

# Value of Combination of the A<sup>2</sup>DS<sup>2</sup> Score and IL-6 in Predicting Stroke-Associated Pneumonia

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**Purpose:** To evaluate the value of the combination of the age, atrial fibrillation, dysphagia, male sex, and National Institutes of Health Stroke Scale (A<sup>2</sup>DS<sup>2</sup>) score and serum interleukin 6 (IL-6) concentration in predicting stroke-associated pneumonia (SAP).

**Patients and Methods:** A total of 398 patients with acute ischemic stroke (AIS) from the medical ward was included in this retrospective study. They were divided into the SAP group and non-SAP group according to the diagnostic criteria of SAP. Multivariate analysis was performed to analyze the association between the A<sup>2</sup>DS<sup>2</sup> score, serum IL-6 concentration, and SAP using a backward stepwise logistic regression model. The receiver operating characteristic (ROC) curve was used to evaluate the value of the A<sup>2</sup>DS<sup>2</sup> score, serum IL-6 concentration and combination of A<sup>2</sup>DS<sup>2</sup> score and IL-6 in predicting SAP.

**Results:** SAP was diagnosed in 70 patients (17.6%). Multivariate analysis showed that the A<sup>2</sup>DS<sup>2</sup> score (odds ratio [OR]: 2.25, 95% confidence interval [CI]: 1.17–4.99,  $P=0.017$ ) and serum IL-6 concentration (OR: 1.76, 95% CI: 1.44–1.95,  $P<0.001$ ) was independently associated with SAP after adjusting for age, smoking, hypertension, hyperlipidemia, and atrial fibrillation. When the A<sup>2</sup>DS<sup>2</sup> score, serum IL-6 concentration and combination of A<sup>2</sup>DS<sup>2</sup> score and IL-6 were employed to predict SAP, the AUC was 0.824 (SE: 0.026, 95% CI: 0.773–0.875), 0.715 (SE: 0.034, 95% CI: 0.641–0.788) and 0.917 (SE: 0.015, 95% CI: 0.887–0.946), respectively. The AUC of combinative prediction was significantly higher than independent prediction (0.917 vs. 0.824,  $Z=3.098$ ,  $P<0.001$ ; 0.917 vs. 0.715,  $Z=5.436$ ,  $P<0.001$ ).

**Conclusion:** The addition of serum IL-6 to the A<sup>2</sup>DS<sup>2</sup> score could significantly enhance the AUC of predicting SAP in AIS patients from the medical ward.

**Keywords:** stroke-associated pneumonia; SAP, A<sup>2</sup>DS<sup>2</sup> score, interleukin 6, multivariate analysis, receiver operating characteristic curve; ROC

## Introduction

Stroke is one of the most common cerebrovascular diseases with high incidence and mortality.<sup>1</sup> Acute ischemic stroke (AIS) is the most common type of stroke, accounting for 80% of the total stroke cases.<sup>2</sup> Many complications occur following a stroke, such as pneumonia, epilepsy, hemorrhagic transformation, secondary infections, etc. Stroke-associated pneumonia (SAP) is a frequent and feared complication after acute stroke, associated with increased mortality and length of hospital stay and poor prognosis.<sup>3–6</sup> Thus, early detection and appropriate treatment for SAP should be emphasized in order to improve the prognosis of stroke patients.

Many baseline clinical variables may predispose individuals to SAP, such as age, the severity of stroke, dysphagia, location, and type of stroke, etc.<sup>7–10</sup> Several

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risk stratification scores for predicting SAP have been derived based on these routinely available variables. Among them, the Age, Atrial Fibrillation, Dysphagia, Male sex, and National Institutes of Health Stroke Scale ( $A^2DS^2$ ) score proposed by Hoffmann et al is a simple and effective tool for predicting SAP during hospitalization,<sup>11</sup> which may have the best performance in identifying patients at high risk of SAP.<sup>12,13</sup> Stroke is associated with altered systemic immunity, predisposing patients to infections and immunosuppression.<sup>14</sup> Therefore, biomarkers involved in the immune changes and systemic inflammatory response may be associated with occurrence of SAP. A study has demonstrated that interleukin 6 (IL-6) may be a reliable biomarker for prediction of stroke-associated infection (SAI) after AIS.<sup>15</sup> However, the value of the combination of the  $A^2DS^2$  score and IL-6 in predicting SAP remains unclarified. In this study, the value of a combination of the  $A^2DS^2$  score and serum IL-6 concentration in predicting SAP was evaluated with the receiver operating characteristic (ROC) curve through a single center retrospective case series study.

