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Computed tomography and clinical parameters predict intracerebral hemorrhage expansion

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Abstract

This study aimed to evaluate the association of imaging signs, and to establish a predictive model through selecting highly relevant imaging signs in combination with clinical parameters for hematoma expansion.

Intracerebral Hemorrhage (ICH) patients who received 2 consecutive noncontrast computed tomography scans were examined and recruited through January 2014 to December 2020. Demographic information and clinical characteristics were collected. Two experienced radiologists reviewed baseline noncontrast computed tomography images to assess the imaging characteristics. Correlation analysis was analyzed with Pearson and Spearman correlation tests. The association between clinical and imaging predictors with hematoma expansion was evaluated in multivariate models. Receiver operating characteristic (ROC) curve analysis was adopted to evaluate predictive performance.

A total of 232 ICH patients, with mean age of 59.73 years, and 31% of female were included, among which, 32 patients occurred with hematoma expansion. For sex, ICH density, low density in hematoma, the midline shift, and Glasgow Coma Scale score, liquid level, H-tra, edema Cor, H Volume, time from onset to examination, there were significant differences between the 2 groups. As for imaging signs, only blend sign showed a significant difference, that patients with blend sign had a higher incidence of ICH expansion. The logistic analysis found that radiation attenuation, liquid level, the midline shift, Glasgow Coma Scale score, history of ischemic stroke, and smoking could predict the occurrence of ICH expansion.

In summary, the model combined radiological characteristics with clinical indicators showed considerable predictive performance. Further validation is needed to verify the findings and help transfer to clinical practice.

Abbreviations: CTA = CT angiography, GCS = Glasgow Coma Scale, ICH = intracerebral hemorrhage, NCCT = noncontrast computed tomography, ROC = receiver operating characteristic.

Keywords: clinical parameters, computed tomography markers, hematoma expansion, intracerebral hemorrhage, predict model

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for 10% to 30% of all strokes and is the most devastating subtype of stroke, with a mortality rate of more than 40% within 30 days.[1–3] Hematoma expansion is an independent predictor of early deterioration and poor prognosis, also a potential therapeutic target in clinical trials.[4] Accurate identification of high-risk patients with hematoma expansion may help with the right decisions for clinical treatment.

Spot signs and leakage signs on CT angiography (CTA) are promising and effective predictors of hematoma expansion.[5,6] However, the high requirements of imaging equipment, contraindications to contrast agents, and expensive examination costs have restricted CTA as a routine method of ICH. While noncontrast computed tomography (NCCT), a more widely used tool to diagnose and evaluate ICH in clinical practice, can not only provide information on the size and shape of the hematoma, but also reflect the heterogeneity of density.[7,8] Many CT imaging features, including blend sign, black hole sign, and island sign have been reported to help predict hematoma expansion.[7,9,10] However, whether there is synergistic effect among these features on hematoma expansion prediction has not been determined. This study aims to evaluate the association of each imaging signs, and to establish a predictive model through selecting highly relevant imaging signs in combination with clinical parameters.

2. Participants and methods

2.1. Participants

This study was approved by the Ethics Committee of The General Hospital of Western Theater Command and written informed consent was obtained from all participants.

ICH patients who received 2 consecutive NCCT scans were examined and recruited through January 2014 to December

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2020. The baseline NCCT scan was examined in the early stage of ICH (within 6 hours after ICH symptoms onset) and NCCT re-examination was conducted within 24 hours of the baseline NCCT scan. Patients were excluded as the followings:

1. traumatic brain injury;
2. secondary hemorrhage, such as venous malformation, brain aneurysm, brain tumor associated hemorrhage, sinus embolism, and hemorrhagic cerebral infarction;
3. no surgical intervention prior re-examination;
4. primary ventricular hemorrhage;
5. CT image with severe artifacts;
6. baseline cerebral hemorrhage volume less than 1 ml.

2.2. Data collection

Demographic information (age, gender) and clinical characteristics (history of hypertension, ischemic stroke, diabetes mellites, smoking and alcoholic drinking, and baseline Glasgow Coma Scale [GCS] score) were collected.

