



An ANAS Nomogram to Predict the Risk of Hospital-Acquired Pneumonia in Patients with Acute Ischemic Stroke

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Abstract

Acute ischemic stroke (AIS) patients are at high risk of acquiring infections such as pneumonia, which is a preventable stroke complication associated with unfavorable outcome. We aimed to develop and validate a novel nomogram model for individualized prediction of hospital-acquired pneumonia (HAP) in AIS patients. This is a retrospective study of AIS patients between May 2013 to May 2018. Data dimension reduction and feature selection were performed using Lasso regression model. Age, NHSS score on admission and other potential variables were integrated into a logistic regression model to develop the nomogram. The discriminative performance of the nomogram was assessed by using area under the curve (AUC) of receiver-operating characteristic (ROC) and calibration of risk prediction model by using the Hosmer-Lemeshow test. The study comprised 1,823 eligible AIS patients for developing the ANAS nomogram and was randomly dichotomized into training (n=1094) and test (n=729) sets. Age, NHSS score on admission, atrial fibrillation, and prestroke mRS (ANAS) were independent predictors for HAP in AIS patients. The AUC-ROC of the ANAS nomogram was 0.816 (95% CI 0.779-0.854) in the training cohort and 0.807 (95% CI 0.765-0.849) in the test cohort. The Hosmer-Lemeshow goodness-of-fit test demonstrated good calibration (p=0.1876) in the training sets and (p=0.5591) in the test sets. The ANAS nomogram is a reliable tool that may help alert clinicians to adopt individualized preventive measures in patients with a high risk of developing HAP based on routinely available variables potentially increasing its practicality in routine care settings and clinical trials.

Keywords

Acute ischemic stroke; Hospital-acquired Pneumonia; Prediction; Nomogram

Introduction

The recent advancements in the acute management and treatment of stroke have led to a reduction in mortality and hospitalization. However, medical complications occurring during hospital stay not only increase hospitalization costs and length of stay but also influence clinical consequences in stroke survivors [1-3]. Pneumonia is reportedly the most recurrent severe complication of stroke and has a reported prevalence of about 10% with a strong influence on morbidity and mortality in stroke patients [4-6]. Therefore, early identification of patients at high risk of developing hospital-acquired pneumonia (HAP) poststroke is of great significance to provide a practical approach in the prevention, increased nursing, and allocation of appropriate medical resources and apt treatment of HAP post-acute ischemic stroke (AIS).

Several scores [7-12] such as A2DS2 (Age, Atrial fibrillation [AF], Dysphagia, Sex, Stroke Severity using the National Institutes of Health Stroke Scale [NIHSS] score) and ISAN score which include variables of sex, age, pre-stroke independence, and NIHSS score on admission have been developed over the years with the objective of predicting pneumonia in stroke patients. Stroke severity and age have been recognized as the strongest predictors of Stroke-associated Pneumonia (SAP) [7-12]. However, the adaptability and ease of these

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scores in routine clinical care for predicting the risk of HAP in stroke are limited by a moderate predictive performance.

A number of studies have shown that nomograms present a more improved outcome than scores that employ grouping of risks [13-18]. Recently, a nomogram was developed by Huang et al. [19] for individualized prediction of stroke-associated pneumonia (SAP) based on 983 AIS patients, the nomogram proved superior to previous risk scores. The use of continuous variables including age and NIHSS, a nomogram is a visual statistical instrument that integrates various variables to generate a scoring system that computes the probability of a particular outcome for an individual patient.

In this analysis, we aimed to develop and validate a simple and clinically useful model that incorporates variables routinely available on admission for individualized prediction of HAP in AIS patients.

