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Original Article

Serum iron and A(2)DS(2) score in stroke-associated pneumonia

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Abstract: To evaluate the efficacy of serum biomarkers such as iron, procalcitonin (PCT), C-reactive protein (CRP) and A(2)DS(2) scores at hospital admission to predict the onset and severity of stroke-associated pneumonia (SAP), 101 patients with acute stroke were selected and divided into the control and SAP group. Compared with control group, no significant differences were discovered in age, sex, vascular risk factors including hypertension, diabetes and hyperlipidemia, chronic lung disease of SAP group, while a significantly higher level was found in incidence of dysphagia, NIHSS score, A(2)DS(2) score, CURB-65 score, serum iron, serum ferritin, PCT and CRP ($P < 0.01$). The receiver operating characteristic curve showed that serum iron, serum ferritin, PCT, CRP, A(2)DS(2) score and CURB-65 score had relatively high values in the SAP prediction (all $P < 0.01$, all AUC > 0.5). When combined ferritin, PCT, and A(2)DS(2) scores and other indicators with CRP for SAP prediction, the model had a larger area under the curve (AUC) and higher specificity than individual prediction models. Spearman regression analysis presented that serum iron, serum ferritin and A(2)DS(2) score were highly correlated with CURB-65 score ($P < 0.01$). It was suggested that Serum iron and A(2)DS(2) score measured at admission were effective indicators in SAP prediction which could be used for SAP screening and severity prediction. Besides, the specificity in SAP prediction could be improved when Serum iron and A(2)DS(2) score combined with CRP.

Keywords: Stroke-associated pneumonia, serum iron, procalcitonin, C-reactive protein, A(2)DS(2) score, CURB-65 score

Introduction

Pneumonia is a common complication after stroke. It has been reported that 6 to 31.3% of patients with stroke will develop pneumonia [1-5]. In Neurological Intensive Care Unit, the prevalence of pneumonia after stroke might be even higher, with pneumonia as the leading cause of death [6]. Pneumonia not only aggravated post-stroke neurological and cognitive dysfunction, but also increased the incidence of post-stroke depression [7], thus lead to a significant increase of 30-day mortality and 1-year mortality.

The term stroke associated pneumonia (SAP) was first proposed by Hilker, *et al*., in 2003 at the Affiliated Hospital of the University of Cologne in Germany [8]. Currently, there are no widely accepted and authoritative guidelines for clinical practice of SAP. In some published expert consensus about SAP [9], the evidence basis for many diagnosis and treatment methods are mostly from the basic and clinical studies on community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), few of them were based on patients with SAP. Considering the different characteristics between stroke and non-stroke patients, it's necessary to carry out more studies based on SAP patients, in order to optimize the diagnosis and treatment of SAP. In this study, we focused on the predicting factors of SAP. Based on the patients with acute stroke, we evaluated the roles of some biomarkers including serum iron, procalcitonin (PCT), C-reactive protein (CRP), and scoring systems including A(2)DS(2) score and CURB-65 score in the occurrence and severity of SAP.

Materials and methods

Ethical statement

The study was reviewed and approved by the Institutional Ethics Committee of Tenth People's

Table 1. Comparison of basic information and clinical data between the two groups

	Control group (n = 50)	SAP group (n = 51)	P
Age ≥ 75 years old, % (n)	46.0 (23)	47.1 (24)	0.915
Percentage of males, % (n)	52.0 (26)	51.0 (26)	0.918
NIHSS score	2.34 ± 1.97	5.25 ± 2.26	0.000
Atrial fibrillation, % (n)	8.0 (4)	29.4 (15)	0.006
Dysphagia, % (n)	6.0 (3)	45.1 (23)	0.000
Hypertension, % (n)	70.0 (35)	72.5 (37)	0.777
Diabetes, % (n)	32.0 (16)	33.3 (17)	0.886
Hyperlipemia, % (n)	38.0 (19)	37.3 (19)	0.938
Chronic lung disease, % (n)	8.0 (4)	9.8 (5)	0.750

hospital affiliated with Tongji University and conducted in compliance with the guidelines of the National Health and Medical Research Council of the United Kingdom. Informed consent was obtained from all subjects.

