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CXCL10 predicts autoimmune features and a favorable clinical course in patients with IIP: post hoc analysis of a prospective and multicenter cohort study

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Abstract

Background Interstitial pneumonia with autoimmune features (IPAF), which does not meet any of the criteria for connective tissue diseases (CTD), has been attracting an attention in patients with idiopathic interstitial pneumonia (IIP). However, the biomarkers that reflect the clinical course of these patients have not been fully elucidated.

Objective To identify useful serum biomarkers reflecting CTD-related features and favorable prognoses in patients with IIP.

Methods This was a post hoc analysis of a prospective and multicenter cohort study between 2015 and 2020. Newly diagnosed patients with IIP were consecutively enrolled, and 74 autoimmune features and autoantibodies were comprehensively checked during IIP diagnosis. Serum levels of CXCL10, CXCL1, CCL2, BAFF, angiopoietin-2, and leptin were evaluated at the time of IIP diagnosis.

Results Two hundred twenty-two patients (159 men and 63 women) with IIP were enrolled. The median observation duration was 36 months. The median age was 71 years old, and median %forced vital capacity (FVC) was 84.1% at the time of IIP diagnosis. The proportion of patients who met the classification criteria for IPAF was 11.7%. In patients with high serum CXCL10, changes in both %FVC and %diffusion lung capacity for carbon monoxide at one year were significantly higher than those in patients with low CXCL10 ($p=0.014$ and $p=0.009$, respectively), whereas these changes were not significant for other chemokines and cytokines. High CXCL10 levels were associated with acute/subacute onset ($p<0.001$) and the diagnosis of nonspecific interstitial pneumonia with organizing pneumonia overlap ($p=0.003$). High CXCL10 levels were related to a higher classification of IPAF (relative risk for IPAF was 3.320,

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95%CI: 1.571–7.019, $p=0.003$) and lower classification of progressive pulmonary fibrosis (PPF; relative risk for PPF was 0.309, 95%CI: 0.100-0.953, $p=0.027$) compared to those with low CXCL10. Finally, survival was higher in patients with IPF and high CXCL10 ($p=0.044$), and high CXCL10 was a significant prognostic factor in multivariate Cox proportional hazards models (hazard ratio 0.368, $p=0.005$).

Conclusions High serum levels of CXCL10 are associated with CTD-related features, the favorable clinical course, and survival in patients with IIP, especially IPF.

Clinical trial number Not applicable.

Keywords Interstitial pneumonia with autoimmune features, Idiopathic interstitial pneumonia, Nonspecific interstitial pneumonia, Organizing pneumonia, C-X-C motif chemokine 10

Introduction

The number of patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) is the second highest after those with idiopathic interstitial pneumonias (IIP), especially idiopathic pulmonary fibrosis (IPF) [1]. The most important differences between CTD-ILD and IPF are the treatment response and prognosis. Generally, patients with CTD-ILD respond favorably to immunosuppressive therapy and have a better prognosis than those with IPF [2–5]. In contrast, patients with IPF do not respond to immunosuppressive therapy [6], and have a poorer prognosis than those with CTD-ILD [2–5]. However, antifibrotic agents can slow the annual decline of forced vital capacity (FVC) in patients with IPF [7, 8]. Therefore, differential diagnosis is pivotal for the selection of appropriate treatments. In addition, some patients with IIP have autoimmune features but do not meet any defined CTD criteria [9–12]. This condition is called interstitial pneumonia with autoimmune features (IPAF) [9]. Conflicting results regarding the prognostic effects of IPAF have been reported since the initial reports of IPAF [3, 13–18]. In our previous prospective study, autoimmune symptoms/signs and serum autoantibodies were systematically checked using checklists including 74 CTD-related items at the time of IIP diagnosis. The presence of consolidation opacity on high-resolution computed tomography (HRCT) and diagnosis by multidisciplinary discussion of nonspecific interstitial pneumonia (NSIP) with organizing pneumonia (OP) were associated with IPAF [12]. To precisely and easily detect ILD with autoimmune features without such thorough examination of faint CTD-like findings, novel and useful biomarkers are needed in clinical practice.

In terms of chemokines and cytokines in CTD-ILD or IPAF, C-X-C motif chemokine ligand (CXCL) 10/interferon (IFN)-γ-induced protein 10 (IP-10) [19–22], CXCL1 [23], C-C motif chemokine ligand (CCL) 2 [20, 22], B-cell activating factor (BAFF)/B-lymphocyte stimulator (BLyS) [24, 25], angiopoietin (ANGP)-2 [26], and leptin [27, 28] are closely associated with the pathogenesis of autoimmunity. Especially, CXCL10/IP-10 is secreted by several cells including T-lymphocytes, monocytes, natural killer (NK) cells, and NK T (NKT) cells in response to helper T-lymphocytes (Th) 1 cells and IFN-γ [21], and the serum and tissue expressions of CXCL10 are increased in rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis, Sjögren's syndrome (SS), and systemic lupus erythematosus (SLE) [19, 21]. Furthermore, the higher serum CXCL10 level was found in SSc patients with ILD compared to those without ILD [20].

In the present study, serum levels of CTD-related chemokines and cytokines in serum were evaluated during IIP diagnosis. Furthermore, the relationships between these cytokines/chemokines and clinical characteristics, findings on HRCT or surgical lung biopsy specimens, and the clinical course were examined. To the best of our knowledge, this is the first study to demonstrate the comprehensive effects of CTD-associated chemokines and cytokines, especially CXCL10, on the longitudinal clinical course and prognosis in patients with IIP.

Methods

Study design and participants

This was a post hoc analysis of a prospective and multicenter study (PAIR-2 cohort study) [12]. Briefly, in our previous study, consecutive patients with IIPs aged ≥ 15 years who had visited or been referred to respiratory departments were prospectively enrolled and followed up from 2015 to 2022 [12]. Patients diagnosed with systemic autoimmune diseases within 3 months of the initial diagnosis of IIPs were excluded from the study [12]. Furthermore, patients with interstitial lung diseases other than IIP, such as hypersensitivity pneumonitis and drug-induced pneumonitis, were excluded. Chest HRCT and serum samples were collected at the time of diagnosis of IIP, and lung histopathological specimens from surgical lung biopsies were also evaluated if performed. Diagnoses of IIP were made by expert pulmonologists, radiologists, and pathologists through multidisciplinary discussion. In addition, detailed radiological and pathological findings were evaluated by each of two pulmonary radiologists (HS and HS) and two pulmonary pathologists (MK and HT), respectively. Systemic autoimmune

diseases were excluded based on the criteria described in a previous study [12]. Enrolled patients were checked annually for their conditions and survival.

The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval number: E14-123) and registered in the University Hospital Medical Information Network (UMIN) system (http://www.umin.ac.jp/, ID: UMIN000015370). This study was performed in accordance with the approved protocol and the 1964 Helsinki Declaration as amended. Informed consent was obtained from all the patients.

Data collection and evaluation of CTD-related features

Clinical data were obtained at the time of IIP diagnosis. Acute, subacute, and chronic IIP were defined as durations of <1 month, 1–3 months, and ≥3 months, respectively, from the onset of respiratory symptoms to the diagnosis of IIP. At the time of diagnosis of IIP, 74 autoimmune features related to CTD, such as arthritis, skin rash, and autoantibodies, were systemically searched according to the "Checklists for detecting CTD-related features" [12] in collaboration with specialists in other areas.