Methods

Study design and participants

A cohort study was carried out on AIS patients' data gathered retrospectively in the Nanjing First Hospital (China) Stroke Registry database (NFHSR). All AIS Patients that were admitted at the Nanjing First Hospital from May 2013 to May 2018 were included. All patients or their legal representatives have duly given their written informed consent, and the scientific use of the data obtained from NFHSR was approved by the Ethics Committees of Nanjing First Hospital in accordance with the Helsinki declaration and internal protocol. Baseline characteristics, demographics, comorbidities, and NIHSS on admission, outcomes and laboratory characteristics during hospitalization were documented. In a bid to avoid aspiration in this study, nasogastric tube interventions were performed on the elderly and comatose patients. In effect, both dysphagia and coma status could imply the presence of nasogastric tube.

Clinical Outcome: The primary outcome measure was a diagnosis of HAP by two neurologists who were blinded to this study during the first seven days of admission following AIS onset. The diagnosis of HAP was undertaken according to the modified Centres for Disease Control and Prevention criteria of hospital-acquired pneumonia [20], on the grounds of clinical and laboratory indicators of respiratory tract infection, and corroborated by chest x-ray and CT scan [21].

Inclusion and exclusion criteria

This study only included AIS patients with comprehensive clinical, demographic and laboratory data at the time of admission. Age ≥ 18 were eligible for inclusion. Patients were excluded from the analysis with prestroke modified Rankin scale (mRS) score unknown, incomplete data, patients treated with endovascular procedure were also excluded. In addition, patients with mRS score >4 and NIHSS >35 were excluded from our study as such patients represent serious neurological deficit or death. A number of candidate variables were analysed in this study and this is elaborated as follows: (1) demographics: age, sex; (2) medical history: hypertension, diabetes mellitus, hyperlipidaemia, coronary artery disease, atrial fibrillation, congestive heart failure, valvular heart disease, peripheral vascular disease, transient ischemic attack, previous stroke, previous cerebral haemorrhage, smoking, drinking; (3) comorbidity: coronary artery disease, cardiac insufficiency, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidaemia, pneumonia; (4) NIHSS score and prestroke mRS scores.

Statistical Analysis

Randomly, the NFHSR cohort was dichotomized into training and test sets using the R software (version 3.5.2). Three-fifth of the cohort was used to generate the prediction model and 2/5 to validate the model. One-sample Kolmogorov-Smirnov test was used to test for normality. Continuous variables were defined as median value and interquartile range. Proportions were attained for categorical variables, dividing the number of events by the summation number

excluding unidentified cases. In the assessment, the Mann-Whitney U-test for continuous variables was employed to investigate the differences of the diverse groups. Also, Fisher's exact test which is referred to as the χ^2 test was employed to examine distinctions between categorical variables.

The ANAS nomogram was generated by entering the pre-established predictors into a logistic regression model. The OR and its 95% CI were hence calculated for the variables found to be remarkably related to the principal endpoint in the multivariate analysis. The statistical analysis was carried out using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), Stata version 13.0 (Stata Corporation, College Station, TX, USA) statistical software, and the statistical software package R, version 3.3.3 (R Development Core Team, Auckland, New Zealand). In the study, data dimension reduction was carried out with the aid of a Lasso regression model. Lasso regression model was also employed in the choosing of the most significant prognostic characteristics from the primary data. Collinearity of variables that entered the multivariate logistic regression analysis was assessed by the variation inflation factors (<2 being considered non-significant) and condition index (<30 being considered non-significant).

The ANAS nomogram allows discrimination of patients with and without HAP, the predictive accuracy of the nomogram model was assessed by calculation of the area under the curve (AUC) of the receiver-operating characteristic. Calibration plot was used to undertake calibration, and the predicted probabilities were plotted against the frequency of the observed negative outcome. The prediction of a well-calibrated model should be mirrored by a 45° diagonal line. Moreover, since the model was internally validated using bootstrap resampling, all predictive equations appear to be over fitted to the original sample. All tests were two-sided, and $p < 0.05$ was seen as statistically significant.