## Patients and Methods

### Patients

Consecutive patients with AIS were retrospectively enrolled in the medical ward of Central Hospital of Jiangjin District, Chongqing between July 2016 and October 2019. Inclusion criteria included: 1) patients confirmed by cranial magnetic resonance imaging (MRI) or computed tomography (CT) within 24 h after admission; 2) patients admitted within 7 days following onset of stroke; and 3) patients with complete clinical data. Exclusion criteria included: 1) pre-existing pneumonia before admission; 2) transient ischemic attack (TIA); 3) lacking the  $A^2DS^2$  scoring items; 4) patients who were died or discharged within 3 days following onset of stroke; 5) preventive antibiotic therapy; 6) active infection or pyrexia within the 2 weeks before admission; 7) other post-stroke infections (non-SAP); 8) patients with ventilation who develop pneumonia during the first 7 days after the onset of stroke; 9) medical history of any other central nervous system disease, such as cerebral hemorrhage, brain trauma, hydrocephalus, Parkinson's disease, etc. This study was performed in accordance with the Declaration of Helsinki and permitted by the Ethics Committee of Central Hospital of Jiangjin District, Chongqing. All patients provided written informed

consent, and that consent was obtained from the study participants prior to study commencement.

### Diagnosis of SAP

SAP was diagnosed retrospectively from medical records by two experienced neurologists according to the modified Centers for Disease Control and Prevention criteria for hospital-acquired pneumonia,<sup>16</sup> based on clinical and laboratory examinations, including cough, fever, new purulent sputum, positive sputum culture, or auscultatory respiratory crackles. Suspected pneumonia patients, based on clinical symptoms and typical chest X-ray were diagnosed and confirmed through sputum cultures and chest CT.<sup>17</sup>

### Data Collection

The following data were collected, including demographic data (sex and age), vascular risk factors (smoking, drinking, diabetes, hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, and previous history of stroke or TIA), laboratory examinations at admission (triacylglycerol [TG], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], glycosylated hemoglobin [GHb], and total cholesterol [TC]), duration from stroke onset to admission, Trial of org 10,172 in acute stroke treatment (TOAST) classification (Large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined, and undetermined), treatment methods (intravenous thrombolysis, anticoagulants, statins, and antiplatelet agents), and the  $A^2DS^2$  score at admission.

The  $A^2DS^2$  score included the following items:<sup>11</sup> 1) 1 point for age  $\geq 75$ -years-old; 2) 1 point for atrial fibrillation that was diagnosed by standard electrocardiogram or Holter monitor; 3) 2 points for dysphagia; 4) 1 point for male sex; and 5) 5 points for a National Institute of Health stroke scale (NIHSS) score  $>16$  points and 3 points for an NIHSS score ranging from 5 to 15 points.

### Detection of Serum IL-6 Concentrations

All patients were collected for blood samples within 24 h of admission, following overnight fasting. Serums were separated through centrifugation at 3000 g for 10 min and then stored at  $-80^{\circ}\text{C}$ . Serum IL-6 concentrations were detected using Human IL-6 ELISA Kit (abcam, Shanghai, China) through the colorimetric method. Detection was performed strictly following the manufacturer's instructions.

