Original Article

Comparison of clinical scores for predicting stroke-associated pneumonia after intracerebral hemorrhage (ICH): potential tools for personalized care and clinical trials for ICH

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Background: This study aimed to systematically compare the discrimination and calibration of 5 clinical scores for stroke-associated pneumonia (SAP) after intracerebral hemorrhage (ICH).

Methods: We derived a validation cohort from the Beijing Registration of Intracerebral Hemorrhage. SAP was then diagnosed according to the Center for Disease Control and Prevention's criteria for hospital-acquired pneumonia. The area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow goodness-of-fit test were used to assess model discrimination and calibration.

Results: A total of 1964 patients were enrolled in the study. The mean age was 56.8±14.4 years, and 67.6% were male. The median National Institutes of Health Stroke Scale (NIHSS) score at admission was 11 [interquartile range (IQR), 3–21], while the median length of stay (LOS) was 16 days (IQR, 8–22 days). A total of 575 (29.2%) patients were diagnosed with in-hospital SAP after ICH. The AUROC of the 5 clinical scores ranged from 0.732 to 0.800. In comparing these scores, we found that the ICH-associated pneumonia score-B (ICH-APS-B 0.800; 95% CI: 0.780–0.820; P<0.001) showed a statistically better discrimination than did the other risk models (all P<0.001). Furthermore, all clinical scores performed better in patients with an LOS >72 h. The ICH-APS-B (0.827; 95% CI: 0.806–0.848; P<0.001) still showed statistically better discrimination than did the other risk models in patients with an LOS longer than 72 hours. The Hosmer-Lemeshow test also revealed that the ICH-APS-B. had the largest Cox and Snell R2 result for in-hospital SAP after ICH.

Conclusions: Among the 5 models for predicting SAP after ICH, the ICH-APS-B showed the best predictive performance, suggests it may be a useful tool for implementing the personalized care of patients and conducting clinical trials of SAP after ICH.

Keywords: Intracerebral hemorrhage (ICH); stroke-associated pneumonia (SAP); risk score; discrimination; calibration

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Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for approximately 15–20% of all strokes and is one of the leading causes of mortality and morbidity worldwide (1,2). Despite advances being made in medical knowledge, treatment for ICH remains strictly supportive, with few evidence-based interventions currently available (3,4).

Stroke-associated pneumonia (SAP) is a common medical complication after stroke and has a significant impact on patient outcomes. Evidence has shown that SAP not only increases the length of stay (LOS) in hospital and medical costs, but is also an important risk factor for poststroke mortality and morbidity (5). In addition, pneumonia has been found to increase the risk of several non-pneumonia-related medical complications, such as deep vein thrombosis, gastrointestinal bleeding, and atrial fibrillation (6). In a previous study, SAP was also found to be more common in patients with ICH than in those with acute ischemic stroke (AIS) (6,7). These data point to the need for more aggressive SAP prophylaxis among patients with ICH.

Several clinical scores have been developed for predicting SAP after ICH, such as the Veterans Health Administration (VHA) risk score (8), intracerebral hemorrhage-associated pneumonia score (ICH-APS; both ICH-APS-A and ICH-ASP-B) (9), the integer-based pneumonia risk score (ISAN) (10), the ACCD4 (age ≥75 years =1; congestive heart failure =1; dysarthria =1; dysphagia =4) (11), and the Preventive Antibiotics in Stroke Study (PASS) score (12). In the current study, the ISAN (10), ACCD4 (11), and PASS (12) scores were used for ICH patients in the derivation cohort, while the ICH-APS-A (9) and ICH-APS-B (9) scores were used exclusively for the ICH validation cohort (Tables S1,S2). Although a few of these ICH risk models have been internally or externally validated, none are universally accepted or consistently used in routine clinical practice or clinical research. In addition, with many grading systems available, it is becoming increasingly difficult for clinicians and researchers to determine which risk model provides the optimal predictability and reliability in clinical practice and clinical trials. Therefore, we believe it is necessary to conduct a head-to-head comparison of these models in an independent cohort.

In this study, we aimed to systematically compare the discrimination and calibration of 5 clinical scores for in-hospital SAP after ICH following the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) guideline (13,14). We present the following article in accordance with the Standards for Reporting Diagnostic Accuracy Studies (STARD) reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-4046/rc).

Methods

Validation cohort

This was a multicenter, prospective, observational cohort study, with the validation cohort being derived from the Beijing Registration of Intracerebral Hemorrhage (15). A total of 13 hospitals in the Beijing area participated. To be eligible, patients had to meet the following criteria: (I) age 18 years or older; (II) hospitalized with a primary diagnosis of spontaneous ICH and confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI); (III) direct admission to hospital from a physician's clinic or emergency department; and (IV) written informed consent from patients or their legal representatives. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board (IRB) of the Beijing Tiantan Hospital (No. KY2014-023-02), and informed consent was given by all patients.

