Journal of the American Heart Association

ORIGINAL RESEARCH

Prediction of Neurological Deterioration After Intracerebral Hemorrhage: The SIGNALS Score

Quanwei He, MD, PhD;* Hongxiu Guo, MD;* Rentang Bi, MD;* Shaoli Chen, MD; Jing Shen, MD, PhD; Chunnan Long, MD; Man Li, MD, PhD; Yuanpeng Xia, MD, PhD; Lei Zhang, MD; Zhou Sun, MD; Xiaolu Chen, MD, PhD; Zhaowei Wang, MD; Daokai Gong, MD; Jingwen Xu, MD; Dondya Zhu, MD, PhD; Yan Wan, MD, PhD; Bo Hu, MD, PhD

BACKGROUND: Intracerebral hemorrhage is the most disabling and lethal form of stroke. We aimed to develop a novel clinical score for neurological deterioration during hospitalization after intracerebral hemorrhage.

METHODS AND RESULTS: We analyzed data from the CHERRY (Chinese Cerebral Hemorrhage: Mechanism and Intervention) study. Two-thirds of eligible patients were randomly allocated into the training cohort (n=1027) and one-third into the validation cohort (n=515). Multivariable logistic regression was used to identify factors associated with neurological deterioration (an increase in National Institutes of Health Stroke Scale of ≥4 or death) within 15 days after symptom onset. A prediction score was developed based on regression coefficients derived from the logistic model. The site, size, gender, National Institutes of Health Stroke Scale, age, leukocyte, sugar (SIGNALS) score was developed as a sum of individual points (0–8) based on site (1 point for infratentorial location), size (3 points for >20 mL of supratentorial hematoma volume or 2 points for >10 mL of infratentorial hematoma volume), sex (1 point for male sex), National Institutes of Health Stroke Scale score (1 point for >10), age (1 point for ≥70 years), white blood cell (1 point for>9.0×10^9/L), and fasting blood glucose (1 point>7.0 mmol/L). The proportion of patients who suffered from neurological deterioration increased with higher SIGNALS score, showing good discrimination and good calibration in the training cohort (C statistic, 0.821; Hosmer-Lemeshow test, P=0.687) and in the validation cohort (C statistic, 0.848; Hosmer-Lemeshow test, P=0.592), respectively.

CONCLUSIONS: The SIGNALS score reliably predicts the risk of in-hospital neurological deterioration of patients with intracerebral hemorrhage.

Key Words: intracerebral hemorrhage ■ neurological deterioration ■ prognosis ■ SIGNALS score

See Editorial by Li and Goldstein

Intracerebral hemorrhage (ICH), despite accounting for only 10% to 15% of stroke, is the most disabling and lethal form.[1,2] Because of the lack of effective therapies, ≈18% of patients with ICH suffer from neurological deterioration (ND) during hospitalization,[3–5] which portends major disability or even death. A model to predict the risk of ND during hospitalization for patients with ICH is urgently required by both neurologists and patients. On the one hand, it contributes to further identify risk factors, fine tune therapeutic

Correspondence to: Yan Wan, MD, Phd, Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. 1277 Jiefang Avenue, Wuhan 430022, China. Email: wanyanalan@163.com and Bo Hu, MD, Phd, Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China. Email: hubo@mail.hust.edu.cn

*Q. He, H. Guo, and R. Bi contributed equally and share first authorship.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026379

For Sources of Funding and Disclosures, see page 7.

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

CLINICAL PERSPECTIVE

What Is New?

- We developed the site, size, gender, National Institutes of Health Stroke Scale, age, leukocyte, sugar (SIGNALS) score, a novel clinical predictive model to predict neurological deterioration within 15 days after intracerebral hemorrhage (ICH).
- The SIGNALS score demonstrated good calibration and discrimination in training and validation cohorts, respectively.
- The SIGNALS score presents better discriminative ability to predict 30-day poor outcome after ICH, compared with 3 existing ICH scores (the original ICH score, ICH-Grading Scale and modified Emergency Department ICH Scale).

What Are the Clinical Implications?

- We developed a novel clinical score to predict neurological deterioration during hospitalization after ICH, which features good calibration and discrimination.
- Predicting early neurological deterioration for patients with ICH is conducive to risk stratification of ICH and timely clinical decision making, both helpful for patients and clinicians.

Nonstandard Abbreviations and Acronyms

CHERRY	Chinese Cerebral Hemorrhage: Mechanism and Intervention Study
FBG	fasting blood glucose
ICH	intracerebral hemorrhage
ND	neurological deterioration
NIHSS	National Institutes of Health Stroke Scale

strategies, and accurately predict long-term outcomes. On the other hand, it determines the possible clinical cost-effectiveness for the patients and their families, and facilitates a positive clinician-patient relationship. However, few studies have focused on predictors, and there was no model of in-hospital ND after ICH.

Previously, studies have identified some risk factors of ND, including age, hematoma volume, hematoma expansion, intraventricular hemorrhage, National Institutes of Health Stroke Scale (NIHSS) score, systolic blood pressure, serum leukocyte counts, and blood glucose levels.[6–10] In spite of unquestionable progress, they generally result from small-sample, single-center observational research or pool analysis of randomized controlled trials, which received no large-scale validation and formed no prognostic model.