Results

A total of 3,419 AIS patients from May 2013 to May 2018 from the NFHSR database were identified. Out of the 3,419 patients captured in the NFHSR cohort, 1073 (31.4%) patients lack previous mRS score. Patients were excluded because of incomplete data at baseline (incomplete NIHSS) ($n=282$; 8.2%), age ($n=11$) and comorbidity ($n=25$), unknown medical history ($n=31$), and 174 (5.0%) patients treated with endovascular procedure were excluded. Thus, the final study cohort used in this analysis comprised of 1,823 patients (median age 68 years; IQR 60-78 years). The clinical and demographic characteristics of the patients in the training ($n=1094$) and test ($n=729$) cohorts are provided in Table 1. The proportion of patients with HAP after AIS was similar between the two cohorts: 18.6% in the training cohort and 18.1% in the test cohort. To develop the ANAS nomogram for prediction of HAP in AIS patients, four pre-established predictors were entered into a logistic regression model in the multivariate analysis: age (OR: 1.029; 95% CI: 1.016-1.042; $p < 0.0001$), NIHSS score on admission (OR: 1.172; 95% CI: 1.143-1.203; $p < 0.0001$), previous mRS score (OR: 1.321; 95% CI: 1.151-1.516 $P < 0.0001$) and atrial fibrillation (OR: 2.493; 95% CI: 1.785-3.480; $p < 0.0001$), (Table 2, Figure 1). No significant statistical collinearity was observed for any of the 4 independent risk factors that entered the multivariate logistic regression analysis. The logistic regression model resulted: $\text{Log}(p[x]/1-p[x]) = -4.514 + (0.023 \times \text{age}) + (0.170 \times \text{NIHSS score}) + (0.356 \times \text{previous mRS score}) + (0.936 \times \text{atrial fibrillation})$; where $p(x)$ was the probability of risk of HAP after AIS.

The building of the nomogram was fundamentally characterized by pictorially allotting initial score to every one of the four independent predictive indicators while bearing a point reach of 0 to 100. The resultant summed up score was subsequently determined by tallying the allotted initial scores. In the end, converted into an individual risk of HAP after AIS expressed in percentage that is, within the reach of 0 to 100%. From the results obtained, it was prognosticated that the nomogram's increased summed up score significantly had to do with the increased tendency of developing HAP following AIS whereas the

	Training	Testing	P value
Patients, n (%)	1094	729	
Demographics			
Age (years), median (IQR)	67.5 (60-76)	69 (60-78)	0.272
Gender, n (%)			0.444
Male, n (%)	724 (66.2)	495 (67.9)	
Female, n (%)	370 (33.8)	234 (32.1)	
Medical history, n (%)			
Hypertension	779 (71.2)	526 (72.2)	0.661
Diabetes mellitus	312 (28.5)	214 (29.4)	0.700
Hyperlipidemia	27 (2.5)	17 (2.3)	0.853
Coronary artery disease	123 (11.2)	90 (12.3)	0.473
Atrial fibrillation	126 (11.5)	77 (10.6)	0.525
Congestive heart failure	0 (0)	1 (0.1)	0.220
Valvular heart disease	21 (1.9)	8 (1.1)	0.169
Peripheral vascular disease	1 (0.1)	1 (0.1)	0.772
Transient ischemic attack	5 (0.5)	1 (0.1)	0.243
Previous stroke	168 (15.4)	127 (17.4)	0.241
Previous cerebral hemorrhage	27 (2.5)	17 (2.3)	0.853
Smoking, n (%)			0.709
Never smoker	511 (46.7)	345 (47.3)	
Current smoker	438 (40.0)	297 (40.7)	
Former smoker	145 (13.3)	87 (11.9)	
Drinking, n (%)			0.858
Never drinker	658 (60.1)	429 (58.8)	
Current drinker	327 (29.9)	225 (30.9)	
Former drinker	109 (10.0)	75 (10.3)	
Comorbidity, n (%)			
Coronary artery disease	124 (11.3)	100 (13.7)	0.129
Cardiac insufficiency	36 (3.3)	18 (2.5)	0.311
Atrial fibrillation	171 (15.6)	112 (15.4)	0.877
Diabetes mellitus	402 (36.7)	271 (37.2)	0.853
Hypertension	875 (80.0)	580 (79.6)	0.826
Hyperlipidemia	113 (10.3)	52 (7.1)	0.085
Pneumonia	204 (18.6)	132 (18.1)	0.771
Baseline data			
NIHSS score, median (IQR)	3 (2-6)	3 (2-6)	0.327
Previous mRS scores, median (IQR)	0 (0-0)	0 (0-0)	0.621

NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale.

Table 1: Demographic and laboratory characteristics in Training and Test Cohorts

	OR	Error	Wald	P	95% CI
Age	1.029	0.007	4.40	P<0.0001	1.016-1.042
NIHSS on admission	1.172	0.015	12.23	P<0.0001	1.143-1.203
Prestroke mRS	1.321	0.093	3.97	P<0.0001	1.151-1.516
Atrial fibrillation	2.493	0.424	5.36	P<0.0001	1.785-3.480

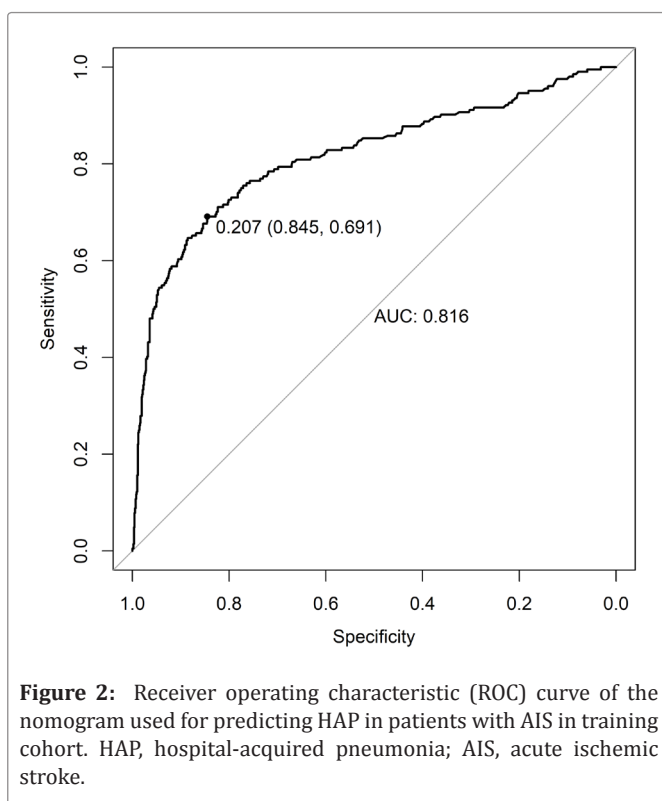
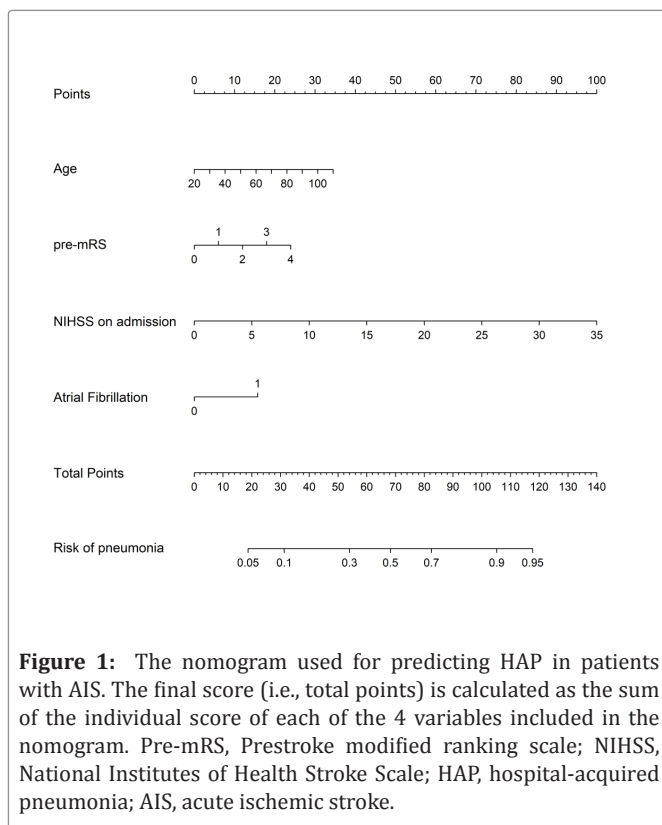
NIHSS: National Institutes of Health Stroke Scale; CI: confidence intervals; mRS: modified Rankin Scale

