Original Article

Interleukin-11 in idiopathic pulmonary fibrosis: predictive value of prognosis and acute exacerbation

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Background: Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease with a poor prognosis and unknown aetiology. We have recently clarified the prognostic value of the serum platelet-derived growth factor (PDGF) level in patients with IPF. Interleukin (IL)-11 is a member of the IL-6 family, and *in vivo* and *in vitro* studies have suggested that it has profibrotic effects in pulmonary fibrosis. In this study, we investigated the predictive value of the serum IL-11 level in patients with IPF for survival and occurrence of acute exacerbation (AE).

Methods: This retrospective study included 68 patients with IPF diagnosed according to the 2018 guideline. Serum PDGF levels were measured using the Bio-Plex method and serum IL-11 levels using enzyme-linked immune-sorbent assay. Cytokine production per lung volume was evaluated using the serum cytokine/percent predicted forced vital capacity (%FVC) value.

Results: Forty-six patients were male and the median age was 67 years. The serum IL-11/%FVC value was significantly correlated with the percent predicted diffusing capacity of carbon monoxide (ρ=–0.518, P<0.001) and modified Medical Research Council score for shortness of breath (mMRC) (ρ=0.335, P=0.006) by Spearman's rank correlation analysis. Multivariate Cox proportional hazard regression analysis revealed that the serum IL-11/%FVC value was a significant prognostic factor after adjustment for the serum PDGF/%FVC value and other clinical parameters including mMRC and lymphocyte percentage in bronchoalveolar lavage [hazard ratio (HR): 88.540, 95% confidence interval (CI): 1.905–4,115.686, P=0.022]. IL-11/%FVC value was also a significant predictor of AE after adjustment for age and PDGF/%FVC (HR: 1,815.443, 95% CI: 10.49–314,109.219, P=0.004).

Conclusions: The serum IL-11/%FVC value was an independent predictor of prognosis and AE occurrence in patients with IPF, and the IL-11 level appeared to show pathophysiologic value in IPF.

Keywords: Idiopathic pulmonary fibrosis (IPF); platelet-derived growth factor (PDGF); interleukin-11 (IL-11); survival; acute exacerbation (AE)

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease of unknown aetiology and has a poor prognosis (1-3). Some patients with IPF experienced rapid deterioration, known as acute exacerbation (AE), which is the most prevalent cause of death in patients with IPF (1-4). Various cytokines have been associated with the inflammation and fibrosis involved in the pathogenesis of IPF (5,6). However, there has been limited research on serum cytokine levels as predictors of survival and AE occurrence in IPF (7). We have previously shown that the serum platelet-derived growth factor (PDGF) level can predict survival and AE in these patients (8).

Interleukin (IL)-11 is a member of the IL-6 cytokine family and is secreted by resident fibroblasts in response to profibrotic stimuli, including transforming growth factor (TGF)-β, IL-13, and fibroblast growth factor-2. IL-11 is thought to play an important role in pulmonary fibrosis (9-11). However, whether the serum IL-11 level can predict survival in patients with IPF is unknown. In this study, we measured the serum IL-11 level in patients with IPF and investigated its predictive significance for survival and AE occurrence. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-876/rc).

Highlight box

Key findings

- In this study, we measured the serum IL-11 level in patients with IPF and investigated its predictive significance for survival and AE occurrence. The serum IL-11/%FVC value was an independent predictor of prognosis and AE occurrence in patients with IPF, and the IL-11 level appeared to show pathophysiologic value in IPF.

What is known and what is new?

- IL-11 is a member of the IL-6 family, and in vivo and in vitro studies have suggested that it has profibrotic effects in pulmonary fibrosis.
- This manuscript added significance of serum IL-11 levels to predict survival and AE occurrence of IPF.

What is the implication, and what should change now?

- Serum IL-11 level appeared to show pathophysiologic roles in IPF. IL-11 might be a target molecule for treatment of IPF.

