



A Novel FAND Nomogram to Predict the Risk of Stroke-Associated Pneumonia in Acute Ischemic Stroke patients with Mechanical Thrombectomy

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Abstract

Background: The timely prediction in the risk of Stroke-Associated Pneumonia (SAP) in Acute Ischemic stroke (AIS) patients with Mechanical thrombectomy (MT) treatment is of high priority, given the rise in AIS mortality as a result. Although prior extensive research has been conducted in SAP preventive management and therapeutics, ischemic stroke patients are still at serious risk of contracting SAP infections following certain medical procedures like Mechanical thrombectomy, a care standard for AIS patients. The predictive accuracy of patients with higher infection risk and adjusting therapeutic strategies accordingly will not only provide an enhanced preventive measure perspective but also significantly improve patient outcomes. Hence, our study was aimed at the validation and development of a novel predictive tool for risk stratification and individualized predictions of SAP occurrence in AIS patients with MT.

Methods: A multicenter retrospective study was executed with 405 AIS patients with MT and admitted to the three Chinese stroke units. The major measure of outcome was to estimate the risk of SAP through the integration of the following four predictors FBG, Age, NIHSS, and Diastolic blood pressure (FAND) into a nomogram. Assessed on the multivariate logistic model, a nomogram was constructed, using the area under the receiver-operating characteristic curve to evaluate the discriminative performance and the Hosmer–Lemeshow test for risk prediction model calibration.

Results: Age (OR:1.039; 95%CI 1.017-1.062; p=0.001), NIHSS(National Institutes of Health Stroke Scale) score on admission(OR:1.066; 95%CI: 1.030-1.103; p< 0.0001), diastolic blood pressure (OR 1.023; 95% CI 1.006-1.040: p=0.008), Fasting blood glucose (OR 1.1444; 95% CI 1.029-1.271; p=0.013) remained independent predictors of SAP integrated into the FAND nomogram after AIS Chinese patients with MT. The Hosmer–Lemeshow goodness-of fit-test expressed good calibration (p-value: 0.496) and Area under the curve of 0.737 was exhibited for functional impairment prediction.

Conclusion: The FAND nomogram is a novel prognostic model developed and validated in Chinese AIS patients with MT may aid in preventive measure strategies and predict poor patient outcomes.

Keywords

Nomogram; Stroke-Associated Pneumonia; Mechanical Thrombectomy; Acute Ischemic Stroke; Chinese

Introduction

Acute ischemic stroke (AIS) continues to be a major cause of short and long term mortality and morbidity [1,2]. Mechanical thrombectomy (MT) has proven highly effective in AIS therapy due to the significantly higher vessel recanalization and 24 hour treatment ability [3-7]. Post-surgical complications remain frequent as a considerable amount of AIS-related deaths are directly attributed to suffered complications [8]. Stroke-Associated

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Pneumonia (SAP) is a lower respiratory tract infection in the lungs occurring roughly 48-72 hours after clinical admission and is rapidly emerging as a crucial patient safety concern [9]. Pneumonia is reportedly the most dominant, dangerous and recurrent severe AIS complication with an estimated mortality rate of about 30% and an 8 to 12% attributable mortality rate in stroke survivors increasing in-hospital admission by approximately six days [10-14]. However, the incidence of SAP is relative to the study population with older patients being at higher risk of infection. Considering the demographic increase in the elderly and longer life expectancy in china, a rise in the future number of patients experiencing complications after AIS is predictable [15]. Although preventive intervention measures carried out by clinics show an impressive decrease in hospitalization and mortality rates, clinical complications have not been completely eliminated and infection rates are expected to rise within the next few years. Therefore, early prediction of SAP onset after AIS is of great significance in providing a reasonable approach to clinical and therapeutic management [16-18].

The vast majority of comprehensive research conducted on SAP has primarily centered around diagnosis rather than eliminating infection prognosis which is equally important [19]. Gaining insight into important factors in the prognosis of this condition might be challenging but highly necessary in accurately predicting patient outcomes, suggesting reasonable clinical and treatment management approach, and giving patients and their loved ones a better understanding of AIS [7,20]. Regardless of several scores constructed with the aim of predicting pneumonia emergence in stroke patients such as ISAN score, the PANTHERIS score, A2DS2 (Age, Atrial fibrillation [AF], Dysphagia, Sex, Stroke Severity using National Institutes of Health Stroke Scale [NIHSS] score), Chumbler's score, Functional Bedside Aspiration Screen (FBAS score) and Stroke-Associated Pneumonia Score (acute ischemic stroke-associated pneumonia score, AIS-APS) there are still restrictions on the accumulative effect in clinical care practice by moderate predictive performance [21-26].

