CORRELATIONS BETWEEN THE EXPRESSION OF CYFRA21-1, DCR3, AND CARCINOEMBRYONIC ANTIGEN AND THE SEVERITY OF IDIOPATHIC INTERSTITIAL PNEUMONIA

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ABSTRACT

Objective: *To analyze the correlations between the expression of cytokeratin 19 (CYFRA21-1), decoy receptor 3 (DcR3), and carcinoembryonic antigen (CEA) and the severity of idiopathic interstitial pneumonia (IIP).*

Methods: *From September 2018 to August 2019, 34 patients with IIP, 34 patients with nonspecific interstitial pneumonia, and 34 healthy controls were selected as the IIP group, while 34 patients with nonspecific interstitial pneumonia were selected as the control group. Enzyme-linked immunosorbent assay (ELISA) was used to detect changes in the serum CYFRA21-1, DcR3, and CEA levels. Forced vital capacity (FVC), forced expiratory volume (FEV1), FEV1/FVC, and carbon monoxide diffusion capacity (DLCO) were detected by a pulmonary function instrument; chest high-resolution CT (HRCT) score was used for each group. Spearman correlation analysis was used to analyze the correlations between CYFRA21-1, DcR3, and CEA levels and pulmonary function and HRCT score.*

Results: *Compared with the normal control group, the serum CYFRA21-1, DcR3, and CEA levels in the IIP and NSIP groups were significantly increased (P<0.05), and the serum CYFRA21-1, DcR3, and CEA levels in the IIP group were significantly higher than those in the NSIP group (P<0.05). Compared with the normal control group, the lung function indexes of the IIP and NSIP groups were significantly decreased (P<0.05), and the IIP group was significantly lower than the NSIP group; the difference was statistically significant (P<0.05). The changes in serum CYFRA21-1, DcR3, and CEA levels were significantly positively correlated with HRCT scores (P<0.05), while serum CYFRA21-1, DcR3, and CEA levels were negatively correlated with lung function indexes (P<0.05).*

Conclusion: *The serum CYFRA21-1, DcR3, and CEA levels in patients with IIP are higher, and have significant correlation with the severity of IIP in those patients. Joint detection is conducive to timely assessment and monitoring of disease development in IIP patients, and provides a new method for the treatment of IIP patients.*

Keywords: *CYFRA21-1, DcR3, CEA, idiopathic interstitial pneumonia, severity, correlation.*

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Introduction

Idiopathic interstitial pneumonia (IIP), also known as idiopathic interstitial fibrosis (IIP), is a group of diffuse, progressive lower respiratory lung diseases of unknown origin that primarily affect the interstitium of the lungs. In some patients, pulmonary parenchyma, pulmonary vessels, and airway involvement may occur simultaneously. The clinical manifestations of IIP are progressive dyspnea, poor prognosis, and high mortality. Patient mortality is often due to pulmonary insufficiency and heart failure[1-2]. The pathogenesis of IIP is unknown, and it is highly prone to comorbidity with other diseases. Therefore, early diagnosis and treatment of IIP is of great importance for improving the prognosis and reducing the mortality rate of the disease. In recent years, serum tumor markers have

played an important role in the diagnosis of lung diseases. Cytokeratin 19 fragment (CYFRA21-1) is a new tumor marker commonly used in clinical diagnosis of lung cancer. It exists primarily in tumor epithelial cytoplasm and is released into body fluids when tumor cells are necrotic. Decoy receptor 3 (DCR3) is a secretory protein that plays an important role in cell activity and differentiation as well as the regulation of immune function by competitively binding the same ligand with functional receptors[3]. Carcinoembryonic antigen (CEA) is a protein complex rich in polysaccharides, and which is mainly used in clinical diagnosis, prognosis evaluation, and efficacy detection of malignant tumors.

However, the correlations between these factors and the severity of IIP requires further investigation. The purpose of this study was therefore to investigate the correlations between the expression of serum CYFRA21-1, DCR3, and CEA and the severity of IIP in patients.

Materials and methods

General information

All studies were approved by the ethics committee of the hospital. Thirty-four patients with IIP who were first diagnosed and treated in our hospital from September 2018 to August 2019 were selected as the IIP group. Participants were aged 42-63 years old, and included 19 men and 15 women.

