The efficacy of modified neutrophil alkaline phosphatase score, serum IL-6, IL-18 and CC16 levels on the prognosis of moderate and severe COPD patients.

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Abstract

Objective: Our objective is to analyse the efficacy of modified Neutrophil Alkaline Phosphatase (NAP) score, serum Interleukin-6 (IL-6), IL-18 and human Clara cell secretory 16-kD protein (CC16) on the prognosis of moderate and severe Chronic Obstructive Pulmonary Disease (COPD) patients, which provides a reference to predict the prognosis of COPD patients.

Methods: 182 moderate and severe COPD patients admitted in our hospital during April 2012 to April 2015 were included in the observation group, and 150 healthy people were included in the control group for prospective analysis. Serum IL-6, IL-18 and CC16 levels were detected and the differences were analysed. Pearson's correlation analysis was used to analyse the correlation of modified NAP score, serum IL-6, IL-18 and CC16 levels with pulmonary function, 2 y acute exacerbation times and 6 min walk distance in moderate and severe COPD patients (P<0.05).

Results: The serum IL-6 and IL-18 in the observation group were higher than the control group, and CC16 was lower than the control group, which were statistically significant (P<0.05). In the observation group, NAP score was normal in 104 patients and abnormal in 78 patients, the second day serum IL-6, IL-18 and CC16 were statistically different between patients with normal and abnormal NAP scores (P<0.05). Pearson's correlation analysis showed that NAP score, IL-6 and IL-18 were positively correlated with the 2 y acute exacerbation times, and negatively correlated with FEV1, FEV1/FVC and 6 min walk distance. CC16 was negatively correlated with the 2 y acute exacerbation times, and positively correlated with FEV1, FEV1/FVC and 6 min walk distance (P<0.05).

Conclusion: Modified NAP score, serum IL-6, IL-18 and CC16 levels are closely correlated to the prognosis of moderate and severe COPD patients. Evaluation of the patient prognosis and actively intervention based on this can improve the life quality of patients.

Keywords: Chronic obstructive pulmonary disease, Modified neutrophil alkaline phosphatase score, Interleukin, Human Clara cell secretory protein, Prognosis.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by continuous airflow limitation, which does not only affect the lung but also causes the systemic adverse reactions. It can significantly affect the work and life of patients, and it is also the fifth life-threatening disease worldwide [1-3]. Compared with mild COPD, there is higher risk of acute exacerbation in moderate and severe COPD patients, furthermore, the pulmonary function is decreased faster and the prognosis is worse. Thus, at present most of the studies focus on predicting the clinical prognosis of moderate and severe COPD patients in order to evaluate the risk of acute exacerbation in the early stage and then intervene [4-7]. The previous studies have shown that Interleukin-6 (IL-6), IL-18 and human Clara cell secretory 16-kD protein (CC16) may be involved in the progress of COPD, and modified Neutrophil Alkaline Phosphatase (NAP) score can provide a reference for the evaluation of the life quality of COPD patients through the infectious condition and clinical symptoms [8-15]. However, there has been no report related to the evaluation of moderate and severe COPD patients' prognosis by modified NAP score and serum IL-6, IL-18 and CC16 levels. In this study, 182 patients and 150 healthy people were selected for prospective controlled analysis.

Materials and Methods

182 moderate and severe COPD patients admitted in our hospital during April, 2012-April, 2015 were included in the observation group, and 150 healthy people were included in the control group. In the observation group there were 108 male patients and 74 female patients, the age was 44-81 years old and the average age was (67.25 ± 11.43 y) old, the Body Mass Index (BMI) was (24.37 ± 3.91 kg/m^2); in the control group there were 87 male patients and 63 female patients, the age was 42-80 y old and the average age was (68.04 ± 11.29 y) old, the BMI was (24.66 ± 3.35 kg/m^2). The gender ratio, age and BMI were not statistically different between two groups (P>0.05), which was statistically comparable. This study was approved by the Ethics Committee in our hospital, and all the patients were informed and they signed the informed consent form.