Methods

This study had a single-centre retrospective design. A search of the National Hospital Organization Kinki-Chuo Chest Medical Center database identified 94 consecutive patients who had been diagnosed with IPF between 2004 and 2009 according to the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guidelines for IPF (2). Two patients with AE at the time of diagnosis of IPF were excluded. Serum samples obtained at the time of diagnosis were available for 68 of the 92 patients and stored in -30℃ freezer with minimal door opening. The 2018 ATS/ERS/JRS/ALAT guidelines for IPF were used to reconfirm the diagnosis of IPF in all cases (3). We measured the serum IL-11 and PDGF levels in the 68 patients and the serum IL-11 level in 20 healthy controls.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the National Hospital Organization Kinki-Chuo Chest Medical Center Institutional Review Board (approval Nos. 651 and 365). All participants provided written informed consent for inclusion of their data in the study. Samples of healthy controls were obtained from our hospital staffs who offered their cooperation in the interstitial lung disease research during their medical check-up for the clinical study, which was approved by the institutional review board (approval No. 586).

Clinical parameters at time of diagnosis of IPF

Clinical findings at the time of diagnosis of IPF, including age, sex, body mass index, smoking status, modified Medical Research Council (mMRC) score (12), and pulmonary function test results, were retrospectively collected from the medical records. Pulmonary function tests, including percent predicted forced vital capacity (%FVC) and percent predicted diffusing capacity of carbon monoxide (%DLco), were performed using a Chestac 8080 spirometer (Chest, Tokyo, Japan). Bronchoalveolar lavage was performed via a flexible bronchoscope as previously described (13).

Diagnosis of AE in IPF

AE in IPF was diagnosed according to the Japanese

Respiratory Society diagnostic criteria as follows: (I) within one month of the chronic course of IPF disease progression, the following three conditions should be satisfied: (i) progressively worsening dyspnoea, (ii) new ground glass opacities evident on high-resolution computed tomography (CT) scans superimposed on a background reticular or honeycomb pattern , and (iii) a reduction of resting partial pressure of oxygen in arterial blood (PaO_2) by more than 10 Torr (mmHg) compared to previous measurements; and (II) exclusion of obvious causes of acutely impaired respiratory function, such as infection, pneumothorax, cancer, pulmonary embolism, and congestive cardiac failure (8,14).

Apparent infections were carefully excluded by measuring antibodies for Mycoplasma pneumoniae and Chlamydia pneumonia, β-D glucan, cytomegalovirus antigen and bacterial cultures of blood and sputum. Congestive heart failure was excluded by echocardiography and pulmonary embolism was excluded by contrast CT and/or echo-Doppler examination.

Measurement of serum IL-11

Serum IL-11 levels were measured by enzyme-linked immunosorbent assay (ELISA) using a Human IL-11 Quantikine ELISA Kit (R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturer's instructions.

Measurement of serum PDGF

In our previous study, we measured the serum levels of multiple cytokines, including PDGF-BB, in 69 patients with IPF using the Bio-Plex Suspension Array System with the Bio-Plex Pro Human Cytokine Group Panel (Bio-Rad Laboratories Inc., Hercules, CA, USA) according to the manufacturer's instructions and demonstrated the significance of PDGF in predicting survival in patients with IPF (8). However, in the present study, we could not measure the IL-11 in one patient because all of the patients' serum sample had been used and lost in previous experiments.

Physiological value of our novel serum cytokine/%FVC parameter

It is important to know whether or not the serum cytokine level is associated with the severity of IPF (7). In patients with IPF, the production of fibrotic cytokines is thought to increase in fibrotic lung lesions (6). However, the volume of a lung with these fibrotic lesions decreases with disease progression (15), and total cytokine production may not be associated with the severity of IPF. For example, if half of the lung becomes fibrotic, the volume of lung affected by fibrosis shrinks to one-fifth, and local cytokine production per fibrotic lung volume increases five-fold, then, the total cytokine production in the fibrotic lung might be same as that in the normal lung. As a result, serum levels of the cytokine might be same as those in a normal control subject. Therefore, serum cytokine levels may not be correlated with the severity of IPF or predict survival (8). Hence, we hypothesized that "total cytokine production/forced vital capacity" can approximate total cytokine production/lung volume and suggest local cytokine production and that this parameter is associated with the severity of IPF.

