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Correlation between Cystatin C and Pulmonary Hypertension in Patients with Idiopathic Pulmonary Fibrosis

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Abstract **Objective**: To analyze the relationship between Cystatin C and pulmonary arterial hypertension in patients with idiopathic pulmonary fibrosis. **Methods:** A clinical cohort of sixty-eight idiopathic pulmonary fibrosis patients and forty normal individuals was established. All the cases were obtained from department of respiratory in the fifth affiliated hospital of Sun Yat-Sen University from May 2009 to May 2017. Data including basic information, Cystatin C, echocardiography parameters of each patients were recorded. Then the serum Cystatin C between the two groups was compared. The correlation between Cystatin C and pulmonary arterial hypertension in patients with idiopathic pulmonary fibrosis was evaluated. **Results:** The serum Cystatin C level in IPF patients was observed higher than that in normal cases with significant difference ($P < 0.001$). Patients with increased level of serum Cystatin C had statistical significant higher ($P < 0.05$) Cystatin C and Echocardiography parameters including RAD, RVDd, PA, velocity of TR, and pulmonary arterial. The Cystatin C serum concentrations were positively correlated with RAD, RVDD, velocity of TR, and pulmonary arterial pressure. Multiple linear regression (stepwise method) analysis showed that the serum Cystatin C was positively correlated with pulmonary arterial pressure with the maximum impact, suggesting that the concentration of serum Cystatin C was one significant factor in PH of PIF patients($P < 0.001$). **Conclusions:** The serum Cystatin C level is found to be elevated in IPF patients. The serum Cystatin C concentration in IPF patients was positively correlated with pulmonary arterial pressure. Cystatin C may play a role in patients with IPF and it bears great potential to be exploited as a PH biomarker in IPF patients.

Keywords Cystatin C, Pulmonary Hypertension, Idiopathic Pulmonary Fibrosis, Echocardiography

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare lung disease of chronic progressive fibrosing interstitial pneumonia of unknown origin which leads rapidly to death [1]. It is the most common one of the interstitial lung disease. Epidemiological studies suggest that the incidence of IPF has been increasing steadily over the last two to three decades [2]. IPF attracts intense attention due to the complexity of its pathogenesis, difficulty in early diagnosis, irreversibility in disease progression, easy combination of other diseases. Currently, Effective therapies are urgently lacking along with poor prognosis, that short median survival rate of 3 years after diagnosis[3].The presence of pulmonary hypertension (PH), which can lead to right ventricular dysfunction, has been associated with higher mortality in patients with IPF[4, 5]. So examinating pulmonary artery pressure of IPF patients with PH is important.

Cystatin C is a highly sensitive endogenous marker of renal filtration that outperforms creatinine-based estimation of glomerular filtration rate [6]. However, multiple studies have shown that Cystatin C also predicts left heart failure and overall cardiovascular mortality [7, 8]. Recently, study found that Cystatin C may be exploited as a biomarker in the evaluation of PH [9].

Echocardiography is a non-invasive imaging assessment of PH based on estimation of right ventricular systolic pressure. Besides that, the value of echocardiography also lie in the assessment of RV morphological and functional adaptation to PH. Using echocardiography, we tested the hypothesis that Cystatin C accurately correlates with PH of patients with IPF by means of analyzing the relationship between Cystatin C and PH.

2. Materials and Methods

2.1. Subjects

We retrospectively reviewed 68 patients with IPF who underwent an initial evaluation of echocardiography in the department of respiratory of our hospital from May 2009 to May 2017 as observational group. 40 normal individuals were also enrolled in this study as control group.

2.2. Exclusive Criteria

The following patients were excluded: 1) Patients with other respiratory disease: chronic obstructive pulmonary disease, primary pulmonary hypertension, pulmonary hypertension induced by other diseases, infectious disease of the pulmonary, pleural effusion, pneumothorax, lung cancer. 2) Patients with cardiovascular disease: heart failure, acute coronary syndrome, hypertension, pulmonary heart disease, cerebral infarction, cerebral hemorrhage. 3) Patients with liver and kidney dysfunction. 4) Patients with diabetes and hyperthyroidism. 5) Patients with incomplete clinical data.

