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Comparison of Clinical Scores for Predicting Stroke-Associated Pneumonia After Acute Ischemic Stroke

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Keywords: comparison | risk score | stroke | stroke-associated pneumonia

ABSTRACT

Objectives: To compare the discrimination and calibration of six risk scoring systems in the assessment of patients with stroke-associated pneumonia (SAP) after acute ischemic stroke.

Methods: The validation cohort was derived from the Third China National Stroke Registry. SAP was diagnosed according to the criteria for hospital-acquired pneumonia of the Centers for Disease Control and Prevention. The area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow goodness-of-fit test were used to assess discrimination and calibration.

Results: A total of 12,071 patients were included in the study and 606 (5.02%) patients were diagnosed with in-hospital SAP after ischemic stroke. The AUROC of the six clinical scores ranged from 0.660 to 0.752. In the pairwise comparison, the AIS-APS score (0.752, 95% CI = 0.730–0.773, $p < 0.001$) showed significantly better discrimination than the other risk models, except the PASS score. The AIS-APS score had the largest Cox and Snell R^2 for in-hospital SAP after ischemic stroke. In the subgroup analysis, among patients over 61 years of age, all TOAST subtypes except small vessel disease, length of hospital stay longer than 8 days, male and female sex, different groups stratified by admission NIHSS score and time from onset to arrival, the AIS-APS score showed better discrimination than other risk models with regard to SAP after AIS.

Conclusions: Our study compared the discrimination and calibration of the Kwon Pneumonia Score, A2DS2 score, PANTHERIS score, AIS-APS score, ISAN score, and PASS score in SAP identification; of these, the AIS-APS score showed the best performance.

1 | Introduction

Stroke-associated pneumonia (SAP) is one of the most common complications after stroke. Evidence has shown that SAP not only increases medical costs [1] but also is an important risk factor for mortality and morbidity after stroke [2, 3]. Antibiotic prevention of SAP was not demonstrated to be beneficial in 2 large phase III trials (STROKE-INF [4] and PASS [5]). Predicting SAP risk could allow the application of preventive interventions to reduce the incidence among the highest-risk patients and could facilitate appropriate patient selection for clinical trials assessing preventive interventions.

A variety of SAP risk scales, such as the Kwon Pneumonia Score [6], A2DS2 scale [7], Preventive Antibacterial Therapy in Acute Ischemic Stroke (PANTHERIS [8]) scale, Acute Ischemic Stroke-associated Pneumonia Scale (AIS-APS [9]), ISAN scale [10], and Pneumonia-Associated Septic Shock (PASS [11]), Chumbler's

score [12], have been developed. With many grading systems available, it is becoming increasingly difficult for clinicians and researchers to assess which risk models provide optimal predictability and reliability in clinical practice and clinical trials. Our aim was to compare these six clinical scales in the Third China National Stroke Registry (CNSR-III), a large, multicenter and prospective cohort study.

2 | Methods

2.1 | Validation Cohort

The validation cohort was derived from the CNSR-III, which was a large, multicenter, prospective cohort study. Two hundred and one hospitals in China participated in the study. This study included patients meeting the following criteria: (1) age older than 18 years; (2) hospitalization with a primary diagnosis of ischemic stroke confirmed by brain CT or MRI; (3) no more than 7 days from the onset of symptoms to enrollment; and (4) informed consent from the patient or a legally authorized representative (primarily their spouse, parents, or adult children, unless otherwise indicated). Besides, we omitted individuals with incomplete data and those who had not been subjected to SAP evaluations. The protocol of the CNSR-III study was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers [13].

2.2 | Data Collection and Definition of Variables

An electronic data capture system (EDC) was developed and used for data collection. Participating centers collected data, which were submitted online using an electronic signature (unique username and password). For this study, the following candidate variables were analyzed: (1) demographics: age and sex; (2) vascular risk factors: hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary artery disease, history of stroke/TIA, current smoking, and excess alcohol consumption; (3) preexisting comorbidities: congestive heart failure, valvular heart disease, peripheral artery disease, chronic obstructive pulmonary disease (COPD), hepatic cirrhosis, peptic ulcer or previous gastrointestinal bleeding (GIB), renal failure, arthritis, dementia, and cancer; (4) prestroke dependence (mRS ≥ 3); (5) admission stroke severity based on the National Institutes of Health Stroke Scale (NIHSS) score; (6) symptoms of dysphagia; (7) Oxfordshire Community Stroke Project (OCSP) subtype; (8) admission blood glucose; and (9) length of hospital stay (LOS).