Subjects

A total of 160 stroke patients with or without stroke-associated pneumonia (SAP) who were consecutively admitted to the Department of Neurology in Shanghai Tenth People's Hospital between January, 2013 and April, 2013 were potential subjects of the study. After exclusion of those who were discharged or deceased within 24 hours and those who had cardiac arrest requiring cardiopulmonary resuscitation and an artificial respirator for assisted respiration, fever and pneumonia revealed by chest X-ray and chest CT, tumors, iron-deficiency anemia requiring iron supplementation or bacterial infection with the use of prophylactic antibiotics prior to admission, 101 patients were finally recruited. Acute stroke was diagnosed according to the criteria released by the Chinese Medical Association at its 4th National Academic Conference on Cerebral Vessels in 1995 [10]. SAP was diagnosed on the basis of the 2010's Chinese Expert Consensus on Diagnosis and Treatment of Stroke-associated Pneumonia [11].

Clinical assessments

At admission, information on basic demographics including age and gender was collected. Body temperature was measured. Chest X-ray or CT scanning was performed. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS). The risk of post stroke pneumonia was predicted using the 10-point A(2)DS(2) scoring system (Age ≥ 75 years = 1, atrial fibrillation = 1, dysphagia = 2, male = 1, stroke severity, NIHSS score, 0-4 = 0, 5-15 = 3, ≥ 16 = 5) developed by Hoffmann and colleagues [12] and the CURB-65 (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater) scoring system recommended in the USA community-acquired pneumonia (CAP) guidelines [13].

Laboratory investigation

Within 24 h after admission, fasting venous blood was collected in the morning and sent to the laboratory within 30 min. Serum concentrations of iron, ferritin, CRP and PCT were measured by a colorimetric endpoint assay with commercial kits from Roche-China (Shanghai, China), by a chemiluminescence assay with kits from Roche China, by an immunofluorescence assay (double antibody sandwich assay) with kits from the Boditech Med RNC (Seoul, South Korea), and by a chemiluminescence assay with kits from Shenzhen New Industries Biomedical Engineering Co., Ltd. (Shenzhen, Guangdong, China), respectively.

Statistical analysis

Categorical data were expressed as percentage and analyzed by chi-square test, corrected chi-square test or Fisher's exact test according to sample size and distribution of theoretical values. Continuous variables (quantitative data) were expressed as mean ± standard deviation and analyzed by independent sample t-test. The homogeneity of variance (normal distribution) of the data was examined by Levine's homogeneity test of variance. The value of individual indicators in SAP prediction was determined by receiver operating characteristic (ROC) curves drawn according to the distribution of sensitivity and specificity at different sites within the area under the curve (AUC). The value of a combination of multiple indicators in SAP prediction was determined by logistic regression analysis combined with ROC curves.

Table 2. Comparison of clinical scores and blood indicators between the two groups

	Control group (n = 50)	SAP group (n = 51)	P
C-reactive protein (mg/L)	11.14 ± 11.58	50.71 ± 37.50	0.000
Serum procalcitonin (ng/ml)	0.35 ± 0.16	0.75 ± 0.48	0.000
Serum iron (umol/L)	14.11 ± 4.67	8.52 ± 3.84	0.000
Serum ferritin	301.66 ± 175.98	648.25 ± 309.98	0.000
A(2)DS(2) score (points)	2.34 ± 1.97	5.25 ± 2.26	0.000
CURB-65 score (points)	0.68 ± 0.68	2.06 ± 0.95	0.000

The correlations of serum iron with CURB-65 score and other indicators were analyzed by Spearman correlation analysis. Differences were considered statistically significant when $P < 0.05$. All analyses were performed with the statistical software SPSS version 18.0 (Chicago, IL, USA).

Results

Comparison of basic information and clinical data between the two groups

The SAP group and the control group had no significant differences in age, gender, various vascular risk factors and other basic data ($P > 0.05$), but the former had a significantly higher incidence of dysphagia and higher NIHSS score ($P < 0.01$), as shown in **Table 1**.

Comparison of serum iron, serum ferritin, PCT, CRP and A(2)DS(2) score between the two groups

The SAP group had significantly a higher A(2)DS(2) and CURB-65 score and serum iron, ferritin, PCT and CRP than the control group ($P < 0.01$), as shown in **Table 2**.

Comparisons of the serum iron, serum ferritin, serum PCT, CRP and A(2)DS(2) score in SAP prediction

The ROC curve showed that serum iron, serum ferritin, PCT, CRP, the A(2)DS(2) score and the CURB-65 score had relatively high values in SAP prediction (all $P < 0.01$, all AUC > 0.5), as shown in **Table 3**.

Values of combination of multiple indicators in SAP prediction

Serum iron, serum ferritin, PCT, the A(2)DS(2) score and other indicators were combined with CRP for SAP prediction, the model had a larger AUC and higher specificity than the individual prediction models, as shown in **Table 4**.