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: (I) demographics; (II) time from onset to hospitalization (hours); (III) stroke risk factors, including hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of stroke/transient ischemic attack (TIA), myocardial infarction, heart failure, and current smoking or alcohol consumption; (IV) prestroke modified Rankin Scale (mRS) score; (V) preadmission antithrombotic medications; (VI) admission stroke severity based on the National Institutes of Health Stroke Scale (NIHSS) score and the Glasgow Coma Scale (GCS) score; (VII) admission blood pressure (mmHg); (VIII) admission laboratory tests; (IX) neuroimaging variables, including hematoma volume (measured using the ABC/2 method) (16), hematoma location (supratentorial or infratentorial ICH), intraventricular extension (presence or absence), and subarachnoid extension

(presence or absence); (X) etiology diagnosis (primary or secondary ICH); (XI) surgical treatment (craniotomy evacuation, minimally invasive surgical therapy, or brain ventricle puncture and drainage); (XII) withdrawal of medical care; and (XIII) LOS in hospital.

Diagnosis of SAP

In-hospital SAP was diagnosed by the treating physician according to the Center for Disease Control and Prevention's criteria for hospital-acquired pneumonia (17,18). This included a basis of clinical and laboratory indices of respiratory tract infection (fever, cough, new purulent sputum, and auscultatory respiratory crackles) and was supported by typical chest X-ray findings. In this study, the occurrence of prestroke pneumonia was not considered.

Statistical analysis

For our statistical analysis, categorical variables are summarized as proportions, while continuous variables are summarized with mean and SD, or median and interquartile range (IQR). Chi-square or Fisher's exact test was used to compare categorical variables, and a Mann-Whitney test or independent *t*-test was employed to compare continuous variables between groups. Through a systematic search, we identified 6 clinical scores which could be used to predict SAP after ICH. However, the VHA score (8) could not be validated in the study as we did not have information on "found down at symptom onset". This left us with 5 clinical scores for our study: ICH-APS-A (9), ICH-ASP-B (9), ISAN (10), ACCD4 (11), and PASS (12). Discrimination was assessed by calculating the area under the receiver operating characteristic curve (AUROC) (13,14). Pairwise AUROC was compared with Delong's method (19). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at each risk model's maximum Youden index. Calibration, on the other hand, was evaluated using a Hosmer-Lemeshow goodness-of-fit test, and observed versus predicted risk was plotted according to 10 deciles of the predicted risk. We were then able to calculate the Cox and Snell R^2 and Nagelkerke R^2 (13,14). As the Hosmer-Lemeshow test has been shown to be overly sensitive (20), we also used Pearson correlation coefficient to calculate the observed and predicted risk. All tests were 2-tailed, and statistical significance was determined at a P level of .05. Statistical analysis was conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA), SPSS 26.0 (IBM Corp., Armonk, NY, USA), and MedCalc 12.3 (MedCalc Software Ltd., Ostend, Belgium) software.

Results

Patient characteristics

From December 2014 to September 2016, a total of 1964 patients were enrolled in the Beijing Registration of Intracerebral Hemorrhage. Their clinical characteristics are shown in *Table 1*. The mean age was 56.8±14.4 years, and 67.6% were male. The median time from onset to hospitalization was 4.0 h (IQR, 1.90–11.1 h), and the median NIHSS and GCS score on admission was 11 (IQR, 3–21) and 14 (IQR, 8–15), respectively. The median hematoma volume on CT was 15.8 cm^3 (IQR, 6.0–38.6 cm^3), while the median LOS was 16 days (IQR, 8–22 days). A total of 575 (29.2%) patients were diagnosed with in-hospital SAP after ICH. Compared to patients without in-hospital SAP, those with in-hospital SAP after ICH were older and had a higher proportion of dysphagia, dysarthria, hematoma intraventricular extension, and subarachnoid extension. Furthermore, they had received surgical treatment and had a higher NIHSS score (at admission), blood pressure, blood glucose level, and hematoma volume, as well as a longer LOS (*Table 1*).

LOS and in-hospital SAP after ICH

Previous studies have shown that predicting SAP with a clinical score is more effective for patients who survive 48–72 h after ICH. For this reason, we performed a sensitivity analysis by LOS. Patient characteristics stratified by LOS (≤72 *vs.* >72 h) are shown in *Table 2*. Compared to patients with an LOS >72 h, those with an LOS ≤72 h had a significantly higher NIHSS score (P<0.001) upon admission, a lower GCS score (P<0.001), and a larger hematoma volume (P<0.001). However, the proportion of in-hospital SAP between the 2 groups was not statistically significant (30.2% *vs.* 29.2%; P=0.75). It was also found that patients with an LOS ≤72 h had a significantly higher rate of in-hospital mortality (40.6% *vs.* 7.4%; P<0.001) and withdrawal of medical care (18.4% *vs.* 5.7%; P<0.001; *Table 2*).

