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Risk factors of acute stroke associated pneumonia and predictive value of serum amyloid A combined with neutrophil-to-lymphocyte ratio

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Abstract

Objectives: This study aimed to explore the risk factors for stroke-associated pneumonia (SAP) and assess the predictive value of Serum Amyloid A (SAA) combined with neutrophil-to-lymphocyte ratio (NLR) on SAP. *Methods:* The study included acute ischemic stroke (AIS) patients from January 2021 to June 2022 in our hospital. The patients' history of chronic diseases, the clinical characteristics, and the laboratory testing data were recorded. SPSS 22 was used for statistical analysis. Receiver operating characteristics (ROC) curves and logistic regression analysis were used to identify independent predictors. *Results:* We studied 356 patients with AIS, of which 19.4% (n = 69) developed SAP. In the SAP group, the patients with higher the proportion of hypertension, coronary heart disease and higher the NIHSS score were older, the blood glucose, neutrophil count, NLR and SAA of the SAP group were significantly higher than the Non-SAP group . Multiple logistic regression analysis for SAP showed that age , NIHSS,SAA and NLR were independent risk factors for SAP. For SAA alone, the area under the curve (AUC) in the ROC curve was 0.765, For NLR alone, the AUC was 0.840. When SAA combined with NLR, the AUC increased to 0.853. we created a 4-item prediction model, the AUC increased to 0.881.
Conclusion: Age, NIHSS, SAA and NLR were independent risk factors for SAP. When SAA combined with NLR, its predictive value for SAP was higher than its alone, the value of prediction for SAP appeared to be much stronger when SAA and NLR incorporated in a prediction model including age, and NIHSS.

Keywords: Stroke-associated pneumonia, neutrophil-to-lymphocyte ratio, serum amyloid A, acute ischemic stroke, risk factors

INTRODUCTION

Stroke-associated pneumonia (SAP) is one of the most common complications after stroke with an incidence ranging from 7% to 38% in China.[1] Previous studies[2-4] have shown that SAP is an important risk factor for costly stroke care, prolonged hospital stay, and poor prognosis. SAP has several known risk factors, but the sensitivity is not high At present, there are many prediction models for SAP. However, most of them are based on clinical presentations with various items, making SAP prediction complex and difficult.[5] SAA and NLR are easily available indicators of inflammation with predictive value superior to traditional indicators.[6] This study retrospectively analyzed the clinical data of acute stroke patients admitted to the Department of Neurology of our hospital. This study analyzed the risk factors of SAP, and evaluated the predictive value of early SAA combined with NLR for SAP.

METHODS

Objective

The study stroke patients were recruited from the Department of Neurology, Hangzhou First People's Hospital. The patients were aged 26-85 years seen in the period from January 2021 to June 2022. The inclusion criteria were: patients with complete medical records; patients satisfying the diagnostic criteria of stroke. The diagnosis of acute ischemic stroke conformed to the clinical diagnostic criteria of ischemic stroke in the Chinese guidelines for the diagnosis and treatment

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of AIS.[7] The patients were new acute cerebral stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI); hospitalization within 3 days of symptom onset; and hospitalization for more than 7 days.

The exclusion criteria were: Previous history of dysphagia, long-term indwelling nasogastric tube, previous hematologic, inflammatory or autoimmune disorders, advanced tumors,recent surgery, infections preceding stroke, use of antibiotics <24 h before admission, use of immunosuppressants on admission, severe liver , kidney dysfunction and severe cardiopulmonary dysfunction.

Clinical evaluation

We collected the demographic data (such as age, gender) and medical history (such as hypertension, diabetes, coronary heart disease, hyperlipidemia and smoking history) of these patients. The clinical data that were collected included NIHSS score on admission, whether SAP occurred within 7 days after hospitalization, CT and MRI for the diagnosis of stroke. The laboratory results of all patients were obtained within 24 h after admission, including blood glucose, uric acid count, SAA count, neutrophil count, and lymphocyte count. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

The patients in this study were divided into two groups, with and without associated pneumonia. SAP was diagnosed based on the 2015 Diagnostic Consensus[8] according to clinical and laboratory examinations and was confirmed through sputum culture results and chest CT scans retrospectively.

Statistical analysis

SPSS Statistics 25 was used for statistical analyses. Continuous data were expressed as mean ± standard deviation, and the t-test was used for comparisons between groups. Quantitative data were expressed as the number of cases and percentages (n [%]), and the $\chi 2$ test or Fisher's exact probability method was used for inter-group comparisons with classification Multivariate logistic regression analysis determined the independent risk factors for SAP. A receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to evaluate the ability of SAA, NLR and multiple items combined to predict SAP. To judge the sensitivity and specificity of NLR in predicting SAP, the best cut-off value was set as the value corresponding to the maximum You den index (sensitivity – [1–specificity]). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of SAP and non-SAP patients with AIS.

