

# Intracerebral Hemorrhage Progression Score: A Novel Risk Score to Predict Neurological Deterioration after Intracerebral Hemorrhage

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Dear Sir:

Spontaneous intracerebral hemorrhage (ICH) accounts for approximately 20% of all strokes and is a leading cause of mortality and morbidity worldwide.<sup>1</sup> Despite advances in medical research, the treatment for ICH remains strictly supportive.<sup>2,3</sup> Efforts are ongoing to develop new targets for improving outcomes after ICH.<sup>4</sup>

In-hospital neurological deterioration affects approximately 10% to 30% of the patients with ICH,<sup>5-7</sup> which includes early and delayed neurological deterioration. Thus, preventing in-hospital neurological deterioration after ICH is a logical step and represents a promising approach to improve outcomes after ICH. Currently, no valid risk model is available to identify high-risk populations for neurological deterioration after ICH in routine clinical practice or clinical trials. In this study, we aimed to develop a risk score (ICH progression score) to predict in-hospital neurological deterioration after ICH using routinely collected variables at presentation.

The derivation and internal validation cohorts were obtained from the Beijing Registration of Intracerebral Hemorrhage.<sup>8</sup> External validation was based on the China National Stroke Registry<sup>9</sup> and the in-hospital medical complications after acute stroke (iMCAS) study.<sup>10</sup>

In this study, in-hospital neurological deterioration after ICH was defined as an episode in which a patient experienced a persistent increase in National Institutes of Health Stroke Scale

score  $\geq 4$ , a decline in Glasgow Coma Scale (GCS) score  $\geq 2$ , or death during hospitalization.

The baseline characteristics of the derivation cohort and the internal and external validation cohorts are presented in Table 1. Univariate and multivariate analyses for predictors of in-hospital neurological deterioration after ICH in the derivation cohort are shown in Supplementary Tables 1 and 2. To derive an integer value for each predictor, the  $\beta$  coefficients were multiplied by four and rounded to the closest integer. Finally, age, sex, medical history of diabetes mellitus and atrial fibrillation, GCS score, dysphagia, hematoma location, hamartoma volume, and blood glucose level were included in the ICH progression score. The ICH progression scores ranged from 0 to 32 (Table 2). The five-level risk categories were assigned in six-point increments. The rate of in-hospital neurological deterioration increased steadily with increasing ICH progression scores (Figure 1).

The predictive performance (area under the receiver operating characteristic curve [AUROC]) of the ICH progression score in the derivation ( $n=1,309$ ) and internal validation cohorts ( $n=655$ ) was 0.840 (95% confidence interval [CI], 0.813 to 0.867) and 0.845 (95% CI, 0.808 to 0.881) (Supplementary Table 3). The predicted and observed risks of in-hospital neurological deterioration after ICH were in close agreement according to the 10 deciles of predicted risk in the derivation ( $r=0.96$ ,  $P<0.001$ ) and internal validation ( $r=0.95$ ,  $P<0.001$ ) cohorts (Supplementary Figure 1A and B). In external validation cohort-1 ( $n=3,255$ ) and -2 ( $n=314$ ), the ICH progression score

