Establishment of prediction score for hematoma expansion after intracerebral hemorrhage

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DOI:
10.21203/rs.2.306/v1

SUBJECT AREAS
Internal Medicine Specialties

KEYWORDS
Intracerebral hemorrhage; Hematoma expansion; Non-enhanced CT; Prediction; Score
Abstract

**Background:** Identification of intracerebral hemorrhage (ICH) patients at risk of hematoma expansion (HE) could facilitate the selection of candidates likely to benefit from therapies aiming to minimize ICH growth. We, therefore, aimed to develop a prediction score for HE that can be quickly used during the critical phase.

**Methods:** A retrospective analysis of clinical features of 317 ICH patients in the Second Affiliated Hospital of Soochow University from January, 2016 to May, 2018 was conducted. Independent risk factors of HE were obtained according to multiple logistic regression, and a prediction score was established and preliminarily evaluated.

**Results:** History of anticoagulants, ultraearly hematoma growth ≥ 2.7ml/h, GCS ≤ 8, and non-enhanced CT signs (island sign, black hole sign, blend sign, niveau formation) exist one or more, were independent risk factors for HE (P < 0.05). The C statistics of score was 0.854 (95%CI, 0.803~0.904; P < 0.001); calibration was outstanding (c2 = 3.323, P = 0.344); decision curve analysis showed the score was safe and reliable, with high net benefit. After dichotomized, the sensitivity, specificity and accuracy of the high-risk group (score ≥ 4.5) were 0.77, 0.85 and 0.83, respectively.

**Conclusion** The score can accurately identify high-risk individuals with HE, swift guide treatment decisions, and can also be used in clinical trials.

**Keywords:** Intracerebral hemorrhage; Hematoma expansion; Non-enhanced CT; Prediction; Score.

**Background**

It is well known that intracerebral hemorrhage (ICH) is the second most common type of stroke, accounting for 10~15% of all stroke events\[1\]. The fatality rate is relatively high, only 12~39% survivors have the ability to live independently\[2\]. Early hematoma
expansion (HE) occurs in 20~30% of ICH patients [3]. Multiple studies have shown that [1,4-6] HE is not only the most important determinant of increase of disability and fatality rates, but also the only target for human intervention. Therefore, it is of great value to use simple and effective predictors to screen out the high-risk patients who may have HE, and make targeted treatments to curb the early deterioration of ICH and improve the prognosis. The present study conducted a retrospective clinical research on 317 ICH patients, analyzed the relevant factors of HE, established a prediction score and made a preliminary evaluation.

Methods

Study population

Patients with ICH in the Second Affiliated Hospital of Soochow University from January, 2016 to May, 2018 were consecutively registered. Inclusion criteria: 1. The first CT scan was performed within 24h after the onset, and the diagnosis was acute ICH; 2. Age≥18. Exclusion criteria: 1. Secondary ICH (cerebral tumor, traumatic brain injury, arteriovenous malformation, cerebral aneurysm, hemorrhagic transformation of cerebral infarction); 2. Emergency surgery before the second CT scan; 3. CT was not re-examined within 72h after the first scan. A total of 317 eligible ICH patients were enrolled. The study was approved by the ethical committee of the Second Affiliated Hospital of Soochow University (JD-LK-2018-067-01). All study protocols and procedures were conducted in accordance with the declaration of Helsinki. Because this study was a retrospective observational study, patient information was anonymized and deidentified before analysis. Therefore, the need for patient consent was waived.

Research design

Retrospective study was conducted to record the clinical data of patients by referring to
electronic medical records, and the subjects were divided into HE group and non-HE group. HE was defined as an increase of hematoma volume >33% or absolute hematoma growth >6 mL from initial non-contrast CT (NCCT) scan\(^3,4,7,8\). Specific NCCT signs (island sign, black hole sign, blend sign, edema, niveau formation) were all identified and recorded, definitions refer to previous studies\(^9,10\). The two observers (neuroradiologist and neurologist) were blind to the information and outcome of patients, independently evaluated the first and second scans of NCCT. Disagreements were decided by consensus decision.

