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Establishment of a Scale for Predicting Early Hematoma Enlargement of Spontaneous Intracerebral Hemorrhage Based on Non-Contrast CT Signs

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ABSTRACT

AIM: This study aimed to optimize the Spontaneous intracerebral hemorrhage (sICH) early hematoma expansion prediction scoring table to adopt appropriate clinical treatment plans and improve the prognosis of sICH patients.

MATERIAL and METHODS: A total of 150 patients with sICH were enrolled, and 44 had early hematoma expansion. According to the selection and exclusion criteria, the study subjects were screened, their NCCT characteristic signs and clinical data were analyzed statistically. The established prediction score was applied to the follow-up study cohort to conduct a pilot study, and the t-test and ROC curve were used to evaluate its predictive ability.

RESULTS: Statistical analysis found that initial hematoma volume, GCS score, and NCCT special signs were independent risk factors for early hematoma expansion after sICH ($p<0.05$). Thus, a score table was established. Subjects with ≥10 were divided into high-risk group, 6-8 comprised the medium-risk group, and ≤4 were divided into low-risk group. Among 17 patients with acute sICH, 7 developed early hematoma enlargement. The prediction accuracy was 92.41% in the low-risk group, 98.06% in the medium-risk group, and 84.61% in the high-risk group.

CONCLUSION: This optimized prediction score table based on the special signs of NCCT shows the high prediction accuracy of sICH early hematoma.

KEYWORDS: Spontaneous intracerebral hemorrhage, Early hematoma enlargement, Prediction rating table, Noncontrast CT signs

INTRODUCTION

Spontaneous intracerebral hemorrhage (sICH) accounts for about 10-15% of all types of stroke and has a high mortality and disability rate than ischemic stroke (48) (58% of sICH patients die within 1 year, neurologic dysfunction persisted in 67% ofpatients). The main causes of sICH are various forms of small vessel diseases (4), among which hypertensive cerebral hemorrhage is the most common, and other causes include vascular malformations, cerebral venous sinus thrombosis, tumors, and the use of anticoagulants. Noncontrast computed tomography (NCCT) is a conventional imaging method for the diagnosis of acute sICH and has been widely used as the first choice for monitoring intracranial conditions. The parameters of NCCT, along with various clinical criteria, have been used to create practical scoring protocols that predict (early hematoma enlargement). According to Brott criteria (8), hematoma enlargement is defined as an increase in hematoma volume by >33% or an increase of >6 mL in the newly diagnosed CT compared to the next review to assess prognosis (1). Actively implemented interventions (including surgery and drug therapy) can improve the clinical outcome after sICH (4). Therefore, identifying patients with sICH who are at risk of hematoma enlargement

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is essential for the diagnosis, treatment plan, and prediction of prognosis. Chinese Stroke Association guidelines for clinical management of intracerebral hemorrhage in 2019 (10) stated that CT angiography (CTA) examination should be performed routinely in competent hospitals. In addition to excluding secondary intracerebral hemorrhage, CTA "point sign" is a risk factor for hematoma enlargement of sICH. Factors such as CT hematoma volume at first diagnosis, "Blend sign." and "Island sign" on NCCT should be comprehensively considered in assessing the risk of hematoma enlargement.

CTA "point sign" is a reliable and effective marker of hematoma enlargement, clinical deterioration, and poor prognosis in sICH (12). However, its evaluation requires CTA, which is not a routine test in the diagnostic examination of acute sICH. In a large randomized controlled trial (35), <20% of patients with sICH received CTA within 8 h of onset. Two randomized controlled trials (RCTs) selected sICH patients for CTA screening (16,33) were terminated prematurely due to difficulties in recruiting subjects. These failures highlight the need for CTA-independent strategies for predicting hematoma enlargement and adverse outcomes, and hence, NCCT special signs have emerged as an alternative to CTA "point signs" to rapidly identify patients at a high risk of early hematoma enlargement and with adverse clinical outcomes (46).

NCCT is the recommended imaging test of choice for the diagnosis of sICH both for routine review and monitoring, as well as the assessment of the sudden deterioration of the patient's condition. sICH mainly occurs in the basal ganglia region, followed by the lobes, cerebellum, and pontines. The proportions of hypertension, amyloidosis, arteriovenous malformation (AVM), and unknown sICH hemorrhage were 46.2%, 10.3%, 7.69%, and 35.9%, respectively (25). Acute sICH hematoma is usually round or oval in shape (17), and its CT value is usually 30–80 Hounsfield unit (HU). NCCT can also locate the hematoma, which is crucial in determining the etiology of bleeding and the prognosis of patients. Many recent studies (1) have shown some specific signs in NCCT that can predict hematoma enlargement in early sICH.

MATERIAL and METHODS

Clinical Data

Retrospective Analysis to Establish a Prediction Table

From the image database of The Second Affiliated Hospital of Soochow University, patients diagnosed from August 2018 to June 2020 were screened for spontaneous intracerebral hemorrhage (sICH). The inclusion criteria were as follows: 1) Initial CT was performed within 24 h after the onset of disease and was diagnosed as acute sICH; 2) Age ≥18-years-old. The exclusion criteria were as follows: 1) cerebral tumor stroke, AVM, aneurysm, spontaneous subarachnoid hemorrhage, cerebral infarction, and brain stem hemorrhage; 2) CT was not reexamined within 24 h after initial diagnosis; 3) Surgical treatment was performed before CT review. After the above criteria screening, 150 cases of sICH patients admitted to our hospital were analyzed retrospectively. The hematoma enlargement was diagnosed based on Brott criteria (8). It was defined as >33% increase in hematoma volume or >6 mL increase in the initial CT compared to the next review CT. According to the definition of early hematoma enlargement, all patients were divided into two groups: the enlarged hematoma and the stable hematoma. The clinical data of the two groups of patients, including gender, age, hospital blood pressure (systolic pressure), important medical history (such as diabetes, hypertension, cerebral infarction), Glasgow Coma Scale(GCS) score, hematoma volume, the first time and the subsequent review of CT, CT hematoma CT value on average, hematoma, laboratory examination results (hemoglobin, Ca^{2+}, K^{+}, D-dimer), prognosis, and specific signs of NCCT (island, mixed, black hole, and liquid level), were collected. A flowchart of study design as shown in Figure 1.

Pilot Study Verification Rating Table

A pilot study was conducted to explore the correlation between early hematoma enlargement and predictive rating scale. Patients with acute sICH admitted to The Second Affiliated Hospital of Soochow University (Suzhou, China) from October 2020 to January 2021 were recruited in this study. The exposed factors were mainly at the level of prediction score, and the observation outcomes served as the expected final outcome of early hematoma enlargement and the failure of early hematoma enlargement. The classification was based on uniform criteria (the criteria for early hematoma enlargement were Brott criteria) 1), defined as an increase in hematoma volume >33% or an increase of ≥6 mL on the initial CT compared to the next review CT. Experimental group: sICH patients with early hematoma enlargement were selected. Control group: sICH patients without early hematoma enlargement. Inclusion criteria: 1) Initial CT was performed within 24 h after disease onset and diagnosed as acute sICH; 2) ≥18-years-old; 3) CT reexamination was performed within 8 h. Exclusion criteria: 1) Brain tumor stroke, AVM, aneurysm, spontaneous subarachnoid hemorrhage, cerebral infarction, and brain stem hemorrhage; 2) CT was not reexamined within 8 h after initial diagnosis; 3) Surgical treatment was performed before CT review. The clinical data of two groups of patients, including gender, age, medical history (such as diabetes, hypertension, and cerebral infarction), GCS score, hematoma volume, the first time and the subsequent review of CT, CT hematoma, CT value on average, hematoma, NCCT special signs (Island sign, Blend sign, Black hole sign, Fluid levels), and prediction score.

