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The establishment of a stroke-associated pneumonia predictive scoring system

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Abstract

Background & Objective: Stroke-associated pneumonia (SAP) is a common complication of ischemic stroke, increasing the length of hospital stay and costs, and affecting prognosis. This study aimed to determine the incidence of SAP, investigate the risk factors that lead to SAP to facilitate a more targeted response to the prevention of SAP. *Methods:* A retrospective study was performed to analyze the factors that predict SAP in an acute stroke population from a university affiliated hospital in Fujian, China. A SAP risk score table was constructed. *Results:* A total of 1,016 patients with acute cerebral infarction were enrolled. The incidence of SAP was 13.58%. Multivariate regression analysis found that age, NIHSS, GCS scores, dysphagia, heart failure, creatinine, and proton pump inhibitors (PPIs) use were independently associated with SAP. Based on the data, a SAP risk score table was constructed with age > 75 years -2 points, NIHSS ≥ 16 -2 points, GCS score ≤ 8 -1.5 points, dysphagia - 5 points, heart failure - 1.5 points, creatinine - 1 point, PPIs use - 1.5 points, a total of 14.5 points. The optimal value was 3 points.
Conclusions: Age, NIHSS, GCS score, dysphagia, heart failure, creatinine, and PPIs use were predictive of SAP.

Keywords: Ischemic stroke, stroke-associated pneumonia, prediction score

INTRODUCTION

In 2003, Professor Hilker of Germany first used the term "stroke-associated pneumonia" (SAP) to describe the inflammation of the lung parenchyma infected in patients with acute stroke within 72 hours of admission who were without previous pulmonary infection.[1] Clinical studies have shown that SAP not only increases hospitalization days and costs, but is also the main cause of poor prognosis and death in patients during acute phase.[2]

Currently, there are many studies on SAP-related risk factors both in China and abroad. The risk factors examined include gender, age, stroke type (cerebral hemorrhage, cerebral infarction), onset time, National Institute of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS score), swallowing function, nasal feeding, mechanical ventilation, previous medical history (hypertension, diabetes, atrial fibrillation, heart failure, smoking history, renal insufficiency, nutritional disorders), position (lying, raising the bed), and use of gastric mucosal protective agents.[3-8]

This study aimed to investigate the risk factors of SAP, its correlation with the development of SAP, and establish a predictive score table for ischemic stroke with SAP, which can provide a basis for SAP prevention and treatment.

METHODS

Collection of data

Acute cerebral infarct patients admitted to the Department of Neurology, the First Hospital of Quanzhou, from 1st January 2019 to 31st December 2020 were retrospectively analyzed. The inclusion criteria were: medical history and imaging (CT/MRI) that meet the diagnostic criteria for acute cerebral infarction; symptom onset ≤ 7 days; age ≥ 18 years old; no pulmonary infection or infection outside the lungs during admission, and admission within 48 hours of the disease onset (including the incubation period). Exclusion criteria were: other comorbidities (such as severe heart and lung disease, severe liver and kidney dysfunction); underlying

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autoimmune diseases or diseases affecting immune function; have received mechanical ventilation antibiotics, or immunosuppressive agents that may affect the observed indicators; other physiological or pathological conditions that may affect the indicators; and those with incomplete data. The data collected include gender (male, female), age in years (≤75, >75), stroke site (partial anterior circulation, complete anterior circulation, posterior circulation, multiple anterior and posterior circulation), onset time (<3 days, 3-7 days), NIHSS (0-4, 5-15, ≥16), GCS score (>12,9-12, ≤8), dysphagia, comorbidities (hypertension, diabetes, atrial fibrillation, heart failure), history of smoking, initial laboratory tests (albumin, creatinine), use of proton pump inhibitor (PPIs), and whether SAP occurred during hospitalization (based on the US National Centers for Disease Control and Prevention (CDC) 2015 recommended diagnostic criteria for acute stroke patients[9]).

Statistical analysis

The collected data were statistically analyzed with SPSS 20.0 software, and the test level was bilateral P<0.05. Gender, age, onset time, dysphagia, comorbidities (hypertension, diabetes, atrial fibrillation, heart failure), smoking history, and related medications (PPIs) were two-category variables, and four-factor analysis was performed using a four-square-square chi-square test. The stroke site, NIHSS, and GCS scores were categorical variables. Chi-square test was used for univariate analysis based on whether or not the stroke-related pneumonia was combined. (If there is any theoretical frequency <5 in the four-table or R*C table, then using Fisher's exact probability method). Albumin and creatinine are numerical variables. Firstly, the normal distribution test proves whether the four groups of data are normal distribution. If the normal distribution is consistent, then the mean and variance are calculated separately. The homogeneity test of variance, independent sample t test or correction is used. The method of testing; if non-normal distribution, the Wilcoxon rank sum test is used to verify the relationship between each factor and SAP.