**Statistical analyses**

Statistical analyses were performed using SPSS 25.0, Stata 15, and Rstudio. Data presented as mean±standard deviation (SD) for variables with normal distribution and compared using student’s t test. Non-normally distributed continuous variables were compared across quartiles and tested for statistical significance using Mann-Whitney \(U\) test. Differences in categorical variables were compared using \(c^2\) test. In order to establish the score, measurement data were converted into categorical data, and the cut-off values were obtained by using the quartile, Youden index of receiver operating characteristic (ROC) curve and recursive partitioning as appropriate. To avoid collinearity of variables, partial repeated ones were professionally removed. Categorical variables with \(P<0.05\) between groups were included in the multivariate logistic regression. As a result, risk factors with \(P<0.05\) in regression were added into score. The score was created based on the parameter estimates (\(\beta\) coefficients) from the regression. The assigned scores for each item were derived by summing the \(\beta\) coefficients (\(B\)), calculating the point for each risk factor as \(4\times(\beta_i/B)\) and the point was rounded to the nearest integer. Novel measures of score performance were utilized, including c-index for
discrimination, Hosmer-Lemeshow goodness-of-fit statistic for calibration and decision curve analysis (DCA) for clinical utility. A two-tailed $P<0.05$ was considered statistically significant.

Results

**Baseline characteristics of Patients**

Baseline characteristics of participants are shown in Table 1. A total of 317 eligible patients were recruited in our study, including 200 males (63.1%). The average age was 64 years old (IQR, 52~74). HE was observed in 87 patients (27.4%); inter-reader reliability was very good (kappa=0.85). History of anticoagulants, D-Dimer ≥ 0.65mg/L, potassium ≤ 3.1mmol/L, ultraearly hematoma growth (uHG) ≥ 2.7ml/h, GCS ≤ 8, and NCCT signs (island sign, black hole sign, blend sign, niveau formation) exist one or more, were risk factors of HE ($P<0.05$). Then the above risk factors were included in multivariate logistic regression, and the detailed results were shown in Table 2. Finally, it was concluded that the history of anticoagulants, ultraearly hematoma growth ≥ 2.7ml/h, GCS ≤ 8, and NCCT signs (island sign, black hole sign, blend sign, niveau formation) exist one or more, were independent risk factors of HE ($P < 0.05$).

**Establishment of prediction score and preliminary evaluation**

The independent risk factors were included in the model, and score was created based on the parameter estimates (β coefficients), as shown in Table 3. Further, the ROC curve of score is shown in Figure 1. The C statistic was 0.854, 95%CI (0.803~0.904), $P<0.001$, and the discrimination ability was excellent. Calibration plot is shown in Figure 2, the fitting line conformed to 45 degrees, passed through the origin, the maximum deviation was 0.070, and the average deviation was 0.028. Hosmer-Lemeshow goodness-of-fit test presented strong accuracy ($c^2=3.323, P=0.344$). DCA curve proved score clinically
practical, as shown in Figure 3. Curve of score is far from both curve of treat all and curve of treat none, with high net benefit, a wide range of optional threshold probability, so it’s safe and reliable. Table 4 shows the results of the score. In general, the incidence of HE increases with higher scores. When 4.5 was taken as the cutoff value to dichotomize the score, the incidence of HE was 66.3% in high risk group (score ≥ 4.5) compared with 9.3% in low risk group (score < 3). The sensitivity, specificity, and overall accuracy of the high risk group were 0.77, 0.85 and 0.83, respectively.

Discussion

In this study, we showed that the history of anticoagulants was an independent risk factor for HE, while the history of antiplatelets was not. Previous studies [5,11] have pointed out that the history of antiplatelets was negatively correlated with the prognosis of neurological function, but it’s relationship with HE was highly controversial. The differences may be attributed to the definition of hematoma enlargement, sample size, or demographic factors. In addition, edema [3,9] was reported as an independent risk factor while niveau formation was not, which was inconsistent with our study. The reason may be that there was a lack of consensus on criteria for identifying signs when there was coexistence or overlap between different NCCT signs. Another possibility is that observers lack standardized training.