Image Acquisition and Image Analysis

Patients were scanned using the same CT (GE Bright Speed 16-slice spiral CT) scan parameters, and NCCT imaging was obtained within the standard time limit. First, all NCCT images were evaluated by two neurosurgeons (One for 3 years and one for 25 years) blinded to the patient's clinical data for the presence of NCCT-specific signs (Island sign, Blend sign, Black hole sign, Fluid levels). Next, hematoma volumes were measured on primary and subsequent CT scans and calculated using 3D Slicer software (version 4.9.0; Harvard University, Massachusetts, USA; Figure 2). The mean CT values of hematomas were also measured, and the hematomas were classified according to the sites: basal ganglia hemorrhage,

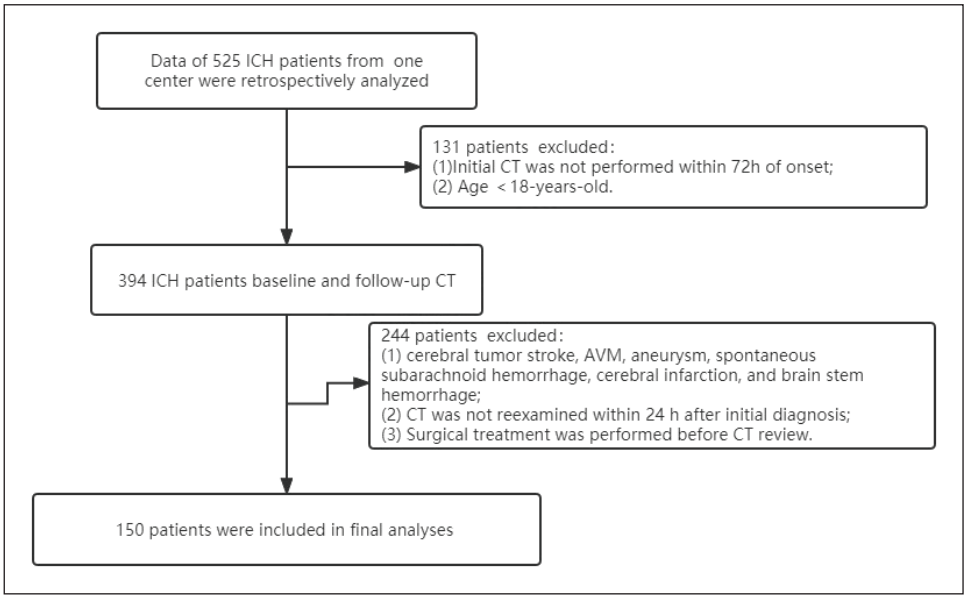

Figure 1: The flowchart of study design.

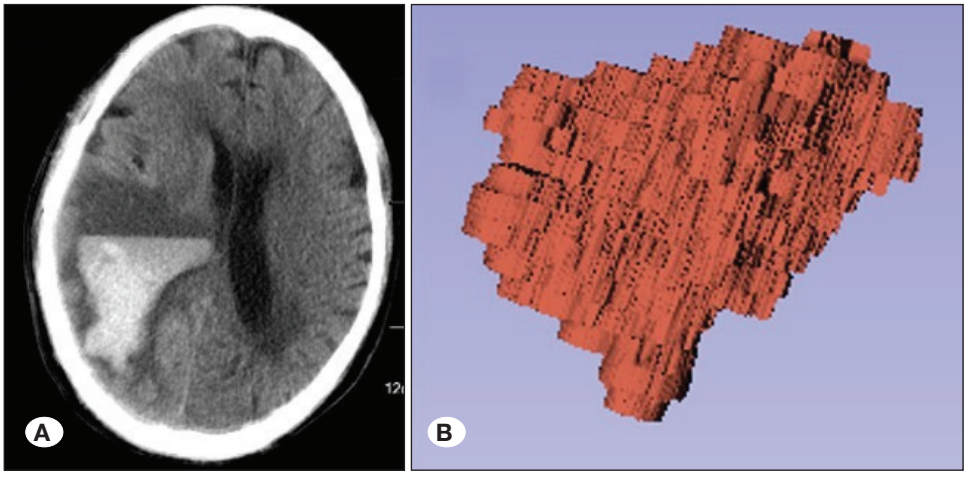

Figure 2: Measurement method of sICH hematoma on NCCT image. **A)** CT image of irregular sICH; **B)** Use 3Dslicer software to carry out 3D reconstruction effect drawing (convenient for accurate calculation of hematoma volume). The images were obtained from the image database of the Second Affiliated Hospital of Soochow University.

cerebral lobe hemorrhage, cerebellar hemorrhage, thalamic hemorrhage, and intraventricular hematoma (changes in intraventricular hematoma volume were not included in early hematoma enlargement).

Ethical Review

This project was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (JD LK-2018-067-01).

Statistical Methods

Retrospective study

Statistical software SPSS 26.0 and Prism 8.4.0 were used for data processing and analysis. The consistency of the image judgments between the two physicians was assessed by Kappa test. Continuous variables were summarized using the appropriate mean (M) or median (interquartile range (IQR)) value, and discrete variables were summarized using counts (%). Univariate analysis was performed by χ^2 test, Fisher's exact test, t-test, and Mann–Whitney test, and $p<0.05$ was considered statistically significant. Multivariate logistic regression models were used to identify factors that were independently associated with significant hematoma enlargement. The variables associated with the outcomes in univariate analysis ($p<0.05$) were input into the nominal logistic model. The receiver operating characteristic curve (ROC), calibration curve, and decision curve analysis (DCA) were used to evaluate the discrimination ability of the model. The Mean square error (MSE) test assesses its accuracy. Finally, the incidence of early hematoma enlargement under different scores was estimated and compared to evaluate the reliability of the prediction table.

Pilot Study

A single-blind trial was conducted by recording patients' data when they were not informed of the clinical data evaluation and the outcomes. To evaluate the initial diagnosis and review CT images, the researchers calculated hematoma volumes

using standard software using 3D Slicer software (version 4.9.0; Harvard University) and processed the hematoma volume obtained from the initial CT scan, and the follow-up CT scan was compared and grouped. Statistical software SPSS 26.0 and Prism 8.4.0 were utilized for data processing and analysis. Continuous variables were summarized using the appropriate M or median (IQR) values, and discrete variables were summarized using counts (%). The measurement data conformed to the normal distribution was represented by $\overline{x}$ ± s, and the score was tested by single-sample Kolmogorov-Smirnovtest to detect whether it complied with the normal distribution. The t-test was used for comparison between groups, and the ROC curve was used to evaluate the predictive power of the score.