Univariate analysis of the variables that were statistically significant in relation to the occurrence of SAP using the logistic multivariate regression analysis model to rule out factors that were considered to be indirectly related to statistics. And the regression coefficient (β value) were translated into independent risk factor in the SAP prediction score table, and set the smallest β value to "1", and divide the β value of each risk factor by the smallest β value and get the corresponding Score, After the decimal point, the 0.25 is 0, the 0.25-0.75 is 0.5, and more than 0.75 is 1. The SAP predictive scoring system for ischemic stroke patients is established.

All the cases enrolled were scored using the established SAP predictive scoring system, and the ROC curve was drawn as the end point of SAP, and the sensitivity and specificity of the area under the ROC curve and the critical value were calculated. The A2DS2 scores were scored for all enrolled cases, and the ROC curve was drawn. The area under the curve of the score and the A2DS2 score, sensitivity, specificity and other indicators were compared.

RESULTS

General situation and single factor analysis

From 1st January 2019 to 31st December 2020, a total of 1,538 patients with acute cerebral infarction were admitted to the Department of Neurology, the First Hospital of Quanzhou. Of these, insufficient data was excluded in 25 cases, symptom onset longer than 7 days in 253 cases, malignant tumor in 25 cases, had an associated immune system disease in 7 cases, and preceding pulmonary disease in 4 cases, infection outside the lung on admission in 62 cases, severe renal insufficiency in 7 cases, severe cardiac insufficiency in 9 cases, mechanical ventilation in 2 cases, acute gastrointestinal hemorrhage in 8 cases, and pulmonary infection within 48 hours of admission in 119 cases. All together 522 cases were excluded, and 1,016 cases were included in this study, out of which 138 cases had SAP. The incidence of SAP was 13.58%.

Chi-square test was performed on the 1,016 cases Among the 701 males, there were 88 pneumonia, the SAP incidence was 19.69%. Of the 315 female, there were 50 cases of pneumonia, the SAP incidence was 15.87%, the difference was not statistically significant (P = 0.166). The results of the chi-square test of the remaining variables are shown in Table 1. Age, stroke location, onset time, NIHSS, GCS score, dysphagia, atrial fibrillation, heart failure, creatinine, and PPIs were all significantly associated with SAP. (P<0.05).

The normal distribution test showed that the numerical variable data albumin and creatinine were all of normal distribution. The mean and

Table 1: Univariate analysis: categorical variable chi-square test

Variables		Not combined with SAP	Combined with SAP	Total	The incidence of SAP (%)	χ^2	P values
Gender	Man	613	88	701	19.69	2.04	0.166
	Women	613	50	315	15.87		
Age	≤75	725	84	809	10.38	34.63	< 0.05
	> 75	153	54	207	26.08		
Stroke position	Partial anterior circulation	511	41	552	7.43	92.24	< 0.05
	Complete anterior circulation	73	49	122	16.67		
	posterior circulation	204	30	234	12.82		
	Multiple	90	18	108	40.16		
Onset time	< 3	603	109	712	15.3	6.042	< 0.05
	3-7	275	29	304	9.54		
NIHSS	≤4	532	32	564	5.67	165.3	< 0.05
	5-15	316	62	378	16.4		
	≥16	30	44	74	59.46		
GCS score	> 12	796	77	873	8.82	132.4	< 0.05
	9-12	64	36	100	36		
	≤8	18	25	43	58.14		
Dysphagia	Yes	131	98	229	42.8	214.9	< 0.05
	No	747	40	787	5.08		
Hypertension	Yes	643	111	754	14.72	3.231	0.076
	No	235	27	262	10.31		
Diabetes	Yes	271	49	320	15.31	1.191	0.279
	No	607	89	696	12.79		
Atrial fibrillation	Yes	140	53	193	27.46	39.09	< 0.05
	No	738	85	823	10.39		
Heart failure	Yes	37	26	63	41.27	43.86	< 0.05
	No	841	112	953	11.75		
Smoking	Yes	380	56	436	12.8	0.355	0.58
	No	498	82	580	14.14		
PPIs	Yes	199	65	264	24.62	37.02	< 0.05
	No	679	73	752	9.7		

