ORIGINAL RESEARCH

Analysis of Correlation Between Serum Hypoxia-Inducible Factor-1α, Uric Acid, and Inflammatory Factor Levels and Lung Function in Patients with AECOPD

Sumin Deng, MM; Taofeng Zhu, MD; Cen Wang, BM; Xinnan Gu, BM; Jun Zhang, BM; Qin Lu, MM; Yan Yang, MM; Xiuqin Ma, MM

ABSTRACT

Objective • To investigate the correlation between the serum hypoxia-inducible factor-1α, uric acid, inflammatory factor levels, and lung function in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods • The clinical data of patients with chronic obstructive pulmonary disease (40 cases) from March 2020 to March 2021 were retrospectively analyzed. According to the disease condition in patients with chronic obstructive pulmonary disease, they were divided into acute exacerbation stage (observation group, 20 cases) and stable stage (control group, 20 cases). All patients' basic data such as age, sex, and course of disease were collected and sorted out, and the serum hypoxia-inducible factor-1α, uric acid, inflammatory factor levels (procalcitonin, interleukin-6, and high-sensitivity C-reactive protein), and the index of their pulmonary function were measured. The profiles of serum hypoxia-inducible factor-1 alpha and uric acid, levels of inflammatory factors, and pulmonary function indices were measured and compared between the observation and control groups. The correlation between patients' serum hypoxia-inducible factor-1α, uric acid, and inflammatory factors and lung function was analyzed.

Results • There was no difference in basic data between the observation group and the control group, $P > .05$. Serum hypoxia-inducible factor-1α, uric acid, and levels of inflammatory factors were all higher in the observation group than the control group, and the differences are significant ($P < .05$). There was significant difference in lung function indexes between the observation group and the control group ($P < .05$). Serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor levels were negatively associated with pulmonary function indices.

Conclusion • The more serious the condition of AECOPD patients is, the levels of serum hypoxia inducible factor -1α, uric acid and inflammatory factors gradually increase, and the lung function tends to decline. (*Altern Ther Health Med.* 2023;29(8):214-220).

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a very common disease in respiratory medicine. In 2017, the number of people with chronic respiratory diseases was estimated at 544.9 million, of which about 55% were COPD. In 2019, COPD was the third leading cause of death worldwide. However, the prevalence of COPD is expected to increase. The risk factors for COPD are diverse, and macroscopic generalization is a combination of individual susceptibility factors and environmental factors. Individual factors include genetic factors, age and sex, lung growth and development, bronchial asthma and airway hyper-responsiveness, and low body mass index. Environmental factors include tobacco, fuel smoke, air pollution, occupational dust, infections and chronic bronchitis, and socioeconomic status.

The main disease feature is irreversible airflow limitation.[1,2] The main symptoms of COPD are chronic cough, sputum production, and difficulty in breathing. Patients with early COPD may have no obvious symptoms which become increasingly significant as the disease progresses; cough and sputum production usually appear early in the disease, and later stages are characterized by dyspnea. Symptom characteristics and evolution: (1) Chronic cough: is a common symptom of COPD. Cough symptoms appear slowly and persist for many years, mainly in the morning and at night. (2) Sputum cough: mostly cough accompanied by symptoms, sputum is often white mucus serous, often in the morning when getting up with severe cough, coughing up more mucus serous sputum after the symptoms are relieved; in acute

exacerbations, sputum can become mucopurulent and not easy to cough up. (3) Shortness of breath or dyspnea: it only appears during exertion in the early stage, and then gradually worsens, so that it is difficult to breathe during daily activities and even rest; dyspnea after activity is a "hallmark symptom" of COPD. (4) Chest tightness and wheezing: some patients have obvious chest tightness and wheezing, which is not a specific symptom of COPD, which is common in patients with severe or acute exacerbations. During the stable period of COPD, patients will not have very obvious clinical symptoms, but in the acute exacerbation period, it may lead to the exacerbation of the disease, damage the body's lung function and reduce airway function, and then cause adverse events such as respiratory failure.[3,4] AECOPD mainly refers to the situation involving aggravation of persistent clinical symptoms such as increased sputum volume, purulent sputum, shortness of breath, and cough in patients with COPD in a relatively short period of time, accompanied by the occurrence of various inflammatory reactions at the same time.[5,6] The occurrence of inflammatory reactions will in turn affect the lung function in patients, resulting in the continuous deterioration of the disease.[7,8]