## Statistical Analysis

The SPSS version 22.0 (SPSS Inc., USA) was used to perform statistical analysis and significance was set at two-sided  $P < 0.05$ . Kolmogorov–Smirnov test was used to evaluate the distribution of quantitative data. Normally distributed data were expressed as mean  $\pm$  standard deviation, and the Student's  $t$  test was used to compare intergroup differences; and non-normally distributed data were expressed as median ( $M$ ) and interquartile range ( $IQR$ ), and Mann–Whitney  $U$ -test was used to compare intergroup differences. Qualitative data were expressed as percentages or ratios (%), and the Chi-square test was used to compare intergroup differences. Variables with two-sided  $P < 0.10$  in univariate analysis were then included in multivariate analysis employing a backward stepwise *logistic* regression model. ROC curve was used to evaluate the predictive value. The ROC curve, used to evaluate the predictive value of a combination of the  $A^2DS^2$  score and serum IL-6 concentration, was drawn with the probability derived from the *logistic* regression model. The area under curve (AUC) was compared with the  $Z$  test.

## Results

### General Data

A total of 451 consecutive patients with AIS were enrolled. Among them, 8 patients were excluded due to being transferred to the Department of Neurosurgery for surgical treatment, 25 patients due to incomplete clinical data, and 20 patients due to meeting the exclusion criteria. Finally, 398 patients were included in this study. They included 238 males (59.8%) and 160 females (40.2%) with an average age of (62 $\pm$ 9) years. SAP was diagnosed in 70 patients (17.6%). The average time of SAP onset was (4.12 $\pm$ 1.57) d after admission.

### Univariate Analysis

Univariate analysis (Table 1) demonstrated that age, smoking, hypertension, atrial fibrillation, the serum IL-6 concentration, and  $A^2DS^2$  score were statistically different between AIS patients with SAP and without SAP ( $P < 0.05$ ), and the rest of the variables were not statistically different ( $P > 0.05$ ).

The average concentration of serum IL-6 was (1.46  $\pm$  0.30) ng/mL. Stroke severity was evaluated with the NIHSS. The serum IL-6 concentration was higher in AIS patients with an NIHSS score  $\geq 5$  than in AIS patients with an NIHSS score  $< 5$  (1.48 $\pm$ 0.32 vs. 1.40 $\pm$ 0.26,  $n_1=109$ ,  $n_2=289$ ,  $t=2.335$ ,  $P=0.020$ ). Lesion size was divided into

large ( $>50 \times 50$  mm and  $> 5$  slices), moderate ( $\leq 15 \times 15$  mm and  $> 5$  slices or  $> 50 \times 50$  mm and  $\leq 5$  slices), and small ( $\leq 15 \times 15$  mm and  $\leq 5$  slices). The serum IL-6 concentration demonstrated the tendency of large infarct volume  $>$  moderate infarct volume  $>$  small infarct volume (1.54 $\pm$ 0.34 vs. 1.43 $\pm$ 0.29 vs. 1.30 $\pm$ 0.21,  $n_1=192$ ,  $n_2=119$ ,  $n_3=87$ , all  $P < 0.05$ ).

### Multivariate Analysis

Age, smoking, hypertension, hyperlipidemia, atrial fibrillation, the  $A^2DS^2$  score, and serum IL-6 concentration were included in a backward stepwise *logistic* regression model. The results of multivariate analysis showed that the serum IL-6 concentration (odds ratio [OR]: 1.76, 95% confidence interval [CI]: 1.44–1.95,  $P < 0.001$ ) and  $A^2DS^2$  score (OR: 2.25, 95% CI: 1.17–4.99,  $P=0.017$ ) were independently associated with SAP after adjusting for age, smoking, hypertension, hyperlipidemia, and atrial fibrillation.

### Predictive Value

When the  $A^2DS^2$  score, serum IL-6 concentration and combination of  $A^2DS^2$  score and IL-6 were employed to predict SAP, the AUC was 0.824 (SE: 0.026, 95% CI: 0.773–0.875), 0.715 (SE: 0.034, 95% CI: 0.641–0.788) and 0.917 (SE: 0.015, 95% CI: 0.887–0.946), respectively (Figure 1). The AUC of combinative prediction was significantly higher than independent prediction (0.917 vs. 0.824,  $Z=3.098$ ,  $P < 0.001$ ; 0.917 vs. 0.715,  $Z=5.436$ ,  $P < 0.001$ ). The clinical utility indexes for the  $A^2DS^2$  score, serum IL-6 concentration, and combination of the  $A^2DS^2$  score, and IL-6 in predicting SAP are shown in Table 2.