IIP group inclusion criteria involved the following:

• Progressive dyspnea with no clear cause;

• Surgical biopsy showing that the histology was consistent with the common interstitial pneumonia-like changes;

• Pulmonary function examination showing restrictive ventilation dysfunction with decreased diffusion function;

• Routine chest radiographs and high-resolution CT (HRCT) examination of the chest revealing diffuse reticular nodules or honeycomb lung in both lower lungs and subpleura.

In addition, 34 patients with non-specific interstitial pneumonia (NSIP) who visited our hospital during the same period were selected as the NSIP group. Participants in this group were aged 41-62 years old, and included 16 men and 18 women.

NSIP group inclusion criteria involved the following:

• Dyspnea and cough; pulmonary function showing restricted ventilation disorder;

• Diffuse reticular opacity in both lower lungs or subpleura detected by HRCT, but no subpleural lung tissue involved.

Finally, 34 healthy subjects were selected as the normal control group. Patients in the IIP and NSIP groups were diagnosed in accordance with the diagnostic criteria of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) for idiopathic interstitial pneumonia (2013 edition[4].

Exclusion criteria were:

• Age ≤18 years old, ≥80 years old;

• Suffering from various acute or chronic infectious diseases;

• Insufficiency of heart, kidney, or liver.

All patients or their family members were informed of the study and signed their informed consent. There was no statistical significance in gender, age, or other general data among the three groups (P≥0.05), which showed comparability. See Table 1 for details.

Group	n	Gender (M/F)	Age (year)
Control group	34	17/17	56.71±9.42
IIP group	34	19/15	56.31±9.11
NSIP group	34	16/18	56.89±9.53
F		0.236	0.0708
P		0.627	0.9652

Table 1: Comparison and analysis of demographic data from all three groups ($\bar{x}\pm s$).

Blood sample collection

Blood sample collection involved collecting 5ml of fasting venous blood from the normal control group in the morning following their passing of the physical examination. After admission and diagnosis, 5ml of fasting venous blood from patients in the IIP and NSIP groups was taken from the hospital and placed at room temperature for 30min. After centrifugation at 3000r/min for 10min, the upper serum was taken and stored at -80°C for later use.

Observation indexes

Enzyme-linked immunosorbent assay (ELISA) (Shanghai Enzyme Linked Biotechnology Co., Ltd.) was used to determine changes in serum levels of CYFRA21-1, DCR3, and CEA. All operations were conducted in strict accordance with the instructions of the instrument and kit.

A lung function meter (Japan Minato lung function tester AS-507, Beijing Ze'ao Medical Technology Co., Ltd.) was used to detect forced

vital capacity (FVC%), forced expiratory volume in the first second (FEV1%), FEV1 percentage of vital capacity (FEV1/FVC), and carbon monoxide dispersion (DLCO). The reference value of normal lung function in Chinese adults was used as the normal predicted value.

HRCT score

The Muller method was used to score the HRCT of each group. Ground-glass, mesh, and honeycomb changes were scored, respectively (the three change scoring criteria were all referred to with HRCT scoring criteria, and the sum of the three change scores was the total HRCT score). HRCT scoring criteria are shown in Table 2 below.

Scope of lesions	Score
No lesions	0 point
The lesion range is ≤ 5%	1 point
The lesion range is 5~25%	2 points
The lesion range is 25~50%	3 points
The lesion range is 50~75%	4 points
The lesion range is > 75	5 points

Table 2: HRCT scores.
Note: The total score of ground glass sample change, mesh sample change, and honeycomb sample change is the HRCT score.

Statistical analysis

SPSS 20.0 statistical software was used for data statistics, and standard deviation ($\bar{x}\pm s$) was used to represent measurement data. One-way analysis of variance was used for comparison between multiple groups, LSD-t test was used for pairwise comparison, and Spearman correlation analysis was used for correlation between factors and severity of disease. The comparison between the data was deemed statistically significant if P<0.05.

