Respiratory Medicine 224 (2024) 107577

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Radiological and histopathological features and treatment response by subtypes of interstitial pneumonia with autoimmune features: A prospective, multicentre cohort study

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ARTICLE INFO

Keywords:
Interstitial pneumonia with autoimmune features
Idiopathic interstitial pneumonia
Nonspecific interstitial pneumonia
Organizing pneumonia
Anti-aminoacyl tRNA synthetase (ARS) antibody

ABSTRACT

Background: Patients with idiopathic interstitial pneumonia (IIP) have a favourable prognosis when they have interstitial pneumonia with autoimmune features (IPAF). However, precise IPAF-related findings from high-resolution computed tomography (HRCT) and lung histopathological specimens and the treatment response have not been fully determined. Therefore, this study was conducted to evaluate the relationship between findings on HRCT or lung histopathological specimens and the progression of interstitial pneumonia in patients with IPAF.

Methods: This multicentre cohort study prospectively enrolled consecutive patients with IIP. At the diagnosis of IIP, we systematically evaluated 74 features suggestive of connective tissue diseases and followed them up. HRCT, lung specimens, serum antibodies, and the clinical course were also evaluated.

Results: Among 222 patients with IIP, 26 (11.7%) fulfilled the IPAF criteria. During a median observation period of 36 months, patients with IPAF showed better survival than those without IPAF ($p = 0.034$). While histopathological findings were not related to IPAF, nonspecific interstitial pneumonia (NSIP) with organizing pneumonia (OP) overlap was the most prevalent HRCT pattern ($p < 0.001$) and the consolidation opacity was the

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https://doi.org/10.1016/j.rmed.2024.107577
Received 30 December 2023; Received in revised form 7 February 2024; Accepted 20 February 2024
Available online 24 February 2024

most common radiological finding in IPAF ($p = 0.017$). Furthermore, in patients with IPAF, the diagnosis of COP or NSIP with OP overlap was associated with a higher increase in %FVC in 1 year than in those with idiopathic pulmonary fibrosis, NSIP, or unclassifiable IIP ($p = 0.002$).
Conclusions: This study shows the presence of consolidation opacity on HRCT and the diagnosis of COP or NSIP with OP overlap are associated with IPAF and its favourable treatment response in patients with IPAF.

1. Introduction

Patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) are frequently seen in clinical practice. CTD-ILD is the most important differential diagnosis of idiopathic interstitial pneumonias (IIPs) with a focus on idiopathic pulmonary fibrosis (IPF). The most important differences between CTD-ILD and IPF are the response to immunosuppressive therapy and the prognosis. Patients with CTD have characteristic extrapulmonary manifestations, such as skin rash and arthralgia, and the prognosis in patients with CTD-ILD is much better than that in those with IPF [1–3]. Therefore, discriminating between these two different diseases is important in clinical practice. However, some patients with IIP have autoimmune features, but do not meet any defined CTD criteria [4].

Fischer et al. proposed comprehensive criteria for interstitial pneumonia with autoimmune features (IPAF) in 2015 as a platform for future studies [5]. Conflicting results regarding the prognostic effects of IPAF were reported after the initial reports of IPAF [2,6–11], probably because these studies were retrospectively designed. Additionally, autoimmune symptoms/signs or autoantibodies were not systematically evaluated at the diagnosis of IIPs. Therefore, a long-term prospective study that systematically examines autoimmune features at the diagnosis of IIPs is critical to precisely evaluate patients with IPAF. Recently, we conducted a long-term, nationwide, prospective study and found that IPAF classification or patients with autoimmune features regardless of IPAF was significantly associated with a favourable prognosis (Prognostic Analysis of IIPs with Rheumatologic features: PAIR cohort study) [12]. However, precise IPAF-related findings on high-resolution computed tomography (HRCT) and those in lung histopathological specimens have not been fully determined. Furthermore, the treatment response for each type of IIP in patients with IPAF is not well known. Therefore, this study was conducted to evaluate the relationship between findings on HRCT or lung histopathological specimens and the progression of interstitial pneumonia in patients with IPAF.

In this study, we systematically evaluated autoimmune symptoms/signs and serum autoantibodies using checklists including 74 CTD-related items at the diagnosis, and followed up patients for a long period (median observation period: 36 months). In patients with IPAF, findings on HRCT and lung histopathological specimens were studied in detail, and the treatment responses in each type of IIP were compared.

2. Methods

2.1. Study design and participants

In this multicentre study (PAIR-2 cohort study), consecutive patients with IIPs aged 15 years or older who had visited or been referred to respiratory departments were prospectively enrolled and followed up from 2015 to 2022, similar to our previous study [12]. All diagnoses of IPF and other IIPs were made in accordance with the 2011 international guidelines for IPF [13], the 2013 international statement for IIPs [14], and the morphologic domain of IPAF criteria [5,15]. These diagnoses were decided using multidisciplinary discussion (MDD) by expert pulmonologists together with radiologists and pathologists with more than 10 years of experience. 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. Patients diagnosed with defined systemic autoimmune diseases within 3 months from the initial diagnosis of IIPs were excluded from the study. Systemic autoimmune diseases were excluded on the basis of the following criteria: 2010 American College of Rheumatology (ACR)/The European Alliance of Associations for Rheumatology (EULAR) classification criteria for rheumatoid arthritis [16], 2012 ACR classification criteria for Sjögren's Syndrome [17], Bohan and Peter criteria for polymyositis/dermatomyositis (PM/DM) [18], 2013 ACR/EULAR classification criteria for systemic sclerosis [19], 1997 ACR revised classification criteria [20] and/or 2012 Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus [21], 1989 criteria for mixed connective tissue disease [22], and the 2007 classification algorithm of antineutrophil cytoplasmic antibody-associated vasculitis [23]. The enrolled patients were checked annually regarding their conditions and survival. The relationships between autoimmune features and the prognosis were prospectively analysed in this observational study.

The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval number: E14-123), and this study was 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 patients.