COPD exacerbations can be classified as mild (requiring short-acting bronchodilator therapy only), moderate (with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), and severe (requiring hospitalization or emergency or ICU therapy). The risk assessment of acute exacerbations is based on the number of exacerbations in the previous year, and is assessed as a high-risk group if there have been two or more moderate/severe exacerbations in the previous year, or if one or more hospitalizations for exacerbations have occurred.

The predictors of future exacerbation risk are mainly a history of previous exacerbations, other symptoms, lung function, eosinophil count, etc. On the other hand, serum hypoxia-inducible factor-1α belongs to heterodimers, when the vasomotor substances regulated by hypoxia-inducible factor-1α are out of balance, it will lead to the continuous contraction of pulmonary blood vessels, and lead to pathological changes in the body, which will further lead to pulmonary heart disease and multiple organ failure, and plays an essential part in the progression of COPD.

Other studies have shown that under hypoxia, uric acid will increase abnormally, and there is a close correlation between high level of uric acid and inflammatory responses.[9,10] Therefore, uric acid has its irreplaceable clinical significance in the diagnosis of AECOPD patients. The purpose of this article was to explore the correlation between the serum hypoxia-inducible factor-1α, uric acid, inflammatory factor levels, and lung function in patients with AECOPD. Relevant data studies are shown below.

DATA AND METHODS

General Information

The clinical data of patients with COPD (40 cases) from March 2020 to March 2021 were retrospectively analyzed. According to the disease condition in patients with COPD, they were divided into acute exacerbation stage (observation group, 20 cases) and stable stage (control group, 20 cases).

Inclusion criteria: (1) Patients with a high completeness of clinical data; (2) the patients who were diagnosed as COPD by clinical examination and imaging; and (3) the patients who met the clinical diagnostic criteria for COPD.

Exclusion criteria: (1) Those with malignant tumor; (2) those with severe impairment of liver and kidney function; and (3) those who were unable to cooperate with the study.

Methods

All patients' basic data such as age, sex, and course of disease were collected and sorted out, and the serum hypoxia-inducible factor-1α, uric acid, inflammatory factor levels (procalcitonin, interleukin-6, and high-sensitivity C-reactive protein), and the index of their pulmonary function (percentage of the first-second mandatory expiratory capacity to the forecast value and the ratio of the first-second mandatory expiratory capacity to the mandatory vital capacity) were measured.

Determination of serum hypoxia-inducible factor-1α and uric acid: 5ml of peripheral venous blood samples of the patients were drawn, placed in an EDTA tube, sent to the laboratory within 30 minutes, centrifuged at a speed of 4000 rpm, and the upper serum was extracted after 10 minutes. The serum was stored at -20 °C, and then the serum hypoxia-inducible factor-1α was tested by enzyme-linked immunosorbent assay. The blood uric acid level of the subjects was measured by a full-automatic biochemical analyzer with the model of Olympus AU640.

Determination of inflammatory factor levels: 2ml of venous blood samples of patients in fasting state were drawn, injected into vacuum blood collection vessels, centrifugation was carried out at 2000 rpm in 2 minutes, and then the levels of calcitonin, Interleukin-6, and high-sensitivity C-reactive protein were measured by enzyme-linked immunoassay (ELISA).

Measurement of lung function indicators: the lung function tester of Beijing MaBang msa99 provided by Shandong Boke Scientific Instruments Co., Ltd. was used to measure the percentage of exertional expiratory volume in one second versus the expected value and the ratio of exertional expiratory volume in one second to exertional vital capacity.

