Comparison of Prognostic Models of Spontaneous Intracerebral Hemorrhage: Potential Tools for Personalized Care and Clinical Trial in ICH

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Research

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Abstract

Background: Several prognostic models have been developed for spontaneous intracerebral hemorrhage (ICH); however, none of them have been consistently used in routine clinical practice or clinical research. In the study, we systematically compared 27 ICH models with regard to mortality and functional outcome at 1-month, 3-month and 1-year after ICH.

Methods: The validation cohort was derived from the Beijing Registration of Intracerebral Hemorrhage. Poor functional outcome was defined as modified Rankin Scale score (mRS) ≥ 3 at 1-month, 3-month and 1-year after ICH, respectively. The area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow goodness-of-fit test were used to assess model discrimination and calibration. Moderate, good, excellent and outstanding discrimination were predefined as AUROC of 0.75-0.79, 0.80-0.84, 0.85-0.89 and above 0.90, respectively.

Results: A total number of 1575 patients were included. The mean age was 57.2 ± 14.3 and 67.2% were male. The median NIHSS score on admission was 11 (IQR: 3-21). For predicting mortality at 3-month after ICH, AUROC of 27 ICH models ranged from 0.604 to 0.856. One model showed excellent discrimination; fifteen models demonstrated good discrimination; and seven models demonstrated moderate discrimination. In pairwise comparison, the ICH-FOS (0.856, 95%CI=0.835-0.878, $P < 0.001$) showed statistically better discrimination than other models for mortality at 3-month after ICH (all $P < 0.05$). For predicting poor functional outcome (mRS ≥ 3) at 3-month after ICH, AUROC of 27 ICH models ranged from 0.602 to 0.880. Five models showed excellent discrimination; six models demonstrated good discrimination; and ten models demonstrated moderate discrimination. In pairwise comparison with other prediction models, the ICH-FOS was superior in predicting poor functional outcome at 3-month after ICH (all $P < 0.001$). Several risk models were well calibrated (Hosmer-Lemeshow test $P > 0.05$) for mortality and poor functional outcome at 3-month after ICH, however, the ICH-FOS showed the largest Cox and Snell R-square. Similar results were verified for mortality and poor functional outcome at 1-month and 1-year after ICH.

Conclusion: Several risk models are externally validated to be effective for risk stratification and outcome prediction after ICH, especially the ICH-FOS, which would be useful tools for personalized care and clinical trial in ICH.

Background

Spontaneous intracerebral hemorrhage (ICH) accounts for approximately 15–20% of all strokes and is one of leading causes of mortality and morbidity worldwide[1, 2]. Despite advances in medical knowledge, treatment for ICH remains strictly supportive with not many evidence-based interventions currently available[3, 4]. Effort continues over the development of accurate, reliable and practical clinical grading scales and outcome prediction models for ICH[5], which would be useful for data-driven discussion with patients or families, personalized care and clinical trial.

During the past decades, several prognostic models have been proposed for predicting mortality and functional outcome after ICH. In early stage, ICH models were mainly presented as equations and were not convenient for clinical practice. In 2001, Hemphill et al introduced the original ICH score, which represents as one of the first simple and easily assessable clinical grading scale for ICH[6]. Since then, a number of modifications to the original ICH score and other pragmatic ICH scores have been developed[5]. Although some of these ICH risk models have been internally or externally validated, none of them has been universally accepted and consistently used in routine clinical practice and clinical research. In addition, with many ICH grading system available, it is becoming increasingly difficult for clinician and researcher to determine which risk models provide optimal predictability and reliability in clinical practice and clinical trials. Therefore, it is necessary to conduct head-to-head comparison of ICH models in an independent cohort.

In the study, we aimed to systematically compare discrimination and calibration of ICH risk models with regard to mortality and functional outcome at 1-month, 3-month and 1-year after ICH following the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guideline[7, 8].

Methods

Validation cohort

The validation cohort was derived from the Beijing Registration of Intracerebral Hemorrhage, which was a multicenter, prospective and observational cohort study. A total number of thirteen hospitals in Beijing area participated in the study. Trained research coordinators at each hospital reviewed medical records daily to identify, consent and enroll consecutively eligible patients. To be eligible for the study, subjects had to meet the following criteria: (1) age 18 years or older; (2) hospitalized with a primary diagnosis of spontaneous ICH and confirmed by brain CT or MRI[9]; (3) direct admission to hospital from a physician's clinic or emergency department; (4) written informed consent from patients or their legal representatives. All patients were diagnosed by a certified vascular neurologist. Demographics, medical history, medications, pre-stroke modified Rankin Scale (mRS) score, neurological deficit on admission, blood pressure, laboratory test, neuroimaging, treatment, medical complications and follow-up information during 1-year after onset were prospectively recorded. The study protocol was approved by the Institutional Review Board (IRB) of the Beijing Tiantan Hospital (KY2014-023-02) and written informed consent was obtained.

Data Collection And Definition Of Variables

A standardized electronic case report form (eCRF) was used for data collection. Participating centers collected data and submitted it online to the coordinating center at Beijing Tiantan Hospital. For this study, the following candidate variables were analyzed: (1) demographics (age and gender); (2) time from onset to hospital; (3) stroke risk factors: hypertension (history of hypertension or anti-hypertensive medication use), diabetes mellitus (history of diabetes mellitus or anti-diabetic medication use), dyslipidemia (history of dyslipidemia or lipid-lowering medication use), atrial fibrillation (history of atrial fibrillation or documentation of atrial fibrillation on admission), history of stroke/TIA, myocardial infarction, heart failure, current smoking, and heavy alcohol consumption (≥ 2 standard alcohol beverage per day); (4) pre-admission antithrombotic medications (anticoagulation and antiplatelet agents); (5) pre-stroke mRS score; (6) admission stroke severity based on the National Institutes of Health Stroke Scale score (NIHSS) and the Glasgow Coma Scale (GCS) score; (7) admission systolic and diastolic blood pressure (mmHg); (8) admission laboratory tests (white blood cell count, blood glucose, and creatinine); (9) neuroimaging variables: intracerebral hemorrhage volume (measured using the ABC/2 method[10]), hematoma location (supratentorial or infratentorial ICH), intraventricular extension (presence or absence) and subarachnoid extension (presence or absence). All images were prospectively viewed by a trained neuroradiologist blinded to clinical data. (10) etiology diagnosis at discharge (primary or secondary ICH); (11) surgical treatment (craniotomy evacuation, minimal-invasive surgical therapy or brain ventricle puncture and drainage); (12) withdrawal of medical care; and (13) length of hospital stay (LOS).