A nomogram is a reliable statistical tool that generates individualized approximation, faster prognostic prediction and continuous probability estimation of certain outcomes in a given patient, it is developed by the mathematical visualization of complex formula through Cox proportional hazards analysis or multivariate logistic regression and the incorporation of some continuous variables as a scoring system [27-29]. Nomograms are an integral constituent of modern clinical intervention and have been extensively integrated and validated in a wide array of medical applications [30-34]. To date however, no nomogram models had been found to predict the risk of SAP in Chinese AIS patients with MT.

The purpose of this study was advancing and validating a nomogram model through the incorporation of variables promptly accessible at the patient time of admission for the individualized prediction of SAP after AIS that could directly aid individual treatment for AIS patients and provide relevant therapeutic preventive measures for patients with a higher risk of SAP.

Methods

Study design, participants, and procedures

A retrospective study was conducted based on data sequentially recorded from 405 patients between the period of January 2014 to February 2019. The AIS patients had been admitted to three-stroke units The First. Affiliated Hospital (People's Hospital of Hunan Province), Nanjing First Hospital and Changsha Central Hospital respectively. After MT therapy, each patient gave consent to the use of their information for research purposes and the scientific data obtained was approved for research by the three hospital ethics committees in correlation with internal protocol and Helsinki Declaration. All studies executed under the consent of the Local Institutional Review Board.

Patients admitted with comprehensive clinical, demographic and laboratory information were solely considered for this research. The study's exclusion criteria were no SAP infection, age unknown or age <18, absence of FBG, anterior circulation stroke TOAST, no Coronary heart disease medical history, therapy onset interval of over 24h, incomplete data, and an unknown National Institutes of Health Stroke Scale (NIHSS) score on admission.

The following were recorded, sex, age, medical history such as diabetes mellitus, hypertension, coronary artery disease, hyperlipidemia, transient ischemic stroke, previous cerebral infarction, atrial fibrillation, previous cerebral hemorrhage etc. diastolic blood pressure, NIHSS score on admission and FBG (fasting blood glucose). The diagnosis of SAP in AIS patients with MT through antibiotic treatment stimulation following admission was the clinical outcome.

Statistical analysis

The nomogram generation was based on assigning a graphic preliminary score to each of the 4 independent predictors with point range within 1-100 and then summed up to generate a total score. Finally, they were converted into an individual risk of SAP expressed in the percentile range of 0-100%. Predictions suggested a higher total nomogram score in association with higher probability of SAP and a lower score associated with lower probability of SAP diagnosis.

The median value and interquartile range were set as continuous variables while using the Mann-Whitney U-test for univariate comparison to explore the cohort differences. The expression of categorical variables was alternatively expressed as the division of events numbers by the total amount except unknown or missing cases. Proportional differences were assessed by the χ^2 test or Fisher's exact test. The SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), Stata version 13.0 (StataCorp, College Station, TX, USA) statistical software and the statistical software package R version 3.5.2 (R Development Core Team, Auckland, New Zealand) was used in the statistical analysis.

The FAND nomogram model was then constructed to predict the probability of SAP in AIS patients with MT. In the nomogram generation, a multivariate logistic regression analysis was conducted in a stepwise order which included, age, Fasting Blood Glucose (FBG), NIHSS score on admission and Diastolic BP (blood pressure) as pre-established variables, all with a univariate analysis probability value at < 0.10.

The foremost model was then selected based on the Akaike information criterion. The Condition Index (<30 considered as non-significant) and Variation Inflation Factor Analysis (VIF, <2 considered as non-significant) of variable co-linearity combinations were used in the analysis of multivariate logistic. In the multivariate model, calculation of the odds ratio and 95% confidence interval were carried out for significantly associated primary endpoint variables.

Model performance was assessed by method of discrimination (which is utilizing the start score to unrelated dividing pneumonia patients from patients without pneumonia) or the calibration method (SAP prediction distance relative to actual patient outcome). The predictive accuracy of the nomogram model was evaluated through the calculation of the area below the receiver operating characteristic curve (AUC-ROC). Visual assessment was used in the test cohort through a calibration plot to determine the similarities between actual outcomes and outcomes predicted, where probability predicted was plotted against recorded pneumonia. Using a 45° line as a perfect calibration indication, the match between the value predicted and the actual patient's risk was assessed. Furthermore, internal validation of the model was obtained with the use of 2000 bootstrap samples. Every test was two-sided and if the value of probability was < 0.05 was considered statistically significant.