Observation Indicators

Basic data like age, gender, and disease duration were compared between the two groups. The serum hypoxia-inducible factor-1α profiles, uric acid profiles, uric acid profiles, and pulmonary function indices of the observed and control groups were compared. The correlation between patients' serum hypoxia-inducible factor-1α, uric acid, and inflammatory factors and lung function was analyzed.

Criteria for different disease stages: (1) Stable stage: chronic blockage lung disease confirmed by X-ray and CT, with a ratio of expired exertional volume to expired vital capacity in one second of less than 70% after inhalation of

Table 1. Comparison of Age, Sex, Disease Duration, and other Basic Data Between the Two Groups

Group	Number of cases	Age (years) $\bar{x} \pm s$	Gender (male / female)	Disease duration (1-2 years /3-4 years)
Observation group	20	56.66 ± 2.21	11/9	8/12
Control group	20	56.69 ± 2.23	12/8	9/11
t/χ^2		0.043	0.102	0.102
P value		.966	.749	.749

Table 2. Comparison of Serum Hypoxia-Inducible Factor-1α Situation Between Observation Group and Control Group (pg/ml)

Group	Number of cases	Serum hypoxia-inducible factor-1α
Observation group	20	43.44 ± 3.52
Control group	20	35.83 ± 7.95
t		3.914
P value		.000

bronchodilators. (2) Acute attack stage: after inhalation of bronchodilators, the forced expiratory volume in one second accounts for less than 70% of the forced vital capacity, while the forced expiratory volume in one second is greater than or equal to 80%.

Statistical Treatment

SPSS 24.0 software was adopted for analysis, and the metric data were expressed as ($\bar{x} \pm s$) with *t* test, the statistical data were expressed as rates with χ^2 test, and Pearson linear correlation was applied to analyze the correlation between groups, and $P < .05$ was considered as a difference that is statistically meaningful.

RESULTS

Comparison of the age, sex, disease duration, and other basic data of the two groups

The observed group did not vary from the control group in terms of age, gender, disease duration, and other basic data, $P > .05$. Refer to Table 1 and Figures 1, 2, and 3.

Comparison of the serum hypoxia-inducible factor-1α situation between the observation group and the control group

Serum hypoxia-inducible factor-1α in the observation group was higher than in the control group, and the difference was statistically meaningful ($P < .05$). Refer to Table 2 and Figure 4.

Comparison of uric acid between the observation group and the control group

The uric acid in the observation group was higher than the control group, and the difference was meaningful, $P < .05$. Refer to Table 3 and Figure 5.

Figure 1. Comparison of Basic Data of Age Between the Two Groups

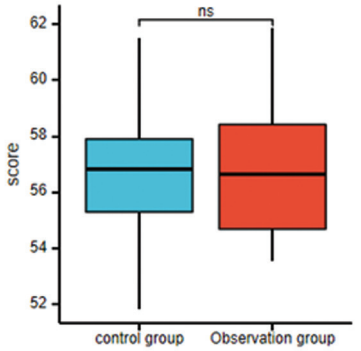


Figure 2. Comparison of Basic Data of Gender Between Two Groups

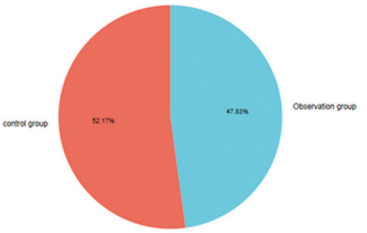


Figure 3. Comparison of Basic Data of Disease Duration Between the Two Groups

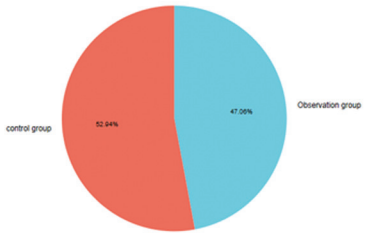


Figure 4. Comparison of Serum Hypoxia-Inducible Factor-1α Situation Between Observation Group and Control Group