Analysis on correlations between serum iron, serum ferritin and A(2)DS(2) score and CURB-65 score

Spearman correlation analysis showed that serum iron, serum ferritin, procalcitonin and the A(2)DS(2) score were highly correlated with the CURB-65 score ($P < 0.01$), and therefore could be used to predict the severity of pneumonia, as shown in **Table 5**.

Discussions

CRP is an acute phase reactant synthetized by the liver when tissue injury occurs and has become one of the most recognized inflammatory markers. When inflammation progresses, CRP will quickly return to normal, and its' increased effective range is positively correlated with infection severity. In order to find the indicators for evaluating infection occurrence and predicting short-term and long-term prognosis, Diedler J, et al. [14], investigated the CRP levels in 247 patients with supratentorial intracerebral hemorrhage. The result using the multivariate model, the maximum value of CRP was an independent predictive factor for poor prognosis (mRS > 2) (OR: 1.72, 95% CI: 1.12-2.64, P = 0.013). Chalmers JD, et al. [15], conducted a prospective study on patients with pneumonia to measure CRP at the time of admission and 4 days after admission and observed the 30-day mortality. In total 570 cases were included in the study, and the results showed that the 30-day mortality rate was 9.6% and low levels of CRP showed highly negative (survival rate) predictive ability (CRP < 10 mg/L = 100%, CRP < 50 mg/L = 99.1%, CRP < 100 mg/L = 98.9%, CRP < 200 mg/L = 94.9%) for SAP. When CRP on Day 4 was compared with that on Day 1, the patients with a marked decrease of less than 50% showed higher 30-day mortality (OR 24.5, 6.4-93.4, P < 0.001). In this case, CRP is an independent marker in predicting the severity of pneumonia. In this study, we found that when CRP was independently used to predict the occurrence of SAP, the sensitivity was 96.2%

Table 3. Comparison of values of clinical scores and blood indicators in SAP prediction

	Critical value	AUC (95% CI)	P	Sensitivity	Specificity
Serum iron (umol/L)	10.25	0.835 (0.755-0.915)	0.000	78.0%	72.5%
Serum procalcitonin (ng/ml)	0.405	0.840 (0.761-0.919)	0.000	78.4%	72.0%
Serum ferritin	405.25	0.845 (0.768-0.921)	0.000	80.4%	72.0%
C-reactive protein (mg/L)	14.95	0.924 (0.869-0.979)	0.000	98.0%	76.0%
A(2)DS(2) score	2.50	0.827 (0.746-0.908)	0.000	96.1%	66.0%
CURB-65 score	1.50	0.877 (0.810-0.944)	0.000	76.5%	88.0%

Table 4. Comparison of combinations of multiple indicators in SAP prediction

	AUC (95% CI)	P	Sensitivity	Specificity
CRP + serum iron	0.930 (0.880-0.980)	0.000	94.1%	84.0%
CRP + serum ferritin	0.938 (0.892-0.984)	0.000	94.1%	84.0%
CRP + procalcitonin	0.957 (0.923-0.991)	0.000	98.0%	82.0%
CRP + A(2)DS(2) score	0.953 (0.912-0.993)	0.000	94.1%	84.0%
CRP + CURB-65 score	0.951 (0.909-0.992)	0.000	92.2%	90.0%

and the specificity was 86.5% ($P < 0.01$), showing an advantage among all of the serological indicators.

Certainly, there are limitations for CRP: CRP is a non-specific protein, and in addition to infection, many other factors, such as trauma and bleeding, can also cause an increased expression. Di Napoli M, et al. [16], made a prospective multi-center clinical study of 223 patients with spontaneous intracerebral hemorrhage and found that CRP significantly increased 48 hours after cerebral hemorrhage, which may interfere with the determination of infection and severity by CRP. Because CRP is produced in the liver, in cases of chronic liver disease and severe hepatic dysfunction, it may not increase significantly or could even decrease [17]. Mackenzie I, et al. [18], in retrospect analyzed 126 patients with bacteremia and found that serum CRP levels in 33 patients with hepatic dysfunction (median: 103 mg/L, internal distance: 29-204 mg/L) was significantly lower than in other patients with normal liver function (median: 146 mg/L, internal distance: 74->250 mg/L). This indicates that one should be cautious when using CRP to diagnose and detect bacteremia in patients with liver disease. However, in recent years, some researchers have proposed different opinions. Tsiakalos A, et al. [19], made a study on acute phase proteins in patients with cirrhosis and found that serum CRP > 55.8 mg/L had relatively high sensitivity (79%) and specificity (96%), as well as high diagnostic accuracy (92%) in the diagnosis of bacterial infections. Korppi M, et al. [20], analyzed the results of CRP in 209 inpatients serologically and determined the samples to be either bacterial or a viral infection and found that different from bacterial infections or viral infections that might have no increase in CRP.