## Discussion

SAP refers to pneumonia happening during the first 7 days after the onset of stroke in non-ventilated patients,<sup>17</sup> and its incidence is reported to range from 2.3% to 44%.<sup>18–21</sup> It is a common and severe complication after acute stroke, associated with increased mortality and length of hospital stay, and poor prognosis.<sup>3–6</sup> Studies have shown that SAP can increase the 30-day, 1-year, and 3-year mortality significantly.<sup>19,22,23</sup> Patients with SAP have a threefold increased risk in the 30-day mortality after adjusting for severity of admission, compared to patients without SAP.<sup>19</sup> Therefore, early detection and appropriate treatment of SAP is of critical importance for reducing mortality and improving the clinical prognosis of stroke patients.

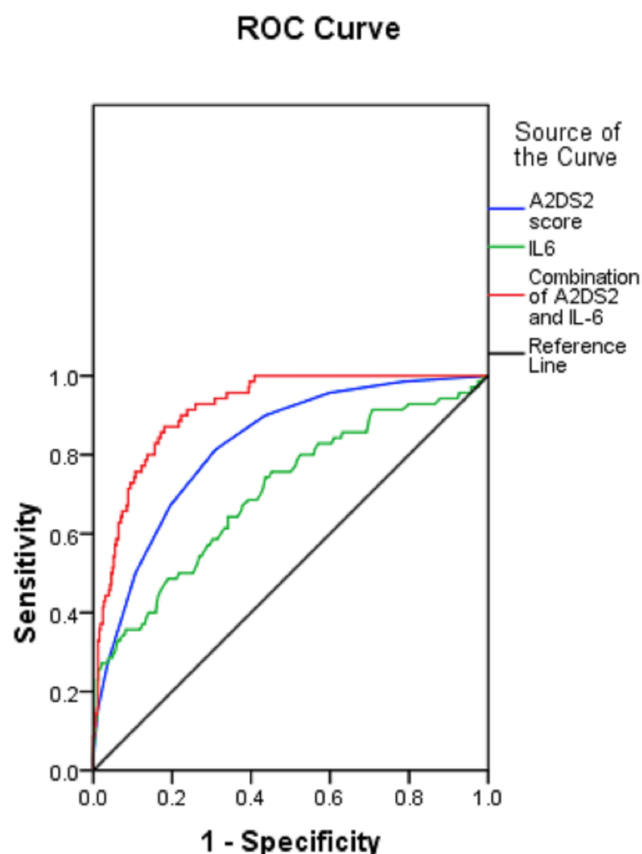
**Table 1** Results of Univariate Analysis Between AIS Patients With SAP and Without SAP