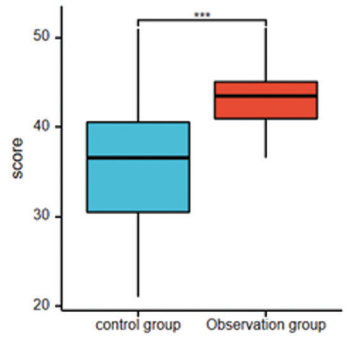


Table 3. Comparison of Uric Acid in the Observing Group and the Control Group (umol/l)

Group	Number of cases	uric acid
Observation group	20	377.41 ± 39.53
Control group	20	180.43 ± 21.33
t		19.612
P value		.000

Table 4. Comparing the Levels of Inflammatory Factors in the Observation Group and the Control Group

Group	Number of cases	Procalcitonin (pg/ml)	IL-6 (pg/ml)	High-sensitivity C-reactive protein (mg/ml)
Observation group	20	7.99 ± 1.41	53.33 ± 5.55	5.44 ± 0.55
control group	20	4.44 ± 1.11	45.55 ± 3.21	3.22 ± 0.32
t		8.847	5.427	15.602
P value		.000	.000	.000

Table 5. A Comparative of Pulmonary Function Indexes Between the Observation Group and the Control Group

Group	Number of cases	Percentage of forced expiratory volume in the first second to the expected value (%)	Ratio of forced expiratory volume in the first second to forced vital capacity (%)
Observation group	20	55.99 ± 2.22	57.99 ± 3.11
Control group	20	41.12 ± 2.33	45.54 ± 1.23
t		20.663	16.648
P value		.000	.000

Comparison of the levels of inflammatory factors between the observation group and the control group

The levels of inflammatory factors (calcitonin, Interleukin 6, and high-sensitivity C-reactive protein) in the observed group were above those in the control group, and the difference was meaningful, $P < .05$. Refer to Table 4 and Figure 6.

Comparing the pulmonary function indexes of the observation group and the control group

There was significant difference in lung function indexes between the observation group and the control group ($P < .05$). Refer to Table 5 and Figure 7.

Analysis of the correlation between patients' serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor levels and lung function

Serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor levels (procalcitonin, interleukin-6, and high-sensitivity C-reactive protein) were negatively correlated with lung function indicators. See Table 6 and Figure 8-17.

Figure 5. Comparison of Uric Acid Situation Between the Observation Group and the Control Group

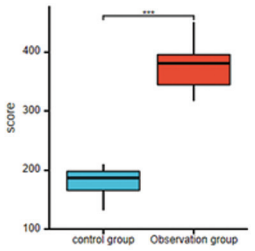


Figure 6. Comparison of Inflammatory Factor Levels Between the Observation Group and the Control Group

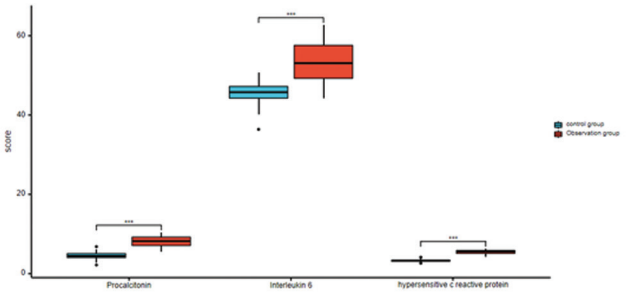


Figure 7. Comparison of Lung Function Indicators Between the Observation Group and the Control Group