Functional Outcome Assessment

The modified Rankin Scale was used to evaluate functional outcome during 1 year after ICH. Central follow-up blinded to baseline variables was made by telephone interview by trained interviewers based on a standardized interview protocol. For patients who lost to follow-up, we made telephone follow-up interview once a week for three times. In the study, poor functional outcome was defined as mRS ≥ 3 at 1-month, 3-month and 1-year after ICH.

Statistical analysis

Continuous variables were summarized with mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were summarized as proportions. Chi-square or Fisher exact test was used to compare categorical variables and Mann-Whitney test or independent t-test was employed to compare continuous variables between groups.

The primary criterion for selecting ICH model was whether all elements required for the model was available in our dataset and finally 27 existing ICH risk models met this criterion: the Tuhim's Eq. (1991)[11], Broderick's score (1993)[12], Lisk's Eq. (1994)[13], Mase's Eq. (1995)[14], original ICH Score (2001)[6], Hallevy's score (2002)[15], modified ICH Score (2003)[16],

Shaya's score (2005)[17], Essen ICH score (2006)[18], Weimar' equation-I (2006)[19], GP on STAGE score (2006)[20], ICH-GS (2007)[21], FUNC Score (2008)[22], MICH Score (2008)[23], Huang's score (2008)[24], simplified ICH score (2009)[25], Weimar' equation-II (2009)[26], IVH score (2010)[27], Kinshasa ICH score (2012)[28], ICH index (2012)[29], ICH-FOS (2013)[30], EDICH score (2014)[31], CAA-ICH score (2016)[32], Ho's score (2016)[33], Safatli's score (2016)[34], max-ICH score (2017)[35] and ICHOP score (2017)[36].

The resulting ICH models were validated by assessing model discrimination and calibration[7, 8]. Discrimination was assessed by calculating the area under the receiver operating characteristic curve (AUROC). In the study, moderate, good, excellent and outstanding discrimination were predefined as AUROC of 0.75–0.79, 0.80–0.84, 0.85–0.89 and above 0.90, respectively. Due to that existing ICH models were designed for predicting outcomes at different time points after onset, we compared discrimination of ICH models with regard to mortality and poor functional outcome at 1-month, 3-month and 1-year after ICH, respectively. Pairwise AUROC was compared by using Delong's method[37] and sensitivity, specificity, positive predict value (PPV), and negative predictive value (NPV) were calculated at each risk models' maximum Youden Index. Calibration was assessed by performing the Hosmer-Lemeshow goodness-of-fit test and plot of observed versus predicted risk according to 10 deciles of the predicted risk. The Cox and Snell R-square and Nagelkerke R-square of the Hosmer-Lemeshow goodness-of-fit test were calculated.

All tests were 2-tailed and statistical significance was determined at α level of 0.05. Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC), SPSS 19.0 (SPSS Inc., Chicago, IL), and Medcalc software 12.3 (MedCalc).

Results

Patient characteristics

From December 2014 to September 2016, a total number of 1964 patients were enrolled in the Beijing Registration of Intracerebral Hemorrhage. Among them, we were unable to obtain follow-up information in 389, yielding 1575 patients with requisite data for the present analysis (An additional figure shows this in more detail [see Additional Fig. 1]). The clinical characteristics of the study patients are shown in Table 1. The mean age was 57.2 ± 14.3 and 67.2% were male. The median time from onset to hospital was 4.0 hours (IQR: 1.83–11.1). The median NIHSS and GCS score on admission was 11 (IQR: 3–21) and 14 (IQR: 8–15), respectively. A total number of 1438 (91.3) was diagnosed with primary ICH and 137 (8.7%) secondary ICH at discharge. The median length of hospital stay was 16 days (IQR: 8–22). There were 104 (6.6%) patients in whom withdraw of care was instituted during hospitalization. The median mRS score at 1-month, 3-month and 1-year after onset was 4 (IQR: 1–5), 3 (IQR: 1–5) and 2 (IQR: 1–6), respectively. The baseline characteristics of patients included ($n = 1575$) and those excluded ($n = 389$) are listed in additional Table 1 (An additional table shows this in more detail [see Additional Table 1]). They were not statistically different in initial NIHSS score, GCS score, hematoma volume and withdraw of care.

Table 1
Patient characteristics

	Overall (n = 1575)
Demographics	
Age, y, median (IQR)	57.2 ± 14.3
Gender (male), n (%)	1061 (67.2)
Onset to hospital (hours), median (IQR)	4.00 (1.83–11.1)
Risk factors, n (%)	
Hypertension	1093 (69.4)
Diabetes mellitus	236 (15.0)
Dyslipidemia	150 (9.5)
Atrial fibrillation	23 (1.5)
History of stroke/TIA	263 (16.7)
Myocardial infarction	35 (2.2)
Heart failure	7 (0.4)
Current smoker	511 (32.4)
Heavy alcohol consumption	589 (37.4)
Pre-admission anticoagulation, n (%)	17 (1.1)
Pre-admission antiplatelet, n (%)	246 (15.6)
Pre-stroke mRS score, median (IQR)	0 (0–0)
Admission NIHSS score, median (IQR)	11 (3–21)
Admission GCS score, median (IQR)	14 (8–15)
Admission SBP (mm Hg), median (IQR)	164 (147–187)
Admission DBP (mm Hg), median (IQR)	95 (82–109)
Admission WBC, 10 ⁹ /L, median (IQR)	9.83 (7.41–13.1)
Admission glucose (mmol/L), median (IQR)	7.4 (6.1–9.3)
Admission creatinine (mmol/L), median (IQR)	63.8 (52.7–77.2)
Hematoma location	
Supratentorial ICH, n (%)	1384 (87.9)
Infratentorial ICH, n (%)	191 (12.1)
Hematoma volume (cm ³), median (IQR)	16.1 (6.2–39.5)
Intraventricular extension, n (%)	181 (11.5)

Abbreviation: IQR, Interquartile Range; TIA, Transient Ischemic Attack; NIHSS, National Institutes of Health Stroke Scale score; GCS, Glasgow Coma Scale; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Cell Count; ICH, Intracerebral Hemorrhage; mRS, modified Rankin Scale.