We aimed to develop a novel clinical score for ND during hospitalization after ICH with demographic data, clinical presentations, imaging findings, and biochemical tests in the CHERRY (Chinese Cerebral Hemorrhage: Mechanism and Intervention) study. Furthermore, we compared its performance with other existing scores predicting 1-month poor outcome after ICH, including the ICH score,[11] Intracerebral Hemorrhage Grading Scale,[12] and modified Emergency Department ICH Scale.[13] Moreover, we compared its performance with other independent predictors previous reported with regard to ND, and validated them in the present analysis.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. We performed an analysis of data from the CHERRY study. Consecutive patients presenting with spontaneous ICH were admitted to 31 hospital centers between December 2018 and June 2021. Patients were included if they were aged ≥18 years, diagnosed as spontaneous ICH with computed tomography, and hospitalized within 24 hours after symptom onset. Patients were excluded if they met any of the following criteria: (1) hemorrhages derived from trauma, primary subarachnoid hemorrhage, hemorrhagic conversion from ischemic stroke, and thrombolysis; (2) survivors without records of NIHSS at admission and hospitalization within 15 days; (3) imaging and baseline information was not available. Of note, patients with ICH secondary to vascular anomalies, such as arterial aneurysm, arteriovenous malformation, and moyamoya, were not excluded in the present analysis. Two-thirds of eligible patients were randomly allocated into the training cohort, and the remaining one-third of patients were allocated into the validation cohort. The study protocol was approved by the research ethics committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (ethical approval number: 2018-S485). All participants signed a written informed consent before enrollment.

Clinical and Imaging Data Collection

Demographic characteristics and clinical variables were collected, including age, sex, medical history (hypertension, diabetes, ischemic heart disease, ischemic stroke), medication history (prior use of antithrombotic and antihypertensive agents), admission vitals (onset-to-admission time, baseline systolic blood pressure, diastolic blood pressure, and NIHSS score), imaging

data (hematoma location, hematoma volume, and intraventricular hemorrhage), and laboratory tests (white blood cell [WBC], platelet, fasting blood glucose [FBG], and international normalized ratio). Medication history was defined as taking antithrombotic (antiplatelet or anticoagulation) or antihypertensive agents within 30 days before hospitalization for ICH. Admission NIHSS score was used for assessing the baseline neurological deficits. Imaging analyses were performed by experienced neurologists based on the initial computed tomography scan, in which hematoma volume was calculated using the ABC/2 formula. All available information was collected from patients and their relatives, hospital records, and general practitioners.

Outcome

The primary outcome was ND occurrence within 15 days after ICH. Based on the NIHSS score or survival state from medical records, the ND was defined as an NIHSS score increased by ≥4 points or death attributable to ICH.

Statistical Analysis

For univariate analyses, continuous variables were reported as mean with SD or median with interquartile range, and were analyzed using the Student *t* test and Mann-Whitney *U* test for normally distributed variables and nonnormally distributed variables, respectively. Categorical variables were presented as frequency with percentage and were analyzed using a χ^2 test. All variables with $P<0.1$ in the univariate analysis were considered for multivariate logistic regression analysis. Nonnormally distributed continuous variables (age, NIHSS score, hematoma volume, FBG, WBC) were categorized based on receiver operating characteristic (ROC) curve analysis in the multivariate analysis. Factors retaining significance in the multivariate model were included in the final scoring system for predicting ND.

The site, size, gender, NIHSS, age, leukocyte, sugar (SIGNALS) score was generated using independent variables associated with ND in a multiple logistic regression model, with weighting based on the strength of the association with β coefficients. The SIGNALS score was tested both in the training cohort and in the validation cohort. Calibration was assessed by the Hosmer-Lemeshow test to determine goodness of fit. Discrimination was measured by area under the curve (AUC) and C statistic to predict accuracy. Pairwise AUC differences between SIGNALS score and other prediction models were tested by the Delong method.[14] All tests were 2-tailed. and $P<0.05$ was considered significant. Statistical analyses were performed using SPSS software (version 26.0; IBM, Armonk, NY) and R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

There were 4248 patients enrolled into the CHERRY study between December 2018 and June 2021. After an exclusion of 25 patients with nonspontaneous ICH, 778 patients who presented exceeding 24 hours from symptom onset, 1789 patients who lacked data on ND within 15 days after ICH, and 114 who patients lacked important clinical and imaging information, 1542 patients were included in the current analysis (Figure S1). The median age was 63 years (interquartile range, 51–71 years), and 67.6% were men. A total of 308 (20%) patients suffered from ND within 15 days after ICH. Two-thirds of the eligible patients (n=1027) were randomly allocated into the training cohort and one-third (n=515) into the validation cohort.

The clinical characteristics of the patients in the training and validation cohorts are shown in Table S1. No significant differences were found between patients of the 2 cohorts. The proportion of patients with ND was 20.0% in the training cohort and 19.2% in the validation cohort. In the training group, patients with ND were more likely to present with higher NIHSS score, higher systolic blood pressure, larger hematoma volume, the presence of intraventricular hemorrhage, higher WBC counts, and higher FBG levels than did patients without ND.