We also hypothesized that (I) total cytokine production can be evaluated by multiplying serum cytokine levels by blood volume, (II) blood volume is proportional to body size, and (III) body size is proportional to the predicted FVC. Hence, "total cytokine production/FVC" can be derived as follows: serum cytokine level × blood volume/FVC, serum cytokine level × body size/FVC, serum cytokine level/FVC/body size, serum cytokine level/FVC/predicted FVC, and finally, serum cytokine level/%FVC.

Having demonstrated the pathophysiological importance of PDGF using the serum PDGF/%FVC value in a previous study (8), we similarly used the serum IL-11/%FVC value to evaluate the importance of IL-11 in the present study.

Statistical analysis

Continuous variables are presented as the median and interquartile range and categorical variables as the number and percentage. The %FVC was not known in healthy controls but was assumed to be 100%. Hence, serum IL-11/%FVC values were calculated using the serum levels of IL-11/100 in healthy controls. The values for continuous variables in the two groups were compared using the Wilcoxon rank-sum test. The correlation between the two parameters was examined using Spearman's rank correlation analysis.

The significance of each clinical parameter and serum levels of IL-11 and PDGF as predictors of survival and AE occurrence were determined by univariate and multivariate Cox proportional hazards regression analyses with a

Table 1 Patient demographics, clinical parameters, and serum cytokine levels

Parameter	Frequency (%) or median (IQR)	
	Patents with IPF (n=68)	Healthy controls (n=20)
Clinical parameters		
Sex, male/female	56/12 (82.4/17.6)	10/10 (50.0/50.0)[¶]
Age, years	67 [60–72]	56 [55–58][¶]
Smoking, NS/ES or CS	9/59 (13.2/86.8)	8/12[¶]
Diagnosis of IPF, clinical/SLB	35/33 (51.5/48.5)	–
BMI	24.9 (23.0–26.2)	–
mMRC score, <2/≥2	46/22 (67.6/32.4)	–
%FVC*, %	76.9 (63.8–90.1)	–
%DLco**, %	52.7 (37.3–62.9)	–
KL-6*, ×100 U/mL	8.23 (5.85–12.00)	–
SP-D**, ×10 ng/mL	18.1 (10.9–30.4)	–
Neutrophils in BAL*, %	2.2 (0.8–5.6)	–
Lymphocytes in BAL*, %	6.6 (3.4–12.4)	–
Pirfenidone, yes/no	10/58 (14.7/85.3)	–
Corticosteroids, yes/no	31/37 (45.6/54.4)	–
Corticosteroid before AE, yes/no	15/53 (22.1/77.9)	–
Occurrence of AE, yes/no	21/47 (30.9/69.1)	–
Last observation: dead/alive	31/37 (45.6/54.4)	–
Observation period, days	1,295 (547–1,873)	–
Median survival time, days	2,079	–
Serum cytokines		
IL-11, pg/mL	14.5 (12.7–16.6)	15.3 (14.1–18.9)[#]
PDGF, pg/mL	163.0 (64.0–472.1)	–
IL-11/%FVC	0.196 (0.150–0.252)	0.153 (0.141–0.189)[¶§]
PDGF/%FVC	2.67 (0.89–5.99)	–

*n=67, **n=66, n=68 for other parameters. [¶], significant differences were observed with P values of 0.006, <0.001, <0.001, and 0.014 for sex, age, smoking, and IL-11/%FVC, respectively; [#], NS, P=0.066; [§], IL-11/%FVC was calculated as the %FVC of healthy controls was hypothesized to be 100. IQR, interquartile range; IPF, idiopathic pulmonary fibrosis; NS, non-smoker; ES, ex-smoker; CS, current smoker; SLB, surgical lung biopsy; BMI, body mass index; mMRC, modified Medical Research Council score for shortness of breath; %FVC, percent predicted forced vital capacity; %DLco, percent predicted diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; BAL, bronchoalveolar lavage; AE, acute exacerbation; IL, interleukin; PDGF, platelet-derived growth factor.

stepwise selection method. The serum cytokine/% FVC value was used to compare local production of each cytokine according to lung volume.