**Table 1.** Baseline characteristics

Characteristic	Overall cohort (n=1,964)	Derivation cohort (n=1,309)	Internal validation cohort (n=655)	<i>P</i> *	External validation cohort-1 (n=3,255)	External validation cohort-2 (n=314)
Age (yr)	56.8±14.4	56.8±14.6	56.9±13.9	0.19	62.1±13.1	54.7±14.2
Male sex	1,327 (67.6)	866 (67.7)	441 (67.3)	0.87	1,995 (61.3)	221 (70.4)
Onset to hospital (hr)	4.0 (1.90–11.0)	4.0 (1.92–11.0)	3.9 (1.97–11.0)	0.76	10.0 (2.41–29.3)	78 (24–96)
Risk factors						
Hypertension	1,367 (69.6)	908 (69.4)	459 (70.1)	0.75	2,210 (67.9)	208 (66.9)
Diabetes mellitus	289 (14.7)	196 (15.0)	93 (14.2)	0.65	290 (8.9)	41 (13.1)
Dyslipidemia	184 (9.4)	109 (8.3)	75 (11.5)	0.03	230 (7.1)	36 (11.5)
Atrial fibrillation	30 (1.5)	20 (1.5)	10 (1.5)	0.99	54 (1.7)	10 (3.2)
History of stroke/TIA	309 (15.7)	208 (15.9)	101 (15.4)	0.79	889 (27.3)	48 (15.3)
Myocardial infarction	38 (1.9)	20 (1.5)	18 (2.7)	0.06	204 (6.3)	26 (8.3)
Heart failure	8 (0.4)	6 (0.5)	2 (0.3)	0.62	19 (0.6)	3 (1.0)
Current smoker	628 (32.0)	403 (30.8)	225 (34.4)	0.11	1,228 (37.7)	120 (38.2)
Alcohol consumption	716 (36.5)	470 (35.9)	246 (37.6)	0.47	367 (11.3)	166 (52)
Pre-admission anticoagulation	21 (1.1)	14 (1.1)	7 (1.1)	0.99	32 (1.0)	5 (1.6)
Pre-admission antiplatelet	277 (14.1)	181 (13.8)	96 (14.7)	0.62	291 (8.9)	25 (7.9)
Pre-stroke mRS score	0 (0–0)	0 (0–0)	0 (0–0)	0.36	0 (0–0)	0 (0–0)
Admission NIHSS score	11 (3–21)	11 (3–21)	11 (4–21)	0.89	9 (3–16)	4 (1–10)
Admission GCS score	14 (8–15)	14 (8–15)	14 (9–15)	0.26	14 (9–15)	15 (14–15)
Admission dysphagia	666 (33.9)	441 (33.7)	225 (34.4)	0.77	220 (6.8)	24 (7.6)
Admission SBP (mm Hg)	165 (147–186)	164 (146–186)	167 (150–187)	0.10	160 (147–180)	158 (140–171)
Admission DBP (mm Hg)	96 (82–109)	95 (81–108)	98 (84–110)	0.10	95 (87–106)	93 (83–104)
Hematoma location				0.91		
Supratentorial ICH	1,752 (89.2)	1,167 (89.2)	585 (89.3)		2,862 (87.9)	282 (89.8)
Infratentorial ICH	212 (10.8)	142 (10.8)	70 (10.7)		393 (12.1)	32 (10.2)
Hematoma volume (cm <sup>3</sup> )	15.8 (6.0–38.6)	15.5 (5.9–37.0)	16.7 (6.6–40.0)	0.20	12.6 (5.5–28.0)	15 (10–30)
Intraventricular extension	655 (33.4)	430 (32.8)	225 (34.4)	0.51	962 (29.6)	109 (34.7)
Subarachnoid extension	264 (13.4)	182 (13.9)	82 (12.5)	0.39	190 (5.8)	30 (9.6)
Admission WBC (10 <sup>9</sup> /L)	9.79 (7.35–13.0)	9.68 (7.29–12.9)	10.0 (7.56–13.0)	0.26	8.7 (6.7–11.3)	8.83 (7.34–11.0)
Admission glucose (mmol/L)	7.31 (6.08–9.20)	7.26 (6.05–9.10)	7.49 (6.13–9.40)	0.20	6.3 (5.7–7.5)	5.04 (4.37–6.07)
Admission creatinine (μmol/L)	63.4 (52.7–77.0)	63.1 (52.3–76.6)	63.9 (53.8–77.0)	0.17	77.0 (62.0–92.0)	61.7 (52.1–72.1)
Etiology diagnosis				0.86		
Primary ICH	1,785 (90.9)	1,193 (91.1)	592 (90.4)		-	277 (88.2)
Secondary ICH	159 (8.1)	103 (7.3)	56 (8.5)		-	34 (10.8)
Primary IVH	20 (1.0)	13 (1.0)	7 (1.1)		-	...
Withdrawal of medical care	139 (7.1)	99 (7.6)	40 (6.1)	0.24	404 (12.4)	21 (6.7)
Surgical treatment	366 (18.6)	251 (19.2)	115 (17.6)	0.39	206 (6.3)	43 (13.7)
Length of hospital stay	16 (8–22)	16 (9–22)	16 (8–22)	0.99	18 (11–26)	14 (12–18)
In-hospital neurological deterioration	373 (19.0)	250 (19.1)	123 (18.8)	0.87	476 (14.6)	18 (5.7)

Values are presented as mean±standard deviation, median (interquartile range), or number (%).

TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; WBC, white cell count; IVH, intraventricular hemorrhage.

\**P* denotes a significant test between the derivation and internal validation cohorts.

showed good discrimination with an AUROC of 0.810 (95% CI, 0.789 to 0.832) and 0.831 (95% CI, 0.696 to 0.966) (Supplementary Table 3). The plot of observed versus the predicted risk of in-hospital neurological deterioration after ICH showed a high correlation between observed and predicted risk in the external validation cohort-1 ( $r=0.93$ ,  $P<0.001$ ) and -2 ( $r=0.91$ ,  $P<0.001$ ) (Supplementary Figure 1C and D). The Hosmer–Lemeshow test was not significant in the tested cohorts (all  $P>0.05$ ). The Snell R-square and Nagelkerke R-square values of the Hosmer–Lemeshow goodness-of-fit test are shown in Supplementary Table 4. In the sensitivity analysis, the ICH progression

score showed similar good discrimination in several subgroups of patients with different clinical characteristics (AUROC range, 0.772 to 0.883) (Supplementary Table 5).

To the best of our knowledge, this is the first study to develop a risk score to predict in-hospital neurological deterioration after ICH. The ICH progression score is unique as it was derived from a large, multicenter, and prospective ICH cohort, which included consecutive patients with ICH, was outside of clinical trials, and was more reflective of real-world clinical practice. Additionally, the ICH progression score consists of factors that are readily available at the presentation. Using a simple score, it can easily be applied in clinical practice or clinical trials.

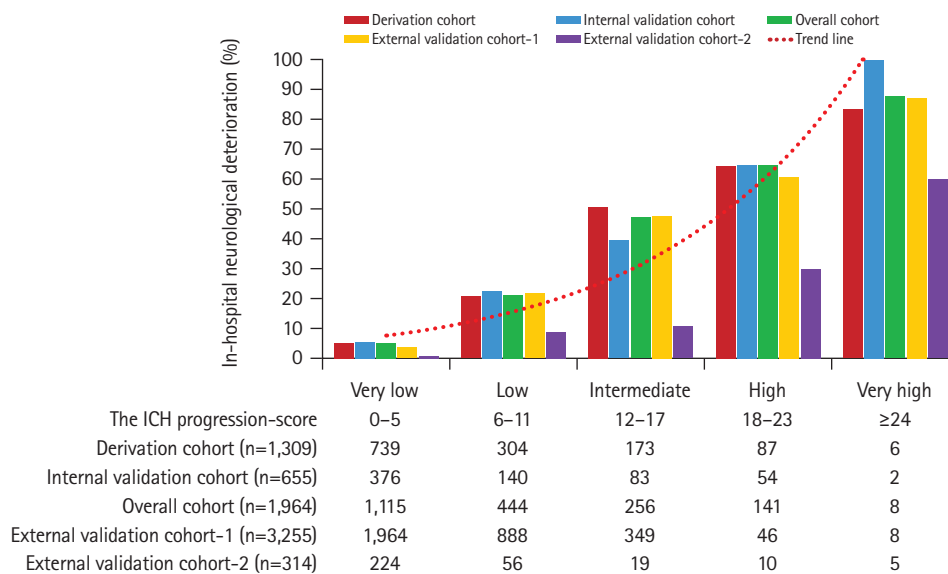
The predictive performance of the ICH progression score was shown to be accurate in risk stratification and outcome prediction in the derivation, internal, and external validation cohorts (AUROC range, 0.810 to 0.845), respectively. In addition, in the sensitivity analysis, the ICH progression score was valid in several prespecified subgroups of patients with different clinical characteristics.