All images were examined using the same scanning pattern in the 64-layer spiral CT scanner (LightSpeed VCT, GE). Scan conditions 100–120KV, 125–200 mAs, layer thickness 3.00 mm, layer spacing 3.00 mm. Two experienced radiologists (Wang P and Du FZ), who had 12 and 16 years' experience of neuroimaging diagnosis respectively, reviewed baseline NCCT images to assess the following characteristics:

1. position: deep (basal ganglia, hypothalamus, internal capsule, callosum, or corona radiata), and brain lobe (frontal lobe, temporal lobe, occipital lobe, or multiple lobes), brain stem, cerebellum, or others;
2. shape: circle/ellipse, cast, or irregular;
3. density: uniform or uneven;
4. low density in hematoma: yes or no;
5. swirl sign: yes or no;
6. blend sign: yes or no;
7. black hole sign: yes or no;
8. island sign: yes or no;
9. satellite sign: yes or no; and
10. edema: no, mild, moderate, or severe.

The results of the 2 radiologists' readings were tested by Kappa, with a credibility value of 0.86 and a range of 0.63 and 0.9.

The criteria for each of these imaging signs were as follows:

Swirl sign: swirling hypodense or isodense region inside the hyperdense hematoma, with clear boundaries.[11] (Fig. 1A)
Blend sign: uneven densities, with an attenuating difference of at least 18 Hounsfield units (Hu) between the 2 areas of different densities.[9] (Fig. 1B)
Black hole sign: hypodense encapsulated within the hyperattenuating hematoma, with a density difference of at least 28 Hu between 2 areas of differing densities.[7] (Fig. 1C)
Island sign: more than 3 separate small hematomas, all of which were scattered and separated from the main hematoma; or more than 4 separate small hematomas, partial or all of which were connected to the main hematoma.[10] (Fig. 1D)
Satellite sign: any small hematoma that was completely isolated from the main hematoma. The shortest distance between the small hematoma and main hematoma was 1–20 mm.[12] (Fig. 2A)
Liquid level and ***the midline shift*** were shown in Figure 2B and C, respectively.

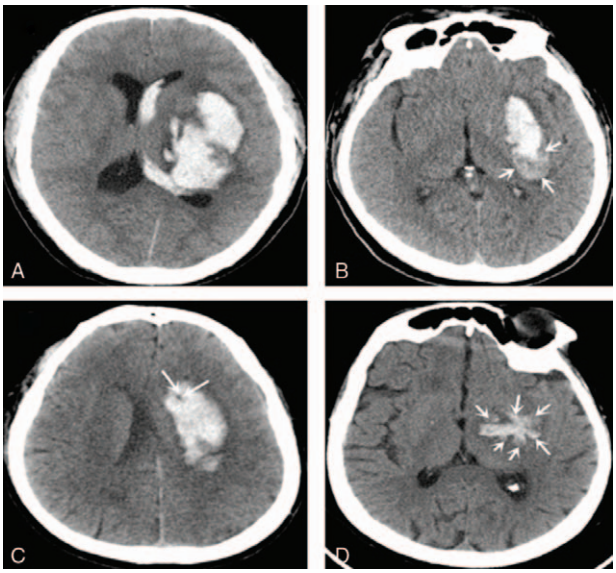

Figure 1. Imaging signs (A) Swirl sign, (B) Blend sign, (C) Black hole sign, (D) Island sign.

Hematoma expansion was defined as hemorrhage volume growth of more than 6 mL or a 33% increase over baseline volume.[13] Using artificial sketch ROI, python was used to calculate hemorrhage volume and volume changes.

2.3. Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) or median (quartile range), and categorical variables were calculated with counts. Mann–Whitney *U* test, independent *t*-test, square test, and Fisher exact test were used for one-way variance analysis. Correlation analysis was analyzed with Pearson and Spearman correlation tests. The association between clinical and imaging predictors and hematoma expansion was evaluated in multivariate models. ROC curve analysis was adopted to evaluate predictive performance. Based on the Maximum Youden Index, the area under the ROC curve (AUC), sensitivity, specificity and accuracy were calculated. Furthermore, the patients were divided into training and validation set with the ratio of 7:3 based on gender and age. A total of 1370 imaging omics features were extracted. The model was constructed and verified through ROC curve after data balancing, standardization, and feature screening. The effectiveness of imaging omics features in predicting hematoma expansion was evaluated by comparing with radiologists' routine diagnostic performance. Two-sided P value $<.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (Version 23.0, IBM Corporation, NY).

