemorrhage	10(8.3)	13(6.7)	0.590	12(7.5)	11(7.1)	0.878

ICH indicates intracerebral hemorrhage; CT, computed tomography; HE, hematoma expansion; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; IQR, inter-quartile range; SD, standard deviation; mRS, modified Rankin scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; RHE, revised hematoma expansion.

Table S3. Multivariable Logistic Regression Models of NCCT Markers and The Definitions of Active Bleeding for Primary and Secondary Outcome.

Variables	Primary Outcome (mRS 4-6)*		Secondary Outcome (mRS 3-6)[#]	
	Adjusted OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Definitions of Active Bleeding				
Hematoma expansion	4.75 (2.28-9.88)	**<0.001**	3.93 (1.91-8.10)	**<0.001**
IVH growth	7.65 (3.22-18.20)	**<0.001**	8.22 (2.91-23.21)	**<0.001**
RHE	5.02 (2.53-9.96)	**<0.001**	4.20 (2.15-8.23)	**<0.001**
NCCT markers				
Blend sign	5.83 (2.42-14.02)	**<0.001**	6.48 (2.71-15.46)	**<0.001**
Black hole sign	6.89 (2.27-20.87)	**0.001**	4.17 (1.41-12.28)	**0.010**
Island sign	5.02 (1.95-12.96)	**0.001**	5.24 (1.90-14.48)	**0.001**
Expansion-prone hematoma	7.51 (3.48-16.23)	**<0.001**	6.38 (3.16-12.87)	**<0.001**

NCCT indicates noncontrast computed tomography; CT, computed tomography; IVH, intraventricular hemorrhage; RHE, revised hematoma expansion; mRS, modified Rankin scale; OR, Odds Ratio; CI, Confidence Interval.

*Adjusted for age, sex, baseline intracerebral hemorrhage volume, baseline IVH volume, presence of IVH on initial CT, baseline glasgow coma scale, and ICH location.

[#]Adjusted for age, sex, baseline intracerebral hemorrhage volume, baseline IVH volume, presence of IVH on initial CT, baseline glasgow coma scale, time from onset to initial CT, and ICH location.

Figure S1. Representative images showed the NCCT markers and the revised hematoma expansion resulting from recognition of each NCCT marker.

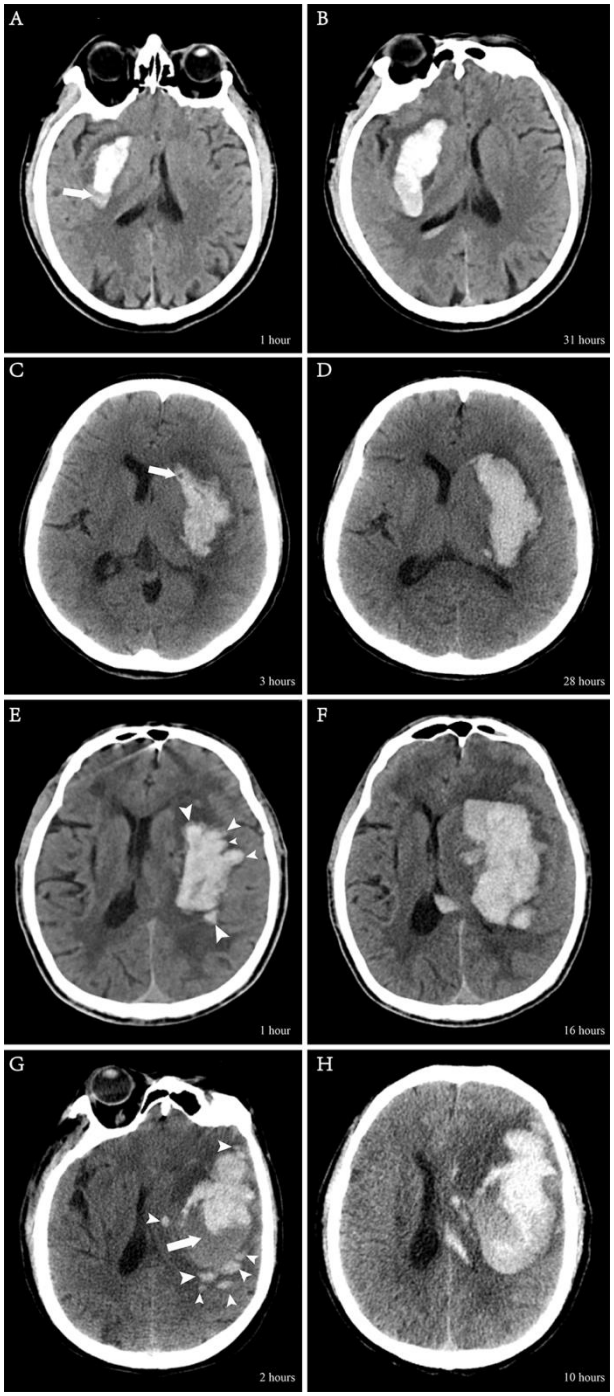

Illustration of a hematoma with blend sign (arrowhead, A, 1 hour after ICH onset), black hole sign (arrowhead, C, 3 hours after ICH onset), island sign (arrows, E, 1 hour after ICH onset), and blend sign (arrowheads) with coexisting island sign (arrows) (G, 2 hours after ICH onset) on the initial CT scan, and the corresponding revised hematoma expansion (B, D, F, and H) presented on the follow-up CT scan, respectively. The interval time from ICH onset to follow-up CT scan of B, D, F, and H were 31 hours, 28 hours, 16 hours and 10 hours, respectively. NCCT: Non-contrast computed tomography, ICH: Intracerebral hemorrhage.