RESULTS

Retrospective Study to Establish a Prediction Rating Table

A total of 150 patients with acute sICH were included in this study. Among them, 44 (29.33%) cases developed early hematoma enlargement. The two physicians had high consistency in judging NCCT signs (Kappa values >0.75). The mean age was 60.87 ± 15.84-years-old. The cohort comprised 102 (68.00%) males and 48 (32.00%) females. The mean systolic blood pressure was 166.95 ± 28.42 mmHg, mean hemoglobin 132.16 ± 16.46 g/L, mean K^+ 3.72 mmol/L, mean Ca^{2+} 0.59 mg/L, and mean D-dimer was 2.21. The mean CT scan time from onset to first diagnosis was 7 h. The CT time from onset to the first diagnosis was <6 h in 102 (68.00%) cases. After admission, the GCS score was recorded in all patients, including 14 (9.33%) cases with GCS score ≤5, 47 (31.33%) cases with GCS scores between 6 and 8, and 89 (59.33%) cases with GCS score ≥9. The average initial hematoma volume was about 26 mL, the initial hematoma volume was ≤18 mL in 75 (50.00%) cases, the initial hematoma volume was between 18 and 45 mL in 47 (31.33%) cases, and with >45 mL in 28 (18.67%) cases. Moreover, 114 (76.00%) cases had a history of hypertension, 27 (18.00%) cases had a history of diabetes, 9 (6.00%) cases had creatinine ≥141 μmol/L (renal insufficiency), and 8 (5.33%) cases ingested anticoagulant drugs. The cohort comprised of 36 (24.00%) cases with Island sign, 45 (30.00%) cases with Blend sign, 10 (6.67%) cases with Black hole sign, and 3 (2.00%) cases with Fluid levelssign. There were more than two special signs of NCCT and 73 (48.67%) cases exhibited at least one of island or Blend signs, while 16 (10.67%) patients had poor prognosis (Table I). Interestingly, significant differences were observed in the initial hematoma volume (≤18 mL, 18-45 mL, >45 mL), GCS score (≤ 5, 6-8, ≥9), average HU minimum value of hematoma, Island sign, Blend sign, and NCCT special sign ≥2, and at least one of these was island or Blend signs ($p<0.05$) between enlarged and stable hematoma groups.

The above risk factors were included in the multivariate Logistic regression analysis, and it was found that initial hematoma volume, GCS score, island sign, mixed sign, and NCCT special signs were ≥2, and at least one of them was island sign or mixed sign as independent risk factors for early hematoma enlargement after sICH ($p<0.05$).

Finally, the prediction rating table was obtained (the total score was 2-14 points, Table II). The area under the ROC curve of the rating scale was 0.858 (95% confidence interval (CI): 0.791-0.924, $p<0.001$), indicating that the rating scale had a strong predictive power. Furthermore, according to Pearson's chi-square test, the significance (Sig) was <0.01 and <0.05, indicating that the probability of early hematoma enlargement increased with the increase in the predictive score.

A total of 150 patients were divided into groups according to the predictive score: 4, 6, and 8. Among them, 26 patients were classified as the high-risk group with a score ≥10. The incidence of early hematoma enlargement was 84.61% (22/26), and the standard error of mean (SEM) was 0.109. The score was 6-8, and 45 cases were divided into the moderate-risk group. The incidence of early hematoma enlargement was 35.56% (16/45), and SEM was 0.150. A total of 79 patients were divided into the low-risk group with score ≤4, and the incidence of early enlarged hematoma was 7.59% (6/79) with SEM 0.274 (all P-values were <0.01). The area under the ROC curve between groups was 0.821 (95% CI: 0.743-0.900), indicating the high reliability of the grouping method. The sensitivity, specificity, and accuracy of the prediction rating scale were 0.95, 0.57, and 0.87, respectively. The DCA decision curve (Figure 3) was different in the two extreme cases, and the range of selectable threshold was large, indicating that this prediction rating scale had strong clinical practicability. The calibration curves (Figure 4) showed that x^2 =2.122 and p=0.713, indicating that the accuracy of this prediction rating table was satisfactory. The error among the MSE groups was 6.701, and the loss of function was small, indicating high accuracy of this prediction rating table.

Verify the Prediction Rating Table in the Pilot Study

A total of 17 patients with acute sICH were included in this study. A total of 7 (41.17%) of the 17 patients developed early hematoma enlargement (included in the experimental group), while 10 (58.83%) did not develop early hematoma enlargement (included in the control group). Clinical data were collected after admission (see Table III) and predicted scores were made. The probability of early hematoma enlargement was as follows: 2 points (0%,0/3),4 points (0%,0/3), 6 points (20.00%,1/5), 8 points (66.33%,2/3), 10 points (100%,3/3), 12 points (100%,1/1); Prediction accuracy (low risk group =92.41%, medium risk group =98.06%, high risk group =84.61%). The comparison of general data between the experimental group (n=7) and the control group (n=10) is shown in Table III. The above data were compared with the prediction score in this prediction rating table, and t test was performed, t=3.972 ($p=0.001 < 0.05$), indicating that the prediction score could significantly reflect the probability of early hematoma enlargement. Univariate analysis of predictive score showed that OR =1.666 > 1, 95%CI (1.043 ~ 2.661), indicating that predictive score was an independent predictor of early hematoma enlargement. The ROC curve of pilot study score was drawn, AUC=0.914,95%CI (0.782 ~ 1.000).

Table I: Comparison of Data Between the Enlarged Hematoma Group and the Stable Hematoma Group