Hematoma heterogeneity is currently recognized as an independent risk factor of HE, but the definition and scale of irregular shape and density heterogeneity were subjective, immature and lack of strict standard consensus, which may lead to ambiguity, so this study did not apply this indicator. CTA spot sign is a popular marker of increased risk of HE at present, with relatively high specificity. But it is expensive and increases radiation. Emergency CTA examination is unavailable in most hospitals, and patients with allergy to
contrast medium or renal insufficiency are out of bound. For critically patients with unstable vital signs, CTA potentially delays the disease and leads to medical malpractice. Multi-center clinical trials\[^{12}\] have confirmed that the actual diagnostic capacity of CTA had not reached the theoretical level, suggesting that NCCT signs could be a reliable substitute for CTA spot sign. NCCT has strong universality and is widely used in the world, which can improve the compliance of patients, thus increases the number of patients enrolled and plays a pivotal role in clinical trials. Sakuta\[^{13}\] declared that the accuracy of the National Institute of Health Stroke Scale (NIHSS) in predicting HE was higher than that of Glasgow Coma Scale (GCS), and emphasized that human had dominant hemispheres of brain. When bleeding occurs in different hemispheres, the assessment of consciousness level or speech ability will be inevitably inaccurate. However, in the standard version of GCS score, when two sides of the score are different, the higher side shall be prevail, so the above concerns may be unnecessary. Most of patients in Sakuta's research had normal consciousness, so NIHSS may be more reflective of mild or moderate neurological impairment than GCS. However, some patients in this study were in critical condition. Due to secondary vascular injury (such as avalanche effect\[^{14}\]), the accuracy of GCS was not necessarily inferior to that of NIHSS. This may imply that GCS and NIHSS can be compatible and complementary according to different situation.

Some models\[^{9,13,15-19}\] had been published, but there are following defects: 1. Models are complex and user-unfriendly, which cannot apply to all patients. 2. Most models are only focused on the accuracy in mathematical statistics instead of the practical significance. 3. Most models only used ROC curve for evaluation. However, good discriminating ability does not mean high accuracy. If the harm caused by false negative is tremendous, ROC curve will not intuitively present this information, which is eventually ignored by
researchers. In comparison, the current study has higher professionalism and accuracy in modeling, and it is the first time to conduct a multidimensional systematic evaluation of the model (identification ability, accuracy, clinical practicability). Furthermore, our results are significantly better than the previous versions. The cut-off value was 4.5 in this model to divide the score into the high risk group and the low risk group, because the incidence of HE at this point was significantly higher than the average one. It is worth mentioning that no patients with a score of 4 were found, due to the fact that NCCT signs and low GCS scores are more likely to occur when hematomas are large. So there is a greater probability of uHG≥2.7ml/h when the above two co-exist. Thanks for the good specificity of score, it can be used in clinical trials of hemostatic drugs to screen out the groups that benefit most from HE targeted intervention, paving the way for standardized treatment and research of ICH. For example, high risk group (score≥4.5) requires intensive care, blood pressure control, early surgery or transfer to a higher level of medical center, which is also suitable for clinical trials of hemostasis treatment; low risk group (score <4.5) is unlikely to benefit from hemostasis therapy and minimize potential side effects like thrombogenesis. HE generally occurs within 6 hours after the onset, leaving a limited time gap for the HE preventing strategies. Therefore, it is crucial to quickly assess the risk of HE. Compared with nomograph, score is concise, which can be calculated within minutes of a patient's arrival in the emergency room, gets rid of the previous versions limitations, enables doctors of any medical institutions to swift make personalized treatment plans with limited information.

This study has some limitations. 1. It is limited by the nature of retrospective research. Relevant data could only be obtained from medical records, so some valuable details might be missed. 2. The study was carried out at a single-center, with a small sample size and no external validation. Before applied in clinical practice, multi-center prospective
studies with large samples are required for external validation. 3. The time from onset to CT scan was sometimes inaccurate or even unknown, and only be roughly estimated (wake-up strokes). 4. HE generally occurs within 6 hours after the onset. Patients who received initial CT scan later may have developed HE but failed to be detected, which will affect the proportion of HE occurrence. 5. Several studies [7-9,14-16] have confirmed that HE is an independent risk factor for early deterioration of neurological function and poor long-term prognosis. To avoid repeated studies, the association between score and prognosis of neurological function had not been clarified for the definition of HE. Our study was mainly based on neuroimaging. 6. A small number of patients were excluded from the study due to early death, abandonment of treatment and emergency surgery. This is a recurring flaw in observational studies that will inevitably lead to selection bias. This group of people is generally considered to have the highest incidence of HE, excluding them contributes to underestimate its real predictive power.

Conclusions

In conclusion, our model has excellent identification ability, good accuracy and clinical utility. Score is universal and feasible, accurately identifies high-risk individuals of HE, swift guides treatments and also serves clinical trials. But prospective studies are required for external validation before application.