2.2. Data collection and evaluation of CTD-related features

Clinical data were obtained at the diagnosis of IIP. Acute, subacute, and chronic IIPs were defined as a duration of <1 month, 1–3 months, and ≥ 3 months, respectively, from the onset of respiratory symptoms to the diagnosis of IIP. At the diagnosis of IIPs, 74 autoimmune features related to CTD, such as arthritis, skin rash, and autoantibodies, were systemically searched for according to the "Checklists for detecting CTD-related features" (Supplementary Table S1), in collaboration with specialists in other areas, including rheumatologists, dermatologists, ophthalmologists, and otolaryngologists. However, these specialists other than those in the respiratory field did not always participate in the MDD.

2.3. Statistical analysis

Statistical analyses were performed using JMP 13.1.0 (SAS Institute Inc., Cary, NC, USA) and EZR 1.41 [24]. Categorical data were compared using the χ^2 test or Fisher's exact probability test for independence. Continuous data were analysed 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 of IIP (AE) was estimated considering death before AE as a competing event, and analysed using Gray's method. The relationships between variables and mortality were

Table
1Clinical characteristics and pulmonary function tests 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)

Data are presented as median (range) or n (%).
Abbreviations; IP: interstitial pneumonia, FVC: forced vital capacity, DLCO: diffusion lung capacity for carbon monoxide.

evaluated by Cox proportional hazards regression analysis. All tests were two-sided and statistical significance was set at $p < 0.05$.

3. Results

3.1. Clinical characteristics, physiological findings, and clinical classifications of IIP

Initially, we prospectively enrolled 226 consecutive patients with IIP who had visited or been referred to respiratory departments (Supplementary Fig. S1). Four patients were excluded from this study. Therefore, 222 patients with IIP were included. The clinical characteristics of all patients with IIP are shown in Table 1. The participants had a median age of 71 years, 159 (71.6%) were men, and 185 (83%) showed a chronic onset. Forced vital capacity (FVC) was preserved (median: 84.1%), whereas the diffusion lung capacity for carbon monoxide (DL_{CO}) was impaired (median: 67.8%). The median observation period was 36 months. The diagnoses of 222 patients with IIPs are shown in Supplementary Fig. S2. Eighty-three (37.4%) patients had IPF, 14 (6.3%) had cryptogenic organizing pneumonia (COP), 9 (4.1%) had nonspecific interstitial pneumonia (NSIP), 17 (7.7%) had NSIP with OP overlap, and 71 (32%) had unclassifiable IIP (UCIIP).

3.2. Prevalence and characteristics of patients with IPAF

In all patients with IIPs, the most frequent CTD-related symptom/sign was dry symptoms or findings (7.7%), followed by a mucocutaneous lesion (5.9%) and polyarticular pain or swelling (2.3%) (Supplementary Table S2). Serological data and positivity of autoantibodies are shown in Supplementary Table S3. The frequency of antinuclear antibody (ANA) at a threshold of 1:320 titre was 4.5%. The frequency of rheumatoid factor (RF) at a threshold of 30 IU/mL (2 × the upper limit of normal) was 8.3%. Among CTD-specific autoantibodies, the frequencies of anti-cyclic citrullinated peptide (CCP) antibody, anti-aminoacyl tRNA synthetase (ARS) antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody were 4.2%, 3.8%, and 4.1%, respectively. A comparison of these data between patients with IPAF and those without IPAF is also shown in Supplementary Tables S2 and S3.

The percentages of patients with IIP who met the criteria of IPAF are shown in Fig. 1. In all patients, the percentage of patients fulfilling the IPAF criteria was 11.7% (26 patients). The proportions of IPAF in each group of patients with IPF or non-IPF were 7.2% and 14.4%, respectively ($p = 0.098$, Fig. 1A). With regard to each domain of IPAF, 24 of 26 (92.3%) patients with IPAF fulfilled the morphologic and serologic domain (Fig. 1B and Supplementary Table S4). With regard to each type of IIP, patients who met the IPAF criteria had higher rates of NSIP, COP, and NSIP with OP overlap, and lower rates of IPF and smoking-related ILD than those without IPAF (Fig. 1C, $p = 0.002$). Comparisons of