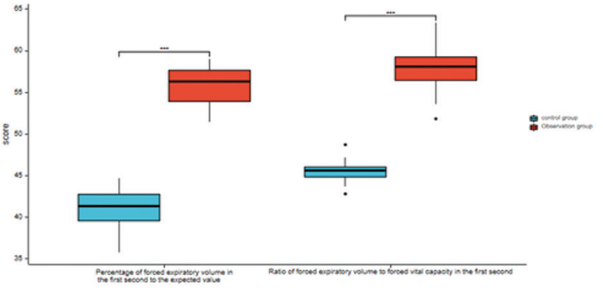


Figure 8. Analysis of the Correlation Between Patients' Serum Hypoxia-Inducible Factor-1α and Percentage of Forcible Expiratory Volume in One Second Versus Predicted Value

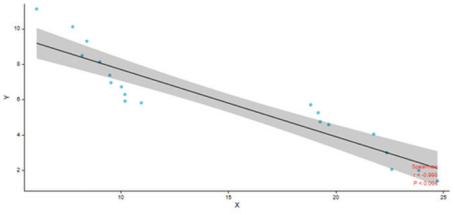


Figure 9. Analysis of the Correlation Between Patients' Serum Hypoxia-Inducible Factor-1α and Ratio of Forcible Expiratory Volume to Forcible Vital Capacity in One Second

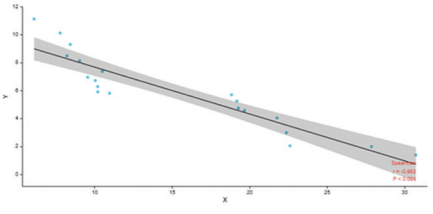


Table 6. Analysis of Correlation Between Patients' Serum Hypoxia-Inducible Factor-1α, Uric Acid, and Inflammatory Factor Levels and Lung Function

Index	Serum hypoxia-inducible factor-1α		uric acid		Procalcitonin		Interleukin 6		High-sensitivity C-reactive protein	
	R value	*P* value	R value	*P* value	R value	*P* value	R value	*P* value	R value	*P* value
Percentage of forcible expiratory volume in one second to the expected value	-0.998	<.05	-0.983	<.05	-0.983	<.05	-0.970	<.05	-0.964	<.05
Ratio of forcible expiratory volume in one second to forcible vital capacity	-0.983	<.05	-0.998	<.05	-0.974	<.05	-0.988	<.05	-0.956	<.05

Figure 10. Analysis of the Correlation Between Uric Acid and the Percentage of Forced Expiratory Volume in the First Second in the Predicted Value

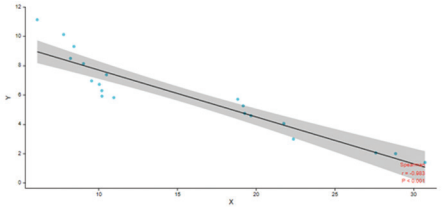


Figure 11. Analysis of the Correlation Between Uric Acid and the Ratio of Forcible Expiratory Volume to Forcible Vital Capacity within One Second

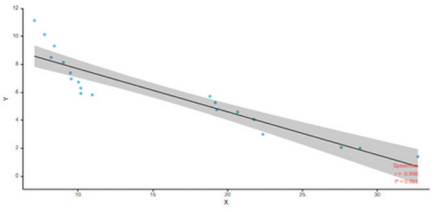


Figure 12. Analysis of the Correlation in the Percentage of Forceful Expiratory Volume within One Second of Calcitonin and Predicted Values

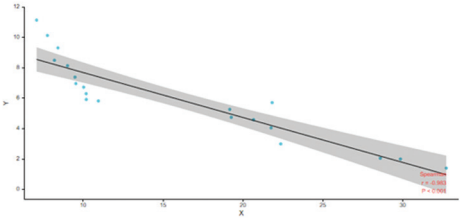


Figure 13. Analysis of the Correlation Between Procalcitonin and the Ratio of Forcible Expiratory Volume to Forcible Vital Capacity within One Second