In-hospital neurological deterioration, whether early or late, was significantly associated with short- and long-term death, poor functional outcome, cognition, and quality of life after ICH.<sup>5-7</sup> Using the ICH progression score, clinicians can identify patients at high risk of developing in-hospital neurological deterioration after ICH. Early prediction of in-hospital neurological deterioration after ICH would help identify vulnerable patients and implement tailored preventive strategies. In addition, it could be used as a selection criterion in nonrandomized studies to control for case-mix variation and in controlled studies. The

**Table 2.** Scoring system of the intracerebral hemorrhage progression score

Item	Score
Age ≥80 years	2
Male sex (yes)	2
History of diabetes mellitus (yes)	2
History of atrial fibrillation (yes)	7
Admission GCS score ≤8 (yes)	6
Dysphagia on admission (yes)	3
Infratentorial hematoma location (yes)	2
Hematoma volume (mL)	
Supratentorial ≤39 or infratentorial ≤4	0
Supratentorial 40–69 or infratentorial 5–10	4
Supratentorial ≥70 or infratentorial ≥11	5
Blood glucose >11.1 mmol/L	3
<b>Total</b>	<b>32</b>

GCS, Glasgow Coma Scale.



**Figure 1.** In-hospital neurological deterioration after intracerebral hemorrhage (ICH) according to the ICH progression score. The figure shows that the proportion of in-hospital neurological deterioration after ICH increased steadily with higher ICH progression scores in the derivation (n=1,309), internal validation (n=655), and two external valuation cohorts (n=3,255 and n=314).

potential etiology of in-hospital neurological deterioration after ICH might be heterogeneous and dynamically changing. For example, at the early stage after ICH (e.g., within 24 hours after onset), hematoma expansion, intraventricular hemorrhage, and rapidly increased intracranial pressure might be potential causes of neurological deterioration, and at the later stage after ICH (e.g., 24 hours to 14 days after onset), pre-hematoma edema, hydrocephalus, infection, and other medical complications might cause the condition of ICH patients to worsen. Based on the potential risk and etiology of in-hospital neurological deterioration after ICH, clinicians should apply tailored preventive and treatment strategies.

Our study had some limitations. First, we cannot rule out the possibility that additional baseline variables (unmeasured confounders) might have an impact on the risk of in-hospital neurological deterioration after ICH. Second, our study included only hospitalized patients, and patients who died in the emergency department or were treated in outpatient clinics were not included. Finally, both the derivation and validation cohorts were derived from the Asian population.

In summary, the ICH progression score is a valid clinical grading scale for predicting in-hospital neurological deterioration after ICH at presentation and would be a useful tool for personalized care and clinical trials in the prevention of in-hospital neurological deterioration after ICH.

The study protocol was approved by the Institutional Review Board (IRB) of the Beijing Tiantan Hospital (KY2014-023-02). Written informed consent from patients or their legal representatives.

## Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2022.00619>.

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**Supplementary Table 1.** Univariable predictor of in-hospital neurological deterioration after ICH in the derivation cohort (n=1,309)