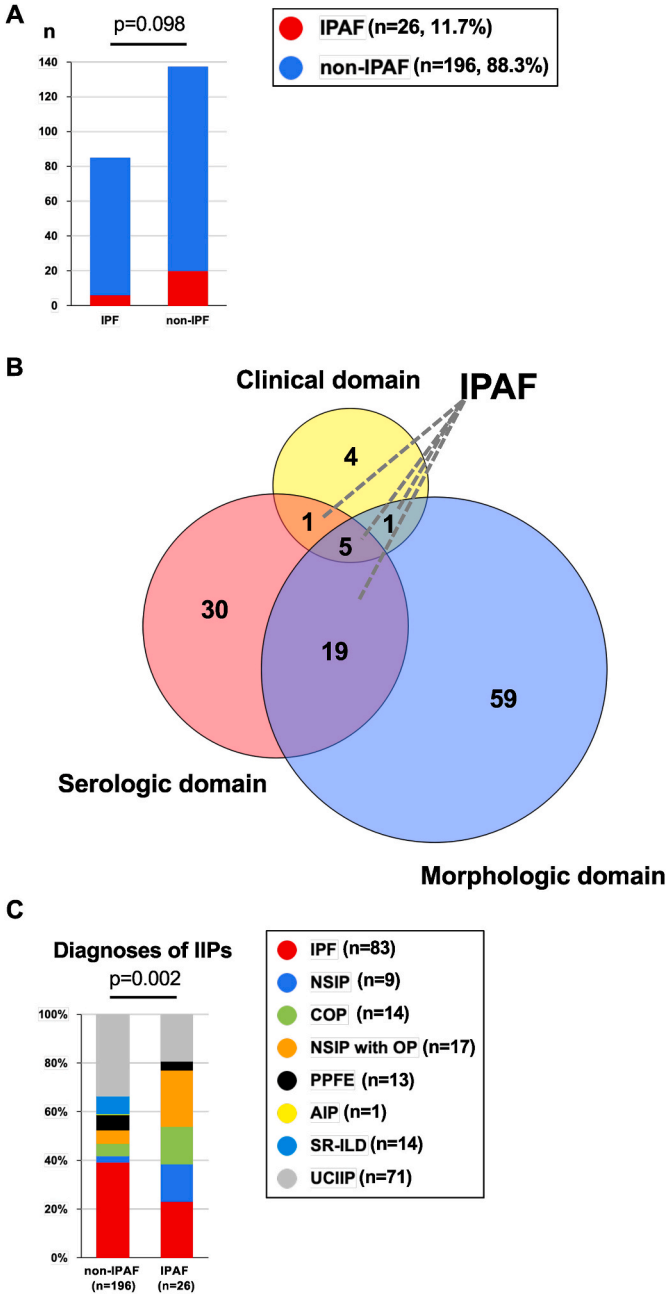

Fig. 1. Proportion of IPAF in patients with IIP and the types of IIPs in patients with IPAF. At the diagnosis of IIP, 74 autoimmune features related to CTD, including arthritis, skin rash, and autoantibodies, were systemically searched for according to the "Checklists for detecting CTD-related features". In all patients with IIPs, the percentage of patients who fulfilled the criteria of IPAF was 11.7% (26 patients). The proportion of IPAF in each group of patients with and without IPF or non-IPF was 7.2% and 14.4%, respectively, and tended to be higher in patients without IPF ($p = 0.098$, A). Twenty-four of 26 (92.3%) patients with IPAF fulfilled both the morphologic and serologic domains (B). Among each classification of IIP, patients who met the IPAF criteria had more NSIP, COP, and NSIP with OP overlap, and the proportion of IPF was decreased ($p = 0.002$, C). In patients with IPAF, the most common diagnosis of IIP was NSIP with OP overlap. IPAF: interstitial pneumonia with autoimmune features, CTD: connective tissue disease, IIP: idiopathic interstitial pneumonia, IPF: idiopathic pulmonary fibrosis, NSIP: nonspecific interstitial pneumonia, COP: cryptogenic organizing pneumonia, PPFE: pleuroparenchymal fibroelastosis, AIP: acute interstitial pneumonia, SR-ILD: smoking-related interstitial lung disease, UCIIP: unclassifiable idiopathic interstitial pneumonia.

Table
2Comparisons of patient characteristics between patients with and without IPAF.

	IPAF (n = 26) (median (range))	non-IPAF (n = 196) (median (range))	p-value
Age, yo	70 (45, 80)	71 (42, 87)	0.710
Female, n (%)	10 (38.5)	53 (27.0)	0.237
Observation period, months	47.5 (11, 85)	36 (0, 68)	0.023
Smoking history, n (%) current/ex/never	4 (15)/14 (54)/8 (31)	29 (15)/111 (57)/56 (28)	0.963
Motives for hospital visit, n (%) symptoms/medical check-up/others	18 (69)/7 (27)/1 (4)	91 (47)/93 (47)/12 (6)	0.087
Onset forms, n (%) acute/subacute/chronic/unknown	5 (19)/3 (12)/18 (69)/0 (0)	13 (7)/14 (7)/167 (85)/2 (1)	0.160
FVC, % predicted	74.9 (52.0, 130.7)	84.5 (28.1, 146.6)	0.255
DL_{CO}, % predicted	65.8 (34.8, 114.5)	69.3 (13.4, 154.4)	0.499
BAL Total cell count, $x10^5$/mL	1.80 (0.27, 11.0)	1.70 (0.16, 34.3)	0.629
Macrophage, %	71.0 (1, 97)	84.5 (7, 99.5)	0.052
Lymphocyte, %	12.5 (1, 69)	6.8 (0, 82.3)	0.092
Eosinophil, %	2.5 (0, 25.6)	1.5 (0, 20)	0.216
Neutrophil, %	2.3 (0, 73)	2.2 (0, 70)	0.995
Prognosis; dead, n (%)	3 (11.5)	55 (28.1)	0.053

Data are presented as median (range) or n (%).
Abbreviations; IPAF: interstitial pneumonia with autoimmune features, FVC: forced vital capacity, DL_{CO}: diffusion lung capacity for carbon monoxide, HRCT: high-resolution computed tomography, GGA: ground-glass attenuation, IPF: idiopathic pulmonary fibrosis, AE: acute exacerbation, CP: chronic progression of IIPs.