Results

Comparison of serum CYFRA21-1, DCR3, and CEA in normal control group, IIP group, and NSIP group

Compared with those in the normal control group, serum levels of CYFRA21-1, DCR3, and CEA in the IIP and NSIP groups were significantly increased (P<0.05). Furthermore, those of the IIP group were significantly higher than those of the NSIP group; the difference was statistically significant (P<0.05). The complete data are listed in Table 3.

Group	n	CYFRA21-1 (ng/ml)	DcR3 (ng/ml)	CEA (ng/ml)
Control group	34	1.57±0.81	0.23±0.04	3.54±1.36
NSIP group	34	5.03±3.23*	0.56±0.41*	4.75±3.21*
IIP group	34	6.61±3.11*#	2.89±1.15*#	7.53±7.32*#
F		208.748	190.365	75.946
P		<0.001	<0.001	<0.001

Table 3: Comparative analysis of serum CYFRA21-1, DCR3, and CEA levels in the three groups ($\bar{x}\pm s$).
*Note: *indicates comparison with the normal control group, P<0.05; #indicates comparison with the NSIP group, P<0.05.*

Comparison of lung function among normal control group, IIP group, and NSIP group

Compared with the normal control group, lung function indexes in the IIP and NSIP groups were significantly decreased (P<0.05), and those of the IIP group were significantly lower than in the NSIP group; the difference was statistically significant (P<0.05). Complete data are shown in Table 4.

Group	Control group (n=34)	NSIP (n=34)	IIP (n=34)	F	P
FEV1 (%)	89.21±9.13	78.24±4.32*	68.56±5.63*#	19.064	<0.001
FVC (%)	77.52±11.33	64.86±5.42*	55.52±8.36*#	16.456	<0.001
FEV1/FVC	99.87±18.65	85.26±7.45*	72.11±10.58*#	13.421	<0.001
DLCO (%)	78.65±8.54	47.35±3.74*	40.35±5.69*#	20.965	<0.001

Table 4: Comparative analysis of lung function in the three groups ($\bar{x}\pm s$).
*Note: *indicates comparison with the normal control group, P<0.05; #indicates comparison with the NSIP group, P<0.05.*

Spearman correlation analysis

Spearman correlation analysis showed that the changes in serum CYFRA21-1, DCR3, and CEA levels in IIP patients were significantly positively correlated with HRCT scores (P<0.05), while serum CYFRA21-1, DCR3, and CEA levels were significantly negatively correlated with lung function indexes (P<0.05). Complete data are shown in Table 5.

	CYFRA21-1		DcR3		CEA	
	r	*P*	*r*	*P*	*r*	*P*
HRCT	2.423	0.035	3.451	0.027	0.186	0.045
FEV_1 (%)	-3.654	0.044	-3.568	0.048	0.354	0.012
FVC (%)	-0.175	0.010	-0.107	0.041	-0.131	0.005
FEV_1/FVC	-0.214	0.023	-0.261	0.007	-0.451	0.032
DLCO (%)	-0.118	0.015	-0.507	0.002	-0.415	0.008

Table 5: Correlation between changes in serum CYFRA21-1, DCR3, and CEA levels and HRCT scores and lung function ($\bar{x}\pm s$).

Discussion

The pathological process of IIP consists primarily of facial chronic alveolar inflammation with slow progress or alveolar structural disorder. This can lead to the destruction of alveolar structure and the formation of complete fibrosis and vesicular cellular lung, mainly occurring in pulmonary interstitium, peripheral airways, pulmonary small vessels, and alveoli and other parts[5-6]. A series of complications such as respiratory failure, emphysema, bronchioliectasis, pulmonary heart disease, spontaneous pneumothorax, and pulmonary hypertrophic osteoarthropathy can occur in patients with IIP in the early stages, while alveolar cell carcinoma, oat cell carcinoma, lung adenocarcinoma, and other diseases can often occur in patients in advanced stages[7]. The prognosis for IIP is poor, and the five-year survival rate is only 50-60%. Therefore, clinical researchers have become increasingly concerned with how to improve the survival rate and quality of life for IIP patients. In recent years, several studies have found that differences in biological marker levels can reflect the severity of the disease, which plays an important role in early disease assessment for IIP patients.