Variable	Increment/categories	OR	95% CI	P
<b>Demographics</b>				
Age (yr)	1 Year increase	1.013	1.005–1.021	<0.001
Male sex (yes)	Male vs. Female	1.303	1.016–1.672	0.030
Onset to hospital (hr)	1 Hour increase	1.000	1.000–1.000	0.650
<b>Risk factors</b>				
Hypertension	Yes vs. No	1.258	0.924–1.718	0.140
Diabetes mellitus	Yes vs. No	1.723	1.213–2.447	0.002
Dyslipidemia	Yes vs. No	0.948	0.571–1.572	0.830
Atrial fibrillation	Yes vs. No	2.905	1.387–6.084	0.005
History of stroke/TIA	Yes vs. No	1.428	1.069–1.908	0.020
Myocardial infarction	Yes vs. No	0.962	0.420–2.203	0.920
Heart failure	Yes vs. No	1.424	0.286–7.084	0.660
Current smoker	Yes vs. No	1.042	0.819–1.326	0.730
Alcohol consumption	Yes vs. No	1.120	0.888–1.413	0.330
Pre-admission anticoagulation	Yes vs. No	1.337	0.487–3.674	0.570
Pre-admission antiplatelet	Yes vs. No	1.545	1.146–2.081	0.004
Pre-stroke mRS score	1 Grade increase	1.110	0.975–1.264	0.110
Admission NIHSS score	1 Point increase	1.105	1.092–1.118	<0.001
Admission GCS score	1 Point decrease	1.311	1.272–1.350	<0.001
Admission dysphagia	Yes vs. No	5.009	3.942–6.365	<0.001
Admission SBP	1 mm Hg increase	1.015	1.011–1.019	<0.001
Admission DBP	1 mm Hg increase	1.009	1.003–1.015	0.004
Hematoma location	Infratentorial vs. Supratentorial	1.815	1.314–2.506	<0.001
Hematoma volume	1 mL increase	1.024	1.020–1.028	<0.001
Intraventricular extension	Yes vs. No	1.884	1.496–2.371	<0.001
Subarachnoid extension	Yes vs. No	2.278	1.708–3.040	<0.001
Admission WBC	1×10 <sup>9</sup> /L increase	1.167	1.138–1.196	<0.001
Admission glucose	1×mmol/L increase	1.136	1.100–1.173	<0.001
Admission creatinine	1×μmol/L increase	1.000	1.000–1.001	0.350
<b>Etiology diagnosis</b>				
Primary ICH	Primary ICH vs. IVH	0.969	0.322–2.916	0.950
Secondary ICH	Secondary ICH vs. IVH	0.609	0.186–1.997	0.410
Surgical treatment	Yes vs. No	1.926	1.481–2.505	<0.001

ICH, intracerebral hemorrhage; OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white cell count; IVH, intraventricular hemorrhage.

**Supplementary Table 2.** Multivariable predictors of in-hospital neurological deterioration after ICH in the derivation cohort (n=1,309)

Variable	$\beta$ -coefficients	SE	Adjusted OR*	95% CI	P
Model intercept	-4.719				
Age (1 year increase)	0.012	0.005	1.012	1.001–1.023	0.030
Male sex	0.389	0.167	1.476	1.064–2.048	0.020
History of diabetes mellitus (yes)	0.451	0.187	1.570	1.089–2.265	0.020
History of atrial fibrillation (yes)	1.832	0.484	6.244	2.418–16.12	<0.001
GCS (1 point decrease)	0.161	0.020	1.175	1.129–1.223	<0.001
Dysphagia on admission (yes)	0.804	0.160	2.234	1.632–3.059	<0.001
Hematoma location (infratentorial)	0.524	0.226	1.688	1.084–2.630	0.020
Hematoma volume (1 ml increase)	0.013	0.002	1.013	1.008–1.017	<0.001
Blood glucose (per 1 mmol/L increase)	0.069	0.016	1.071	1.037–1.106	<0.001

ICH, intracerebral hemorrhage; SE, standard error; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale.

\*Multivariable logistic regression adjusted for demographics, time from onset to hospitalization, stroke risk factors, pre-admission antithrombotic medications, pre-stroke dependence, admission National Institutes of Health Stroke Scale and GCS scores, blood pressure, hematoma volume, hematoma location, intraventricular and subarachnoid extension, etiology, withdrawal of medical care, and blood glucose levels.

**Supplementary Table 3.** Predictive performance of ICH progression score with regard to in-hospital neurological deterioration after ICH

Variable	AUROC	95% CI	P*	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
In the derivation cohort (n=1,309)	0.840	0.813–0.867	<0.0001	0.533	8	0.752	0.781	0.448	0.930
In the internal validation cohort (n=655)	0.845	0.808–0.881	<0.0001	0.546	8	0.756	0.790	0.454	0.933
In the overall cohort (n=1,964)	0.841	0.820–0.861	<0.0001	0.537	8	0.753	0.783	0.450	0.931
In the external validation cohort (n=3,255)	0.810	0.789–0.832	<0.0001	0.474	8	0.733	0.741	0.326	0.942
In the external validation cohort (n=314)	0.831	0.696–0.966	<0.0001	0.659	8	0.786	0.873	0.224	0.989

ICH, intracerebral hemorrhage; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

\*P indicated significance test of AUROC. Null hypothesis is that true area=0.5.

