ADVISING score: a reliable grading scale based on injury and response for intracerebral haemorrhage

Yan Wan,[1] Hongxiu Guo,[1] Shaoli Chen,[1] Jiang Chang,[2] David Wang ,[3]
Rentang Bi,[1] Man Li,[1] Ke Shi,[2] Zhaowei Wang,[4] Daokai Gong,[5] Jingwen Xu,[6]
Quanwei He ,[1] Bo Hu [1]

ABSTRACT

Background Intracerebral haemorrhage (ICH) is the most devastating form of stroke causing high morbidity and mortality. We aimed to develop a novel clinical score incorporating multisystem markers to predict functional dependence at 90 days after ICH.

Methods We analysed data from Chinese Cerebral Hemorrhage: Mechanism and Intervention study. Multivariable logistic regression analysis was used to identify the factors associated with 90-day functional dependency (the modified Rankin Scale ≥3) after ICH and develop the ADVISING scoring system. To test the scoring system, a total of 2111 patients from Hubei province were included as the training cohort, and 733 patients from other three provinces in China were included as an external validation cohort.

Results We found nine variables to be significantly associated with functional dependency and included in the ADVISING score system: age, deep location of haematoma, volume of haematoma, National Institutes of Health Stroke Scale, aspartate transaminase, international normalised ratio, neutrophil-lymphocyte ratio, fasting blood glucose and glomerular filtration rate. Individuals were divided into 12 different categories by using these nine potential predictors. The proportion of patients who were functionally dependent increased with higher ADVISING scores, which showed good discrimination and calibration in both the training cohort (C-statistic, 0.866; p value of Hosmer-Lemeshow test, 0.195) and validation cohort (C-statistic, 0.884; p value of Hosmer-Lemeshow test, 0.853). The ADVISING score also showed better discriminative performance compared with the other five existing ICH scores (p<0.001).

Conclusions ADVISING score is a reliable tool to predict functional dependency at 90 days after ICH.

INTRODUCTION

Intracerebral haemorrhage (ICH) is the second most common stroke subtype and accounts for 15%–30% of stroke cases worldwide. ICH is associated with 50% of stroke-related mortality (approximately 2.8 million deaths per year) and is twice as fatal as ischaemic stroke.[1–3] Many ICH scoring systems have been developed to predict the patient's outcome. These scoring systems assess the prognosis of ICH at different stages. For in-hospital or 30 days after ICH, there are ICH score[4] and simplified ICH score.[5] For intermediate-term predictive models (3 months after ICH), there are ICH Grading Scale (ICH-GS),[6] ICH Outcomes Project (ICHOP) score,[7] the functional outcome (FUNC) score[8] and Essen-ICH score.[9] For long-term outcome (6 months or 1 year after ICH), there are modified ICH (MICH) score,[10] max ICH score[11] and ICH Functional Outcome Score (ICH-FOS).[12] Efforts were made to improve the model discrimination and calibration, and predictors of models were optimised by adding single or several laboratory indicators to the clinical characteristics.

Limitations of prior studies include small sample size from single centre or not sufficiently validated, using Glasgow Outcome Score or Barthel Index but not modified Rankin Scale (mRS) to measure outcome. Most scoring systems include only indicators of adverse effects of haematoma, but not the indicators of multiple system injuries and responses after ICH, including organs such as liver,[13] and kidney,[14] inflammation,[15] coagulation[16] and metabolic disorders,[17] which may worsen the prognosis in patients with ICH. Thus, integration of important clinical predictors of ICH reflecting multisystem responses into the prognostic model may improve the assessment of poor outcomes after ICH (online supplemental file 2, graphical abstract).

In this study, we aimed to develop a novel tool incorporating multisystem markers to predict 90-day poor outcome in Chinese patients with ICH based on a multicentre cohort study. Its performance was also compared with other five recognised scoring systems, including the ICH score, ICH-FOS, ICH-GS, ICHOP score and MICH score.

METHODS
Study population
We developed the model using data from the Chinese Cerebral Hemorrhage: Mechanism

and Intervention (CHEERY) cohort study, which is a multicentre Chinese programme that included consecutive patients with spontaneous ICH admitted to 31 stroke centres from December 2018 to June 2021. Patients were included if they were older than 18 years and diagnosed with a spontaneous ICH on CT. Patients were excluded if they had: (1) brain haemorrhage deriving from trauma, primary subarachnoid haemorrhage, haemorrhagic conversion from ischaemic stroke and thrombolysis; (2) onset to admission more than 7 days; (3) baseline clinical and imaging information unavailable; and (4) lost to follow-up at 90 days. A total of 4248 patients had an ICH event and 2844 patients were included in this final analysis. Of those, 2111 eligible participants from 19 centres in Hubei province were designated as the training cohort, and the remaining 733 participants from five centres of other three provinces were designated as the validation cohort. Informed consent was obtained from all participants prior to the enrolment.