Abbreviations

ICH: Intracerebral hemorrhage HE: Hematoma expansion C statistics: Area under the curve NCCT: Non-contrast computed tomography SD: Standard deviation ROC: Receiver operating characteristic DCA: Decision curve analysis NIHSS: National Institute of Health Stroke Scale GCS: Glasgow Coma Scale IQR: Interquartile range SBP: Systolic blood pressure Hb: Hemoglobin INR: International sensitivity index uHG: Ultraearly hematoma
growth OR: Odds ratio  CI: Confidence interval  Emax: Maximum deviation of probability

Eavg: Average deviation of probability

Declarations

Acknowledgements

The authors thank the participants and all who were involved in our study.

Funding

This work was supported by the Natural Natural Science Foundation of China[81602183] and Postgraduate Practice Innovation Program of Jiangsu Province (SJCX18_0855). The fund body took no part in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

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

Authors’ contributions

XYK study concept and design, analysis and interpretation of data, drafting of the manuscript. WQ acquisition of data, analysis and interpretation of data, drafting of the manuscript. JD acquisition of data, analysis and interpretation of data and revision of the drafting of the manuscript. ZYQ obtaining funding, study concept and design, study supervision or coordination, revision of the drafting of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethical committee of the Second Affiliated Hospital of Soochow University (JD-LK-2018-067-01). All study protocols and procedures were conducted in accordance with the declaration of Helsinki. Because this study was a retrospective observational study, patient information was anonymized and deidentified
before analysis. Therefore, the need for patient consent was waived by the ethical committee of the Second Affiliated Hospital of Soochow University.

**Consent for publication**

Because this study was a retrospective observational study, patient information was anonymized and deidentified before analysis. Therefore, the need for patient consent was waived.

**Competing interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Tables

Table 1: Baseline clinical characteristics of patients with and without HE
| Variables                                      | Total n=317 | HE n=87 | Non HE n=230 | P       |
|------------------------------------------------|-------------|---------|--------------|---------|
| Age, y (IQR)                                   | 64[52–74]   | 66[52–75] | 64[52–73]    | 0.497   |
| Sex, male, n (%)                               | 200[63.1]   | 53[60.9] | 147[63.9]    | 0.622   |
| Hypertension, n (%)                            | 239[75.4]   | 66[75.9] | 173[75.2]    | 0.905   |
| Diabetes mellitus, n(%)                        | 48[15.1]    | 11[12.6] | 37[16.1]     | 0.445   |
| Chronic Kidney Disease, n(%)                   | 13[4.1]     | 6[6.9]   | 7[3.0]       | 0.220   |
| Antiplatelets, n(%)                            | 20[6.3]     | 5[5.7]   | 15[6.5]      | 0.800   |
| Recurrent ICH, n(%)                            | 30[9.5]     | 8[9.2]   | 22[9.6]      | <0.001  |
| SBP, mmHg (IQR)                                | 163[148–180]| 162[148–182]| 165[148–175]| 0.630   |
| Platelet, *10^9/L (IQR)                        | 196[163–240]| 185[149–229]| 204[165–243.5]| 0.032   |
| INR, n(IQR)                                    | 1.03[0.98–1.08]| 1.03[0.98–1.08]| 1.02[0.98–1.07]| 0.358   |
| D-Dimer, mg/L (SD)                             | 0.77[0.41–1.15]| 0.98[0.61–1.41]| 0.72[0.39–1.08]| 0.001   |
| Potassium, mmol/L (IQR)                        | 3.57[3.29–3.88]| 3.54[3.16–3.76]| 3.59[3.34–3.90]| 0.040   |
| Calcium, mmol/L (IQR)                          | 2.24[2.17–2.32]| 2.24[2.16–2.31]| 2.25[2.17–2.32]| 0.351   |
| Time to initial CT scan, h (IQR)               | 3[2–6]      | 2.5[2–4]| 3[2–7.25]    | 0.003   |
| Baseline ICH volume, mL (IQR)                  | 8[4.5–18]| 23[10–40]| 6[3.5–13]| <0.001  |
| uHG, ml/h (IQR)                                | 2.8[1–7.5]| 8[3.78–15.33]| 1.78[0.7–4.58]| <0.001  |
| Supratentorial ICH, n(%)                       | 284[89.6]| 82[94.3]| 202[87.8]| 0.095   |
| Intraventricular ICH, n(%)                     | 106[33.4]| 35[40.2]| 71[30.9]| 0.115   |
| GCS, n(IQR)                                    | 13[11–14]| 11[9–13]| 13[11–15]| <0.001  |
| GCS≤8, n(%)                                    | 43[3.6]| 30[34.5]| 13[5.7]| <0.001  |
| Island sign, n(%)                              | 59[18.6]| 51[58.6]| 8[3.5]| <0.001  |
| Black hole sign, n(%)                          | 74[23.3]| 45[51.7]| 25[12.6]| <0.001  |
| Blend sign, n(%)                               | 28[8.8]| 16[18.4]| 12[5.2]| <0.001  |
| Edema, n(%)                                    | 37[11.7]| 15[17.2]| 22[9.6]| 0.058   |
| Niveau formation, n(%)                         | 18[5.7]| 16[18.4]| 2[0.9]| <0.001  |
| NCCT signs (island sign, black hole sign, blend sign, niveau formation) exist one or more, n(%) | 109[34.4]| 63[72.4]| 46[20]| <0.001  |

