



Seroradiologic prognostic evaluation of acute exacerbation in patients with idiopathic interstitial pneumonia: a retrospective observational study

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Background: We previously reported that high-resolution computed tomography (HRCT) patterns and certain serum marker levels can predict survival in patients with acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) and in those with idiopathic interstitial pneumonias (IIPs). The utility of serum marker changes before and during AE has not been previously evaluated. This study aimed to clarify whether changes in serum marker levels could improve the prognostic significance of HRCT patterns in patients with AE-IIPs.

Methods: Seventy-seven patients (60 males, 17 females) with AE-IIP diagnosed between 2004 and 2016 and whose serum Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D levels were measured before and at the onset of AE were enrolled in this study. The HRCT pattern of each patient was classified as diffuse, multifocal, or peripheral. We examined the prognostic significance of the HRCT pattern, increased serum marker levels, and a combination of these parameters using Cox proportional hazard regression analysis.

Results: Fifty-three patients had IPF and 24 had non-IPF IIP. A serum KL-6 level that was increased compared with the level in the stable state ($\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$) was a significantly poor prognostic factor in patients with a multifocal pattern. Multivariate Cox analysis identified long-term oxygen therapy, a partial oxygen tension/fraction of inspired oxygen ratio ≤ 200 Torr, and an elevated SP-D level during a stable state to be significantly poor prognostic factors in all patients. A diffuse HRCT pattern was not a significant prognostic factor in an AE-IIP in multivariate analysis after adjustment; however, a multifocal pattern accompanying a $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$ or a diffuse pattern was a significantly poor prognostic factor than a peripheral pattern or a multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$.

Conclusions: Combining the HRCT pattern and the $\Delta\text{KL-6}/\text{ST-KL-6}$ value can improve our ability to predict the survival of AE-IIP patients.

Keywords: Acute exacerbation (AE); idiopathic interstitial pneumonia (IIP); idiopathic pulmonary fibrosis (IPF); prognosis; Krebs von den Lungen-6; high-resolution computed tomography (HRCT)

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease of unknown etiology and has a poor prognosis (1,2). It is characterized by progressive worsening of dyspnea and lung function; however, for unknown reasons, some patients with IPF experience rapid and often fatal disease progression (3-6). This type of rapid progression is known as acute exacerbations (AEs) of IPF (AE-IPF). AEs were first reported in IPF but have since been reported in other types of idiopathic interstitial pneumonias (IIPs) (7,8). We have recently reported the frequency of AE of IIP (AE-IIP) (8) and demonstrated similar survival rates in AE-IPF and AE of non-IPF IIP (9). AE of non-IPF interstitial lung diseases (ILDs), including non-IPF IIP, chronic hypersensitivity pneumonia, and collagen vascular disease associated-interstitial pneumonias, is an important healthcare issue (10).

A diagnosis of IPF (11), respiratory dysfunction (9) and use of corticosteroids (9) during periods of a stable state, a lower partial oxygen tension (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (9), and higher lactate dehydrogenase and inflammatory parameters at the onset of AE-IPF (12) have been reported to be significantly poor prognostic factors (13). High-resolution computed tomography (HRCT) findings are also an important predictor of the prognosis of AE-IPF patients. Akira *et al.* classified HRCT findings at the onset of AE-IPF into three patterns, i.e., peripheral, multifocal, or diffuse, and reported a worse prognosis in AE-IPF patients with a diffuse pattern than in those with a peripheral or multifocal pattern (14). They found that a radiologically diffuse pattern suggested a pathologic outcome of diffuse alveolar damage (DAD) and that a peripheral pattern was suggestive of organizing pneumonia (OP) (14).

Krebs von den Lungen (KL)-6 (15) and surfactant protein (SP)-D (16) are serum biomarkers of ILDs, and prognostic significance was suggested in IPF and the other IIPs. Furthermore, KL-6 can predict the occurrence of AE in IPF and IIPs (8,17) and is a significant prognostic factor in AE-IPF (18,19). We previously reported that SP-D is a significant prognostic factor in AE-IIPs (9). Although serum biomarker levels are often found to be elevated at the onset of AE compared to the levels recorded previously during a stable state, their prognostic significance and association with HRCT patterns of AE-IPF have not been examined. This clinical study aimed to answer these clinical questions in AE-IIP patients.

Methods

Study population

We retrospectively identified 113 patients with AE-IIPs diagnosed between 2004 and 2016 at Kinki-Chuo Chest Medical Center (KCCMC). Seventy-seven patients whose serum KL-6 and SP-D levels had been measured within the 6 months before and at the time of onset of AE were enrolled in the study (see *Figure S1*).

Clinical data for the 77 cases were collected from the medical records (*Table 1*). Sixty of the patients were male and the median age was 72 years. The underlying IIP was IPF in 53 cases and non-IPF in 24. Twenty-one patients were treated with prednisolone before the onset of AE and long-term oxygen therapy (LTOT) had been initiated in 31 cases.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by our institutional review board (approval number 650, July 23, 2018). The need for patient consent was waived in view of the retrospective nature of the study and the anonymity of the data.

Diagnosis of underlying IIPs

Bronchoalveolar lavage (BAL) and/or transbronchial lung biopsy (TBLB) was performed while diagnosing IIP in 58 of the 77 cases. Twenty-five surgical lung biopsy (SLB) specimens and one autopsy specimen were pathologically evaluated. Underlying IPF was diagnosed based on the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guideline for diagnosis and management of IPF (2). The IPF group included 53 patients, 24 of whom had SLB-proven idiopathic usual interstitial pneumonia (UIP) and 1 had autopsy-proven UIP. They were classified into definite ($n=20$), possible IPF ($n=5$), and clinically diagnosed IPF cases ($n=28$) with UIP HRCT pattern. The remaining 24 patients comprised the non-IPF IIP group ($n=24$); one patient was diagnosed with nonspecific interstitial pneumonia by SLB (20), and the remaining 23 had unclassifiable IIP without SLB evaluation and did not have cryptogenic OP after clinical evaluation with ($n=17$) or without ($n=6$) bronchoscopic findings. Our cohort did not include patients with collagen vascular disease associated-interstitial pneumonia diagnosed using specific diagnostic

Table 1 Demographics of patients with AE-IIPs

Parameters	Total cases (n=77)
Before AE	
Age, years	72 (66.5–76.5)
Sex, male/female	60/17
Smoking, NS/CS or Ex	19/58
Smoking, NS/Ex/CS	19/48/10
Smoking pack index	30 (4.2–50.0)
IPF/non-IPF	53/24
HRCT UIP/possible/inconsistent	45/13/19
Combined pulmonary fibrosis and emphysema on HRCT, yes/no	19/58
Bronchoscopy at the diagnosis of underlying IIPs, yes/no	58/19
Lymphocytes in BAL, %	9.3 (4.0–16.9)
Neutrophils in BAL, %	3.1 (1.5–8.2)
Eosinophils in BAL, %	2.0 (0.8–4.3)
%FVC [†]	70.3 (57.0–89.2)
FEV1/FVC [†] , %	84.9 (79.1–89.1)
%DLCO [#]	51.0 (37.6–60.5)
SLB or autopsy for underlying IIPs, yes/no	26/51
Autoantibody, yes/no	16/61
PSL before AE, yes/no	16/61
Immunosuppressants, yes/no	21/56
Initial immunosuppressants, AZP/CyA/CPA	11/4/1
Pirfenidone, yes/no	7/70
LTOT, yes/no	31/46
ST-KL-6, U/mL	1,230 (710–1,960)
ST-SP-D, ng/mL	182 (117–271)
DM, yes/no	25/52
OMI or angina, yes/no	8/69
Cerebral infarction, yes/no	5/72
At the onset of AE	
PaO ₂ /FiO ₂ ratio, Torr	151 (84–223)
WBC/μL	10,000 (8,000–12,900)
CRP, mg/dL	11.1 (4.5–13.9)
IgG, mg/dL	1,430 (1,210–1,930)
AE-KL-6, U/mL	1,690 (900–2,168)
ΔKL-6/ST-KL-6	0.211 (0.055–0.526)

Table 1 (continued)

Table 1 (continued)

Parameters	Total cases (n=77)
AE-SP-D, ng/mL	254 (173–450)
Δ SP-D/ST-SP-D	0.410 (0.066–1.371)
HRCT, diffuse/non-diffuse	21/56
HRCT, diffuse/multifocal/peripheral	21/38/18
Treatment for AE	
Intravenous high-dose methylprednisolone, yes/no	76/1
Initial dose of PSL, mg/kg	0.923 (0.692–0.990)
Initial dose of PSL, <0.6/≥0.6 mg/kg	16/61
Immunosuppressant, yes/no	39/38
CPA pulse, yes/no	13/64
AZP/CyA	22/6
Recombinant soluble thrombomodulin, yes/no	12/65
PPV within a month from the start of treatment, yes/no	28/49
NPPV/IPPV [§]	23/7
PMX-DHP therapy [†] , yes/no	17/60
Pirfenidone, yes/no	6/71
Interval of serum marker measurement days*	50 (34–83)
Interval from the symptomatic onset of AE to treatment, days	5 (2–9)

The data are presented as the frequency or median (interquartile range) is presented for each parameter. [¶]Spirometry was performed in 73 cases. [#]DLco was performed in 65 cases. [§]Cases treated with both NPPV and IPPV were classified as IPPV-treated cases. [†]Patients who received PMX-DHP therapy for the second AE were not included as PMX-DHP therapy-treated cases. *Interval days of serum marker measurement from stable state to onset of AE. AE, acute exacerbation; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; AZP, azathioprine; CPA, cyclophosphamide; CRP, C-reactive protein; CS, current smoker; CyA, cyclosporine A; DM, diabetes mellitus; EX, ex-smoker; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusing capacity of carbon monoxide; IgG, immunoglobulin G; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; IPPV, invasive positive pressure ventilation; KL-6, Krebs von den Lungen-6; LTOT, long-term oxygen therapy; NE, not evaluable; NPPV, non-invasive positive pressure ventilation; non-IPF, non-IPF IIPs; NS, non-smoker; OMI, old myocardial infarction; P/F ratio, PaO₂/FiO₂ ratio; PMX-DHP therapy, hemoperfusion therapy with polymyxin B-immobilized fiber column; PPV, positive pressure ventilation; PSL, prednisolone; SP-D, surfactant protein-D; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; WBC, white blood cells; Δ KL-6, increase in KL-6 at onset of acute exacerbation as compared with the stable state; Δ SP-D, increase in SP-D at onset of acute exacerbation as compared with the stable state.

criteria. Serum autoantibody positivity was evaluated based on the criterion of “interstitial pneumonia with autoimmune features (IPAF)” in the serological domain (21). Anti-neutrophil cytoplasmic antibody levels were also evaluated. Of 16 patients with positive autoantibodies, one showed Reynaud’s phenomenon and satisfied the IPAF criteria. Chronic hypersensitivity pneumonia was ruled out based on clinical and bronchoscopic findings. Percentages of lymphocytes in BAL were less than 40%, except in two

cases (22). Granulomatous lesions were not detected on TBLB specimens. HRCT did not show prominent mosaic attenuation (22).