Comparison of model discrimination for in-hospital SAP

Figure 1 shows the discrimination of the 5 clinical scores regarding in-hospital SAP after ICH. The AUROC of

Table 1 Baseline characteristics

Variable	Overall (n=1,964)	Without SAP (n=1,389)	With SAP (n=575)	P value
Demographics				
Age, years	56.8±14.4	55.9±14.1	59.0±14.6	<0.001
Gender (male), n (%)	1,327 (67.6)	925 (66.6)	402 (69.9)	0.16
Onset to hospital (h), median (IQR)	4.0 (1.90–11.0)	4.13 (1.98–12.8)	3.45 (1.82–8.00)	0.001
Risk factors, n (%)				
Hypertension	1,367 (69.6)	955 (68.8)	412 (71.7)	0.22
Diabetes mellitus	289 (14.7)	205 (14.8)	84 (14.6)	1.00
Dyslipidemia	184 (9.4)	138 (9.9)	46 (8.0)	0.20
Atrial fibrillation	30 (1.5)	19 (1.4)	11 (1.9)	0.42
History of stroke/TIA	309 (15.7)	199 (14.3)	110 (19.1)	0.01
Myocardial infarction	38 (1.9)	25 (1.8)	13 (2.3)	0.47
Heart failure	8 (0.4)	5 (0.4)	3 (0.5)	0.70
Current smoker	628 (32.0)	421 (30.3)	207 (36.0)	0.02
Alcohol consumption	716 (36.5)	500 (36.0)	216 (37.6)	0.53
Preadmission anticoagulation, n (%)	21 (1.1)	13 (0.9)	8 (1.4)	0.46
Preadmission antiplatelet, n (%)	277 (14.1)	178 (12.8)	99 (17.2)	0.01
Preadmission statins, n (%)	113 (5.8)	72 (5.2)	41 (7.1)	0.11
Prestroke mRS score, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.02
Admission NIHSS score, median [IQR]	11 [3–21]	8 [2–15]	20 [12–27]	<0.001
Admission GCS score, median [IQR]	14 [8–15]	14 [12–15]	9 [6–13]	<0.001
Admission dysphagia, n (%)	666 (33.9)	286 (20.6)	380 (66.1)	<0.001
Admission dysarthria, n (%)	918 (46.7)	599 (43.1)	319 (55.5)	<0.001
Admission SBP (mmHg), median [IQR]	165 [147–186]	161 [145–182]	173 [150–191]	<0.001
Admission DBP (mmHg), median [IQR]	96 [82–109]	95 [81–108]	98 [84–110]	0.009
Admission WBC, 10^9/L, median (IQR)	9.79 (7.35–13.0)	9.14 (7.03–11.9)	11.5 (8.30–14.7)	<0.001
Admission glucose (mmol/L), median (IQR)	5.85 (4.89–7.39)	5.54 (4.72–6.93)	6.57 (5.53–8.14)	<0.001
Admission creatinine (μmol/L), median (IQR)	63.4 (52.7–77.0)	63.1 (52.9–76.5)	63.8 (52.0–77.1)	0.89
Hematoma location, n (%)				0.17
Supratentorial ICH	1,752 (89.2)	1,248 (89.8)	504 (87.7)	
Infratentorial ICH	212 (10.8)	141 (10.2)	71 (12.3)	
Hematoma volume (cm^3), median (IQR)	15.8 (6.0–38.6)	12.0 (5.0–28.1)	30.0 (12.8–59.3)	<0.001
Intraventricular extension, n (%)	655 (33.4)	368 (26.5)	287 (49.9)	<0.001
Subarachnoid extension, n (%)	264 (13.4)	152 (10.9)	112 (19.9)	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Overall (n=1,964)	Without SAP (n=1,389)	With SAP (n=575)	P value
Etiology diagnosis, n (%)				0.61
Primary ICH	1,785 (90.9)	1,259 (90.6)	526 (91.5)	
Secondary ICH	159 (8.1)	117 (8.4)	42 (7.3)	
Primary IVH	20 (1.0)	13 (0.9)	7 (1.2)	
Withdrawal of medical care, n (%)	139 (7.1)	86 (6.2)	53 (9.2)	0.02
Surgical treatment, n (%)	366 (18.6)	159 (11.4)	207 (36.0)	<0.001
Length of hospital stay, median [IQR]	16 [8–22]	15 [8–20]	19 [8–29]	<0.001

SAP, stroke-associated pneumonia; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale score; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; IVH, intraventricular hemorrhage; TIA, transient ischemic stroke.