Clinical and imaging data collection

Demographic and clinical characteristics collected on admission include age, sex, medical history (ischaemic stroke, ischaemic heart disease, hypertension, diabetes, hyperlipidaemia), prestroke mRS, systolic blood pressure (SBP), National Institutes of Health Stroke Scale (NIHSS), imaging information (haematoma location, haematoma volume and intraventricular haemorrhage (IVH)) and laboratory tests (white cell count, haemoglobin (Hb), platelet (PLT), neutrophil-lymphocyte ratio (NLR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, uric acid (UA), fasting blood glucose (FBG), international normalised ratio (INR); glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation).[18] The laboratory variables on admission from all 31 stroke centres were uniformly converted before statistical analysis. Initial CT scans were analysed by experienced neurologists and the ABC/2 formula was used to calculate haematoma volume. The ICH location was considered as deep if the origin of the haemorrhage appeared to be in thalamus, basal ganglia, internal capsule, deep periventricular white matter, brainstem and cerebellum. Haemorrhages originating in both deep and lobar were also considered as deep location.

Outcome

The mRS score at 90 days was obtained by telephone calls or messages from patients or their relatives. We determined the 90-day functional dependence (mRS, 3–6) as the outcome of this study.

Statistical analysis

Continuous and ordinal variables (age, SBP, NIHSS, haematoma volume, Hb, PLT, NLR, ALT, AST, GFR, FBG, UA, INR) were categorised based on clinical significance. All variables were presented as frequency with percentage and were analysed using χ^2 test. Variables that reached $p<0.05$ in the univariate analysis were considered for multivariable analysis.

A scoring system predicting functional dependence was developed from the multiple logistic regression model. Significant variables associated with 90-day functional dependence in multivariate model were included in the ADVISING score and were weighted to assign scoring points based on the strength of association with β coefficients. Specifically, we used β coefficients of haematoma volume (30–60 mL) as a specified parameter (B), and the assigned scores for each item were calculated using the formula of βi/B and the point was rounded to the closest integer (the parameter <1 was assigned a score of 1). Hosmer-Lemeshow test was performed to assess calibration, while C-statistic was calculated to measure discrimination in both training and validation cohorts.

Furthermore, we compared the discrimination of the ADVISING score and prior ICH scores for 90-day functional dependence (mRS ≥3) after ICH in the validation cohort. Five existing ICH scores (MICH score, ICHOP score, original ICH score, ICH-GS and ICH-FOS) were selected since their components were available in our database. Pairwise areas under the curve (AUCs) between ADVISING score and other ICH scores were compared using Delong's method to evaluate the strengths of model discrimination. We also conducted the other two ways, net reclassification index (NRI) and integrated discrimination improvement (IDI), to further assess the superiority of our score compared with others.

All tests were two tailed and $p<0.05$ was considered significant. Statistical analyses were performed using SPSS software (V.26.0) and R software (V.4.1.2).

RESULTS
Patient characteristics

From 1 December 2018 to 30 June 2021, a total of 4248 patients experienced an ICH event in the CHEERY study. Of those, 1404 patients were excluded (25 patients for non-spontaneous ICH, 87 patients for the onset to admission time >7 days, 532 patients for lack of imaging data, 701 patients for lack of clinical data and 59 patients for lack of information on 90-day mRS), and the remaining 2844 patients were included in the final analysis (online supplemental figure S1). Online supplemental table S1 shows comparisons of baseline characteristics between the excluded and the included data sets. Compared with excluded samples, the analysed data set had a lower rate of IVH occurrence and better 90-day outcomes. After exclusion of patients with IVH extension accompanied with unavailable haematoma volume (which was not calculated for irregular shapes), these differences were eliminated. A total of 2111 (74.2%) eligible patients from 19 stroke centres of Hubei province were included in the training