Variables	All Patients (n=398)	Patients without SAP (n=328)	Patients with SAP (n=70)	P
Male (n, %)	238(59.8%)	192(58.5%)	46(65.7%)	0.266
Age (years, mean±standard)	62±9	61±9	67±12	<0.001
Vascular risk factors (n, %)				
Smoking	89(22.4%)	65(19.8%)	24(34.3%)	0.008
Hypertension	286(71.9%)	228(69.5%)	58(82.9%)	0.024
Hyperlipidemia	62(15.6%)	46(14.0%)	16(22.9%)	0.064
Diabetes	58(14.6%)	45(13.7%)	13(18.6%)	0.296
Coronary heart disease	19(4.8%)	14(4.3%)	5(7.1%)	0.350*
Atrial fibrillation	29(7.3%)	19(5.8%)	10(14.3%)	0.013
Previous history of stroke or TIA	27(6.8%)	20(6.1%)	7(10.0%)	0.291*
Drinking	184(46.2%)	147(44.8%)	37(52.9%)	0.221
Laboratory examinations (mean±standard)				
Total cholesterol (mmol/L)	4.58±0.85	4.60±0.86	4.49±0.80	0.312
triacylglycerol (mmol/L)	1.34±0.61	1.32±0.59	1.43±0.70	0.216
Low density lipoprotein cholesterol (mmol/L)	2.83±0.74	2.80±0.69	2.97±0.97	0.178
High density lipoprotein cholesterol (mmol/L)	1.03±0.45	1.04±0.48	0.98±0.31	0.182
Glycosylated hemoglobin (%)	5.44±1.93	5.39±1.88	5.67±2.16	0.325
IL-6 (ng/mL)	1.46±0.30	1.43±0.28	1.62±0.37	<0.001
Duration from stroke onset to admission (h, mean ±standard)	18.87±6.92	19.02±6.99	18.17±6.59	0.343
TOAST classification (n, %)				
Large artery atherosclerosis	124(31.2%)	101(30.8%)	23(32.9%)	0.727
Small vessel occlusion	104(26.1%)	89(27.1%)	15 (21.4%)	
Cardioembolism	88(22.1%)	74(22.6%)	14(20.0%)	
Other determined	36(9.0%)	28(8.5%)	8(11.4%)	
Undetermined	46(11.6%)	36(11.0%)	10(14.3%)	
Treatment methods (n, %)				
Intravenous thrombolysis	29(7.3%)	21(6.4%)	8(11.4%)	0.142
Antiplatelet agents	310(77.9%)	253(77.1%)	57(81.4%)	0.432
Anticoagulants	108(27.1%)	86 (26.2%)	22(31.4%)	0.374
Statins	336(84.4%)	275(83.8%)	61(87.1%)	0.489
A <sup>2</sup> DS score (M, IQR)	3(4)	2(3)	6(3)	<0.001
Distribution of A <sup>2</sup> DS <sup>2</sup> score (n, %)				
0	71(17.8%)	70(21.3%)	1(1.4%)	<0.001*
1	64(16.1%)	62(18.9%)	2(2.9%)	
2	57(14.3%)	53(16.2%)	4(5.7%)	
3	47(11.8%)	41(12.5%)	6(8.6%)	
4	48(12.1%)	38(11.6%)	10(14.3%)	
5	41(10.3%)	29(8.8%)	12(17.1%)	
6	39(9.8%)	23(7.0%)	16(22.9%)	
7	16(4.0%)	8(2.4%)	8(11.4%)	
8	9(2.3%)	3(0.9%)	6(8.6%)	
9	4(1.0%)	1(0.3%)	3(4.3%)	
10	2(0.5%)	0(0)	2(2.9%)	

Note: \*Fisher's Exact Test.

The A<sup>2</sup>DS<sup>2</sup> score, in which scoring items includes age, atrial fibrillation, dysphagia, male sex, and NIHSS,<sup>11</sup> has been confirmed to be a simple and effective tool in predicting

SAP during hospitalization in several counties, including Spain,<sup>12</sup> Singapore,<sup>13</sup> France,<sup>18</sup> Denmark,<sup>24</sup> the UK,<sup>25</sup> and China.<sup>26–28</sup> The A<sup>2</sup>DS<sup>2</sup> score has a total score of 10.



**Figure 1** ROC curves for the A<sup>2</sup>DS<sup>2</sup> score, serum IL-6 concentration and combination of A<sup>2</sup>DS<sup>2</sup> score and IL-6 in predicting SAP.

Hoffmann et al demonstrated that the best cut-off of the A<sup>2</sup>DS<sup>2</sup> score was 4.5, and a cut-off of  $\geq 4$  had a sensitivity of 91% and a specificity of 57%.<sup>11</sup> Li et al showed that the best cut-off of the A<sup>2</sup>DS<sup>2</sup> score was 4.5 when it was applied to the Chinese population, and the AUC was up to 0.836.<sup>27</sup> Therefore, the A<sup>2</sup>DS<sup>2</sup> score had a high predictive value. In our study, the AUC of the A<sup>2</sup>DS<sup>2</sup> score applied in predicting SAP was 0.824, and the best cut-off was 5.