Predictors of ND After ICH

In univariate analysis, several factors (age, male sex, medical history of ischemic heart disease and ischemic stroke, baseline systolic blood pressure, NIHSS score, infratentorial location, hematoma volume, intraventricular hemorrhage, WBC, FBG) were found to be associated with ND after ICH (Table 1). In multivariate logistic regression analysis, 7 variables remained statistically significant: age ≥70 years (odds ratio [OR], 1.5 [95% CI, 1.0–2.2]; $P=0.033$), male sex (OR, 2.0 [95% CI, 1.3–3.1]; $P=0.001$), NIHSS score >10 (OR, 1.8 [95% CI, 1.2–2.6]; $P=0.007$), infratentorial location (OR, 2.3 [95% CI, 1.2–4.3]; $P=0.010$), hematoma volume (supratentorial hematoma >20 mL: OR, 6.7 [95% CI, 4.3–10.5]; $P<0.001$; infratentorial hematoma >10 mL: OR, 3.9 [95% CI, 1.8–8.7]; $P=0.001$), FBG >7.0 mmol/L (OR, 2.0 [95% CI, 1.4–2.9]; $P<0.001$), and WBC >9.0×10^9/L (OR, 1.6 [95% CI, 1.1–2.3]; $P=0.012$) (Table 2). The value corresponding to the best performance on ROC curve analysis was rounded to the closest integer as the cutoff value for clinical application. These 7 factors were identified as independent predictors for ND after ICH and were then used for creating the prediction score.

The SIGNALS Score

The SIGNALS score was developed from logistic regression analysis of the training subset (n=1027).

Table 1. Univariate Analysis Comparing Patients With and Without Neurological Deterioration in the Training Cohort

Characteristics	Neurological deterioration		*P* value
	Yes, N=209	No, N=818	
Demographic data			
Age, y	66 (54–75)	62 (53–71)	0.012*
Male sex	159 (76.1)	541 (66.1)	0.006*
Medical and medication history			
Ischemic heart disease	19 (9.1)	37 (4.5)	0.009*
Ischemic stroke	29 (13.9)	76 (9.3)	0.051*
Hypertension	141 (67.5)	520 (63.6)	0.294
Diabetes	23 (11.0)	72 (8.8)	0.327
Antithrombotic agent	13 (6.2)	32 (3.9)	0.146
Antihypertensive agent	28 (13.4)	127 (15.5)	0.443
Clinical presentations			
Onset-to-admission time, h	3.0 (2.0–5.0)	4.0 (2.0–8.0)	<0.001*
SBP, mm Hg	176.8 ±34.9	168.6 ±28.9	0.002*
DBP, mm Hg	98.1±19.3	96.7±16.9	0.365
Baseline NIHSS	19 (10–30)	8 (3–15)	<0.001*
Imaging findings			
Infratentorial location	45 (21.5)	127 (15.5)	0.038*
ICH volume, mL	30.0 (15.0–52.0)	8.7 (4.0–22.1)	<0.001*
IVH	62 (29.7)	139 (17.0)	<0.001*
Laboratory values			
WBC, $\times 10^9$/L	10.2 (7.7–13.2)	8.0 (6.3–10.8)	<0.001*
Platelets, $\times 10^9$/L	192.4±76.2	195.4±65.0	0.587
FBG, mmol/L	7.7 (6.0–9.3)	6.1 (5.1–7.6)	<0.001*
INR	1.0 (0.9–1.1)	1.0 (0.9–1.1)	0.202

Continuous variables were reported as mean±SD or median (IQR), and categorical variables were presented as n (%). DBP indicates diastolic blood pressure; FBG, fasting blood glucose; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; IVH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SBP indicates systolic blood pressure; and WBC, white blood cell count.

*$P<0.05$.

Integral scores (0–3) were assigned to each of the 7 independent predictors based on their regression coefficients of the outcome. As a sum of individual points (0–8 points), the SIGNALS score consists of site (1 point for infratentorial location), size (3 points for >20 mL of supratentorial hematoma volume or 2 points for >10 mL of infratentorial hematoma volume), sex (1 point for male sex), NIHSS score (1 point for >10), age (1 point for ≥70 years), leukocyte (1 point for WBC >9.0×10^9/L), and sugar (1 point for FBG >7.0 mmol/L) (Table 3).

In the training subset, the C statistic was 0.821 (95% CI, 0.790–0.852), and the *P* value of the Hosmer-Lemeshow goodness of fit test was 0.687. The model was then tested in the validation cohort, showing good discrimination, with the C statistic 0.848 (95% CI, 0.811–0.886) and good calibration with Hosmer-Lemeshow goodness-of-fit *P* value of 0.592.

The proportion of patients experiencing ND by the score is shown in Table 3. In general, the proportion increased with higher scores, with 1.8% to 77.3% in the training subset and 0% to 68.8% in the validation subset, corresponding to a total score from 0 to 8 points. Based on these findings, 2 risk levels predicting ND after ICH of the training and validation cohorts were obtained: low (0–4, 7.8% versus 8.8%) and high (5–8, 44.4% versus 44.4%), with the cutoff value determined based on the optimal performance of ROC curve analysis. Subjects with a score ≥5 predicted ND with 0.746 and 0.677 sensitivity and 0.762 and 0.798 specificity in the training and validation cohorts, respectively (Table 4).