3. Results

3.1. Baseline characteristics

A total of 232 patients with ICH (mean age of 59.73 years, range from 29–93 years; female 72 [31%]) were included, among which, 32 patients occurred with hematoma expansion. The demographic and clinical characteristics was shown in Table 1. There was no significant difference in age, history of hyperten-

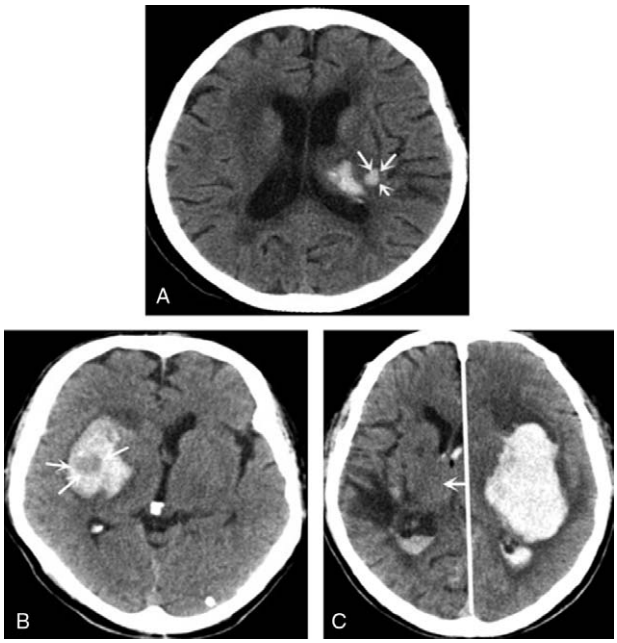

Figure 2. Imaging signs (A) Satellite sign, (B) Liquid level, (C) The midline shift.

sion, diabetes mellitus, ischemic stroke, smoking, alcohol drinking, baseline ICH volume, hematoma location, and ICH shape. ($P > .05$). However, for sex, ICH density, low density in hematoma, the midline shift, and GCS score, liquid level, H-tra, edema Cor, H Volume, time from onset to examination, there were significant differences between the 2 groups. As for imaging signs, only blend sign showed a significant difference, that patients with blend sign had a higher incidence of ICH expansion.

3.2. Correlation analysis for ICH expansion with clinical characteristics

The results of correlation analysis showed that sex (male, $r=0.133$), H-tra (correlation coefficient $r=0171$), H-Cor ($r=0.161$), edema tra ($r=0.183$), edema Cor ($r=0.138$), H volume ($r=0.137$), and bleeding speed ($r=0.294$) was positively correlated with ICH expansion. While GCS score ($r=-0.228$), and time from onset to examination ($r=-0.154$) was negatively associated with ICH expansion.

3.3. Correlation analysis for ICH expansion with imaging characteristics

The results of correlation analysis showed that liquid level ($r=0.176$), blend sign ($r=0.214$), low density in hematoma ($r=0.200$), and the midline shift ($r=0.209$) was positively correlated with ICH expansion. While ICH location ($r=-0.139$), and density ($r=-0.153$) was negatively associated with ICH expansion.

3.4. Prediction model for ICH expansion

The logistic analysis found that radiation attenuation, liquid level, the midline shift, GCS score, history of ischemic stroke, and smoking could predict the occurrence of ICH expansion. The logistic regression equation was $P=.105$ radiation attenuation + 3.371 liquid level + 1.201 the midline shift - 0.175 GCS score + 1.32 history of ischemic stroke + 1.065 smoking −8.322. When the Cut-off value = 0.057, the model had the best fitting, with the sensitivity = 0.969, 1-specifity = 0.365, Youden index = 0.604, and area under the Curve (AUC) of receiver operating characteristic (ROC) = 0.92. (Fig. 3) After screening, the support vector machine (SVM) method used 11 imaging omics features to construct the hematoma expansion prediction model with the best performance. In the training set, the AUC was 0.94, the sensitivity and specificity were 86.9% and 89.6%, respectively, and the diagnostic accuracy rate was 85.7%. While, the AUC of the prediction model in the validation set was 0.78, with the sensitivity and specificity of 68.9% and 83.3%, and the diagnostic accuracy rate of 88.9%.

3.5. Correlation between measurements

In addition, there was a high correlation between some measurements. The results showed that smoking and alcohol drinking was highly correlated with sex ($r=0.540$ and 0.444, respectively). ICH density was highly correlated with ICH shape, swirl sign, blend sign, black hole sign ($r=0.612$, 0.547, 0.699, 0.392, respectively). Swirl sign was highly correlated blend sign, and black hole sign ($r=0.630$ and 0.379). In addition, blend sign had a correlation with black hole sign ($r=0.476$), and island sign had a correlation with satellite sign ($r=0.709$).