Measurements of serum chemokines and cytokines

At the time of diagnosis of IIP, serum levels of CXCL10/IP-10 and leptin were evaluated by single enzyme-linked immunosorbent assay (ELISA, Quantikine® R&D system). Serum levels of CXCL1, CCL2, BAFF/BLyS, and ANGP-2 were measured by magnetic bead-based multiplex assay (Luminex® Human Discovery Assay; R&D system). In the multiplex assay, when the assay results were below the working range, the values were assigned to the midpoint between zero and the lower limit of the working range (applicable to CXCL1). When the results were above the working range of the assay, the values were assigned to the upper limit of the working range (applicable to CCL2) [29].

Statistical analysis

Statistical analyses were performed using JMP 13.1.0 (SAS Institute Inc., Cary, NC, USA) and EZR 1.41 [30]. Categorical data were compared using the χ^2 test or Fisher's exact probability test for independence. Continuous data were analyzed using the Wilcoxon rank-sum test. The overall survival of patients was estimated using the Kaplan–Meier method, and the curves were compared using the log-rank test. The occurrence of acute exacerbation (AE) of IIP was estimated by considering death before AE as a competing event and analyzed using Gray's method. The relationships between the variables and mortality were evaluated using Cox proportional hazards regression analysis. All tests were two-sided, and statistical significance was set at $p<0.05$.

Results

Clinical characteristics, physiological findings, and clinical classifications of IIP

A total of 226 patients with IIP who had visited or been referred to respiratory departments, were prospectively and consecutively enrolled. In the current study, as described in Supplementary Fig. 1, two patients were excluded due to a diagnosis of hypersensitivity pneumonitis after enrollment, and two patients were excluded due to withdrawal of informed consent. Consequently, four patients were excluded from the study, and 222 patients with IIP were included. The clinical characteristics and lung physiology of all the patients are shown in Table 1. The median age of patients was 71 years, 159 (71.6%) were men, and median observation period was 36 months. FVC during IIP diagnosis was preserved (median, 84.1%), whereas the diffusion lung capacity for carbon monoxide (DL_{CO}) was slightly impaired (median, 67.8%). As for the diagnoses of 222 patients with IIP, 83 (37.4%) patients had IPF, 14 (6.3%) had cryptogenic OP (COP), 9 (4.1%) had NSIP, 17 (7.7%) had NSIP with OP overlap, and 71 (32%) had unclassifiable IIP (UCIIP) [12].

Serum levels of chemokines and cytokines, and relationship with physiological parameters

Serum chemokine and cytokine levels were measured at the time of IIP diagnosis. These chemokines and cytokines included CXCL1, CXCL10, CCL2, ANGP-2, BAFF/BLyS, and leptin, which are associated with the pathogenesis of CTDs (Table 1). The volcano plots show Wilcoxon rank-sum test p-values between patients with high and low serum chemokines/cytokines levels and the changes in %FVC or $\%DL_{CO}$ in one year (the median change in the high group − the median change in the low group) (Fig. 1). Serum CXCL10 level was the only significant chemokine indicating that high CXCL10 levels (divided by the mean value of 73.12 pg/mL) could predict an increase in %FVC (Figs. 1A and 2C; $p=0.014$) and $\%DL_{CO}$ (Figs. 1B and 2D; $p=0.009$) one year after the diagnosis of IIP. In contrast, high ANGP-2, BAFF, leptin, CXCL1, and CCL2 levels were not significantly associated with positive changes in %FVC or $\%DL_{CO}$ at one year. The baseline %FVC at the time of IIP diagnosis did not differ between patients with high serum CXCL10 levels and those with low CXCL10 levels (Fig. 2A). Patients with high CXCL10 level were more frequently treated with immunosuppressive therapies including corticosteroids and immunosuppressants ($p<0.001$, Fig. 2B). In terms of detailed treatment selection by the attending doctors on-site, patients with acute/subacute onset (Supplementary Fig. 2B, $p<0.001$) and those who met the classification criteria for IPAF (Supplementary Fig. 2C, $p=0.035$) received more immunosuppressive therapy. Furthermore, the IPAF morphologic domain (Supplementary