	Overall (n = 1575)
Subarachnoid extension, n (%)	230 (14.6)
Etiology diagnosis	
Primary ICH	1438 (91.3)
Secondary ICH	137 (8.7)
Withdrawal of medical care, n (%)	104 (6.6)
Surgical treatment	312 (19.8)
Length of hospital stay, median (IQR)	16 (8–22)
Outcomes within 1-year after onset	
mRS score at 1-month after onset, median (IQR)	4 (1–5)
mortality at 1-month after onset, n (%)	313 (19.9)
mRS ≥ 3 at 1-month after onset, n (%)	966 (61.3)
mRS score at 3-month after onset, median (IQR)	3 (1–5)
mortality at 3-month after onset, n (%)	337 (21.4)
mRS ≥ 3 at 3-month after onset, n (%)	869 (55.2)
mRS score at 1-year after onset, median (IQR)	2 (1–6)
mortality at 1-year after onset, n (%)	399 (25.3)
mRS ≥ 3 at 1-year after onset, n (%)	774 (49.1)
Abbreviation: IQR, Interquartile Range; TIA, Transient Ischemic Attack; NIHSS, National Institutes of Health Stroke Scale score; GCS, Glasgow Coma Scale; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Cell Count; ICH, Intracerebral Hemorrhage; mRS, modified Rankin Scale.	

Predictive Performance For Mortality After Ich

Discrimination. Figure 1 shows discrimination of 27 ICH models with regard to mortality and poor functional outcome (mRS ≥ 3) at 1-month, 3-month and 1-year after ICH, respectively. For predicting 3-month mortality after ICH, AUROC of 27 ICH risk models ranged from 0.604 to 0.856. Among them, one model (The ICH-FOS) showed excellent discrimination with AUROC between 0.85 and 0.89; fifteen risk models demonstrated good discrimination with AUROC between 0.80 and 0.84 including the Essen ICH score, Weimar' equation-II, GP on STAGE score, EDICH score, modified ICH Score, Huang's score, ICHOP score, Lisk's equation, CAA-ICH score, FUNC Score, simplified ICH score, ICH index, IVH score, max-ICH score and Mase's equation; and seven risk models demonstrated moderate discrimination with AUROC between 0.75 and 0.79 (Table 2) (An additional figure shows this in more detail [see Additional Fig. 2]). The sensitivity, specificity, PPV, NPV and maximum Youden Index of 27 ICH models for predicting 3-month mortality after ICH are shown in Table 2. The ICH-FOS showed the maximum Youden Index. In pairwise comparison, the ICH-FOS (0.856, 95% CI = 0.835–0.878, $P < 0.001$) showed statistically better discrimination than other risk models for mortality at 3-month after ICH (all $P < 0.05$). Similar results were found with regard to mortality at 1-month and 1-year after ICH (Additional tables show this in more detail [see Additional Table 2–3]).

Table 2

Discrimination of ICH risk models with regard to mortality and poor functional outcome (mRS $\geq$ 3) at 3-month after ICH (n = 1575)

	AUROC	95% CI	Δ AUROC*	P value ^{&}	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
Mortality at 3-month after ICH										
The ICH-FOS (2013)	0.856	0.835–0.878	Reference		0.577	8	0.798	0.779	0.500	0.934
The Essen ICH score (2006)	0.839	0.820–0.857	0.017	0.02	0.566	4	0.777	0.788	0.501	0.929
Weimar' equation-II (2009)	0.836	0.817–0.854	0.020	0.03	0.561	...	0.756	0.805	0.514	0.924
The GP on STAGE score (2006)	0.836	0.816–0.854	0.020	0.03	0.571	...	0.750	0.821	0.534	0.924
The EDICH score (2014)	0.836	0.817–0.854	0.020	0.04	0.567	2	0.730	0.837	0.550	0.919
The modified ICH Score (2003)	0.835	0.815–0.853	0.021	< 0.001	0.551	2	0.765	0.785	0.493	0.925
Huang's score (2008)	0.829	0.809–0.847	0.027	< 0.001	0.571	3	0.715	0.856	0.575	0.917
ICHOP (2018)	0.828	0.809–0.847	0.028	< 0.001	0.557	5	0.744	0.812	0.520	0.921
Lisk's Eq. (1994)	0.827	0.807–0.845	0.029	< 0.001	0.553	...	0.727	0.826	0.533	0.917
CAA- ICH score (2016)	0.827	0.807–0.845	0.029	< 0.001	0.519	1	0.872	0.647	0.403	0.949
The FUNC Score (2008)	0.825	0.805–0.843	0.031	< 0.001	0.538	7	0.845	0.692	0.429	0.943
The simplified ICH score (2009)	0.825	0.805–0.844	0.031	< 0.001	0.508	7	0.649	0.858	0.556	0.900

* Δ AUROC denotes the difference in AUROC between the ICH-FOS and compared scores with regard to mortality and poor functional outcome at 3-month after ICH.

[&] P value of comparing paired AUROC with Delong's method.

Abbreviation: ICH, Intracerebral Hemorrhage; AUROC, Area Under the Receiver Operating Characteristic Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

	AUROC	95% CI	Δ AUROC*	P value ^{&}	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
The ICH index (2012)	0.821	0.801–0.840	0.035	< 0.001	0.530	...	0.747	0.782	0.484	0.919
The IVH score (2010)	0.818	0.798–0.837	0.038	< 0.001	0.555	1	0.836	0.718	0.448	0.942
max-ICH (2017)	0.813	0.793–0.832	0.043	< 0.001	0.519	2	0.854	0.665	0.410	0.944
Mase's Eq. (1995)	0.809	0.788–0.828	0.047	< 0.001	0.512	...	0.798	0.714	0.432	0.928
The original ICH Score (2001)	0.797	0.777–0.817	0.059	< 0.001	0.475	1	0.768	0.707	0.417	0.918
The ICH-GS (2007)	0.797	0.777–0.817	0.059	< 0.001	0.475	1	0.768	0.707	0.417	0.918
The MICH Score (2008)	0.794	0.774–0.814	0.062	< 0.001	0.465	1	0.768	0.696	0.409	0.917
Broderick's score (1993)	0.776	0.754–0.797	0.080	< 0.001	0.521	...	0.835	0.686	0.394	0.945
Ho's score (2016)	0.772	0.751–0.793	0.084	< 0.001	0.476	...	0.774	0.702	0.415	0.919
Hallevy's score (2002)	0.770	0.748–0.790	0.086	< 0.001	0.402	2	0.685	0.716	0.397	0.893
Tuhim's Eq. (1991)	0.761	0.739–0.782	0.095	< 0.001	0.441	...	0.655	0.785	0.455	0.893
The Kinshasa ICH score (2012)	0.683	0.659–0.706	0.173	< 0.001	0.320	6	0.646	0.673	0.350	0.875
Shaya's score (2005)	0.636	0.611–0.659	0.220	< 0.001	0.247	2	0.599	0.647	0.317	0.856
Weimar' equation-I (2006)	0.632	0.607–0.655	0.224	< 0.001	0.192	...	0.549	0.643	0.296	0.839
Safatli's score (2016)	0.604	0.579–0.628	0.252	< 0.001	0.207	0	0.299	0.907	0.470	0.826
Poor functional outcome (mRS $\geq$ 3) at 3-month after ICH										
* Δ AUROC denotes the difference in AUROC between the ICH-FOS and compared scores with regard to mortality and poor functional outcome at 3-month after ICH.										
^{&} P value of comparing paired AUROC with Delong's method.										
Abbreviation: ICH, Intracerebral Hemorrhage; AUROC, Area Under the Receiver Operating Characteristic Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value.										