2.3 | Diagnosis of SAP

SAP was diagnosed according to modified Centers for Disease Control and Prevention (CDC) criteria by trained and experienced physicians [14, 15]. SAP was defined as having at least one of the following: (1) fever (>38°C) with no other recognized cause; (2) leukopenia (<4000 WBC/mm3) or leukocytosis ($>12{,}000$ WBC/mm3); and (3) for adults ≥ 70 year old, altered mental status with no other recognized cause; plus at least 2 of the following: (1) new onset of purulent sputum, a change in sputum characteristics over a 24-h period, increased respiratory secretions, or increased suctioning requirements; (2) new onset or worsening cough, dyspnea, or tachypnea (respiratory rate >25/min); (3) rales, crackles, or bronchial breath sounds; and 4. worsening gas exchange (e.g., O_2 desaturation [e.g., $PaO_2/FiO_2 \leq 240$], increased oxygen requirements*); plus ≥ 2 serial chest radiographs† (CXR) with at least 1 of the following: new or progressive and persistent infiltrate, consolidation, or cavitation. In patients without underlying pulmonary or cardiac disease, 1 definitive chest radiograph was acceptable. Definitive SAP and probable SAP were diagnosed when additional diagnostic CXR changes were present or absent, respectively. In this study, pneumonia occurring before stroke was not considered.

2.4 | Statistical Analysis

Categorical variables are expressed as proportions. Continuous variables are expressed as the mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). In univariate analysis, categorical variables were compared with the χ^2 test or Fisher's exact test. Continuous variables were compared with Student's *t*-test if the parameters had a normal distribution and the Mann–Whitney *U*-test if not.

Seven clinical scores that could be used to predict SAP after ischemic stroke were identified by a systematic search. Among them, Chumbler's score could not be validated in our study due to missing information for "Found-down at symptom onset". Finally, we included six clinical scores in our study: the AIS-APS, pneumonia, A2DS2, PANTHERIS, ISAN, and PASS.

Discrimination was assessed by calculating the area under the receiver operating characteristic curve (AUROC). Pairwise AUROC was compared by using Delong's method. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at each risk model's maximum Youden Index value. Calibration was assessed by performing the Hosmer-Lemeshow goodness-of-fit test and plotting the observed versus predicted risk according to 10 deciles of the predicted risk. The Cox and Snell R^2 and Nagelkerke R^2 of the Hosmer-Lemeshow goodness-of-fit test were calculated [16, 17].

All tests were two-tailed and statistical significance was indicated at the level of 0.05. Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC), SPSS 26.0 (SPSS Inc., Chicago, IL), and MedCalc software 12.3 (MedCalc).

3 | Results

3.1 | Patient Characteristics

From August 2015 to March 2018, a total of 15,166 patients were enrolled in the CNSR-III, and 12,071 patients met our standards (Figure 1). The clinical characteristics are shown in Table 1. The mean age was 62 ± 11 years, and 68.14% of participants were male. The median NIHSS score on admission was 3 (IQR: 1–6). The median length of hospital stay was 13 days (IQR: 10–15). A total of 606 (5.02%) patients were diagnosed with in-hospital SAP after ischemic stroke. Compared