Table 1 Baseline characteristics and outcomes of the study

Characteristics	Total cohort (n=2844)	Training cohort (n=2111)	Validation cohort (n=733)	P value
Demographic characteristics				
Age (years)	62 (53–70)	62 (53–71)	60 (51–68)	**<0.001**
Male	1920 (67.5)	1421 (67.3)	499 (68.1)	0.704
Medical history				
Ischaemic stroke	288 (10.1)	183 (8.7)	105 (14.3)	**<0.001**
Ischaemic heart disease	99 (3.5)	76 (3.6)	23 (3.1)	0.556
Hypertension	1838 (64.6)	1362 (64.5)	476 (64.9)	0.838
Hyperlipidaemia	69 (2.4)	47 (2.2)	22 (3.0)	0.240
Diabetes	261 (9.2)	188 (8.9)	73 (10.0)	0.395
Admission characteristics				
Prestroke mRS	0 (0–0)	0 (0–0)	0 (0–0)	**0.008**
SBP (mm Hg)	167 (150–187)	167 (150–187)	167 (151–187)	0.334
Baseline NIHSS	8 (4–15)	7 (3–14)	11 (5–17)	**<0.001**
Deep location	2336 (82.1)	1723 (81.6)	613 (83.6)	0.221
Volume of haematoma (mL)	12.0 (5.0–26.0)	12.0 (5.0–25.0)	12.0 (5.1–30.0)	0.141
IVH	321 (11.3)	237 (11.2)	84 (11.5)	0.864
Admission laboratory values				
White cell count (×10^9/L)	8.4 (6.4–10.9)	8.2 (6.3–10.7)	8.8 (6.9–11.8)	**<0.001**
Hb (g/L)	136 (124–147)	135 (123–146)	139 (126–151)	**<0.001**
PLT (×10^9/L)	195 (155–238)	188 (149–231)	215 (175–260)	**<0.001**
ANC (×10^9/L)	6.3 (4.5–9.1)	6.2 (4.5–8.9)	6.5 (4.6–9.6)	**0.019**
ALC (×10^9/L)	1.2 (0.8–1.6)	1.1 (0.8–1.6)	1.3 (0.9–1.9)	**<0.001**
ALT (U/L)	18 (13–26)	18 (13–26)	19 (14–27)	**0.005**
AST (U/L)	23 (18–30)	23 (18–30)	23 (18–30)	0.933
GFR (mL/min/1.73 m^2)	94 (80–104)	93 (80–103)	95 (81–106)	**0.006**
UA (µmol/L)	308 (243–383)	311 (244–388)	307(238-369)	**0.003**
FBG (mmol/L)	6.2 (5.3–7.7)	6.1 (5.2–7.7)	6.5 (5.5–7.9)	**0.001**
INR	1.0 (0.9–1.1)	1.0 (1.0–1.1)	0.9 (0.9–1.0)	**<0.001**
Outcome				
Death at 90 days	469 (16.5)	337 (16.0)	132 (18.0)	0.199
mRS at 90 days				
0–2	1405 (49.4)	1074 (50.9)	331 (45.2)	**0.008**
3–6	1439 (50.6)	1037 (49.1)	402 (54.8)	

Continuous and ordinal variables were reported as median (IQR), and categorical variables were presented as n (%).
P<0.05 was represented in bold type.

ALC, absolute lymphocyte count; ALT, glutamic pyruvic transaminase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; FBG, fasting blood glucose; GFR, glomerular filtration rate; Hb, haemoglobin; INR, international normalised ratio; IVH, intraventricular haemorrhage; mRS, modified Rankin Scale NIHSS, National Institutes of Health Stroke Scale; PLT, platelet; SBP, systolic blood pressure; UA, uric acid.

cohort, while 733 (25.8%) patients from five stroke centres of other three provinces were included in the validation cohort. The median age of the included patients was 62 (IQR 53–70) years, and 67.5% of them were male. A total of 1439 (50.6%) were functionally dependent (mRS ≥3) at 90 days after ICH. Patients in the training cohort were older, had a lower rate of ischaemic stroke and a lower baseline NIHSS, and less proportion of 90-day functional dependence. Patient characteristics and outcomes of the training, validation and total cohorts were listed in table 1.

Univariate analysis of associations with 90-day functional dependence after ICH

Table 2 showed the univariate analysis of variables associated with 90-day functional dependence (mRS ≥3) in the training cohort. For clinical applicability, continuous and ordinal variables were categorised and the

Table 2 Univariate analysis comparing patients with and without functional dependence in training cohort

| | mRS (3–6) | | |
	Yes (n=1037)	No (n=1074)	P value
Demographic characteristics			
Age (years)			
<60	406 (39.2)	498 (46.4)	**0.001**
≥60	631 (60.8)	576 (53.6)	
Male	684 (66.0)	737 (68.6)	0.192
Medical history			
Ischaemic stroke	102 (9.8)	81 (7.5)	0.061
Ischaemic heart disease	42 (4.1)	34 (3.2)	0.276
Hypertension	672 (64.8)	690 (64.2)	0.789
Hyperlipidaemia	20 (1.9)	27 (2.5)	0.362
Diabetes	101 (9.7)	87 (8.1)	0.186
Admission characteristics			
Prestroke mRS	0 (0–0)	0 (0–0)	0.062
SBP (mm Hg)			
<180	628 (45.4)	754 (54.6)	**<0.001**
≥180	409 (56.1)	320 (43.9)	
Baseline NIHSS			
0–3	69 (6.7)	501 (46.6)	**<0.001**
4–5	54 (5.2)	222 (20.7)	
6–14	468 (45.1)	295 (27.5)	
15–40	446 (43.0)	56 (5.2)	
Deep location			
Yes	882 (85.1)	841 (78.3)	**<0.001**
No	155 (14.9)	233 (21.7)	
Volume of haematoma (mL)			
<30	675 (65.1)	988 (92.0)	**<0.001**
30–60	271 (26.1)	77 (7.2)	
>60	91 (8.8)	9 (0.8)	
IVH	159 (15.3)	78 (7.3)	**<0.001**
Admission laboratory values			
White cell count >10×10^9/L	420 (40.5)	219 (20.4)	**<0.001**
Hb <120 g/L	241 (23.2)	179 (16.7)	**<0.001**
PLT <100×10^9/L	71 (6.8)	64 (6.0)	0.405
NLR >10	338 (32.6)	167 (15.5)	**<0.001**
ALT >40 U/L	111 (10.7)	94 (8.8)	0.130
AST >40 U/L	167 (16.1)	63 (5.9)	**<0.001**
GFR <90 mL/min/1.73 m^2	468 (45.1)	410 (38.2)	**0.001**
UA >420 µmol/L	202 (19.5)	183 (17.0)	0.147
FBG ≥7.0 mmol/L	437 (42.1)	279 (26.0)	**<0.001**
INR ≥1.2	121 (11.7)	58 (5.4)	**<0.001**

