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Value of plasma AGEs and sRAGE expression in predicting the occurrence of ARDS in elderly COPD patients

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ABSTRACT

This study aimed to explore the diagnostic value of advanced glycation end products (AGEs) and soluble receptors for advanced glycation end products (sRAGE) by detecting the expression levels of AGEs and sRAGE in the plasma of elderly patients with chronic obstructive pulmonary disease (COPD) combined with acute respiratory distress syndrome (ARDS). For this purpose, 110 COPD patients were divided into the elderly COPD group (n=95) and the elderly COPD combined with the ARDS group (n=15). An additional 100 healthy people were recruited as the control group. All patients were assessed with Acute Physiology and Chronic Health Evaluation (APACHE II score) after admission. The levels of AGEs and sRAGE in the plasma were measured by enzyme-linked immunosorbent assay. Results showed that compared with the elderly COPD group, the APACHE II score was significantly higher in the elderly COPD combined with ARDS group ($P < 0.05$); the level of plasma AGEs in the control group, the elderly COPD group, and the elderly COPD combined with ARDS group decreased in turn ($P < 0.05$), and the level of sRAGE increased in turn ($P < 0.05$). Pearson analysis exhibited that the plasma AGEs level was negatively correlated with the APACHE II score ($r = -0.681$, $P < 0.05$), and plasma sRAGE level was positively correlated with the APACHE II score ($r = 0.653$, $P < 0.05$). Binary Logistic analysis demonstrated that AGEs were the protective factor for ARDS in elderly COPD patients ($P < 0.05$), and sRAGE was the risk factor for ARDS in elderly COPD patients ($P < 0.05$). The areas under the curve of plasma AGEs, sRAGE, and their combination in the prediction of ARDS in elderly COPD patients were 0.860 (95%CI: 0.785-0.935), 0.756 (95%CI: 0.659-0.853), and 0.882 (95%CI: 0.813-0.951), respectively. The decreased level of AGEs and the increased level of sRAGE in the plasma of COPD patients with ARDS are associated with the disease severity and have a certain diagnostic value for ARDS in COPD patients, which may be potential markers for the clinical diagnosis of COPD combined with ARDS.

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Introduction

Acute respiratory distress syndrome (ARDS) is a respiratory failure syndrome characterized by hypoxemia and changes in respiratory system mechanisms and is a major cause of morbidity and mortality in intensive care unit patients (1). The elderly population has a high incidence of COPD. Chronic obstructive pulmonary disease (COPD) combined with ARDS can be detected clinically, which may even lead to disability or death in the elderly. Most elderly people experience a progressive decline in lung function, dyspnea, fatigue, and inability to take care of themselves in daily life. A recent epidemiological survey of ARDS patients in ICUs in 50 countries/regions exhibits that ARDS accounts for 10.4% of all ICU admissions worldwide and the total mortality rate is as high as 35.3% (2). To date, no pharmacological treatment has been shown to improve the mortality or prognosis of ARDS, and the only accepted treatment is to support the use of lung-protective mechanical ventilation strategies designed to minimize lung damage by limiting the tidal volume and reducing average airway pressure (3). Taken together, it is very important to find the factors and predictors that affect the incidence of COPD with ARDS. Advanced glycation end products (AGEs) are a large class of heterogeneous compounds, which can be formed through nonenzymatic glycosylation/oxidation of reducing sugars with the free amino groups of proteins (4). Soluble receptor for advanced glycation end products (sRAGE), a pattern recognition protein, belongs to the receptor immunoglobulin superfamily and can identify various ligands, containing AGEs, S100 calcium-binding protein, and modified low-density lipoprotein (5). A previous study demonstrated that the level of sRAGE in the alveoli of ARDS patients was significantly higher than that of patients treated with mechanical ventilation, and the level of AGEs was significantly diminished (6). This study aims to investigate the diagnostic value of AGEs and sRAGE in COPD patients combined with ARDS by detecting the expression levels of AGEs and sRAGE in their plasma to provide some evidence for the early clinical diagnosis of the disease.