Risk factors	Total number (n=150)	Hematoma enlargement group (n=44)	Stable hematoma group (n=106)	p
Age (±s)	60.87 ± 15.84	63.95 ± 16.44	59.59 ± 15.48	0.160
Male (n,%)	102 (68.00)	33 (75.00)	69 (65.09)	0.065
SBP (mmHg, ±s)	166.95 (28.42)	163.50 (27.21)	168.90 (29.25)	0.538
CT time from onset to first diagnosis (h;M,IQR)	7.65 (3.8)	6.59 (2.7)	7.66 (3.8)	0.096
CT time from onset to first diagnosis ≤6h (n,%)	102 (68.00)	33 (75.00)	69 (65.09)	0.379
Initial hematoma volume (mL; M,IQR)	26.02 (10.33)	45.16 (12.61)	17.92 (8.25)	0.017
Initial hematoma volume ≤18mL (n,%)	75 (50.00)	9 (20.45)	66 (62.26)	0.028
Initial hematoma volume in 18-45mL (n,%)	47 (31.33)	14 (31.81)	33 (31.13)	0.028
Initial hematoma volume >45mL (n,%)	28 (18.67)	21 (47.73)	7 (6.60)	0.028
GCS score ≤8 (n,%)	14 (9.33)	11 (25.00)	3 (2.83)	0.011
GCS score 6~12 (n,%)	47 (31.33)	11 (25.00)	36 (33.96)	0.011
GCS score ≥12 (n,%)	89 (59.33)	22 (50.00)	67 (63.21)	0.011
Hypertension (n,%)	114 (76.00)	33 (75.00)	81 (76.41)	0.572
Diabetes (n,%)	27 (18.00)	10 (22.73)	17 (16.04)	0.329
Hemoglobin (g/L; $\overline{x}$ ±s)	132.16 (16.46)	130.05 (17.27)	133.36 (16.09)	0.369
Potassium ions (mmol/L; M, IQR)	3.72 (3.38, 3.95)	3.69 (3.48, 3.98)	3.72 (3.35, 3.94)	0.870
D-dimer (mg/L; M, IQR)	0.59 (0.28, 1.26)	0.63 (0.36, 1.12)	0.53 (0.25, 1.42)	0.624
Calcium ions (mmol/L; M, IQR)	2.21 (2.13, 2.29)	2.20 (2.09, 2.29)	2.23 (2.14, 2.29)	0.466
Creatinine ≥141 (n,%)	9 (6.00)	5 (11.36)	4 (3.77)	0.609
Anticoagulant drugs (n, %)	8 (5.33)	3 (6.82)	5 (4.72)	0.953
Island sign (n,%)	36 (24.00)	27 (61.36)	9 (8.49)	0.032
Mixed sign (n,%)	45 (30.00)	31 (70.45)	14 (13.21)	0.010
Black hole sign (n,%)	10 (6.67)	6 (13.63)	4 (3.77)	0.900
Liquid level sign (n,%)	3 (2.00)	2 (4.54)	1 (0.94)	0.835
There are at least 2 special signs of NCCT and at least one of them is island sign or mixed sign (n,%)	73 (48.67)	40 (90.90)	28 (26.41)	0.001
Hematoma HU MAX ($\overline{x}$ ±s)	64.29 ± 4.98	63.98 ± 4.71	65.02 ± 4.79	0.447
Hematoma HU MIN ($\overline{x}$ ±s)	53.25 ± 5.04	50.77 ± 4.98	54.60 ± 4.95	0.018
Hematoma HU difference (M, IQR)	11 (7.15)	12 (9.17)	11 (7.14)	0.241
The hematoma parts				
Basal ganglia region (n, %)	137 (79.33)	40 (80.00)	97 (79.24)	
The cerebellum (n, %)	1 (0.58)	0	1 (0.81)	
Lobes (n, %)	34 (19.8)	10 (20.00)	24 (13.87)	
The thalamus (n, %)	14 (8.09)	0	14 (11.38)	
Intraventricular hematoma (n, %)	37 (21.38)	20 (40.00)	17 (9.56)	0.250
Poor prognosis (n, %)	16 (10.67)	11 (22.00)	5 (1.79)	0.121

Note: *Arithmetic mean;* ***S:*** *standard deviation;* ***N:*** *quantity;* ***M:*** *arithmetic mean;* ***IQR:*** *quartile;* ***SBP:*** *systolic blood pressure;* ***GCS:*** *Glasgow Scale;* ***HU:*** *Hounsfield unit value;* ***MIN:*** *minimum value;* ***Max:*** *The maximum.*

Table II: sICH Score for Early Hematoma Enlargement Prediction Based on NCCT Signs

Parameter	Score
GCS score	
≤5	5
6~8	3
≥9	1
Initial hematoma volume	
≤18 mL	1
18~45 mL	3
>45 mL	5
NCCT signs	
Only island sign	2
Only mixed sign	2
There are at least 2 special signs of NCCT and at least one of them is island sign or mixed sign	4
Absence (or only black hole sign)	0
Total score	2~14

Note: GCS: *Glasgow Scale; Score ≥10 was classified as high risk group, score 6-8 as medium risk group, score ≤4 as low risk group.*

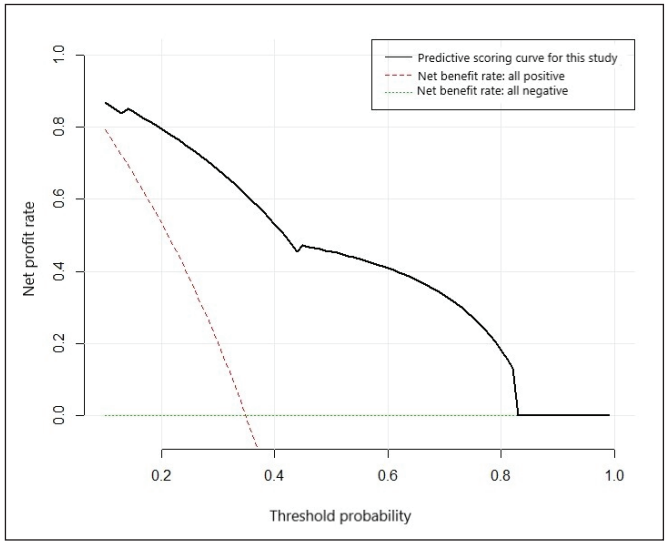

Figure 3: DCA curve of the predicted score. The horizontal line represents the situation where all samples are negative, i.e. no hematoma enlargement. The oblique line indicates that all samples are positive, that is, all hematomas are enlarged. The curve is based on the model curve, far from the above two extreme cases, showing good clinical practicability.

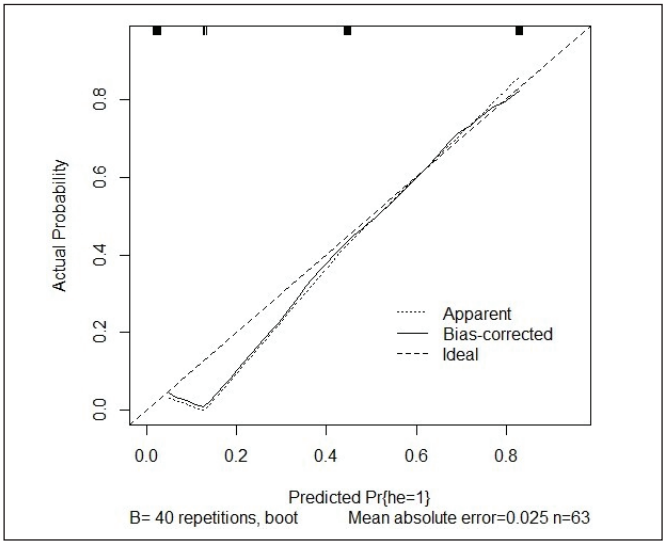

Figure 4: Calibration curve. The curve of the forecast table is close to the ideal curve, and the prediction accuracy is high.