An expert in diffuse lung diseases (TA) and a chest radiologist (MA) retrospectively reviewed the de-identified HRCT films obtained before the onset of AE and classified them into a UIP pattern (n=45), a possible UIP pattern (n=13), or inconsistent with a UIP pattern (n=19) according to the guideline’s criteria (2). All patients with possible

UIP patterns had traction bronchiectasis. Emphysema was diagnosed based on Schmidt *et al.*'s HRCT scan criteria (23). Patients complicated with moderate or severe emphysema were described as having combined pulmonary fibrosis and emphysema.

Diagnosis and treatment of AE-IIPs

AE-IIPs were diagnosed according to the modified Japanese Respiratory Society (24) criteria for AE-IPF (Supplementary File). Apparent infection was excluded; however, AE-IIPs triggered by infection may have been included because endotracheal aspiration or bronchoalveolar lavage was performed in 12 patients. SLB was not performed for the diagnosis of AE-IIPs. The AE-IIPs were generally treated with prednisolone following intravenous administration of methylprednisolone for three consecutive days with/without an immunosuppressant (9) and treatment in detail was shown in *Table 1*.

HRCT findings at diagnosis of AE-IIPs

The HRCT pattern at the onset of AE was classified by three chest radiologists (MA, TO, SS) as peripheral, multifocal, or diffuse (14) (see *Figure S2*). The HRCT pattern was then classified as diffuse or non-diffuse (peripheral or multifocal).

Measurement of serum markers and related parameters

We measured serum markers, including KL-6 and SP-D, using commercially available enzyme-linked immunosorbent assay (ELISA) kits, i.e., ED046 (Eizai, Tokyo, Japan) and SP-D ELISA (Yamasa, Tokyo, Japan) using cut-off levels of 500 U/mL and 110 ng/mL, respectively (25). These markers were measured both at the onset of AE (AE-KL-6 and AE-SP-D) and within the 6 months before AE when the disease was stable (ST-KL-6 and ST-SP-D). The measurement interval between stable state and AE onset was 50 days (median) and less than 90 days in 62 cases (80.5%). We compared the increase in serum levels of these markers (Δ KL-6 and Δ SP-D) and the rate of increase in serum markers when compared with the stable state (Δ KL-6/ST-KL-6 and Δ SP-D/ST-SP-D). Median values of Δ KL-6/ST-KL-6 and Δ SP-D/ST-SP-D were 0.211 and 0.410, respectively, and the two parameters were categorized into a higher and a lower group by their median values.

Statistical analysis

Continuous variables were presented as medians with interquartile range. We compared all parameters in the AE-IIP cases with the three HRCT patterns using the Kruskal-Wallis test, Mann-Whitney *U* test or Fisher's exact test. Kaplan-Meier analysis and Wilcoxon test were used to examine survival. Univariate Cox proportional hazards regression analysis was used to calculate the hazard ratio for each parameter and predict survival after AE. Multicollinearity of each parameter was examined by correlating the regression coefficient calculated by multivariate Cox proportional hazard regression analysis. If absolute values of correlation coefficients of two parameters were more than 0.7, one of the parameters with a higher *P* value for hazard ratio was excluded from the multivariate analysis. Spearman's rank correlation was additionally performed for all the parameters. If the correlation of two parameters was significant ($P < 0.05$) with $\rho > 0.7$, one of the parameters with a higher *P* value for hazard ratio were excluded from the multivariate analysis. Using the remaining parameters, prognostic factors in AE-IIP patients were determined by multivariate analysis with a stepwise selection procedure. All analyses were performed in all patients and separately for patients with AE-IIP according to whether the HRCT pattern was peripheral, multifocal, or diffuse. Statistical significance was inferred at $P < 0.05$. All statistical analyses were performed using SPSS v. 24 for Macintosh software (IBM Corp., Armonk, NY, USA).

Results

Patient demographics

There was no significant difference in survival between patients with AE-IPF and those with AE of non-IPF IIP ($P = 0.875$, log-rank test). Furthermore, the clinical parameters in patients with AE-IPF were similar to those in patients with AE of non-IPF IIP, except for patient sex, smoking history, smoking pack index, and percentages of lymphocytes in BAL (see *Table S1*). Hence, the analysis was performed for all AE-IIP cases.

The patient demographics are shown in *Table 1*. The median age at the diagnosis of AE-IIP was 72 years and 60 patients were male. The median survival time (MST) in all cases was 61 days. Serum levels of KL-6 ($P < 0.001$) and SP-D ($P < 0.001$) at the time of AE increased significantly when compared with the stable state before AE (Wilcoxon signed-rank test).

HRCT pattern and prognosis

The HRCT pattern for AE-IIP cases was diffuse (n=21), multifocal (n=38), or peripheral (n=18). The MST in patients with AE-IIP and a diffuse pattern was significantly worse than that in those with a peripheral pattern (12 vs. 115 days, P=0.017) and tended to be worse than in those with a multifocal pattern (12 vs. 67 days, P=0.059; *Figure 1A*). MST in patients with AE-IIP and a diffuse pattern was worse than that in those with a non-diffuse pattern (n=56, 73 days), including both peripheral and multifocal patterns, (P=0.014, Wilcoxon test; *Figure 1B*).

Differences in clinical features according to HRCT pattern

The white blood cell, lactate dehydrogenase, Δ KL-6, AE-SP-D, Δ SP-D, and Δ SP-D/ST-SP-D values were significantly higher in patients with the diffuse pattern than in those with a multifocal pattern (*Table 2*, Mann-Whitney *U* test). The PaO₂/FiO₂ ratio also tended to be lower when the pattern was diffuse than when it was multifocal. The clinical features and treatment before and at the onset of AE were identical in AE-IIPs with a multifocal or peripheral pattern (*Table 2*).

Prognostic factors according to HRCT pattern

Prognostic factors in all patients were evaluated by univariate Cox proportional hazard regression analysis (*Table 3*). Using the parameters remaining after exclusion due to multi-collinearity evaluation (see *Table S2*) and Spearman's rank correlation (see *Table S3*), multivariate Cox proportional hazard regression analysis with the stepwise selection method was performed for all cases and separately for the three HRCT patterns (*Table 4*). In all cases, implementation of LTOT before AE, a higher ST-SP-D, and a PaO₂/FiO₂ ratio \leq 200 Torr were significantly poor prognostic factors in multivariate analysis. Multivariate analysis revealed a higher AE-KL-6 in the presence of a peripheral pattern, a PaO₂/FiO₂ ratio \leq 200 Torr, a lower Δ KL-6/ST-KL-6 value (\leq 0.211) in the presence of a multifocal pattern, and a higher ST-SP-D value in the presence of a diffuse pattern as significantly poor prognostic factors.

Classification of AE-IIP patients with HRCT pattern and Δ KL-6/ST-KL-6

We have classified AE-IIPs into four groups; diffuse

pattern, peripheral pattern, multifocal pattern with lower Δ KL-6/ST-KL-6 (\leq 0.211), and multifocal pattern with higher Δ KL-6/ST-KL-6 ($>$ 0.211). Survival with a multifocal pattern and lower Δ KL-6/ST-KL-6 (\leq 0.211) was significantly worse than with a higher Δ KL-6/ST-KL-6 ($>$ 0.211) (*Figure 1C*, P=0.002, Wilcoxon test). There was no significant difference between the diffuse pattern and multifocal pattern with Δ KL-6/ST-KL-6 \leq 0.211 (P=0.689) or between the peripheral pattern and multifocal pattern with Δ KL-6/ST-KL-6 $>$ 0.211 (P=0.279).

Difference in clinical features between multifocal patterns with higher and lower Δ KL-6/ST-KL-6

In a multifocal pattern with lower Δ KL-6/ST-KL-6 (\leq 0.211), the Δ KL-6, Δ SP-D, Δ SP-D/ST-SPD and PaO₂/FiO₂ ratio were significantly lower and the frequency of LTOT was significantly higher than that with a higher Δ KL-6/ST-KL-6 (see *Table S4*). ST-KL-6 and ST-SP-D in multifocal pattern with lower Δ KL-6/ST-KL-6 tended to be higher than that with higher Δ KL-6/ST-KL-6 (see *Table S4*).

Difference in clinical features between the diffuse pattern and multifocal pattern with lower Δ KL-6/ST-KL-6

Background parameters before AE and PaO₂/FIO₂ ratio at the onset of AE were similar in the two groups. White blood cells, lactate dehydrogenase, Δ KL-6, Δ KL-6/ST-KL-6, AE-SP-D, Δ SP-D, and Δ SP-D/ST-SPD of the diffuse pattern was significantly higher than those of the multifocal pattern with lower Δ KL-6/ST-KL-6 (see *Table S5*).

Difference in clinical features between peripheral pattern and multifocal patterns with higher Δ KL-6/ST-KL-6

Background parameters except for sex were similar in both groups (see *Table S6*). Multifocal patterns with higher Δ KL-6/ST-KL-6 showed a higher Δ KL-6, more frequently a higher Δ KL-6/ST-KL-6 ($>$ 0.211), and a lower ST-SP-D than peripheral patterns (see *Table S6*).

Proposed classification of AE-IIPs using HRCT pattern and Δ KL-6/ST-KL-6

We divided the AE-IIPs into two groups, i.e., a group with a diffuse or multifocal pattern and a lower Δ KL-6/ST-KL-6 and a group with a peripheral or multifocal pattern