4. Discussion

In this retrospective study, we built 1 model with a combination of radiological and clinical predictors of hematoma expansion, and provided a quick way to identify patients who were at a high risk of hematoma expansion. NCCT-based radiological models reduced the need for CTA testing when selecting patients who might benefit from hemostatic therapy, especially when CTA was not available or in patients who were contraindicated to contrast agent reactions, or had severe kidney diseases.

The overall incidence of hematoma expansion in ICH patients was 13.8%, which was slightly lower than previous studies.[14] This study found that sex (male), liquid level, low density in hematoma, the midline shift, and blend sign was positively correlated with hematoma expansion, while ICH location, density, and GCS score had a negative correlation with hematoma expansion.

The clinical parameters investigated in this study were all widely used in clinical practice, and NCCT markers were all widely available, and could be rapidly evaluated. Although the CTA spot was the strongest predictor in hematoma expansion prediction, emergency CTA is not always available in many hospitals.[8] Various NCCT markers, including swirl sign, blend sign, black hole sign, island sign, and satellite sign reflecting hematoma density heterogeneity, have been evaluated for hematoma expansion prediction. Selariu et al found that patients with swirl sign exhibited larger ICH-volume, compared with those without swirl sign, and swirl sign was an independent predictor of death at 1 month.[15] Li et al found that blend sign could be easily identified on NCCT scans, which could be used as an independent predictor of hematoma expansion with a high sensitivity and specificity.[9] In addition, in a study that included 182 ICH patients, blend sign was found to have a high correlation with the Spot sign and was a reliable predictor for secondary neurological deterioration.[16] Furthermore, black hole sign and island sign had also been proven as an independent, simple and

Table 1

Comparison of baseline demographic and CT imaging characteristics between patients with and without hematoma expansion.

Characteristics	Hematoma expansion		Methods	*P*
	Yes (n = 32)	No (n = 200)		
Age, mean (SD)	60 (14)	60 (13)	*U* test	.745
Female, n (%)	5 (2)	67 (29)	Fisher's exact test	**.042**
Disease history				
Hypertension	25 (11)	152 (66)	Chi-Squared	.793
Diabetes Mellitus	5 (2)	26 (11)	Fisher's exact test	.685
Ischemic stroke	12 (5)	48 (21)	Fisher's exact test	.105
Smoking	17 (3)	78 (34)	Fisher's exact test	.131
Alcohol drinking	15 (6)	87 (38)	chi-square	.721
Use of anticoagulants	1 (0)	4 (2)	Fisher's exact test	.684
Hematoma -Tra (mm)	43.9	36.5	*U* test	**.007**
Hematoma -Cor (mm)	26.4	22.3	*U* test	**.013**
Hematoma -Sig (mm)	41.1	38.2	*U* test	.522
Edema -Tra (mm)	56.3	45.9	*t*-test	**.005**
Edema -Cor (mm)	34.1	29.4	*U* test	.09
Edema -Sig (mm)	44.6	43.5	*U* test	.805
Edema volume (ml)	22.809	19.708	*U* test	.342
Hematoma volume (ml)	29.849	20.859	*U* test	**.03**
Radiation attenuation	65.2	63.4	*U* test	.167
bleeding speed	10.151	3.938	*U* test	**.001**
Time (onset to examination, h)	5.3	10.3	*U* test	**.001**
ICH location			Crosstabs	.331
Basal ganglia	23 (10)	100 (43)		
Hypothalamus	3 (1)	40 (17)		
Internal capsule	0 (0)	1 (0)		
Callosum	2 (1)	4 (2)		
Corona radiata	1 (0)	6 (3)		
Frontal lobe	1 (0)	12 (5)		
Temporal lobe	0 (0)	10 (4)		
Occipital lobe	0 (0)	14 (6)		
Multiple lobes	1 (0)	4 (2)		
Brain stem	1 (0)	5 (2)		
Cerebellum	0 (0)	4 (2)		
ICH shape			Crosstabs	.324
Circle / ellipse	13 (6)	88 (34)		
Cast	0 (0)	11 (5)		
Irregular	19 (8)	101 (44)		
ICH density			Crosstabs	**.020**
Uniform	24 (10)	106 (46)		
Uneven	8 (3)	94 (41)		
Liquid level	2 (1)	1 (0)	Fisher's exact test	**.008**
Low density in hematoma	23 (10)	86 (37)	Chi-Squared test	**.002**
The midline shift	18 (8)	56 (24)	Chi-Squared test	**.001**
Imaging Signs				
Swirl sign, n (%)	19 (8)	84 (36)	Chi-Squared test	.066
Blend sign, n (%)	24 (10)	88 (38)	Chi-Squared test	**.011**
Black hole sign, n (%)	10 (4)	45 (19)	Fisher's exact test	.280
Island sign, n (%)	8 (3)	45 (19)	Fisher's exact test	.755
Satellite sign, n (%)	10 (4)	76 (33)	Fisher's exact test	.463
Edema			Crosstabs	.417
None	0 (0)	7 (3)		
Mild	27 (12)	154 (66)		
Moderate	4 (2)	37 (16)		
Severe	1 (0)	2 (1)		
Baseline GCS score			Crosstabs	**.015**
3–9	9 (4)	17 (7)		
10–12	7 (3)	42 (18)		
13–15	16 (7)	141 (61)		