Table 2: Significant predictors of Hospital-acquired pneumonia in patients with acute ischemic stroke

reduced summed up score was considerably related to the reduced probability of HAP after AIS.

The AUC-receiver operating characteristic value of the ANAS nomogram was 0.816 (95% CI: 0.779-0.854) in the training cohort (Figure 2). The model was validated in the test cohort with AUC-ROC value of 0.807 (95% CI: 0.765-0.849) (Figure 3). The age values exhibited a modest diagnostic accuracy for identifying patients with HAP after AIS, displaying an AUC of 0.682 (95% CI: 0.640-0.724;

p<0.0001). The NIHSS scores on admission exhibited a good diagnostic accuracy for identifying patients with HAP post-AIS, displaying an AUC of 0.787 (95% CI: 0.749-0.824; p<0.0001). The total number of patients with a risk probability of <10% was 565/1094 (51.5%), and only 35 (6.2%) of these were diagnosed with HAP after AIS (0.828 sensitivity, 0.596 specificity, 0.938 negative predictive value, and 0.319 positive predictive value). The total number of patients with a risk probability of < 40% was 950/1094 (86.8%), 101 of whom



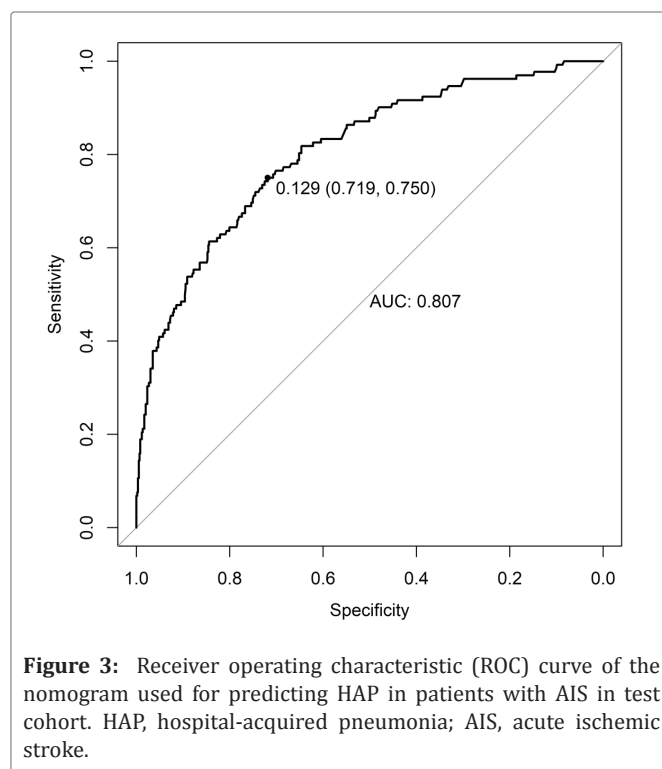
had HAP after AIS (0.505 sensitivity, 0.954 specificity, 0.894 negative predictive value, and 0.715 positive predictive value). Finally, the total number of patients with a high-risk probability (i.e., >80%) was 40/1094 (3.7%), the vast majority of whom (31/40; 77.5%) had a HAP after AIS (0.152 sensitivity, 0.99 specificity, 0.836 negative predictive value, and 0.775 positive predictive value).