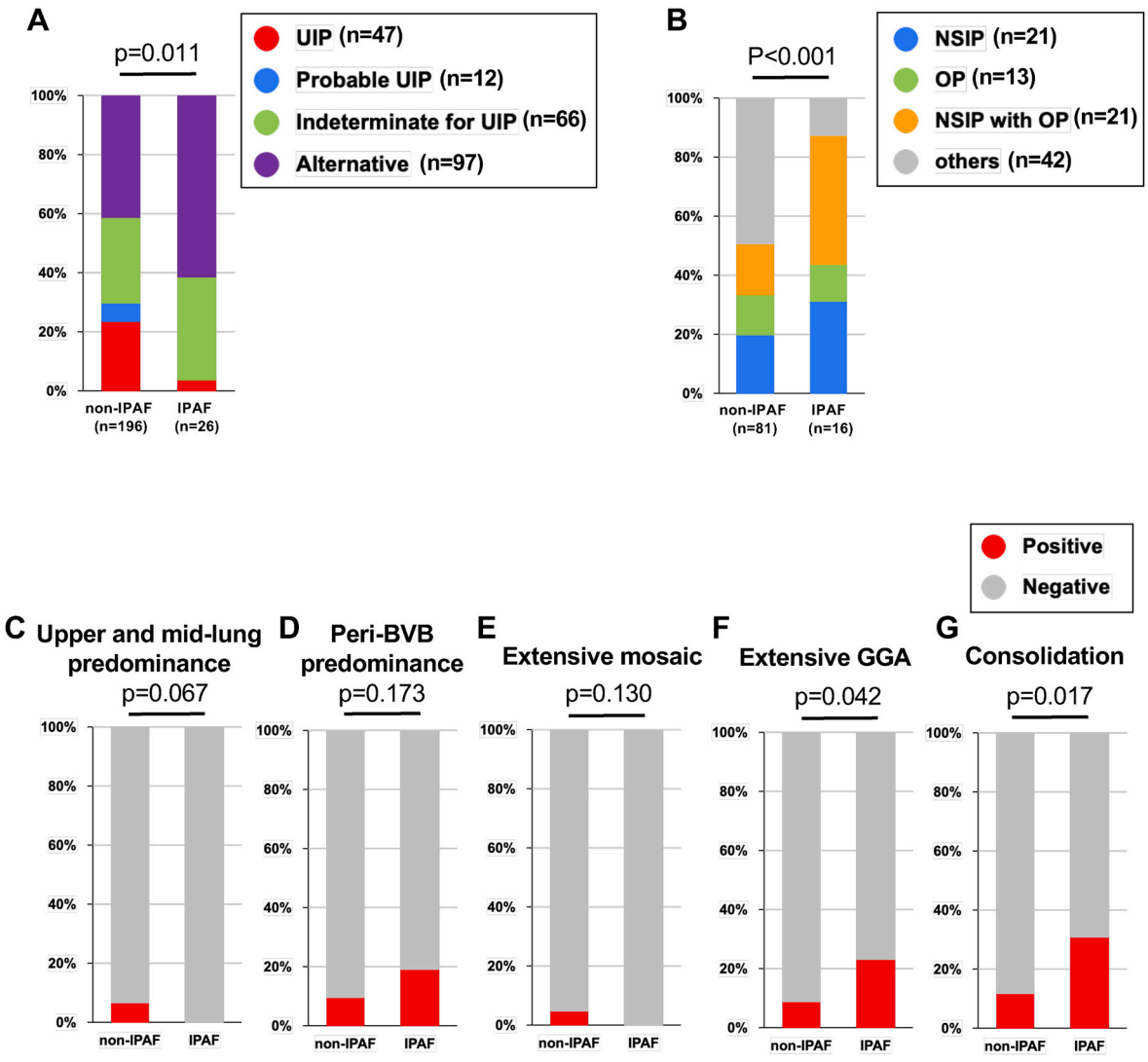

Fig. 2. Findings on HRCT in patients with IPAF. Using the guideline for IPF [13,25], the proportion of the alternative pattern was higher in patients with IPAF than in those without IPAF ($p = 0.011$, A). With regard to the IPAF-related HRCT pattern, based on the morphologic domain of IPAF criteria [5], the NSIP with OP overlap pattern was the most common, and its proportion was significantly higher in patients with IPAF than in those without IPAF ($p < 0.001$, B). With regard to each CTD-related finding on HRCT, upper and mid-lung predominance ($p = 0.067$, C), peri-broncho vascular bundle predominance ($p = 0.173$, D), or extensive mosaic attenuation ($p = 0.130$, E) were not different between the groups. However, the rates of extensive GGA ($p = 0.042$, F) and consolidation opacity ($p = 0.017$, G) were significantly higher in patients with IPAF than in those without IPAF. The relative risk of IPAF was 2.596 when extensive GGA was present (95% CI: 1.162, 5.798) and it was 2.738 when consolidation was present (95% CI: 1.305, 5.747) on HRCT. IPAF: interstitial pneumonia with autoimmune features, HRCT: high-resolution computed tomography, CTD: connective tissue disease, GGA: ground-glass attenuation.

Table
3Comparisons of the positive rates of autoantibodies between patients with IPAF and those without IPAF (only antibodies that have significant difference).

	IPAF (n = 26) [%]	non-IPAF (n = 196) [%]	p-value
Any disease specific Abs, ANA, RF	96.2	18.9	<0.001
Anti-ARS Ab	33.3	0	<0.001
ANA ≥320	26.9	1.5	<0.001
RF ≥ 30	26.1	6.1	0.006
Anti-Scl70 Ab	12.0	0	<0.001
Anti-Centromere Ab	12.0	1.1	0.009
Anti-RNP Ab	15.4	0	<0.001
Anti-CCP Ab	17.4	2.6	0.008
Anti-Sm Ab	8.0	0.6	0.028

Abbreviations; IPAF: interstitial pneumonia with autoimmune features, Ab: antibody, ANA: antinuclear antibody, RF: rheumatoid factor, ARS: anti-aminoacyl tRNA synthetase, RNP: ribonucleoprotein, CCP: cyclic citrullinated peptide, Sm: Smith.

clinical characteristics, pulmonary function data, and findings of bronchoalveolar lavage (BAL) between patients with and without IPAF are shown in Table 2. Although age and sex were similar in the two groups, the proportions of patients who had symptoms and that of lymphocytes in BAL tended to be higher in patients with IPAF than in those without IPAF. Baseline FVC and DL_{CO} tended to be lower in patients with IPAF than in those without IPAF.

3.3. Findings on HRCT in patients with IPAF

On HRCT, based on the guideline for IPF [13,25], the proportion of an "alternative pattern" in patients with IPAF was significantly higher than that in those without IPAF (p = 0.011, Fig. 2A). With regard to IPAF-related HRCT patterns in an alternative pattern for IPF (n = 97), based on the morphologic domain of IPAF criteria [5], the proportion of the NSIP with OP overlap pattern was the most common, and was significantly higher in patients with IPAF than in those without IPAF (p < 0.001, Fig. 2B). With regard to each CTD-related finding on HRCT, there was no difference in upper and mid-lung predominance (p = 0.067), peri-broncho vascular bundle (BVB) predominance (p = 0.173), or extensive mosaic attenuation (p = 0.130) (Fig. 2C–E) between the groups. However, the presence of extensive ground-glass attenuation (GGA) (p = 0.042, Fig. 2F) and consolidation opacity (p = 0.017, Fig. 2G) was significantly higher in patients with IPAF than in those without IPAF. The relative risk of IPAF was 2.596 when extensive GGA was present (95% confidence interval [CI]: 1.162, 5.798) and it was 2.738 when consolidation was present (95% CI: 1.305, 5.747) on HRCT.