Materials and Methods

General information

This study was approved by the Ethics Committee of our Hospital. All the family members of the subjects signed informed consent. The protocol of the study was

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designed and approved by institutional review board and accordingly a total of 110 COPD patients admitted and diagnosed in the Respiratory Department of our Hospital from January 2017 to January 2018 were enrolled as subjects. All COPD patients were diagnosed following the *Guideline for primary care of chronic obstructive pulmonary disease (2018)* revised by the Respiratory Branch of the Chinese Medical Association [7]. According to the presence and absence of ARDS, they were assigned to two groups. The elderly COPD group (n=95) contained 55 males and 40 females, aged 58-86 years old, with a mean age of (68.59±8.36) years old. The elderly COPD combined with the ARDS group (n=15) consisted of 9 males and 6 females, aged 59-87 years old, with a mean age of (69.13±8.89) years old. The diagnosis of ARDS is in line with the new diagnostic criteria for ARDS (Berlin Definition) revised by the European Society of Intensive Care Medicine in Berlin, Germany in 2012 [8]. An additional 100 healthy people who received physical examination in our hospital during the same period were recruited as the control group, including 56 males and 44 females, aged 57-89 years old with a mean age of (68.92±8.62) years. There was no significant difference in age and sex among the three groups ($P > 0.05$), and baseline data were comparable.

Inclusion criteria of COPD patients with ARDS: (1) All patients met the above diagnostic criteria for COPD and ARDS. (2) The patients had complete clinical data. (3) Patients with non-neurological diseases or lung cancer were examined with the nervous system and electronic computed tomography. Exclusion criteria: (1) systemic immune deficiency or immune disorder; (2) pulmonary heart disease, pulmonary embolism, pulmonary hypertension; (3) thick sputum or a large number of airway secretions, receiving tracheal surgery recently; (4) lethargy and neurological dysfunction.

Main reagents and instruments

Enzyme-linked immunosorbent assay (ELISA) kit for plasma AGEs (Tianjin Reagent Biotech Co., LTD., Tianjin, China), ELISA kit for plasma sRAGE (Y-Y Chemical Reagents, Shanghai, China), KHB ST-360 microplate reader (Wuhan Zhongmei Technology Co., Ltd., Wuhan, China), low-temperature high-speed centrifuge (Thermo Fisher Scientific, Waltham, MA, USA), and -80°C ultra-low temperature freezer (Haier Group, Qingdao, China).

Methods

Specimen collection

5 mL of peripheral venous blood was collected from all patients within 1 h after admission and from physical examination subjects on the day of examination. The blood was placed in a tube containing sodium citrate anticoagulant and mixed upside down. The blood was maintained in place for 30 min and centrifuged at room temperature and 3000 rpm/min for 15 min. The supernatant was piped into EP tubes and stored in a -80°C freezer for further use.

Detection of plasma AGEs and sRAGE levels

Frozen plasma samples were removed from the -80°C freezer and thawed. The levels of AGEs and sRAGE in the plasma were determined by ELISA. All operations were conducted in strict accordance with the instrument and kit instructions.

Acute Physiology and Chronic Health Evaluation (APACHE II Score) Scale

APACHE II score is composed of three parts: A, B, and C. A: Acute physiological score, with 12 variables, each variable selects the maximum or minimum value within the first 24 h after admission to the ICU. B: Age points were divided into five age groups, the older you are, the higher the score. C: Chronic health points, refer to patients with a history of severe organ dysfunction or impaired immune function before hospitalization, including 2 points for elective surgery and 5 points for non-surgical or emergency surgery. The maximum theoretical value of the APACHE II score is 71 points. Patients with more than 15 points are classified as severe, while patients with less than 15 points are classified as non-severe. The higher score indicates a more serious disease.

Statistical methods

SPSS 20.0 statistical software was applied to analyze the data. The measurement data were expressed as the mean ± standard error. An independent sample t-test was used between the two groups. Count data were expressed as n and analyzed using the χ^2 test. The Pearson method was employed to analyze the correlation between plasma AGEs and sRAGE levels and APACHE II scores in aged COPD patients. Logistic regression analysis was utilized to analyze the influencing factors of ARDS in aged COPD patients. Receiver operating characteristic (ROC) curves were used to analyze the diagnostic efficiency of plasma AGEs and sRAGE levels for ARDS in aged COPD patients. A value of $P < 0.05$ was considered statistically significant.