Table 2 Baseline characteristics stratified by length of stay

Variable	Overall (n=1,964)	LOS ≤72 h (n=212)	LOS >72 h (n=1,752)	P value
Demographics				
Age (years)	56.8±14.4	57.1±13.3	56.7±14.4	0.73
Gender (male), n (%)	1,327 (67.6)	145 (68.4)	1,182 (67.5)	0.82
Onset to hospital (h), median (IQR)	4.0 (1.90–11.0)	4.01 (1.92–12.5)	3.28 (1.98–5.96)	<0.001
Risk factors, n (%)				
Hypertension	1,367 (69.6)	152 (71.7)	1,215 (69.3)	0.53
Diabetes mellitus	289 (14.7)	34 (16.0)	255 (14.6)	0.53
Dyslipidemia	184 (9.4)	22 (10.4)	162 (9.2)	0.62
Atrial fibrillation	30 (1.5)	4 (1.9)	26 (1.5)	0.41
History of stroke/TIA	309 (15.7)	27 (12.7)	282 (16.1)	0.23
Myocardial infarction	38 (1.9)	5 (2.4)	33 (1.9)	0.60
Heart failure	8 (0.4)	2 (0.9)	6 (0.3)	0.21
Current smoker	628 (32.0)	60 (28.3)	568 (32.4)	0.24
Alcohol consumption	716 (36.5)	70 (33.0)	646 (36.9)	0.29
Preadmission anticoagulation, n (%)	21 (1.1)	2 (0.9)	19 (1.1)	1.00
Preadmission antiplatelet, n (%)	277 (14.1)	29 (13.7)	248 (14.2)	0.92
Prestroke mRS score, median [IQR]	0 [0–0]	0 [0–0]	0 [0–0]	0.38
Admission NIHSS score, median [IQR]	11 [3–21]	26 [12–33]	10 [3–18]	<0.001
Admission GCS score, median [IQR]	14 [8–15]	6 [3–13]	14 [10–15]	<0.001
Admission dysphagia, n (%)	666 (33.9)	104 (49.1)	562 (32.1)	<0.001
Admission dysarthria, n (%)	918 (46.7)	128 (60.4)	790 (45.1)	<0.001
Admission SBP (mmHg), median [IQR]	165 [147–186]	173 [150–200]	164 [146–185]	<0.001
Admission DBP (mmHg), median [IQR]	96 [82–109]	97 [85–110]	95 [82–102]	0.15

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Overall (n=1,964)	LOS ≤72 h (n=212)	LOS >72 h (n=1,752)	P value
Admission WBC, 10^9/L, median (IQR)	9.79 (7.35–13.0)	12.4 (9.31–17.3)	9.49 (7.20–12.4)	<0.001
Admission glucose (mmol/L), median (IQR)	5.85 (4.89–7.39)	8.84 (6.84–11.6)	7.18 (6.02–8.88)	<0.001
Admission creatinine (μmol/L), median (IQR)	63.4 (52.7–77.0)	64.9 (53.6–83.0)	63.1 (52.6–76.2)	0.17
Hematoma location, n (%)				<0.001
Supratentorial ICH	1,752 (89.2)	172 (81.1)	1,580 (90.2)	
Infratentorial ICH	212 (10.8)	40 (18.9)	172 (9.8)	
Hematoma volume (cm^3), median (IQR)	15.8 (6.0–38.6)	40.9 (12.0–78.1)	15.0 (5.8–34.8)	<0.001
Intraventricular extension, n (%)	655 (33.4)	79 (37.3)	576 (32.9)	0.21
Subarachnoid extension, n (%)	264 (13.4)	55 (25.9)	209 (11.9)	<0.001
Etiology diagnosis, n (%)				0.02
Primary ICH	1,785 (90.9)	204 (96.2)	1,581 (90.2)	
Secondary ICH	159 (8.1)	7 (3.3)	152 (8.7)	
Primary IVH	20 (1.0)	1 (0.5)	19 (1.1)	
Withdrawal of medical care, n (%)	139 (7.1)	39 (18.4)	100 (5.7)	<0.001
Surgical treatment, n (%)	366 (18.6)	18 (8.5)	348 (19.9)	<0.001
In-hospital SAP, n (%)	575 (29.3)	64 (30.2)	511 (29.2)	0.75
In-hospital mortality, n (%)	216 (11.0)	86 (40.6)	130 (7.4)	<0.001

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale score; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; TIA, transient ischemic stroke; IVH, intraventricular hemorrhage; LOS, length of stay; SAP, stroke-associated pneumonia.