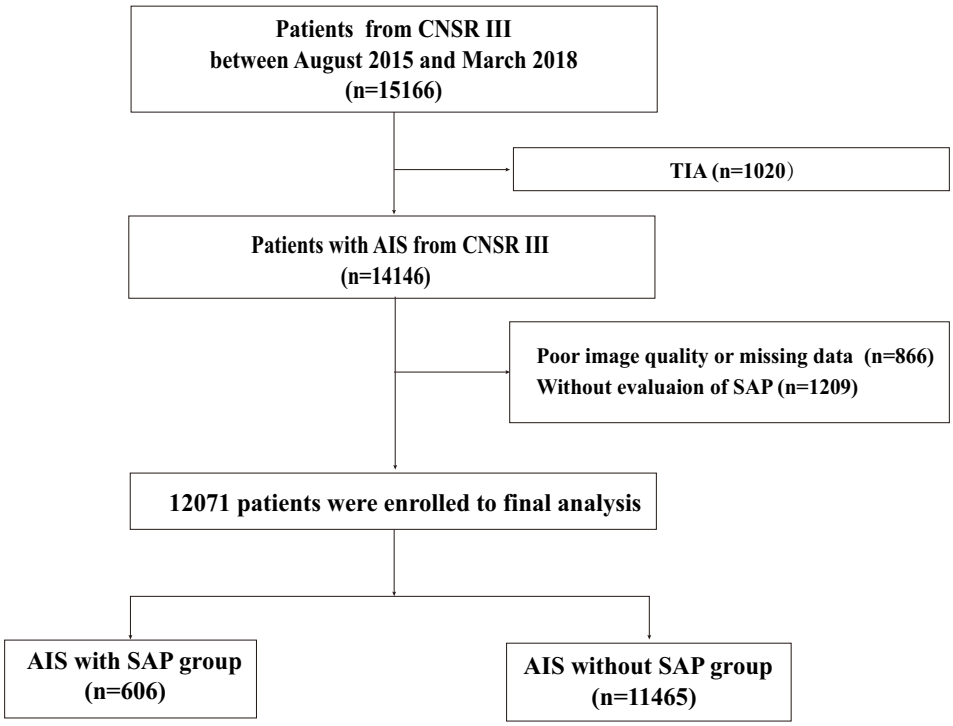

FIGURE 1 | Flow chart of patient enrolment in our study. AIS, acute ischemic stroke; SAP, stroke-associated pneumonia.

to patients without SAP, those with SAP after ischemic stroke were older and had a higher proportion of atrial fibrillation, coronary artery disease, history of stroke/TIA, congestive heart failure, COPD, cancer, and dysphagia; higher prestroke dependence and admission blood glucose; and longer length of hospital stay (Table 1).

The incidence of SAP was summarized by group statistics. There was a significantly higher proportion of SAP among patients who were elderly and had higher NIHSS scores ($p < 0.0001$). The proportion of SAP between groups stratified by sex was not significantly different (5.17% vs. 4.71%, $p = 0.28$) (Table 1).

In the cohort of 606 patients diagnosed with SAP, a total of 492 patients underwent microbiological testing. The etiological analysis revealed that 232 cases (47.15%) were attributed to gram-negative bacilli, specifically 107 cases of *Klebsiella pneumoniae* and 125 cases of *Escherichia coli*. Additionally, 78 cases (15.85%) were identified as anaerobic bacterial infections, with 28 cases of Prevotella species and 50 cases of Fusobacterium species. *Staphylococcus aureus* was isolated in 62 cases (12.60%). The remaining 120 cases (24.40%) exhibited polymicrobial infections.

3.2 | Comparison of Model Discrimination for In-Hospital SAP

Table 2 shows the discrimination of six clinical scores with regard to SAP after ischemic stroke. It includes the sensitivity, specificity, PPV, NPV, and maximum Youden Index value for predicting in-hospital SAP after ischemic stroke. The AUROC of the six clinical scores ranged from 0.660 to 0.752. The AIS-APS score showed the maximum Youden Index value. In the pairwise comparison, the AIS-APS score (0.752, 95% CI = 0.730–0.773, $p < 0.001$) showed significantly better discrimination than the other risk models except the PASS score for in-hospital SAP after ischemic stroke (Table 2).

3.3 | Comparison of Model Calibration for In-Hospital SAP

The predicted and observed risk according to 10 deciles of the predicted risk of SAP after AIS was plotted (Figure 2). The results of the Hosmer-Lemeshow test are shown in Table 3. The AIS-APS score, ISAN score and PASS score had a significance level > 0.05 according to the Hosmer–Lemeshow test in the overall cohort, indicating that the observed values were not significantly different from the expected values. The AIS-APS score had the largest Cox and Snell R^2.

3.4 | Sensitivity Analysis

The sensitivity analysis of all models was summarized by group statistics (Table 4). Among patients over 61 years of age, all TOAST subtypes except small vessel disease, length of hospital stay longer than 8 days, male and female sex, different groups stratified by admission NIHSS score and time from onset to arrival, the AIS-APS score showed better discrimination than other risk models with regard to SAP after AIS (Table 4).

4 | Discussion

In this study, we systematically compared the discrimination and calibration of six clinical scores with regard to in-hospital SAP after

TABLE 1 | Clinical characteristics.