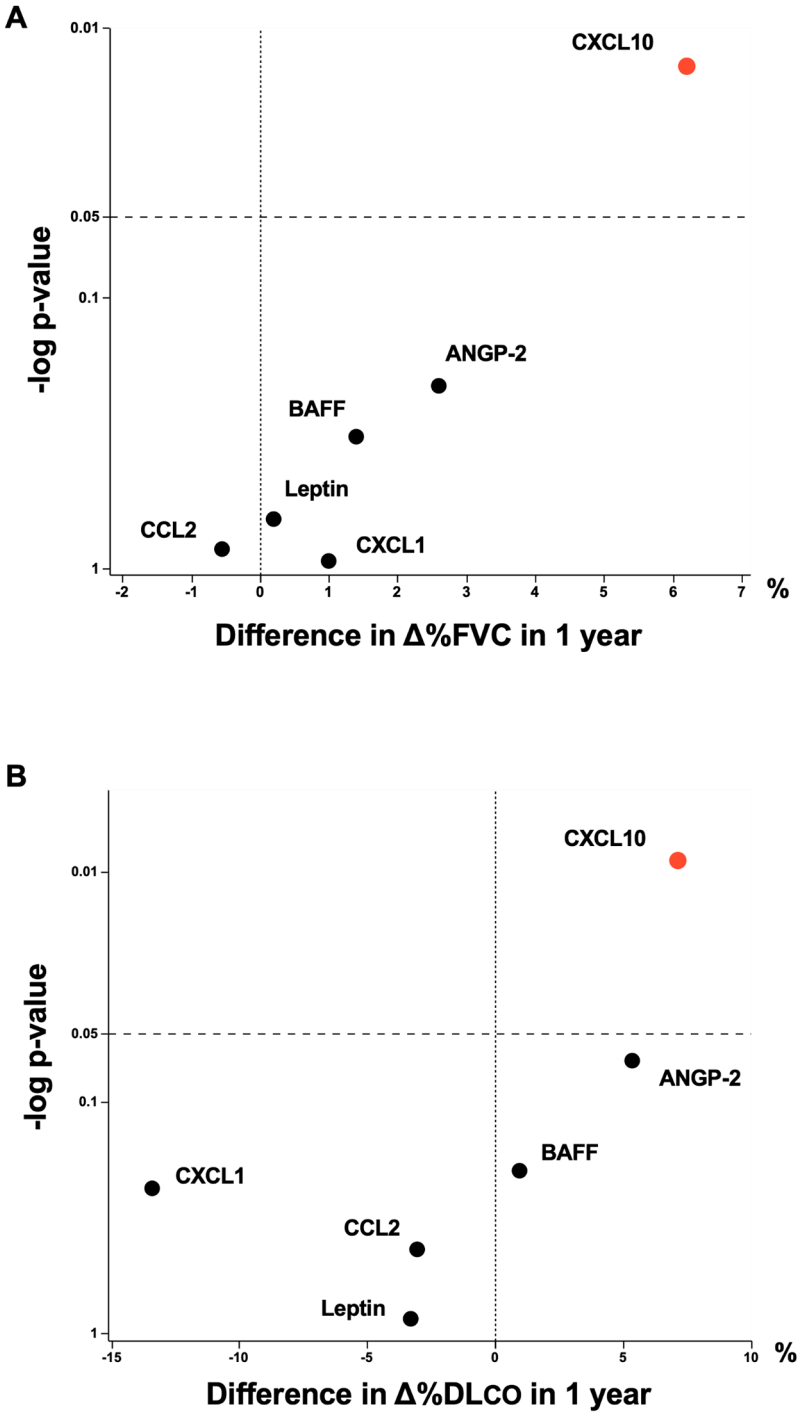

Fig. 1 Serum chemokines/cytokines concentrations and changes in lung physiological parameters. Serum chemokines and cytokines including CXCL1, CXCL10, CCL2, ANGP-2, BAFF/BLyS, and leptin, which are related to the pathogenesis of CTDs, were measured at the time of IIP diagnosis. The volcano plots show Wilcoxon rank-sum test p-values of chemokines/cytokines for the changes in %FVC (**A**) or $\%DL_{CO}$ (**B**). Serum CXCL10 level is a sole significant chemokine, indicating that high CXCL10 level (divided by the mean value of 73.12 pg/mL) can predict the increase of %FVC ($p = 0.014$, **A**) and $\%DL_{CO}$ ($p = 0.009$, **B**) one year after IIP diagnosis. CTD, connective tissue disease; IIP, idiopathic interstitial pneumonia; CXCL, C-X-C motif chemokine ligand; CCL, C-C motif chemokine ligand; BAFF: B-cell activating factor; BLyS, B-lymphocyte stimulator; ANGP, angiopoietin; FVC, forced vital capacity; DL_{CO}, the diffusion lung capacity for carbon monoxide

Table 1 Clinical characteristics, pulmonary function tests, and serum markers in all patients with IIPs

	n **= 222 (median (range))**
Age at the diagnosis of IIPs, yo	71 (42, 87)
Gender, male / female, n (%)	159 (71.6) / 63 (28.4)
Smoking history, n (%) current / ex / never	33 (15) / 125 (56) / 64 (29)
Observation period, months	36 (0, 85)
Family history of IP, n (%)	22 (10.1)
Motives for hospital visit, n symptoms / medical check-up / others	100 (45) / 109 (49) / 13 (6)
Onset forms, n (%) acute / subacute / chronic / unknown	18 (8) / 17 (8) / 185 (83) / 2 (1)
Surgical lung biopsy, n (%)	56 (25.2)
FVC, % predicted	84.1 (28.1, 146.6)
DL_{CO}, % predicted	67.8 (13.4, 154.4)
CXCL10, pg/mL (mean ± SD)	73.12 ± 198.18
CXCL1, pg/mL (mean ± SD)	99.93 ± 151.23
CCL2, pg/mL (mean ± SD)	320.80 ± 374.11
ANGP-2, ng/mL (mean ± SD)	3.26 ± 1.64
BAFF/BLyS, ng/mL (mean ± SD)	1.37 ± 0.52
Leptin, ng/mL (mean ± SD)	6.25 ± 6.69

Data are presented as median (range) or n (%)

Abbreviations; IP: interstitial pneumonia, FVC: forced vital capacity, DL_{CO}: diffusion lung capacity for carbon monoxide, CXCL: C-X-C motif chemokine ligand, ANGP: angiopoietin, BAFF/BLyS: B-cell activating factor/ B-lymphocyte stimulator, CCL: C-C motif chemokine ligand

Fig. 2F, $p<0.001$), but not the clinical domain (Supplementary Fig. 2D, $p=0.712$) or serologic domain (Supplementary Fig. 2E, $p=0.236$), was significantly associated with the more frequent administration of immunosuppressive therapy. Changes in %FVC (Fig. 2C) and $\%DL_{CO}$ (Fig. 2D) at one year were significantly greater in patients with high CXCL10 levels than in those with low CXCL10 levels ($p=0.014$ and 0.009, respectively).

Diagnoses of IIP, classification of IPAF, and clinical characteristics in patients with high CXCL10

In patients with high CXCL10 levels, the proportions of NSIP with OP overlap, COP, and NSIP increased, whereas that of IPF decreased ($p=0.003$; Fig. 3A and B). In patients with high CXCL10 levels, increased acute/subacute onset was found (Fig. 3D), and hospital visits due to any symptom tended to increased (Fig. 3C). In addition, higher systemic autoimmune disease-specific autoantibody positivity was found ($p=0.002$, Fig. 3E), especially for anti-aminoacyl tRNA synthetase antibody, which was more positive in patients with high CXCL10 than in those with low CXCL10 ($p=0.017$). More patients with IPAF had high CXCL10 levels ($p=0.003$, Fig. 3F), and the relative risk of high CXCL10 levels for IPAF classification was 3.320 (95% confidence interval [CI]: 1.571–7.019). As for other ILD-associated biomarkers, no significant and strong relationships were observed between serum CXCL10 levels and KL-6 or SP-D levels ($r=0.150$ and r=-0.009, Supplementary Fig. 3A and 3B). A representative HRCT pattern of NSIP with OP overlap is shown in Fig. 4A. A 76 year-old man visited our hospital because of dry cough. The patient tested positive for rheumatoid factor (49.9 IU/mL), anti-Scl-70 antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA). This case was classified as having IPAF and had a high serum CXCL10 level (688 pg/mL). Regarding the HRCT findings, more consolidation opacities were found in patients with high CXCL10 levels ($p=0.002$, Fig. 4B). In addition, according to the guideline for IPF [31], a higher proportion of alternative pattern for IPF and a lower proportion of usual interstitial pneumonia (UIP)/probable UIP patterns on HRCT were found, but not significantly, in patients with high CXCL10 levels than in those with low CXCL10 levels ($p=0.078$, Fig. 4C). Regarding surgical lung biopsy specimens, no significant differences in systemic autoimmune disease-like findings (interstitial lymphoid aggregates with germinal centers, prominent plasmacytic infiltration, dense perivascular collagen, and extensive pleuritis) were observed between the two groups ($p=0.302$, Fig. 4D).

Progressive pulmonary fibrosis (PPF), acute exacerbation of IIP (AE-IIP), and survival in patients with high CXCL10

As shown in Fig. 2B, patients with high CXCL10 were more frequently treated with immunosuppressive therapy, and the %FVC (Fig. 2C) and $\%DL_{CO}$ (Fig. 2D) were significantly higher in patients with high CXCL10 levels than in those with low CXCL10 levels. Furthermore, patients with high CXCL10 levels showed significant improvements in respiratory symptoms ($p<0.001$, Fig. 5A) and opacities on HRCT ($p=0.002$, Fig. 5B). Less number of patients with high CXCL10 met the criteria for PPF one year after IIP diagnosis [31] ($p=0.012$, Fig. 5C), and the relative risk of high CXCL10 for PPF was 0.309 ($p=0.012$, 95%CI: 0.100-0.953). In addition, the cumulative incidence of AE of IIP tended to be lower in patients with high CXCL10 levels than in those with low CXCL10 levels (IPF: Gray's test, $p=0.126$, Fig. 5D; non-IPF: $p=0.384$, Fig. 5E). The development of systemic autoimmune diseases after IIP diagnosis was not related to the serum CXCL10 concentration (log-rank test, $p=0.698$).

