Original Article

Platelet-derived growth factor can predict survival and acute exacerbation in patients with idiopathic pulmonary fibrosis

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Background: Idiopathic pulmonary fibrosis is a fibrotic disease of unknown aetiology and has a poor prognosis. Some patients experience episodes of rapid deterioration known as acute exacerbations (AEs), which are often fatal. This study aimed to clarify whether serum cytokine levels can predict the outcome of idiopathic pulmonary fibrosis.

Methods: This retrospective study included 69 patients with idiopathic pulmonary fibrosis diagnosed according to the 2018 guideline. AE of idiopathic pulmonary fibrosis was diagnosed using the Japanese Respiratory Society criteria. Serum levels of 27 cytokines were measured using the Bio-Plex method. Cytokine production was estimated per lung volume using the serum cytokine level/percent predicted forced vital capacity (%FVC) value. The ability of the serum cytokine level and serum cytokine level/%FVC value to predict the prognosis and AE was examined in a univariate Cox proportional hazards regression model; significant factors were subjected to multivariate analysis with adjustment for significant clinical parameters, including the modified Medical Research Council score.

Results: The study included 57 men and 12 women (median age, 67 years). The modified Medical Research Council score was ≤1 in 47 patients and ≥2 in 22. None of the serum cytokine levels measured could predict survival or AE; however, the serum platelet-derived growth factor/%FVC and interleukin-9/%FVC values were significant prognostic factors and the serum platelet-derived growth factor/%FVC and interleukin-13/%FVC values were significant predictors of AE. Serum platelet-derived growth factor/%FVC alone was a significant predictor of the prognosis and AE after adjustment for clinical parameters.

Conclusions: The prognosis of idiopathic pulmonary fibrosis and AEs of the disease could be predicted by the serum platelet-derived growth factor/%FVC value.

Keywords: Acute exacerbation (AE); idiopathic pulmonary fibrosis; platelet-derived growth factor; prognosis; survival

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease with an unknown aetiology and a poor prognosis (1-3). Patients with IPF usually experience a slow progressive decline in lung function over time; however, for unknown reasons, some patients experience episodes of rapid deterioration known as acute exacerbations (AEs), which are often fatal (1,4-6). Predictors of the prognosis of IPF reportedly include a decline in the percent predicted forced vital capacity (%FVC), the percent predicted diffusing capacity of carbon monoxide (%DLco), the modified Medical Research Council (mMRC) score, and desaturation

on the 6-minute walk test (1). Some of these parameters have also been identified to predict AE in patients with IPF (6,7) and mainly reflect the severity of IPF.

Various cytokines have been associated with the inflammation and fibrosis involved in the pathogenesis of IPF (8) and their levels in serum have been found to be different from those in controls (9). However, there has been limited research on serum cytokine levels as prognostic factors in IPF. Inoue *et al.* reported that serum eotaxin/CC chemokine ligand (CCL)18, interleukin (IL)-6, and IL-8 levels were significant prognostic factors (10). Another study examined cytokine levels in bronchoalveolar lavage (BAL) fluid (BALF) and found that IL-8, monocyte chemoattractant protein (MCP)-1, and vascular endothelial growth factor (VEGF) levels were significantly higher in patients with IPF than in controls (11). However, the ability of serum cytokine levels to predict AE has not been examined in patients with IPF.

Nintedanib has been found to inhibit signal transduction of receptors for platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and VEGF (12) and its efficacy in IPF suggests that these cytokines have pathophysiological significance. Moreover, *in vitro* and *in vivo* investigations have demonstrated an association between serum levels of these cytokines and pulmonary fibrosis (13-19). However, whether or not serum levels of these cytokines can predict survival in patients with IPF and AE of the disease has yet to be clarified. Therefore, in this study, we measured the serum levels of cytokines associated with inflammation, fibrosis, and angiogenesis in these patients and investigated their ability to predict survival and AE of IPF.

We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1418/rc).

Methods

The study had a retrospective design and was approved by the National Hospital Organization Kinki-Chuo Chest Medical Center institutional review board (approval numbers 651 and 365) and performed in accordance with the Declaration of Helsinki (as revised in 2013). All study participants provided written informed consent for inclusion of their data in the study.

Subjects

Patients were selected for enrolment in this single-centre, retrospective observational study as follows. A search of the National Hospital Organization Kinki-Chuo Chest Medical Center database between 2004 and 2009 identified 94 consecutive patients diagnosed to have IPF according to the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) IPF guidelines (2). Two patients who had AE at the time of diagnosis of IPF were excluded. Serum samples obtained at the time of diagnosis of IPF were available for 71 of the 92 patients; however, samples for two of these patients had already been used in another study. Therefore, we were able to collect serum samples for 69 patients with a diagnosis of IPF. After reconfirming the diagnosis of IPF in all cases using the 2018 ATS/ERS/JRS/ALAT IPF guideline (3), we measured serum cytokine levels in these patients and in 30 healthy controls.

Diagnosis of AE in IPF

AE of 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 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 (20,21). Apparent infections were carefully excluded by measuring antibodies for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in paired sera, β-D glucan, cytomegalovirus antigen (22) and bacterial cultures of blood and sputum. Congestive heart failure was excluded by echocardiography. Pulmonary embolism was excluded by contrast CT and/or echo-Doppler examination.

Clinical findings at time of diagnosis

Clinical findings at the time of diagnosis of IPF were

obtained retrospectively from the medical records and included age, sex, body mass index, smoking status, mMRC score (23) and pulmonary function test results. Pulmonary function tests, including FVC and DLco, were performed using a Chestac 8080 spirometer (Chest, Tokyo, Japan). BAL was performed via a flexible bronchoscope as previously described (24).