Categorical variables were presented as n (%).
P<0.05 was represented in bold type.
ALT, glutamic pyruvic transaminase; AST, aspartate aminotransferase; FBG, fasting blood glucose; GFR, glomerular filtration rate; Hb, haemoglobin; INR, international normalised ratio; IVH, intraventricular haemorrhage; mRS, modified Rankin ScaleNIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio; PLT, platelet; SBP, systolic blood pressure; UA, uric acid.

Table 3 Multivariate analysis for factors associated with functional dependence in training cohort

Predictor variable	aOR (95% CI)	P value
Age ≥60 years	1.4 (1.1 to 1.8)	**0.003**
SBP ≥180 mm Hg	1.1 (0.9 to 1.4)	0.412
NIHSS score		
0–3	1.0	**<0.001**
4–5	1.8 (1.2 to 2.7)	
6–14	10.9 (8.0 to 14.9)	
15–40	34.5 (23.2 to 51.3)	
Deep location	1.5 (1.1 to 2.1)	**0.014**
Volume of haematoma (mL)		
<30	1.0	**<0.001**
30–60	2.8 (1.9 to 4.0)	
>60	4.7 (2.1 to 10.8)	
IVH	1.1 (0.8 to 1.7)	0.560
Hb <120 g/L	1.3 (1.0 to 1.7)	0.081
NLR >10	1.7 (1.3 to 2.3)	**<0.001**
AST >40 U/L	2.4 (1.6 to 3.5)	**<0.001**
GFR <90 mL/min/1.73 m^2	1.4 (1.1 to 1.8)	**0.007**
FBG ≥7.0 mmol/L	1.5 (1.2 to 1.9)	**0.001**
INR ≥1.2	1.6 (1.0 to 2.4)	**0.046**

P<0.05 was represented in bold type.
aOR, adjusted OR; AST, aspartate aminotransferase; FBG, fasting blood glucose; GFR, glomerular filtration rate; Hb, haemoglobin; INR, international normalised ratio; IVH, intraventricular haemorrhage; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio; SBP, systolic blood pressure.

cut-off values were chosen based on clinical implications. Patients who suffered from functional dependence were more likely ≥60 years of age, had SBP ≥180 mm Hg and a baseline NIHSS ≥6. Their ICHs had a deeper location and IVH, and haematoma volume was ≥30 mL. Abnormal clinical laboratory values included white cell count >10×10^9/L, Hb <120 g/L, NLR >10, AST >40 U/L, GFR <90 mL/min/1.73 m^2, FBG ≥7.0 mmol/L and INR ≥1.2.

Predictors of 90-day functional dependence after ICH
Multivariable logistic regression model was built to identify independent predictors of functional dependence at 90 days after ICH. After adjusting for confounding factors, nine variables were identified as independent predictors of functional dependence, including age ≥60 years, NIHSS score, deep location, haematoma volume, NLR >10, AST >40 U/L, GFR <90 mL/min/1.73 m^2, FBG ≥7.0 mmol/L and INR ≥1.2. No statistical significance was observed at the associations with SBP (≥180 vs <180 mm Hg, OR 1.1; 95% CI 0.9 to 1.4; p=0.412), IVH (OR 1.1; 95% CI 0.8 to 1.7; p=0.560) or Hb (<120 vs ≥120 g/L, OR 1.3; 95% CI 1.0 to 1.7; p=0.081) (table 3).

Table 4 Determinants of the ADVISING score

Predictors	Score
Age (years)	
<60	0
≥60	1
Deep location	
No	0
Yes	1
Volume of haematoma (mL)	
<30	0
30–60	1
>60	2
NIHSS score	
0–3	0
4–5	1
6–14	2
15–40	3
AST (U/L)	
≤40	0
>40	1
INR	
<1.2	0
≥1.2	1
NLR	
≤10	0
>10	1
GFR (mL/min/1.73 m^2)	
≥90	0
<90	1
FBG (mmol/L)	
<7.0	0
≥7.0	1
Total score	12

Letters underlined were used to create the name of the current intracerebral haemorrhage (ICH) model, ADVISING.
AST, aspartate aminotransferase; FBG, fasting blood glucose; GFR, glomerular filtration rate; INR, international normalised ratio; NIHSS, National Institutes of Health Stroke Scale NLR, neutrophil-lymphocyte ratio.