	Overall ($n = 12,071$)	With SAP ($n = 606$)	Without SAP ($n = 11,465$)	p
Demographics				
Age, years, median (IQR)	62 (54–70)	70 (62–77)	62 (54–70)	< 0.001
Gender (male), *n* (%)	8225 (68.14)	425 (70.13)	7800 (68.03)	0.280
Vascular risk factor, *n* (%)				
Hypertension	8832 (73.17)	457 (75.41)	8375 (73.05)	0.200
Diabetes mellitus	3796 (31.45)	192 (31.68)	3604 (31.43)	0.900
Dyslipidemia	4351 (36.05)	183 (30.20)	4168 (36.35)	0.0021
Atrial fibrillation	754 (6.25)	105 (17.33)	649 (5.66)	< 0.001
Coronary artery disease	1771 (14.67)	145 (23.93)	1626 (14.18)	< 0.001
History of stroke/TIA	2666 (22.09)	162 (26.73)	2504 (21.84)	0.005
Current smoking	3798 (31.46)	163 (26.90)	3635 (31.71)	0.013
Excess alcohol consumption	1716 (14.22)	76 (12.54)	1640 (14.30)	0.226
Preexisting comorbidities, *n* (%)				
Congestive heart failure	1226 (10.16)	99 (16.34)	1127 (9.83)	< 0.001
Valvular heart disease	42 (0.35)	4 (0.66)	38 (0.33)	0.158
Peripheral artery disease	86 (0.71)	5 (0.83)	81 (0.71)	0.622
COPD	101 (0.84)	32 (5.28)	69 (0.60)	< 0.001
Hepatic cirrhosis	22 (0.18)	0 (0.00)	22 (0.19)	0.625
Peptic ulcer or previous GIB	139 (1.15)	8 (1.32)	131 (1.14)	0.690
Renal failure	98 (0.81)	6 (0.99)	92 (0.80)	0.638
Arthritis	258 (2.14)	10 (1.65)	248 (2.16)	0.395
Dementia	43 (0.36)	3 (0.50)	40 (0.35)	0.476
Cancer	105 (0.87)	12 (1.98)	93 (0.81)	0.003
Pre-stroke dependence (mRS > 3), *n* (%)	529 (4.38)	49 (8.09)	480 (4.19)	< 0.001
Admission NIHSS score, median (IQR)	3 (1–6)	5 (2–10)	3 (1–5)	< 0.001
Symptom of dysphagia, *n* (%)	561 (4.65)	147 (24.26)	414 (3.61)	< 0.001
OCSP subtype, *n* (%)				
Partial anterior circulation infarct (PACI)	6811 (56.42)	356 (58.75)	6455 (56.30)	< 0.001
Total anterior circulation infarct (TACI)	191 (1.58)	24 (3.96)	167 (1.46)	
Lacunar infarction (LACI)	2556 (21.17)	66 (10.89)	2490 (21.72)	
Posterior circulation infarct (POCI)	2513 (20.82)	160 (26.40)	2353 (20.52)	
Admission blood glucose (mmol/L), median (IQR)	5.52 (4.9–6.88)	5.74 (5.04–7.24)	5.51 (4.89–6.84)	< 0.001
Length of hospital stay (days), median (IQR)	13 (10–15)	15 (12–21)	13 (10–15)	< 0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; GIB, gastrointestinal bleeding; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; SAP, stroke-associated pneumonia; TIA, transient ischemic attack; mRS, modified Rankin Scale.

TABLE 2 | Comparison of discrimination of international SAP risk models.

	AUROC	95% CI	Δ AUROC[a]	*p*[b]	Youden Index	Cutoff	Sensitivity	Specificity	PPV	NPV
AIS-APS score (2012)	0.752	0.730–0.773	Reference	—	0.385	7	0.597	0.787	0.129	0.026
Pneumonia score (2006)	0.703	0.682–0.724	0.049	<0.001	0.323	2	0.634	0.689	0.097	0.027
A^2DS^2 score (2012)	0.703	0.681–0.726	0.049	<0.001	0.318	1	0.724	0.594	0.086	0.024
PANTHERIS (2013)	0.660	0.640–0.680	0.092	<0.001	0.226	1	0.860	0.366	0.067	0.020
ISAN score (2015)	0.714	0.692–0.736	0.038	<0.001	0.314	1	0.568	0.746	0.106	0.030
PASS score (2018)	0.728	0.705–0.750	0.024	0.003	0.338	10	0.480	0.858	0.152	0.031

Abbreviations: AIS, acute ischemic stroke; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SAP, stroke-associated pneumonia.
[a]Δ AUROC denotes the difference in AUROC between the AIS-PS and compared scores with regard to in-hospital SAP after AIS.
[b]*p* value of comparing paired AUROC with Delong's method.