**Supplementary Table 4.** Calibration of the ICH progression score with regard to in-hospital neurological deterioration after ICH

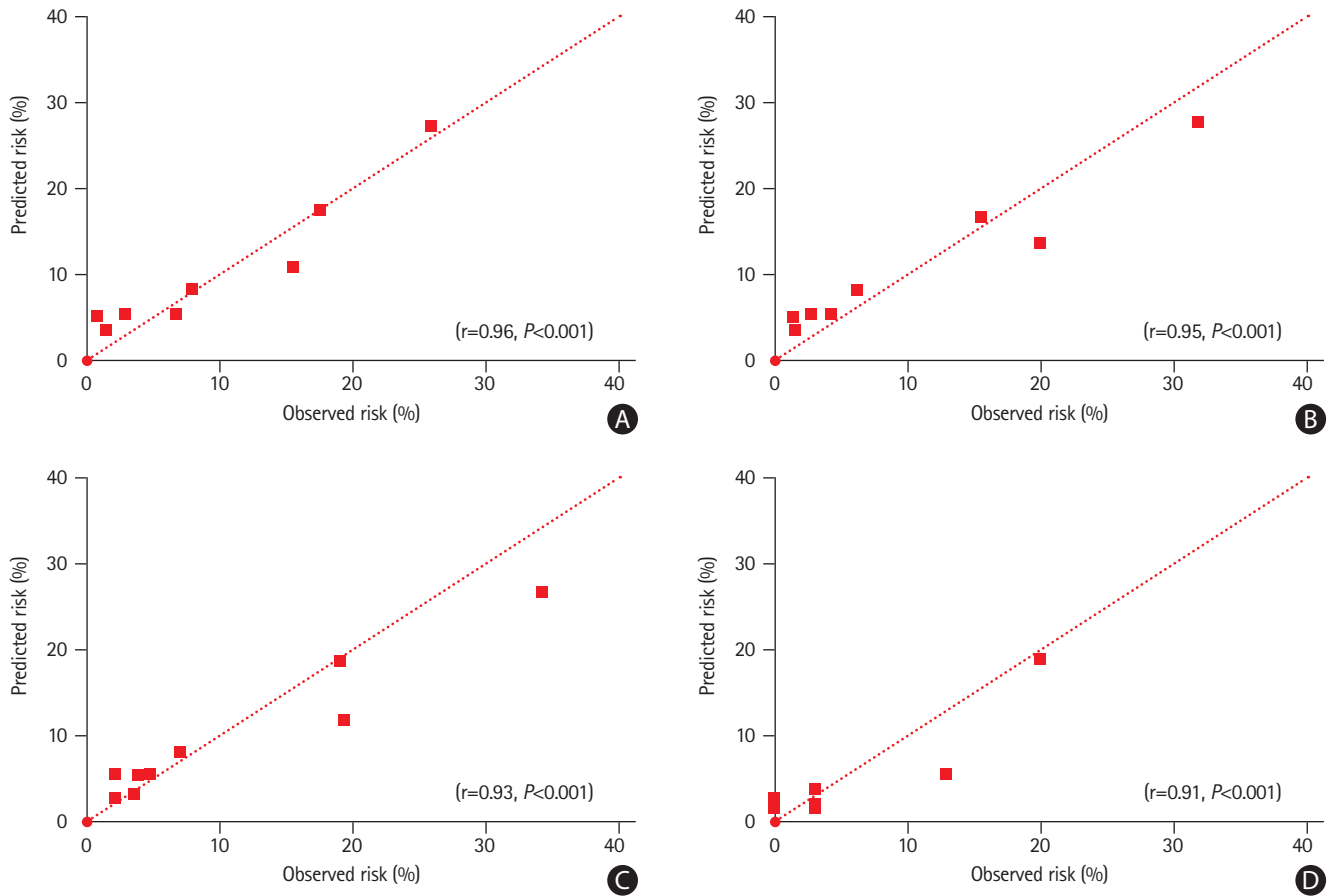
Cohort	Goodness of fit test		
	P	Cox and Snell R <sup>2</sup>	Nagelkerke R <sup>2</sup>
Derivation cohort (n=1,309)	0.16	0.213	0.341
Internal validation cohort (n=655)	0.10	0.222	0.358
External validation cohort-1 (n=3,255)	0.09	0.158	0.279
External validation cohort-2 (n=314)	0.15	0.095	0.195