Results

Comparison of AGEs and sRAGE expression levels in the plasma of subjects

Compared with the elderly COPD group, the APACHE II score was significantly increased in the elderly COPD combined with the ARDS group ($P < 0.05$). The levels of plasma AGEs were significantly decreased successively, while the levels of sRAGE were significantly increased successively in the control group, elderly COPD group, and elderly COPD combined with the ARDS group ($P < 0.05$; Table 1).

Correlation between plasma AGEs and sRAGE levels and APACHE II scores in elderly COPD patients

Pearson analysis exhibited that plasma AGEs level was negatively correlated with APACHE II score (r=-0.681, $P < 0.05$); plasma sRAGE level was positively correlated with APACHE II score (r=0.653, $P < 0.05$; Figure 1).

Logistic regression analysis of the influencing factors of ARDS in elderly COPD patients

Binary logistic regression analysis was conducted with the occurrence of ARDS in elderly COPD patients as the dependent variable and plasma AGEs and sRAGE levels as independent variables. The results demonstrated that AGEs were the protective factor for ARDS in elderly COPD patients ($P < 0.05$). sRAGE is an independent risk factor for ARDS in elderly COPD patients ($P < 0.05$; Table 2).

Table 1. Comparison of plasma expression levels of AGEs and sRAGE.

Group	*n*	APACHE II score	AGEs (μg/mL)	sRAGE (pg/mL)
Control	100	-	48.62±9.28	285.46±85.29
Elderly COPD	95	13.75±3.21	34.26±6.63	357.16±106.25
Elderly COPD combined with ARDS	15	20.53±5.16	21.48±4.65	769.25±216.24
t/F	-	6.924	194.511	167.769
P	-	0.000	0.000	0.000

Table 2. Logistic regression analysis of influencing factors for ARDS in aged COPD patients.

Item	β	SE	wald χ^2	*P*	*OR*	95%*CI*
AGEs	-0.241	0.112	4.622	0.031	0.786	0.631-0.979
sRAGE	0.710	0.121	35.056	0.000	2.035	1.608-2.575

ROC analysis of plasma AGEs and sRAGE levels in the diagnosis of ARDS in elderly COPD patients

ROC curve analysis results displayed that the areas under the curve of plasma AGEs and sRAGE to predict ARDS in aged COPD patients were 0.860 (95%CI: 0.785~0.935) and 0.756 (95%CI: 0.659~0.853), respectively, with cutoff values of 27.191 μg/mL and 443.158 pg/mL, the sensitivity of 86.0% and 80.0%, and the specificity of 78.0% and 68.0%, respectively. The area under the curve for predicting ARDS in elderly COPD patients by combined detection was 0.882 (95%CI: 0.813~0.951), with a sensitivity of 72.0% and specificity of 96.0% (Figure 2).

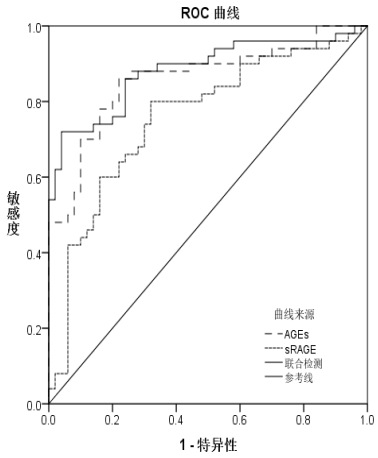

Figure 2. ROC analysis of plasma AGEs and sRAGE levels in the diagnosis of ARDS in elderly COPD patients.

Discussion

COPD is characterized by incompletely reversible airflow obstruction, in which the lungs exhibit a progressive inflammatory response to harmful particles or gases. After respiratory tract lesions, if these COPD patients are combined with infection and shock and the imbalance between pro-inflammatory factors and anti-inflammatory factors occurs, leading to uncontrolled disease, extensive pulmonary exudation, and alveolar edema, and oxygen exchange disorders, thereby resulting in ARDS (9). ARDS is a common cause of respiratory failure and death in critically ill patients, and its clinical characteristics are diffuse alveolar epithelial and pulmonary endothelial injury, inducing pulmonary edema with increased permeability, alveolar filling, and respiratory failure (10). The three criteria for defining ARDS in the 2012 Berlin definition include (i) onset within 1 week of the onset of a known clinical infection or new or worsening respiratory symptoms. (ii) Chest X-ray or computed tomography cannot fully explain bilateral opacity, effusion, lobular/pulmonary collapse, or nodules. (iii) Respiratory failure cannot be fully explained by heart failure or fluid excess (11). ARDS is characterized by rapid onset, rapid development, poor outcome, and high mortality, which bring heavy mental pressure and medical burden to ARDS patients and their families. With a deep understanding of the inflammatory mechanism, a variety of inflammatory factors has been found to be involved in the occurrence and development of ARDS.