The bias-corrected calibration plot for the nomogram model demonstrated good agreement between predictors calculated with the ANAS nomogram and actual HAP after AIS in the training cohort

(Figure 4) and test cohort (Figure 5). An adequate fit of the model predicting the risk of HAP after AIS was revealed by Calibration graphic. The Hosmer-Lemeshow goodness-of-fit test demonstrated good calibration of the monogram in both trainings ($p=0.1876$) and ($p=0.5591$) test sets.

Discussion

Despite advancements in the area of stroke, the impact of HAP on morbidity and mortality in patients with stroke has affected this progress in current times [22]. Therefore, early identification of patients that have been diagnosed with AIS and consequently have increased risk of HAP could be a valuable perspective to provide a reasonable approach in the prevention, increased individualized monitoring, and allocation of relevant medical resources. Several prognostic scores [7-12] have been developed to predict the risk of HAP after stroke. It is imperative to note that, the various scores and models for individualized prediction of HAP are influenced by the application of dichotomization of prognosticators which include age and prestroke mRS. Interestingly, dichotomization presents a downside in the sense that it does not employ the use of within-category information and hence results in data being lost. Therefore, our study aimed to develop a simple, visual and reliable clinically useful tool for predicting the risk of HAP in AIS patients. Owing to this reason, the ANAS nomogram was developed based on variables that were provided at first-hand on admission. The ANAS nomogram could prove more preferable to previous prognostic models that fundamentally employ archaic risk-grouping categorization which tends to reduce the predictive accuracy. In contrast to previous scores, it is important to acknowledge that this novel study is the foremost to render a graphical model, and this provides a more effective prognostic tool for predicting the risk of HAP in patients with AIS from 5 to 95%. This is demonstrated in Figure 1. The ANAS nomogram is a visual computation instrument, incorporating 4 clinical factors all of which are routinely obtainable on hospitalization to predict HAP after AIS. The ANAS nomogram offers an individualized prediction of HAP, which is entirely based on the individual's characteristics potentially increasing its practical applicability in the conducting of clinical trials as well as in the delivery of regular procedural care. Additionally, by integrating all relevant and informative predictors of a patient, the ANAS nomograms provide better predictive accuracy for HAP than models based on risk grouping. Simultaneously, the discriminative



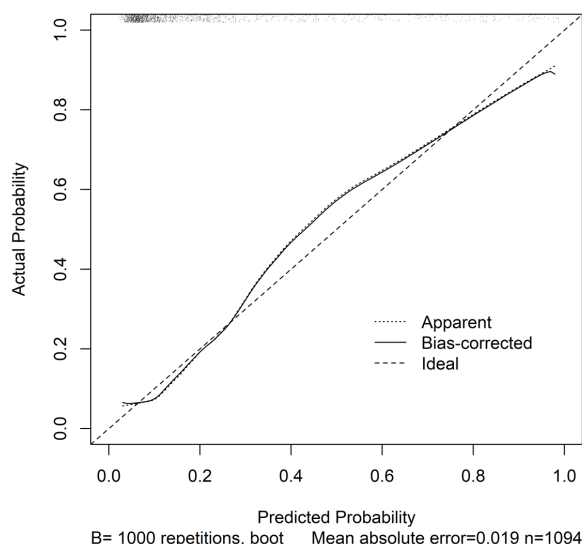


Figure 4: The calibration plot for the nomogram used for predicting HAP in patients with AIS in training cohort. Dashed line is reference line where an ideal nomogram would lie. Dotted line is the performance of the nomogram, while the solid line corrects for any bias in the nomogram. HAP, hospital-acquired pneumonia; AIS, acute ischemic stroke.