Results

Data from a total number of 405 AIS patients admitted to the three Chinese stroke units and treated with MT was compiled. Patients were excluded from the study research for no SAP diagnosis ($n=9$; 2.2%), unknown NIHSS score on admission ($n=1$; 0.2%), lack of FBG ($n=45$; 11.1%), no anterior circulation stroke ($n=6$; 1.5%), lack of TOAST ($n=11$; 2.7%), no history with Coronary artery disease ($n=24$; 5.9%), and patients <18 years old were also excluded from this research. Hence, the total number of only 305 patients with a complete data record useful in generation of the nomogram model participated in the study (Median age 72 years; IQR 62 – 79.5 years). The proportion of patients with SAP was calculated as 64.9% (198/305).

All clinical, laboratory and demographic data generated from the study population were stated in **Table 1**. Values included: age (67 versus 75; $p<0.0001$), NIHSS score on admission (12 versus 16; $p<0.0001$), Diastolic blood pressure (81 versus 86; $p=0.017$) and FBG (5.17 versus 6.71; $p<0.0001$) were all found to be significant in SAP prediction in AIS patients with MT.

During the process of FAND nomogram development for the prediction of SAP in AIS patients with MT, four non-categorical significant predictors were entered into a logistics regression model in the multivariate analysis: Age (OR:1.039; 95%CI 1.017-1.062; $p=0.001$), NIHSS score on admission (OR:1.066; 95%CI: 1.030-1.103; $p<0.0001$), diastolic blood pressure (OR 1.023; 95% CI 1.006-1.040; $p=0.008$), Fasting blood glucose (OR 1.144; 95% CI 1.029-1.271; $p=0.013$) (Figure 1, Table 2). There was no significant co linearity observable for any of the four risk factors imputed in the multivariate regression analysis. Logistic regression model results were $\text{Log}(p(x)/1 - p(x)) = -5.846 + (0.038 \times \text{age}) + (0.064 \times \text{NIHSS score}) + (0.134 \times \text{fasting blood glucose}) + (0.023 \times \text{diastolic blood pressure})$; where $p(x)$ was the probability of risk of SAP in AIS patients with MT.

The model was internally validated through the employment of 2000 bootstrap samples with AUC-ROC value of 0.737 (95%CI: 0.679-0.795) (Figure 2). The age values with AUC of 0.655 (95% CI: 0.592 – 0.718; $p<0.0001$). The scores of NIHSS on admission displaying an AUC of 0.670 (95% CI: 0.606 – 0.734; $p<0.0001$) and the FBG with an AUC of 0.652 (95% CI: 0.586 – 0.718; $p<0.0001$) all showed diagnostic accuracy in the identification of hospital-acquired pneumonia patients. The overall number of patients with a risk probability of <20% was 6/305 (2.0%), and only one of these were acquired pneumonia (0.99 sensitivity, 0.05 specificity, 0.66 positive predictive value and, 0.83 negative predictive value). All patients with a risk probability <40% were 37/305 (12.1%), 12 of whom (32.4%) had acquired pneumonia (0.94 sensitivity, 0.23 specificity, 0.69 positive predictive value and 0.68 negative predictive value). Lastly, the total number of high-risk probability patients (i.e., >80%) was 77/305 (25.2%). There was a vast predominance in patients (69/77; 89.6%) with poor prognosis (0.35 sensitivity, 0.93 specificity, 0.90 positive predictive value and 0.43 negative predictive value). The FAND nomogram model bias-corrected calibration plot illustrates good agreement between FAND nomogram predictors and verified SAP (Figure 3). Hosmer-Lemeshow test P-value: 0.496 showed a good nomogram calibration in the goodness-of-fit test. Further, the mean variance inflation factor (VIF) was 1.03 indicating no multi-collinearity between predictors and was considered non-significant.