All statistical analyses were performed using SPSS for Macintosh (version 26; IBM Corp., Armonk, NY, USA). Statistical significance was set at P<0.05.

Results

Patient demographics, clinical characteristics, and serum cytokine levels

Fifty-six of the 68 patients with IPF were men and 59 had a smoking history (*Table 1*). The median age was 67 years

Table 2 Correlation between cytokine related parameters and other severity markers*

Parameters	mMRC score		%DLco	
	ρ	P value	ρ	P value
IL-11	–0.148	0.228	–0.153	0.221
PDGF	0.066	0.595	0.037	0.767
IL-11/%FVC	0.335	0.006	–0.518	<0.001
PDGF/%FVC	0.202	0099	–0.119	0.343

*, correlation was evaluated using Spearman's rank correlation analysis. mMRC, modified Medical Research Council; %DLco, percent predicted value of diffusing capacity of carbon monoxide; IL, interleukin; PDGF, platelet-derived growth factor; %FVC, percent predicted value of forced vital capacity.

(range, 60–72 years). There was no significant difference in the serum IL-11 level between the 68 patients with IPF and the 20 healthy controls; however, the serum IL-11/%FVC value was significantly higher in patients with IPF (P=0.014).

Serum cytokine/%FVC values and severity parameters

The IL-11/%FVC value was significantly correlated with the mMRC score for shortness of breath (ρ=0.335, P=0.006) and %DLco (ρ=–0.518, P<0.001); however, the IL-11, PDGF, and PDGF/%FVC values were not correlated with either of these two parameters (*Table 2*). There was a significant correlation between the IL-11/%FVC and PDGF/%FVC values (ρ=0.308, P=0.01).

Clinical parameters predicting survival

Univariate and multivariate Cox proportional hazards regression analyses identified %FVC, mMRC score, and percentage of lymphocytes in bronchoalveolar lavage fluid to be significant prognostic factors in patients with IPF (*Table 3*).

Serum IL-11/%FVC value as a prognostic factor in IPF

Serum IL-11 and PDGF levels alone were not significant prognostic factors (*Table 3*). However, both the IL-11/%FVC value and the PDGF/%FVC value were significant prognostic factors in univariate Cox proportional hazards regression analysis. As shown in *Table 4*, the IL-11/%FVC value was also a significant prognostic factor after adjustment for PDGF/%FVC and other significant clinical factors mentioned in *Table 3*.

Clinical parameters predicting AE

Univariate and multivariate Cox proportional hazards regression analyses identified %FVC and age to be significant predictors of AE occurrence in patients with IPF (*Table 5*).

Serum IL-11/%FVC value as a predictor of AE occurrence

Serum IL-11 and PDGF levels alone were not significant predictors of AE occurrence (*Table 3*). However, the univariate Cox proportional hazards regression analysis revealed that PDGF/%FVC value was a significant predictor of AE occurrence and IL-11/%FVC tended to predict AE. Multivariate analysis using these two parameters (model 1 in *Table 6*) showed similar results. However, the IL-11/%FVC value was a significant predictor of AE occurrence after adjustment for PDGF/%FVC and age, which was a significant clinical factor mentioned in *Table 5* (model 2 in *Table 6*).

Discussion

The findings of this study highlight the significance of the IL-11/%FVC value as a predictor of survival in patients with IPF. This value was also a significant factor after adjustment for the PDGF/%FVC value and other significant clinical parameters in multivariate Cox proportional hazards regression analysis. In addition, IL-11/%FVC was a significant predictor of AE occurrence after adjustment for the PDGF/%FVC and age.