DISCUSSION

In China, due to the aging population, the incidence of sICH was high (10). The early detection of the high-risk factors for early hematoma enlargement is crucial for the development of treatment strategies and the improvement of the diagnosis and treatment of sICH in the region. The application of NCCT signs to predict the early expansion of hematoma is recommended in the 2019 Chinese Multidisciplinary Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage (6). Based

Table III: Comparison of Clinical Data Between sICH Patients in the Experimental Group and Control Group

Risk factors	The experimental group (n=7)	The control group (n=10)
Age (years; $\overline{x}$ ±*s*)	66.82 ± 14.14	68.43 ± 10.61
Male (n,%)	5 (62.50)	5 (50.00)
GCS score (M, IQR)	11.13 (9.13)	11.29 (10.14)
Hematoma volume (mL; M, IQR)	26.35 (20.51)	23.13 (10.25)
Hematoma mean HU (±*s*)	50.86 ± 2.83	51.95 ± 0.71
Island sign (n,%)	2 (28.57)	1 (10.00)
Mixed sign (n,%)	6 (85.71)	3 (30.00)
Black hole sign (n,%)	3 (42.86)	0 (6.67)
Liquid level sign (n,%)	1 (14.28)	0
NCCT special signs ≥2 and at least one of them is island sign or mixed sign (n,%)	6 (85.71)	1 (10.00)
Predictive score (M, IQR)	6.17 (6.10)	5.33 (2.6)

Note: *Arithmetic mean;* ***S:*** *Standard deviation;* ***N:*** *Quantity;* ***M:*** *Arithmetic average;* ***IQR:*** *Quartile;* ***HU:*** *Hounsfield unit value.*

on a previous preliminary study (24), the prediction rating scale was improved, enabling the clinicians to predict the possibility of early hematoma enlargement in sICH. The routine examination results determined the diagnosis and treatment plan, especially the choice of surgical intervention when the patients were received the first time. The current results showed that the high-risk factors associated with early hematoma enlargement were initial hematoma volume, GCS score, Island sign, Blend sign, NCCT special sign ≥2, and at least one of them was Island sign or Blend sign.

Fujii et al. demonstrated that a low GCS score is a major risk factor for hematoma enlargement, and continuous bleeding is likely to lead to severe neurological damage and large hematoma (14). Nonetheless, it is not clear why patients with impaired consciousness have a high incidence of hematoma enlargement. Although disturbance of consciousness is an independent predictor of hematoma growth, it is currently not considered an independent risk factor for hematoma growth because disturbance of consciousness occurs naturally after sICH and worsens with hematoma growth. Also, a causal correlation cannot be established between GCS score and early hematoma enlargement based on the observational studies. Becker et al. demonstrated that a low GCS score is associated with a less persistent bleeding tendency (5).

Previous studies have shown that NCCT special signs are associated with hematoma enlargement independently (2) because the NCCT application is broad and usually the first choice for neurosurgical diseases. The findings may have the significance to improve the prognosis and contribute towards expanding hematoma resistance crowd positioning, which might benefit from the crowd. Other studies (27,32) have shown that the stroke cascade may be the cause of continued enlargement of hematoma, and the initial bleeding may cause tearing of the peripheral blood vessels, leading to continued bleeding (and possibly sequential bleeding). The uneven density within the hematoma may reflect different bleeding stages and thus have a role in discriminating whether the hematoma will expand further (3,13). Miyahara et al. speculated that enhancing the "point sign" on CTA was the gold standard for the early expansion of sICH (32). However, in the diagnosis and treatment of emergency sICH in China, all hospitals could not use CTA. In addition, CTA is expensive, and the radiation dose is significantly higher than that of NCCT. The presence of an iodine contrast agent also increases the risk of patients with chronic kidney disease (CKD) (20), and CKD is an independent risk factor for ischemic and hemorrhagic stroke. In addition, the disease is associated with neurological dysfunction, poor outcomes, and high mortality after stroke. Among patients with sICH, hematoma volume was 2.3-fold higher in patients with moderate to severe CKD than in the general population. Therefore, NCCT has an advantage in predicting early hematoma enlargement in sICH. Without a CTA test, this scale may be used to select treatment options, such as controlled hypotension, hemostasis, surgical treatment, or specific anticoagulant reversal strategies, for those at high risk. It also helps to select treatment options for patients with ICH; with limited resources, it can be divided into routine stroke unit care, intensive care, and emergency surgery based on patient risk assessment.

This study verified that confounding sign is an independent predictor of hematoma enlargement. Since there is an obvious overlap between the definition of Black hole sign and confounding sign (29,30), and data analysis showed that confounding sign is more sensitive than Black hole sign, the presence of confounding sign can better indicate the instability of hematoma (41). Similarly, Island signs (28) are independent predictors of hematoma enlargement. The single-center study on Island signs by Li was the first to report that Island signs

can be used as predictors of hematoma enlargement and poor functional prognosis with high specificity in the detection of hematoma enlargement. In addition to Li, who first described the hybrid sign and Black hole sign, Boulouis et al. (n=1029) and Morotti et al. (n=989) also conducted two large studies, wherein NCCT-specific signs were independent predictors of hematoma enlargement (7,34). A recent meta-analysis of five studies (n=2248) (45) found that the combined sensitivity and specificity of the mixed syndrome were 0.39 (95% CI: 0.16-0.46) and 0.92 (95% CI: 0.88–0.95), respectively, indicating that mixed syndrome has a low sensitivity and high specificity. Another meta-analysis of the five studies (47) (n=1495) showed that the combination sensitivity and specificity for Black hole signs were 0.30 (95% CI: 0.20-0.41) and 0.91 (95% CI: 0.87-0.94), respectively. These findings suggested that NCCT-specific signs are highly associated with early hematoma enlargement (26). For fluid level sign (21), the appearance of this sign could reflect the abnormal coagulation function of the patient, accompanied by the decrease in blood coagulation ability, persistent bleeding, and the change in body position, indicating stratified hematoma. Since the fluid level is rarely seen in patients with sICH, and only 3 patients in the data collected from the present study showed this sign, a larger database is needed for further analysis. Subsequently, various CT signs were summarized based on the above studies (7,28,29,34,41,45). The author found that the positive predictive value (40%) of low-density signs was extremely low, and hence, it was not included in the statistical data for analysis in this study.

On the other hand, after comparing the hematoma volume, the authors found that Island signs and Blend signs were mainly present in large hematomas (31/36 patients with Island signs had CT hematoma volume >18 mL at initial diagnosis. Among 45 patients with Blend signs, 36 had CT hematoma volume >18 mL at initial diagnosis. Therefore, hematoma volume is also an important independent predictor of early hematoma enlargement in sICH patients (18). To date, the inclusion criteria and clinical grading scales (including the sICH score) for most trials (9) have used a 30-mL hematoma cutoff to identify patients at risk of poor prognosis. However, in the study by Kim et al., 18 mL in the basal ganglia was the critical value of hematoma volume, with maximum sensitivity and specificity (21). Hematomas of >45 mL were significantly associated with high mortality, which was consistent with the results of the present study. In order to calculate the hematoma volume of irregular and discontinuous hematomas, we used 3D Slicer software after 3D reconstruction. Currently, clinicians use the ellipsoid method to measure sICH hematoma volume on NCCT (31). In most clinical situations, the ellipsoid method ((A×B×C) /2, where A is the front and rear diameter, B is the width, and C is the height) is sufficient. However, the hematoma volume calculated by the ellipsoid method is about 20% larger than that calculated by the application software. Therefore, in patients with various indicators close to surgical indications, the application of the 3D reconstruction software provides an accurate assessment of the hematoma volume and prepares for emergency surgery. However, before surgery, 3D Slicer software can also be used to locate the hematoma by mobile phone (37) and achieve the desired surgical effect.