Discussion

Ischemic stroke continues to be a leading cause of death and disability. An astonishing 87 percent of all stroke cases are ischemic resulting in as many as 6.7 million deaths worldwide [30]. Irrespective of the exponential advancement of MT devices and extensive recognition of the procedure as an advanced surgical alternative in AIS therapy due to the comparative simplicity and efficacy patients are still at risk of acquiring postoperative SAP. SAP continues to pose a major threat clinically considering the significant increase in mortality through patient immobilization, fever and, organ failure as a result of shock. Over 50,000 deaths (i.e. 1.6 deaths in 10,000 people)

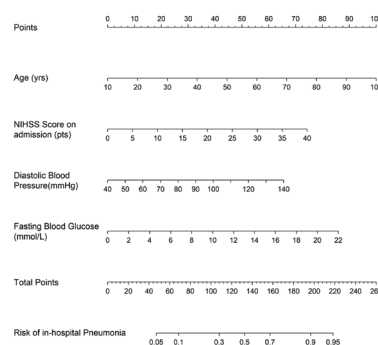


Figure 1: The FAND nomogram used for predicting SAP in AIS patients with MT. The final score (i.e., total points) is calculated as the sum of the individual score of each of the 4 variables included in the nomogram. SAP: Stroke-Associated Pneumonia; AIS: acute ischemic stroke; MT: Mechanical thrombectomy

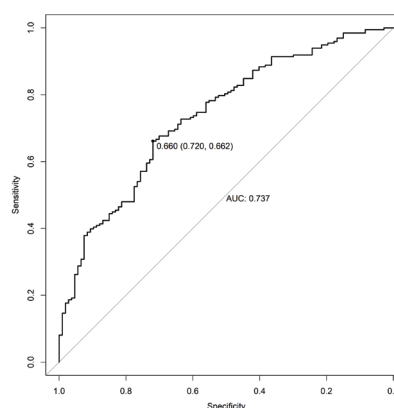


Figure 2: Receiver operating characteristic (ROC) curve of the FAND nomogram used for predicting SAP in AIS patients with MT. SAP: Stroke-Associated Pneumonia; AIS: acute ischemic stroke; MT: Mechanical thrombectomy

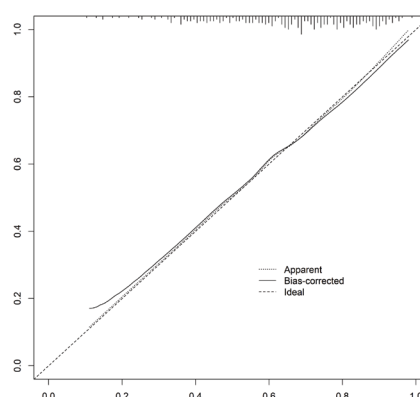


Figure 3: The calibration plot for the FAND nomogram used for predicting SAP in AIS patients with MT. Dashed line is reference line where an ideal nomogram would lie. Dotted line is the performance of the nomogram, while the solid line corrects for any bias in the nomogram. SAP: Stroke-Associated Pneumonia; AIS: acute ischemic stroke; MT: Mechanical thrombectomy

	No SAP	SAP	P
Patients, n (%)	107	198	
Age (years), median (IQR)	67(58-75)	75(64-81)	<0.0001*#
Sex, n (%)			0.860
Male, n (%)	67(62.6)	126(63.6)	
Female, n (%)	40(37.4)	72(36.4)	
Medical history, n (%)			
Hypertension	70(65.4)	147(74.2)	0.105*
Diabetes mellitus	19(17.8)	42(21.2)	0.472
Hyperlipidemia	4(3.7)	8(4.0)	1.000*
Coronary artery disease	16(15.0)	46(23.2)	0.086*
Atrial fibrillation	27(30.7)	56(37.3)	0.141*
Transient ischemic attack	0(0)	3(1.5)	0.554
Previous cerebral infarction	22(20.6)	42(21.2)	0.894
Previous cerebral hemorrhage	5(4.7)	3(1.5)	0.204
Smoking, n (%)			0.265
Never smoker	61(57.0)	117(59.4)	
Former smoker	8(7.5)	24(12.2)	
Current smoker	38(35.5)	56(28.4)	
Baseline data			
NIHSS score on admission, median (IQR)	12(7-17)	16(12-21)	<0.0001*#
Systolic BP, mmHg, median (IQR)	138(123-156)	144(130-159)	0.130#
Diastolic BP, mmHg, median (IQR)	81(72-93)	86(77-99)	0.017*#
INR, median (IQR)	1.00(0.95-1.06)	0.99(0.94-1.08)	0.834#
Creatinine, umol/L, median (IQR)	64.00(57.00-80.00)	74.00(61.0-92.0)	0.006*#
FBG, mmol/L, median (IQR)	5.71(4.89-7.16)	6.71(5.73-8.23)	<0.0001*#
Platelet count, 10 ⁹ /L, median (IQR)	179(141-224)	176(143-225)	
TC, mmol/L, median (IQR)	4.30(3.54-5.09)	4.25(3.49-4.97)	0.646#
TG, mmol/L, median (IQR)	1.08(0.77-1.52)	1.04(0.74-1.50)	0.517#
LDL, mmol/l, median (IQR)	2.69(2.01-3.29)	2.51(1.96-3.09)	0.217#
HbA1c, %, median (IQR)	5.80(5.50-6.30)	5.90(5.50-6.40)	0.662#
UA, umol/l, median (IQR)	267.00(227.00-371.00)	319.50(221.6-385.5)	0.165#
Anterior circulation stroke, n (%)	88(82.2)	157(79.3)	0.536
Posterior circulation stroke, n (%)	21(19.6)	44(22.2)	0.597
TOAST classification			0.119
Large artery atherosclerosis, n (%)	42(39.3)	55(27.8)	
Cardioembolism, n (%)	45(42.1)	115(58.1)	
Others, n (%)	20(18.6)	11(14.1)	
Intravenous thrombolysis, n (%)			0.095*
No thrombolysis	70(65.4)	110(55.6)	
Thrombolysis	37(34.6)	88(44.4)	
Interval from onset to treatment, min, median (IQR)	325(243-450)	270(198-380)	0.006*#