Comparison Between SIGNALS Score and Other Predictors

To test the performance of the predictive scoring system, we compared AUCs among the SIGNALS score and other 3 existing ICH scores (the original ICH score, Intracerebral Hemorrhage Grading Scale, and modified Emergency Department ICH Scale) predicting a 1-month poor outcome after ICH in the total cohort

Table 2. Multivariate Analysis for Factors Associated With Neurological Deterioration in the Training Cohort

Predictor variable	OR (95% CI)	*P* value
Age ≥70 y	1.5 (1.0–2.2)	0.033*
Male sex	2.0 (1.3–3.1)	0.001*
Ischemic heart disease	1.5 (0.8–3.0)	0.254
Ischemic stroke	1.5 (0.9–2.5)	0.164
Onset-to-admission time ≤3 h	1.3 (0.9–1.9)	0.173
SBP	1.0 (1.0–1.0)	0.290
NIHSS score >10	1.8 (1.2–2.6)	0.007*
Infratentorial location	2.3 (1.2–4.3)	0.010*
Hematoma volume, cm^3		
Supratentorial >20	6.7 (4.3–10.5)	<0.001*
Supratentorial ≤20	1.0	
Infratentorial >10	3.9 (1.8–8.7)	0.001*
Infratentorial ≤10	1.0	
IVH	0.9 (0.6–1.3)	0.545
FBG >7.0 mmol/L	2.0 (1.4–2.9)	<0.001*
WBC >9.0×10^9/L	1.6 (1.1–2.3)	0.012*

FBG indicates fasting blood glucose; IVH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; and WBC, white blood cell count.
*P<0.05.

(N=1542). For ND after ICH, AUCs ranged from 0.769 to 0.827 (Intracerebral Hemorrhage Grading Scale, 0.769; modified Emergency Department ICH Scale, 0.792; ICH score, 0.803; SIGNALS score, 0.827). The SIGNALS score showed the highest AUC, and Delong tests of pairwise AUC differences had statistical significance (P<0.005) (Table 5). The Figure shows ROCs of the mentioned scores with regard to ND after ICH.

We also compared AUCs between the SIGNALS score and other independent predictors with regard to ND and validated them in the present analysis in the total cohort (N=1542). AUCs ranged from 0.568 to 0.827 (age, 0.568; FBG, 0.646; WBC, 0.651; NIHSS score, 0.752; hematoma volume, 0.767; SIGNALS score, 0.827). The SIGNALS model presented the highest AUC, and Delong tests of pairwise AUC differences were statistically significant (all P<0.001). In addition, compared with individual predictors, the SIGNALS model showed the largest Youden Index (0.501) with high sensitivity (0.724) and specificity (0.774) (Table S2). Figure S2 shows ROCs of the SIGNALS score and other variables with regard to ND after ICH.

DISCUSSION

We developed and validated a novel clinical score named the SIGNALS score as a combined application of age, male sex, baseline NIHSS score, infratentorial location, hematoma volume, FBG, and WBC count to predict ND within 15 days after ICH, with a total score

Table 3. Determinants of the SIGNALS Score

Component	Points
Site	
Supratentorial location	0
Infratentorial location	1
Size, hematoma volume, cm^3	
Supratentorial location	
≤20	0
>20	3
Infratentorial location	
≤10	0
>10	2
Sex	
Women	0
Men	1
NIHSS score	
≤10	0
>10	1
Age, y	
<70	0
≥70	1
Leukocyte, WBC, ×10^9/L	
≤9.0	0
>9.0	1
Sugar, FBG, mmol/L	
≤7.0	0
>7.0	1
Total score	0–8

FBG indicates fasting blood glucose; NIHSS, National Institutes of Health Stroke Scale; SIGNALS, site, size, gender, National Institutes of Health Stroke Scrore, age, leukocyte, sugar; and WBC, white blood cell count.

ranging from 0 to 8. Moreover, the predictive model presents excellent discriminative and calibrated ability in the derivation cohort, which is further confirmed in the validation cohort, that have the potential to become a facile and practical clinical tool.

The present results are credible from the perspective of both clinical characteristics and pathophysiology. The baseline characteristics and the incidence of ND are relatively close to previous studies.[11,15,16] The risk factors included in the model have been shown to be associated with neurological deterioration after ICH. For instance, entrance peripheral leukocytes into the central nervous system may represent a more severe type of inflammation.[17] High blood glucose levels may promote brain edema via oxidative stress, leading to worse neurological deficits.[18] It is worth mentioning that continuous variables, such as WBC and FBG, were transformed into categorical variables in the scale for clinical applicability, and the cutoff values determined according to the optimal performance of ROC curve analysis were simple and practical for clinicians.

Table 4. Proportion of Patients Experiencing Neurological Deterioration Stratified by the SIGNALS Score

	Neurological deterioration within 15 days after intracerebral hemorrhage	
	Training cohort, N=1027	Validation cohort, N=515
C statistics (95% CI)	0.821 (0.790–0.852)	0.848 (0.811–0.886)
Score		
0	1/56 (1.8)	0/27 (0.0)
1	5/189 (2.6)	0/94 (0.0)
2	13/204 (6.4)	7/110 (6.4)
3	18/132 (13.6)	10/77 (13.0)
4	16/95 (16.8)	15/56 (26.8)
5	34/106 (32.1)	11/44 (25.0)
6	53/136 (39.0)	24/60 (40.0)
7	52/87 (59.8)	21/31 (67.7)
8	17/22 (77.3)	11/16 (68.8)
Dichotomized score		
0–4	53/676 (7.8)	32/364 (8.8)
5–8	156/351 (44.4)	67/151 (44.4)
Dichotomized test characteristics (95% CI)		
Sensitivity	0.746 (0.681–0.803)	0.677 (0.574–0.765)
Specificity	0.762 (0.731–0.790)	0.798 (0.756–0.835)
PPV	0.444 (0.392–0.498)	0.444 (0.364–0.527)
NPV	0.922 (0.898–0.940)	0.912 (0.877–0.938)
PLR	3.131 (2.706–3.622)	3.352 (2.651–4.238)
NLR	0.333 (0.264–0.420)	0.405 (0.304–0.539)

The proportion of patients was represented as n/N (%). NLR indicates negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; and SIGNALS, site, size, gender, National Institutes of Health Stroke Score, age, leukocyte, sugar.