Table 5 Proportion of patients with functional dependence stratified by ADVISING score

	90-day functional dependence after ICH	
	Training cohort (n=2111)	Validation cohort (n=733)
C-statistic (95% CI)	0.866 (0.850 to 0.881)	0.884 (0.861 to 0.908)
Score		
0	3/23 (13.0)	0/4 (0)
1	7/132 (5.3)	2/39 (5.1)
2	25/222 (11.3)	5/59 (8.5)
3	83/377 (22.0)	26/121 (21.5)
4	177/396 (44.7)	76/149 (51.0)
5	215/363 (59.2)	96/139 (69.1)
6	207/255 (81.2)	67/87 (77.0)
7	156/176 (88.6)	55/60 (91.7)
8	103/106 (97.2)	43/43 (100.0)
9	38/38 (100.0)	25/25 (100.0)
10	20/20 (100.0)	7/7 (100.0)
11	2/2 (100.0)	–
12	1/1 (100.0)	–
Dichotomised score		
0–4	295/1150 (25.7)	109/372 (29.3)
5–12	742/961 (77.2)	293/361 (81.2)
Dichotomised test characteristics (95% CI)		
Sensitivity	0.716 (0.687 to 0.743)	0.729 (0.682 to 0.771)
Specificity	0.796 (0.770 to 0.820)	0.795 (0.746 to 0.836)
PPV	0.772 (0.744 to 0.798)	0.812 (0.767 to 0.850)
NPV	0.743 (0.717 to 0.768)	0.707 (0.657 to 0.752)
PLR	3.509 (3.099 to 3.973)	3.548 (2.847 to 4.421)
NLR	0.357 (0.324 to 0.394)	0.341 (0.290 to 0.401)

The proportion of patients was represented as n/N (%).
ICH, intracerebral haemorrhage; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.
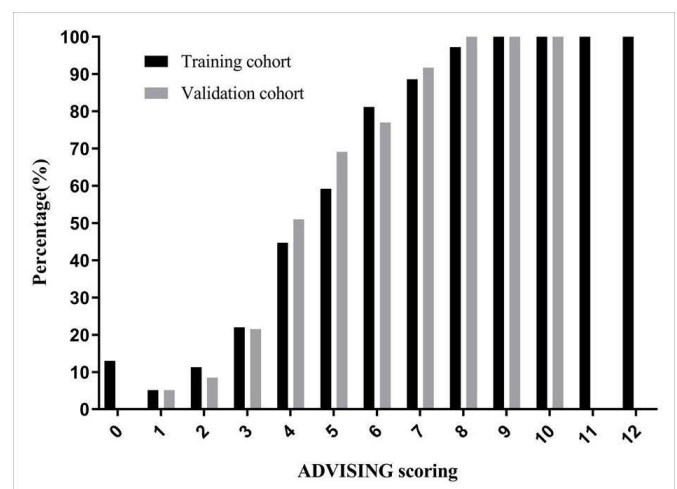
The ADVISING score

The ADVISING (age, deep location, volume of haematoma, NIHSS score, AST, INR, NLR, GFR, FBG) score was thus developed based on the multivariate logistic analysis result in the training cohort. Each of the nine predictors in the scoring system was weighted and points assigned based on the strength of association with β coefficients. The range of ADVISING scores was between 0 and 12, with a score ≥9 indicating a hundred per cent of functional dependence (mRS ≥3) (table 4). In fact, the proportion of patients who suffered from functional dependence at 90 days increased with higher scores both in training cohort and validation cohort, as shown

Figure 1 The proportion of patients suffering from functional dependence at 90 days in training and validation cohorts.
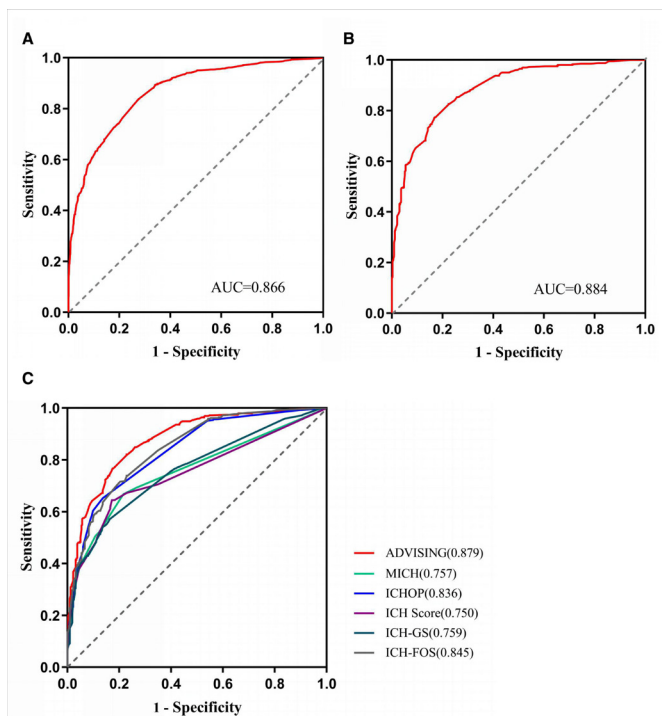
Figure 2 Receiver operating characteristic (ROC) curve for 90-day functional dependence (modified Rankin Scale (mRS) ≥3). (A) ROC curve of ADVISING score in training cohort. (B) ROC curve of ADVISING score in validation cohort. (C) ROCs of ADVISING score and the other five intracerebral haemorrhage (ICH) scores in validation cohort. The values in parenthesis in (B) and (C) are areas under the curve (AUCs). ICH-FOS, ICH Functional Outcome Score; ICH-GS, ICH Grading Scale; ICHOP, ICH Outcomes Project; MICH, modified ICH.