Evaluation of serum biomarkers

Serum Krebs von den Lungen (KL)-6 (25) and surfactant protein (SP)-D (26) levels were measured using commercial enzyme-linked immunosorbent assay kits (KL-6: Eizai, Tokyo, Japan; SP-D: Kyowa Medex, Tokyo, Japan) with respective cut-off levels of 500 U/mL and 110 ng/mL (27). Cytokine levels in the serum samples were quantified 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. The cytokines measured included IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, CCL11, basic FGF (b-FGF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, IFN-γ inducible protein 10 (IP-10)/CXC chemokine ligand (CXCL)10, MCP-1/CCL2, macrophage inflammatory protein (MIP)-1α/CCL3, MIP-1β/CCL4, PDGF-BB, regulated on activation, normal T-cell expressed and secreted (RANTES)/CCL5, tumor necrosis factor (TNF)-α, and VEGF. In each patient, cytokine levels beyond the upper or lower limits were defined to be in the upper range or half of the lower range, respectively.

Assuming that the cytokines associated with pulmonary fibrosis would be produced mainly in the lungs, we decided that it would be more meaningful to measure the level of each cytokine in the lung rather than the serum level. We hypothesized that systemic production of cytokines in patients with a more restrictive abnormality would be reflected by increased local cytokine production in the lung. Systemic production of cytokines was roughly estimated by multiplying the serum level by "body size". In this way, we could compare production of each cytokine according to lung volume using the following formula: serum cytokine level × body size/FVC, i.e., the serum cytokine level/(FVC/body size). FVC/body size could be expected to show a positive correlation with FVC/pFVC, i.e., %FVC, if the predicted FVC (pFVC) in each case was calculated using body size. Therefore, we estimated local production of each cytokine according to lung volume using the serum cytokine level/%FVC value.

Statistical analysis

Continuous variables are presented as the median and interquartile range and categorical variables as the number and percentage. The significance of each clinical parameter and serum cytokine level as a predictor of survival and AE was evaluated by univariate and multivariate Cox proportional hazards regression analyses with a stepwise selection method.

All statistical calculations were performed using SPSS for Macintosh (version 26; IBM Corp., Armonk, NY, USA). A P value <0.05 was considered statistically significant.

Results

Patient demographics

Fifty-seven of the 69 patients with IPF were male and 60 had a smoking history. Median (IQR) age was 67 [61–72] years old. Twenty-one patients experienced AE and 31 died during a median observation period of 1,289 days (*Table 1*). This study included 30 healthy volunteers, with a median age (IQR) of 56 [54–59], of whom 15 were females and 13 were non-smokers. They were significantly younger (P<0.001, Mann-Whitney U test) and included significantly more females (P=0.001, Chi-square test) and non-smokers (P<0.001, Chi-square test) than IPF patients.

Clinical parameters predicting a poor prognosis and AE of IPF

Univariate Cox proportional hazards regression analysis identified lower %FVC, lower %DLco, an mMRC score ≥2, higher serum levels of KL-6 and SP-D, and higher percentages of neutrophils in BAL to be significant predictors of a poor prognosis. Multivariate analysis with stepwise selection indicated that higher %FVC, an mMRC score ≥2, and lower percentages of lymphocytes in BAL were predictors of shorter survival in patients with IPF (*Table 2*).

Univariate Cox proportional hazards regression analysis revealed lower %FVC, an mMRC score ≥2, higher serum levels of KL-6 and SP-D, and higher percentages of neutrophils in BAL to be significant predictors of AE.

Table 1 Patient demographics

Parameters	Frequency (%) or median (IQR)
Gender, male/female	57/12 (82.6/17.4)
Age, yrs	67 [61–72]
Smoking. NS/ES or CS	9/60 (13.0/87.0)
Diagnosis of IPF, Clinical/SLB	35/34 (50.7/49.3)
BMI	24.8 (23.1–26.1)
mMRC, <2/≥2	47/22 (68.1/3.19)
%FVC*, %	76.5 (64.0–89.4)
%DLco**, %	52.2 (37.5–62.3)
KL-6*, ×100 U/mL	8.35 (5.85–11.97)
SP-D**, ×10 ng/mL	18.4 (11.0–30.7)
Neutrophils in BAL*, %	2.3 (0.8–5.6)
Lymphocytes in BAL*, %	7.3 (3.4–12.4)
Pirfenidone, yes/no	10/59
Corticosteroids, yes/no	31/38
Corticosteroid before AE, yes/no	15/54
Occurrence of acute exacerbation, yes/no	21/48 (30.4/69.6)
Last observation: dead/alive	31/38 (44.9/55.1)
Observation period, days	1,289 (578–1,867)

*, n=68; **, n=67, n=69 for the other parameters. IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; BMI, body mass index; mMRC, modified Medical Research Council score for shortness of breathe; FVC, forced vital capacity; DLco, diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D.

Multivariate analysis with stepwise selection confirmed a lower %FVC and an mMRC score ≥2 (*Table 3*) to be significant predictors of AE.

Serum cytokine levels in patients with IPF

Serum levels of IL-1ra (P<0.001), IL-2 (P=0.007), IL-6 (P=0.001), IL-10 (P=0.001), IL-12 (P<0.001), G-CSF (P=0.001), and PDGF (P<0.001) were significantly higher and those of IL-9 (P=0.005), MIP-1β (P<0.001), and RANTES (P=0.016) were significantly lower in patients with IPF than in controls (*Table 4*).