We also found that the mean HU of hematoma was negatively correlated with the increase in sICH during the initial NCCT scan (19). The increase in HU in the hematoma might reflect the contraction process of the in-situ clot. When bleeding occurs, platelets aggregate to form a temporarily closed environment, and fibrinogen is converted to fibrin polymer to form a viscoelastic thrombus, followed by clot contraction, which is the final step in the maturation of a blood clot to enhance its hemostasis. The lower the mean HU of a hematoma on the first NCCT scan, the higher the association with early hematoma enlargement, and it may reflect insufficient clot contraction for hemostasis. The mean HU of a hematoma shows a linear correlation with HBC and platelet count. The contraction of blood clots is driven by the contractile force of platelets and transmitted through the fibrin network (22,23,42). During this process, changes in the shape of the red blood cells occur that build up the clot in the first few hours. When the clot contracts, the HU of the clot increases as red blood cell compaction increases (43). The initial upward trend of HU of the hematoma in this study may reflect the dynamic process of clot contraction. The platelet cytoskeleton system provides clot contractility to the platelet fibrin network, which is stronger in the presence of red blood cells (11). Low density within a hematoma is a recently confirmed radiographic marker of early hematoma enlargement. Although the underlying mechanism may be unclear, it reflects persistent bleeding or local clot contraction (38). The mean HU value of the hematoma might provide an explanation for the re-enlargement of the hematoma, and the difference in mean HU value of the initial and subsequent stage dynamics suggests the hemostasis of clot contraction in sICH. The current results also suggested that the mean HU value in hematomas is a risk factor for early hematoma enlargement. The average HU of hematoma requires high image quality, is not as intuitive as that of NCCT special signs, and has certain limitations. However, the average HU of hematoma may be more predictive than signs of low density within the hematoma. With the development of imaging techniques, the quantitative analysis of the HU value of hematomas may help in identifying patients at high risk of ICH hematoma enlargement and guide the development of anti-expansion strategies for future clinical diagnosis and treatment.

sICH is a dynamic process, and the incidence of early hematoma enlargement decreases with the increase in the time interval from the onset to initial CT diagnosis (36,39,40,44). The earlier a patient is admitted to sICH, the more likely he/she is to develop early hematoma enlargement. In several different rating scales (36,39,44), the initial CT diagnosis time was 2.5 hours, 3 hours and 5 hours, respectively. Obviously, the time of initial CT diagnosis varies from region to region, and its inclusion in the scoring system is only applicable to local conditions. The parameters indicate that China needs to strengthen the efforts to popularize relevant medical knowledge, guide sICH patients to see a doctor in time, and actively promote the construction of a stroke center system.

A previous study introduced the concept of hematoma growth (HG), i.e., HG=hematoma volume difference between newly diagnosed CT and reexamined CT/scan time interval between

newly diagnosed CT and reexamined CT. The study showed that Hg ≥4.7 mL/h is an independent risk factor for hematoma enlargement, early neurological deterioration, and poor prognosis (24). However, as an outcome variable (at least two NCCT images at different time points were required), Hg was limited in the evaluation of acute sICH and hence, was not included in the statistical data in this study.

Although a causal correlation between anticoagulant use and hematoma enlargement seems logical, the risk of bleeding associated with anticoagulants is common in the gastrointestinal tract, and three cohort studies and three case-control studies reported an association between anticoagulants and hematoma enlargement in early sICH. In most studies, low-dose aspirin was not associated with a significantly increased risk of sICH. In case-control studies (15), low-dose aspirin therapy was associated with a relative risk (RR) of 1.0 (95% CI: 0.8–1.2) in sICH and not with early hematoma enlargement in sICH. In cohort studies, anticoagulants were associated with an RR of 1.5 (95% CI: 1.4-1.7) in patients with sICH, with a slight association with hematoma enlargement in early sICH. Notably, many rating scales (9,19,31,37) use warfarin as the representative of anticoagulant drugs. However, at present, the anticoagulant drugs are mainly aspirin, and hence, the current clinical utilization rate of the above rating scales may not be high.

Herein, we found that the high-risk factors associated with early hematoma enlargement in sICH were initial hematoma volume, GCS score, and special NCCT signs. Based on these factors, a scale for predicting early hematoma enlargement after sICH was established, and pilot study verification was performed. Since the data of initial hematoma volume, GCS score, and NCCT special signs are readily available at the time of initial diagnosis, the scale could be used to predict the risk of sICH. We also used the 3DSlicer software for 3D reconstruction in the calculation of hematoma volume and found that the accuracy was much higher than the traditional method, and it could be utilized in surgical treatment. The Kappa test showed good inter-observer consistency, indicating that NCCT signs are easier to identify, less affected by work experience, and even lower-level physicians can obtain more objective results. However, in the high-risk group, the prediction accuracy of the model was lower than in the previous two groups. The main reason is that the sample size of the pilot test is small, only 17 patients, so it may lead to a decrease in the accuracy of the model and an increase in error, and the sample size needs to be expanded to solve this problem in subsequent experiments. Compared to other international scoring tables, this scale is more suitable for the current medical environment in China. This study suggested stratified clinical management based on the patient prediction score scale. Patients at high risk of enlarged hematoma may require intensive care, transfer to a higher-level medical center, and surgical treatment; patients at moderate risk need close attention and timely intervention; Low-risk patients can be treated conservatively to avoid the waste of medical resources and iatrogenic injury.

Nevertheless, the present study has the following limitations: (1) It has the inherent defects of a single-center study, and no intra-observer consistency study was conducted, which has some influence on the statistical results. (2) The statistical sample size is small. In addition, high-risk sICH patients are often excluded from the study due to the need for emergency surgical intervention or death or abandonment of treatment, leading to a decrease in clinical samples and statistical bias. Therefore, large sample size and multi-center study will be needed in the future to validate the scale. (3) After the first CT diagnosis of sICH patients, the time interval of CT reexamination could not be consistent, which might lead to data bias.

CONCLUSION

The retrospective research verification and preliminary prospective verification emphasized that our score can accurately identify high-risk individuals with early hematoma enlargement, guide clinical treatment, provide a reference, and aid clinical trials. However, before the scoring can be applied to routine clinical work, a large-scale multi-center joint prospective study is essential.

Main messages

1. The number of deaths from stroke has been increasing year by year. To assess the risk of hematoma expansion, hematoma volume and NCCT (non-contrast CT signs) factors should be considered comprehensively in the initial diagnosis and treatment guidelines of CT.
2. The patient's data can be obtained at the first visit, so the scoring table established in this study can give full play to its timeliness in predicting the risk of sICH.
3. The 3DSlicer software is used for three-dimensional reconstruction when calculating the volume of the hematoma. The accuracy is much higher than that of the traditional method, and it can be further positioned during surgical treatment, and has high clinical practical value.