in table 5 and figure 1. In order to promote the clinical practice of ADVISING score, we dichotomised the score to 0–4 for low risk and 5–12 for high risk of functional dependence, and determined. The cut-off value was based on the optimal performance of receiver operating characteristic (ROC) curve analysis. Among them, 742 (77.2%) patients in the training cohort and 293 (81.2%) in the validation cohort had a score ≥5, which predicted 71.6% and 72.9% sensitivity, and 79.6% and 79.5% specificity in the training and validation cohorts, respectively. The detailed information dichotomised test characteristics were shown in table 5.

The ADVISING score demonstrated good discrimination and calibration in training cohort (C-statistic, 0.866; p value of Hosmer-Lemeshow test, 0.195) and validation cohort (C-statistic, 0.884; p value of Hosmer-Lemeshow test, 0.853). Figure 2A,B shows the ROC of the model.

Comparing the ADVISING score with five other existing ICH scores

We compared the discriminative performance of the ADVISING score with five existing ICH scores including MICH score, ICHOP score, original ICH score, ICH-GS and ICH-FOS in the validation cohort (n=733). Among them, 27 patients were excluded for missing information

on elements of other scores. The comparison of screening characteristics and scores between the ADVISING score and the previous risk scores was shown in online supplemental table S2. For functional dependence at 90 days after ICH, AUCs ranged from 0.750 to 0.879 (ICH score, 0.750; MICH score, 0.757; ICH-GS, 0.759; ICHOP score, 0.836; ICH-FOS, 0.845; ADVISING score, 0.879). The ADVISING score had the highest AUC. The pairwise difference in AUCs between the ADVISING and other scores showed statistical significance (all p<0.001) (online supplemental table S3). Figure 2C showed the ROCs of the mentioned scores with regard to functional dependence (mRS ≥3) at 90 days. To better evaluate the performance of predicting scores, we further calculated NRI and IDI in validation cohort (n=706). Reclassifications for patients with and without functional dependence were summarised in online supplemental table S4. The cut-off of 50% for risk categories was chosen based on the actual 90-day dependence rate reported in previous literature.[19] Both NRI and IDI were estimated to be greater than zero (p<0.001) in pairwise comparison, with the greatest net gain in the reclassified 18.4% proportion and the highest improved ability in discrimination of 19.6%, suggesting that the ADVISING score had a significant improvement in performance compared with the other five existing ICH scores.

DISCUSSION

We developed a novel prognostic scoring system for patients with spontaneous ICH from the nationwide multicentre samples in the CHEERY study. ADVISING score exhibited excellent discriminative ability, and was well calibrated and validated in the external cohort. Compared with other ICH scoring models, ADVISING score was developed including well-recognised predictors for prognosis, and selecting multisystem indicators to reflect the damage of other organs after ICH, which is expected to provide the new train of thoughts for screen, diagnosis, prophylaxis and treatment of ICH.

Growing evidence suggests that stroke is a systemic disease affecting many organ systems beyond the brain. Injuries after ICH consist of two main parts: one is the primary injury, including clot removal, haematoma expansion and ischaemia; the secondary injury included thrombin formation, inflammation, complement interaction, Hb fluctuation, iron deposition, free radical formation, glutamate release, cell death pathway apoptosis, etc.[20] Stroke-related systemic responses and inflammatory/immune dysregulations may play important roles in brain injury, recovery and outcome.[21]

Multiple organ injuries after ICH include liver, kidney and coagulation system, mainly caused by circulating inflammatory factors and oxidative stress products.[15 16 22–24] Above all, liver injury usually leads to further haemostatic disorders. Population-based studies have found that patients with ICH have an increased rate of liver dysfunction, including fibrosis and cirrhosis, with

significant impairment of PLT aggregation and reduction of α2 antifibrinolytic activity, which in turn increase risks of ICH.[25 26] As a sensitive marker of liver function, AST was associated with worsening of clinical outcomes in ICH.[13] Second, renal function impairment, characterised by endothelial dysfunction and lipohyalinosis, is also a common complication after ICH.[27–29] Patients with ICH with chronic renal insufficiency have more white matter changes, haematoma growth and perihaematoma oedema,[30 31] possibly due to renal insufficiency inhibiting coagulation system and PLT function through microparticles and microRNA.[32] GFR, as a common indicator reflecting renal function, was identified as an independent predictor of in-hospital mortality after ICH in a previous study.[14] In addition, reactive hyperglycaemia, mediated by cortisol and norepinephrine, induces the opening of the blood–brain barrier and causes vasogenic cerebral oedema by directly inducing neuronal apoptosis, increasing inflammatory cytokines such as tumour necrosis factor alpha and interleukin-1 and promoting the production of oxygen-free radicals after ICH.[33 34] Finally, our study found that higher baseline INR was associated with a 3-month poor outcome, which was in line with the previous study.[16] In our study, we combined the above multisystem injury markers with traditional prognostic predictors and generated a novel prognostic system for patients with ICH.