Table 1: Clinical, demographic and laboratory data of study population.

SAP, Stroke-Associated Pneumonia, INR International normalized ratios, FBG Fasting blood glucose, TC total cholesterol, TG triglyceride, LDL Low density lipoprotein, HbA1c Glycated hemoglobin, UA Uric Acid, TOAST Trial of ORG 10172 in Acute Stroke Treatment. *included into the multiple logistic regression models ($P < 0.1$). Additionally, traditional stroke risk factor such as atrial fibrillation was added into the model. # calculated using Mann-Whitney U test.

	OR	Error	Wald	P	95% CI
Age	1.039	0.011	3.45	0.001	1.017-1.062
NIHSS on admission	1.066	0.018	3.68	P<0.0001	1.030-1.103
Diastolic blood pressure	1.023	0.009	2.64	0.008	1.006-1.040
FBG	1.144	0.062	2.49	0.013	1.029-1.271

Table 2: Significant predictors of SAP in AIS patients with MT.

SAP: Stroke-Associated Pneumonia; AIS: acute ischemic stroke; MT: Mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; FBG, fasting blood glucose.

were reportedly due to pneumonia in the year 2015 alone [18]. The early prediction of pneumonia onset in AIS patients following MT treatment ought to be a prominent perspective on accurate and systematic clinical and therapeutic management [9,22-23,35,36].

Previous nomogram models and prognostic scores have identified Age and NIHSS score as independent unfavorable outcome predictors in stroke patients. However, the categorization or dichotomization of predictors has been a major limitation as the risk grouping system by 2 or 4 in independent continuous variables has proven to be statistically inefficient and significantly decrease predictive accuracy. A major disadvantage of dichotomization is the lack of incorporating in-category information often resulting in information diminution.

For proper estimation of specific clinical outcomes based on distinctive inputs at clinical interactions, a nomogram (graphical statistical predictive model) was constructed [24]. The FAND nomogram development was based on pre and post-treatment pre-established independent variables and through the combinational assessment of these four putative predictors readily available at time of admission; Age (OR:1.039; 95%CI 1.017-1.062; p=0.001), Fasting Blood Glucose (OR: 1.066; 95%CI: 1.030-1.103); p<0.0001), Diastolic blood pressure (OR 1.023; 95%CI 1.006-1.040: p=0.008) and NIHSS score (OR 1.1444; 95%CI 1.029-1.271; p=0.013) with NIHSS baseline score as the most proficient SAP predictor although age, FBG and diastolic blood pressure remained significant continuous variables. The nomogram presented a more dependable prognostic tool for the individualized prediction of SAP with a 5-95 percentile range in AIS Chinese patients. The discriminative performance of the model was good, efficient and proved relevant even following the adjustment of other clinical and demographic variables.