PCT is a prohormone without hormonal activity and is mainly used for diagnosis of bacterial infections, sepsis and disease monitoring. Simon L, et al. [21], made a meta-analysis of 905 patients and found that in cases of systemic bacterial infections, fungi, parasites, rickettsia and tuberculosis infection, PCT levels increased significantly, while in the case of viral infections, PCT levels might increase mildly, thus PCT's sensitivity in diagnosis of infection was (88%, 95% CI: 80-93%) and its specificity was (81%, 95% CI: 67-90%). The PCT increased range is correlated with the severity and prognosis of infection. de Jager CP, et al. [22], found that PCT was a valuable tool for clinical evaluation and follow-up of pneumonia caused by Legionella pneumophila. This was considerably better than WBC, CRP and CURB-65 score, and it had higher clinical values in pneumonia differential diagnosis, prognosis and efficacy observation. After a stroke, a high fever could lead to the difficult identification of pulmonary embolism and pneumonia. Köktürk N, et al. [23], made a surveying analysis on 46 patients (including patients with pulmonary embolism and pneumonia complicated by fever). PCT can be used to identify pulmonary embolism and pneumonia, and it was found that in the first day of initial diagnosis, PCT levels in the patients with pneumonia (2.24 ± 0.99 ng/ml) were significantly higher than in the patients

Table 5. Analysis on correlations between serum iron, serum ferritin, procalcitonin and A(2)DS(2) score and CURB-65 score

	Correlation coefficient	P
Serum iron and CURB-65 score	-0.500	0.000
Serum ferritin and CURB-65 score	0.470	0.000
Procalcitonin and CURB-65 score	0.363	0.000
A(2)DS(2) score and CURB-65 score	0.645	0.000

with pulmonary embolism (0.48 ± 0.77 ng/ml). After 3 days of antibiotic therapy, the PCT levels decreased significantly (0.92 ± 0.62 ng/ml, $P < 0.001$). Schuetz P, et al. [24], found in a multicenter randomized controlled study on 1359 patients with pneumonia conducted in 2006-2008 that the PCT values could guide use of antibiotics. This assures the ensuring safety and efficacy, and it could reduce the time of antibiotic use, reduce antibiotic-related adverse events, and reduce the emergence of multiple resistant bacteria. A prospective cohort study conducted in Switzerland in 2010 showed that first PCT value after admission could accurately predict positive blood culture results ($P < 0.01$), reduce the numbers of blood cultures, and thus save medical costs [25].

Holm A, et al. [26], made a prospective observational study on 364 patients with pneumonia, and analyzed chest X-rays, microculture and CRP and PCT tests. The results indicated that both PCT and CRP values could well predict the occurrence and severity of inflammation and the need for hospitalization. But no signs indicated that PCT was lower than CRP. In this study, we also found when PCT was independently used to predict the occurrence of SAP, its sensitivity was only 76.9% and specificity was only 62.2% ($P < 0.01$), and lower than those of other serological markers. Krüger S, et al. [27, 28], made a CAPNETZ study to follow up 991 inpatients for 28 days and found that the PCT had a lower accuracy in predicting the short and long-term mortality of post-stroke infections than adrenomedullin and was significantly affected by the use of antibiotics.

The iron element is an essential trace element constituting the human body. Venezuelan scientists made a test in mice and horses and discovered that in the early infection stage, phagocytic cells are stimulated to synthetize and release certain cytokines, and these cytokines stimulate ferritin synthesis and will cause iron to be released from other cells or an external iron molecule will bind with it and results in decreased serum iron and increased serum ferritin. Increased serum ferritin level has immunosuppressive effects, because it can inhibit lymphocyte proliferation [29]. Many researchers found in further studies that decreased serum iron could prevent infection, because too much free iron in the blood cannot improve body immunity and will be swallowed by bacteria resulting in mass proliferation of bacteria and aggravated infection. Sengoelge G, *et al.* [30], found that iron is not only an essential nutrient in the human body, but has potential risks. It can affect the production of endothelial cells and cytokines, cause oxidative stress, and even support bacterial growth. Intravenous iron therapy may accelerate the formation of hydroxyl radicals in catalysts, thus causing infection in patients with iron overload. It was reported that researchers found in a mouse model that S. aureus obtained iron from hemoglobin through the surface iron adjusting system to meet the need for bacterial reproduction [31]. Da Silva CB, *et al* [32], measured a significantly lower serum iron level in infected rats than in non-infected rates ($P < 0.05$), and serum ferritin level was significantly higher than in non-infected rats ($P < 0.01$). Grieger TA, Kluger MJ, *et al*.[33, 34], made a test of bacterial infections in lizards and rabbits and found that fever and decreased serum iron level could be a defense response of the host, and iron supplementing iron therapy would increase the mortality of the experimental infected animals. Animals utilize iron sequestration as a means of defense from microbes. Iron is a nutrient required for bacterial reproduction, but hosts (i.e. human) have developed mechanisms to sequester iron in various ways such that the amount of free iron in the body is low and bacteria have difficulties to reproduce. When the body is infected, it will release a variety of endogenous anti-inflammatory mediators, which can not only increase body temperature, but also further reduce the amount of free iron that can be accessed by bacteria in the blood. Therefore, low serum iron levels will benefit infected patients. Phillip Klebba, *et al.* [35], found that bacteria must