	AUROC	95% CI	Δ AUROC*	P value ^{&}	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
The ICH-FOS (2013)	0.880	0.863–0.896	Reference		0.588	4	0.756	0.832	0.848	0.734
The Essen ICH score (2006)	0.862	0.843–0.878	0.018	< 0.001	0.554	2	0.784	0.769	0.808	0.743
max-ICH (2017)	0.862	0.844–0.878	0.018	< 0.001	0.562	1	0.872	0.690	0.777	0.814
Weimar' equation-II (2009)	0.853	0.835–0.870	0.027	< 0.001	0.535	...	0.848	0.687	0.770	0.786
ICHOP (2018)	0.850	0.832–0.867	0.030	< 0.001	0.533	3	0.735	0.798	0.818	0.710
Hallevy's score (2002)	0.840	0.821–0.858	0.040	< 0.001	0.550	1	0.850	0.703	0.778	0.791
The modified ICH Score (2003)	0.818	0.798–0.837	0.062	< 0.001	0.489	1	0.716	0.772	0.796	0.689
Lisk's Eq. (1994)	0.815	0.795–0.834	0.065	< 0.001	0.485	...	0.558	0.927	0.905	0.630
The GP on STAGE score (2006)	0.811	0.791–0.830	0.069	< 0.001	0.494	...	0.680	0.813	0.819	0.673
Mase's Eq. (1995)	0.807	0.787–0.827	0.073	< 0.001	0.478	...	0.631	0.848	0.837	0.650
The IVH score (2010)	0.806	0.786–0.825	0.074	< 0.001	0.501	1	0.624	0.876	0.862	0.654
The FUNC Score (2008)	0.797	0.776–0.817	0.083	< 0.001	0.495	7	0.644	0.850	0.842	0.660
The MICH Score (2008)	0.792	0.771–0.811	0.088	< 0.001	0.451	1	0.605	0.846	0.830	0.635
CAA- ICH score (2016)	0.791	0.770–0.811	0.089	< 0.001	0.495	1	0.685	0.809	0.816	0.676
The ICH index (2012)	0.787	0.766–0.807	0.093	< 0.001	0.450	...	0.676	0.774	0.787	0.660

* Δ AUROC denotes the difference in AUROC between the ICH-FOS and compared scores with regard to mortality and poor functional outcome at 3-month after ICH.

[&] P value of comparing paired AUROC with Delong's method.

Abbreviation: ICH, Intracerebral Hemorrhage; AUROC, Area Under the Receiver Operating Characteristic Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

	AUROC	95% CI	Δ AUROC*	P value&	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
The simplified ICH score (2009)	0.786	0.765–0.806	0.094	< 0.001	0.469	6	0.675	0.794	0.802	0.665
The EDICH score (2014)	0.772	0.751–0.793	0.108	< 0.001	0.446	1	0.659	0.786	0.793	0.652
Broderick's score (1993)	0.771	0.749–0.791	0.109	< 0.001	0.453	...	0.713	0.740	0.772	0.677
The original ICH Score (2001)	0.768	0.746–0.789	0.112	< 0.001	0.429	1	0.586	0.842	0.821	0.623
The ICH-GS (2007)	0.768	0.746–0.789	0.112	< 0.001	0.429	1	0.586	0.842	0.821	0.623
Huang's score (2008)	0.766	0.744–0.787	0.114	< 0.001	0.456	1	0.627	0.829	0.820	0.643
Tuhim's Eq. (1991)	0.741	0.719–0.763	0.139	< 0.001	0.379	...	0.478	0.901	0.856	0.583
Ho's score (2016)	0.739	0.716–0.760	0.141	< 0.001	0.432	...	0.611	0.821	0.808	0.631
The Kinshasa ICH score (2012)	0.721	0.698–0.743	0.159	< 0.001	0.391	6	0.570	0.821	0.797	0.608
Shaya's score (2005)	0.716	0.693–0.739	0.164	< 0.001	0.379	2	0.575	0.804	0.784	0.605
Weimar' equation-I (2006)	0.691	0.667–0.714	0.189	< 0.001	0.271	...	0.655	0.615	0.678	0.592
Safatli's score (2016)	0.602	0.577–0.626	0.278	< 0.001	0.203	0	0.227	0.975	0.921	0.506
* Δ AUROC denotes the difference in AUROC between the ICH-FOS and compared scores with regard to mortality and poor functional outcome at 3-month after ICH.										
& P value of comparing paired AUROC with Delong's method.										
Abbreviation: ICH, Intracerebral Hemorrhage; AUROC, Area Under the Receiver Operating Characteristic Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value.										