The significance of the serum levels of each cytokine in terms of the prognosis and prediction of AE was evaluated by Cox proportional hazards regression analysis. None of the cytokine levels could predict survival (*Table 5*) or AE (*Table 6*) in patients with IPF.

No significant correlation was found between the serum level of any cytokine and %FVC (*Table 7*). Serum levels of IL-12, G-CSF, GM-CSF, MIP-1α, MIP-1β were significantly associated with percentages of neutrophils in BAL, and serum levels of IL-15, MCP-1, and MIP-1α had significant correlation with percentages of lymphocytes in BAL (*Table 7*).

Ability of serum cytokine levels per %FVC to predict a poor prognosis and AE

We evaluated the ability of serum cytokine levels per %FVC to predict a poor prognosis and AE by Cox proportional hazards regression analysis.

Univariate Cox analysis revealed that IL-1ra/%FVC, IL-7/%FVC, IL-9/%FVC, IL-17/%FVC, eotaxin/%FVC, b-FGF/%FVC, and PDGF/%FVC were significant predictors of poor survival. IL-9/%FVC and PDGF/%FVC were identified to be significant factors in multivariate analysis with stepwise selection (*Table 8*). After adjustment for significant prognostic clinical factors other than %FVC (i.e., the mMRC score and lymphocyte percentages in BAL at the time of diagnosis of IPF), the PDGF/%FVC value was found to be a significant prognostic factor (*Table 8*).

The serum IL-7/%FVC, IL-9/%FVC, IL-13/%FVC, IL-17/%FVC, eotaxin/%FVC, b-FGF/%FVC, and PDGF/%FVC values were significant predictors of AE in IPF by univariate analysis (*Table 9*). Multivariate analysis with stepwise selection revealed that IL-13/%FVC and PDGF/%FVC were significant predictors of AE. After adjustment for significant clinical predictors of AE other than %FVC (i.e., the mMRC score at the time of diagnosis of IPF), the PDGF/%FVC value was a significant predictor of AE (*Table 9*).

Correlation between serum cytokine levels per %FVC and mMRC score

Correlation between serum cytokine levels per %FVC and mMRC score was examined by spearman's rank correlation (*Table 10*). IL-1β/%FVC, IL-7/%FVC, IL-9/%FVC, IL-13/%FVC, IL15/%FVC, IL17/%FVC, eotaxin/%FVC, b-FGF/%FVC, IFNγ/%FVC, and TNFα/%FVC was significantly correlated with mMRC score. In addition, IL-4/%FVC and PDGF/%FVC tended to be correlated with

Table 2 Univariate and multivariate Cox proportional hazard regression analysis to evaluated prognostic factors

Parameters	HR	95% CI	P value
Univariate analysis			
Gender, male *vs.* female	0.987	0.403–2.416	0.978
Age	1.027	0.980–1.076	0.272
Smoking, CS or ES *vs.* NS	0.877	0.336–2.289	0.789
Diagnosis of IPF, Clinical *vs.* SLB	1.696	0.831–3.460	0.147
BMI	0.939	0.839–1.051	0.277
mMRC, ≥2 *vs.* <2	4.591	2.247–9.380	<0.001
%FVC*	0.950	0.930–0.971	<0.001
%DLco**	0.960	0.939–0.983	0.001
Neutrophils in BAL*, %	1.087	1.011–1.169	0.025
Lymphocytes in BAL*, %	0.973	0.919–1.029	0.338
KL-6*, ×100 U/mL	1.056	1.018–1.095	0.004
SP-D*, ×10 ng/mL	1.020	1.005–1.036	0.009
Multivariate analysis stepwise selection procedure			
%FVC	0.955	0.930–0.982	0.001
mMRC, ≥2 *vs.* <2	2.824	1.265–6.305	0.011
Lymphocytes in BAL, %	0.927	0.866–0.991	0.027

Prognostic significance of each parameter was evaluated by univariate Cox proportional hazard regression analysis. Multivariate analysis with stepwise method was performed using all parameters to clarify prognostic factors. *, n=68; **, n=67, n=69 for the other parameters. HR, hazard ratio; CI, confidence interval; IPF, idiopathic pulmonary fibrosis; BMI, body mass index; mMRC, modified Medical Research Council score for shortness of breathe; %FVC, percent predicted value of forced vital capacity; %DLco, percent predicted value of diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein.

mMRC score.

Similarly to %FVC, mMRC score suggests severity of IPF patients. Predictive role of another parameter "serum cytokine levels/mMRC" for prognosis and AE occurrence was examined by Cox proportional hazard regression analysis with stepwise selection procedure (*Table 11*). PDGF/mMRC and eotaxin/mMRC was a significant prognostic factor. PDGF/mMRC and IL-9/mMRC was a significant predictor for AE occurrence.

Discussion

In this study, we measured serum cytokine levels in patients with IPF at the time of diagnosis and assessed their ability to predict the outcome in these patients. Serum cytokine levels were not associated with the %FVC and could not predict outcome of IPF. However, we identified a new parameter, namely the serum cytokine level/%FVC value, the results for which suggest that PDGF is an important determinant of both survival and AE in patients with IPF. Similar parameter, the serum cytokine level/mMRC, also suggested importance of PDGF as a predictor of mortality and AE occurrence.