3.4. Findings on histopathological specimens and relationship with IPAF or HRCT findings

There was no significant difference in histological pattern between patients with IPAF and those without IPAF (Supplementary Fig. S3A). With regard to histopathological finding, which is suggestive of CTD, the proportion of interstitial lymphoid aggregates with germinal centres (p = 0.265), prominent plasmacytic infiltration (p = 0.813), dense perivascular collagen (p = 0.365), and extensive pleuritis (p = 0.554) were similar in the two groups (Supplementary Figs. S3B–E). However, five of six patients with IPAF and IPF showed interstitial lymphoid aggregates with germinal centres. Furthermore, the relationships between CTD-related findings on HRCT and those on histopathological specimens were evaluated. The presence of consolidation opacity on HRCT was significantly related to histopathological patterns of NSIP, OP, and NSIP with OP, while that of extensive GGA on HRCT was not (Supplementary Figs. S4A and B). The relationships between histopathological patterns and HRCT patterns of ILD are shown in Supplementary Fig. S4C. The NSIP with OP pattern on HRCT was consistent with the histopathological NSIP, OP, and NSIP with OP patterns. The four histopathological findings (interstitial lymphoid aggregates with germinal centres, prominent plasmacytic infiltration, dense perivascular collagen, and extensive pleuritis) were defined as CTD-related histopathological findings. However, there were no significant differences in the five CTD-related findings on HRCT (upper and mid-lung predominance, peri- BVB predominance, extensive mosaic attenuation, extensive GGA, and consolidation opacity) between patients with CTD-related histopathological findings and those without these findings (Supplementary Figs. S4D–H).

3.5. Autoantibodies in patients with IPAF

Significant differences in the positive rates of the following antibodies were found between patients with IPAF and those without IPAF: anti-ARS antibody, ANA titre ≥1:320, RF concentrations ≥30 IU/mL, anti-Scl70 antibody, anti-centromere antibody, anti-ribonucleoprotein antibody, anti-CCP antibody, and anti-Smith (Sm) antibody (Table 3). There were no significant differences in the positive rates of other antibodies measured (Supplementary Table S3). More than 90% of patients with IPAF were positive for any CTD-specific autoantibody (p < 0.001), and the most common autoantibody in patients with IPAF was anti-ARS antibody (p < 0.001) (Table 3). In addition, ANA≥1:320 titre (p < 0.001), RF ≥ 30 IU/mL (p = 0.006), anti-Scl70 antibody (p < 0.001), anti-centromere antibody (p = 0.009), anti-ribonucleoprotein (RNP) antibody (p < 0.001), anti-CCP antibody (p = 0.008), and anti-Sm antibody (p = 0.028) were significantly higher in patients with IPAF than in those without IPAF (Table 3). Half of patients with IPAF were positive for consolidation opacity on HRCT or anti-ARS antibody (p < 0.001, Supplementary Fig. S8A), and its relative risk for IPAF was 4.261 (95% CI: 2.475, 7.336).

3.6. Comparison of treatment response and the survival between patients with IPAF and those without IPAF

More patients with IPAF (19/26, 73.1%) were treated mainly with immunosuppressive therapy than those without IPAF (p = 0.035, Fig. 3A). One year after the diagnosis of IIP, patients with IPAF showed a better improvement in respiratory symptoms (p < 0.001, Fig. 3B) and a change in FVC (p = 0.013, Fig. 3D) than those without IPAF. Lung opacities on HRCT tended to be improved in patients with IPAF (p = 0.109, Fig. 3C). The proportion of patients who met the classification criteria of progressive pulmonary fibrosis (PPF) [26] tended to be lower in patients with IPAF than in those without IPAF (8.3% vs. 20.8%, p = 0.114). Furthermore, patients with IPAF tended to have a lower frequency of AE-IIP than those without IPAF (Gray test, p = 0.218, Fig. 3E). During the observation period, seven (3.2%) patients developed systemic autoimmune diseases, including rheumatoid arthritis (n = 4, 57%), microscopic polyarteritis (n = 2, 29%), and systemic lupus erythematosus (n = 1, 14%) (Supplementary Fig. S5). Patients with IPAF had a significantly better prognosis than those without IPAF (p = 0.034, Fig. 3F), and this difference in survival became more striking when these patients were limited to those who received treatment for IIP (p = 0.014, Fig. 3G). Patients who only met one IPAF domain did not show a significantly better prognosis (Supplementary Figs. S7A–C). Most patients who only met one IPAF domain showed chronic onset of IIP and