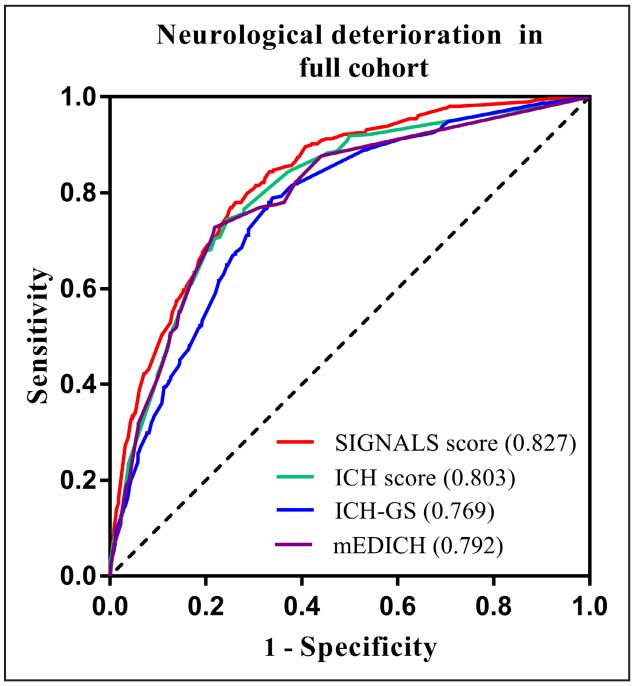


Figure 1. Receiver operating characteristics of the SIGNALS score and other existing scores with regard to neurological deterioration after ICH in the full cohort.
The values in parenthesis are areas under the receiver operating characteristic curve. ICH indicates intracerebral hemorrhage; ICH-GS, Intracerebral Hemorrhage Grading Scale; mEDICH, modified Emergency Department ICH Scale; and SIGNALS, site, size, gender, National Institutes of Health Stroke Scale, age, leukocyte, sugar.

Over the past decades, several prognostic models have been developed for studying ICH, but they are limited by reliability and accuracy, and few are universally accepted and applicated clinically.[5,19–22] Meanwhile, almost all of the existing models focus on 1-month, 3-month, 6-month, or 12-month poor outcomes after ICH, ignoring ND in the early period after ICH. Predicting early ND for patients with ICH is important for clinical decision making, helpful for both patients and clinicians. For example, patients with early ND may need more early intensive care unit care and necessary surgical intervention. Also, early ND is a predictor for long-term poor prognosis after ICH. Thus, a special model to predict early ND is quite necessary. In this study, for the first time we developed a simple and operable model to predict ND within ≈2 weeks after ICH.

To test the performance of the SIGNALS score, we compared its AUCs with the other 3 existing ICH scores (the original ICH score, Intracerebral Hemorrhage Grading Scale, and modified Emergency Department ICH Scale), and it showed that the highest AUC and Delong tests of pairwise AUCs were significantly different. When compared to other single variables with regard to ND after ICH, the SIGNALS model showed the largest Youden Index (0.501), with high sensitivity (0.724) and specificity (0.774). These results indicated

Table 5. Comparison in Predictive Power of the SIGNALS Score and Other ICH Scores

ICH scores	Neurological deterioration AUC (95% CI)	Difference between AUCs (95% CI)	*Z* score	*P* value
SIGNALS	0.827 (0.803–0.852)	…	…	…
ICH	0.803 (0.776–0.830)	0.024 (0.005–0.043)	2.463	0.014
ICH-GS	0.769 (0.741–0.797)	0.058 (0.037–0.079)	5.312	<0.001
mEDICH	0.792 (0.764–0.821)	0.035 (0.015–0.054)	3.514	<0.001

AUC indicates area under the curve; ICH, intracerebral hemorrhage; ICH-GS, Intracerebral Hemorrhage Grading Scale; mEDICH, modified Emergency Department ICH Scale; and SIGNALS, site, size, gender, National Institutes of Health Stroke Scale, age, leukocyte, sugar.

that the SIGNALS score may be a reliable tool for predicting ND after ICH. Of note, more validations are needed in larger ICH cohorts and other ethnic groups.

Our study shows several strengths. Based on a large-sample multicenter study, consecutive participants from both large teaching hospitals and primary care providers were included. Little heterogeneity is present in the statistics, because all included participants had distinctive ICH clinical characteristics and played no part in other clinical trials. New independent predictors, including WBC count and FBG, were added into the risk prediction model.

The score has significant limitations. Patients with ICH involved in both supratentorial and infratentorial were not included in the present analysis. We proposed to calculate the score of these patients using supratentorial and infratentorial methods, respectively, and take the maximum as the measured score. Confounding factors that are not measured may affect the results in this observational study. There was no independent external validation for an available additional cohort. Hematoma expansion was not included as a predictor in the scale for the inconsistent time of neuroimaging follow-up.

CONCLUSIONS

We developed a novel clinical score to predict ND during hospitalization after ICH that features good calibration and discrimination.

ARTICLE INFORMATION

Received April 12, 2022; accepted May 2, 2022.