Other studies have investigated serum cytokine levels as biomarkers of the severity of IPF and its prognosis. Serum IL-8 has been reported to be a significant prognostic factor in IPF (28) and to show a significant negative correlation with %FVC (29); however, IL-2, IL-4, IL-10, IL-12, and IFN-γ did not have no significant correlation with %FVC (29). De Lauretis *et al.* reported that the serum IL-6 level can predict progression of IPF and mortality (30). Serum CCL18 was correlated with a change in %FVC and %TLC, not with %FVC. Patients with IPF and a serum CCL18 level >150 ng/mL were reported to have significantly poor survival than those with a lower CCL18 level (31). The results of our study that none of the

Table 3 Univariate and multivariate Cox proportional hazard regression analysis to evaluated predictive factors of occurrence of acute exacerbation in IPF

Parameters	HR	95% CI	P value
Univariate analysis			
Gender, Male *vs.* Female	0.987	0.328–2.913	0.968
Age	1.044	0.984–1.108	0.156
Smoking, CS or ES *vs.* NS	0.654	0.219–1.949	0.446
Diagnosis of IPF, Clinical *vs.* SLB	1.742	0.728–4.168	0.212
BMI	1.000	0.873–1.146	0.999
mMRC, ≥2 *vs.* <2	4.367	1.819–10.483	0.001
%FVC*	0.953	0.930–0.977	<0.001
%DLco**	0.973	0.947–0.999	0.039
Neutrophils in BAL*, %	1.083	1.004–1.169	0.040
Lymphocytes in BAL*, %	0.994	0.934–1.059	0.861
KL-6*, ×100 U/mL	1.063	1.021–1.106	0.003
SP-D*, ×10 ng/mL	1.018	1.001–1.035	0.036
Multivariate analysis with stepwise selection procedure			
%FVC	0.962	0.935–0.989	0.007
mMRC, ≥2 *vs.* <2	2.741	1.063–7.066	0.037

*, n=68; **, n=67, n=69 for the other parameters. Prognostic significance of each parameter was evaluated by univariate Cox proportional hazard regression analysis. Multivariate analysis with stepwise method was performed using all parameters to clarify prognostic factors. HR, hazard ratio; CI, confidence interval; IPF, idiopathic pulmonary fibrosis; BMI, body mass index; mMRC, modified Medical Research Council score for shortness of breathe; %FVC, percent predicted value of forced vital capacity; %DLco, percent predicted value of diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein.

serum cytokine levels were associated with %FVC is not inconsistent with previous reports. Serum levels of some cytokines associated with inflammation were correlated with cell populations of BAL in our study. This might be because serum levels of inflammatory cytokines were proportional to local cytokine levels in the lung volume.

An investigation of acute respiratory distress syndrome associated with mould infection suggested that the prognostic significance of cytokine levels in BALF might be better than those in serum in IPF (32). In that study, the prognosis could not be predicted by the serum IL-6 level in patients with mould infection complicated by viral or bacterial infection but could be predicted by IL-6 in BALF. Another IPF study found that the MCP-1 (CCL2) level in BALF was higher in non-survivors than in survivors but that serum CCL2 was not associated with mortality (33). Cytokine levels in BALF reflect intrapulmonary cytokine production; however, BAL is not always easy to perform in patients with IPF. Moreover, cytokine levels in BALF do not necessarily reflect cytokine production per lung volume and BAL is not always obtained from the area of fibrosis. We hypothesized that cytokines associated with fibrosis would be produced mainly in the lung and that cytokine production per lung volume would be the parameter with the best predictive ability. Therefore, we decided to use the serum cytokine level/%FVC value to estimate the prognostic significance of each cytokine.

In this study, univariate analysis revealed that the IL-1ra/%FVC, IL-7/%FVC, IL-9/%FVC, IL-17/%FVC, eotaxin/%FVC, b-FGF/%FVC, and PDGF/%FVC values were significant predictors of poor survival and most of these parameters were significantly correlated with mMRC, suggesting severity of IPF. These results show our new parameters might be useful to evaluate severity and mortality of IPF. Most of these cytokines have been associated with pulmonary fibrosis (13,15,16,34-37),

Table 4 Serum cytokines of IPF and healthy volunteers*

Parameters	IPF (n=69)	Healthy volunteers (n=30)	P value
IL-1 ra	82.61 (65.20–110.00)	57.99 (27.49–79.05)	<0.001
IL-2	0.5600 (0.3500–0.9550)	0.3900 (0.0150–0.6700)	0.007
IL-6	0.6800 (0.4700–1.3150)	0.3400 (0.1700–0.8175)	0.001
IL-9	37.36 (21.78–38.85)	46.49 (33.14–49.09)	0.005
IL-10	0.4200 (0.1300–1.0800)	0.0450 (0.0150–0.3250)	0.001
IL-12	0.4400 (0.2800–0.7200)	0.1250 (0.0150–0.3275)	<0.001
G-CSF	13.130 (8.660–21.575)	6.635 (2.350–11.282)	0.001
PDGF-BB	158.38 (64.58–466.49)	63.07 (53.17–113.27)	<0.001
MIP-1β/CCL4	113.29 (51.42–263.53)	621.71 (264.96–884.63)	<0.001
RANTES/CCL5	3,415 (2,865–4,656)	4,447 (3,332–5,061)	0.016
VEGF-A	2.010 (2.010–16.925)	0.615 (0.615–5.796)	<0.001
IL-1β	0.4000 (0.2000–0.565)	0.4000 (0.2775–0.6500)	0.799
IL-4	0.5500 (0.4100–0.8150)	0.5050 (0.3825–0.850)	0.417
IL-5	0.0300 (0.0150–1.8150)	0.0300 (0.0300–0.8325)	0.087
IL-7	3.740 (2.980–5.170)	4.180 (2.280–5.320)	0.921
IL-8	2.840 (2.090–3.870)	1.925 (1.487–3.327)	0.053
IL-13	0.5300 (0.3650–0.9500)	0.6300 (0.2700–1.0675)	0.957
IL-15	13.81 (13.81–15.34)	7.8550 (0.7350–16.095)	0.096
IL-17	3.470 (2.450–4.055)	3.330 (2.285–4.182)	0.451
Eotaxin/CCL11	34.82 (26.16–47.52)	34.14 (28.79–46.87)	0.775
b-FGF	8.740 (6.815–10.135)	9.190 (8.107–9.980)	0.379
GM-CSF	0.030 (0.2500–0.5500)	0.1150 (0.010–0.4375)	0.542
IFNγ	2.120 (1.535–3.700)	2.430 (1.202–3.595)	0.840
IP-10/CXCL10	321.71 (246.28–460.07)	325.29 (235.13–443.72)	0.982
MCP-1/CCL2	9.930 (6.820–14.645)	9.060 (6.110–12.397)	0.426
MIP-1α/CCL3	0.7500 (0.4700–1.5150)	0.5900 (0.3650–1.9775)	0.479
TNF-α	13.62 10.35–15.59)	15.04 (10.78–15.72)	0.428