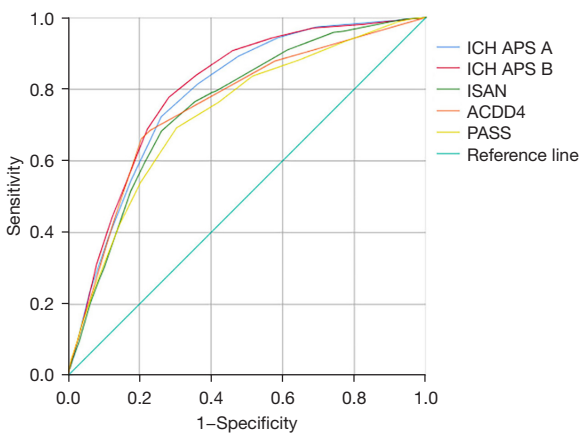

Figure 1 Predictive performance of clinical scores regarding in-hospital SAP after ICH (n=1,964). PASS, Preventive Antibiotics in Stroke Study Score; ISAN, integer-based pneumonia risk score; ACCD4, an 8-point pneumonia prediction scale (age ≥75 years =1; congestive heart failure =1; dysarthria =1; dysphagia =4); ICH-APS, intracerebral hemorrhage-associated pneumonia score; SAP, stroke-associated pneumonia.

the 5 scores ranged from 0.732 to 0.800 (*Table 3*). The sensitivity, specificity, PPV, NPV, and maximum Youden index for predicting in-hospital SAP after ICH are shown in *Table 3*. We found that the ICH-SAP-B had the maximum value in the Youden index. In the comparison of scores, the ICH-APS-B (0.800; 95% CI: 0.780–0.820; P<0.001) also showed a statistically better discrimination than did the other risk models for in-hospital SAP after ICH (all P<0.001). However, all risk models showed a much better discrimination in patients with an LOS >72 h (*Table 3*). Among these patients with an LOS >72 h, the ICH-APS-B (0.827; 95% CI: 0.806–0.848; P<0.001) still showed statistically better discrimination for in-hospital SAP after ICH than did the other risk models (all P<0.001).

Comparison of model calibration for in-hospital SAP

We plotted the predicted and observed risk according to 10 deciles of the predicted risk of in-hospital SAP after

Table 3 Discrimination of risk models regarding in-hospital SAP after ICH

Variable	AUROC	95% CI	Δ AUROC*	P value[&]	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
Overall cohort (N=1,964)										
ICH-APS-B (2014)	0.800	0.780–0.820	Reference		0.495	6	0.777	0.718	0.533	0.886
ICH-APS-A (2014)	0.787	0.766–0.808	0.013	<0.001	0.462	6	0.724	0.739	0.534	0.866
ISAN (2015)	0.755	0.732–0.777	0.045	<0.001	0.421	8	0.683	0.737	0.519	0.849
ACDD4 (2017)	0.755	0.735–0.774	0.045	<0.001	0.456	3	0.662	0.794	0.571	0.850
PASS (2018)	0.732	0.708–0.756	0.068	<0.001	0.388	6	0.692	0.696	0.485	0.845
LOS ≤72 h (N=288)										
ICH-APS-B (2014)	0.639	0.574–0.703	Reference		0.265	6	0.830	0.435	0.392	0.853
ICH-APS-A (2014)	0.637	0.573–0.702	0.002	0.92	0.272	6	0.773	0.500	0.405	0.833
ISAN (2015)	0.599	0.533–0.665	0.040	0.09	0.214	9	0.784	0.430	0.377	0.819
ACDD4 (2017)	0.648	0.580–0.716	0.009	0.73	0.319	2	0.704	0.615	0.446	0.826
PASS (2018)	0.627	0.556–0.697	0.012	0,70	0.249	7	0.534	0.715	0.452	0.777
LOS >72 h (N=1,676)										
ICH-APS-B (2014)	0.827	0.806–0.848	Reference		0.533	6	0.768	0.765	0.573	0.890
ICH-APS-A (2014)	0.811	0.789–0.832	0.016	<0.001	0.493	6	0.714	0.779	0.570	0.869
ISAN (2015)	0.780	0.756–0.804	0.047	<0.001	0.455	8	0.661	0.793	0.568	0.851
ACDD4 (2017)	0.773	0.747–0.798	0.055	<0.001	0.482	1	0.679	0.802	0.585	0.859
PASS (2018)	0.750	0.724–0.775	0.077	<0.001	0.421	6	0.702	0.718	0.505	0.855

*, Δ AUROC denotes the difference in AUROC between the ICH-SAP-B and the other scores regarding SAP after ICH; [&], P value of comparing paired AUROC with Delong's method. ICH, intracerebral hemorrhage; AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; PASS, Preventive Antibiotics in Stroke Study Score; LOS, length of stay; ISAN, integer-based pneumonia risk score; ACCD4, an 8-point pneumonia prediction scale (age ≥75 years =1; congestive heart failure =1; dysarthria =1; dysphagia =4); ICH-APS, intracerebral hemorrhage–associated pneumonia score.