Affiliations

Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China (Q.H., H.G., R.B., S.C., J.S., C.L., M.L., Y.X., L.Z., Z.S., X.C., Y.W., B.H.); Department of Neurology, Qianjiang Central Hospital, Qianjiang, Hubei Province, China (Z.W.); Department of Neurology, Jingzhou Central Hospital, Jingzhou, Hubei Province, China (D.G.); Department of Neurology, Honghu People's Hospital, Honghu, Hubei Province, China (J.X.); and School of Pharmacy, Nanjing Medical University, Nanjing, Jiangsu Province, China (D.Z.).

Acknowledgments

The authors appreciate Y. Wang and X. Zhao for their kind technical and statistical support, and all of the participants and investigators in the CHERRY study.

Sources of Funding

This work was supported by the National Natural Science Foundation of China (number 82071335 to Q.H., number 81901214 to Y.W., number 81820108010 to B.H.), and the National Key Research and Development Program of China (number 2018YFC1312200 to B.H.).

Disclosures

None.

Supplemental Material

Tables S1–S2
Figures S1–S2

REFERENCES

1. Schrag M, Kirshner H. Management of intracerebral hemorrhage: JACC focus seminar. *J Am Coll Cardiol.* 2020;75:1819–1831. doi: 10.1016/j.jacc.2019.10.066
2. O'Carroll CB, Brown BL, Freeman WD. Intracerebral hemorrhage: a common yet disproportionately deadly stroke subtype. *Mayo Clin Proc*. 2021;96:1639–1654. doi: 10.1016/j.mayocp.2020.10.034
3. Ren H, Han R, Chen X, Liu X, Wan J, Wang L, Yang X, Wang J. Potential therapeutic targets for intracerebral hemorrhage-associated inflammation: an update. *J Cereb Blood Flow Metab*. 2020;40:1752–1768. doi: 10.1177/0271678X20923551
4. Xi G, Strahle J, Hua Y, Keep RF. Progress in translational research on intracerebral hemorrhage: is there an end in sight? *Prog Neurobiol*. 2014;115:45–63. doi: 10.1016/j.pneurobio.2013.09.007
5. Lord AS, Gilmore E, Choi HA, Mayer SA, Collaboration V-I. Time course and predictors of neurological deterioration after intracerebral hemorrhage. *Stroke*. 2015;46:647–652. doi: 10.1161/STROKEAHA.114.007704
6. Law ZK, Dineen R, England TJ, Cala L, Mistri AK, Appleton JP, Ozturk S, Bereczki D, Ciccone A, Bath PM, et al. Predictors and outcomes of neurological deterioration in intracerebral hemorrhage: results from the tich-2 randomized controlled trial. *Transl Stroke Res*. 2021;12:275–283. doi: 10.1007/s12975-020-00845-6
7. Okazaki S, Yamamoto H, Foster LD, Fukuda-Doi M, Koga M, Ihara M, Toyoda K, Palesch YY, Qureshi AI. Late neurological deterioration after acute intracerebral hemorrhage: a post hoc analysis of the atach-2 trial. *Cerebrovasc Dis (Basel, Switzerland)*. 2020;49:26–31. doi: 10.1159/000506117
8. You S, Zheng D, Delcourt C, Sato S, Cao Y, Zhang S, Yang J, Wang X, Lindley RI, Robinson T, et al. Determinants of early versus delayed neurological deterioration in intracerebral hemorrhage. *Stroke* 2019;50:1409–1414, doi: 10.1161/STROKEAHA.118.024403
9. Qi H, Wang D, Deng X, Pang X. Lymphocyte-to-monocyte ratio is an independent predictor for neurological deterioration and 90-day mortality in spontaneous intracerebral hemorrhage. *Med Sci Monit*. 2018;24:9282–9291. doi: 10.12659/MSM.911645
10. Ovesen C, Christensen AF, Havsteen I, Krarup Hansen C, Rosenbaum S, Kurt E, Christensen H. Prediction and prognostication of neurological deterioration in patients with acute ich: a hospital-based cohort study. *BMJ Open.* 2015;5:e008563. doi: 10.1136/bmjopen-2015-008563
11. Hemphill JC III, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ich score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891–897. doi: 10.1161/01.STR.32.4.891
12. Ruiz-Sandoval J, Chiquete E, Romero-Vargas S, Padilla-Martínez J, González-Cornejo S. Grading scale for prediction of outcome in primary intracerebral hemorrhages. *Stroke*. 2007;38:1641–1644. doi: 10.1161/STROKEAHA.106.478222
13. Masotti L, Di Napoli M, Godoy DA, Lorenzini G. Predictive ability of a modified version of emergency department intracerebral hemorrhage grading scale for short-term prognosis of intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2015;24:1100–1104. doi: 10.1016/j.jstrokecerebrovasdis.2015.01.013
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837. doi: 10.2307/2531595
15. Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, Vashkevich A, McNamara KA, Valant V, Schwab K, et al. Predicting hematoma expansion after primary intracerebral hemorrhage. *JAMA Neurol*. 2014;71:158–164. doi: 10.1001/jamaneurol.2013.5433
16. Haapaniemi E, Strbian D, Rossi C, Putaala J, Sipi T, Mustanoja S, Sairanen T, Curtze S, Satopaa J, Roivainen R, et al. The cave score for predicting late seizures after intracerebral hemorrhage. *Stroke*. 2014;45:1971–1976. doi: 10.1161/STROKEAHA.114.004686
17. Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. *Prog Neurobiol*. 2014;115:25–44. doi: 10.1016/j.pneurobio.2013.11.003
18. Chiu C, Chen C, Shen C, Chin L, Ma H, Chuang H, Cho D, Chu C, Chang C. Hyperglycemia exacerbates intracerebral hemorrhage via the downregulation of aquaporin-4: temporal assessment with magnetic resonance imaging. *Stroke*. 2013;44:1682–1689. doi: 10.1161/STROKEAHA.113.675983
19. Sorimachi T, Fujii Y. Early neurological change in patients with spontaneous supratentorial intracerebral hemorrhage. *J Clin Neurosci*. 2010;17:1367–1371. doi: 10.1016/j.jocn.2010.02.024