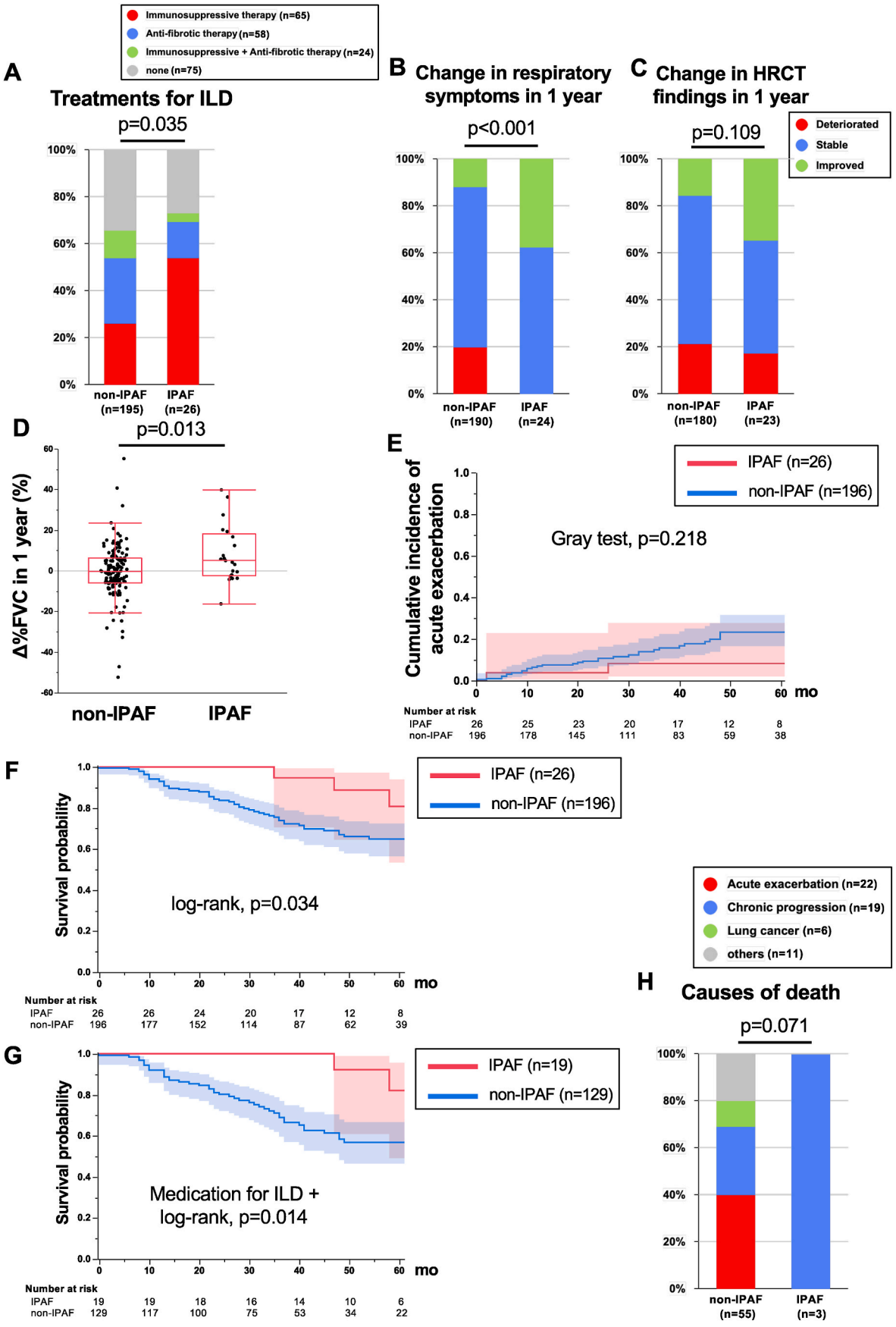

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Fig. 3. Treatment and survival in patients with IPAF or those without IPAF. More patients with IPAF (19/26, 73.1%) were treated mainly with immunosuppressive therapy than those without IPAF ($p = 0.035$, A). One year after the diagnosis of IIP, patients with IPAF showed a significant improvement in respiratory symptoms ($p < 0.001$, B) and ΔFVC ($p = 0.013$, D). HRCT findings tended to improve in patients with IPAF ($p = 0.109$, C). With regard to the development of acute exacerbation of IIP, patients with IPAF tended to have a lower frequency of acute exacerbation of IIP (Gray test, $p = 0.218$, E). With regard to survival, patients with IPAF had a significantly better prognosis than those without IPAF ($p = 0.034$, F). This difference in survival increased when these patients were limited to those who received treatment for IIP ($p = 0.014$, G). Although only three patients with IPAF died, the cause of death was chronic progression of IIP in all of these patients, and acute exacerbation of IIP was not found (H). IPAF: interstitial pneumonia with autoimmune features, FVC: forced vital capacity, HRCT: high-resolution computed tomography, IIP: idiopathic interstitial pneumonia.

were diagnosed as having IPF or UCIIP, but not with COP or NSIP with OP overlap. However, patients who were positive for consolidation opacity on HRCT or anti-ARS antibody received more immunosuppressive therapy (Supplementary Fig. S8C) and showed a significantly better survival than those who were not positive (log-rank test, $p = 0.023$, Supplementary Fig. S8D). These patients mainly consisted of those with COP or NSIP with OP overlap (72.2%, Supplementary Fig. S8B). Only three patients with IPAF died. The cause of death was chronic progression of IIP, and no AE-IIP was found in these three patients with IPAF (Fig. 3H). These effects of IPAF on the prognosis and frequency of AE-IIP were not widely affected by the diagnosis of IPF/non-IPF (Supplementary Fig. S6).

3.7. Comparison of the treatment response and survival between patients with IPAF and those without IPAF with UCIIP

We studied patients without IPAF who had UCIIP ($n = 66$). The treatment response and survival in these patients were compared with those in patients with IPAF including IPF. A significantly higher proportion of patients with IPAF were treated mainly with immunosuppressive therapy than those without IPAF with UCIIP ($p = 0.006$, Fig. 4A). One year after the diagnosis of IIP, patients with IPAF showed a better improvement in respiratory symptoms ($p < 0.001$, Fig. 4B), lung opacities on HRCT ($p = 0.004$, Fig. 4C), and a change in FVC ($p = 0.009$, Fig. 4D) than those without IPAF with UCIIP. The proportion of patients who met the classification criteria of PPF [26] tended to be lower in patients with IPAF than in those without IPAF with UCIIP (8.3% vs. 19.7%, $p = 0.180$). Furthermore, patients with IPAF tended to have a lower frequency of AE-IIP than those without IPAF with UCIIP (Gray test, $p = 0.113$, Fig. 4E). Patients with IPAF had a significantly better prognosis than those without IPAF with UCIIP ($p = 0.048$, Fig. 4F). This difference in survival became more pronounced when these patients were limited to those who received treatment for IIP ($p = 0.010$, Fig. 4G). The cause of death was a mixture of chronic progression of IIP, AE-IIP, and lung cancer in patients without IPAF with UCIIP, while it was limited to chronic progression of IIP in patients with IPAF ($p = 0.151$, Fig. 4H).

3.8. Evaluation of prognostic factors in patients with IIPs

Prognostic factors were evaluated using Cox proportional hazards models of mortality in all patients with IIPs. In univariate models, CTD-related symptoms or auto-antibodies were not significant prognostic factors (Supplementary Table S5). However, IPAF (hazard ratio [HR]: 0.304, $p = 0.017$), the diagnosis of COP or NSIP with OP overlap (HR: 0.302, $p = 0.016$), and the presence of consolidation opacity on HRCT or anti-ARS antibody (HR: 0.325, $p = 0.011$) were significant prognostic factors. Significant factors in univariable models and other important CTD-related factors are also shown in multivariable models adjusted for age, sex, FVC, and the diagnosis of IPF/non-IPF (Table 4). Even after adjustments, IPAF classification (HR: 0.287, $p = 0.014$) and the diagnosis of COP or NSIP with OP overlap (HR: 0.162, $p = 0.002$) were still significant prognostic factors in patients with IIP. Furthermore, the presence of consolidation opacity on HRCT or anti-ARS antibody was a significant prognostic factor (HR: 0.317, $p = 0.017$).