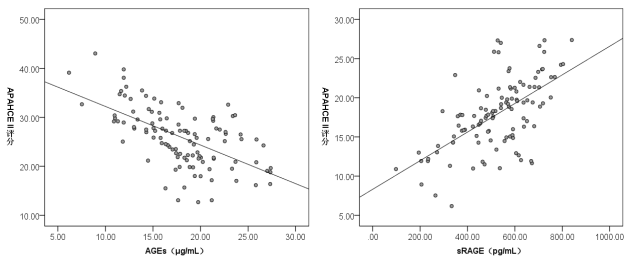

Figure 1. Correlation between plasma AGEs and sRAGE levels and APACHE II score in elderly COPD patients.

AGEs are a group of compounds from different origins that are generated through spontaneous reactions between reducing sugars and the free amino groups in amino acids, as well as through other reactions, including the oxidation of sugars, lipids, and amino acids, to produce reactive aldehydes covalently bound to proteins. Previous studies have confirmed that AGEs are associated with oxidative stress and inflammation, and long-term inflammatory responses lead to many chronic diseases, such as cardiovascular disease, diabetes, and COPD (12-13). sRAGE is an extensively studied receptor for AGEs. sRAGE is a multiligand single-transmembrane receptor and a member of the immunoglobulin superfamily of cell surface molecules. AGEs bind to sRAGE to stimulate various inflammatory signal transduction pathways, promote the release of inflammatory cytokines, and participate in inflammatory responses. In addition, sRAGE also has the binding site of transcriptional factor nuclear factor-κB (NF-κB) and has been proven to be the direct target gene of NF-κB signal transduction (14, 15). The activation of NF-κB during inflammation increases the expression of sRAGE and generates a positive feedback cycle, which can transform the transient proinflammatory response into a chronic

pathophysiological state (14), suggesting that the chronic progression of COPD patients may be associated with the chronic pathologic state of the sRAGE-NF-κB pathway. In this study, the APACHE II score of the elderly COPD combined with ARDS group was significantly higher than that of the elderly COPD group; the levels of plasma AGEs decreased successively and the levels of sRAGE increased successively in the control group, the elderly COPD group, and the elderly COPD combined with ARDS group. It is indicated that plasma AGEs and sRAGE may be associated with ARDS in aged COPD patients. In the present study, Pearson analysis showed that plasma AGEs level was negatively correlated with APACHE II score, while plasma sRAGE level was positively correlated with APACHE II score. Binary logistic regression analysis displayed that AGEs were protective factors for ARDS in senile COPD patients and sRAGE was a risk factor for ARDS in senile COPD patients. It is suggested that plasma AGEs and sRAGE are associated with the severity of the disease. The increased level of plasma AGEs may predict the improvement of COPD, and the increased level of plasma sRAGE may predict the deterioration of COPD to ARDS. A previous study exhibited that a higher baseline plasma sRAGE level was associated with higher 90-day mortality in ARDS patients (15). Our ROC curve analysis results exhibited that plasma AGEs and sRAGE could well predict ARDS in elderly COPD patients. Combined detection has higher diagnostic efficacy in predicting ARDS in elderly COPD patients. These findings suggest that both of them may be potential markers for the diagnosis of ARDS in elderly COPD patients.

In conclusion, the diminished expression level of AGEs and increased expression level of sRAGE in the plasma of COPD patients with ARDS are strongly associated with the disease severity and are independent risk factors for ARDS in COPD patients. Both of them can predict the occurrence of ARDS in elderly COPD patients and may be potential markers for the clinical diagnosis of COPD combined with ARDS. This study has the limitation of not including the co-detection of pulmonary function indicators or other inflammation-related factors. The role of plasma AGEs and sRAGE levels in elderly COPD patients combined with ARDS deserves further investigation.

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