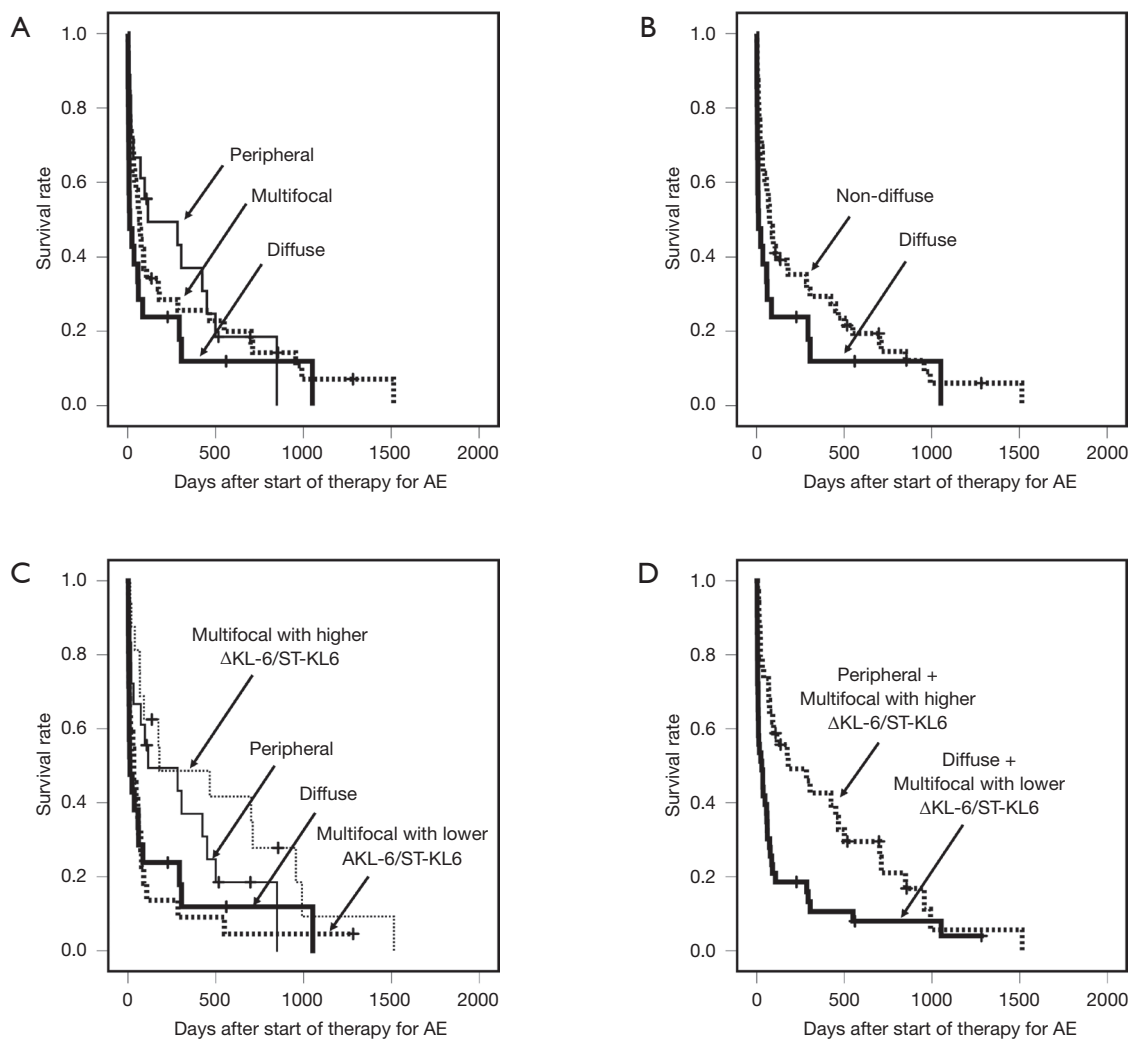


Figure 1 (A) Kaplan-Meier curves showing survival of patients with AE-IIPs according to whether the HRCT pattern was peripheral (n=18, thin line; MST 115 days), multifocal (n=38, dotted line; MST 67 days), or diffuse (n=21, thick line; MST 12 days). Survival in patients with the peripheral pattern was significantly better (P=0.017), while survival in those with the multifocal pattern (P=0.059) tended to be better than in those with the diffuse pattern (Wilcoxon test). Survival in patients with the peripheral pattern was similar to that in those with the multifocal pattern (P=0.349). (B) Kaplan-Meier curves showing that patients with AE-IIPs and a non-diffuse, i.e., peripheral or multifocal pattern, had better survival (n=56, dotted line; MST 73 days) than those with a diffuse pattern (thick line; P=0.014, Wilcoxon test). (C) Kaplan-Meier curves showing the survival of patients who had AE-IIPs with a diffuse pattern (n=21, thick line; MST 12 days), peripheral pattern (n=18, thin line; MST 115 days), multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$ (n=22, thick dotted line; MST 34 days), or multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$ (n=16, thin dotted line; MST 180 days). There was a significant difference in survival between patients with the peripheral pattern and those with the multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$ (P=0.021, Wilcoxon test), and between patients with the diffuse pattern and those with the multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$ (P=0.002, Wilcoxon test). However, there was no significant difference between patients with the diffuse pattern and multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$ (P=0.689) or between patients with the peripheral pattern and multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$ (P=0.279). Survival with a multifocal pattern and lower $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$ was significantly worse than with a higher $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$ (P=0.002, Wilcoxon test). (D) Kaplan-Meier curves showing that the survival of patients with AE-IIPs having the diffuse or multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$ (n=43, thick line; MST 29 days) was worse than the survival of those with the peripheral or multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$ (n=34, thin line; MST 180 days; P<0.0001, Wilcoxon test). AE, acute exacerbation; HRCT, high-resolution computed tomography; IIPs, idiopathic interstitial pneumonia; MST, median survival time; ST-KL-6, KL-6 during a stable state; $\Delta\text{KL-6}$, increase in KL-6 at the onset of AE compared with that during the stable state.

Table 2 Comparison of clinical parameters in patients with AE-IIP according to the diffuse, multifocal, or peripheral pattern

Parameter	Diffuse (n=21)	Multifocal (n=38)	Peripheral (n=18)	P value [§]
Before AE				
Age, years	72.0 (65.0–78.5)	72.5 (67.5–75.0)	68.5 (65.0–74.3)	0.471
Sex, male/female	16/5	27/11	17/1	0.119
IPF/non-IPF	11/10	26/12	16/2	0.053
HRCT, UIP/possible/inconsistent	9/7/5	24/4/10	12/2/4	0.255
CPFE on HRCT, yes/no	2/19	11/27	6/12	0.098
Bronchoscopy, yes/no	17/4	29/9	12/6	0.576
Lymphocyte in BAL, %	7.0 (3.3–18.4)	12.8 (6.0–20.7)	6.2 (3.3–11.4)	0.090
Neutrophils in BAL, %	2.6 (1.2–7.4)	3.2 (1.6–9.8)	4.4 (2.1–6.9)	0.599
Eosinophils in BAL, %	3.0 (1.2–5.5)	1.6 (0.7–3.6)	1.95 (1.0–3.4)	0.420
%FVC*	70.6 (59.3–88.3)	68.2 (56.2–82.0)	78.1 (52.4–95.4)	0.696
FEV1/FVC, %	88.5 (80.6–90.1)	84.1 (79.7–88.6)	86.1 (74.1–88.9)	0.375
%DLco*	54.8 (35.6–64.9)	49.4 (35.8–59.9)	50.3 (39.2–59.6)	0.795
SLB or autopsy, yes/no	6/15	12/26	8/10	0.573
Autoantibody, yes/no	3/18	9/29	4/14	0.757
Smoking status, NS/CS or ES	6/15	11/27	2/16	0.331
Smoking status, NS/ES/CS	6/14/1	11/22/5	2/12/4	0.383
Smoking pack index	15 (0–53)	30 (0–50)	33 (23–51)	0.600
LTOT, yes/no	10/11	15/23	6/12	0.652
Prednisolone, yes/no	6/15	11/27	4/14	0.779
Immunosuppressants, yes/no	5/16	9/29	2/16	0.546
AZP/CyA/CPA	2/2/1	7/2/0	2/0/0	
At the onset of AE				
PaO ₂ /FiO ₂ ratio, Torr	121 (66–179) [§]	181 (92–231)	186 (131–222)	0.081
PaO ₂ /FiO ₂ ratio ≤200/>200	18/3	24/14	11/7	0.146
PaO ₂ /FiO ₂ ratio, ≤100/>100 & ≤200/>200	9/9/3	10/14/14	3/8/7	0.254
WBC/μL	12,400 (10,200–15,100) ^{¶#}	8,300 (6,800–11,525)	10,750 (8,075–13,275)	0.001
LDH, U/mL	400 (336–433) ^{¶#}	348.5 (283.5–401.0)	342.0 (264.5–391.0)	0.024
CRP, mg/dL	12.3 (8.4–15.1)	10.0 (4.6–13.3)	10.6 (3.3–14.1)	0.423
IgG, ×100 mg/dL	13.9 (10.2–17.2)	15.7 (12.1–18.3)	14.8 (10.2–19.9)	0.670
AE-KL-6, U/L	1,868 (1,443–2,322)	1,757 (927–2,412)	1,150 (921–1,839)	0.159
ST-KL-6, U/mL	1,210 (671–2,175)	1,229 (816–2,045)	1,170 (467–1,688)	0.507
ΔKL-6, U/mL	550 (139–1,069) [#]	240 (6–553)	235 (19–513)	0.131
ΔKL-6/ST-KL-6	0.230 (0.091–1.346)	0.188 (0.007–0.481)	0.263 (0.013–0.819)	0.378
ΔKL-6/ST-KL-6, ≤0.211/>0.211 [†]	9/12	22/16	8/10	0.455

Table 2 (continued)

Table 2 (continued)

Parameter	Diffuse (n=21)	Multifocal (n=38)	Peripheral (n=18)	P value [§]
AE-SP-D, ng/mL	411 (231–587) [#]	241 (146–383)	251 (190–531)	0.023
ST-SP-D, ng/mL	181 (123–335)	176 (114–236)	216 (117–368)	0.301
ΔSP-D, ng/mL	207 (42–297) [#]	41 (–4–176)	54 (–26–160)	0.041
ΔSP-D/ST-SP-D	0.836 (0.241–2.138) [#]	0.288 (–0.041–0.863)	0.383 (–0.098–1.251)	0.070
ΔSP-D/ST-SP-D, ≤0.410/>0.410 [‡]	6/15	22/16	9/9	0.122
Observation period, days	61 (10–299)	67 (14–330)	111 (19–463)	0.051
Interval of serum marker measurement**, days	69 (40–106)	46 (30–77)	49 (30–70)	0.320
Interval from the symptomatic onset of AE to treatment, days	3 (1–6)	5 (2–8)	7 (1–10)	0.192
Interval from AE diagnosis to treatment ^ε , days	0 (0–0)	0 (0–2)	0 (0–2)	0.028

Categorical variables are presented as a number and continuous variables as the median (interquartile range). [§]The distribution of all categorical parameters between the three HRCT patterns was compared by Fisher's exact test and distribution of continuous variables were compared between the three HRCT patterns by the Kruskal-Wallis one-way analysis of variance. Dunn-Bonferroni post-hoc analysis revealed a significant difference between the diffuse and multifocal patterns ([#]P<0.05). Mann-Whitney *U* test revealed a significant difference between the diffuse and multifocal patterns ([‡]P<0.05). PaO₂/FiO₂ ratio of diffuse pattern tended to be lower than that of the multifocal pattern (^εP=0.079). *Pulmonary function test was performed in the diffuse pattern (Spirometry 20 cases, DLco 17 cases), multifocal pattern (Spirometry 37 cases, DLco 32 cases), peripheral pattern (Spirometry 16 cases, DLco 16 cases). [†]ΔKL-6/ST-KL-6 was divided into higher/lower by its median value, 0.211. [‡]ΔSP-D/ST-SP-D was divided into higher/lower by its median value, 0.410. There was no significant difference in the treatment received, including initial dose of prednisolone, frequency of administration of immunosuppressants, soluble thrombomodulin and anti-fibrotic drugs, PMX-DHP therapy, and positive pressure ventilation within 1 month of onset of AE for AE-IIPs, according to the HRCT pattern determined by the Wilcoxon rank sum test or Fisher's exact test. **Interval of days between serum marker measurement in the stable state and that after onset of AE. ^εThe interval was ≤2 days for all cases. There was a significant difference in the interval between three HRCT patterns. Treatment was started on the same day as the diagnosis of AE for all diffuse AE-IIP cases. The intervals for multifocal pattern and peripheral pattern were > 0 day in 11 and 4 cases, respectively. AE, acute exacerbation; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; AZP, azathioprine; BAL, bronchoalveolar lavage; CPA, cyclophosphamide; CPFE, combined pulmonary fibrosis and emphysema; CRP, C-reactive protein; CS, current smoker; CyA, cyclosporine A; ES, ex-smoker; FEV₁, forced expiratory volume in 1 second; FiO₂, fraction of inspired oxygen; FVC, forced vital capacity; DLco; diffusing capacity of carbon monoxide; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; NS, non-smoker; PaO₂, partial oxygen tension; SLB, surgical lung biopsy; SP-D, surfactant protein-D; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; ΔKL-6, increase in KL-6 at onset of acute exacerbation when compared with the stable state; ΔSP-D, increase in SP-D at onset of acute exacerbation when compared with the stable state; WBC, white blood cells

and a higher ΔKL-6/ST-KL-6 (Figure 1D). Wilcoxon test revealed the significant survival difference between the two groups (P<0.0001, Figure 1D). After adjustment for other prognostic factors, a diffuse or multifocal pattern with a lower ΔKL-6/ST-KL-6 was a significantly poor prognostic factor (Table 5), although a diffuse pattern alone was not. Similarly, none of the three patterns seen on HRCT were significant prognostic factors.