ICH, intracerebral hemorrhage.

**Supplementary Table 5.** Sensitivity analysis of ICH progression score in the Beijing Registration of Intracerebral Hemorrhage (n=1,964)

Subgroups	AUROC	95% CI	P
<b>Age (yr)</b>			
<80 (n=1,847)	0.843	0.820–0.865	<0.001
≥80 (n=117)	0.815	0.728–0.902	<0.001
<b>Sex</b>			
Male (n=1,327)	0.832	0.805–0.809	<0.001
Female (n=637)	0.857	0.819–0.895	<0.001
<b>History of hypertension</b>			
Yes (n=597)	0.846	0.821–0.872	<0.001
No (n=1,367)	0.830	0.788–0.871	<0.001
<b>History of diabetes mellitus</b>			
Yes (n=289)	0.850	0.803–0.897	<0.001
No (n=1675)	0.838	0.814–0.863	<0.001
<b>Pre-antithrombotic agents</b>			
Yes (n=294)	0.796	0.736–0.855	<0.001
No (n=1,670)	0.850	0.826–0.873	<0.001
<b>Hematoma location</b>			
Supratentorial (n=1,752)	0.834	0.810–0.858	<0.001
Infratentorial (n=212)	0.874	0.827–0.921	<0.001
<b>Hematoma volume (mL)</b>			
<15 (n=880)	0.811	0.757–0.865	<0.001
≥15 (n=1,084)	0.792	0.760–0.823	<0.001
<b>Intraventricular extension</b>			
Yes (n=655)	0.819	0.784–0.855	<0.001
No (n=1,309)	0.845	0.816–0.874	<0.001
<b>Subarachnoid extension</b>			
Yes (n=264)	0.772	0.713–0.831	<0.001
No (n=1,700)	0.846	0.822–0.871	<0.001
<b>Etiology of ICH</b>			
Primary ICH (n=1,785)	0.843	0.820–0.865	<0.001
Secondary ICH (n=159)	0.831	0.731–0.932	<0.001
<b>Surgical treatment</b>			
Yes (n=366)	0.791	0.730–0.852	<0.001
No (n=1,598)	0.883	0.860–0.906	<0.001
<b>Length of hospital stay (day)</b>			
≤7 (n=443)	0.842	0.805–0.879	<0.001
>7 (n=1,521)	0.784	0.747–0.822	<0.001
<b>Withdraw of medical care</b>			
Yes (n=139)	0.770	0.669–0.871	<0.001
No (n=1,825)	0.845	0.820–0.869	<0.001

ICH, intracerebral hemorrhage; AUROC, area under the receiver operating characteristic curve; CI, confidence interval.



**Supplementary Figure 1.** Plot of observed versus predicted risk of neurological deterioration after intracerebral hemorrhage (ICH) in the derivation and validation cohorts. Plot of observed versus predicted risk of in-hospital neurological deterioration after ICH in the derivation, internal, and external validation cohorts according to 10 deciles of predicted risk. Overall, there was a very high correlation between the observed and predicted risks in the derivation cohort (A) ( $n=1,309$ ;  $r=0.96$ ;  $P<0.001$ ), internal validation cohort (B) ( $n=655$ ;  $r=0.95$ ;  $P<0.001$ ), external validation cohort-1 (C) ( $n=3,255$ ;  $r=0.93$ ,  $P<0.001$ ), and external validation cohort-2 (D) ( $n=314$ ;  $r=0.91$ ,  $P<0.001$ ), which indicated excellent calibration.