Previous *in vitro* studies have suggested the importance of IL-11 in pulmonary fibrosis. The IL-11 receptor is

Table 3 Results of univariate and multivariate Cox proportional hazards regression analyses of potential prognostic factors

Parameter	HR	95% CI	P value
Univariate analysis			
Sex, male *vs.* female	0.998	0.408–2.442	0.996
Age	1.030	0.982–1.081	0.229
Smoking, CS or ES *vs.* NS	0.890	0.341–2.324	0.812
Diagnosis of IPF, clinical *vs.* SLB	1.660	0.813–3.386	0.164
BMI	0.940	0.840–1.051	0.279
mMRC score, ≥2 *vs.* <2	4.519	2.211–9.237	<0.001
%FVC*	0.950	0.930–0.971	<0.001
%DLco**	0.961	0.939–0.983	0.001
Neutrophils in BAL*, %	1.090	1.015–1.172	0.018
Lymphocytes in BAL*, %	0.973	0.920–1.029	0.342
KL-6*, ×100 U/mL	1.055	1.018–1.094	0.004
SP-D*, ×10 ng/mL	1.021	1.005–1.036	0.008
PDGF, pg/mL	1.001	1.000–1.002	0.136
IL-11, pg/mL	1.002	0.951–1.056	0.950
Multivariate analysis with stepwise selection procedure			
%FVC	0.955	0.930–0.981	0.001
mMRC score, ≥2 *vs.* <2	2.732	1.224–6.097	0.014
Lymphocytes in BAL, %	0.927	0.867–0.992	0.028

The prognostic significance of each parameter was evaluated in a univariate Cox proportional hazards regression model. Multivariate analysis with a stepwise method was performed to identify prognostic factors using all parameters, except for serum IL-11 and PDGF levels. *n=67, **n=66, n=68 for other parameters. HR, hazard ratio; CI, confidence interval; CS, current smoker; ES, ex-smoker; NS, non-smoker; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; BMI, body mass index; mMRC, modified Medical Research Council; %FVC, percent predicted value of forced vital capacity; %DLco, percent predicted value of diffusing capacity of carbon monoxide; BAL, bronchoalveolar lavage; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; PDGF, platelet-derived growth factor; IL, interleukin.

highly expressed in fibroblasts, smooth muscle cells, and alveolar epithelial cells (AECs). Stimulation of IL-11 upregulates expression of collagen type 1 and α-smooth muscle actin in lung fibroblasts and induces proliferation of normal and IPF-derived lung fibroblasts (16). IL-11 secretion was induced in mouse fibroblasts stimulated by other fibrotic cytokines, including TGF-β1, oncostatin M, IL-13, fibroblast growth factor, PDGF, and endothelin 1 (9). Hence, IL-11 is thought to be a master regulator of tissue fibrosis (11). IL-11 forms an autocrine and maladaptive loop in AECs, which secrete IL-11 in response to stimulation by TGF-β and viral infection, and in turn, IL-11 induces death of AECs (10,17,18). IL-11 has also been associated with epithelial-mesenchymal transition (10). Hence, IL-11 exerts profibrotic effects through multiple pathophysiological processes, including proliferation of fibroblasts, deposition of collagen, and alveolar epithelial injury.

An immunohistochemical study found that IL-11 was significantly upregulated in the IPF lung (9) and another study found that IL-11 genes were overexpressed in IPF fibroblasts in comparison with controls (19). The hydroxyproline content in the lung, which suggests the extent of lung fibrosis, was significantly higher in IL-11 transgenic mice than in littermate controls. Secretion of

Table 4 Prognostic significance of the IL-11/%FVC value as determined by Cox proportional hazards regression analysis

Parameters*	HR**	95% CI	P value
Univariate analysis			
IL-11/%FVC	13.177	1.119–155.129	0.040
PDGF/%FVC	1.117	1.041–1.198	0.002
Multivariate analysis			
Model 1[¶]			
IL-11/%FVC	18.140	1.174–280.401	0.038
PDGF/%FVC	1.116	1.041–1.196	0.002
Model 2[#]			
IL-11/%FVC	88.540	1.905–4,115.686	0.022
PDGF/%FVC	1.081	1.002–1.116	0.044
Lymphocytes in BAL, %	0.943	0.891–0.998	0.044
mMRC score, ≥2 *vs.* <2	4.317	2.055–9.069	<0.001