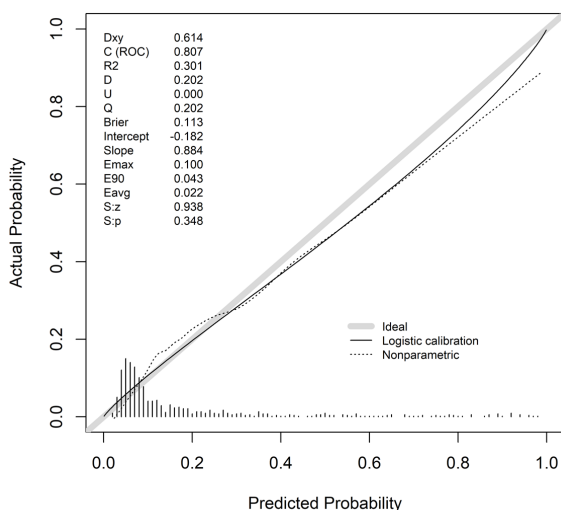


Figure 5: The calibration plot for the nomogram used for predicting HAP in patients with AIS in test cohort. Dashed line is a reference line where an ideal nomogram would lie. Dotted line is the performance of the nomogram, while the solid line corrects for any bias in the nomogram. HAP, hospital-acquired pneumonia; AIS, acute ischemic stroke.

performance of the ANAS nomogram proved good in the training and test cohorts.

Consistent with earlier reports [5,7,10,12,23-31], we confirmed that age, NHISS on admission, prestroke mRS and atrial fibrillation were significantly associated with HAP after AIS. As observed from the nomogram in this current research work, a greater than 80% likelihood border range was inferred. This likelihood border marker was associated with a positive value of prognostication which was 0.775. A more exact prediction of the risk of HAP after AIS was further enhanced by the positive value of prediction of 0.775. As opposed to the resultant nomogram, a greater than 80 % border marker, a risk

cut-off of less than 10% remarkably showed a more negative value of prediction, which was 0.938. The tendency of developing HAP after AIS is accurately excluded by the negative value of prediction mentioned earlier.

Findings of our study showed that NHISS on admission is the strongest independent predictor of HAP after AIS, while age, prestroke mRS score, and atrial fibrillation are significant independent predictors of HAP. Our results demonstrated that advancement in age was independently related to HAP as demonstrated in previous research [7,10,12,24-26]. The tendency to develop HAP is significantly increased in patients that are above 80 years old. This observed predisposition may be accounted for by the incidence of a compromised immune system coupled with comorbid medical conditions such as obstructive airways disease and cardiac conditions, as well as dysphagia and its associated risks in the elderly, as consequent to the advancement in age [32].

A deteriorated level of consciousness and neurological impairment are related to a significantly increased NHISS score [33]. NHISS on admission was the strongest, significant independent predictor for the development of HAP and it maintained significant impact even after an alteration of other demographic and clinical factors. Patients with a characteristically intense level of neurological damage are much more predisposed to develop HAP after AIS, with reference to previous research [7,12,23,26-29,34]. Patients with altered level of consciousness usually experience a higher incidence of neurological deficits and are less able to guard their airways thereby increasing their predisposition to develop pneumonia. More so, this evaluative work showed that AF is an independent risk factor for HAP in AIS patients. Although AF is an established marker of prediction, not many studies have reported it in available literature. A recent study inferred that AF itself is an independent risk factor for HAP [31]. In the event of AF, the incidence of pulmonary infection may be increased by the presence of decreased cardiac output as well as pulmonary congestion which may result from atrial irregular processes.

Importantly, we also found that the association between prestroke mRS and HAP after AIS. mRS is a standard of disability worldwide that is ubiquitously employed in the assessment of stroke when focusing on functional outcome [35]. A study by Quinn et al. [36] inferred that a higher score of prestroke mRS resulted in a higher likelihood of the patient to experience unfavourable results, increase the duration of hospital stay and medical complications such as pneumonia. Correspondingly, with reference to former research work by Chen et al. [37], there was an agreeable relationship between hospitalization time and HAP.