*, serum cytokine levels (pg/mL) of IPF and healthy volunteers were compared with Mann-Whitney U test. IL, interleukin; CCL, CC chemokine ligand; bFGF, basic fibroblast growth factor; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IP-10, IFN-γ inducible protein; CXCL, CXC chemokine ligand; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

probably because the pathophysiology of IPF involves fibrosis more than inflammation. IPF is thought to develop as a result of recurrent injury to alveolar epithelial cells (AECs), which have been associated with endoplasmic reticulum stress and apoptosis of these cells and from aberrant and uncontrolled wound healing thereafter (38). Our multivariate analysis suggested that the PDGF/%FVC value was the most important predictor of survival in IPF.

PDGF has potent fibrotic activity, activating both proliferation of fibroblasts and collagen synthesis. PDGF

Table 5 Prognostic significance of serum cytokines determined by univariate Cox proportional hazard regression analysis

Parameters*	HR**	95% CI	P value
IL-1β	0.596	0.232–1.532	0.283
IL-ra	1.000	0.993–1.007	0.983
IL-2	0.847	0.488–1.470	0.555
IL-4	0.465	0.146–1.479	0.195
IL-5	0.970	0.856–1.100	0.638
IL-6	0.892	0.665–1.198	0.447
IL-7	0.946	0.765–1.170	0.610
IL-8	0.988	0.964–1.013	0.356
IL-9	1.002	0.972–1.033	0.908
IL-10	0.763	0.404–1.440	0.404
IL-12	1.005	0.764–1.320	0.973
IL-13	1.039	0.868–1.234	0.678
IL-15	0.994	0.974–1.015	0.585
IL-17	0.917	0.736–1.144	0.443
Eotaxin/CCL11	0.987	0.957–1.018	0.398
b-FGF	0.974	0.861–1.103	0.682
G-CSF	0.991	0.977–1.005	0.226
GM-CSF	0.780	0.371–1.641	0.513
IFNγ	0.897	0.723–1.114	0.327
IP-10/CXCL10	0.999	0.997–1.001	0.368
MCP-1/CCL2	0.960	0.908–1.015	0.147
MIP-1α/CCL3	0.967	0.920–1.017	0.194
PDGF-BB	1.001	1.000–1.002	0.122
MIP-1β/CCL4	0.999	0.997–1.001	0.234
RANTES/CCL5	1.000	1.000–1.000	0.405
TNF-α	0.966	0.916–1.018	0.190
VEGF-A	0.991	0.961–1.023	0.585

*, cytokine levels were used as pg/mL; **, HR >1 means an increase in each continuous parameter indicating high risk of mortality. AE, acute exacerbation; b-FGF, basic fibroblast growth factor; CCL, CC chemokine ligand; CI, confidence interval; CXCL, CXC chemokine ligand; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; HRCT, high-resolution computed tomography; IFN, interferon; IIP, idiopathic interstitial pneumonia; IL, interleukin; IP-10, IFN-γ inducible protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Table 6 AE predictive significance of serum cytokines determined by univariate Cox proportional hazard regression analysis

Parameters*	HR**	95% CI	P value
IL-1β	0.587	0.183–1.886	0.371
IL-ra	1.001	0.994–1.008	0.813
IL-2	0.975	0.535–1.779	0.935
IL-4	0.779	0.227–2.668	0.690
IL-5	1.021	0.906–1.151	0.731
IL-6	0.906	0.654–1.253	0.550
IL-7	1.001	0.790–1.267	0.995
IL-8	0.995	0.971–1.019	0.655
IL-9	0.998	0.955–1.022	0.473
IL-10	0.910	0.447–1.853	0.796
IL-12	0.970	0.691–1.361	0.858
IL-13	1.074	0.889–1.297	0.458
IL-15	1.000	0.978–1.022	0.978
IL-17	0.919	0.701–1.206	0.544
Eotaxin/CCL11	1.004	0.968–1.041	0.830
b-FGF	0.967	0.830–1.126	0.666
G-CSF	0.998	0.984–1.012	0.760
GM-CSF	0.956	0.453–2.018	0.905
IFNγ	0.936	0.751–1.168	0.560
IP-10/CXCL10	0.999	0.998–1.001	0.587
MCP-1/CCL2	0.957	0.894–1.025	0.208
MIP-1α/CCL3	0.981	0.939–1.025	0.383
PDGF-BB	1.001	1.000–1.002	0.054
MIP-1β/CCL4	0.999	0.997–1.0011	0.304
RANTES/CCL5	1.000	1.000–1.000	0.599
TNF-α	0.964	0.902–1.029	0.272
VEGF-A	1.005	0.977–1.035	0.716