ICH (Figure S1). The results of the Hosmer-Lemeshow test are shown in *Table 4*. In the overall cohort, the Hosmer-Lemeshow test showed that the ICH-APS-B had a significance level greater than .05, indicating that the observed values were not statistically different from the expected values. The ICH-SAP-B had the largest Cox and Snell R^2. Similar results were found for patients with an LOS >72 h. As the Hosmer-Lemeshow test has been shown to be overly sensitive to trivial deviations from the ideal fit, Pearson correlation coefficient was also used to calculate the predicted and observed risk. All the correlation coefficients of the 5 models were greater than 0.90 (all P<0.001), and the ICH-SAP-B had the largest Pearson correlation coefficient.

Discussion

In this study, we systematically compared the discrimination and calibration of 5 clinical scores regarding in-hospital SAP after ICH. The AUROC ranged from 0.732 to 0.800 in the overall cohort. Through a comparative analysis, we found the ICH-APS-B showed statistically better discrimination than did the other risk models in terms of in-hospital SAP after ICH. Furthermore, all risk models showed much better discrimination among patients with an LOS >72 h. The ICH-APS-B still showed statistically better discrimination than did the other risk models for in-hospital SAP after ICH in patients with an LOS >72 h. The Hosmer-Lemeshow test also revealed that the ICH-SAP-B had the largest Cox and Snell R^2 among patients with an LOS >72 h.

Previous studies have shown that clinical scores for predicting SAP performed better in sensitivity analyses for patient survival beyond 48–72 h after ICH (9,10). We found the potential reasons for this to be worth investigating. To

Table 4 Calibration of risk models regarding in-hospital SAP after ICH

International ICH models	Goodness-of-fit test regarding SAP after ICH		
	P value	Cox and Snell R^2	Nagelkerke R^2
Overall cohort (N=1,964)			
ICH-APS-B (2014)	0.08	0.210	0.299
ICH-APS-A (2014)	<0.05	0.194	0.277
ISAN (2015)	<0.05	0.155	0.221
ACDD4 (2017)	<0.05	0.178	0.253
PASS (2018)	<0.05	0.128	0.183
LOS ≤72 h (N=288)			
ICH-APS-B (2014)	0.05	0.055	0.078
ICH-APS-A (2014)	0.09	0.053	0.074
ISAN (2015)	0.04	0.030	0.043
ACDD4 (2017)	0.30	0.072	0.102
PASS (2018)	0.37	0.036	0.050
LOS >72 h (N=1,676)			
ICH-APS-B (2014)	0.10	0.251	0.358
ICH-APS-A (2014)	<0.05	0.228	0.326
ISAN (2015)	<0.05	0.190	0.271
ACDD4 (2017)	0.09	0.202	0.288
PASS (2018)	<0.05	0.149	0.212

ICH-APS, intracerebral hemorrhage–associated pneumonia score; ISAN, integer-based pneumonia risk score; ACCD4, an 8-point pneumonia prediction scale (age ≥75 years =1; congestive heart failure =1; dysarthria =1; dysphagia =4); PASS, Preventive Antibiotics in Stroke Study Score; LOS, length of stay.

this end, we compared the baseline characteristics of patients with an LOS ≤72 h and those with an LOS >72 h and found that patients with a shorter LOS had a significantly more severe neurological deficit on admission as indicated by a higher NIHSS score, lower GCS score, and larger hematoma volume. However, these factors did not correspond to an increased risk of in-hospital SAP after ICH. The rates of in-hospital SAP between the 2 groups were not statistically different. Furthermore, we found that patients with a shorter LOS had a significantly higher proportion of in-hospital mortality and withdrawal of medical care (*Table 2*). For our study, limited data were available about the time course of SAP after stroke. However, previous studies have reported a 3-day (IQR, 2–5) median time from onset to diagnosis of SAP after ICH), a 4-day median for AIS (IQR, 2–7), and a 5-day median for subarachnoid hemorrhage (SAH; IQR, 3–7) (21). Therefore, based on these data, we conjectured that the contradiction between neurological severity and risk of in-hospital SAP after ICH in patients with an LOS ≤72 h might be due to the patient dying or leaving hospital before the pneumonia occurred. For this patient subgroup of in-hospital pneumonia after ICH, this might be a potential reason for the lower sensitivity of these clinical scores. Despite advances in medical knowledge, treatment for ICH remains strictly supportive, with few evidence-based interventions currently available (3,4). Evidence has shown that SAP not only increases LOS and medical costs, but is also an important risk factor for poststroke mortality and morbidity. In addition, a previous study has shown the rate of SAP to be higher among patients with ICH than those with AIS (6). These data suggest that compared to patients with AIS, patients with ICH require a more aggressive SAP prophylaxis. Several clinical scores have been developed for predicting SAP after ICH. Although some