Elevated blood leucocyte count was associated with higher disease severity, larger ICH volume and worse outcomes.[35] Lower lymphocyte count was associated with larger haematoma volume and an independent predictor of risk of infection and 3-month mortality in ICH.[36] Previous studies showed that NLR may be a useful biomarker for stroke severity and outcome, and higher NLR is associated with larger baseline haematoma volume and higher initial NIHSS.[37 38] In our study, NLR was also included in the ADVISING score, which reflected the inflammatory and immune dimension of stroke-related systemic injuries and responses.

The robustness of this study is driven by large-sample, nationwide multicentre data. However, this study also had several limitations. First, this study only included data on Chinese people. Second, outcome data at 3 months were analyzed only, long outcomes like 1 year or 3 years of follow-up need further studies. In the mean time, the outcome was assessed by telephone interview and text, which are not as accurate as a face-to-face interview. Third, the laboratory variables were only drawn once on admission and we could not observe the dynamic changes of these indicators. Fourth, continuous and ordinal variables were transformed into categorical variables in the scale, with cut-off values determined according to the frequently used clinical implications rather than ROC analysis, which may be not statistically rigorous. Fifth, some patients with IVH were excluded for lacking of haematoma volume (which was not calculated for irregular shapes), leading to lower IVH occurrence rate and better outcomes of the analysed data set compared with excluded samples. Furthermore, we chose logistic regression model for creating this scoring system in order to compare this one with previous established models. Advanced methods including machine learning may be used in our future work to overcome the shortcomings of logistic regression. In addition, to better understand the mechanisms and interactions of multisystem injury after ICH, animal studies on biochemical mechanisms were expected in the future work.

In conclusion, we developed and independently validated a novel clinical prediction score for patients with ICH for their clinical outcomes, which features good calibration and discrimination.

Author affiliations
[1]Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[3]Neurovascular Division, Department of Neurology, Barrow Neurological Institute/Saint Joseph Hospital Medical Center, Phoenix, Arizona, USA
[4]Department of Neurology, Qianjiang Central Hospital, Qianjiang, Hubei, China
[5]Department of Neurology, Jingzhou Central Hospital, Jingzhou, Hubei, China
[6]Department of Neurology, Honghu People's Hospital, Honghu, Hubei, China

ORCID iDs
David Wang http://orcid.org/0000-0003-2277-4608
Quanwei He http://orcid.org/0000-0002-8318-6976
Bo Hu http://orcid.org/0000-0003-1462-8854