20. Sun W, Peacock A, Becker J, Phillips-Bute B, Laskowitz DT, James ML. Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage. *J Clin Neurosci*. 2012;19:1096–1100. doi: 10.1016/j.jocn.2011.11.020
21. Sun W, Pan W, Kranz PG, Hailey CE, Williamson RA, Sun W, Laskowitz DT, James ML. Predictors of late neurological deterioration after spontaneous intracerebral hemorrhage. *Neurocrit Care*. 2013;19:299–305. doi: 10.1007/s12028-013-9894-2
22. Fan JS, Chen YC, Huang HH, How CK, Yen DH, Huang MS. The association between on-scene blood pressure and early neurological deterioration in patients with spontaneous intracerebral haemorrhage. *Emerg Med J*. 2015;32:239–243. doi: 10.1136/emermed-2013-203114

Supplemental Material

Table S1. Baseline characteristics and outcomes of the study.

Characteristics	Training cohort (N=1027)	Validation cohort (N=515)	*P* Value*
Demographic data			
Age, years	63 (54-71)	62 (54-71)	0.462
Male	700 (68.2)	434 (66.6)	0.537
Medical and medication history			
Ischemic heart disease	105 (10.2)	52 (10.1)	0.938
Ischemic stroke	56(5.5)	20 (3.9)	0.179
Hypertension	661(64.4)	335 (65.0)	0.790
Diabetes	95 (9.3)	50 (9.7)	0.771
Antithrombotic agent	45(4.4)	25 (4.9)	0.674
Antihypertensive agent	155 (15.1)	86 (16.7)	0.413
Clinical presentations			
Onset-to-admission time, h	3.0(2.0-7.0)	4.0(2.0-8.0)	0.095
SBP, mm Hg	170.3±30.4	171.0±31.5	0.660
DBP, mm Hg	97.0±17.4	97.4±18.5	0.679
Baseline NIHSS	9 (4-19)	10 (4-20)	0.654
Imaging findings			
Infratentorial location	172 (16.7)	89 (17.3)	0.792
ICH volume, cm^3	10.7 (5.0-30.0)	11.0 (4.5-25.0)	0.299
IVH	201 (19.6)	96 (18.6)	0.662
Laboratory values			
White blood cell count, $*10^9/L$	8.4 (6.5-11.3)	8.6 (6.3-11.4)	0.961
Platelet, $*10^9/L$	194.8±67.4	194.3±67.7	0.912
Fasting blood-glucose, mmol/L	6.3 (5.2-8.0)	6.4 (5.3-7.9)	0.837
International normalized ratio	1.0 (0.9-1.1)	1.0 (0.9-1.1)	0.310

Continuous variables were reported as mean ± SD or median (IQR), and categorical variables were presented as n (%). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; NIHSS, the National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; ND, neurological deterioration; SD, standard deviation; IQR, interquartile.

* All P value ＞0.05.

Table S2. Discrimination of SIGNALS score and other variables with regard to ND after ICH (n=1542).

	AUC	95% CI	Δ AUC	P value	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
SIGNALS score	0.827	0.803-0.852	reference		0.501	4	0.724	0.774	0.444	0.918
Age, years	0.568	0.530-0.606	0.259	<0.001	0.148	70	0.403	0.724	0.267	0.829
Hematoma volume, ml	0.767	0.737-0.797	0.06	<0.001	0.466	15	0.753	0.703	0.388	0.919
NIHSS score	0.752	0.722-0.781	0.075	<0.001	0.389	10	0.737	0.639	0.337	0.907
FBG, mmol/L	0.646	0.612-0.681	0.181	<0.001	0.277	7	0.591	0.673	0.313	0.868
WBC, $*10^9$/L	0.651	0.617-0.685	0.176	<0.001	0.277	9	0.656	0.612	0.297	0.877

ND indicates neurological deterioration; ICH, intracerebral hemorrhage; NIHSS, the National Institutes of Health Stroke Scale; FBG, fasting blood-glucose; WBC, white blood cell count; AUC, area under receiver operating characteristic curve; CI indicates confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Figure S1. The flowchart of patient selection.