Table 3
Calibration of ICH risk models with regard to mortality and functional outcome at 3-month after ICH (n = 1575)

International ICH models	Goodness of fit test with regard to mortality at 3-month after onset			International ICH models	Goodness of fit test with regard to poor functional outcome (mRS $\geq$ 3) at 3-month after onset		
	P value	Cox and Snell R ²	Nagelkerke R ²		P value	Cox and Snell R ²	Nagelkerke R ²
The ICH-FOS (2013)	> 0.05	0.249	0.376	The ICH-FOS (2013)	> 0.05	0.399	0.535
The modified ICH Score (2003)	> 0.05	0.237	0.367	max-ICH (2017)	> 0.05	0.373	0.50
The GP on STAGE score (2006)	> 0.05	0.232	0.365	Hallevy's score (2002)	> 0.05	0.337	0.45
CAA- ICH score (2016)	> 0.05	0.229	0.354	The modified ICH Score (2003)	> 0.05	0.301	0.403
Lisk's Eq. (1994)	> 0.05	0.224	0.347	The IVH score (2010)	> 0.05	0.287	0.384
The ICH index (2012)	> 0.05	0.217	0.336	The FUNC Score (2008)	> 0.05	0.273	0.366
The original ICH Score (2001)	> 0.05	0.193	0.299	CAA- ICH score (2016)	> 0.05	0.264	0.354
The ICH-GS (2007)	> 0.05	0.193	0.299	The MICH Score (2008)	> 0.05	0.263	0.351
Weimar' equation-I (2006)	> 0.05	0.044	0.068	The ICH index (2012)	> 0.05	0.234	0.313
The Essen ICH score (2006)	< 0.05	0.245	0.379	Weimar' equation-I (2006)	> 0.05	0.109	0.146
The simplified ICH score (2009)	< 0.05	0.243	0.375	The Essen ICH score (2006)	< 0.05	0.363	0.486
The EDICH score (2014)	< 0.05	0.242	0.374	ICHOP (2018)	< 0.05	0.346	0.463
Weimar' equation-II (2009)	< 0.05	0.241	0.373	Weimar' equation-I (2006)	< 0.05	0.306	0.410
Huang's score (2008)	< 0.05	0.231	0.358	The GP on STAGE score (2006)	< 0.05	0.291	0.39
ICHOP (2018)	< 0.05	0.227	0.351	Lisk's Eq. (1994)	< 0.05	0.284	0.38
Broderick's score (1993)	< 0.05	0.215	0.333	Mase's Eq. (1995)	< 0.05	0.271	0.363
The FUNC Score (2008)	< 0.05	0.209	0.323	The simplified ICH score (2009)	< 0.05	0.26	0.348
Mase's Eq. (1995)	< 0.05	0.193	0.299	Huang's score (2008)	< 0.05	0.249	0.333
max-ICH (2017)	< 0.05	0.193	0.298	The EDICH score (2014)	< 0.05	0.239	0.321

Abbreviation: ICH, Intracerebral Hemorrhage; mRS, modified Rankin Scale.

International ICH models	Goodness of fit test with regard to mortality at 3-month after onset			International ICH models	Goodness of fit test with regard to poor functional outcome (mRS ≥ 3) at 3-month after onset		
	P value	Cox and Snell R ²	Nagelkerke R ²		P value	Cox and Snell R ²	Nagelkerke R ²
The IVH score (2010)	< 0.05	0.189	0.292	The original ICH Score (2001)	< 0.05	0.233	0.312
The MICH Score (2008)	< 0.05	0.185	0.286	The ICH-GS (2007)	< 0.05	0.233	0.312
Ho's score (2016)	< 0.05	0.170	0.263	Broderick's score (1993)	< 0.05	0.217	0.291
Hallevy's score (2002)	< 0.05	0.147	0.228	Ho's score (2016)	< 0.05	0.215	0.288
Tuhrim's Eq. (1991)	< 0.05	0.143	0.221	Tuhrim's Eq. (1991)	< 0.05	0.201	0.268
The Kinshasa ICH score (2012)	< 0.05	0.077	0.119	The Kinshasa ICH score (2012)	< 0.05	0.161	0.216
Shaya's score (2005)	< 0.05	0.059	0.091	Shaya's score (2005)	< 0.05	0.16	0.214
Safatli's score (2016)	< 0.05	0.051	0.079	Safatli's score (2016)	< 0.05	0.098	0.131
Abbreviation: ICH, Intracerebral Hemorrhage; mRS, modified Rankin Scale.							

Calibration. The predicted and observed risk according to 10 deciles of the predicted risk of mortality at 3-month after ICH was plotted (An additional figure shows this in more detail [see Additional Fig. 4]). The results of Hosmer-Lemeshow test are shown in Table 3. Nine models have a significance level of Hosmer-Lemeshow test greater than 0.05, as indicated that the observed values are not statistically different from the expected values. Among them, the risk models with top three largest Cox and Snell R-square were the ICH-FOS, modified ICH Score and GP on STAGE score, respectively. Similar results were verified for mortality at 1-month and 1-year after ICH (Additional tables shows this in more detail [see Additional table4-5]).

Predictive Performance For Poor Functional Outcome After Ich

Discrimination. For predicting poor functional outcome (mRS ≥ 3) at 3-month after ICH, AUROC of 27 ICH risk models ranged from 0.602 to 0.880. The ICH-FOS score (AUROC = 0.880; 95% CI = 0.864–0.897; $P < 0.001$), Essen ICH score (AUROC = 0.862; 95% CI = 0.843–0.878; $P < 0.001$), max-ICH score (AUROC = 0.862; 95% CI = 0.844–0.878; $P < 0.001$), Weimer's equation-II (AUROC = 0.853; 95% CI = 0.835–0.872; $P < 0.001$) and ICHOP scores (AUROC = 0.850; 95% CI = 0.832–0.867; $P < 0.001$) demonstrated excellent discrimination with AUROC between 0.85 and 0.89. Six risk models showed good discrimination with AUROC between 0.80 and 0.84, including the Hallevy's score, modified ICH Score, Lisk's equation, GP on STAGE score, Mase's equation and IVH score. Ten risk models demonstrated moderate discrimination with AUROC between 0.75 and 0.79 (Table 2) (An additional figure shows this in more detail [see Additional Fig. 3]). The sensitivity, specificity, PPV, NPV and maximum Youden Index of ICH risk models with regard to poor functional outcome at 3-month after onset are shown in Table 2. The ICH-FOS showed the maximum Youden Index. In pairwise comparison with other prediction models, the ICH-FOS was superior in predicting poor functional outcome at 3-month after ICH (all $P < 0.001$). Similar results were found with regard to poor functional outcome at 1-month and 1-year after ICH (Additional tables show this in more detail [see Additional Table2-3]).