The ANAS nomogram is a useful tool that could aid the facilitation of the spark of awareness in clinicians to adopt individualized preventive measures in patients with increased suspicious, follow-up counseling and patient counseling. Additionally, early intervention and allocation of medical resources may lower the risk of complications and improve prognosis after acute stroke.

The present study has a number of strengths. First, our study is unique in the sense that, the ANAS nomogram is a simple graphic prognostic model developed with the definite aim of predicting the risk of HAP in patients with AIS. By integrating clinical variables that are readily obtainable following admission, the ANAS nomogram has the capability to generate an individual risk of developing HAP after AIS. Additionally, the nomogram prognostications are customized to suit the probable adverse effects stirred by the associated features of stroke as specific to a patient. Relatively, this is rather more significant against the results of the general group peers. For example, in this first instance, a 50-year-old patient (11.5 points) with NHISS on admission score of 10 (28.6 points), prestroke mRS of 1 (0.99 points) and atrial fibrillation of 1 (15.7 points), with a total score of 56.8 points will have 35% risk of developing HAP after AIS. In this other instance, a 78-year-old patient (22.2 points) with NHISS

on admission score of 20 (57.1 points), prestroke mRS of 2 (11.98 points) and atrial fibrillation of 1 (15.7 points), with a total score of 107.1 points will have > 90% risk of developing HAP after AIS. Second, our ANAS nomogram only requires easily accessible variables that are available on hospital admission. Laboratory data and variables such as swallowing test [11] and mechanical ventilation [12] were not included in our nomogram as such variables are not always readily available on admission. The ANAS nomogram could be used to predict individual risk of developing HAP on hospital arrival and as such could be useful in tailored counseling of a patient as well as developing follow-up schedules.

A couple of shortcomings were identified in this study. First, the collection of data was carried out in a single center and was streamlined in a retrospective fashion thereby causing much data lost which might have influenced the final outcome. Second, dysphasia a known predictor for HAP was absent in the cohort. This study's precision in predicting the likelihood of developing HAP in AIS patients is improbable to be affected by the neglect of dysphasia from the ANAS nomogram as dysphasia is associated with higher NHISS on admission and advancement in age [38,39]. Regardless of these identified shortcomings, this research work is a novel endeavour to build a nomogram model for individualized risk prediction of HAP in patients with AIS. Finally, external validation in an entirely different cohort of patients is vehemently recommended.

Conclusion

We developed a nomogram based on clinical variables routinely available on hospitalization, it is an effective prognostic tool used for individualized prediction of risk of HAP in patients with AIS. The identification of early predictors of HAP is of immense significance for clinical care providers, thus the ANAS nomogram will help clinicians to provide appropriate clinical information and care to patients and their families and also aid in the classification of likely unfavorable outcomes in clinical as well as research settings. Thus, the ANAS nomogram is a promising tool that provides a new and improved model of predicting individualized risk of HAP in patients with AIS.

Author Contributions

Linda Nyame, Enoch Kwaw-Nimeson and Yang Zou contributed equally to this work. Jian-Jian Zou, Jun-shan Zhou and Chun-Lian Jiang conceived, designed and supervised the study. Jun-shan Zhou, Xiang-Liang Chen, and Yu-Kai Liu acquired the data. Linda Nyame, Enoch Kwaw-Nimeson, Xiang Li and Zheng Zhao analyzed and interpreted the data, provided statistical analysis, had full access to all of the data in the study, and are responsible for the integrity of the data and the accuracy of the data analysis. Linda Nyame, Mako Ibrahim and Chao Sun drafted the manuscript, Jian-Jian Zou, Chun-Lian Jiang and Yang Zou critically revised the manuscript for important intellectual content.

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Disclosure Statement

The authors have declared that they have no conflicts of interest regarding the content of this article.

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