Our proposed classification of AE-IIP patients can predict the survival of AE-IPF (n=53) (Table 6) after

adjustment for other prognostic factors, although univariate analysis cannot show the significant survival difference (P=0.057, Wilcoxon test) (Figure 2). The classification can also predict survival AE-IIP patients who were diagnosed between 2011 and 2016 (n=31) (see Table S7).

Discussion

In this study, we demonstrated that AE-IIP patients with a multifocal HRCT pattern and lower ΔKL-6/ST-KL-6

Table 3 Prognostic factors in patients with AE-IIP (all patients): a univariate Cox proportional hazard regression analysis

Parameter	Univariate		
	HR	95% CI	P value
Age ^{#¶}	0.990	0.963–1.019	0.504
Male sex ^{#¶}	1.260	0.709–2.238	0.431
Smoking status, NS/CS or ES ^{#¶}	1.212	0.680–2.159	0.515
Diagnosis, IPF/non-IPF ^{#¶}	0.959	0.567–1.623	0.876
SLB or autopsy, yes/no [#]	0.928	0.560–1.536	0.771
LTOT before AE, yes/no ^{#¶}	2.122	1.277–3.526	0.004
PaO ₂ /FiO ₂ ratio, Torr	0.997	0.994–1.000	0.075
PaO ₂ /FiO ₂ ratio, Torr, ≤200 vs. >200 ^{#¶}	1.575	1.026–2.417	0.038
WBC/μL [#]	1.000	1.000–1.000	0.928
LDH, U/mL [#]	1.001	0.999–1.004	0.276
CRP, mg/dL [#]	0.981	0.949–1.015	0.271
IgG, ×10 mg/dL ^{#¶}	0.996	0.992–1.000	0.069
AE-KL-6, ×100 U/mL ^{#¶}	1.016	0.994–1.038	0.161
ΔKL-6, ×100 U/mL	1.014	0.969–1.061	0.539
ΔKL-6/ST-KL-6	0.950	0.660–1.367	0.782
ΔKL-6/ST-KL-6, ≤0.211 vs. >0.211 ^{#¶}	1.569	0.970–2.540	0.067
ST-KL-6, ×100 U/mL	1.013	0.990–1.036	0.272
AE-SP-D, ×10 ng/mL	1.007	1.001–1.013	0.021
ΔSP-D, ×10 ng/mL	1.006	0.998–1.015	0.157
ΔSP-D/ST-SP-D	1.013	0.863–1.188	0.876
ΔSP-D/ST-SP-D, ≤0.410 vs. >0.410 [#]	1.251	0.768–2.037	0.368
ST-SP-D, ×10 ng/mL ^{#¶}	1.018	1.003–1.032	0.017
HRCT, diffuse/non-diffuse	1.603	0.941–2.773	0.083

AE, acute exacerbation; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; CI, confidence interval; CRP, C-reactive protein; CS, current smoker; ES, ex-smoker; FiO₂, fraction of inspired oxygen; HR, hazard ratio; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; NS, non-smoker; PaO₂, partial oxygen tension; SLB, surgical lung biopsy; SP-D, surfactant protein-D; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; WBC, white blood cells; ΔKL-6, increase in KL-6 at onset of acute exacerbation when compared with the stable state; ΔSP-D, increase in SP-D at onset of acute exacerbation when compared with the stable state. According to the results of multicollinearity analysis (see Table S2) and Spearman's rank correlation test (see Table S3), 15 parameters were selected (¶) in Table 3. To avoid the multiplicity problem, the parameters of performed SLB or autopsy, WBC, CRP, LDH, and lower ΔSP-D/ST-SP-D with P value >0.20 were excluded. Age and sex were included because they are fundamental parameters. Using the remaining 10 parameters (¶), multivariate COX proportional hazard regression analysis with a stepwise selection procedure was performed to predict the survival of AE-IIPs in Table 4.

value have a worse prognosis than their counterparts with a higher ΔKL-6/ST-KL-6 after adjusting for other prognostic factors; however, the prognosis in both groups is similar if the HRCT pattern is diffuse or peripheral. A multifocal

pattern with a lower ΔKL-6/ST-KL-6 value might correspond histologically to a DAD pattern and that with a higher ΔKL-6/ST-KL-6 to an OP pattern. Therefore, we can divide AE-IIPs into two populations, i.e., according to

Table 4 Prognostic factors for AE-IIPs according to the HRCT pattern at the time of acute exacerbation: a multivariate Cox proportional hazard regression analysis

Parameter	HR	95% CI	P value
All patients			
ST-SP-D, $\times 10$ ng/mL	1.020	1.005–1.036	0.010
LTOT, yes vs. no	1.941	1.130–3.335	0.016
PaO ₂ /FiO ₂ ratio, Torr, ≤ 200 vs. >200	2.037	1.163–3.568	0.013
Peripheral pattern			
AE-KL-6, $\times 100$ U/mL	1.054	1.006–1.104	0.027
Multifocal pattern			
Δ KL-6/ST-KL-6 ≤ 0.211 vs. >0.211	2.760	1.304–5.841	0.008
PaO ₂ /FiO ₂ ratio, Torr, ≤ 200 vs. >200	2.611	1.199–5.684	0.016
Diffuse pattern			
ST-SP-D, $\times 10$ ng/mL	1.037	1.003–1.073	0.033

Multivariate analyses with a stepwise method were performed to predict the survival of all AE-IIP patients, i.e., AE-IIP patients with peripheral, multifocal and diffuse pattern HRCT using the parameters ([†]) shown in *Table 3*. AE, acute exacerbation; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; CI, confidence interval; CRP, C-reactive protein; CS, current smoker; ES, ex-smoker; FiO₂, fraction of inspired oxygen; HR, hazard ratio; HRCT, high-resolution computed tomography; IIPs, idiopathic interstitial pneumonias; KL-6, Krebs von den Lungen-6; LTOT, long-term oxygen therapy; NS, non-smoker; PaO₂, partial oxygen tension; SP-D, surfactant protein-D; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; Δ KL-6, increase in KL-6 at onset of acute exacerbation when compared with the stable state

Table 5 Adjusted prognostic significance of a proposed new classification for AE-IIPs* using the HRCT pattern and serum marker levels** for all AE-IIP patients (n=77)

Parameters	HR	95% CI	P value
Diffuse, multifocal, peripheral			0.258
Diffuse vs. peripheral	1.821	0.891–3.722	0.100
Multifocal vs. peripheral	1.392	0.723–2.682	0.322
Diffuse vs. non-diffuse	1.457	0.843–2.519	0.177
Diffuse or multifocal with Δ KL-6/ST-KL-6 ≤ 0.211 , vs. the others*	1.972	1.169–3.327	0.011

*Proposed new classification for AE-IIPs. **Prognostic significance of these three parameters was adjusted for other prognostic factors for all patients, including a PaO₂/FiO₂ ratio ≤ 200 , ST-SP-D, and long-term oxygen therapy, as shown in *Table 4*. HRCT, high-resolution computed tomography; AE, acute exacerbation; CI, confidence interval; FiO₂, fraction of inspired oxygen; HR, hazard ratio; IIP, idiopathic interstitial pneumonia; PaO₂, partial oxygen tension; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; Δ KL-6, increase in KL-6 at the onset of AE compared with that during the stable state

the possibility of DAD or OP, using the combined criteria of HRCT pattern and the Δ KL-6/ST-KL-6 value, given that the prognosis of the two populations is significantly different after adjusting for other prognostic factors.

The main histologic pattern of AE-IPF is DAD (2,6,26). Previous studies using SLB showed various frequencies of an OP pattern superimposed on a UIP pattern (27,28).

SLB-proven OP in AE-IPF was associated with better survival in both these reports. However, radiologic findings might be more important than histologic findings in general clinical settings when diagnosing AE-IPF and predicting patient survival because morphological overlaps between organizing DAD and OP (29) and sampling errors due to the patchy nature of acute lesions in AE-IPF (27) were

Table 6 Adjusted prognostic significance of a proposed new classification for AE-IIPs* using the HRCT pattern and serum marker levels for AE-IPF patients (n=53)

Parameter	HR	95% CI	P value
Prognostic factors for AE-IPF ^A			
Multivariate analysis with stepwise selection			
LTOT, yes vs. no	2.284	1.219–4.279	0.010
Smoking status, NS vs. CS or ES	2.780	1.148–6.728	0.023
IgG, ×10 mg/dL	0.990	0.984–0.997	0.004
Adjusted prognostic significance by parameters of Part A ^B			
Diffuse, multifocal, peripheral			0.171
Diffuse vs. peripheral	2.274	0.941–5.496	0.068
Multifocal vs. peripheral	1.613	0.806–3.231	0.177
Diffuse vs. non-diffuse	1.685	0.795–3.570	0.174
Diffuse or multifocal with Δ KL-6/ST-KL-6 \leq 0.211, vs. the others*	1.910	1.036–3.521	0.038

*Proposed new classification for AE-IIPs. ^APrognostic factors were evaluated by multivariate Cox proportional hazard regression analysis with stepwise selection procedure using parameters shown in Table 3 (^A). ^BThe prognostic significance of these 3 parameters was adjusted for other prognostic factors, including a smoking history (CS or ES), serum IgG, and LTOT, as shown in A). HRCT, high-resolution computed tomography; AE, acute exacerbation; CI, confidence interval; HR, hazard ratio; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LTOT, long term oxygen therapy; KL-6, Krebs von den Lungen-6; ST-KL-6, KL-6 during a stable state; Δ KL-6, increase in KL-6 at the onset of AE compared with that during the stable state; CS, current smoker; ES, ex-smoker; IgG, immunoglobulin G.

reported.