GCS, Glasgow Coma Scale; HE, hematoma expansion; ICH, intracerebral hemorrhage; IQR, interquartile range; SBP, systolic blood pressure; Hb, hemoglobin; INR, international sensitivity index; NCCT, non-contrast CT; uHG, ultraearily hematoma growth and SD, standard deviation.

Table 2: Multiple logistic regression of HE risk factors

| Variables                                      | B coefficients | OR[95%CI] | P       |
|------------------------------------------------|---------------|-----------|---------|
| Anticoagulants, n(%)                            | 3.212         | 24.83[1.95–315.48] | 0.013   |
| uHG≥2.7ml/h, n(%)                              | 1.688         | 5.41[2.46–11.90]     | <0.001  |
| GCS≤8, n(%)                                     | 1.364         | 3.91[1.63–9.40]      | 0.002   |
| D-Dimer≥0.65mg/L, n(%)                         | 0.633         | 1.86[0.96–3.71]      | 0.068   |
| Potassium≥3.1mmol/L, n(%)                      | 0.705         | 2.02[0.81–5.03]      | 0.130   |
| NCCT signs (island sign, black hole sign, blend sign, niveau formation) exist one or more, n(%) | 1.471         | 4.35[2.24–8.46]      | <0.001  |

GCS, Glasgow Coma Scale; HE, hematoma expansion; ICH, intracerebral hemorrhage; NCCT, non-contrast CT; uHG, ultraearly hematoma growth; OR, odds ratio; CI, confidence interval.
interval.

**Table 3:** HE prediction grading system in ICH

| Variables                                      | Points |
|------------------------------------------------|--------|
| GCS≤8                                          | 2      |
| uHG≥2.7ml/h                                    | 2.5    |
| NCCT signs (island sign, black hole sign, blend sign, niveau formation) exist one or more | 2      |
| Anticoagulants                                 | 4.5    |
| Total                                          | 0–11   |

GCS, Glasgow Coma Scale; HE, hematoma expansion; ICH, intracerebral hemorrhage; NCCT, non-contrast CT; uHG, ultraearly hematoma growth.

**Table 4:** The results of prediction score

| Score | Hematoma expansion [%] | n |
|-------|------------------------|---|
| 0     | 6.2                   | 8/130 |
| 2     | 8.7                   | 2/23  |
| 2.5   | 15.9                  | 10/63 |
| 4.5   | 56.1                  | 37/66 |
| 6.5   | 82.1                  | 23/28 |
| ≥7    | 100                   | 7/7   |

Dichotomized

| ≥4.5 | 9.3          | 20/216 |
| ≥4.5 | 66.3         | 67/101 |

When score ≥4.5

| Sensitivity | 0.77 |
| Specificity | 0.85 |
| Positive predictive value | 0.66 |
| Negative predictive value | 0.91 |
| Overall accuracy | 0.83 |
Figure 1

Receiver operating characteristic curve of prediction score.
Figure 2

Calibration plot of prediction score $E_{\text{max}}$, Maximum deviation of probability;
$E_{\text{avg}}$, average deviation of probability.
Figure 3

Decision curve analysis of prediction score. X, prediction score.

Supplementary Files

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data.xls