*, cytokine levels were used as pg/mL; **, HR >1 means an increase in each continuous parameter indicating high risk of occurrence of acute exacerbation. AE, acute exacerbation; b-FGF, basic fibroblast growth factor; CCL, CC chemokine ligand; CI, confidence interval; CXCL, CXC chemokine ligand; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; HRCT, high-resolution computed tomography; IFN, interferon; IIP, idiopathic interstitial pneumonia; IL, interleukin; IP-10, IFN-γ inducible protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Table 7 Correlation between serum cytokines levels and clinical parameters

Parameters*	ρ (Spearman's rank correlation)				
	%FVC	mMRC (<2/≥2)	Neu in BAL	Lymph in BAL	Corticosteroid before AE
IL-1β	0.021	0.096	0.004	−0.121	0.098
IL-ra	−0.080	−0.114	0.094	−0.218	−0.086
IL-2	0.003	−0.045	0.220	−0.088	0.098
IL-4	0.155	−0.035	0.130	−0.021	−0.030
IL-5	0.181	−0.206	0.144	−0.047	−0.151
IL-6	0.022	−0.164	0.170	−0.079	−0.129
IL-7	0.043	0.012	0.214	0.078	−0.028
IL-8	−0.057	−0.064	0.229	−0.124	−0.124
IL-9	0.108	0.075	−0.001	−0.093	0.022
IL-10	0.060	−0.198	0.070	−0.045	−0.121
IL-12	−0.085	0.049	0.244†	−0.025	0.048
IL-13	−0.072	0.237	0.198	−0.079	0.147
IL-15	0.083	0.087	0.149	0.372‡	0.037
IL-17	0.043	0.087	0.002	−0.082	0.066
Eotaxin/CCL11	−0.013	0.078	0.000	−0.007	0.022
b-FGF	0.046	0.035	0.070	−0.034	0.014
G-CSF	0.072	−0.073	0.299†	−0.128	0.044
GM-CSF	−0.117	0.123	0.264†	0.078	0.143
IFNγ	0.072	0.054	0.237	−0.041	−0.091
IP-10/CXCL10	0.145	−0.381‡	−0.006	−0.034	−0.195
MCP-1/CCL2	0.172	−0.148	0.096	−0.254†	−0.151
MIP-1α/CCL3	0.131	−0.164	0.254†	−0.241†	0.004
PDGF-BB	−0.137	0.072	−0.040	−0.223	0.133
MIP-1β/CCL4	0.038	−0.167	0.239†	0.119	−0.117
RANTES/CCL5	−0.029	−0.130	0.089	−0.087	−0.050
TNF-α	0.117	−0.079	0.013	−0.096	−0.047
VEGF-A	0.009	−0.111	0.115	−0.163	−0.004

†, P<0.05; ‡, P<0.01; *, cytokine levels were used as pg/mL. BAL, bronchoalveolar lavage; b-FGF, basic fibroblast growth factor; CCL, CC chemokine ligand; CI, confidence interval; CXCL, CXC chemokine ligand; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; HRCT, high-resolution computed tomography; IFN, interferon; IIP, idiopathic interstitial pneumonia; IL, interleukin; IP-10, IFN-γ inducible protein; Lymph, lymphocytes; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; mMRC, modified Medical Research Council score for shortness of breathe; Neu, neutrophils; %FVC, percent predicted value of forced vital capacity; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Table 8 Prognostic significance of serum cytokines/%FVC determined by Cox proportional hazard regression analysis

Parameters*	HR**	95% CI	P value
Univariate analysis			
IL-1β/%FVC	12596673	0.000–1.119e^{36}	0.631
IL-1 ra/%FVC	1.416	1.023–1.962	0.036
IL-2/%FVC	145948721	0.000–3.446e^{24}	0.328
IL-4/%FVC	2.566e^{14}	0.000–1.571e^{42}	0.309
IL-5/%FVC	1.346	0.000–8,156.099	0.947
IL-6/%FVC	1.503	0.000–113,740,946	0.965
IL-7/%FVC	33275.167	2.656–416,827,118	0.031
IL-8/%FVC	0.612	0.110–3.401	0.575
IL-9/%FVC	26.515	3.957–177.689	0.001
IL-10/%FVC	1.699	0.000–7.157e^{16}	0.978
IL-12/%FVC	14.147	0.000–1,608,358.47	0.656
IL-13/%FVC	722339.368	0.767–6.806e^{11}	0.055
IL-15/%FVC	1.803	0.479–6.780	0.383
IL-17/%FVC	30,284,237.2	5.062–1.812e^{14}	0.030
Eotaxin (CCL11)/%FVC	5.029	1.263–20.028	0.022
b-FGF/%FVC	29,109.988	37.378–22,671,011.2	0.002
G-CSF/%FVC	0.830	0.312–2.208	0.708
GM-CSF/%FVC	70,967.265	0.000–8,404e^{24}	0.636
IFNγ/%FVC	6.768	0.006–8,148.224	0.597
IP-10 (CXCL10)/%FVC	1.030	0.944–1.125	0.503
MCP-1(CCL2)/%FVC	0.818	0.138–4.835	0.824
MIP-1α (CCL3)/%FVC	0.142	0.004–4.466	0.267
PDGF-BB/%FVC	1.119	1.043–1.200	0.002
MIP-1β (CCL4)/%FVC	0.981	0.903–1.067	0.660
RANTES (CCL5)/%FVC	1.001	0.997–1.006	0.558
TNF-α/%FVC	2.701	0.174–41.909	0.477
VEGF-A/%FVC	1.446	0.244–8.579	0.685
Multivariate analysis with stepwise selection procedure			
IL-9/%FVC	23.957	2.846–201.626	0.003
PDGF-BB/%FVC	1.092	1.018–1.171	0.014
Adjusted by mMRC (≥2 *vs.* <2) and lymphocyte in BAL (%) with stepwise selection procedure			
PDGF-BB/%FVC	1.101	1.022–1.186	0.011
mMRC (≥2 *vs.* <2)	4.083	1.978–8.430	<0.001