3.9. Favourable disease course in patients with IPAF and COP or NSIP with OP overlap

Patients with IPAF were more commonly diagnosed with NSIP with OP overlap or COP than those without IPAF (Fig. 1C). A representative case of NSIP with OP overlap is shown in Fig. 5A and B. This patient was a 67-year-old woman with subacute onset of a dry cough and dry mouth. She was a never-smoker and serum anti-ARS antibody was positive. HRCT showed GGA and patchy consolidation opacity along the BVB mixed with peripheral opacity mainly in the lower lobes (Fig. 5A). Haematoxylin–eosin staining of specimens by a surgical lung biopsy showed spatially and temporally homogenous mononuclear cell infiltration mixed with slight collagen deposition (Fig. 5B). Furthermore, many areas of patchy granulation tissue in air space were found (Fig. 5B). She was classified as IPAF and diagnosed with NSIP with OP overlap by an MDD team meeting. Similar to in this patient, acute/subacute onset was found in 8/26 (30.8%) patients with IPAF. With regard to each type of IIP, patients who met the IPAF criteria with acute/subacute onset had higher rates of COP and NSIP with OP overlap than those with chronic onset (Fig. 5C, $p = 0.002$). No patients had IPF in the acute/subacute group. As shown in Figs. 3A and 73.1% of patients with IPAF were treated mainly with immunosuppressive therapy. In patients with IPAF, the change in %FVC in 1 year was significantly greater in patients with acute/subacute onset than in those with chronic onset (Fig. 5D, $p = 0.003$). Changes in %FVC in each type of IIP are shown in Fig. 5E. The change in %FVC in 1 year was significantly greater in patients with NSIP with OP overlap than in those with IPF ($p = 0.020$). Furthermore, when these IIPs were divided into two groups, patients with COP or NSIP with OP overlap showed a significantly higher increase in %FVC than did those with IPF or NSIP or UCIIP ($p = 0.002$, Fig. 5F). When these patients were limited to those who received treatment, patients with COP or NSIP with OP overlap showed a more striking increase in %FVC ($p = 0.001$, Fig. 5G). These patients with IPAF and COP or NSIP with OP overlap comprised 25% of those who were positive for consolidation opacity on HRCT or anti-ARS antibody (data not shown). Therefore, these subtypes in patients are similar but not identical. With regard to survival, three patients with IPAF died during the observation period (two with NSIP and one with UCIIP). Patients with COP or NSIP with OP overlap tended to have a better prognosis than those with other IIPs in IPAF ($p = 0.201$, Fig. 5H).

4. Discussion

In this multicentre prospective cohort study, 74 autoimmune features were searched at the diagnosis in 222 patients with IIPs, and these patients were followed up for a long period. To the best of our knowledge, this is the first long-term prospective study to comprehensively study IPAF-related findings on HRCT/histopathological specimens and