A total of 356 eligible patients were included, with an average age of 66.49 ± 11.91 years, including 236 males (66.3%) and 120 females (33.7%). The SAP group consisted of 69 patients, with an average age of 73.13±10.48 years, including 46 males (66.7%) and 23 females (33.3%). The non-SAP group consisted of 287 patients, with an average age of 67.43 ± 11.10 years, including 190 males (66.2%) and 97 females (33.8%). Univariate analysis of the clinical data from the two groups demonstrated that members of the SAP group were older, with a higher proportion of hypertension and coronary heart disease, a higher NIHSS score on admission. The blood glucose, neutrophil count, NLR and SAA of the SAP group were significantly higher than those of the Non-SAP group, whereas lymphocyte count was significantly lower than that in the Non-SAP group ($P < 0.05$). (Table 1)

Multivariate logistic regression analysis of risk factors for SAP

Multiple logistic regression analysis for SAP showed that age (OR 1,043, 95% CI 1.004–1.054, $P = 0.000$), NIHSS score (OR 1.176, 95% CI 1.164–1.189, $P = 0.000$), SAA (OR 0.990, 95% CI 0.987–0.991, $P = 0.000$) and NLR (OR 0.958, 95% CI 0.932–0.959, $P = 0.000$), were independent risk factors for SAP. (Table 2).

ROC curve analyses

For SAA alone, the area under the curve (AUC) in the ROC curve was 0.765 (95% CI = 0.696–0.833). The optimal cutoff threshold, sensitivity, and specificity were 12.500,0.652, and 0.774, respectively. For NLR alone, the area under the curve (AUC) in the ROC curve was 0.840 (95% CI = 0.781–0.900). The optimal cutoff threshold, sensitivity, and specificity were 3.710, 0.783, and 0.801, respectively. When the combination of SAA and NLR was used to predict SAP, the AUC increased to 0.853 (95% CI = 0.797–0.910). The optimal cutoff threshold, sensitivity, and specificity were 0.135,0.826, and 0.784, respectively. We created a 4-item prediction

Table 1: Baseline characteristics of SAP and non-SAP patients with AIS

Index	SAP group	Non-SAP group	X/t/Z value	P value
Gender(male, n(%))	46(66.7)	190(66.2)	0.01	0.942
Age(years)	73.13±10.48	67.43±11.10	-4.02	**<0.001**
Hypertension n(%)	63(91.3)	227(79.1)	5.49	**0.019**
Diabetes n(%)	21(30.4)	98(34.1)	0.34	0.557
Coronary heart disease n(%)	15(21.7)	33(11.5)	5.00	**0.025**
Hyperlipidemia n(%)	1(1.4)	25(8.79)	3.33	0.068
Smoke n(%)	17(24.6)	99(34.5)	2.46	0.117
NIHSS score on admission (score)	9.66±6.83	4.02±3.03	-7.69	**<0.001**
Uric acid (umol/L)	298.33±128.11	309.48±83.49	0.92	0.362
Blood glucose (mmol/L)	6.79±3.13	7.52±29.06	-0.221	**0.027**
Neutrophils *10^9/L	7.92±4.45	4.57±1.76	-7.59	**<0.001**
Lymphocyte *10^9/L	1.17±0.57	1.75±0.68	-6.73	**<0.001**
NLR	9.71±12.37	3.07±2.64	-8.78	**<0.001**
SAA (mg/L)	50.45±52.83	15.71±28.29	-6.86	**<0.001**

SAA, Serum Amyloid A; NLR, neutrophil-to-lymphocyte ratio; NIHSS, National Institute of Health Stroke Scale; The bold values represent $p < 0.05$ which is statistically significant.

model, in this model, the AUC increased to 0.881 (95% CI = 0.834–0.929). The optimal cutoff threshold, sensitivity, and specificity were 0.146,0.841, and 0.791, respectively. The results showed its predictive value for SAP was significantly higher than either parameter alone (P<0.05). At the same time, the value of prediction for SAP appears to be much stronger when SAA and NLR incorporated in a prediction model including age, and NIHSS score. (Figure 1, Table 3)

DISCUSSION

SAP is the most common complication among acute stroke and adversely affect clinical outcomes, increases length of hospital stay, the cost of treatment, the high morbidity and mortality in post-stroke patients, and aggravates the financial burden of the national medical health system. Early identification and management of high-risk patients are necessary to prevent the occurence of SAP.[9,10] The incidence rate from different studies varied greatly, depending on the size of each study sample and the severity of the case studied. In this study, the incidence rate of acute SAP was 19.4%, which was in line with previously reported findings.[11-13] The aim of this study was to determine which clinical risk factors independently predict SAP and are sensitive in the early predictors of SAP. The earlier reported risk factors including dysphagia[14], indwelling nasogastric tube, higher NIHSS, age, stroke type[15] and gender[16,17] were identified as independent predictors of SAP. In concordance with previous reports[12,18], we also found that age, NIHSS score, SAA, NLR levels were independent risk predictors for SAP, we did not find an impact of gender to be independent predictor in in these risk factors of our current study.