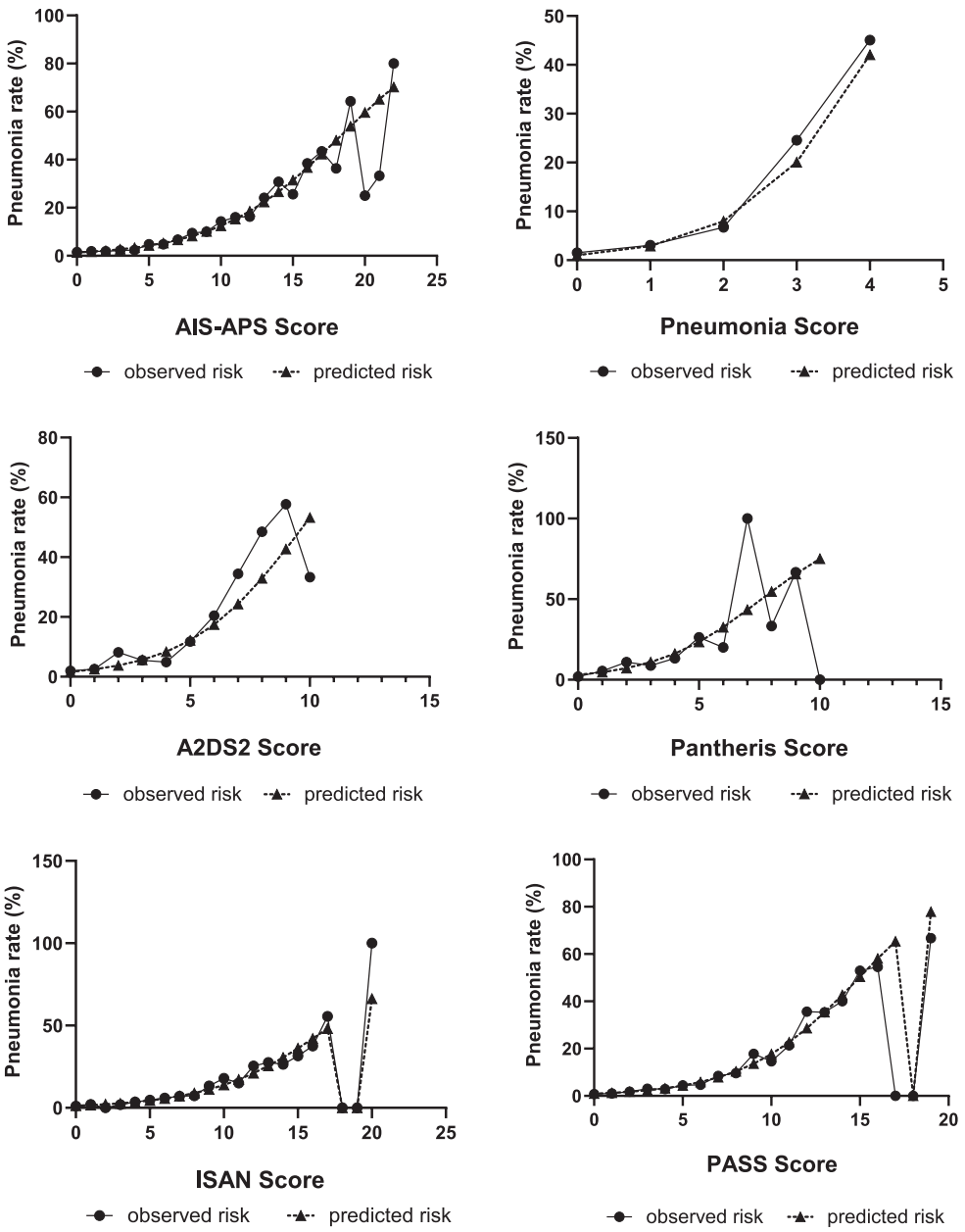

FIGURE 2 | Plot of observed versus predicted risk of SAP after AIS.

TABLE 3 | Comparison of calibration of international SAP risk models.

	Goodness of fit		
	Cox and Snell R^2	**Nagelkerke R^2**	***p***
AIS-APS score (2012)	0.046	0.141	0.372
Pneumonia score (2006)	0.036	0.111	<0.050
A^2DS^2 score (2012)	0.034	0.104	<0.050
PANTHERIS (2013)	0.017	0.051	<0.050
ISAN score (2015)	0.032	0.097	0.091
PASS score (2018)	0.043	0.132	0.177

TABLE 4 | Sensitivity analysis.