2.3. Data Collection

The following data were collected for each patient of both the two groups:1) Basic information of the patients both from the observational group and control group, which include gender, age, weight, height, family history, smoking history and drinking history.2) Laboratory examination results include fasting blood glucose, blood lipids, liver function and kidney function. 3) Echocardiography parameters, which includes right arterial diameter, right ventricular diameter, the doppler velocity of tricuspid regurgitation and estimation of pulmonary artery pressure.

2.4. Statistical Analysis

Continuous measurements were expressed as mean±SDs, and categorical measurements were expressed as frequencies and percentages. Comparisons between baseline data and follow-up data were performed using a paired t-test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables as appropriate. The associations were tested by Spearman correlation analysis. Multivariate Cox regression models were constructed. In all analyses, $P < 0.05$ was considered significant. We performed all statistical comparisons using SPSS Statistics Version 13.0.

3. Result

1 The serum Cystatin C level in the observational group was found higher compared with that in the control group with significant difference($P < 0.001$). The other indicators of baseline information were also compared (Table 1).

2 The patients with IPF in the observational group were divided into two groups, Cystatin C elevated group and Cystatin C nomal group, according to the median of Cystatin C. The differences of echocardiography parameters in the two groups were compared. As result, Cystatin C and Echocardiography parameters including RAD, RVDd, PA, velocity of TR, and pulmonary arterial pressure are found higher in Cystatin C elevated group compared with Cystatin C nomal group with significant difference ($P < 0.05$)(Table 2).

Table 1. Cystatin C and Baseline characteristics

Indicators	Observational group	Control group	P value
n	68	40	
Age(years)	56.26±11.56	54.71±11.22	0.36
BMI(kg/m2)	1.71±0.21	1.70±0.23	0.42
Smoking history(%)	27.94	32.00	0.22
Acohol intake history(%)	12.00	32.00	＜0.001
HR(beats/min)	86.89±13.31	71.01±10.08	0.04
HGB(g/L)	118.6±13.22	128.32±11.21	0.11
FPG(mmol/L)	4.82±0.63	4.63±0.71	0.23
TG(mmol/L)	1.39±0.82	1.43±1.01	0.15
Cr(umol/L)	72.66±16.70	68.22±15.17	0.18
BUN(mmol/L)	4.76±1.87	4.54±1.22	0.21
Cystatin C(mmol/L)	1.17±0.22	0.91±0.18	0.01

Table 2. The comparison of Cystatin C and echocardiography diameters between Cystatin C elevated group and Cystatin C nomal group.

Indicators	Cystatin C elevated group	Cystatin C nomal group	P value
n	34	34	
Cystatin C(mmol/L)	1.22±0.22	1.12±0.18	0.01
RAD(mm)	38.43	33.12	0.01
RVDd(mm)	37.77	32.88	0.03
PA(mm)	27.62	21.23	＜0.001
Vtr(m/s)	2.32	1.36	＜0.001
PAP(mmHg)	29.82	11.40	＜0.001

Table 3. The comparison of Cystatin C between the high pulmonary arterial pressure group and the nomal pulmonary arterial pressure group

Indicators	High PAP group	Normal PAP group	P value
n	21	47	
Cystatin C(mmol/L)	1.30	1.11	＜0.001

Table 4. Related analysis of Cystatin C with RAD, RVDD, velocity of TR, and pulmonary arterial pressure

Indicators	RAD	RVDd	PA	TR	PAP
R	0.348	0.318	0.683	0.521	0.601
P	0.04	.003	＜0.001	0.003	＜0.001