obtain iron from the host to establish a "base" for colonization. Deprivation of iron could cause resistance to diseases by separating antibodies to block the uptake of iron, which can help animals and humans protect themselves against bacterial diseases and provide a new perspective for development of new antibiotics. In this retrospective study, we also discovered when serum iron was independently used to predict the occurrence of SAP, the sensitivity was 78.4% and the specificity was 73.1% ($P < 0.01$). It is also one of the serological markers that could be effectively used in future clinical work. More cases can be collected and combined with bacteriological classification of pathogen detection to study this further. However, it was reported that compared with patients without bacteremia, patients with bacteremia had lower serum iron levels and higher serum ferritin levels, but the differences were not statistically significant [36].

CURB-65 score (disturbance of consciousness = 1 point, blood urea nitrogen > 7 mmol/L (19 mg/L) = 1 point, respiratory rate ≥ 30 times/min = 1 point, SBP < 90 mmHg or DBP ≤ 60 mmHg = 1 point, age ≥ 65 years old = 1 point) is recommended by USA and UK CAP guidelines for evaluation of severity of pneumonia. USA CAP Diagnosis and Treatment Guidelines for Adults 2007 suggest that when CURB-65 score ≥ 2 point, hospitalization is recommended [36]. British Thoracic Society (BTS) CAP Guidelines 2009 suggest that when CURB-65 score = 0 (mortality 0.6%) or 1 (mortality 2.7%), hospitalization is not required. A CURB-65 score = 2 (mortality 6.8%), hospitalization is required or existing hospitalization is shortened and outpatient supervision is required. A CURB-65 score ≥ 3 (mortality 14%), emergency hospitalization is required. A CURB-65 score = 4-5 (mortality 27.8%), ICU admission is required [37]. Loke YK, *et al.* [38], made a meta-analysis and found that a CURB-65 score had a higher specificity and was suitable for the assessment of high-risk patients, but many published reports claimed that most patients with acute stroke developed stress renal dysfunction, including elevated blood urea nitrogen, which might interfere with the accuracy of this score when used in patients with stroke [39].

Hoffmann S, *et al*. [40], made a retrospective analysis of patients with stroke in Berlin, Germany from 2007 to 2009 and proposed a new scoring system for SAP prediction A(2)DS(2) score (Age ≥ 75 years old = 1 point, atrial fibrillation = 1 point, dysphagia = 2 points, male = 1 point, stroke severity, according to NIHSS score, 0-4 = 0, 5-15 = 3 points, ≥ 16 = 5 points), and it could help guide prevention of high-risk patients in SAP treatment (when A(2)DS(2) score increased from 0 to 10 points, while the incidence of pneumonia also increased from 0.3% to 39.4%, ROC AUC = 0.84).

In this study, the A(2)DS(2) score ROC AUC was 0.837, similar to the results in the study on patients with a stroke discovered by German scientists. The sensitivity for SAP prediction was (96.2%, $P < 0.01$), better than the CURB-65 score (84.6%, $P < 0.01$). The specificity was (70.3%, $P < 0.01$), lower than the CURB-65 score (86.5%, $P < 0.01$), and the A(2)DS(2) score combined with the CRP values could further improve the sensitivity (96.2%, $P < 0.01$) and the specificity (91.9%, $P < 0.01$), so it is the first choice in clinical practices when combined with laboratory and clinical indicators.

Therefore, an analysis of serum ferritin, PCT, CRP and the A(2)DS(2) score at admission is an effective way to predict SAP; serum iron, ferritin and the A(2)DS(2) score can not only be used as a SAP monitoring method, but they can also predict the severity of SAP. The serum iron and A(2)DS(2) score combined with CRP can improve the accuracy of SAP prediction.

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Disclosure of conflict of interest

None.

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