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AUTHORSHIP CONTRIBUTION

Study conception and design: ZQ
Data collection: ZL, TZ, XW
Analysis and interpretation of results: QD
Draft manuscript preparation: XK
Critical revision of the article: ZQ
All authors (ZL, XK, QD, TZ, XW, ZQ) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Al-Kawaz MN, Hanley DF, Ziai W: Advances in therapeutic approaches for spontaneous intracerebral hemorrhage. Neurotherapeutics 17:1757-1767, 2020
2. Al-Khaled M, Awwad S, Brüning T: Nontraumatic spontaneous intracerebral hemorrhage: Baseline characteristics and early outcomes. Brain Behav 10:e015122020
3. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, Arima H, Hasegawa H, Oishi M, Godoy DA, Masotti L, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Jang DK, Davalos A, Castillo J, Yao X, Claassen J, Volbers B, Kazui S, Okada Y, Fujimoto S, Toyoda K, Li Q, Khoury J, Delgado P, Sabín JÁ, Hernández-Guillamon M, Prats-Sánchez L, Cai C, Kate MP, McCourt R, Venkatasubramanian C, Diringer MN, Ikeda Y, Worthmann H, Ziai WC, d'Esterre CD, Aviv RI, Raab P, Murai Y, Zazulia AR, Butcher KS, Seyedsaadat SM, Grotta JC, Martí-Fàbregas J, Montaner J, Broderick J, Yamamoto H, Staykov D, Connolly ES, Selim M, Leira R, Moon BH, Demchuk AM, Di Napoli M, Fujii Y, Anderson CS, Rosand J; VISTA-ICH Collaboration; ICH Growth Individual Patient Data Meta-analysis Collaborators: Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: A systematic review and meta-analysis of individual patient data. Lancet Neurol 17:885-894, 2018
4. An SJ, Kim TJ, Yoon BW: Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: An update. J Stroke 19:3-10, 2017
5. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA: Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. Stroke 30:2025-2032, 1999
6. Behrouz R, Azarpazhooh MR, Godoy DA, Hoffmann MW, Masotti L, Parry-Jones AR, Popa-Wagner A, Schreuder FH, Slevin MA, Smith CJ, Di Napoli M; MNEMONICH Steering Committee: The multi-national survey on epidemiology, morbidity, and outcomes in intracerebral haemorrhage (mnemonich). Int J Stroke 10:E86, 2015
7. Boulouis G, Morotti A, Brouwers HB, Charidimou A, Jessel MJ, Auriel E, Pontes-Neto O, Ayres A, Vashkevich A, Schwab KM, Rosand J, Viswanathan A, Gurol ME, Greenberg SM, Goldstein JN: Association between hypodensities detected by computed tomography and hematoma expansion in patients with intracerebral hemorrhage. JAMA Neurol 73:961-968, 2016
8. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J: Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 28:1-5, 1997
9. Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, Vashkevich A, McNamara KA, Valant V, Schwab K, Orzell SC, Bresette LM, Feske SK, Rost NS, Romero JM, Viswanathan A, Chou SH, Greenberg SM, Rosand J, Goldstein JN: Predicting hematoma expansion after primary intracerebral hemorrhage. JAMA Neurol 71:158-164, 2014
10. Cao Y, Yu S, Zhang Q, Yu T, Liu Y, Sun Z, Zhao M, Wang W, Zhao JZ: Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: Executive summary and 2019 update of clinical management of intracerebral hemorrhage. Stroke Vasc Neurol 5:396-402, 2020
11. Cines DB, Lebedeva T, Nagaswami C, Hayes V, Massefski W, Litvinov RI, Rauova L, Lowery TJ, Weisel JW: Clot contraction: Compression of erythrocytes into tightly packed polyhedra and redistribution of platelets and fibrin. Blood 123:1596-1603, 2014
12. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, Kobayashi A, Boulanger JM, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Kosior J, Bhatia R, Tymchuk S, Subramaniam S, Gladstone DJ, Hill MD, Aviv RI; PREDICT/Sunnybrook ICH CTA study group: Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet Neurol 11:307-314, 2012
13. Eslami V, Tahsili-Fahadan P, Rivera-Lara L, Gandhi D, Ali H, Parry-Jones A, Nelson LS, Thompson RE, Nekoobakht-Tak S, Dlugash R, McBee N, Awad I, Hanley DF, Ziai WC: Influence of intracerebral hemorrhage location on outcomes in patients with severe intraventricular hemorrhage. Stroke 50:1688-1695, 2019
14. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R: Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. Stroke 29:1160-1166, 1998
15. García Rodríguez LA, Martín-Pérez M, Hennekens CH, Rothwell PM, Lanas A: Bleeding risk with long-term low-dose aspirin: A systematic review of observational studies. PLoS One 11: e0160046, 2016
16. Gladstone DJ, Aviv RI, Demchuk AM, Hill MD, Thorpe KE, Khoury JC, Sucharew HJ, Al-Ajlan F, Butcher K, Dowlatshahi D, Gubitz G, De Masi S, Hall J, Gregg D, Mamdani M, Shamy M, Swartz RH, Del Campo CM, Cucchiara B, Panagos P, Goldstein JN, Carrozzella J, Jauch EC, Broderick JP, Flaherty ML; SPOTLIGHT and STOP-IT Investigators and Coordinators: Effect of recombinant activated coagulation factor vii on hemorrhage expansion among patients with spot sign-positive acute intracerebral hemorrhage: The spotlight and stop-it randomized clinical trials. JAMA Neurol 76:1493-1501, 2019
17. Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, Mayo SW, Bistran-Hall AJ, Gandhi D, Mould WA, Ullman N, Ali H, Carhuapoma JR, Kase CS, Lees KR, Dawson J, Wilson A, Betz JF, Sugar EA, Hao Y, Avadhani R, Caron JL, Harrigan MR, Carlson AP, Bulters D, LeDoux D, Huang J, Cobb C, Gupta G, Kitagawa R, Chicoine MR, Patel H, Dodd R, Camarata PJ, Wolfe S, Stadnik A, Money PL, Mitchell P, Sarabia R, Harnof S, Barzo P, Unterberg A, Teitelbaum JS, Wang W, Anderson CS, Mendelow AD, Gregson B, Janis S, Vespa P, Ziai W, Zuccarello M, Awad IA; MISTIE III Investigators: Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): A randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet 393:1021-1032, 2019