The inclusion and exclusion criteria

The inclusion criteria of observation group: The patient symptoms were confirmed to the COPD diagnostic criteria made by Respiratory Society, Chinese Medical Association (2013 edition); there was no exacerbation of symptoms or physical signs within 4 w before inclusion, and the clinical phase was stable phase, and clinical classification was moderate or severe (Grades III and IV); the patients who had smoking history had stopped smoking ≥ 6 months when included. The people included in the control group were the healthy people who received physical examination at the Physical Examination Center of our hospital, and those patients didn't have COPD history.

The exclusion criteria: The patients complicated with the diseases that could cause gaspor or dyspnea such as bronchiectasis and active pulmonary tuberculosis; the patients complicated with some other systematic inflammatory diseases, immunodeficiency disease or endocrine disease; the patients received glucocorticoid treatment within 2 w before inclusion; the compliance of patients was poor or the patients refused to participate in this study.

Detection of serum indexes: 0.5 ml fasting elbow venous blood was collected from patients in two groups, and kept at room temperature for 20 min, and then centrifuged at 3000 r/min for 10 min to separate the blood serum. The serum was then transferred into Eppendorf tubes and preserved at -70°C. Serum IL-6, IL-18 and CC16 levels were detected by Enzyme-Linked Immunosorbent Assay (ELISA), the kits were purchased from TSZ Biological Trade Co., Ltd., San Francisco, USA. The levels of serum IL-6, IL-18 and CC16 between two groups were compared.

Calculation of NAP score

Peripheral blood of the patients was collected for blood smear, and rapid modified nitrogen coupling reaction was used to calculate NAP score. The normal range is 150-190.

Follow-up

The patients in the observation group were followed-up by telephone, outpatient follow-up and family visit for 2 years. The 2 y acute exacerbation time was recorded during the follow-up, the pulmonary function was detected at the last follow-up and 6 min walking distance was tested. The pulmonary function was detected by C-8800D pulmonary function testing system (CHEST M. I., INC., Miyagi, Japan), and the indexes included Forced Expiratory Volume in 1 s (FEV1), Forced Vital Capacity (FVC) and their ratio (FEV1/FVC).

Statistical analysis

All the data in this study were analysed by SPSS18.0 (International Business Machines Corp., New York, USA), the enumeration data were presented by (n/%) and analysed by χ^2 test, the measurement data were presented as (x̄ ± s) and analysed by t test. P<0.05 was considered as statistically significant, the Pearson correlation analysis was used to analyse the correlation.

Results

The results of serum indexes

The serum IL-6 and IL-18 in the observation group were higher than the control group, and CC16 was lower than the control group, which were statistically significant (P<0.05), as shown in Table 1. In the observation group, NAP score was normal in 104 patients and abnormal in 78 patients, the second day serum IL-6, IL-18 and CC16 were statistically different in patients with normal and abnormal NAP scores (P<0.05), as shown in Table 2.

Table 1. *Comparison of serum IL-6, IL-18 and CC16 between the patients in two groups (x̄ ± s).*

Index	Observation group (n=182)	Control group (n=150)	t value	P value
IL-6 (pg/ml)	7.56 ± 1.48	2.99 ± 0.68	4.296	<0.05
IL-18 (pg/ml)	47.25 ± 10.76	16.24 ± 3.95	6.581	<0.05
CC16 (ng/ml)	23.08 ± 3.92	41.86 ± 6.40	3.337	<0.05

Table 2. *Comparison of the second day serum IL-6, IL-18 and CC16 levels between patients with different NAP scores (x̄ ± s).*

Index	Normal (n=104)	Abnormal (n=78)	t value	P value
IL-6 (pg/ml)	5.71 ± 1.68	10.68 ± 2.55	8.741	<0.05
IL-18 (pg/ml)	40.32 ± 9.81	52.36 ± 15.05	6.332	<0.05
CC16 (ng/ml)	26.39 ± 5.67	20.24 ± 3.52	6.585	<0.05

Follow-up results

Among 182 patients, 4 patients were lost to follow-up, 13 patients died, and the rest 165 patients were effectively

followed-up. The indexes at the last follow-up: the 2 y acute exacerbation time was 4.33 ± 1.26 times, FEV1 was $49.62 \pm 6.75\%$, FEV1/FVC was 68.62 ± 5.73 and 6 min walk distance was 240.11 ± 39.52 m. Pearson's correlation analysis showed that modified NAP score, IL-6 and IL-18 were positively correlated with the 2 y acute exacerbation times, and negatively correlated with FEV1, FEV1/FVC and 6 min walk distance. CC16 was negatively correlated with the 2 y acute exacerbation times, and positively correlated with FEV1, FEV1/FVC and 6 min walk distance ($P<0.05$), as shown in Table 3.