CYFRA21-1 is a factor formed by activating protease in malignant epithelial cells through the promotion of cell degradation, causing a large number of cytokeratin fragments to be released into the blood and specifically binding with two beads of monoclonal antibodies, KS19.1 and BM19.21[8]. CYFRA21-1 is a novel lung tumor marker discovered in recent years, and is of especially great value in the diagnosis of non-small cell lung cancer. A healthy body's content of CYFRA21-1 is very low; when the body's cells become malignant, CYFRA21-1 can be released from apoptotic cells, thereby causing an increase in the level of CYFRA21-1 in many parts of the body. Rui et al. found that the level of serum concentration of CYFRA21-1 can be used to evaluate the severity and prognosis of the disease[9]. When the level of CYFRA21-1 in patients is high, it indicates that the disease is in a progressive stage or has a poor prognosis; when the level of CYFRA21-1 in patients decreases and then increases, an increase indicates that the disease is at risk of recurrence.

As a member of the tumor necrosis factor receptor superfamily, DCR3 is a soluble deceptive receptor that can competitively bind to Fas ligand and LIGHT and is mainly expressed in tumor cells, participating in tumor immune escape and inhibiting cell apoptosis[10]. Thus, DCR3 plays an important role in autoimmunity, transplantation immunity, tumor immunity, and anti-infection immunity[11-12]. When patients with IIP develop the disease, the level of DCR3 in the body increases rapidly and performs its immunomotor function. CEA is a complex rich in polysaccharides, one which belongs to the immunoglobulin superfamily and is widely present in digestive system carcinoma of endodermal origin and digestive canal tissues of normal embryos[13]. The content of CEA in normal human serum is extremely small. When the content of CEA increases sharply, it can be used as an antigen to cause an immune response in patients. Therefore, it exists as a broad-spectrum tumor marker in clinical practice and is used to assist the diagnosis of malignant tumors, test the efficacy, and judge the prognosis. Chen Lei and Wu Jianqing found that the level of CEA in serum of patients with primary lung cancer was positively correlated with the severity of the patient's illness[14]. CEA can be secreted by bronchiole epithelium and alveolar epithelium; the main pathological change in IIP patients is alveolar structure destruction, leading to complete fibrosis. When the CEA content in IIP patients is increased, the changes in lung function can be predicted.

Chest HRCT is an important index and standard for the diagnosis of interstitial lung diseases, and is considered the preferred method for the diagnosis of diffuse lung diseases. It is mainly a supplement to conventional CT, which is helpful for the differentiation and diagnosis of lung diseases. HRCT can clearly display the fine structures of lung tissues, including blood vessels and interlobular septa, lung lobular airway, lung interstitium, and intrapulmonary nodules, and can depict the fine structures of the lesions, eliminating the need for contrast enhancement during scanning. It mainly reflects the scope of disease involvement, pulmonary fibrosis, and degree of honeycomb lung, and scan results are directly related to the severity of the disease[15]. The results of this study showed that compared with the normal control group, the levels of serum CYFRA21-1, DCR3, and CEA in the IIP and NSIP groups were significantly increased ($P<0.05$), and that the IIP group levels were significantly higher than the NSIP group ($P<0.05$). This result suggests that serum CYFRA21-1, DCR, and CEA are involved in the progression of IIP. Furthermore, Spearman correlation analysis showed that the changes in serum CYFRA21-1, DCR3, and CEA levels in IIP patients were significantly

positively correlated with HRCT scores ($P<0.05$), while serum CYFRA21-1, DCR3, and CEA levels were significantly negatively correlated with lung function indexes ($P<0.05$). These results suggest that serum CYFRA21-1, DCR3, and CEA could indicate the diagnosis of the disease and serve to evaluate the severity of the disease to a certain extent, and that they have a positive clinical significance in IIP classification and diagnosis.

In conclusion, the levels of serum CYFRA21-1, DCR3, and CEA in patients with IIP are high, and are significantly correlated with the severity of the disease in patients with IIP. Combined detection is conducive to timely assessment and monitoring of the disease progression in patients with IIP, and presents a new method for the treatment of patients with IIP.

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