	AIS-APS score	**Pneumonia score**	**A^2DS^2 score**	**PANTHERIS**	**ISAN score**	**PASS score**
Overall cohort	0.752	0.703	0.704	0.660	0.714	0.728
Subgroups						
Age						
≤60	0.639	0.648	0.656	0.590	0.634	0.646
≥61	0.741	0.672	0.704	0.593	0.686	0.710
Gender						
Male	0.745	0.720	0.704	0.661	0.705	0.730
Female	0.770	0.719	0.712	0.660	0.733	0.749
Admission NIHSS						
<3	0.685	0.638	0.653	0.613	0.660	0.658
≥3	0.765	0.721	0.712	0.675	0.711	0.739
Time from onset to arrival (h)						
<6	0.843	0.783	0.797	0.675	0.804	0.826
6–12	0.711	0.646	0.657	0.650	0.687	0.662
12–24	0.732	0.697	0.669	0.655	0.687	0.716
>24	0.741	0.705	0.724	0.670	0.705	0.718
TOAST subtypes						
Large artery stenosis	0.741	0.704	0.699	0.638	0.700	0.725
Small vessel disease	0.643	0.657	0.604	0.579	0.601	0.635
Cardioembolism	0.730	0.672	0.703	0.628	0.692	0.705
Other determined etiology	0.834	0.740	0.601	0.811	0.740	0.754
Undetermined etiology	0.764	0.704	0.711	0.677	0.734	0.738
Length of hospital stay (days)						
≤7	0.814	0.761	0.783	0.671	0.797	0.816
8–13	0.702	0.651	0.643	0.638	0.670	0.666
≥14	0.750	0.710	0.700	0.666	0.705	0.728

AIS. Our results showed that the AIS-APS score and PASS score have good discrimination in SAP risk prediction. Additionally, for the AIS-APS score, this study demonstrated good calibration in the CNSR III cohort. In the subgroup analysis, among patients over 61 years of age, all TOAST subtypes except small vessel disease, length of hospital stay longer than 8 days, male and female sex, different groups stratified by admission NIHSS score and time from onset to arrival, the AIS-APS score showed better discrimination than other risk models with regard to SAP after AIS.

Compared with other risk models, the AIS-APS incorporates chronic obstructive pulmonary disease [18], dysphasia [19], atrial fibrillation [20], glucose [21, 22], and stroke subtypes [21, 23], which are independent predictors of pneumonia after stroke. Maybe it is the reason why AIS-APS score performs best.

The strengths of our study include its international multicenter design and large number of patients. By assessing the six scores that appeared to be most promising for clinical use, we could investigate the optimum way to assess the risk of pneumonia in patients after stroke.

Two large trials (PASS and STROKE-INF) did not support the use of preventive antibiotics in adults with acute stroke because preventive antibiotic therapy did not improve functional outcome after stroke. Patients were selected according to symptoms, and prevention strategies were developed randomly, without consideration of the differences in SAP risk between individuals. We can use these scores to filter patients and design prophylactic antibiotic trials at different risk levels. In addition, SAP prediction can help clinicians focus on high-risk groups and provide specific management to prevent adverse outcomes.

Our study has some limitations that deserve mention. First, our study included only hospitalized patients, and most patients had minor stroke. Second, we did not have all elements required for all risk models. For example, we did not have information about "Found-down at symptom onset", and thus, Chumbler's score could not be validated in the study.

5 | Conclusion

In conclusion, our study compared the discrimination and calibration of the Kwon Pneumonia Score, A2DS score, PANTHERIS score, AIS-APS score, ISAN score, and PASS score in SAP identification, and of these, the AIS-APS score showed the best performance.

Author Contributions

Linlin Wang analyzed the data and drafted the manuscript. Xinyu Liu and Feifei Ma collected the data. Jun Xu, Xingquan Zhao, Anxin Wang, Ruijun Ji and Yongjun Wang revised the manuscript. All authors contributed to the article and approved the submitted version.

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Ethics Statement

The protocol of the CNSR-III study was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers. Informed consent was obtained from all individual participants included in the study. The consent process included a detailed explanation of the study's purpose, procedures, potential risks, and benefits, and participants were given the opportunity to ask questions and receive clear answers. Participants were informed of their right to withdraw from the study at any time without penalty. The informed consent form was translated into Chinese to accommodate participants from different linguistic backgrounds. Measures were taken to ensure the confidentiality of participants' data throughout the data collection, storage, and sharing processes.

Conflicts of Interest

The authors declare no conflicts of interest.

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