Table 3. The correlation of modified NAP score and serum indexes with 2 y acute exacerbation times, 6 min walking distance and pulmonary function (r value).

Index	Times of acute exacerbation	FEV1	FEV1/FVC	6 min walk distance
Modified NAP score	0.633*	-0.419*	-0.516*	-0.487*
IL-6	0.571*	-0.385*	-0.361*	-0.525*
IL-18	0.602*	-0.473*	-0.381*	-0.359*
CC16	-0.580*	0.621*	0.374*	0.525*
Note:*P<0.05				

Discussion

COPD is a disease that significantly affects human health. The morbidity and mortality of COPD are high, which brings severe adverse effects on social economy, patients and their family. Thus, it has been a serious social and public health problem. According to the prediction by World Health Organization, COPD is going to be the 3rd biggest cause of death by 2030, which is 2 times higher than that at present [16-19].

As a common disease that can be prevented and treated, the acute exacerbation of COPD and its complications can seriously affect the severity of COPD and even patient life quality [20-22]. Thus, effectively alleviating pulmonary function degradation and decreasing the times of acute exacerbation are the top priorities of COPD treatment. Accurately predicting the clinical prognosis is the key of targeted intervention measures.

The previous studies have shown that the development of COPD involves a large amount of inflammatory factors, among which IL-6 and IL-18 are most concerned [10]. As a cytokine with various biological activities, in the normal condition IL-6 has immune response effect, and in the pathological condition increase of IL-6 concentration can cause immunologic pathological injury. Our study showed that serum IL-6 level in the moderate and severe COPD was higher than the control group, which is related to the immunosuppression, regulation dysfunction of T lymphocyte and B lymphocyte in COPD patients [23-27]. In the comparison of serum IL-18, we found that IL-18 was significantly increased in moderate and severe COPD patients. IL-18 is mainly secreted by activated mononuclear phagocyte, Type 1 T helper (Th1) cells, B cells and natural killer cell, which can strengthen immune response, promote the secretion of inflammatory factors and cytokines. Meanwhile, as a strong Interferon-γ (IFN-γ) stimulating factor, IL-18 can increase the activity of mononuclear phagocyte through positive feedback to increase inflammatory tissue injury mediated by cellular immunity [10,11]. Thus, as the increase of IL-6 and IL-18, the clinical symptoms and physical signs are aggravated. Also because NAP score can reflect the infectious condition of the body, modified NAP was continuously increased [14].

CC16 is a protein secreted by Clara cells, which has biological activities such as anti-inflammatory, antioxidant and immune regulatory effects. Its serum level can reflect the synthesis and secretion amount by non-ciliated epithelial cell. In this study, CC16 level in moderate and severe COPD patients was significantly lower than the normal people, suggesting that the permeability of blood-air barrier was obviously increased. In that case, the permeability of CC16 from lung epithelial lining fluid into blood along with the concentration gradient is restricted, and the immune defense function is also decreased. Thus the airway epithelial injury is continuously aggravated [28-32]. The correlation results showed that as the increase of serum IL-6, IL-18 levels and the decrease of CC16 level, the pulmonary function was gradually deteriorated, the clinical symptoms and physical signs were gradually aggravated and the exercise capacity was lower, indicating that monitoring the NAP score and serum indexes in COPD patients is significant in predicting the disease prognosis and evaluating the prognosis. In the future clinical practice, exploring the drugs targeting at the regulation of IL-6, IL-18 and CC16, which is hopeful to provide a novel approach for the treatment of COPD patients, is worthy of further attention.

In conclusion, NAP score, serum IL-6, IL-18 and CC16 levels are closely correlated with the clinical prognosis in moderate and severe COPD patients. Based on this, the prognosis of patients can be predicted, which provides a reference for the improvement of patient life quality and a novel approach for the exploration of therapeutic drug for COPD patients.

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