Note: If there is any theoretical frequency <5 in the four-table or R*C table, the Fisher exact probability method is used. NIHSS: National Institute of Health stroke scale, CGS score: Glasgow Coma Scale

variance of SAP and non-SAP cases in each group were then calculated, and the variance of the two groups was tested by the homogeneity of variance. (The albumin group had an F value of 33.086, P<0.05; the creatinine group had an F value of 4.375, P<0.05) The independent sample corrected

Table 2: Logistic multivariate regression analysis

Variables	Standard coefficient (β values)	95%CI	P values
Age	0.121	0.057-0.148	< 0.05
NIHSS	0.118	0.027-0.102	< 0.05
GCS score	0.084	0.011-0.109	< 0.05
Dysphagia	0.319	0.21-0.313	< 0.05
Heart failure	0.087	0.047-0.210	< 0.05
Creatinine	0.067	0.001-0.002	< 0.05
Use of PPIs	0.085	0.025-0.108	< 0.05

Note:. NIHSS: National Institute of Health stroke scale, CGS score: Glasgow Coma Scale proton pump suppression

t-test showed that the T value of albumin group was 0.54, P=0.59; the T value of creatinine group was 2.963, P<0.05. The difference of creatinine between SAP group and non-SAP group was statistically significant.

Logistic multi-factor regression analysis and establishment of SAP prediction score table

After independent sample T test and chi-square test, the factors that were statistically significant effect on SAP were as follow: Age, stroke location, onset time, NIHSS, GCS score, dysphagia, atrial fibrillation, heart failure, creatinine, and PPIs use. Logistic multivariate regression analysis was performed using SPSS20.0 software. The regression coefficients (β values) of each factor were: 0.118, 0.041, 0.007, 0.119, 0.079, 0.317, 0.008, 0.082, 0.064, 0.084. When the test level was P<0.05, the stroke site (P=0.137), onset time (P=0.805), and atrial fibrillation (P=0.797) were considered to be not directly related to the occurrence of SAP. Age, NIHSS, GCS score, dysphagia, heart failure, creatinine, and use of PPIs were considered to be associated with SAP (P<0.05). Excluding the non-statistically significant variables, the selected seven variables were again subjected to logistic multivariate regression analysis. The β values and 95% CI of β were: 0.121, 0.057-0.148; 0.118, 0.027-0.102; 0.084, 0.011-0.109; 0.319, 0.21-0.313; 0.087, 0.047-0.210; 0.067, 0.001-0.002; 0.085, 0.025-0.108, all P values are <0.05 (Table 2).

With the minimum value (creatinine) 0.067 given as "1", and divide each β value by 0.067 to obtain the corresponding score (after the decimal point was less than 0.25, it was 0, 0.25- 0.74 was recorded as 0.5, ≥0.75 was recorded as 1), an SAP ischemic stroke SAP prediction score table was established, as shown in Table 3.

All cases enrolled were scored using the established SAP predictive scoring system, and the occurrence of SAP as the endpoint to draw the ROC curve (Figure 1). The area under the ROC curve was calculated to be 0.855, and the 95% confidence interval was 0.819-0.891 (both sides P<0.05). The point with the highest specificity and sensitivity on the curve is selected, and the critical value is 2.75 points. According to the rule that the score is ≥0.75 after the decimal point is 1 point, the critical value was 3 points and the

Table 3: SAP forecast score table constructed based on the data in this study

Risk factors	Points
>75 years old	2
NIHSS ≥16	2
GCS score ≤8	1.5
dysphagia	5
heart failure	1.5
Creatinine*	1
use of PPIs	1.5

*Note: The center >97umol / L is judged to be elevated creatinine, because the normal value is different, so the application is based on the upper limit of the normal value of the center.

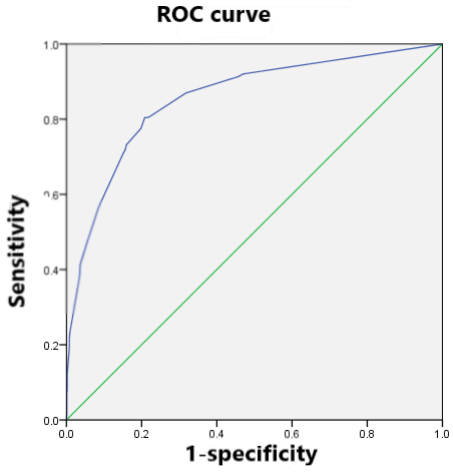

Figure 1: This predicts the scoring system ROC curve based on this study

Note: The area under the curve is 0.855, and the 95% confidence interval is 0.819-0.891. The sensitivity was 80.4% and the specificity was 79.2%.