*, cytokine levels were used as pg/mL; **, HR >1 means an increase in each continuous parameter indicating high risk of mortality. AE, acute exacerbation; b-FGF, basic fibroblast growth factor; BAL, bronchoalveolar lavage; CCL, CC chemokine ligand; CI, confidence interval; CXCL, CXC chemokine ligand; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; HRCT, high-resolution computed tomography; IFN, interferon; IIP, idiopathic interstitial pneumonia; IL, interleukin; IP-10, IFN-γ inducible protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; mMRC, modified Medical Research Council score for shortness of breathe; %FVC, percent predicted value of forced vital capacity; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Table 9 AE predictive significance of serum cytokines/%FVC determined by Cox proportional hazard regression analysis

Parameters*	HR**	95% CI	P value
Univariate analysis			
IL-1β/%FVC	1.257e^{9}	0.000–1.037e^{44}	0.610
IL-ra/%FVC	1.373	0.984–1.917	0.062
IL-2/%FVC	1.915e^{13}	0.000–5.734e^{31}	0.159
IL-4/%FVC	1.101e^{27}	0.008–1.556e^{56}	0.069
IL-5/%FVC	48.713	0.016–145,457.537	0.341
IL-6/%FVC	2.722	0.000–977,650,401	0.919
IL-7/%FVC	98,037.144	4.048–2.374e9	0.026
IL-8/%FVC	0.982	0.176–5.469	0.983
IL-9/%FVC	10.276	1.208–87.378	0.033
IL-10/%FVC	27,592.119	0.000–7.565e^{21}	0.618
IL-12/%FVC	2.256	0.000–1,921,813.53	0.907
IL-13/%FVC	5,427,096.68	2.853–1.032e^{13}	0.036
IL-15/%FVC	2.512	0.644–9.802	0.185
IL-17/%FVC	222,037,044	2.734–1.803e^{16}	0.039
Eotaxin (CCL11)/%FVC	8.611	1.972–37.613	0.004
b-FGF/%FVC	54,703.892	17.649–169,554,985	0.008
G-CSF/%FVC	1.416	0.527–3.800	0.490
GM-CSF/%FVC	66,901,058.1	0.000–4.228e^{24}	0.389
IFNγ/%FVC	5.156	0.005–4,880.085	0.639
IP-10 (CXCL10)/%FVC	1.042	0.945–1.150	0.408
MCP-1(CCL2)/%FVC	0.760	0.112–5.133	0.778
MIP-1α (CCL3)/%FVC	0.381	0.018–7.880	0.532
PDGF-BB/%FVC	1.134	1.052–1.221	0.001
MIP-1β (CCL4)/%FVC	0.982	0.891–1.084	0.723
RANTES (CCL5)/%FVC	1.001	0.996–1.006	0.738
TNF-α/%FVC	3.403	0.125–92.146	0.467
VEGF-A/%FVC	2.716	0.542–13.609	0.224
Multivariate analysis with stepwise selection procedure			
IL-13/%FVC	902,694,187	108.785–7.491e^{15}	0.011
PDGF-BB/%FVC	1.147	1.063–1.238	<0.001
Adjusted by mMRC (≥2 *vs.* <2) with stepwise procedure			
PDGF-BB/%FVC	1.133	1.045–1.228	0.003
mMRC (≥2 *vs.* <2)	4.116	1.692–10.015	0.002

*, cytokine levels were used as pg/mL; **, HR >1 means an increase in each continuous parameter indicating high risk of occurrence of acute exacerbation. AE, acute exacerbation; b-FGF, basic fibroblast growth factor; CCL, CC chemokine ligand; CI, confidence interval; CXCL, CXC chemokine ligand; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; HRCT, high-resolution computed tomography; IFN, interferon; IIP, idiopathic interstitial pneumonia; IL, interleukin; IP-10, IFN-γ inducible protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; mMRC, modified Medical Research Council score for shortness of breathe; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Table 10 Correlation between serum cytokine levels/%FVC and mMRC examined by Spearman's rank correlation

Parameters*	Correlation with mMRC (<2/≥2)	
	ρ	P value
IL-1β/%FVC	0.237	0.049
IL-ra/%FVC	0.194	0.111
IL-2/%FVC	0.003	0.313
IL-4/%FVC	0.231	0.056
IL-5/%FVC	0.003	0.980
IL-6/%FVC	0.019	0.879
IL-7/%FVC	0.251	0.037
IL-8/%FVC	0.108	0.378
IL-9/%FVC	0.443	0.000
IL-10/%FVC	–0.109	0.371
IL-12/%FVC	0.194	0.111
IL-13/%FVC	0.329	0.006
IL-15/%FVC	0.333	0.005
IL-17/%FVC	0.356	0.003
Eotaxin (CCL11)/%FVC	0.365	0.002
b-FGF/%FVC	0.392	0.001
G-CSF/%FVC	0.081	0.507
GM-CSF/%FVC	0.208	0.087
IFNγ/%FVC	0.245	0.042
IP-10 (CXCL10)/%FVC	–0.005	0.970
MCP-1(CCL2)/%FVC	0.117	0.338
MIP-1α (CCL3)/%FVC	–0.006	0.959
PDGF-BB/%FVC	0.205	0.092
MIP-1β (CCL4)/%FVC	0.002	0.990
RANTES (CCL5)/%FVC	0.166	0.174
TNF-α/%FVC	0.278	0.021
VEGF-A/%FVC	0.044	0.721