Stroke is associated with altered systemic immunity, predisposing patients to infections and immunosuppression.<sup>14</sup> Therefore, biomarkers involved in the immune changes and systemic inflammatory response may be able to predict the occurrence of SAP. Pro-inflammatory cytokines have plausible biological actions that predispose towards infection. IL-6 is a pro-inflammatory cytokine and has a significantly elevated level in acute stroke,<sup>29</sup> which is correlated with poor prognosis and larger infarct volumes.<sup>30–32</sup>

IL-6 can activate the production of acute-phase proteins from the liver,<sup>33</sup> including activation of CRP production in AIS.<sup>34</sup> Thus, it may be associated with defense against infections through the acute phase response. In addition, IL-6 may

**Table 2** Clinical Utility Indexes for the A<sup>2</sup>DS<sup>2</sup> Score, Serum IL-6 Concentration and Combination of A<sup>2</sup>DS<sup>2</sup> Score and IL-6 in Predicting SAP

	AUC	SE	P	95% CI	Best Cut-Off	Sensitivity	Specificity	Accuracy	False Positive Rate	False Negative Rate	Positive Predictive Value	Negative Predictive Value	Youden Index
A <sup>2</sup> DS <sup>2</sup> score	0.824	0.026	<0.001	0.773	5	81.40%	68.90%	71.11%	64.15%	5.44%	35.84%	94.56%	0.50
Serum IL-6 concentration	0.715	0.034	<0.001	0.641	1.48	74.30%	56.40%	59.55%	73.33%	8.87%	26.67%	91.13%	0.31
Combination of A <sup>2</sup> DS <sup>2</sup> score and IL-6	0.917	0.015	<0.001	0.887		87.10%	82.00%	82.91%	49.17%	3.24%	50.83%	96.76%	0.69



also play a role in determining cellular immunity. Many studies in animal models and humans have implied that acute stroke may induce depression of the immune system with an elevated susceptibility to infections.<sup>35</sup> The characteristics of stroke-caused immunosuppression include impaired cell-mediated immunity and excessive anti-inflammatory cytokines.<sup>35</sup> Immunosuppression following stroke may, at least in part, be correlated with catecholamine actions on lymphocytes and mechanistic links exist between the autonomic nervous system, the hypothalamic-pituitary-adrenal axis (HPAA), IL-6 and infection.<sup>36–38</sup> Thus, it can be speculated that elevated susceptibility to infections following stroke may, at least partly, be promoted by increased IL-6 levels operating via catecholamines, which in turn cause immunosuppression. Kwan et al demonstrated that patients with SAI, in particular pneumonia, had elevated IL-6 levels and higher mortality, and IL-6 was an independent risk factor of SAI ( $OR = 19.2$ , 95%  $CI$ : 3.68–100).<sup>15</sup> They concluded that IL-6 might be a critical biomarker for the prediction of SAI. In this study, the serum IL-6 concentration was independently associated with occurrence of SAP. The AUC of the serum IL-6 concentration applied in predicting SAP was 0.715, and the best cut-off was 1.48 ng/mL. Moreover, the value of the combination of A<sup>2</sup>DS<sup>2</sup> score and IL-6 in predicting SAP was evaluated. Its AUC was 0.917 with a sensitivity of 87.1% and a specificity of 82.0%, significantly higher than the A<sup>2</sup>DS<sup>2</sup> score or IL-6. The addition of serum IL-6 to the A<sup>2</sup>DS<sup>2</sup> score significantly enhanced the AUC of predicting SAP in AIS patients from the medical ward. In this study, the cost of detecting serum IL-6 concentrations was low (about 25 RMB for each detection). Therefore, serum IL-6 could be applied in screening for SAP in AIS patients from the medical ward.

The limitations of this study included: 1) the sample size was small; and 2) the included patients were from the medical ward; therefore, data characteristics were limited to specific AIS patients.

## Conclusion

The addition of serum IL-6 to the A<sup>2</sup>DS<sup>2</sup> score could significantly enhance the AUC of predicting SAP in AIS patients from the medical ward. Therefore, it could be applied in screening for SAP in AIS patients from the medical ward.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation,

or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

All the authors do not have any conflicts of interest.

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