*, cytokine levels are expressed in pg/mL; **, HR >1 means an increase in each continuous parameter indicating a high risk of mortality; [¶], using two cytokine/%FVC values; [#], using the two significant prognostic factors except for %FVC in *Table 2* and IL-11/%FVC and PDGF/%FVC. Multivariate Cox analysis showed that regression coefficient between IL-11/%FVC and PDGF/%FVC is 0.082. Multicollinearity between IL-11/%FVC and PDGF/%FVC was denied. Spearman rank correlation revealed that rho between IL-11/%FVC and %FVC is –0.777 (P<0.001). Hence, IL-11/%FVC and %FVC is highly correlated and %FVC had better be excluded from the multivariate analysis. IL, interleukin; %FVC, percent predicted value of forced vital capacity; HR, hazard ratio; CI, confidence interval; PDGF, platelet-derived growth factor; BAL, bronchoalveolar lavage; mMRC, modified Medical Research Council.

IL-11 by lung fibroblasts was significantly greater in a mouse model with bleomycin-induced pulmonary fibrosis than in a control lung model (9). Furthermore, attenuation of the effects of IL-11 by administration of anti-IL-11 antibody or use of IL-11 receptor knockout mice reduces the extent of bleomycin-induced pulmonary fibrosis (9).

In contrast with the profibrotic effects of IL-11, recombinant human IL-11-overexpressing mouse lungs are strongly protected from hyperoxia-induced lung injury and death (10,20,21). These observations might be inconsistent with the profibrotic effect of IL-11 shown by Ng *et al.* (9,10). However, this effect is caused by competitive inhibitory effects of recombinant human IL-11 against mouse IL-11 (11).

IL-11 is known to be induced by PDGF (9-11), and we have shown that the IL-11/%FVC value is significantly correlated with the PDGF/%FVC value; however, both IL-11/%FVC and PDGF/%FVC were significant independent predictors of the prognosis in patients with IPF. The mMRC score and %DLco value were significantly associated with the IL-11/%FVC value but not with the PDGF/%FVC value. These findings might reflect the fact that IL-11 is also induced by other fibrotic cytokines, including TGF-β (9-11).

According to the univariate Cox proportional hazard regression analysis, AE can be significantly predicted by PDGF/%FVC but not by IL-11/%FVC. This may be because of differences in the pathophysiologic roles of these cytokines against AECs. PDGF is produced by AECs, and increased PDGF production supposedly reflects the degree of AEC hyperplasia (21,22). IL-11 is also produced by AECs and simultaneously it induces AEC apoptosis (10,17,18), and local IL-11 levels might not be directly associated with AEC hyperplasia. Hyperplastic AECs of IPF can be injured by apoptotic stimuli, and their extensive distribution can lead to AE occurrence (23). Hence, PDGF/%FVC might be a better predictor of AE than IL-11/%FVC although multivariate model 2 (*Table 6*) suggested IL-11/%FVC is also a significant predictor of AE.

This study had several limitations. First, it had a

Table 5 Results of univariate and multivariate Cox proportional hazards regression analyses of potential predictors of occurrence of acute exacerbation

Parameter	HR	95% CI	P value
Univariate analysis			
Sex, male *vs.* female	0.994	0.334–2.962	0.992
Age	1.048	0.986–1.114	0.131
Smoking, CS or ES *vs.* NS	0.664	0.223–1.982	0.463
Diagnosis of IPF, clinical *vs.* SLB	1.701	0.711–4.071	0.233
BMI	1.000	0.874–1.145	0.998
mMRC score, ≥2 *vs.* <2	4.292	1.787–10.310	<0.001
%FVC*	0.953	0.930–0.977	<0.001
%DLco**	0.973	0.948–0.998	0.037
Neutrophils in BAL*, %	1.086	1.007–1.170	0.032
Lymphocytes in BAL*, %	0.995	0.935–1.058	0.862
KL-6*, ×100 U/mL	1.063	1.021–1.106	0.003
SP-D*, ×10 ng/mL	1.018	1.001–1.035	0.033
PDGF, pg/mL	1.001	1.000–1.002	0.060
IL-11, pg/mL	1.001	0.939–1.067	0.979
Multivariate analysis with stepwise selection procedure			
%FVC	0.944	0.918–0.971	<0.001
Age	1.070	1.010–1.134	0.022