In this study, SAP group were older, with a

Table 2: Multivariate logistic regression analysis of risk factors for SAP

Variables	OR value	95%CI	P value
Age	1.043	1.044-1.054	<0.001
Neutrophils	1.610	1.449-1.526	<0.001
Lymphocyte	0.216	0.253-0.317	<0.001
NLR	0.958	0.932-0.959	<0.001
SAA	0.990	0.987-0.991	<0.001
NIHSS score on admission	1.176	1.164-1.189	<0.001

SAA, Serum amyloid A; NLR, neutrophil-to-lymphocyte ratio; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio. CI, confidence interval.

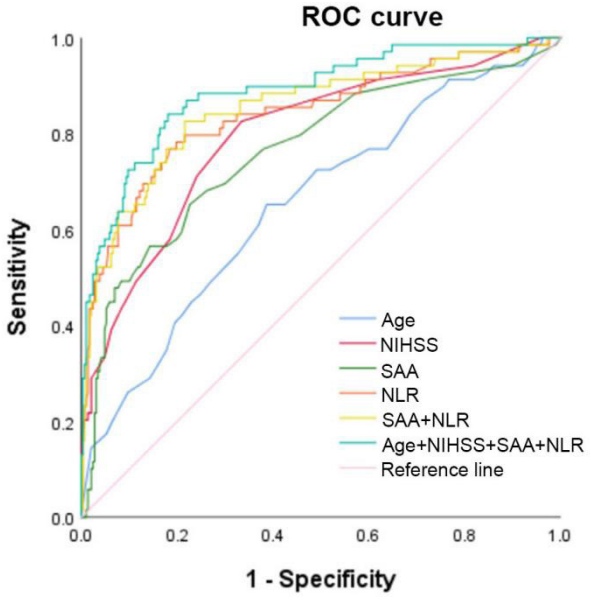

Figure 1. ROC curve
SAA, Serum Amyloid A; NLR, neutrophil-to-lymphocyte ratio; NIHSS, National Institutes of Health Stroke Scale; AUC, area under the curve; The cutoff value were obtained by maximizing the sum of sensitivity and specificity (maximum Youden index)

higher proportion of hypertension and coronary heart disease, and a higher NIHSS score on admission. The blood glucose, neutrophil count, NLR and SAA of the SAP group were significantly higher than those of the Non-SAP group, whereas lymphocyte count was significantly lower than the Non-SAP group. Multiple logistic regression analysis for SAP showed that age, NIHSS score, SAA and NLR were independent risk factors for SAP. Moreover, the combined biomarkers have higher predictive ability than individual biomarkers, these findings may contribute to distinguishing AIS patients with a high risk of developing SAP at an early clinical stage, thereby facilitating timely clinical intervention and appropriate treatment.

SAA and NLR have been previously reported to be potential biomarkers for severity of cerebral infarction.[19-24] Previous studies have also found a link among the SAA, NLR and post-stroke infections, but its predictive value appears to be quite weak. A study of Schweizer *et al*.[18] found that ROC curve analysis of SAA alone showed an AUC of 0.76 (95% CI = 0.69-0.83). They created a 10-item prediction model using age, female sex, baseline NIHSS, hypertension, atrial fibrillation, cardioembolic stroke, thrombolysis or endovascular treatment, WBC, CRP, and PCT, and the AUC of their model increased to 0.81 (95% CI = 0.74–0.88). A study by *Robin Gens et al*.[12] (Reference 12 is Wang *et al*) found that a NLR cut-off value >4.7, ROC curve analysis of NLR alone showed an AUC of 0.66 (95% CI = 0.59–0.73), they also created a 5-item prediction model using NLR ≥ 4.7, age > 75 years, male gender, dysphagia, and NIHSS> 7, and the AUC

Table 3: ROC curve analyses

Parameter	AUC	Cut-off value	Sensitivity	Specificity	P-value
Age	0.656	69.500	0.652	0.613	<0.001
NIHSS	0.796	4.500	0.826	0.666	<0.001
SAA	0.765	12.500	0.652	0.774	<0.001
NLR	0.840	3.710	0.783	0.801	<0.001
SAA+NLR	0.853	0.135	0.826	0.784	<0.001
SAA+NLR+age+NIHSS	0.881	0.146	0.841	0.791	<0.001

increased to 0.84 (95% CI = 0.79–0.89). The two studies mentioned above have relatively low predictive value. In our study, when SAA combined with NLR, the AUC increased to 0.853 (95% CI = 0.797–0.910). In addition, we created a 4-item prediction model using SAA,NLR, age and NIHSS score ,and the AUC of this model increased to 0.881 (95% CI = 0.834–0.929). The optimal sensitivity and specificity were 0.841 and 0.791 respectively. As can be seen, the predictive value of our model for SAP was higher than those two studies. indicate that SAA, NLR were especially useful in predicting SAP when incorporated in a prediction model including age and NIHSS score.