18. Huang Y, Zhang Q, Yang M: A reliable grading system for prediction of hematoma expansion in intracerebral hemorrhage in the basal ganglia. Biosci Trends 12:193-200, 2018
19. Jeong HG, Bang JS, Kim BJ, Bae HJ, Han MK: Hematoma Hounsfield units and expansion of intracerebral hemorrhage: A potential marker of hemostatic clot contraction. Int J Stroke 16:163-171, 2021
20. Jung JM, Kim HJ, Ahn H, Ahn IM, Do Y, Choi JY, Seo WK, Oh K, Cho KH, Yu S: Chronic kidney disease and intravenous thrombolysis in acute stroke: A systematic review and meta-analysis. J Neurol Sci 358:345-350, 2015
21. Kim J, Smith A, Hemphill JC 3rd, Smith WS, Lu Y, Dillon WP, Wintermark M: Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. AJNR Am J Neuroradiol 29:520-525, 2008
22. Kim OV, Litvinov RI, Alber MS, Weisel JW: Quantitative structural mechanobiology of platelet-driven blood clot contraction. Nat Commun 8:1274, 2017
23. Kirchhof K, Welzel T, Mecke C, Zoubaa S, Sartor K: Differentiation of white, mixed, and red thrombi: value of CT in estimation of the prognosis of thrombolysis phantom study. Radiology 228: 126-130, 2003
24. Kong XY, Qian W, Dong J, Qian ZY: Proposal of a prediction score for hematoma expansion after intracerebral hemorrhage. Med Intensiva 45:147-155, 2021
25. Labib MA, Shah M, Kassam AB, Young R, Zucker L, Maioriello A, Britz G, Agbi C, Day JD, Gallia G, Kerr R, Pradilla G, Rovin R, Kulwin C, Bailes J: The safety and feasibility of image-guided brainpath-mediated transsulcul hematoma evacuation: A multicenter study. Neurosurgery 80:515-524, 2017
26. Law ZK, Ali A, Krishnan K, Bischoff A, Appleton JP, Scutt P, Woodhouse L, Pszczolkowski S, Cala LA, Dineen RA, England TJ, Ozturk S, Roffe C, Bereczki D, Ciccone A, Christensen H, Ovesen C, Bath PM, Sprigg N; TICH-2 Investigators: Noncontrast computed tomography signs as predictors of hematoma expansion, clinical outcome, and response to tranexamic acid in acute intracerebral hemorrhage. Stroke 51: 121-128, 2020
27. Leasure AC, Sheth KN, Comeau M, Aldridge C, Worrall BB, Vashkevich A, Rosand J, Langefeld C, Moomaw CJ, Woo D, Falcone GJ: Identification and validation of hematoma volume cutoffs in spontaneous, supratentorial deep intracerebral hemorrhage. Stroke 50:2044-2049, 2019
28. Li Q, Liu QJ, Yang WS, Wang XC, Zhao LB, Xiong X, Li R, Cao D, Zhu D, Wei X, Xie P: Island sign: An imaging predictor for early hematoma expansion and poor outcome in patients with intracerebral hemorrhage. Stroke 48:3019-3025, 2017
29. 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 46:2119-2123, 2015
30. 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 47:1777-1781, 2016
31. Liao R, Liu L, Song B, Wan X, Wang S, Xu J: 3D-slicer software-assisted neuroendoscopic surgery in the treatment of hypertensive cerebral hemorrhage. Comput Math Methods Med 2022:7156598, 2022
32. Miyahara M, Noda R, Yamaguchi S, Tamai Y, Inoue M, Okamoto K, Hara T: New prediction score for hematoma expansion and neurological deterioration after spontaneous intracerebral hemorrhage: A hospital-based retrospective cohort study. J Stroke Cerebrovasc Dis 27:2543-2550, 2018
33. Morotti A, Arba F, Boulouis G, Charidimou A: Noncontrast CT markers of intracerebral hemorrhage expansion and poor outcome: A meta-analysis. Neurology 95:632-643, 2020
34. Morotti A, Boulouis G, Dowlatshahi D, Li Q, Barras CD, Delcourt C, Yu Z, Zheng J, Zhou Z, Aviv RI, Shoamanesh A, Sporns PB, Rosand J, Greenberg SM, Al-Shahi Salman R, Qureshi AI, Demchuk AM, Anderson CS, Goldstein JN, Charidimou A; International NCCT ICH Study Group: Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. Ann Neurol 86:480-492, 2019
35. Morotti A, Brouwers HB, Romero JM, Jessel MJ, Vashkevich A, Schwab K, Afzal MR, Cassarly C, Greenberg SM, Martin RH, Qureshi AI, Rosand J, Goldstein JN; Antihypertensive Treatment of Acute Cerebral Hemorrhage II and Neurological Emergencies Treatment Trials Investigators: Intensive blood pressure reduction and spot sign in intracerebral hemorrhage: A secondary analysis of a randomized clinical trial. JAMA Neurol 74:950-960, 2017
36. Morotti A, Dowlatshahi D, Boulouis G, Al-Ajlan F, Demchuk AM, Aviv RI, Yu L, Schwab K, Romero JM, Gurol ME, Viswanathan A, Anderson CD, Chang Y, Greenberg SM, Qureshi AI, Rosand J, Goldstein JN; ATACH-II, NETT, and PREDICT Investigators: Predicting intracerebral hemorrhage expansion with noncontrast computed tomography: The bat score. Stroke 49:1163-1169, 2018
37. Qiu S, Liu T, Cao G, Wu K, Zhao T: Treatment of intracranial hemorrhage with neuroendoscopy guided by body surface projection. Medicine (Baltimore) 98:e15503, 2019
38. Petersen OF, Espersen JO: How to distinguish between bleeding and coagulated extradural hematomas on the plain CT scanning. Neuroradiology 26:285-292, 1984
39. Poli L, Leuci E, Costa P, De Giuli V, Caria F, Candeloro E, Persico A, Gamba M, Magoni M, Micieli G, Cavallini A, Padovani A, Pezzini A, Morotti A: Validation and comparison of noncontrast ct scores to predict intracerebral hemorrhage expansion. Neurocrit Care 32:804-811, 2020
40. Sakuta K, Sato T, Komatsu T, Sakai K, Terasawa Y, Mitsumura H, Iguchi Y: The nag scale: Noble predictive scale for hematoma expansion in intracerebral hemorrhage. J Stroke Cerebrovasc Dis 27:2606-2612, 2018
41. Selariu E, Zia E, Brizzi M, Abul-Kasim K: Swirl sign in intracerebral haemorrhage: Definition, prevalence, reliability and prognostic value. BMC Neurol 12:109, 2012
42. Tutwiler V, Litvinov RI, Lozhkin AP, Peshkova AD, Lebedeva T, Ataullakhanov FI, Spiller KL, Cines DB, Weisel JW: Kinetics and mechanics of clot contraction are governed by the molecular and cellular composition of the blood. Blood 127: 149-159, 2016

43. Tutwiler V, Wang H, Litvinov RI, Weisel JW, Shenoy VB: Interplay of platelet contractility and elasticity of fibrin/erythrocytes in blood clot retraction. Biophys J 112:714-723, 2017
44. Yao X, Xu Y, Siwila-Sackman E, Wu B, Selim M: The hep score: A nomogram-derived hematoma expansion prediction scale. Neurocrit Care 23:179-187, 2015
45. Yu Z, Zheng J, Guo R, Ma L, Li M, Wang X, Lin S, Li H, You C: Performance of blend sign in predicting hematoma expansion in intracerebral hemorrhage: A meta-analysis. Clin Neurol Neurosurg 163:84-89, 2017
46. Zhang D, Chen J, Xue Q, Du B, Li Y, Chen T, Jiang Y, Hou L, Dong Y, Wang J: Heterogeneity signs on noncontrast computed tomography predict hematoma expansion after intracerebral hemorrhage: A meta-analysis. Biomed Res Int 2018:6038193, 2018
47. Zheng J, Yu Z, Guo R, Li H, You C, Ma L: Meta-analysis of predictive significance of the black hole sign for hematoma expansion in intracerebral hemorrhage. World Neurosurg 115: e711-e716, 2018
48. Ziai WC, Carhuapoma JR: Intracerebral hemorrhage. Continuum (Minneap Minn) 24:1603-1622, 2018