Calibration. The predicted and observed risk according to 10 deciles of the predicted risk of poor functional outcome at 3-month after ICH was plotted in supplementary Fig. 5 (An additional figure shows this in more detail [see Additional Fig. 5]). The results of Hosmer-Lemeshow test are shown in Table 3. Ten risk models have a significance level of Hosmer-Lemeshow test greater than 0.05. Among them, the models with top three largest Cox and Snell R-square of Hosmer-Lemeshow test were the ICH-FOS, max-ICH and Hallevy's score, respectively (Table 3). Similar results were found for poor functional outcome at 1-month and 1-year after ICH (Additional tables show this in more detail [see Additional table 5–7]).

Sensitivity Analysis

We completed prespecified subgroup analyses by age (≤ 59 vs. ≥ 60), gender (female vs. male), hematoma location (supratentorial vs. infratentorial), hematoma volume (≤ 29 vs. ≥ 30 ml), medical care withdrawal (yes vs. no) and surgical treatment (yes vs. no). Although several risk models demonstrated good or excellent discrimination in these subgroups, the ICH-FOS steadily showed the highest AUROC for poor functional outcome ($mRS \geq 3$) at 3-month (Fig. 2A) and 1-year (Fig. 2B) after onset.

Discussion

In the study, we systematically compared discrimination and calibration of 27 ICH risk models with regard to mortality and poor functional outcome at 1-month, 3-month and 1-year after ICH, respectively. For predicting 3-month mortality after ICH, AUROC of 27 ICH risk models ranged from 0.604 to 0.856. Among them, one model showed excellent discrimination and fifteen models demonstrated good discrimination with regard to mortality at 3-month after ICH. For predicting poor functional outcome ($mRS \geq 3$) at 3-month after ICH, AUROC of 27 ICH risk models ranged from 0.602 to 0.880. Five model showed excellent discrimination and six models demonstrated good discrimination for poor functional outcome at 3-month after ICH. In pairwise comparison, the ICH-FOS showed statistically better discrimination than other ICH models for both mortality and poor functional outcomes at 3-month after ICH. Similar results were verified for mortality and poor functional outcome at 1-month and 1-year after ICH.

A lot of literature conveyed that do-not-resuscitate order and withdraw of care contribute to worse outcomes in patients with ICH and majority of available ICH risk models are hindered by this self-fulfilling prophecy[38, 39]. The ideal way to precisely define prognosis after ICH would be to assess it in a cohort in which patients received full support, irrespective of the perceived probable outcome. The Beijing Registration of Intracerebral Hemorrhage had an overall low rate of withdrawal of care (6.6%) and allowed us to get closer to overcoming the self-fulfilling prophecy prejudice.

For a clinical risk model to become effective and widely used, it must be accurate and reliable in risk-stratification and outcome prediction. Our study indicated that among 27 ICH risk models, seventeen models had good or excellent discrimination ($AUROC \geq 0.80$) for predicting mortality at 3-month after ICH; meanwhile, eleven models showed good or excellent discrimination for poor functional outcome ($mRS \geq 3$) at 3-month after ICH (Table 2). Similar results were found for predicting mortality and poor functional outcome at 1-month and 1-year after ICH (Supplementary table 2–3). These results indicated that several ICH risk models are effective for predicting mortality and functional outcomes after ICH, which would be useful for data-driven discussion with patients or families, personalized care and clinical trial.

With several ICH prognostic models available, it is becoming increasingly difficult for clinician and researcher to determine which risk models provide optimal predictability and reliability in clinical practice and clinical trial. In pairwise comparison, the ICH-FOS showed statistically better discrimination than other ICH risk models for both mortality (all $P < 0.05$) and poor functional outcome (all $P < 0.001$) at 3-month after ICH. Similar results were verified for predicting mortality and poor functional outcome at 1-month and 1-year after ICH (Supplementary table 2–3). In addition, in subgroup analysis, the ICH-FOS steadily showed the highest AUROC in prespecified subgroups for poor functional outcome at 3-month and 1-year after ICH (Fig. 2). In calibration analysis, the ICH-FOS showed the largest Cox and Snell R-square of the Hosmer-Lemeshow goodness of fit test for both mortality and poor functional outcome at 1-month, 3-month and 1-year after ICH. These results

were consistent with the original study for developing the ICH-FOS based on the China National Stroke Registry (CNSR)[30]. Together, these results indicated that the ICH-FOS had significantly better discrimination and calibration than compared models for both mortality and poor functional outcome after ICH. Though it is promising, caution need to be taken when interpreting the results: first, the study populations for derivation and validation of these ICH models are different. The baseline characteristics of our study were different from those of western cohorts, such as with younger age of ICH onset, less severity of neurological deficit, smaller hematoma volume, fewer intraventricular extension and lower rate of withdraw of care. Second, the intended outcome (functional outcome vs. mortality), timing (1-month, 3-month, 6-month and 1-year after ICH) and assessment tools (GOS vs. BI vs. mRS) are different for existing ICH models. Finally, there might be complex genetic, social, economic factors as well as regional management philosophies and preferences that are difficult to account for when risk models are developed or applied to a distinct population. These ICH models need to be further validated in more populations and larger samples in the future.

Despite advances in medical knowledge, treatment for ICH remains strictly supportive with not many evidence-based interventions currently available. Medical and surgical treatment, such as blood pressure control[40, 41], hematoma evacuation[42–44], hemostatic therapy[45], neuroprotection[46] have not shown definite benefit in improving ICH functional outcomes. It is the time that we need to rethink about the way how we conduct a clinical trial for improving ICH functional outcome. Currently, we have come into a new era of precision medicine. According to the Precision Medicine Initiative, precision medicine is a medical model that proposes the customization of healthcare, with medical treatment or prevention being tailored to individual patient[47]. In precision medicine, patients are stratified by potential risk and treatment or prevention strategies are developed for patients with specific risk stratification. On the country, in traditional medicine model, patients were grouped by symptoms and signs and treatment or prevention strategies are developed for the average person (one size fit all), with less consideration for the differences between individuals. Prior ICH clinical trials selected patients mainly based on hematoma volume, hematoma location and time window of symptom onset[40–46]. In this way, it is inevitable to include patients with unbalanced, too high, or too low risk of developing poor functional outcome in these clinical trials (An additional figure shows this in more detail [see Additional Fig. 6A]). Inspired by precision medicine model, we could use validated prognostic models to stratify patients by potential risk of developing poor functional outcome after ICH and then test specific intervention in different risk stratifications (An additional figure shows this in more detail [see Additional Fig. 6B]). ICH trials conducted in this way will allow researchers to clarify more accurately which treatment or prevention strategies will work in which risk stratification patients.