Cor = coronal diameter, Sig = sagittal diameter, (mm), Tra = transverse diameter.

Mann–Whitney *U* test, independent *t*-test, Chi-Squared test, Fisher's exact test, Pearson or Spearman correlations tests were used.

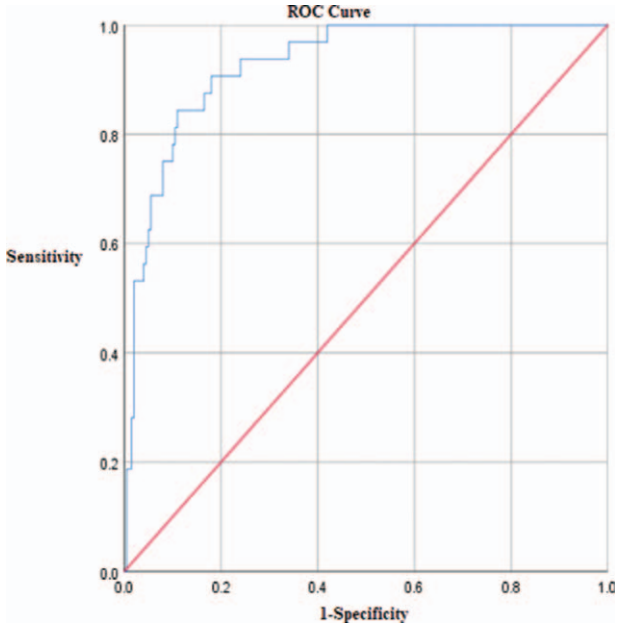

Figure 3. The ROC curve for logistic regression model.

easy-to-use predictor for early hematoma expansion.[7,10] Although a lot of NCCT indications had been found, cross-overlapping definitions and criteria could cause difficulties in clinical applications. In this study, only blend sign was an independent predictor, and included in the prediction model for hematoma expansion.

Furthermore, using a retrospective multicenter cohort study with 520 acute spontaneous ICH patients, Nawabi et al found that the integration of conventional scores and image features had a statistically significant increase in AUC (0.84 [0.83; 0.86], $P < .05$).[17] In this study, the prediction model established in this study together with clinical and imaging parameters had a high sensitivity and specificity for hematoma expansion prediction, with AUC ROC of 0.92.

However, this study had several limitations. First, the retrospective design of this study might cause a selection bias. Second, the sample size was relatively small. Further evidence with large population is warranted to confirm the findings. In addition, there was overlap between the definitions and criteria of these imaging and clinical indicators, making it difficult to standardize the application in clinic practice.

In summary, we validated the traditional NCCT hematoma expansion predictors. The model combined NCCT radiological characteristics with clinical indicators (radiation attenuation, liquid level, the midline shift, GCS score, history of ischemic stroke, and smoking) showed considerable predictive performance. Further validation is needed to verify the findings and help transfer to clinical practice.

Author contributions

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Funding acquisition: Rui Jiang.
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Methodology: Peng Wang, Fa Wu, Yang Wang.
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Supervision: Jianhao Li, Jinping Sheng, Rui Jiang.
Validation: Xiaokun Yang, Hongmei Yu.
Visualization: Peng Wang.
Writing – original draft: Peng Wang, Fa Wu.
Writing – review & editing: Peng Wang, Fa Wu.

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