In our study, a >80% risk limit relative to a 0.90 positive predictive value was derived from the nomogram, providing a more accurate SAP risk. The lower risk limit of <20% was obtained from the nomogram with a more negative predictive value of 0.66, permitting an accurate probability exclusion in SAP diagnosis. Our study results suggested that the score created using variables at time of admission was feasible and reliable. For instance, the FAND nomogram allocated a >95% adverse consequence probability in an 80-year-old patient (76 points) stroke patient, with diastolic blood pressure score of 112 (48 points), FBG at a level of 12.5 (50 points) and NIHSS score of 25 (50 points) and a score total of 224. Alternatively, the nomogram assigns a <10% probability to a 30-year-old (22.5 points) with diastolic blood pressure of 60 (13 points), FBG at a level of 4 (15 points) and NIHSS score of 5 (9 points) with a total score of 59.5 through score conversion into individual probability continuum, The FAND nomogram provides a more precise reclassification of SAP diagnostic outcome.

During the course of our study, we found that elderly patients 80 years old and above were predominantly at a particularly higher risk of SAP infection proving age to be a contributive factor to long-term mortality and pneumonia diagnosis in AIS patients [22]. These predispositions may be conveniently elucidated through medical conditions such as obstructive airway diseases or certain cardiovascular diseases such as high blood pressure, elevated cholesterol and coronary artery disease and also comorbid

compromises in the immune system of the elderly. We also noticed an association between a higher NIHSS score and impaired neurological and consciousness levels [37]. Patients experiencing severe neurological damage levels and those with consciousness level alterations have notably had a higher predisposition to SAP diagnosis with previous study references. Some other important factors associated with SAP after MT treatment in AIS patients included the use of antibiotics and glucocorticoid, Charlson Comorbidity Index (CCI) score and admission in the Intensive care unit (ICU). The management and functional evaluation of these several factors associated with stroke-acquired pneumonia diagnosis especially in elderly patients are recommended and a prime comprehensive possible-complication assessment ought to be carried out earlier in patient admission [38-42].

The FAND nomogram provided a functional decrease in the influence of alternative treatment prognosis since it was developed in compliance with data assembled from AIS patients treated with MT. Therefore, the nomogram could hold an advantage over previous models and prognostic scores comprehending the use of obsolete categorization in patient risk grouping for various risk predictor identification in prior models. Hence, providing better circumstantial information in the facilitation of timely detection in patients with a higher probability of acquiring SAP aiding the relay of prognostic information to patients and their loved ones. The FAND nomogram acts as a visual tool beneficial in leading clinicians and patients to a better AIS treatment approach through individual stroke characterization and prognostications custom made to fit possible adverse effects.

Some research limitations were the comparatively small sample quantity and the retrospective nature of our study. Secondly, an important SAP predictor known as dysphasia was not included in the cohort and could influence the predictive accuracy of the model given dysphagia, age and NIHSS score on admission is related to SAP infection. Neuro-imaging predictors were also absent in this study, the presence of which could have provided higher discriminative performance and enhanced the nomogram's predictive accuracy in AIS patients with MT. Also, during categorical grouping and predictive model generation, limited information on patient's ethnic, racial or geographical information was provided differences that could influence the SAP predictions. Further, our research data was collected based on administrative data manually compiled by a clinicians; it may or may not have been neglected by clinical predictions. Lastly, external validation in different patient's cohort is required. Irrespective of the expressed limitations, our study is the first in our knowledge to develop and validate a prognostic nomogram for the prediction of SAP in Chinese AIS patients treated with MT.

The novel nomogram presented in our research was successfully used as a reliable and efficient tool in the prediction of SAP in AIS patients after receiving MT treatment. The prognosis provided by the FAND nomogram was constructed in compliance with possible adverse effects modeled through individual stroke characterization. In summary, this study suggests that demographic, laboratory and clinical predictors (like age, FBG, NIHSS admission score, and diastolic

blood pressure) may be preferable and more reliable predictors of SAP in AIS patients with MT, which could result in management strategy enhancement and better therapeutic approach by clinicians.

Conclusions

The FAND nomogram provided useful and relatively accurate information through the integration of independent and non-categorical predictors for SAP diagnosis probability in Chinese AIS patients with MT.

Author's Contributions

Belynda Owoya Ochete, Linda Nyame and Yang Zou contributed equally to this work. Zhi-Hong Zhao, Jue Hu and Jian-Jian Zou concept, designed and supervised the study. Chao-Ping Huang, Xue-Mei Li and Ya-Jie Shan acquired the data. Xiang Li and Xiang-Jiang Zhou 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. Belynda Owoya Ochete, Linda Nyame and Mako Ibrahim drafted the manuscript, Yang Zou, Qiong Jie, Yun-Xin Liu and Chun Ge critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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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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