Akira *et al.* were the first to identify the importance of the HRCT pattern when predicting the prognosis of AE-IPF (4,14). Survival was poor in their patients with AE-IPF and a diffuse pattern, which typically corresponds with a pathologic pattern of DAD, and good in those with a peripheral pattern, which usually corresponds with a pathologic pattern of OP (4). There are reports for (30) and against (18) the importance of HRCT patterns in predicting the survival of AE-IPF patients. Silva *et al.* reported histological and radiological discrepancies (28). This may reflect demographic differences in patients with the multifocal AE-IPF pattern, as seen in our study.

In a retrospective study on 58 AE-IPF patients, Akira *et al.* found serial changes from multifocal to diffuse pattern (14). They obtained autopsy specimens from 20 diffuse patients and 3 multifocal patients, all of which showed DAD with UIP (14). However, in an earlier study by the same researchers noted that 3 of 6 patients with AE-IPF and a multifocal pattern improved after high-dose corticosteroid therapy (4). Patients with corticosteroid-responsive AE-IIP and a multifocal pattern might show a pathologic OP pattern. We suspect that patients with a multifocal

pattern constitute a heterogeneous group, possibly with pathologic findings of OP and DAD (4,14). This hypothesis is consistent with the radiologic observation that both cryptogenic OP (31) and acute interstitial pneumonia (32) may show a patchy distribution.

Patients with acute respiratory distress syndrome (ARDS) usually show a DAD histologic pattern and mildly elevated serum KL-6 levels (33) that gradually increase as the illness progresses (34). Nathani *et al.* (33) reported a median KL-6 value of 422 U/mL at onset of ARDS and 588 U/mL 3 days later. Kondo *et al.* reported similar KL-6 levels at the onset of ARDS (34). We suggest that these values might be smaller than expected. However, peak serum KL-6 levels increased to a mean of 1,060.8 U/mL in non-survivors (34) and the elevation of serum KL-6 levels from the baseline to the peak was about 500 U/mL. The increase in KL-6 among non-survivors of ARDS is similar to the median Δ KL-6 value (550 U/mL) in our diffuse AE-IIP patients, whose prognosis was mostly poor. We could not find any other studies that measured Δ KL-6 levels in AE-IIP patients. However, Yokoyama *et al.* reported an elevated KL-6 value at the time of AE-IIP diagnosis and its subsequent increase, especially in patients who were non-

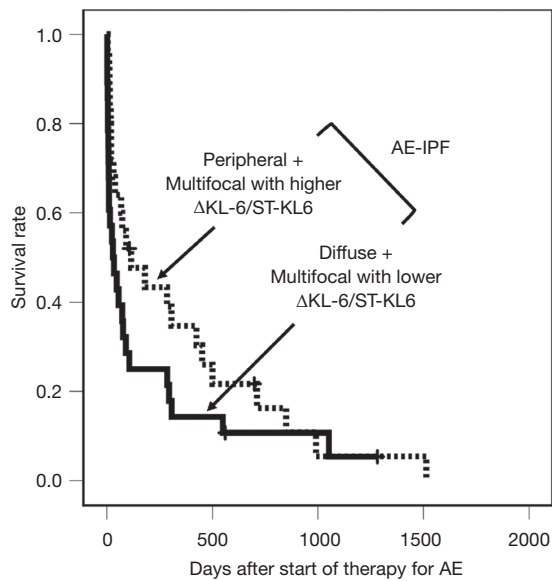


Figure 2 Kaplan-Meier curves showing that survival of patients with AE-IPF and the diffuse pattern or multifocal pattern with $\Delta\text{KL-6/ST-KL-6} \leq 0.211$ ($n=28$, thick line; MST 29 days) tended to be worse than that of those with the peripheral pattern or multifocal pattern and $\Delta\text{KL-6/ST-KL-6} > 0.211$ ($n=25$, thin line; MST 68 days; $P=0.057$, Wilcoxon test). AE, acute exacerbation; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; MST, median survival time; ST-KL-6, KL-6 during a stable state; $\Delta\text{KL-6}$, increase in KL-6 at the onset of AE compared with that during the stable state.

responsive to steroids (35).

Akira *et al.* reported that patients with multifocal patterns may show a pathologic DAD pattern or may progress to a diffuse pattern (14). If a multifocal pattern with a lower $\Delta\text{KL-6/ST-KL-6}$ value indicated an early diffuse pattern, the $\Delta\text{KL-6}$ and $\Delta\text{KL-6/ST-KL-6}$ values in the diffuse pattern would be expected to be significantly larger than those in a multifocal pattern with a lower $\Delta\text{KL-6/ST-KL-6}$, because serum KL-6 levels gradually increase with progression of AE-IIP, and this hypothesis would be consistent with our data (see *Table S5*). Therefore, a multifocal pattern with a lower $\Delta\text{KL-6/ST-KL-6}$ value might indicate an early diffuse pattern and suggest a pathologic DAD pattern. The median $\Delta\text{KL-6}$ value in AE-IIP with a multifocal pattern and a lower $\Delta\text{KL-6/ST-KL-6}$ was 8 U/mL; this figure is consistent with that of previous reports of serum KL-6 levels at the time of onset of ARDS being almost within the normal range (33,34).

In our study, a higher AE-KL-6 in AE-IIPs with a

peripheral pattern suggested a poor prognosis. Okada *et al.* (36) reported that cryptogenic OP with an elevated KL-6 level was suggestive of the presence of traction bronchiectasis and distortion. We found that a higher AE-KL-6 value was a significantly poor prognostic factor for peripheral pattern AE-IIP, which is consistent with Okada *et al.*'s report (36). $\Delta\text{SP-D/ST-SP-D}$ and $\Delta\text{SP-D}$ of AE-IIPs with a multifocal pattern and higher $\Delta\text{KL-6/ST-KL-6}$, reflecting newly appeared acute lesions, was significantly higher than that of AE-IIPs with a multifocal pattern and a lower $\Delta\text{KL-6/ST-KL-6}$ (both $P=0.001$; *Table S4*). These results are consistent with the positive correlation found between serum KL-6 and SP-D levels in patients with cryptogenic OP reported by Yamagishi *et al.* (37) and the hypothesis that pathologic OP has a multifocal pattern with higher $\Delta\text{KL-6/ST-KL-6}$.

SP-D is produced by hyperplastic epithelial cells (38). Patients with IIP and a higher ST-SP-D may have more such cells that are vulnerable to extensive injury by various mechanisms, which would put them at increased risk of a severe AE. This hypothesis is consistent with our finding that a higher ST-SP-D in patients with the diffuse pattern can predict a poor prognosis. ST-SP-D of multifocal pattern and lower $\Delta\text{KL-6/ST-KL-6}$, suggesting histological DAD, tended to be higher than that of multifocal pattern and higher $\Delta\text{KL-6/ST-KL-6}$. Hence, higher ST-SP-D might suggest presence of increased baseline alveolar injury and future occurrence of DAD-type AE.

This study has some limitations. First, it had a retrospective single-center design and included a limited number of patients. Therefore, our results and our proposed classification need to be validated in cohort studies in the future; however, the classification was also a significant prognostic factor for subgroups of our subjects; AE-IPF and AE-IIP diagnosed between 2011 and 2016. Second, the interval between measurements of serum markers in the stable state and those obtained at the time of AE varied from patient to patient; however, in about 80% of cases, the interval was less than 3 months. Third, the link between our proposed classification and pathologic findings was not confirmed by the findings on SLB. Fourth, KL-6 cannot be measured in all countries, so use of more universally available clinical markers to classify AE-IIP with a multifocal pattern would be expected. Fifth, the possibility that we included AE patients with a disease other than an IIP cannot be excluded because most non-IPF IIP cases were diagnosed without SLB. However, the autoantibody positivity rate and HRCT pattern of the underlying IIPs

(UIP, possible UIP, inconsistent with UIP) were not significantly different between the three HRCT patterns at the time of AE (Table 2). Furthermore, Suzuki *et al.* reported that the prognosis of AE-IPF was similar to that of AE of non-IPF ILDs (39) and that the prognosis of AEs of all types of ILDs could be evaluated together.

Conclusions

Combining the HRCT pattern and the Δ KL-6/ST-KL-6 value can improve our ability to predict the survival of AE-IIP patients. We hope that our classification will be evaluated by other investigators in the future.

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Footnote

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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). This retrospective study was approved by the institutional review board of Kinki-Chuo Chest Medical Center (approval number 650, acceptance date: July 23, 2018). The need for patient consent was waived in view of the retrospective nature of the study and the anonymity of the data.

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1 Between 2004 and 2016, we have diagnosed 113 patients
 2 with AE-IIP according to the diagnostic criteria of the
 3 Japanese Respiratory Society (JRS). AE-IIP patients, whose
 4 serum levels of KL-6 and SP-D was evaluated both at the
 5 onset of AE and within 6 months before the onset of AE,
 6 was selected and 77 patients were enrolled in this study.
 7 High-resolution computed tomography (HRCT) films
 8 at the onset of AE was classified into 3 patterns (diffuse,
 9 multifocal and peripheral) according to the criteria of
 10 Akira (14).

12 Diagnostic criteria of acute exacerbation (AE) in 13 Idiopathic interstitial pneumonias (IIPs)

14 AE-IIPs were diagnosed according to the modified AE-IPF
 15 criteria of the Japanese Respiratory Society (25). (I) Within
 16 one month, the following three conditions were all satisfied
 17 during the disease progression of IIPs: (i) progressively
 18 worsening dyspnea; (ii) new ground-glass attenuation (GGA)

20 evident in HRCT superimposed on a background reticular
 21 or honeycomb pattern; and (iii) a reduction in PaO₂ at rest
 22 of more than 10 Torr relative to previous measurements.
 23 (II) Exclusion of obvious causes of acutely impaired
 24 respiratory function, such as infection, pneumothorax,
 25 cancer, pulmonary embolism, or congestive cardiac failure.
 26 Apparent infections were carefully excluded by measuring
 27 antibodies for *Mycoplasma pneumoniae* and *Chlamydia*
 28 *pneumoniae* in paired sera, β-D glucan, Cytomegalovirus
 29 antigen, and bacterial cultures of blood and sputum.

30 We evaluated the HRCT pattern at the onset of AE
 31 according to the classification of Akira (14). For a diffuse
 32 pattern (*Figure S2A*), the ground glass attenuation (GGA)
 33 was homogeneously distributed. For the multifocal pattern
 34 (*Figure S2B*), parenchymal opacification was apparent in
 35 both the central and peripheral regions. For the peripheral
 36 pattern (*Figure S2C*), parenchymal opacification appeared
 37 in the inner peripheral region adjacent to pre-existing
 38 subpleural honeycombing or peripheral interstitial opacity.