Our study has strength and limitation. To the best of our knowledge, we are the first to systematically compare predictive performance of 27 ICH risk models with regard to mortality and functional outcome after ICH in a large independent cohort. The finding of the study will provide important information on selecting prognostic tools for personalized care and clinical trial in ICH. However, our study also has limitation that deserve comment: First, central follow-up blinded to baseline variables was made by telephone interview by trained interviewers based on a standardized interview protocol. For patients who lost to follow-up, we made telephone follow-up interview once a week for three times. Although a lot of effort has been done, there is still a relatively high rate of patients with missing follow-up information during 1-year after ICH. We compared the baseline characteristics of patients included and those excluded and they were not statistically different in admission NIHSS score, GCS score, hematoma volume and withdraw of care. Second, we cannot have all elements required for all ICH models and several ICH risk models cannot be externally validated in the study. Meanwhile, some risk models developed based on machine learning were not included in the study as well. Third, our study included only hospitalized patients and those patients died in emergency room or treated in outpatient clinics were not included. Meanwhile, like most registries, our registry required informed consent and selection bias was inevitable. Finally, validation cohorts originated from Asian population and the ICH models needed to be further validated in different populations.

Conclusion

Several risk models are externally validated to be effective for risk stratification and outcome prediction after ICH, especially the ICH-FOS, which would be useful tools for personalized care and clinical trials in ICH.

List Of Abbreviations

Intracerebral hemorrhage (ICH)

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline

modified Rankin Scale (mRS)

Institutional Review Board (IRB)

electronic case report form (eCRF)

National Institutes of Health Stroke Scale score (NIHSS)

Glasgow Coma Scale (GCS)

Length of hospital stay (LOS)

Standard deviation (SD)

Interquartile range (IQR)

Area under the receiver operating characteristic curve (AUROC)

Positive predict value (PPV)

Negative predictive value (NPV)

China National Stroke Registry (CNSR)

The ICH Functional Outcome Score (ICH-FOS)

Declarations

The study protocol was approved by the Institutional Review Board (IRB) of the Beijing Tiantan Hospital (KY2014-023-02).

All authors are consent for publication.

Availability of data and materials: the corresponding author has the responsibility on behalf of Beijing Registration of Intracerebral Hemorrhage investigators and has full access to the final database. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

Dr. Ruijun Ji reports no disclosures.

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Authors' contributions

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References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN *et al*: **Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association**. *Circulation* 2020, **141**(9):e139-e596.
2. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, Wang L, Jiang Y, Li Y, Wang Y *et al*: **Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults**. *Circulation* 2017, **135**(8):759-771.
3. Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH *et al*: **Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare**

- Professionals From the American Heart Association/American Stroke Association. *Stroke* 2015, **46**(7):2032-2060.
4. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, Forsting M, Harnof S, Klijn CJ, Krieger D *et al*: **European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage.** *Int J Stroke* 2014, **9**(7):840-855.
 5. Gregorio T, Pipa S, Cavaleiro P, Atanasio G, Albuquerque I, Chaves PC, Azevedo L: **Prognostic models for intracerebral hemorrhage: systematic review and meta-analysis.** *BMC Med Res Methodol* 2018, **18**(1):145.
 6. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC: **The ICH score: a simple, reliable grading scale for intracerebral hemorrhage.** *Stroke* 2001, **32**(4):891-897.
 7. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS: **Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration.** *Ann Intern Med* 2015, **162**(1):W1-73.
 8. Collins GS, Reitsma JB, Altman DG, Moons KG: **Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement.** *BMJ* 2015, **350**:g7594.
 9. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT *et al*: **An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** *Stroke* 2013, **44**(7):2064-2089.
 10. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J: **The ABCs of measuring intracerebral hemorrhage volumes.** *Stroke* 1996, **27**(8):1304-1305.
 11. Tuhim S, Dambrosia JM, Price TR, Mohr JP, Wolf PA, Hier DB, Kase CS: **Intracerebral hemorrhage: external validation and extension of a model for prediction of 30-day survival.** *Ann Neurol* 1991, **29**(6):658-663.
 12. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: **Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality.** *Stroke* 1993, **24**(7):987-993.
 13. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC: **Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation.** *Neurology* 1994, **44**(1):133-139.
 14. Mase G, Zorzon M, Biasutti E, Tasca G, Vitrani B, Cazzato G: **Immediate prognosis of primary intracerebral hemorrhage using an easy model for the prediction of survival.** *Acta Neurol Scand* 1995, **91**(4):306-309.
 15. Hallevy C, Ifergane G, Kordysh E, Herishanu Y: **Spontaneous supratentorial intracerebral hemorrhage. Criteria for short-term functional outcome prediction.** *J Neurol* 2002, **249**(12):1704-1709.
 16. Cheung RT, Zou LY: **Use of the original, modified, or new intracerebral hemorrhage score to predict mortality and morbidity after intracerebral hemorrhage.** *Stroke* 2003, **34**(7):1717-1722.
 17. Shaya M, Dubey A, Berk C, Gonzalez-Toledo E, Zhang J, Caldito G, Nanda A: **Factors influencing outcome in intracerebral hematoma: a simple, reliable, and accurate method to grade intracerebral hemorrhage.** *Surg Neurol* 2005, **63**(4):343-348; discussion 348.
 18. Weimar C, Benemann J, Diener HC, German Stroke Study C: **Development and validation of the Essen Intracerebral Haemorrhage Score.** *J Neurol Neurosurg Psychiatry* 2006, **77**(5):601-605.
 19. Weimar C, Roth M, Willig V, Kostopoulos P, Benemann J, Diener HC: **Development and validation of a prognostic model to predict recovery following intracerebral hemorrhage.** *J Neurol* 2006, **253**(6):788-793.
 20. Pongvarin N, Suwanwela NC, Venketasubramanian N, Wong LK, Navarro JC, Bitanga E, Yoon BW, Chang HM, Alam SM, Asian Stroke Advisory P: **Grave prognosis on spontaneous intracerebral haemorrhage: GP on STAGE score.** *J Med Assoc Thai* 2006, **89** Suppl 5:S84-93.
 21. Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S, Padilla-Martinez JJ, Gonzalez-Cornejo S: **Grading scale for prediction of outcome in primary intracerebral hemorrhages.** *Stroke* 2007, **38**(5):1641-1644.
 22. Rost NS, Smith EE, Chang Y, Snider RW, Chanderraj R, Schwab K, FitzMaurice E, Wendell L, Goldstein JN, Greenberg SM *et al*: **Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score.** *Stroke* 2008,

39(8):2304-2309.