Evaluation of prognostic factors and survival in patients with IIP

Prognostic factors were evaluated using Cox proportional hazards models of mortality for all patients with IIP. In univariate models (Supplementary Table 1), age (hazard ratio [HR]: 1.076, $p<0.001$), sex (male, HR: 1.933, $p=0.037$), FVC (L, HR: 0.567, $p=0.002$), DL_{CO} (HR: 0.970, $p<0.001$), walk distance (HR: 0.996, $p=0.004$)

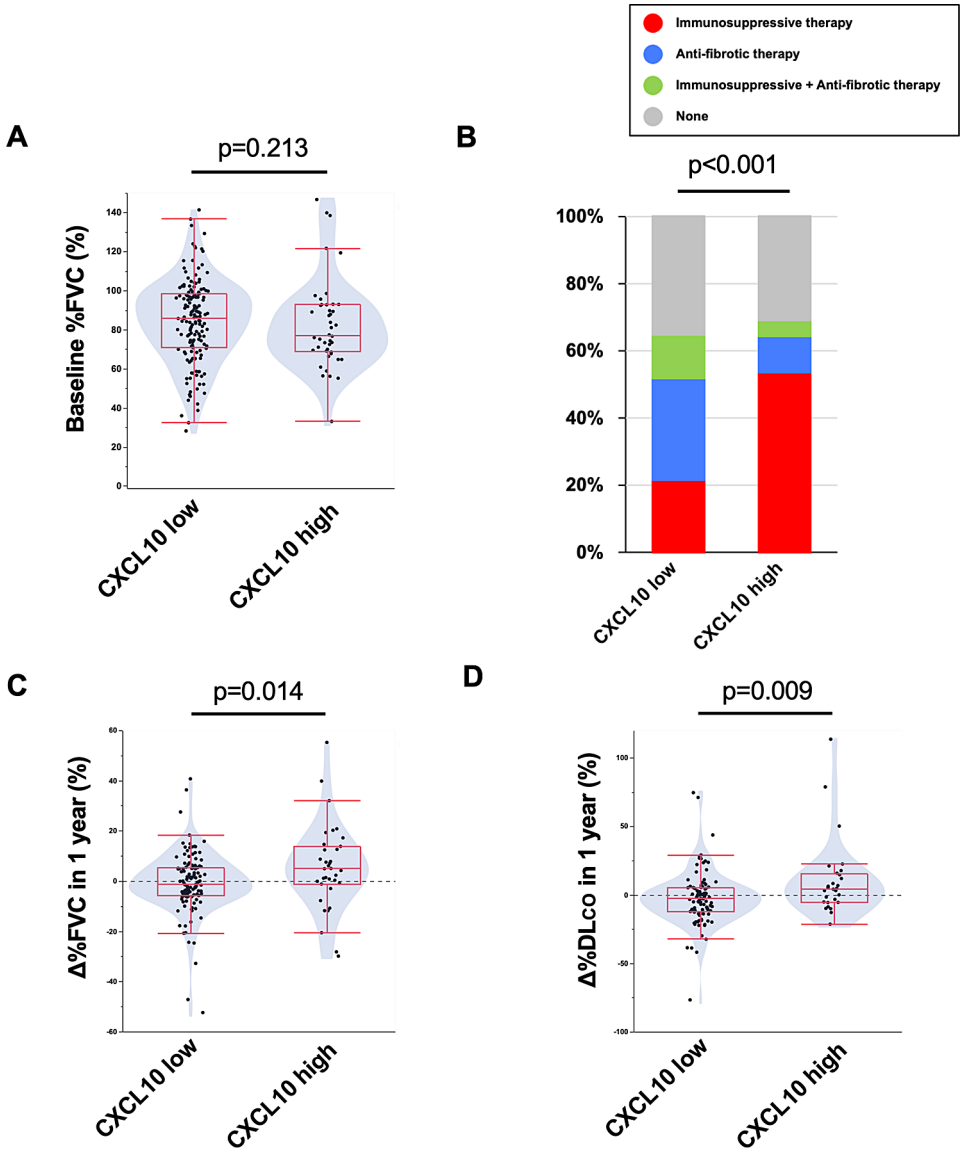

Fig. 2 Treatments and lung physiological parameters in patients with high serum CXCL10. Serum CXCL10 levels were divided into two groups based on the mean value of 73.12 pg/mL. Baseline %FVC at the time of IIP diagnosis were not different between patients with high and low serum CXCL10 levels (**A**). Patients with high CXCL10 level were more frequently treated with immunosuppressive therapies including corticosteroids and immunosuppressants than those with low CXCL10 level (**B**). Changes in %FVC (**C**) and %DL_{CO} (**D**) one year after IIP diagnosis are shown. Changes in %FVC and %DL_{CO} significantly increased in patients with high CXCL10 ($p=0.014$ and $p=0.009$, respectively). CXCL, C-X-C motif chemokine ligand; FVC, forced vital capacity; DL_{CO}, the diffusion lung capacity for carbon monoxide; IIP, idiopathic interstitial pneumonia

and minimum SpO2 in 6-minute walk test (6MWT) (HR: 0.933, $p<0.001$), development of AE-IIP (HR: 6.359, $p<0.001$), change in %FVC in one year (HR: 0.949, $p<0.001$), presence of IPAF (HR: 0.304, $p=0.017$), and presence of PPF (HR: 8.120, $p<0.001$) were significant prognostic factors. In multivariable models adjusted for age, sex, FVC, and the diagnosis of IPF/non-IPF (Table 2), loss of body weight (HR: 20.78, $p=0.045$), DL_{CO} (HR: 0.976, $p<0.001$), minimum SpO2 in 6MWT (HR: 0.930, $p<0.001$), COP or NSIP with OP overlap (HR: 0.162, $p=0.002$), development of AE-IIP (HR: 6.036, $p<0.001$), change in %FVC in one year (HR: 0.934, $p<0.001$), presence of IPAF (HR: 0.287, $p=0.014$), and presence of PPF (HR: 7.315, $p<0.001$) were significant prognostic factors. Among the several chemokines and cytokines measured, a high concentration of serum CXCL10 was a significant and favorable prognostic factor (HR: 0.368, $p=0.005$), whereas CXCL1, CCL2, ANGP-2, BAFF/BLyS, and leptin were not significant (Table 2). Regarding survival, IPF patients with high CXCL10 levels showed a significantly better prognosis (log-rank test, $p=0.044$, Fig. 5F), while non-IPF patients with high CXCL10 levels did not