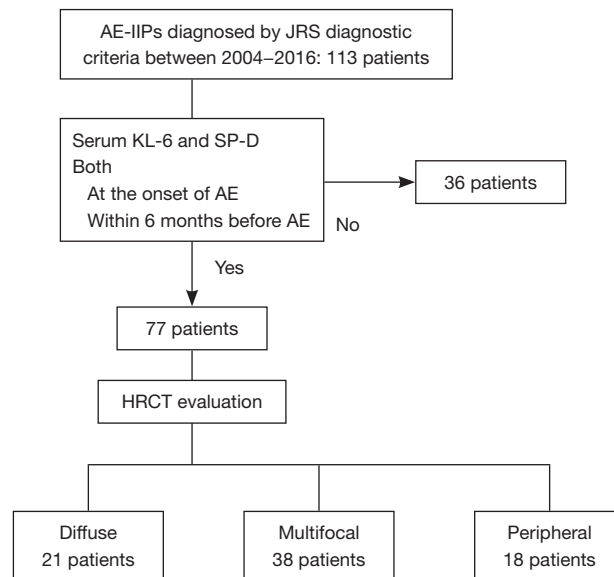


Figure S1 Patients flow in the present study of acute exacerbation (AE) in idiopathic interstitial pneumonias (IIPs).

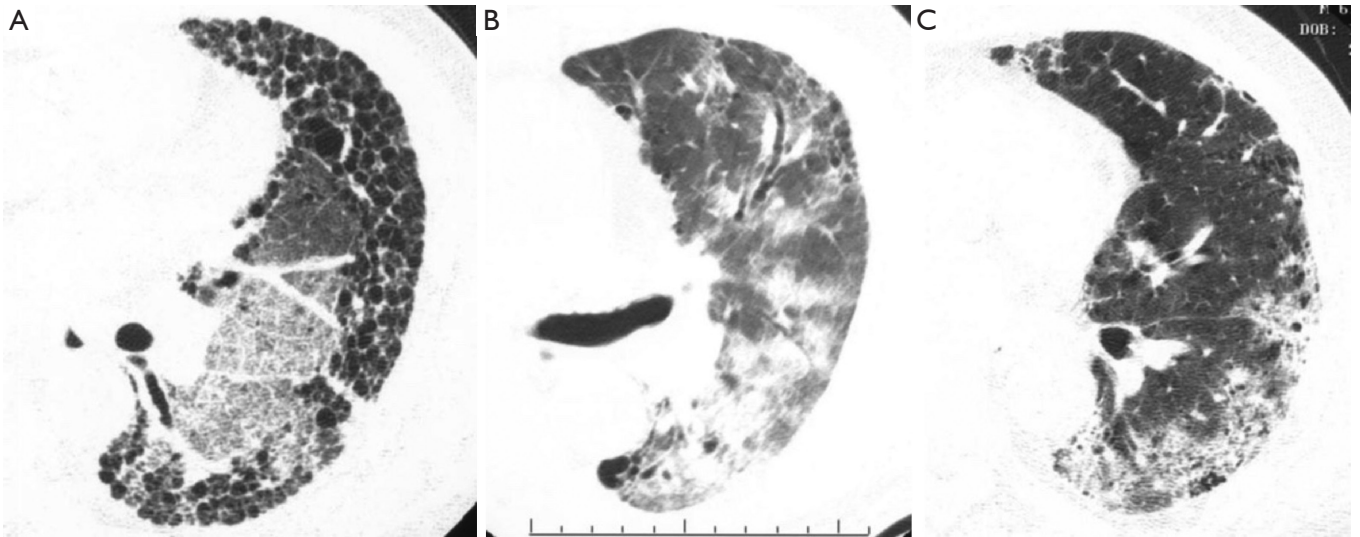


Figure S2 High-resolution computed tomography pattern depicted at the onset of acute exacerbation. Description of data: three high-resolution computed tomography patterns are seen at the onset of acute exacerbation. Examples of the peripheral, multifocal, and diffuse patterns are provided.

Table S1 Patient demographics

Parameters	IPF (n=53)	Non-IPF-IIP (n=24)	P value
Before AE			
Age, years	71 (67–75)	72.5 (63.5–77.8)	0.601
Sex, male/female	45/8	15/9	0.039
Smoking, NS/CS or EX	9/44	10/14	0.026
Smoking, NS/Ex/CS	9/37/7	10/11/3	0.071
Smoking pack index	44 (20–58.5)	14 (0–35.5)	0.002
HRCT, UIP/possible/inconsistent	44/5/4	1**/8/15	<0.001
Combined pulmonary fibrosis and emphysema on HRCT	15/38	4/20	0.394
Bronchoscopy at the diagnosis of underlying IIPs, yes/no	40/13	18/6	0.175
Lymphocytes in BAL, %	6.6 (3.8–12.7)	14.9 (7.9–30.1)	0.027
Neutrophils in BAL, %	3.5 (1.4–10.1)	2.8 (1.7–5.1)	0.573
Eosinophils in BAL, %	2.2 (0.8–5.2)	1.3 (0.2–3.4)	0.165
%FVC [‡]	70.8 (57.4–86.2)	69.3 (56.0–91.3)	0.808
FEV1/FVC [‡] , %	84.5 (78.2–88.8)	88.0 (79.8–90.1)	0.198
%DLCO [§]	45.6 (37.6–59.0)	56.0 (39.5–62.6)	0.340
SLB or autopsy, yes/no	25/28	1/23	<0.001
Autoantibody, yes/no	11/42	5/19	1.000
PSL before AE, yes/no	12/41	9/15	0.269
Pirfenidone, yes/no	3/50	4/20	0.195
LTOT, yes/no	22/31	9/15	0.806
ST-KL-6, U/mL	1,130 (710–1,830)	1,240 (700–2,380)	0.492
ST-SP-D, ng/mL	187 (109–296)	164 (132–226)	0.832
DM, yes/no	20/33	5/19	0.192
OMI or angina, yes/no	5/48	3/21	0.699
Cerebral infarction, yes/no	4/49	1/23	1.000
At the onset of AE			
PaO ₂ /FIO ₂ ratio, Torr	149 (81–223)	182 (91–236)	0.987
PaO ₂ /FIO ₂ ratio ≤200/>200	37/16	16/8	0.796
PaO ₂ /FIO ₂ ratio, ≤100/>100 & ≤200/>200	16/21/16	6/10/8	0.905
WBC/μL	11,500 (8,050–14,050)	9,400 (6,700–10,500)	0.016
CRP, mg/dL	11.1 (4.5–14.7)	10.7 (4.2–13.3)	0.382
IgG, mg/dL	1,570 (1,160–1,960)	1,410 (1,010–1,760)	0.165
AE-KL-6, U/mL	1,540 (930–2,080)	1,890 (1,330–2,840)	0.054
AE-SP-D, ng/mL	249 (170–487)	259 (175–396)	0.808
HRCT, diffuse/non-diffuse	11/42	10/14	0.095
HRCT, diffuse/multifocal/peripheral	11/26/16	10/12/2	0.053
Intravenous high-dose methylprednisolone, yes/no	53/0	23/1	0.312
Initial dose of PSL, mg/Kg	0.914 (0.684–0.980)	0.932 (0.715–1.000)	0.575
Initial dose of PSL, <0.6 mg/kg/≥0.6 mg/kg	12/41	4/20	0.763
Immunosuppressant, yes/no	27/26	12/12	1.000
CPA pulse, yes/no	7/46	6/18	0.209
AZP/CyA	13/9	1/5	0.165
PPV within a month, yes/no	22/31	6/18	0.127
NPPV/IPPV [§]	18/6	5/1	0.255
PMX-DHP therapy [†] , yes/no	14/39	3/21	0.142
Pirfenidone, yes/no	2/51	4/20	0.072
Interval from the symptomatic onset of AE to treatment, days	5 (2–9)	4 (1–5)	0.052
Interval of serum marker measurement*, days	54 (35–89)	45 (30–70)	0.271

AE, acute exacerbation; IIPs, idiopathic interstitial pneumonias; CS, current smoker; EX, ex-smoker; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusing capacity of carbon monoxide; NS, non-smoker; IPF, idiopathic pulmonary fibrosis; Non-IPF, Non-IPF IIPs, LTOT, long-term oxygen therapy; KL-6, Krebs von den Lungen-6; ST-KL-6, KL-6 during a stable state; ST-SP-D; SP-D, surfactant protein-D; ST-SP-D, SP-D during a stable state; DM, diabetes mellitus; OMI, old myocardial infarction; PaO₂, partial oxygen tension; FiO₂, fraction of oxygen tension; WBC, white blood cell; IgG, immunoglobulin G; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; HRCT, high-resolution computed tomography; CRP, C-reactive protein; NE, not evaluable; PSL, prednisolone; CPA, cyclophosphamide; AZP, azathioprine; CyA, cyclosporine A; PPV, positive pressure ventilation; NPPV, non-invasive positive pressure ventilation; IPPV, invasive positive pressure ventilation; PMX-DHP therapy, hemoperfusion therapy with polymyxin B-immobilized fiber column. Frequency or Median (IQR) is presented for each parameter. Parameters in IPF cases and Non-IPF cases were compared using the Fisher's exact test or the Mann-Whitney U test. [‡]Spirometer was performed in 50 IPF cases and in 23 non-IPF cases. [§]DLco was performed in 44 IPF cases and in 21 non-IPF cases. [§]Cases treated with both NPPV and IPPV were classified as IPPV-treated cases. [†]Patients who received PMX-DHP therapy for the second AE were not included in the PMX-DHP therapy-treated cases. *Interval of serum marker measurement from stable state to onset of AE. **This case is SLB-proven nonspecific interstitial pneumonia; however, HRCT pattern at the diagnosis of AE, was UIP pattern with honeycombing.

Table S2 Multicollinearity evaluation: correlation of regression coefficient calculated using parameters in *Table 3* except for HRCT pattern by multivariate Cox proportional hazard regression analysis

No.	Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	Age	B																					
2	Male sex	X	B																				
3	Smoking status, NS/CS or ES	X	X	B																			
4	Diagnosis, IPF/non-IPF	X	X	X	B																		
5	SLB or autopsy, yes/no	X	X	X	X	B																	
6	LTOT before AE, yes/no	X	X	X	X	X	B																
7	PaO ₂ /FiO ₂ ratio, Torr	X	X	X	X	X	X	B															
8	PaO ₂ /FiO ₂ ratio, Torr, ≤200 vs. >200	X	X	X	X	X	X	X	B														
9	WBC/μL	X	X	X	X	X	X	X	X	B													
10	LDH, U/mL	X	X	X	X	X	X	X	X	X	B												
11	CRP, mg/dL	X	X	X	X	X	X	X	X	X	X	B											
12	IgG, ×10 mg/dL	X	X	X	X	X	X	X	X	X	X	X	B										
13	AE-KL-6, ×100 U/mL	X	X	X	X	X	X	X	X	X	X	X	X	B									
14	ΔKL-6, ×100 U/mL	X	X	X	X	X	X	X	X	X	X	X	X	@	B								
15	ΔKL-6/ST-KL-6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	B							
16	ΔKL-6/ST-KL-6, ≤0.211 vs. >0.211	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	B						
17	ST-KL-6, ×100 U/mL	X	X	X	X	X	X	X	X	X	X	X	X	@	@	X	X	B					
18	AE-SP-D, ×10 ng/mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	B				
19	ΔSP-D, ×10 ng/mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	@	B			
20	ΔSP-D/ST-SP-D	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	B		
21	ΔSP-D/ST-SP-D, ≤0.410 vs. >0.410	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	B	
22	ST-SP-D, ×10 ng/mL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	@	@	X	X	B
	Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

B: between same parameters; CC: correlation coefficient of two parameters. X: absolute value of CC<0.5, @: 0.7≤ absolute value of CC, all the other parameters were included in X. AE, acute exacerbation; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; CI, confidence interval' CRP, C-reactive protein; CS, current smoker; ES, ex-smoker; FiO₂, fraction of inspired oxygen; HR, hazard ratio; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; NS, non-smoker; PaO₂, partial oxygen tension; SLB, surgical lung biopsy; SP-D, surfactant protein-D; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; WBC, white blood cells; ΔKL-6, increase in KL-6 at onset of acute exacerbation when compared with the stable state; ΔSP-D, increase in SP-D at onset of acute exacerbation when compared with the stable state.