3. The patients with IPF in the observational group were divided into two groups, high pulmonary arterial pressure group and nomal pulmonary arterial pressure group, according to the pulmonary arterial pressure. The serum level of Cystatin C between the two groups was compared. And we discovered that the serum Cystatin C level in high pulmonary arterial pressure group was found higher compared with the nomal pulmonary arterial pressure group with significant difference(P＜0.001). (P＜0.00)(Table 3).
4. The Cystatin C serum concentrations were positively correlated with RAD, RVDD, velocity of TR, and pulmonary arterial pressure in the observational group (Table 4).
5. Using multiple linear regression (stepwise method) analysis showed that serum Cystatin C concentration, were positively related with pulmonary arterial pressure, where the serum FGP level was negatively correlated. The serum Cystatin C showed the maximum impact on pulmonary arterial pressure, suggesting that the concentration of serum Cystatin C was one significant factor in PH of PIF patients(P <0.001).
6. After grouped according to the factors such as gender, family history, smoking history, alcohol history, the difference of Cystatin C level among any subgroups were not statistically significant ($P \geq 0.05$), except between the two subgroups categorized by alcohol history.

4. Discussion

Cystatin C is a 13-kDa endogenous cysteine proteinase inhibitor and freely filtrated through the glomeruli [10], it is a highly sensitive endogenous marker of renal filtration that outperforms creatinine-based estimation of glomerular filtration rate [11]. However, plenty of studies have shown that Cystatin C associated with cardiac disease [12, 13]. Some other studies also showed that Cystatin C is a potential biomarker for pulmonary arterial hypertension [14]. Consistent with previous results, our study also found that the serum Cystatin C level is elevated in IPF patients and further found that Cystatin C is positively related with pulmonary arterial pressure independent of the kidney function. IPF patients with PH in observational group also revealed higher diameter of RA, RV, PA and velocity of TR. All of these results suggest that Cystatin C may play a role in the development of pulmonary arterial pressure in patients with IPF. Previous study showed the primary role of Cystatin C, which is involved in intracellular and extracellular proteolytic regulation, is to protect cells from endogenous and exogenous proteases and to act as anti-proteases during cathepsin activation [15]. It inhibits activity of endogenous cysteine protease, especially inhibits activity of cathepsin, and protects cells from endogenous or exogenous proteases. There is now a growing body of evidence showing that cysteine cathepsins take part in pulmonary homeostasis. Cathepsins, such as Cathepsin S, Cathepsin B, Cathepsin L and Cathepsin K with elastic tissue dissociation properties, serve as the potent collagenolytic enzymes to hydrolyze various excessive extracellular matrix and basal membrane components of the lung tissue, are also increased in bronchoalveolar lavage fluids of IPF patients [16]. Under normal circumstances, cysteine cathepsins are encapsulated in the lysosome of the cell and separated from other components of the cytoplasm [17].In the pathological state, they were released into the cytoplasm and tissue space due to

the stimulation of some stimulus. And with the increase expression of cysteine cathepsins, the level of Cystatin C, which act as a highly potent inhibitor of cysteine Cats, increased to provide a protective or compensatory effect for our body. With the progress of the disease of IPF, the level of Cystatin C may rise more higher with the continuing release of Cathepsins, and accompany with PH at last. With a range of results of the relationship between Cystatin C and PH, it is reasonable for us to speculate that Cystatin C may play a self-protection or compensation role in patients with IPF and it may have the potential utility as a PH biomarker in IPF patients.

However, there are still some aspects worthy of attention to strengthen our conclusions. Firstly, this study is a retrospective static case analysis, and the medication situation of IPF patients is not considered .So Long-term follow-up with regards to patients' medication to analyze the further causal link between the Cystatin C and IPF warrants further study. Furthermore, large-scale prospective studies with more cases would help to validate our conclusions. The cases included in this study are somewhat limited, so the results still need some large-scale prospective studies to be confirmed.

5. Conclusions

Our results show that the serum Cystatin C level in IPF patients is higher than normal. The serum Cystatin C concentration in IPF patients was positively related with pulmonary arterial pressure. Cystatin C may play a pivotal role in patients with IPF and it bears great potential to be exploited as a PH biomarker in IPF patients.

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