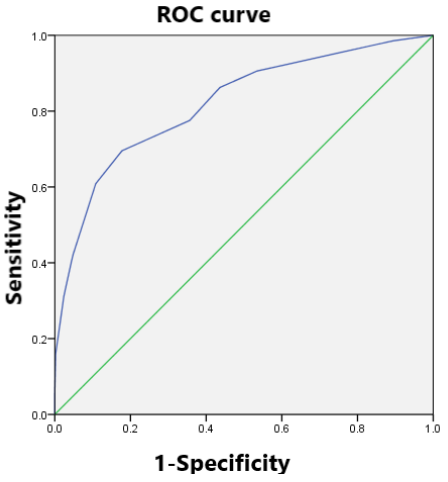

Figure 2: The ROC curse based on A2DS2 score

Note: The area under the curve is 0.819, and the 95% confidence interval is 0.778-0.86.Sensitivity 69.6%, specificity 82.2%

sensitivity is 80.4%. Specificity was 79.2%.

Among 1,016 cases, the score was ≥3 in 293 cases, including 111 cases of pneumonia, and the incidence of pneumonia was 37.88%. The score was <3 points in 723 cases, including 27 cases of pneumonia, and the incidence of pneumonia was 3.73%. The difference was statistically significant (chi-square value $\chi 2$=197.078 bilateral P<0.05).

The A2DS2 score is the current international risk assessment score for SAP. The included risk indicators are: age (1 point), atrial fibrillation (1 point), swallowing dysfunction (2 points), and male (1 point). NIHSS score (5-15 3 points; ≥16 5 points).[5] All the cases in the current study were scored according to A2DS2 and the occurrence of SAP as the endpoint was used to plot the ROC curve (Figure 2). The area under the ROC curve was calculated to be 0.819, the 95% confidence interval was 0.778-0.86 (both sides P<0.05). The point with the highest specificity and sensitivity on the curve (critical value of 3.5 points) was selected. The sensitivity was 69.6% and the specificity was 82.2%. Among 1,016 cases, the score of >3.5 points has 420 cases, with 107 cases of pneumonia; the incidence of pneumonia was 25.48%. With the score of <3.5 points, there were 596 cases, with 31 cases of pneumonia; the incidence of pneumonia was 5.2%. The difference was statistically significant (chi-square value $\chi 2$=86.28, P<0.05).

Compared with the A2DS2 score, our SAP prediction score has a larger area under the curve, with higher sensitivity and slightly lower specificity. Therefore, it is concluded that the ischemic stroke SAP predictive scoring system established in this study can reliably predict the occurrence of SAP.

DISCUSSION

Among the 1,016 patients enrolled in the study, the incidence of SAP was 13.58%. The final logistic multivariate regression analysis of this study identified the following risk factors for SAP: Age, NIHSS, GCS score, dysphagia, atrial fibrillation, heart failure, use of PPP, and elevated creatinine. The established ischemic stroke SAP prediction score table has higher sensitivity and specificity to predict the occurrence of SAP.

Impact of NIHSS, GCS score, age, and dysphagia on SAP

In this study, the age (>75 years old), NIHSS score (≥16), and GCS score (≤8) were selected as the SAP susceptibility scores because their risk scores were 1.5-2.0, which was related to low immunity caused by old age and severity of the stroke. The risk score of dysphagia in this study was the highest (5), as dysphagia may result in aspiration. The importance of dysphagia has been reported in other studies.[10] The risk score of elevated creatinine elevation was the lowest (1). The pathophysiological mechanism of its effect on SAP is uncertain.

Relationship between atrial fibrillation, heart failure and SAP

Atrial fibrillation is considered to be an independent risk factor for SAP in the current literature.[5] The incidence of SAP with atrial fibrillation in this study was 27.46%, and the incidence of SAP without atrial fibrillation was 10.39%. The difference was statistically significant. However, in the subsequent multivariate analysis, the correlation between atrial fibrillation and SAP was not statistically significant; whilst heart failure was considered to be an independent risk factor for SAP. Of the 1,016 cases enrolled in this study, among 140 patients with atrial fibrillation, 44 patients had atrial fibrillation complicated with heart failure, 15 of this 44 patients (34.09%) had SAP. Whereas only 38 of 149 (25.5%) cases of atrial fibrillation without heart failure had SAP. We may conclude here it is the atrial fibrillation combined with heart failure that is at risk of SAP, while atrial fibrillation without heart failure has lower risk, but this remains to be further investigated.