Table S3 Correlation between parameters in *Table 3* except for HRCT pattern by Spearman's rank correlation

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1: Age	B																					
2: Male sex	O	B																				
3: Smoking status, NS/CS or ES	O	O	B																			
4: Diagnosis, IPF/non-IPF	X	O	O	B																		
5: SLB or autopsy, yes/no	X	X	X	O	B																	
6: LTOT before AE, yes/no	X	X	X	X	X	B																
7: PaO ₂ /FiO ₂ ratio, Torr	X	X	X	X	X	O	B															
8: PaO ₂ /FiO ₂ ratio, Torr, ≤200 vs. >200	X	X	X	X	X	X	@	B														
9: WBC/μL	X	X	X	O	X	X	O	X	B													
10: LDH, U/mL	X	X	X	X	X	X	X	X	O	B												
11: CRP, mg/dL	X	X	X	X	X	X	O	O	X	X	B											
12: IgG, ×10 mg/dL	X	X	X	X	X	X	X	X	X	O	X	B										
13: AE-KL-6, ×100 U/mL	X	X	X	X	X	O	O	X	X	O	O	X	B									
14: ΔKL-6, ×100 U/mL	X	X	X	O	X	X	X	X	X	O	X	X	O	B								
15: ΔKL-6/ST-KL-6	X	X	X	X	X	O	X	X	X	O	X	X	X	@	B							
16: ΔKL-6/ST-KL-6, ≤0.211 vs. >0.211	X	X	X	X	X	X	X	X	X	O	X	X	X	O	@	B						
17: ST-KL-6, ×100 U/mL	X	X	X	X	X	O	X	X	X	X	X	X	@	X	O	X	B					
18: AE-SP-D, ×10 ng/mL	X	X	X	X	X	O	X	X	X	O	X	X	O	O	O	X	X	B				
19: ΔSP-D, ×10 ng/mL	X	X	X	X	X	X	X	X	O	O	X	X	X	O	O	X	X	@	B			
20: ΔSP-D/ST-SP-D	X	X	X	X	X	X	X	O	O	O	X	X	X	O	O	O	O	O	@	B		
21: ΔSP-D/ST-SP-D, ≤0.410 vs. >0.410	X	X	X	X	X	X	X	O	O	O	X	X	X	O	O	X	X	O	O	@	B	
22: ST-SP-D, ×10 ng/mL	O	X	X	X	X	O	X	X	X	X	X	X	O	X	O	O	O	O	X	O	O	B
Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

O: rho is less than 0.70 with P value<0.05. @: rho is more than 0.70 with p-value <0.05. X: non-significant correlation. B: between the same parameters. AE, acute exacerbation; AE-KL-6, KL-6 at onset of acute exacerbation; AE-SP-D, SP-D at onset of acute exacerbation; CI, confidence interval' CRP, C-reactive protein; CS, current smoker; ES, ex-smoker; FiO₂, fraction of inspired oxygen; HR, hazard ratio; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; NS, non-smoker; PaO₂, partial oxygen tension; SLB, surgical lung biopsy; SP-D, surfactant protein-D; ST-KL-6, KL-6 during a stable state; ST-SP-D, SP-D during a stable state; WBC, white blood cells; ΔKL-6, increase in KL-6 at onset of acute exacerbation when compared with the stable state; ΔSP-D, increase in SP-D at onset of acute exacerbation when compared with the stable state.

Table S4 Comparison of clinical parameters between patients with AE-IIP and a multifocal pattern with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$ and those with a multifocal pattern and $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$

Parameters	Multifocal with $\Delta\text{KL-6}/\text{ST-KL-6} > 0.211$	Multifocal with $\Delta\text{KL-6}/\text{ST-KL-6} \leq 0.211$	P value [§]
Number of cases	16	22	
Before AE			
Age, years	72.5 (69.0–78.75)	72.0 (65.0–74.25)	0.258
Sex, male/female [¶]	8/8	19/3	0.028
IPF/non-IPF-IIP [¶]	9/7	17/5	0.289
HRCT UIP/possible/inconsistent	9/1/6	15/3/4	0.481
CPFE on HRCT, yes/no	4/12	7/15	0.729
Bronchoscopy, yes/no	12/4	17/5	1.000
Lymphocyte in BAL, %	18.0 (6.2–27.7)	11.8 (5.6–13.8)	0.107
Neutrophils in BAL, %	3.0 (1.9–6.4)	3.8 (1.4–12.6)	0.777
Eosinophils in BAL, %	1.4 (0.6–3.6)	1.6 (0.7–4.1)	0.744
%FVC	73.5 (65.8–89.9)*	61.2 (53.0–76.8)**	0.086
FEV1/FVC, %	79.8 (74.7–86.0)*	85.0 (81.9–89.7)**	0.045
%DLco	52.6 (29.3–60.0)*	43.6 (36.4–60.3)**	0.823
SLB or autopsy, yes/no	5/11	7/15	1.000
Smoking status, NS/CS or ES	5/11	6/16	1.000
Smoking status, NS/ES/CS	5/8/3	6/14/2	0.653
Smoking pack index	22.5 (0–44.7)	47.5 (12.7–66.7)	0.089
LTOT, yes/no	3/13	12/10	0.043
Autoantibody, yes/no	4/12	5/17	1.000
Prednisolone, yes/no	4/12	7/15	0.729
Immunosuppressants, yes/no	4/12	5/17	1.000
At the onset of AE [#]			
PaO ₂ /FIO ₂ ratio, Torr [¶]	225 (101–274)	144 (68–198)	0.033
PaO ₂ /FIO ₂ ratio $\leq 200 / > 200$ [¶]	7/9	17/5	0.047
WBC/ μL [¶]	9,100 (6,700–12,700)	8,000 (6,800–10,000)	0.388
LDH, U/mL [¶]	387 (288–438)	333 (278–363)	0.101
CRP, mg/dL	5.4 (3.5–14.5)	11.4 (5.9–13.3)	0.223
IgG, x100 mg/dL	14.2 (10.6–17.8)	17.0 (12.9–19.8)	0.147
AE-KL-6, U/L	1760 (1150–2180)	1,590 (910–2520)	0.872
ST-KL-6, U/mL	1130 (700–1600)	1,490 (860–2,460)	0.073
$\Delta\text{KL-6}$, U/mL [¶]	568 (421–786)	8 (-110–330)	0.001
$\Delta\text{KL-6}/\text{ST-KL-6}$ [¶]	0.501 (0.423–0.594)	0.053 (-0.114–0.135)	0.001
$\Delta\text{KL-6}/\text{ST-KL-6}$, $\leq 0.211 / > 0.211$ [¶]	0/16	22/0	<0.001
AE-SP-D, ng/mL [¶]	288 (172–434)	220 (118–274)	0.108
ST-SP-D, ng/mL	147.9 (94.3–201.3)	198 (117–255)	0.069
$\Delta\text{SP-D}$, ng/mL [¶]	178 (58–259)	21 (-47–52)	0.001
$\Delta\text{SP-D}/\text{ST-SP-D}$ [¶]	0.821 (0.423–1.942)	0.091 (-0.188–0.291)	0.001
$\Delta\text{SP-D}/\text{ST-SP-D}$, $\leq 0.410 / > 0.410$ [¶]	3/13	19/3	<0.001
Interval of serum marker measurement, days [†]	46 (31–71)	47 (28–97)	0.759
Interval from the symptom onset of AE to treatment, days	5 (4–8)	4 (2–9)	0.413

Definition of abbreviations: AE, acute exacerbation; IIPs, idiopathic interstitial pneumonias; KL-6, Krebs von den Lungen-6; AE-KL-6, KL-6 at the onset of AE; ST-KL-6, KL-6 at stable state; $\Delta\text{KL-6}$, increase in KL-6 at the onset of AE as compared with at stable state. IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; NS, non-smoker; CS, current smoker; ES, ex-smoker; LTOT, long-term oxygen therapy; PaO₂, partial oxygen tension; FIO₂, fraction of oxygen tension; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgG, immunoglobulin G. [§]Categorical data was compared with Fisher's exact test. Continuous variables were presented as median and IQR, and compared with Mann-Whitney U test. [#]Treatment including initial dose of prednisolone, frequency of administration of immunosuppressants, soluble thrombomodulin and anti-fibrotic drugs, PMX-DHP therapy, positive pressure ventilation within one month from the onset of AE for AE-IIPs with each HRCT pattern was not significantly different by Mann-Whitney U test or Fisher's exact test. *Spirometry and DLco was performed in 15 cases. **Spirometry was performed in 22 cases and DLco in 17 cases. [†]Interval of serum marker measurement from stable state to onset of AE. [¶]Distribution and median of the parameters were significantly different among diffuse, peripheral, multifocal with higher $\Delta\text{KL-6}/\text{ST-KL-6}$, and multifocal with lower $\Delta\text{KL-6}/\text{ST-KL-6}$ by Fisher's exact test and Krsukal-Wallis test, respectively.