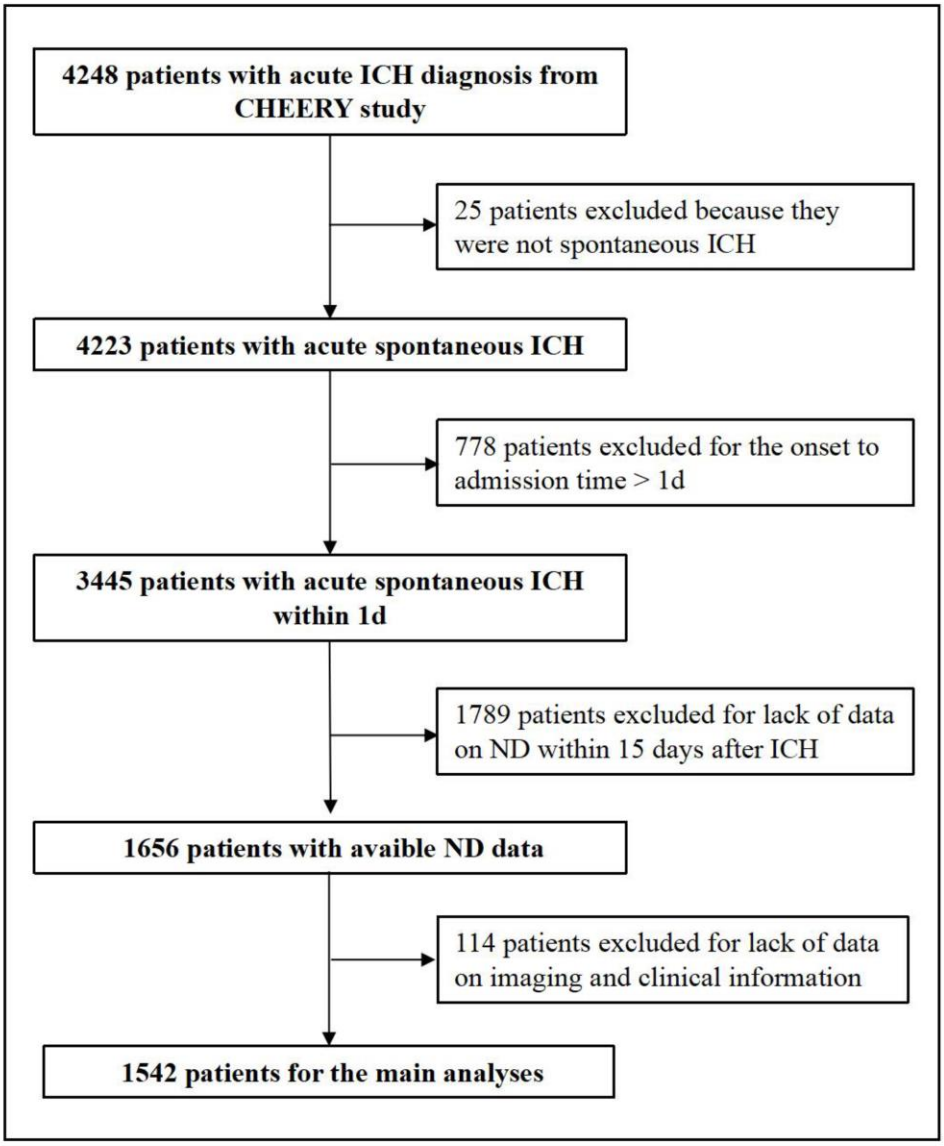
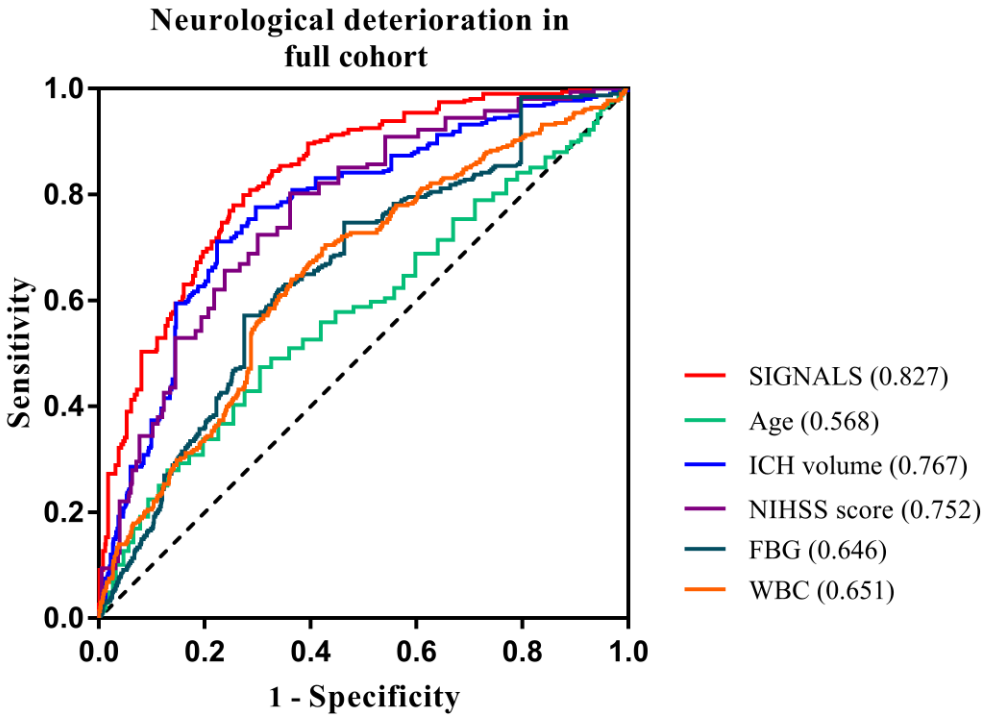


Figure S2. ROCs of the SIGNALS score and other variables with regard to ND after ICH.



ROC indicates receiver operating characteristic; ICH, intracerebral hemorrhage; ND, intracerebral hemorrhage; NIHSS, the National Institutes of Health Stroke Scale; FBG, fasting blood-glucose; WBC, white blood cell count. The value in parenthesis is area under receiver operating characteristic curve.