This study revealed that patients with SAP group had older age, with a higher proportion of hypertension and coronary heart disease, higher NIHSS score on admission, and more severe stroke. The reason was considered to be related to aging-related comorbidities. With an increase in age, a decrease in immune function, a increase in the prevalence of hypertension and coronary heart disease, result in an increased risk of infectious diseases, especially pneumonia. Patients with a high NIHSS score indicated that their conditions were more serious (often complicated with disturbance of consciousness and dysphagia), were relatively bedridden, were more likely to cause aspiration, and were more likely to experience infection leading to SAP. Concurrently, the level of blood glucose in the SAP group was significantly higher than the Non-SAP group ($P < 0.05$), which was consistent with previous reports.[25,26] In patients with acute stroke, blood glucose was increased due to stress reaction, and body immunity was reduced. Meanwhile, the hyperglycemic environment was conducive to the growth and reproduction of bacteria, which aggravated the pulmonary microcirculation disorder and increased the probability of pulmonary infection.[27]

In this study, multiple regression analysis demonstrated that age, NIHSS score, SAA, and NLR, were independent risk factors for SAP. In addition to aging-related comorbidities and severity of stroke ,which are the main causes of SAP, the other most likely mechanism of SAP development is currently inflammatory response and immunosuppression caused by acute stroke.[28-31]

SAA is an acute-phase protein, which is up-regulated by a variety of inflammatory stimuli.[32] In healthy individuals, SAA concentration in serum is ≈1 to 5 μg/mL.[33] However, during an acute-phase reaction, the concentration can increase to 1 mg/mL or even higher.[34] In addition ,that SAA is an ultra-early predictor of SAP in comparison to dysphagia and CRP[35] suggests an incremental prognostic value beyond these traditional risk factors. It is reported that SAA has immunomodulatory activity[36], local inflammation is a part of the reactions within hours after the ischemic event[18], which is rapidly extended to the peripheral circulation by the release of pro-inflammatory cytokines, and that start the systemic inflammatory response by activating peripheral proteins acting as acute-phase reactants, such as SAA, leading to a more severe immunodepression in the following days and increasing the risk of SAP.

The neuroinflammatory process starts immediately in the brain after stroke[37], which triggers a systemic immunodepression mainly through excessive activation of the autonomous nervous system. Manifestations of immunodepression include increased neutrophils, decreased lymphocytes, and elevated NLR levels. Those immune cells enter the brain through the cerebral vessels and meninges[38-41], dying neural cells released danger-associated molecular patterns activating microglia, which in turn produce proinflammatory cytokines , danger-associated molecular patterns and cytokines released into the bloodstream induce an initial short-lasting activation of the systemic immunity, paralleled by rapid and long-lasting immunodepression resulting in increased susceptibility to SAP. Since it is easy to obtain from peripheral blood and relatively cheap, it can be used as a routine indicator of systemic immunodepression in clinical work. It is speculated that SAA and NLR were involved in inflammatory and immunodepression to SAP. Immunomodulatory approaches to counter immunosuppression to prevent stroke-associated pneumonia need to consider and avoid further tissue damage. It needs to explore urgently the promising targets for the prevention of pneumonia and find ways to optimize immune regulation effectively while reducing the occurrence of SAP.

This study has some limitations. First, the research object is a small sample, and the risk factors for SAP were not adequately representative. Additionally, there may not exclude residual confounding effects interfering with ability of SAA and NLR to predict SAP, although we adjusted for multiple potential confounders such as age, NIHSS score, hypertension, coronary heart disease and fasting blood glucose. Finally, we did not measure SAA and NLR levels at different time periods, given that most of SAP patients occur

within the first 48 to 72 hours after stroke. We would need to do further and deeper research on the risk factors for SAP and on the relationship among SAA, NLR and SAP during different periods.

In conclusion, the risk factors for SAP were multifaceted. Age, NIHSS score, SAA and NLR were independent risk factors for SAP. When SAA and NLR were combined, its predictive value for SAP was higher than its alone. At the same time, the value of prediction for SAP appears to be much stronger when SAA and NLR incorporated in a prediction model including age, and NIHSS score. The predictive effect of SAA and NLR on SAP are beneficial to identify high-risk patients, actively control the risk factors, reduce the occurrence of SAP, and improve the prognosis of patients with acute stroke.

DISCLOSURE

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Conflict of interest: None

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