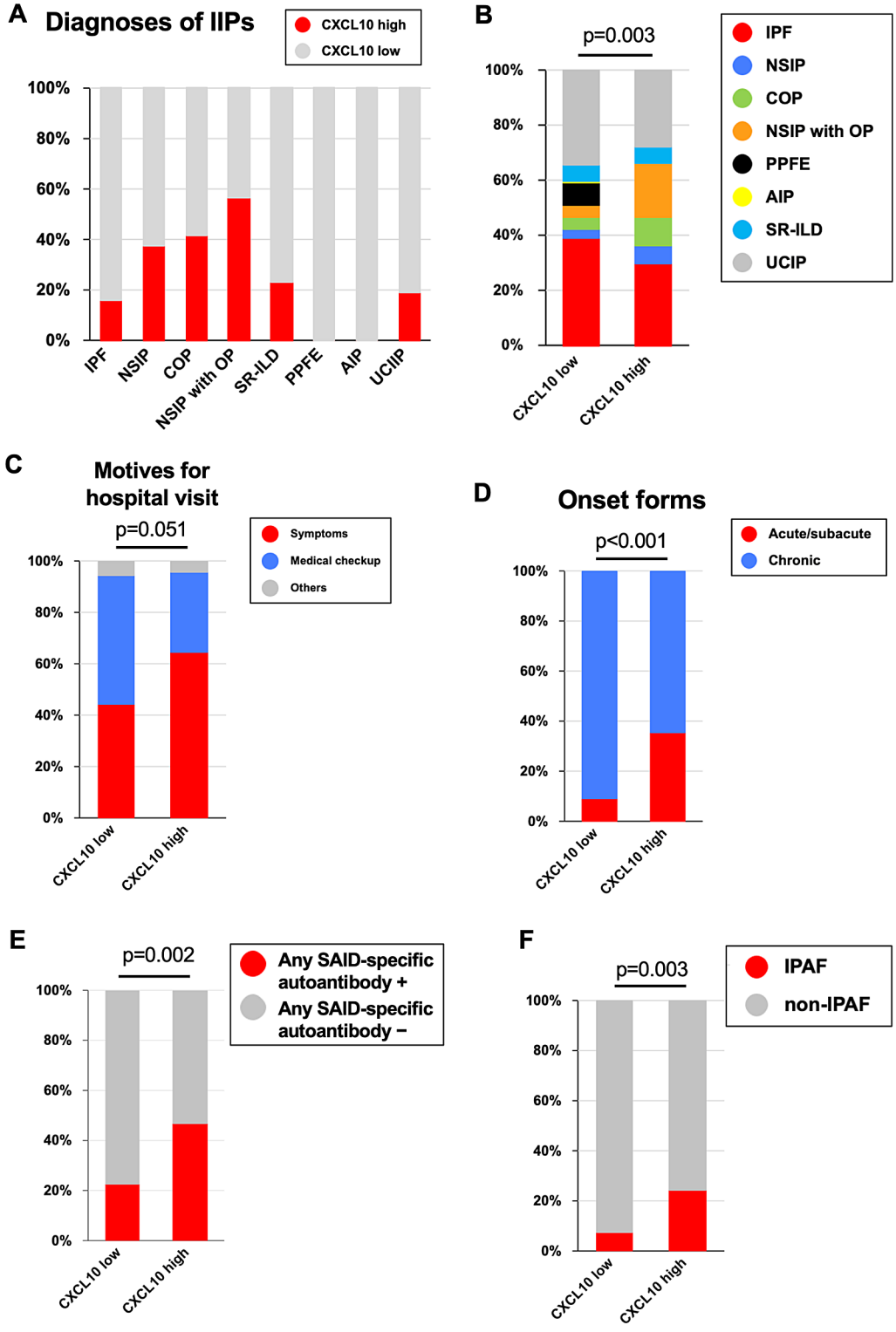

Fig. 3 Diagnoses of IIP, classification of IPAF, and clinical characteristics of patients with high CXCL10. In patients with high CXCL10, the proportions of NSIP with OP overlap, COP, and NSIP increased, while that of IPF decreased ($p=0.003$, **A** and **B**). In patients with high CXCL10, hospital visit due to any symptoms tended to increase ($p=0.051$, **C**), and increased acute/subacute onset was found ($p<0.001$, **D**). Higher systemic autoimmune disease-specific autoantibody positivity was found ($p=0.002$, **E**) and more patients with IPAF ($p=0.003$, **F**) had high CXCL10 levels. IIP, idiopathic interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; CXCL, C-X-C motif chemokine ligand; NSIP, nonspecific interstitial pneumonia; COP, cryptogenic organizing pneumonia; SAID, systemic autoimmune disease