REFERENCES

1. Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. *Intensive Care Med* 2002;28 Suppl 2:s235–40.
2. Schrag M, Kirshner H. Management of intracerebral hemorrhage: JACC focus seminar. *J Am Coll Cardiol* 2020;75:1819–31.
3. O'Carroll CB, Brown BL, Freeman WD. Intracerebral hemorrhage: a common yet disproportionately deadly stroke subtype. *Mayo Clin Proc* 2021;96:1639–54.
4. Hemphill JC, Bonovich DC, Besmertis L, *et al*. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001;32:891–7.
5. Chuang Y-C, Chen Y-M, Peng S-K, *et al*. Risk stratification for predicting 30-day mortality of intracerebral hemorrhage. *Int J Qual Health Care* 2009;21:441–7.
6. Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S, *et al*. Grading scale for prediction of outcome in primary intracerebral hemorrhages. *Stroke* 2007;38:1641–4.
7. Gupta VP, Garton ALA, Sisti JA, *et al*. Prognosticating functional outcome after intracerebral hemorrhage: the ICHOP score. *World Neurosurg* 2017;101:577–83.
8. Rost NS, Smith EE, Chang Y, *et al*. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. *Stroke* 2008;39:2304–9.
9. Weimar C, Benemann J, Diener H-C, *et al*. Development and validation of the Essen intracerebral haemorrhage score. *J Neurol Neurosurg Psychiatry* 2006;77:601–5.
10. Cho D-Y, Chen C-C, Lee W-Y, *et al*. A new Modified Intracerebral Hemorrhage score for treatment decisions in basal ganglia hemorrhage--a randomized trial. *Crit Care Med* 2008;36:2151–6.
11. Sembill JA, Gerner ST, Volbers B, *et al*. Severity assessment in maximally treated ICH patients: the max-ICH score. *Neurology* 2017;89:423–31.
12. Ji R, Shen H, Pan Y, *et al*. A novel risk score to predict 1-year functional outcome after intracerebral hemorrhage and comparison with existing scores. *Crit Care* 2013;17:R275.
13. Tan G, Hao Z, Lei C, *et al*. Subclinical change of liver function could also provide a clue on prognosis for patients with spontaneous intracerebral hemorrhage. *Neurol Sci* 2016;37:1693–700.
14. Rhoney DH, Parker D, Millis SR, *et al*. Kidney dysfunction at the time of intracerebral hemorrhage is associated with increased in-hospital mortality: a retrospective observational cohort study. *Neurol Res* 2012;34:518–21.
15. Lattanzi S, Cagnetti C, Provinciali L, *et al*. Neutrophil-to-Lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. *Stroke* 2016;47:1654–7.
16. Curtze S, Strbian D, Meretoja A, *et al*. Higher baseline international normalized ratio value correlates with higher mortality in intracerebral hemorrhage during warfarin use. *Eur J Neurol* 2014;21:616–22.
17. Koga M, Yamagami H, Okuda S, *et al*. Blood glucose levels during the initial 72h and 3-month functional outcomes in acute intracerebral hemorrhage: the SAMURAI-ICH study. *J Neurol Sci* 2015;350:75–8.
18. Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
19. Liu L, Fuller M, Behymer TP, *et al*. Selective serotonin reuptake inhibitors and intracerebral hemorrhage risk and outcome. *Stroke* 2020;51:1135–41.
20. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol* 2012;11:720–31.
21. Saand AR, Yu F, Chen J, *et al*. Systemic inflammation in hemorrhagic strokes - A novel neurological sign and therapeutic target? *J Cereb Blood Flow Metab* 2019;39:959–88.
22. Hagen M, Sembill JA, Sprügel MI, *et al*. Systemic inflammatory response syndrome and long-term outcome after intracerebral hemorrhage. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e588.
23. Kim HC, Oh SM, Pan W-H, *et al*. Association between alanine aminotransferase and intracerebral hemorrhage in East Asian populations. *Neuroepidemiology* 2013;41:131–8.
24. Zheng D, Sato S, Arima H, *et al*. Estimated GFR and the effect of intensive blood pressure lowering after acute intracerebral hemorrhage. *Am J Kidney Dis* 2016;68:94–102.
25. Fujii Y, Takeuchi S, Tanaka R, *et al*. Liver dysfunction in spontaneous intracerebral hemorrhage. *Neurosurgery* 1994;35:592–6.
26. Lai C-H, Cheng P-Y, Chen Y-Y. Liver cirrhosis and risk of intracerebral hemorrhage: a 9-year follow-up study. *Stroke* 2011;42:2615–7.
27. Li Z, Li Z, Zhou Q, *et al*. Effects of estimated glomerular filtration rate on clinical outcomes in patients with intracerebral hemorrhage. *BMC Neurol* 2022;22:19.
28. Qureshi AI, Huang W, Lobanova I, *et al*. Systolic blood pressure reduction and acute kidney injury in intracerebral hemorrhage. *Stroke* 2020;51:3030–8.
29. Burgess LG, Goyal N, Jones GM, *et al*. Evaluation of acute kidney injury and mortality after intensive blood pressure control in patients with intracerebral hemorrhage. *J Am Heart Assoc* 2018;7. doi:10.1161/JAHA.117.008439. [Epub ahead of print: 13 Apr 2018].
30. Tsai Y-H, Lee M, Lin L-C, *et al*. Association of chronic kidney disease with small vessel disease in patients with hypertensive intracerebral hemorrhage. *Front Neurol* 2018;9:284.
31. Molshatzki N, Orion D, Tsabari R, *et al*. Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. *Cerebrovasc Dis* 2011;31:271–7.
32. Lutz J, Menke J, Sollinger D, *et al*. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant* 2014;29:29–40.
33. Koga M, Yamagami H, Okuda S, *et al*. Blood glucose levels during the initial 72 H and 3-month functional outcomes in acute intracerebral hemorrhage: the SAMURAI-ICH study. *J Neurol Sci* 2015;350:75–8.
34. Saxena A, Anderson CS, Wang X, *et al*. Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: the INTERACT2 study. *Stroke* 2016;47:682–8.
35. Nardi K, Milia P, Eusebi P, *et al*. Admission leukocytosis in acute cerebral ischemia: influence on early outcome. *J Stroke Cerebrovasc Dis* 2012;21:819–24.
36. Li P, Mao L, Liu X, *et al*. Essential role of program death 1-ligand 1 in regulatory T-cell-afforded protection against blood-brain barrier damage after stroke. *Stroke* 2014;45:857–64.
37. Menon G, Johnson SE, Hegde A, *et al*. Neutrophil to lymphocyte ratio - A novel prognostic marker following spontaneous intracerebral haemorrhage. *Clin Neurol Neurosurg* 2021;200:106339.
38. Sun Y, You S, Zhong C, *et al*. Neutrophil to lymphocyte ratio and the hematoma volume and stroke severity in acute intracerebral hemorrhage patients. *Am J Emerg Med* 2017;35:429–33.