The relationship between the use of PPIs and SAP

Acute ischemic stroke, especially when involving large volume of brain, can result in acute stress response, and the use of antiplatelet drugs such as aspirin, both may affect the gastric mucosa. Thus, PPIs are widely used clinically. There are reports that antacids including histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) are associated with increased pneumonia risk in a variety of disease populations.[11] PPIs have a more significant effect on SAP than other stomach-protecting drugs.[12] Our study showed that the incidence of SAP in the group using PPIs was 24.62%, and those not using PPI was 9.7%. The difference was statistically significant. Multivariate regression analysis confirmed the use of PPI as an independent risk factor for SAP. The mechanisms may be related to the use of PPIs, by inhibiting the secretion of gastric acid, lead to the proliferation of the gastrointestinal bacteria, whose regurgitation may have resulted in the SAP.

In conclusion, in this retrospective study of patients with ischemic stroke, the incidence of SAP was 13.58%. Age, NIHSS, GCS score, dysphagia, heart failure, creatinine, and PPI use were identified as major risk factors for SAP. The scores in the constructed predictive score table were: age (>75 years old) 2 points, NIHSS (≥16 points) 2 points, GCS score(≤ 8 points) 1.5, 5 points for dysphagia, 1.5 points for heart failure, 1 point for creatinine, 1.5 points for PPIs, totaling 14.5 points. The area under the ROC curve of the score table is 0.861, the 95% confidence interval is 0.826-0.896($P<0.05$), the optimal value is 3 points, the sensitivity is 84.8%, and the specificity is 75.5%. Compared with the A2DS2 score, the scoring system established in this study is more sensitive in helping to identify the high-risk group in the development of SAP.

REFERENCES

1. Hilker R, Poetter C, Findeisen N, *et al*. Nosocomial pneumonia after stroke:implication for neurological intensive care medicine. Stroke 2003;34;975-81.
2. Kammersgaard LP, Jørgensen HS, Reith J, *et al*. Early infection and prognosis after acute stroke: the Copenhagen Stroke Study. *J Stroke Cerebrovasc Dis* 2001;10:217-21.
3. Ji RJ, Wang D, Shen HP, et al. Interrelationship among common medical complications after acute stroke: pneumonia plays an important role. Stroke 2013;44(12):3436-44.
4. Matz K, Seyfang L, Dachenhausen A, *et al.* Post-stroke pneumonia at the stroke unit – a registry based analysis of contributing and protective factors. *BMC Neurology* 2016; 16:107.
5. Hoffmann S, Malzahn U, Harms H, *et al.* Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke. *Stroke* 2012;43:2617-23.
6. Kumar S, Marchino S, Massaro J, *et al*. ACDD4 score: A simple tool for assessing risk of pneumonia after stroke, J Neurol Sci 2016;372:399-402.
7. Ji RJ, Shen HP, Pan YS, *et al*. Novel risk score to predict pneumonia after acute ischemic stroke. *Stroke* 2013;44:1303-9.
8. Smith CJ, Bray BD, Hoffman A, *et al*. Can a novel clinical risk score improve pneumonia prediction in acute stroke care? A UK multicenter cohort study. *J Am Heart Assoc* 2015;4:e001307.
9. Smith CJ, Kishore AK, Vail A, *et al*. Diagnosis of stroke-associated pneumonia: Recommendations from the Pneumonia in Stroke Consensus Group. *Stroke* 2015;46:2335-40.
10. Sivertsen J, Graverholt B, Espehaug B. Dysphagia screening after acute stroke: a quality improvement project using criteriabased clinical audit. *BMC Nursing* 2017; 16:27.
11. Ho SW, Hsieh MJ, Yang SF, Yeh YT, Wang YH, Yeh CB. Risk of stroke-associated pneumonia with acid-suppressive drugs: A population-based cohort study. *Medicine* 2015; 94(29): e1227.
12. Arai N, Nakamizo T, Ihara H, *et al.* Histamine H2-blocker and proton pump inhibitor use and the risk of pneumonia in acute stroke: A retrospective analysis on susceptible patients. *PLoS ONE* 2017; 12(1):e0169300.