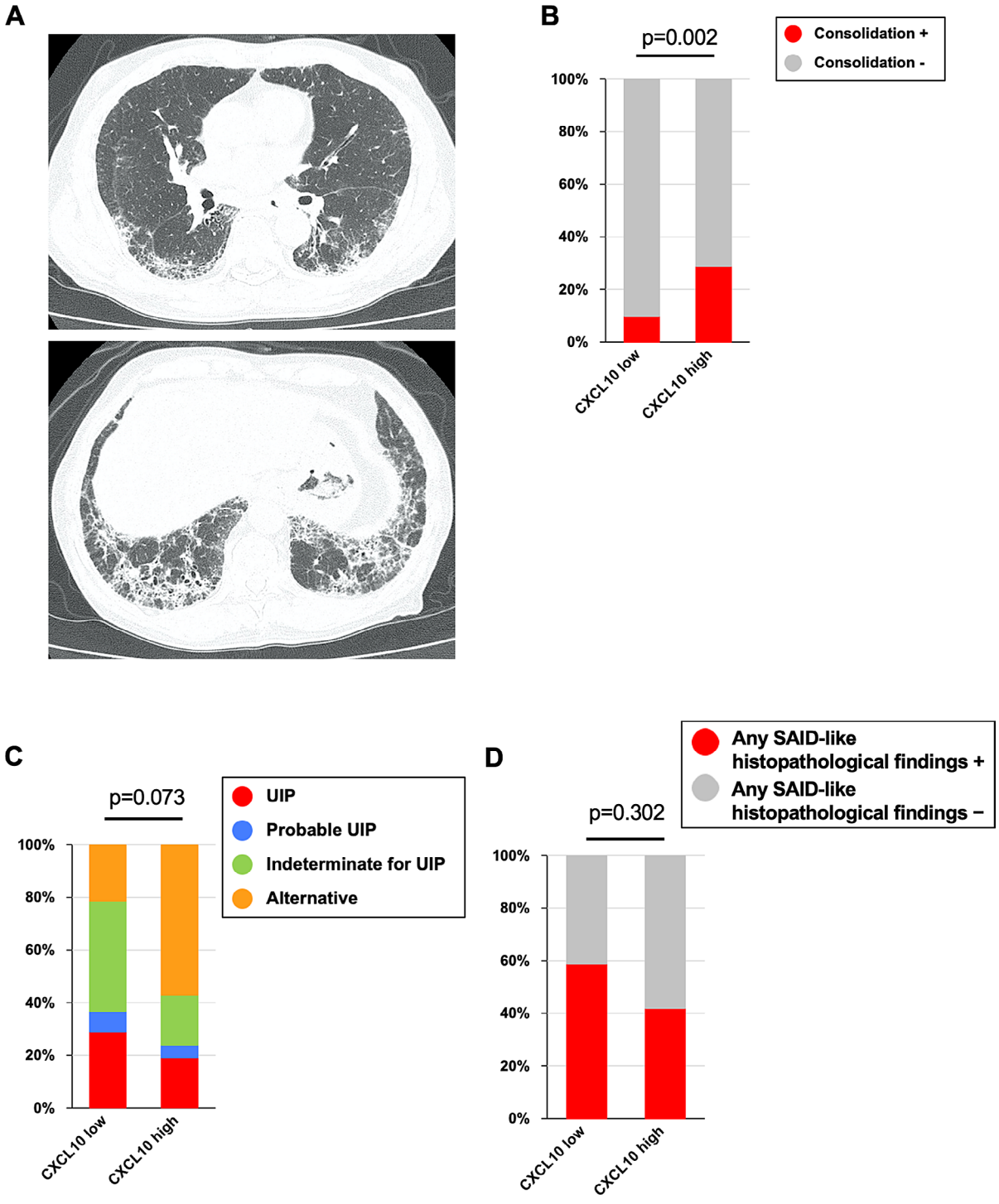

Fig. 4 HRCT findings and lung histopathological specimens of patients with high CXCL10. Representative HRCT pattern of NSIP with OP overlap is shown (**A**). A 76 year-old man visited our hospital because of dry cough. The patient was found positive for rheumatoid factor (49.9 IU/mL), anti-Scl-70 antibody, and MPO-ANCA. This patient was classified as having IPAF and had a high serum CXCL10 level (688 pg/mL). In all patients with IIP, consolidation opacity on HRCT was more frequently found in patients with high CXCL10 level (**B**). According to the guideline for IPF [31], a higher proportion of alternative pattern for IPF and a lower proportion of UIP/probable UIP pattern on HRCT were found, but not significant, in patients with high CXCL10 level compared to those with low CXCL10 level ($p = 0.073$, **C**). Regarding surgical lung biopsy specimens, no significant differences in systemic autoimmune disease-like findings (interstitial lymphoid aggregates with germinal centers, prominent plasmacytic infiltration, dense perivascular collagen, and extensive pleuritis) were observed between the two groups ($p = 0.302$, **D**). HRCT, high-resolution computed tomography; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; IPAF, interstitial pneumonia with autoimmune features; CXCL, C-X-C motif chemokine ligand; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; SAID, systemic autoimmune disease

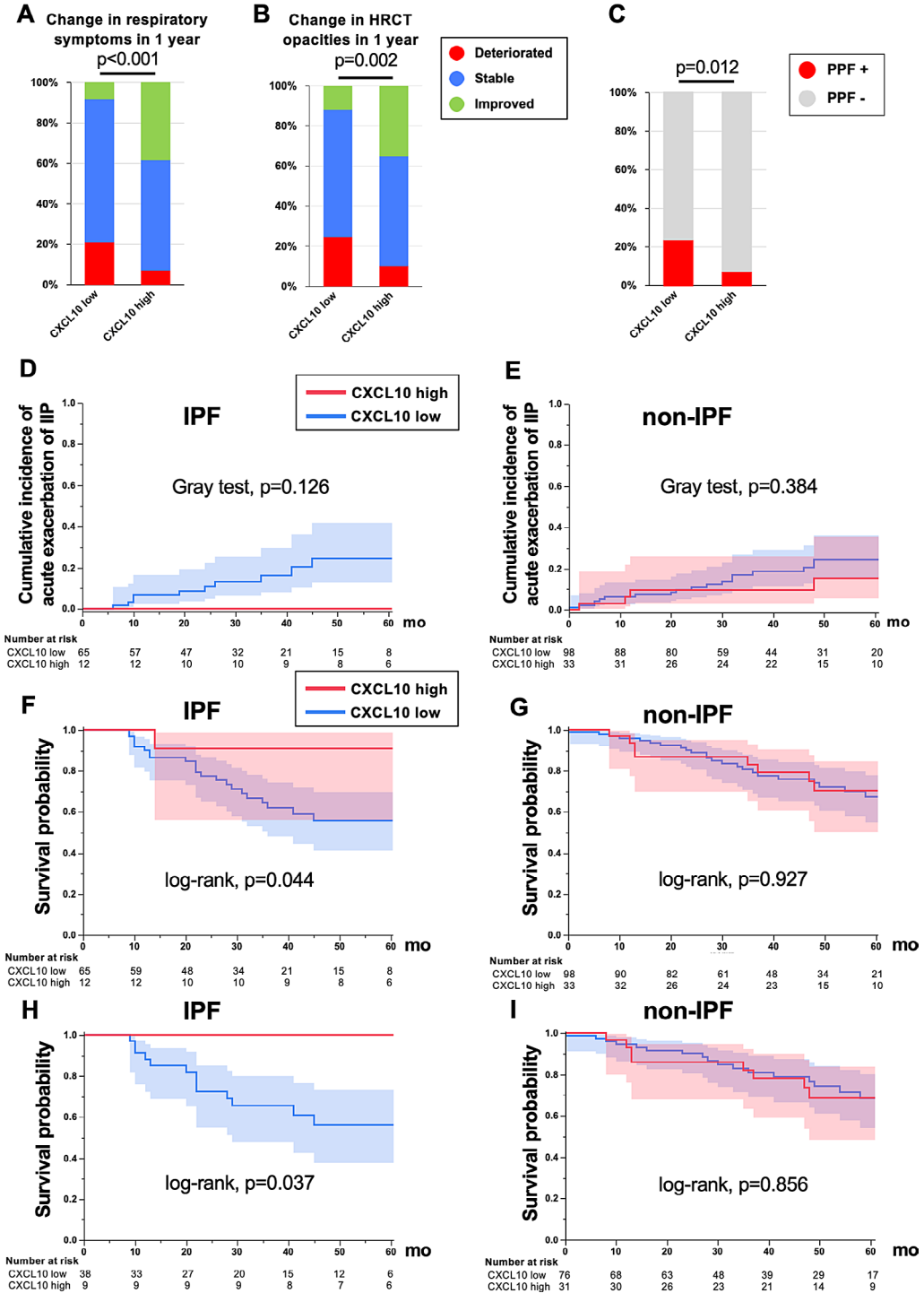

Fig. 5 Clinical course, classification of PPF, occurrence of AE-IIP, and survival in patients with high CXCL10 level. Patients with high CXCL10 level showed significant improvements in respiratory symptoms ($p < 0.001$, **A**) and opacities on HRCT ($p = 0.002$, **B**) at one year. Less number of patients with high CXCL10 met the criteria for PPF one year after IIP diagnosis ($p = 0.012$, **C**), and the relative risk of high CXCL10 level for PPF was 0.309 (95%CI: 0.100-0.953). Cumulative incidence of AE-IIP tended to be lower in patients with high CXCL10 level than in those with low CXCL10 level (IPF: Gray's test, $p = 0.126$, **D**; non-IPF: $p = 0.384$, **E**). IPF patients with high CXCL10 levels showed a significantly better prognosis (log-rank test, $p = 0.044$, **F**), while non-IPF patients with high CXCL10 levels did not ($p = 0.927$, **G**) compared to those with low CXCL10 levels. When patients were limited to those who received immunosuppressive treatments or no treatment, patients with IPF with high CXCL10 level showed significantly better survival than those with low CXCL10 level ($p = 0.037$, **H**), whereas non-IPF patients showed no differences ($p = 0.856$, **I**). PPF, progressive pulmonary fibrosis; AE-IIP, acute exacerbation of idiopathic interstitial pneumonia; CXCL, C-X-C motif chemokine ligand; HRCT, high-resolution computed tomography; CI, confidence interval