*, cytokine levels were used as pg/mL. b-FGF, basic fibroblast growth factor; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; G-CSF; granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; IFN, interferon; IL, interleukin; IP-10, IFN-γ inducible protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; mMRC, modified Medical Research Council score for shortness of breathe; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

functions as a strong chemoattractant for fibrocytes (19), which are associated with pulmonary fibrosis. *In vivo* introduction of the PDGF gene in a rodent model produced histologic findings similar to those in IPF (18). Bleomycin-induced pulmonary fibrosis was inhibited in mice by introduction of the soluble PDGF receptor gene (39) and by imatinib (19) which inhibits PDGF signalling. Furthermore, PDGF mRNA was detected in AECs and alveolar macrophages in patients with IPF (40,41), and production of PDGF by alveolar macrophages from patients with IPF was four times higher than that by those from control donors (42). The results of these studies suggested that serum PDGF is a potentially useful biomarker of the prognosis of IPF; however, clinical significance of serum PDGF levels to predict survival and AE occurrence was not confirmed.

Other studies have found the serum PDGF level to be significantly higher in patients with IPF than in controls (43,44); however, unlike in the present study, its prognostic value was not examined. Zhu *et al.* measured PDGF mRNA in biopsy specimens from patients with IPF as an indicator of intrapulmonary production of PDGF and found no survival difference according to the PDGF mRNA expression level (45), possibly because of their small sample size and the patchy distribution of fibrotic lesions in IPF (1-3). Hence, expression of PDGF in the biopsy specimens might not have reflected typical intrapulmonary PDGF expression. In this study, we found that a higher serum PDGF/%FVC value suggested worse survival in patients with IPF. This finding is consistent with the inhibitory effect of nintedanib on PDGF receptor signal transduction (46).

The pathophysiology of AE in IPF involves acute progression of chronic epithelial damage, which may be triggered by infection, aspiration, and mechanical stretch, and its occurrence is thought to depend on the degree of chronic epithelial damage (4). PDGF produced by alveolar macrophages and hyperplastic AECs is thought to be one of the key molecules in pulmonary fibrosis (40-42). Increased production of PDGF in the lung could reflect the degree of chronic lung injury, meaning that the PDGF/%FVC value can predict both AE and survival in patients with IPF.

This study has several limitations. First, it had a single-centre design and included a limited number of cases. Second, serum samples could not be obtained from all 92 consecutive patients with IPF identified during the study period. We could collect serum samples from only 69 IPF patients. Third, age, gender and smoking history of healthy

Table 11 Predictive role of serum cytokines/mMRC† for prognosis and AE occurrence was examined by Cox proportional hazard regression analysis

Parameters*	HR**	95% CI	P value
Prognosis			
Eotaxin (CCL11)/mMRC	0.918	0.881–0.957	<0.001
PDGF/mMRC	1.002	1.001–1.004	0.002
Adjusted by %FVC with stepwise procedure			
Eotaxin (CCL11)/mMRC	0.918	0.881–0.957	0.002
PDGF/mMRC	1.002	1.001–1.004	0.016
%FVC	0.955	0.930–0.981	0.001
AE occurrence			
IL-9/mMRC	0.880	0.813–0.953	0.002
PDGF/mMRC	1.004	1.001–1.007	0.009
Adjusted by %FVC with stepwise procedure			
IL-9/mMRC	0.904	0.835–0.980	0.014
PDGF/mMRC	1.003	1.001–1.006	0.013
%FVC	0.961	0.933–0.991	0.012

*, cytokine levels were used as pg/mL; **, HR >1 means an increase in each continuous parameter indicating high risk of mortality or occurrence of acute exacerbation; †, the mMRC scores were used in the calculation as the denominator, mMRC scores from 0 to 4 were converted to from 1 to 5. AE, acute exacerbation; CCL, CC chemokine ligand; CI, confidence interval; HR, hazard ratio; IL, interleukin; mMRC, modified Medical Research Council score for shortness of breathe; PDGF, platelet-derived growth factor.

volunteers were significantly different from IPF patients in this study. We cannot deny these differences affected the difference in serum cytokine levels between IPF patients and healthy volunteers; however, Drubaix reported age-dependent decrease in production of PDGF and b-FGF (47). Higher serum levels of these cytokines in IPF patients did not depend on their older ages than healthy volunteers.

Conclusions

This study found that patient survival and AE of IPF could be predicted by the serum PDGF/%FVC value. However, the prognostic importance of this parameter requires validation in further studies. In addition, whether serum levels of PDGF/%FVC can predict the effects of nintedanib on IPF is important problem to be solved in the future studies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1418/rc

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Ingelheim, Taiho, Roche, GALAPAGOS and SAVARA (not related to this study). YI has received lecture fees from Boehringer Ingelheim, Kyorin, GSK and Shionogi (not related to this study). YI has received supports of medical writing from Boehringer Ingelheim about other manuscripts related to other clinical trial (not related to this study). TA has received lecture fees from Boehringer Ingelheim and Shionogi for activities not connected with the submitted work. MH reports a grant from Japanese Society for the Promotion of Science (JSPS), but has no competing interest. 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 numbers 651 and 365) All study participants provided written informed consent for inclusion of their data in the study.

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