risk models have been internally or externally validated, none of them have been universally accepted or consistently used in routine clinical practice and clinical research. In this study's large ICH cohort (n=1,964), the ICH-APS-B showed a statistically better discrimination than did the other risk models regarding in-hospital SAP after ICH. It also displayed the largest Cox and Snell R^2 through the Hosmer-Lemeshow goodness-of-fit test, which was used to predict in-hospital SAP after ICH. Although these results are promising, caution needs to be taken when interpreting the results, as the cohorts used to develop these clinical scores were different. In other words, the ISAN, ACCD4, and PASS scores were only used for ICH patients in the derivation cohort, while the ICH-APS-A and ICH-APS-B scores were used exclusively for the ICH validation cohort. Furthermore, the baseline characteristics between these 2 study groups were different, and there might be complex genetic, social, and 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. Therefore, these clinical scores need to be further validated by a study with a larger sample size.

In 2 recent large, randomized trials [STROKE-INF (22) and PASS (23)], preventive antibiotic therapy did not improve functional outcomes after stroke. These trials selected patients based on symptoms and signs, with a "one-size-fits-all" prevention strategy being developed for the average person. This approach gave less consideration to the differences in SAP risk between individuals. In this way, it was inevitable that they would include patients with an unbalanced, too-high, or too-low risk of developing SAP in their clinical trials. In our study, we found the clinical scores we validated could be used to stratify patients by risk of SAP after stroke, meaning they could aid the testing of prophylactic antibiotics in different risk stratifications. Clinical trials conducted in this way would allow one to more accurately clarify which prophylactic antibiotics will work better for different SAP stratifications. However, whether preventive antibiotic therapy in a high-risk subgroup of SAP patients can improve functional outcomes after ICH requires further investigation.

It is also important to note that our study has certain limitations. First, like all observational studies, we cannot rule out the possibility that additional baseline variables (unmeasured confounders), such as use of angiotensin-converting enzyme inhibitors (24), acid-suppressive medications (25), oral hygiene (26), and biomarkers for stroke-induced immunodepression (27,28), might have some impact on the development of in-hospital SAP after ICH. Second, we could not include all elements required for all risk models. For example, we did not have information about the "found down at symptom onset", and the VHA score (8) could not be validated. Third, our study included only hospitalized patients, and patients who died in the emergency room or who were treated in outpatient clinics were not included. Furthermore, like most registries, our registry required informed consent, and selection bias was therefore inevitable (29). Lastly, the validation cohorts originated from an Asian population, and thus the ICH models need to be further validated in different populations.

Conclusions

In summary, among the 5 models for predicting SAP after ICH, the ICH-APS-B showed the best predictive performance. This indicates that the model can be applied in personalized care and clinical trials of SAP after ICH.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-4046/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-4046/dss

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-4046/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-4046/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board (IRB) of the Beijing Tiantan Hospital (No. KY2014-023-02). Informed consent was given by all patients involved.

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Supplementary

Table S1 Components of the clinical scores used to predict SAP after ICH

Items	ICH-APS-A	ICH-APS-B	ISAN	ACDD4	PASS
Age	✓	✓	✓	✓	✓
Gender			✓		✓
COPD	✓	✓			✓
Diabetes mellitus					
Current smoker	✓	✓			
Excessive alcohol consumption	✓	✓			
Prestroke mRS	✓	✓	✓		✓
Dysphagia	✓	✓		✓	✓
Dysarthria				✓	
Congestive heart failure				✓	
NIHSS	✓	✓	✓		✓
GCS	✓				
Hematoma location	✓	✓			
Ventricular extension	✓				
Hematoma volume		✓			

COPD, chronic obstructive pulmonary disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale score; GCS, Glasgow Coma Scale. SAP, stroke-associated pneumonia; ICH, intracerebral hemorrhage; PASS, Preventive Antibiotics in Stroke Study; ISAN, integer-based pneumonia risk score; ACCD4, an 8-point pneumonia prediction scale (age ≥75 years =1; congestive heart failure =1; dysarthria =1; dysphagia =4). ICH-APS, intracerebral hemorrhage–associated pneumonia score.