Table S5 Comparison of clinical parameters between patients with AE-IIP and a diffuse pattern and those with a multifocal pattern and Δ KL-6/ST-KL-6 ≤ 0.211

Parameters	Diffuse	Multifocal with Δ KL-6/ST-KL-6 ≤ 0.211	P value [§]
Number of cases	21	22	
Before AE			
Age, years	72.0 (65.0–78.5)	72.0 (65.0–74.25)	0.342
Sex, male/female [¶]	16/5	19/3	0.457
IPF/non-IPF-IIP [¶]	11/10	17/5	0.116
HRCT UIP/possible/inconsistent	9/7/5	15/3/4	0.230
CPFE on HRCT, yes/no	2/19	7/15	0.132
Bronchoscopy, yes/no	17/4	17/5	1.000
Lymphocyte in BAL, %	7.0 (3.3–18.4)	11.8 (5.6–13.8)	0.540
Neutrophils in BAL, %	2.6 (1.2–7.4)	3.8 (1.4–12.6)	0.474
Eosinophils in BAL, %	3.0 (1.2–5.5)	1.6 (0.7–4.1)	0.322
%FVC	70.6 (59.3–88.3)*	61.2 (53.0–76.8)**	0.222
FEV1/FVC, %	88.5 (80.6–90.1)*	85.0 (81.9–89.7)**	0.900
%DLco	54.8 (35.6–64.9)*	43.6 (36.4–60.3)**	0.454
SLB or autopsy, yes/no	6/15	7/15	1.000
Smoking status, NS/CS or ES	6/15	6/16	1.000
Smoking status, NS/ES/CS	6/14/1	6/14/2	1.000
Smoking pack index	15 (0–53)	47.5 (12.7–66.7)	0.193
LTOT, yes/no	10/11	12/10	0.763
Autoantibody, yes/no	3/18	5/17	0.698
Prednisolone, yes/no	6/15	7/15	1.000
Immunosuppressants, yes/no	5/16	5/17	1.000
At the onset of AE [#]			
PaO ₂ /FIO ₂ ratio, Torr [¶]	121 (66–179)	144 (68–198)	0.395
PaO ₂ /FIO ₂ ratio [¶] ≤ 200 / >200	18/3	17/5	0.698
WBC/ μ L [¶]	12,400 (10,200–15,100)	8,000 (6,800–10,000)	<0.0001
LDH, U/mL [¶]	400 (336–433)	333 (278–363)	0.003
CRP, mg/dL	12.3 (8.4–15.1)	11.4 (5.9–13.3)	0.395
IgG, $\times 100$ mg/dL	13.9 (10.2–17.2)	17.0 (12.9–19.8)	0.159
AE-KL-6, U/L	1,868 (1,443–2,322)	1,590 (910–2520)	0.430
ST-KL-6, U/mL	1,210 (671–2,175)	1,490 (860–2,460)	0.331
Δ KL-6, U/mL [¶]	550 (139–1,069)	8 (–110–330)	0.001
Δ KL-6/ST-KL-6 [¶]	0.230 (0.091–1.346)	0.053 (–0.114–0.135)	0.001
Δ KL-6/ST-KL-6, ≤ 0.211 / >0.211 [¶]	9/12	22/0	<0.0001
AE-SP-D, ng/mL [¶]	411 (231–587)	220 (118–274)	0.003
ST-SP-D, ng/mL	181 (123–335)	198 (117–255)	0.913
Δ SP-D, ng/mL [¶]	207 (42–297)	21 (–47–52)	0.001
Δ SP-D/ST-SP-D [¶]	0.836 (0.241–2.138)	0.091 (–0.188–0.291)	0.001
Δ SP-D/ST-SP-D, ≤ 0.410 / >0.410 [¶]	6/15	19/3	0.001
Interval of serum marker measurement, days [†]	69 (40–106)	47 (28–97)	0.234
Interval from the symptom onset of AE to treatment, days	3 (1–6)	2 (4–9)	0.459

Definition of abbreviations: AE, acute exacerbation; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; NS, non-smoker; CS, current smoker; ES, ex-smoker; LTOT, long-term oxygen therapy; PaO₂, partial oxygen tension; FIO₂, fraction of oxygen tension; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgG, immunoglobulin G; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; AE-KL-6 (or SP-D), KL-6 (or SP-D) at the onset of acute exacerbation; ST-KL-6 (or SP-D), KL-6 (or SP-D) at stable state; Δ KL-6 (or SP-D), increase in KL-6 (or SP-D) at the onset of acute exacerbation as compared with at stable state. [§]Categorical data was compared with Fisher's exact test. Continuous variables were presented as median and IQR, and compared with Mann-Whitney U test. [#]Treatment including initial dose of prednisolone, frequency of administration of immunosuppressants, soluble thrombomodulin and anti-fibrotic drugs, PMX-DHP therapy, positive pressure ventilation within one month from the onset of AE for AE-IIPs with each HRCT pattern was not significantly different by Wilcoxon rank sum test or Fisher's exact test. *Spirometry was performed in 20 cases and DLco in 17 cases. **Spirometry was performed in 22 cases and DLco in 17 cases. [†]Interval of serum marker measurement from stable state to onset of AE. [¶]Distribution and median of the parameters were significantly different among diffuse, peripheral, multifocal with higher Δ KL-6/ST-KL-6, and multifocal with lower Δ KL-6/ST-KL-6 by Fisher's exact test and Krsukal-Wallis test, respectively.

Table S6 Comparison of clinical parameters between patients with AE-IIP and a multifocal pattern with Δ KL-6/ST-KL-6 >0.211 and those with a peripheral pattern

Parameters	Multifocal with Δ KL-6/ST-KL-6 >0.211	Peripheral	P-value [§]
Number of cases	16	18	
Before AE			
Age, years	72.5 (69.0–78.75)	68.5 (65.0–74.3)	0.117
Sex, male/female [¶]	8/8	17/1	0.006
IPF/non-IPF-IIP [¶]	9/7	16/2	0.052
HRCT UIP/possible/inconsistent	9/1/6	12/2/4	0.578
CPFE on HRCT, yes/no	4/12	6/12	0.715
Bronchoscopy, yes/no	12/4	12/6	0.715
Lymphocyte in BAL, %	18.0 (6.2–27.7)	6.2 (3.3–11.4)	0.012
Neutrophils in BAL, %	3.0 (1.9–6.4)	4.4 (2.1–6.9)	0.590
Eosinophils in BAL, %	1.4 (0.6–3.6)	1.95 (1.0–3.4)	0.630
%FVC	73.5 (65.8–89.9)*	78.1 (52.4–95.4)**	0.922
FEV1/FVC, %	79.8 (74.7–86.0)*	86.1 (74.1–88.9)**	0.401
%DLco	52.6 (29.3–60.0)*	50.3 (39.2–59.6)**	1.000
SLB or autopsy, yes/no	5/11	8/10	0.497
Smoking status, NS/CS or ES	5/11	2/16	0.214
Smoking status, NS/ES/CS	5/8/3	2/12/4	0.408
Smoking pack index	22.5 (0–44.7)	33 (23–51)	0.117
LTOT, yes/no	3/13	6/12	0.448
Autoantibody, yes/no	4/12	4/14	1.000
Prednisolone, yes/no	4/12	4/14	1.000
Immunosuppressants, yes/no	4/12	2/16	1.000
At the onset of AE [#]			
PaO ₂ /FIO ₂ ratio, Torr [¶]	225 (101–274)	186 (131–222)	0.330
PaO ₂ /FIO ₂ ratio ≤ 200 / >200 [¶]	7/9	11/7	0.492
WBC/ μ L [¶]	9,100 (6,700–12,700)	10,750 (8,075–13,275)	0.330
LDH, U/mL [¶]	387 (288–438)	342.0 (264.5–391.0)	0.281
CRP, mg/dL	5.4 (3.5–14.5)	10.6 (3.3–14.1)	0.646
IgG, x100 mg/dL	14.2 (10.6–17.8)	14.8 (10.2–19.9)	0.669
AE-KL-6, U/L	1,760 (1,150–2,180)	1,150 (921–1,839)	0.211
ST-KL-6, U/mL	1,130 (700–1,600)	1,170 (467–1,688)	0.986
Δ KL-6, U/mL [¶]	568 (421–786)	235 (19–513)	0.014
Δ KL-6/ST-KL-6 [¶]	0.501 (0.423–0.594)	0.263 (0.013–0.819)	0.102
Δ KL-6/ST-KL-6, ≤ 0.211 / >0.211 [¶]	0/16	8/10	0.003
AE-SP-D, ng/mL [¶]	288 (172–434)	251 (190–531)	0.825
ST-SP-D, ng/mL	147.9 (94.3–201.3)	216 (117–368)	0.045
Δ SP-D, ng/mL [¶]	178 (58–259)	54 (–26–160)	0.127
Δ SP-D/ST-SP-D [¶]	0.821 (0.423–1.942)	0.383 (–0.098–1.251)	0.231
Δ SP-D/ST-SP-D, ≤ 0.410 / >0.410 [¶]	3/13	9/9	0.071
Interval of serum marker measurement, days [†]	46 (31–71)	49 (30–70)	0.798
Interval from the symptom onset of AE to treatment, days	5 (4–8)	7 (1–10)	0.621

Definition of abbreviations: AE, acute exacerbation; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; NS, non-smoker; CS, current smoker; ES, ex-smoker; LTOT, long-term oxygen therapy; PaO₂, partial oxygen tension; FIO₂, fraction of oxygen tension; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgG, immunoglobulin G; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; AE-KL-6 (or SP-D), KL-6 (or SP-D) at the onset of AE; ST-KL-6 (or SP-D), KL-6 (or SP-D) at stable state; Δ KL-6 (or SP-D), increase in KL-6 (or SP-D) at the onset of AE as compared with at stable state. [§]Categorical data was compared with Fisher's exact test. Continuous variables were presented as median and IQR, and compared with Mann-Whitney U test. [#]: Treatment including initial dose of prednisolone, frequency of administration of immunosuppressants, soluble thrombomodulin and anti-fibrotic drugs, PMX-DHP therapy, positive pressure ventilation within one month from the onset of AE for AE-IIPs with each HRCT pattern was not significantly different by Mann-Whitney U test or Fisher's exact test. *Spirometry and DLco was performed in 15 cases. **Spirometry and DLco was performed in 16 cases. [†]Interval of serum marker measurement from stable state to onset of AE. [¶]Distribution and median of the parameters were significantly different among diffuse, peripheral, multifocal with higher Δ KL-6/ST-KL-6, and multifocal with lower Δ KL-6/ST-KL-6 by Fisher's exact test and Krsukal-Wallis test, respectively.

Table S7 Adjusted prognostic significance of a proposed new classification for AE-IIPs* using the HRCT pattern and serum marker levels for AE-IIP patients between 2011 and 2016 (n=31)

Parameter	HR	95% CI	P value
Prognostic factors for AE-IIP between 2011 and 2016 ^A			
Multivariate analysis with stepwise selection			
LTOT, yes vs. no	2.674	1.037–6.893	0.042
ST-SP-D, ×10 ng/mL	1.044	1.013–1.075	0.004
PaO ₂ /FiO ₂ ratio, Torr, ≤200 vs. >200	3.431	1.145–10.281	0.028
Adjusted prognostic significance by parameters of A ^B			
Diffuse, multifocal, peripheral			0.076
Diffuse vs. peripheral	4.361	1.225–15.529	0.023
Multifocal vs. peripheral	2.790	0.765–10.171	0.120
Diffuse vs. non-diffuse	2.317	0.927–5.794	0.072
Diffuse or multifocal with ΔKL-6/ST-KL-6 ≤0.211, vs. the others*	4.857	1.648–14.314	0.004

*Proposed new classification for AE-IIPs. A, A multivariate Cox proportional hazard regression analysis with stepwise selection procedure was performed using parameters shown in Table 3 (1). B, Prognostic significance of these 3 parameters was adjusted for other prognostic factors for AE-IIP patients, including a PaO₂/FiO₂ ratio ≤200, ST-SP-D, and LTOT, as shown in A). HRCT, high-resolution computed tomography; AE, acute exacerbation; CI, confidence interval; LTOT, long-term oxygen therapy; FiO₂, fraction of inspired oxygen; HR, hazard ratio; IIP, idiopathic interstitial pneumonia; PaO₂, partial oxygen tension; KL-6, Krebs von den Lungen-6; ST-KL-6, KL-6 during a stable state; SP-D, surfactant protein-D; ST-SP-D, SP-D during a stable state; ΔKL-6, increase in KL-6 at the onset of AE compared with that during the stable state.