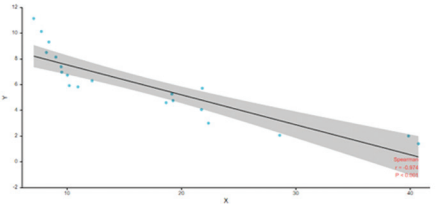


Figure 14. Analysis of the Correlation Between Interleukin-6 and the Percentage of Forced Expiratory Volume in One Second in the Predicted Value

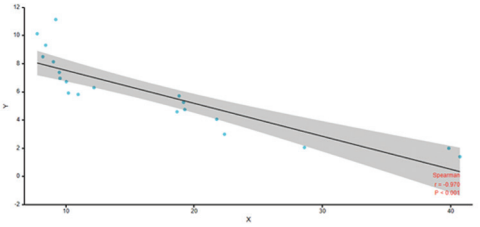


Figure 15. Analysis of the Correlation Between Interleukin-6 and the Ratio of Forced Expiratory Volume in One Second to Forced Vital Capacity

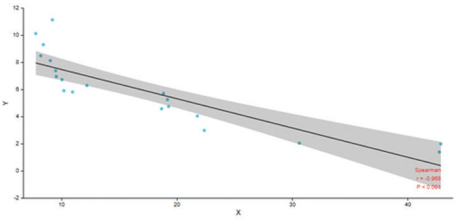


Figure 16. Analysis of the correlation Between Patients' High-Sensitivity C-Reactive Protein and the Percentage of Forced Expiratory Volume in One Second in the Predicted Value

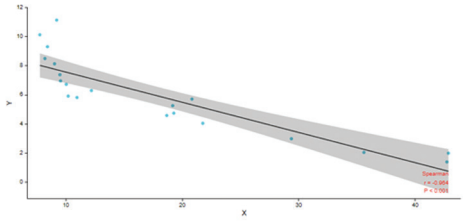
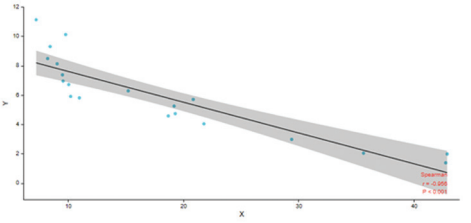


Figure 17. Analysis of the Correlation Between High-Sensitivity C-Reactive Protein and the Ratio of Forced Expiratory Volume in One Second to Forced Vital Capacity



DISCUSSION

COPD is mainly characterized by persistent airflow limitation. The occurrence of this disease is closely related to a variety of abnormal chronic inflammatory reactions, such as cigarette smoke, other harmful gases, and harmful particles. COPD flares repeat with significant respiratory symptoms.[11,12] Clinical intervention can control the disease condition and delay the disease progression by avoiding disease susceptibility factors. If the course of COPD continues to develop, it will affect the lungs and impact lung function. At the same time, the inflammatory reactions will lead to an internal supply imbalance, which is not conducive to other organ functions.[13,14] Although AECOPD patients can relieve clinical symptoms through relevant therapeutic interventions, lung function damage and disease progression in patients may still continue. Hypoxia and inflammatory factors are the key elements that promote the development of disease in patients. It can be seen that the detection of hypoxia, inflammation, and other situations in the body of AECOPD patients can effectively reflect the disease condition in patients, and at the same time can be used as the key point to control the development of the disease.[15,16]