Table S2 Performance of the clinical scores used to predict SAP in the derivation and internal validation cohorts

Model	Stroke subtype	Study design	Sample size of derivation cohort	AUROC	Validation
ICH-APS-B	Spontaneous ICH	Registry	2998	Overall cohort: 0.74 (0.71–0.76); patients with LOS >48 h: 0.77 (0.73–0.81)	Internal
ICH-APS-A	Spontaneous ICH	Registry	2998	Overall cohort: 0.75 (0.72–0.77); patients with LOS >48 h: 0.78 (0.75–0.81)	Internal
ISAN	AIS and ICH	Registry	AIS: 10,635; ICH: 916	Overall cohort: 0.79 (0.77–0.81); patients with ICH: 0.71 (0.66–0.77); patients with LOS >72 h: 0.75 (0.69–0.80)	External
ACDD[4]	AIS and ICH	Retrospective cohort	AIS: 965; ICH: 690	Overall cohort: 0.82 (not reported)	Internal
PASS	AIS and ICH	RCT	AIS: 2,125; ICH: 269	Overall cohort: 0.84 (0.81–0.87)	Internal

AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; AUROC, area under the receiver operating characteristic curve; SAP, stroke-associated pneumonia RCT, randomized controlled trial; LOS, length of stay; PASS, Preventive Antibiotics in Stroke Study; ISAN, integer-based pneumonia risk score; ACCD4, an 8-point pneumonia prediction scale (age ≥75 years =1; congestive heart failure =1; dysarthria =1; dysphagia =4).

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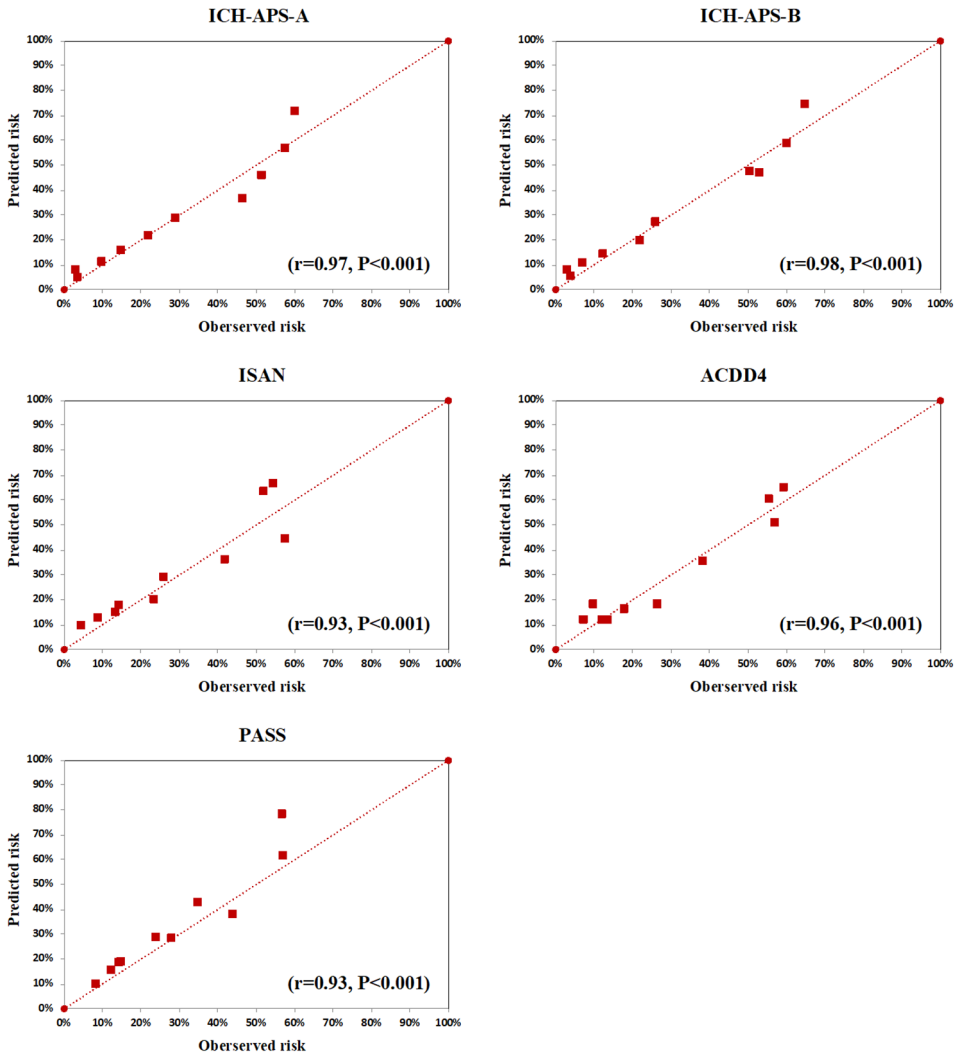

Figure S1 Plot of observed versus predicted risk of in-hospital SAP after ICH in the derivation and validation cohorts (n=1,964). Plot of observed versus predicted risk of in-hospital SAP after ICH for the overall cohorts (according to 10 deciles of predicted risk). All correlation coefficients of the 5 models were greater than 0.90 (all P<0.001), which indicated excellent calibration. The ICH-SAP-B had the largest Pearson correlation coefficient (n=1,964; r=0.98, P<0.001). SAP, stroke-associated pneumonia; ICH, intracerebral hemorrhage.

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