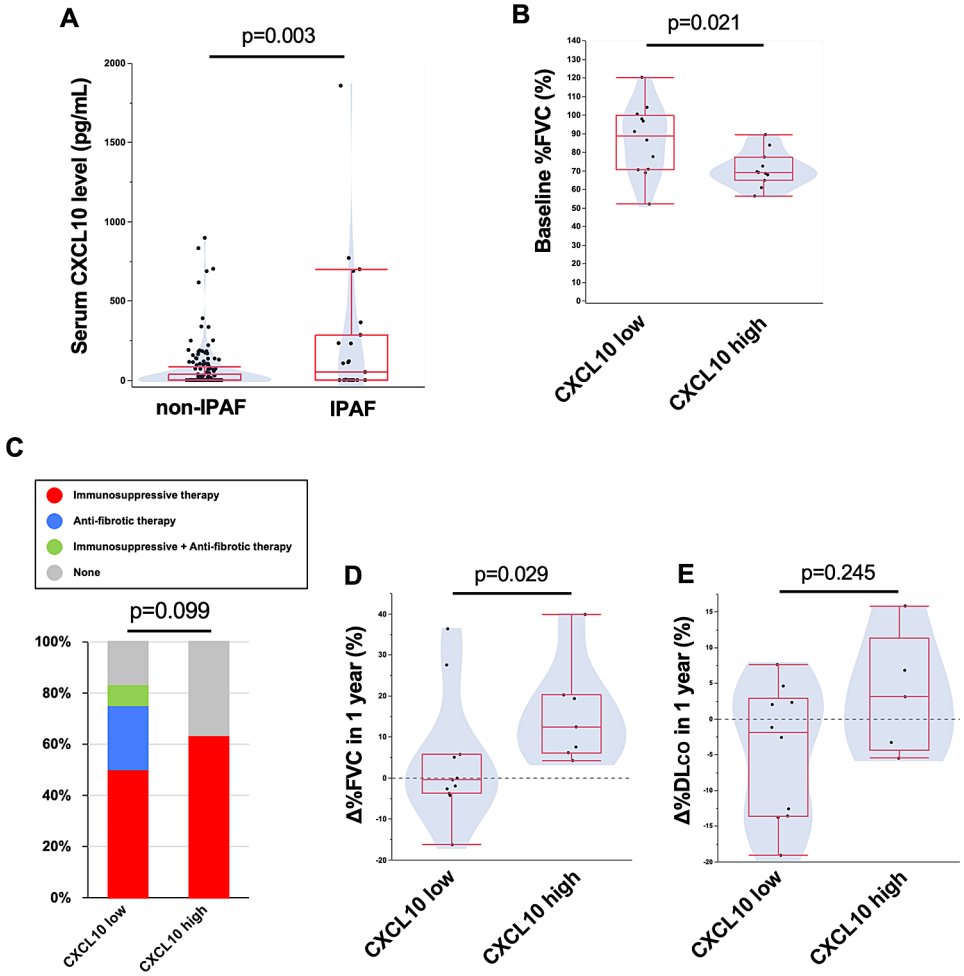

Fig. 6 Serum CXCL10 in patients with IPAF. Patients with IPAF (11.7% of all IIP, 26 patients) showed significantly higher serum CXCL10 level than those without IPAF (median 51 vs. 0 pg/mL and mean 240 vs. 53 pg/mL, $p=0.003$; **A**). At the time of IIP diagnosis, baseline %FVC was significantly lower in patients with high CXCL10 level than in those with low CXCL10 level ($p=0.021$, **B**). Patients with high CXCL10 level tended to receive more immunosuppressive therapy compared to those with low CXCL10 level ($p=0.099$, **C**). Change in %FVC at one year was significantly higher in patients with high CXCL10 level than in those with low CXCL10 level ($p=0.029$, **D**). Change in $\%DL_{CO}$ at one year tended to be higher in patients with high CXCL10 level than in those with low CXCL10 level ($p=0.245$, **E**). CXCL, C-X-C motif chemokine ligand; IPAF, interstitial pneumonia with autoimmune features; FVC, forced vital capacity; DLCO, the diffusion lung capacity for carbon monoxide

($p=0.927$, Fig. 5G) compared to those with low CXCL10 levels. When patients were limited to those who received immunosuppressive treatments or no treatment, IPF patients with high CXCL10 levels showed significantly better survival than did those with low CXCL10 (log-rank test, $p=0.037$; Fig. 5H), whereas non-IPF patients showed no differences (log-rank test, $p=0.856$; Fig. 5I).

CXCL10 in patients with IPAF

Patients with IPAF (11.7% of all IIPs, 26 patients) showed significantly higher levels of serum CXCL10 than those without IPAF (median 51 vs. 0 pg/mL and mean 240 vs. 53 pg/mL; $p=0.003$; Fig. 6A). At the time of IIP diagnosis, baseline %FVC was significantly lower in patients with high CXCL10 levels than in those with low CXCL10 levels ($p=0.021$, Fig. 6B). Patients with high CXCL10 levels tended to receive more with immunosuppressive therapy than those with low CXCL10 levels ($p=0.099$, Fig. 6C). The change in %FVC at one year was significantly higher in patients with high CXCL10 levels ($p=0.029$, Fig. 6D). The change in $\%DL_{CO}$ at one year tended to be higher in patients with high CXCL10 levels than in those with low CXCL10 levels ($p=0.245$, Fig. 6E).

Discussion

In this post hoc analysis of a multicenter prospective cohort study, which searched for 74 autoimmune features at the time of diagnosis in 222 patients with IIP, high serum CXCL10 levels were related to acute/subacute onset, the diagnosis of NSIP with OP overlap, several autoimmune features and IPAF classification, and a favorable clinical course. Furthermore, survival was higher in

Table 2 Multivariable Cox proportional hazards models of mortality adjusted for age, sex, FVC, and the diagnosis of IPF/non-IPF

Variable	Hazard ratio	95% CI		*p*-value
		Lower	Upper	
Mucocutaneous lesion, +	1.050	0.383	2.390	0.916
Joint lesion, +	NC.	0	1.794	0.140
Dry symptoms or findings, +	0.498	0.115	1.443	0.221
Loss of body weight, +	20.78	1.090	122.2	0.045
DL_{CO}, % pred.	0.976	0.962	0.990	< 0.001
Distance in 6MWT, m	0.998	0.995	1.001	0.140
Minimum SpO_2 in 6MWT, %	0.930	0.897	0.967	< 0.001
Extensive GGA on HRCT, +	1.137	0.394	2.605	0.789
Consolidation on HRCT, +	0.397	0.114	1.054	0.065
Anti-ARS antibody, +	0.223	0.012	1.064	0.063
Any SAID-like lung pathological lesion	1.859	0.580	6.394	0.298
IPAF, +	0.287	0.069	0.804	0.014
COP or NSIP with OP overlap, +	0.162	0.026	0.557	0.002
CXCL10 high/low, high	0.368	0.157	0.758	0.005
CXCL1 high/low, high	1.057	0.058	5.160	0.958
CCL2 high/low, high	1.384	0.775	2.407	0.265
ANGP-2 high/low, high	1.059	0.610	1.812	0.835
BAFF/BLyS high/low, high	1.376	0.799	2.395	0.251
Leptin high/low, high	0.776	0.421	1.392	0.399
Development of systemic autoimmune diseases, +	0.554	0.031	2.605	0.524
Development of AE, +	6.036	3.402	10.63	< 0.001
ΔFVC in one year, % pred	0.934	0.908	0.962	< 0.001
PPF, +	7.315	4.063	13.13	< 0.001
Treatments for ILD Immunosuppressive vs. Anti-fibrotic, immunosuppressive	0.738	0.340	1.573	0.431