During the disease development in patients with AECOPD, serum hypoxia-inducible factor-1α, as a nuclear transcription factor that can regulate a series of hypoxia genes, its expression level will increase, so as to regulate the body to adapt to the internal hypoxic environment and avoid other damages due to hypoxia. Therefore, serum hypoxia-inducible factor-1α is involved in the development process of airway, lung tissue, and even systemic inflammation.[17,18] At the same time, inflammatory factors in AECOPD can also act to induce the high expression of serum hypoxia-inducible factor-1α, the two interact with each other, which leads to more and more serious hypoxia and inflammatory reactions in AECOPD patients, causing a vicious cycle.[19,20] An acute COPD is a severe worsening of respiratory symptoms that requires additional treatment. The literature mostly reports 0.5~3.5 acute exacerbations per year in COPD patients, but the actual annual number of acute exacerbations is affected by many factors, and there are large individual differences. Acute exacerbations of COPD are an important part of the COPD course and prevention. Early detection and prompt treatment of exacerbations are essential to reduce the burden of disease. Relevant studies have shown that [21,22] with the participation of serum hypoxia-inducible factor-1α, the inflammatory responses in patients with COPD will gradually aggravate, and the degree of inflammatory infection in patients with acute exacerbation will be higher than that in patients with stable phase, indicating that serum hypoxia-inducible factor-1α is closely related to the pathogenesis of AECOPD, and there is a certain correlation between them. Clinical monitoring of serum hypoxia-inducible factor-1α level can be used to assess the hypoxia and inflammation in patients, and to judge whether the patients are in the acute exacerbation.[23,24] On the other hand, lung function test is the main and common way to diagnose AECOPD, which can effectively judge the degree of airflow limitation in patients through lung function indicators, and then predict the disease development in patients.[25,26] It has been shown that there is a negative correlation between internal serum inflammatory factors and lung function in patients with AECOPD,[27,28] which may be due to the release of inflammatory mediators when chronic inflammation occurs in the lung, which can increase the levels of inflammatory factors and at the same time can cause damage to lung structure, thus affecting lung function. Procalcitonin is a glycoprotein, which is mainly secreted by thyroid cells. It is expressed at a low level in healthy populations, and its expression level will rise rapidly when the body has inflammatory reactions. Therefore, procalcitonin can be used as an effective indicator to reflect the body's inflammatory condition. high-sensitivity C-reactive protein is an inflammatory factor secreted by the liver. It is a sensitive inflammatory indicator of COPD. It has activating effects on the coagulation system of the body and will adversely affect the gas exchange in the lung. Interleukin-6 is also involved in the development of AECOPD patients' disease conditions. It will stimulate the smooth muscle of the airway, which will trigger the contraction of smooth muscle, leading to an increase in the level of the airway mucosa and other conditions. At the same time, it will aggravate the human respiratory tract infection condition. Uric acid is susceptible to a variety of factors. For example, lung function damage will lead to hypoxia which will then increase the level of uric acid, and long-term hypoxia will increase the right ventricular afterload and change the hemodynamics, which, in turn, will affect the expression of serum uric acid. At the same time, the internal inflammatory responses will induce lung injury and lead to high expression of uric acid.[29,30] From the data analyzed in this study, serum hypoxia-inducible factor-1α, uric acid, and level of inflammatory factors (calcitonin, Interleukin 6, and high-sensitivity C-reactive protein) in the observation group was above that in the control group, and the discrepancy was statistically significant ($P<.05$). There was significant difference in lung function indexes between the observation group and the control group ($P<.05$). Serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor were negatively associated with pulmonary function indices. The data all reflected the conclusions of the above text and proved that serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor levels interact with and affect lung function, and thus can be effective indicators for evaluating the disease condition in patients.

In conclusion, the more severe the condition of patients with AECOPD, the serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor levels will gradually increase, and the lung function will show a downward trend. So, the serum hypoxia-inducible factor-1α, uric acid, and inflammatory factor levels are negatively correlated with lung function indicators in patients with AECOPD. The above indicators can be used to effectively evaluate the condition of patients with AECOPD for clinical treatment. This research also has some limitations of application researches, for

example: the patients included are all COPD patients, and the grading of patients' condition in the acute onset period is not considered, which may affect the reliability of data and results and conclusion drawn from therein. Therefore, in the future, more patient types need to be included in the study, so as to overcome the shortcomings of this research.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest.

ACKNOWLEDGEMENT

Thanks to my mentor. Thank you for your guidance and encouragement during the whole research process. Your professional knowledge and rich experience have played a vital role in my thesis writing and research method selection.

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