23. Cho DY, Chen CC, Lee WY, Lee HC, Ho LH: **A new Modified Intracerebral Hemorrhage score for treatment decisions in basal ganglia hemorrhage—a randomized trial.** *Crit Care Med* 2008, **36**(7):2151-2156.
24. Huang BR, Liao CC, Huang WH, Hsu YH, Hsu JC, Yen HC, Lin CL: **Prognostic factors of spontaneous intracerebral haemorrhage in haemodialysis patients and predictors of 30-day mortality.** *Intern Med J* 2008, **38**(7):568-574.
25. Chuang YC, Chen YM, Peng SK, Peng SY: **Risk stratification for predicting 30-day mortality of intracerebral hemorrhage.** *Int J Qual Health Care* 2009, **21**(6):441-447.
26. Weimar C, Ziegler A, Sacco RL, Diener HC, Konig IR, investigators V: **Predicting recovery after intracerebral hemorrhage—an external validation in patients from controlled clinical trials.** *J Neurol* 2009, **256**(3):464-469.
27. Stein M, Luecke M, Preuss M, Boeker DK, Joedicke A, Oertel MF: **Spontaneous intracerebral hemorrhage with ventricular extension and the grading of obstructive hydrocephalus: the prediction of outcome of a special life-threatening entity.** *Neurosurgery* 2010, **67**(5):1243-1251; discussion 1252.
28. Tshikwela ML, Longo-Mbenza B: **Spontaneous intracerebral hemorrhage: Clinical and computed tomography findings in predicting in-hospital mortality in Central Africans.** *J Neurosci Rural Pract* 2012, **3**(2):115-120.
29. Li YF, Luo J, Li Q, Jing YJ, Wang RY, Li RS: **A new simple model for prediction of hospital mortality in patients with intracerebral hemorrhage.** *CNS Neurosci Ther* 2012, **18**(6):482-486.
30. Ji R, Shen H, Pan Y, Wang P, Liu G, Wang Y, Li H, Zhao X, Wang Y, China National Stroke Registry i: **A novel risk score to predict 1-year functional outcome after intracerebral hemorrhage and comparison with existing scores.** *Crit Care* 2013, **17**(6):R275.
31. Zis P, Leivadeas P, Michas D, Kravaritis D, Angelidakis P, Tavernarakis A: **Predicting 30-day case fatality of primary inoperable intracerebral hemorrhage based on findings at the emergency department.** *J Stroke Cerebrovasc Dis* 2014, **23**(7):1928-1933.
32. Lei C, Wu B, Liu M, Zhang S, Yuan R: **Cerebral Amyloid Angiopathy-related Intracerebral Hemorrhage Score For Predicting Outcome.** *Curr Neurovasc Res* 2016, **13**(2):156-162.
33. Ho WM, Lin JR, Wang HH, Liou CW, Chang KC, Lee JD, Peng TY, Yang JT, Chang YJ, Chang CH *et al*: **Prediction of in-hospital stroke mortality in critical care unit.** *Springerplus* 2016, **5**(1):1051.
34. Safatli DA, Gunther A, Schlattmann P, Schwarz F, Kalff R, Ewald C: **Predictors of 30-day mortality in patients with spontaneous primary intracerebral hemorrhage.** *Surg Neurol Int* 2016, **7**(Suppl 18):S510-517.
35. Sembill JA, Gerner ST, Volbers B, Bobinger T, Lucking H, Kloska SP, Schwab S, Huttner HB, Kuramatsu JB: **Severity assessment in maximally treated ICH patients: The max-ICH score.** *Neurology* 2017, **89**(5):423-431.
36. Gupta VP, Garton ALA, Sisti JA, Christophe BR, Lord AS, Lewis AK, Frey HP, Claassen J, Connolly ES, Jr.: **Prognosticating Functional Outcome After Intracerebral Hemorrhage: The ICHOP Score.** *World Neurosurg* 2017, **101**:577-583.
37. 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**(3):837-845.
38. Geurts M, Macleod MR, van Thiel GJ, van Gijn J, Kappelle LJ, van der Worp HB: **End-of-life decisions in patients with severe acute brain injury.** *Lancet Neurol* 2014, **13**(5):515-524.
39. Morgenstern LB, Zahuranec DB, Sanchez BN, Becker KJ, Geraghty M, Hughes R, Norris G, Hemphill JC, 3rd: **Full medical support for intracerebral hemorrhage.** *Neurology* 2015, **84**(17):1739-1744.
40. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B *et al*: **Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage.** *N Engl J Med* 2013, **368**(25):2355-2365.
41. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI *et al*: **Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage.** *N Engl J Med* 2016, **375**(11):1033-1043.
42. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MD, Barer DH, investigators S: **Early surgery versus initial conservative treatment in patients with spontaneous supratentorial**

intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet* 2005, **365**(9457):387-397.

43. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, Investigators SI: **Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial.** *Lancet* 2013, **382**(9890):397-408.
44. Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, Mayo SW, Bistran-Hall AJ, Gandhi D, Mould WA *et al.*: **Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial.** *Lancet* 2019, **393**(10175):1021-1032.
45. Sprigg N, Flaherty K, Appleton JP, Al-Shahi Salman R, Bereczki D, Beridze M, Christensen H, Ciccone A, Collins R, Czulonkowska A *et al.*: **Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial.** *Lancet* 2018, **391**(10135):2107-2115.
46. Selim M, Foster LD, Moy CS, Xi G, Hill MD, Morgenstern LB, Greenberg SM, James ML, Singh V, Clark WM *et al.*: **Deferoxamine mesylate in patients with intracerebral haemorrhage (i-DEF): a multicentre, randomised, placebo-controlled, double-blind phase 2 trial.** *Lancet Neurol* 2019, **18**(5):428-438.
47. Collins FS, Varmus H: **A new initiative on precision medicine.** *N Engl J Med* 2015, **372**(9):793-795.

Figures

Figure 1

Predictive performance of ICH models with regard to mortality and poor functional outcome at 1-month, 3-month and 1-year after onset (n=1575)

Figure 2

Sensitivity analysis of ICH models with regard to poor functional outcome ($mRS \geq 3$) at 3-month and 1-year after onset ($n=1575$)

Supplementary Files

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