The prognostic significance of each parameter was evaluated in a univariate Cox proportional hazards regression model. Multivariate analysis with a stepwise method was performed to identify prognostic factors using all parameters, except for serum IL-11 and PDGF levels. *n=67, **n=66, n=68 for other parameters. HR, hazard ratio; CI, confidence interval; CS, current smoker; ES, ex-smoker; NS, non-smoker; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; BMI, body mass index; mMRC, modified Medical Research Council; %FVC, percent predicted value of forced vital capacity; %DLco, percent predicted value of diffusing capacity of carbon monoxide; BAL, bronchoalveolar lavage; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; PDGF, platelet-derived growth factor; IL, interleukin.

retrospective single-centre design and included a small number of subjects. Second, a validation cohort was not included. Third, the clinical value of the serum cytokine /%FVC value has not been confirmed elsewhere. In our previous study, in which we measured 27 serum cytokines at the time of diagnosis of IPF, serum levels of profibrotic and antifibrotic cytokines including PDGF, fibroblast growth factor, eotaxin, IL-7, IL-9, and IL-17, could not predict survival; however, in univariate analysis, we determined that the serum levels of these cytokines divided by the %FVC value were significant prognostic factors in patients with IPF (8).

Conclusions

In conclusion, a higher IL-11/%FVC value was a significant predictor of a worse prognosis and AE occurrence in IPF, suggesting a significant pathophysiological role of IL-11 in IPF.

Table 6 Predictive significance of the IL-11/%FVC value for occurrence of acute exacerbation determined by multivariate Cox proportional hazards regression analysis

Parameters*	HR**	95% CI	P value
Univariate analysis			
IL-11/%FVC	13.624	0.738–251.395	0.079
PDGF/%FVC	1.132	1.050–1.220	0.001
Multivariate analysis			
Model 1[¶]			
IL-11/%FVC	20.518	0.748–563.105	0.074
PDGF/%FVC	1.131	1.050–1.218	0.001
Model 2[#]			
IL-11/%FVC	1,815.443	10.49–314,109.219	0.004
PDGF/%FVC	1.178	1.079–1.287	<0.001
Age	1.113	1.032–1.200	0.005

*, cytokine levels are expressed in pg/mL; **, HR >1 means an increase in each continuous parameter indicating a high risk of mortality; [¶], using two cytokine/%FVC values; [#], using the one significant prognostic factor (age) except for %FVC in *Table 5* and IL-11/%FVC and PDGF/%FVC. Multivariate Cox analysis showed that regression coefficient between IL-11/%FVC and PDGF/%FVC is 0.126. Hence, multicollinearity between IL-11/%FVC and PDGF/%FVC was denied. Spearman rank correlation revealed that rho between IL-11/%FVC and %FVC is –0.777 (P<0.001) and they were highly correlated, and %FVC had better be excluded from the multivariate analysis. IL, interleukin; %FVC, percent predicted value of forced vital capacity; HR, hazard ratio; CI, confidence interval; PDGF, platelet-derived growth factor.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-876/coif). YI is a consultant or steering/advisory committee member of Boehringer Ingelheim, Roche, SAVARA, and Taiho (not related to this study). YI has received lecture fees from Boehringer Ingelheim, Shionogi, Kyorin, Thermo Fisher, and GSK (not related to this study). TA has received lecture fees from Boehringer Ingelheim and Shionogi for activities not connected with the submitted work. TA received grant from JSPS KAKENHI (Grant No. JP17K09636) and grant from National Hospital Organization (Grant No. H28-NHO [Kokyu]-2). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the National

Hospital Organization Kinki-Chuo Chest Medical Center Institutional Review Board (approval Nos. 651 and 365). All study participants provided written informed consent for inclusion of their data in the study. Samples of healthy controls are obtained from our hospital staffs who offered their cooperation during their medical check-up for the clinical study, which was approved by the institutional review board (approval No. 586).

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