Abbreviations; IPF: idiopathic pulmonary fibrosis, FVC: forced vital capacity, DL_{CO}: diffusion lung capacity for carbon monoxide, 6MWT: 6-minute walk test, GGA: ground glass attenuation, HRCT: high-resolution computed tomography, AE: acute exacerbation, ANA: antinuclear antibody, RF: rheumatoid factor, CK: creatine kinase, ARS: aminoacyl tRNA synthetase, SAID: systemic autoimmune disease, IPAF: interstitial pneumonia with autoimmune features, ILD: interstitial lung diseases, PPF: Progressive pulmonary fibrosis, CXCL: C-X-C motif chemokine ligand, ANGP: angiopoietin, BAFF/BLyS: B-cell activating factor/ B-lymphocyte stimulator, CCL: C-C motif chemokine ligand, confidence interval

patients with IPF and high CXCL10, and high CXCL10 was a significant prognostic factor in multivariable analysis. To the best of our knowledge, this is the first study to show that the longitudinal clinical course and survival of patients with IIP is related to CTD-associated chemokines and cytokines, particularly CXCL10.

Previous studies have reported that patients with CTD-ILD [2–5] or IPAF [11, 12] showed a favorable response primarily to immunosuppressive therapy and a better prognosis than did those with IPF. Although patients with IPF do not respond to immunosuppressive therapy [6], anti-fibrotic agents can slow the decline of FVC [7, 8]. However, in patients with IPAF and IPF, the effects of the IPAF classification on the treatment response to the immunosuppressive therapy and the prognosis of IPF are not clear-cut [3, 14, 15, 17, 32]. Furthermore, our two previous prospective studies also showed that a lack of a significant impact of IPAF on the prognosis of IPF due to the low number of IPAF in patients with IPF [11, 12]. Therefore, novel biomarkers for predicting the responsiveness to immunosuppressive therapy are required.

Serum levels of CXCL9, 10, 11, which are related to the migration of T-lymphocytes, were the highest in CTD-ILD, followed by IPAF and IPF [33]. CXCL10 is secreted from several cells including T-lymphocytes, monocytes, NK cells, and NKT cells in response to Th 1 cells and IFN-γ [21], and is called M1-macrophage-related chemokine [22]. CXCL10 can bind to C-X-C motif chemokine receptor (CXCR) 3 on CD4+and CD8+T-lymphocytes, dendritic cells, and endothelial cells [21]. Therefore, CXCL10 is mainly involved in the recruitment of T-lymphocytes and exerts pro-inflammatory effects [21]. Furthermore, CXCL10 levels are associated with the pathogenesis and disease activity of several CTD, including SLE, SSc, RA, and SS [19, 21, 34], and CXCL10 antagonists decreased CTD disease activity [34]. Higher serum CXCL10 levels have been reported in patients with SSc and ILD [20] and in those with RA and interstitial lung abnormality (ILA) [35] than in those without ILD or ILA. As for IPAF and chemokines/cytokines, plasma CXCL1 level was higher in patients with IPAF than in those with IIP, and higher CXCL1 level was related to higher erythrocyte sedimentation rate, lower DLCO, and higher

frequency of an acute exacerbation of ILD [23]. In addition, Zhang et al. recently reported that CXCL10 levels in bronchoalveolar lavage were the highest among M1-macrophage-related chemokines and cytokines, and that the concentration of CXCL10 was negatively correlated with baseline fibrosis volume in patients with IPAF [22]. In their study, high CCL2 levels were significantly associated with poor survival, while CXCL10 levels were not [22]. Consistent with these results, in our study, high CXCL1 and CCL2 levels were not related to favorable clinical course or prognosis. Furthermore, although the baseline %FVC tended to be lower in patients with high CXCL10 level, the response primarily to immunosuppressive therapy was higher in these patients than in those with low CXCL10 levels. Therefore, high serum CXCL10 levels may be an indicator of autoimmune-related pathogenesis in the lungs and a favorable clinical course in patients with IIP.

Our study had several limitations. First, the number of patients with IIP was small, and these findings need to be validated. Second, this was a post hoc analysis of a multicenter prospective cohort study. Third, treatments for IIPs were not uniform. Therefore, larger prospective studies using uniform treatment regimens are warranted.

Conclusions

In this post hoc analysis of a multicenter prospective cohort study, which searched for 74 autoimmune features at the time of diagnosis in 222 patients with IIP, high serum CXCL10 levels were related to acute/subacute onset, the diagnosis of NSIP with OP overlap, several autoimmune features, and classification of IPAF. In addition, a favorable clinical course was observed in patients with high CXCL10 levels, especially those with IPF. Future studies are required to validate these results and to identify patients with a favorable response to immunosuppressive therapy, especially those with IPF.

Abbreviations

IIP	idiopathic interstitial pneumonia
CTD	connective tissue diseases
IPAF	Interstitial pneumonia with autoimmune features
PPF	progressive pulmonary fibrosis
FVC	forced vital capacity
DL_{CO}	diffusion lung capacity for carbon monoxide
HRCT	high-resolution computed tomography
NSIP	nonspecific interstitial pneumonia
COP	cryptogenic organizing pneumonia
CXCL	C-X-C motif chemokine ligand

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

NE and TS contributed to the study conceptualization, project administration, and funding acquisition. NE, SN, SY, YM, AF, YT, HN, YA, YI, HY, MK, YS, HH, KF, MT, MK, SI, MF, TA, NK, KY, HM, YK, MS, KM, MM, TF, NI, and YN contributed to the data curation. NE, KM, HS, HS, MK, KT, and NO analyzed and interpreted the data. NE drafted the manuscript. NE, YN, HS, HS, MK, KT, NO, and TS contributed to critical revision of important intellectual content. NE, SN, SY, YM, AF, YT, HN, YA, YI, HY, MK, YS, HH, KF, MT, MK, SI, MF, TA, NK, KY, HM, YK, MS, KM, MM, TF, NI, YN, HS, HS, MK, KT, NO, and TS approved the final version of the manuscript to be published.

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Data availability

The raw data collected in this study are not publicly available because of informed consent restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethical approval

The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval number: E14-123) and registered in the University Hospital Medical Information Network (UMIN) system (http://www.umin.ac.jp/, ID: UMIN000015370). This study was performed in accordance with the approved protocol and the 1964 Helsinki Declaration as amended.

Consent for publication

Informed consent was obtained from all the patients.

Competing interests

NE received grants from Boehringer Ingelheim Co., Ltd. Other authors declare no competing interests.

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