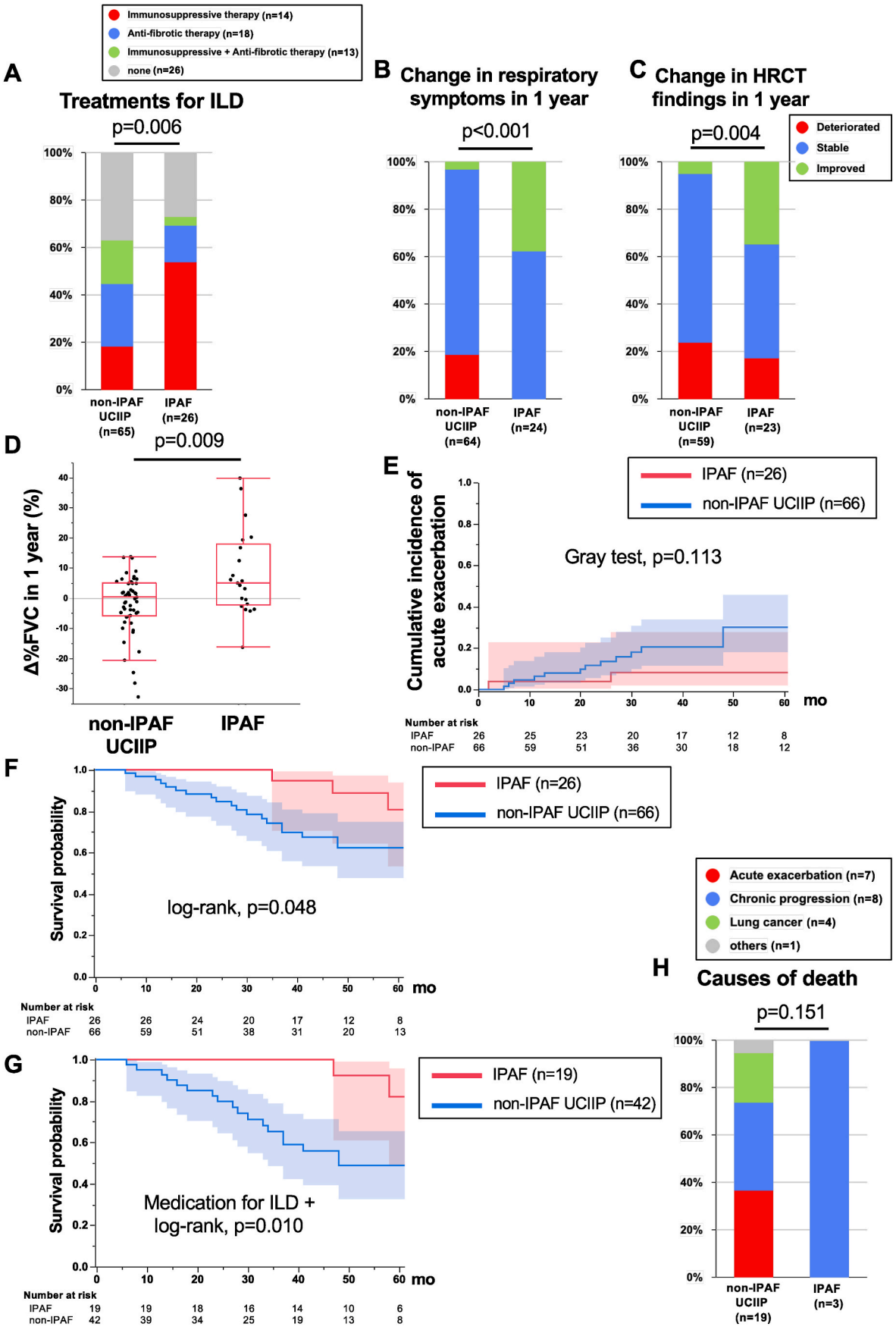

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Fig. 4. Treatment and survival in patients with IPAF and in those without IPAF with UCIIP. Patients without IPAF were limited to those with UCIIP (n = 66). The treatment response and survival in these patients were compared with those in patients with IPAF including IPF. A significantly higher proportion of patients with IPAF were treated mainly with immunosuppressive therapy than those without IPAF with UCIIP (p = 0.006, A). One year after the diagnosis of IIP, patients with IPAF showed a better improvement in respiratory symptoms (p < 0.001, B), lung opacities on HRCT (p = 0.004, C), and a change in FVC (p = 0.009, D) than those without IPAF with UCIIP. Patients with IPAF tended to have a lower frequency of AE-IIP than those without IPAF with UCIIP (Gray test, p = 0.113, E). Patients with IPAF had a significantly better prognosis than those without IPAF with UCIIP (p = 0.048, F). This difference in survival became more pronounced when these patients were limited to those who received treatment for IIP (p = 0.010, G). The causes of death were chronic progression of IIP, AE-IIP, and lung cancer in patients without IPAF with UCIIP, while it was limited to chronic progression of IIP in patients with IPAF (p = 0.151, H). IPAF: interstitial pneumonia with autoimmune features, UCIIP: unclassifiable idiopathic interstitial pneumonia, FVC: forced vital capacity, HRCT: high-resolution computed tomography, IIP: idiopathic interstitial pneumonia.

Table
4Multivariable 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
Consolidation on HRCT or Anti-ARS antibody, +	0.317	0.092	0.831	0.017
Any CTD-like lung pathological lesion	1.859	0.580	6.394	0.298
IPAF, +	0.287	0.069	0.804	0.014
IPAF clinical domain, +	0.722	0.116	2.410	0.642
IPAF serologic domain, +	0.554	0.278	1.025	0.060
IPAF morphologic domain, +	0.775	0.402	1.440	0.427
COP or NSIP with OP overlap, +	0.162	0.026	0.557	0.002
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-min 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, IPAF: interstitial pneumonia with autoimmune features, ILD: interstitial lung diseases, PPF: Progressive pulmonary fibrosis, NC: not calculated.

to evaluate the treatment response in each subtype of IPAF. During a median observation period of 36 months, patients with IPAF showed a better survival than those without IPAF. While histopathological findings were not related to IPAF, the NSIP with OP overlap pattern and consolidation opacity were most commonly observed on HRCT, and anti-ARS antibody was the most common autoantibody in patients with IPAF. Finally, among patients with IPAF, those with COP or NSIP with OP overlap showed a significant higher increase in %FVC in 1 year than those with other IIPs.

The IPAF criteria consist of clinical, serologic, and morphologic domains, and at least two domains need to be met for the classification of IPAF [5]. In these three domains, the serologic and morphologic domains included more patients with IPAF than the clinical domain in the present study, similar to previous studies [12,27,28]. In addition, CTD-related symptoms were not significant prognostic factors in the current study. Therefore, the serologic and morphologic domains may have a relatively large effect on the classification of IPAF and its favourable prognosis in patients with IIP who visit respiratory clinics. However, precise IPAF-related findings on HRCT and lung histopathological specimens have not been previously described.

In this study, consolidation and extensive GGA on HRCT, but not histopathological findings, were related to the classification of IPAF. In particular, consolidation opacity on HRCT was the most prevalent finding in patients with IPAF. Furthermore, with regard to HRCT patterns, the proportion of the NSIP with OP overlap pattern, which is listed in the morphologic domain of the IPAF criteria [5], was higher than that of OP or NSIP pattern in patients with IPAF. Consolidation opacity and OP and NSIP with OP overlap patterns on HRCT are frequently observed in patients with PM/DM-related ILD [29]. In addition, the NSIP with OP overlap pattern showing consolidation opacity on HRCT is related to the development of PM/DM after the initial diagnosis of IIP [15]. Graham et al. also reported that the positivity of myositis-specific antibodies, including anti-ARS antibody, in IPAF were associated with a higher proportion of the OP and NSIP with OP overlap patterns on HRCT and a better prognosis [30]. Even in the current study, patients with IPAF and COP or NSIP with OP overlap showed a higher increase in %FVC than those with other IIPs. Therefore, the classification of IPAF and its better prognosis may be associated with PM/DM-related factors, but not systemic sclerosis-related factors. When patients with IIP have anti-ARS antibody positivity, this disease entity is referred to as anti-synthetase syndrome (ASSD) [31–33]. Recent findings suggest that ASSD is a unique entity with a different clinical phenotype and prognostic factors compared with other forms of IIP or myositis. However, there were no widely accepted and validated definitions or criteria for ASSD at the time of completing the current study (systematically reviewed by Zanframundo G et al., in 2022 [34]). In the near future, we believe that ASSD will be assigned as one of the defined CTDs, and that anti-ARS antibody will be removed from the serologic domain of the IPAF criteria.

This study has several limitations. First, the number of patients with IPAF, especially in those with IPF, was relatively small, and these findings need to be validated. Second, treatments for IIPs were not uniform. Especially in patients with IPF and IPAF, immunosuppressive treatments including corticosteroids may not be harmful, but effective instead, particularly in the early stage of IPF with IPAF. Therefore, larger studies with a uniform treatment regimen are required in the future.

In conclusion, this prospective, multicentre cohort study evaluated patients with IPAF on the basis of a systematic examination of autoimmune features. We determined the clinical significance of consolidation opacity on HRCT and serum anti-ARS antibody in the classification of IPAF. Furthermore, the diagnosis of COP or NSIP with OP overlap was associated with a favourable change in %FVC in patients with IPAF. Future studies are required to validate these results and to modify IPAF criteria for determining the proper treatment selection.

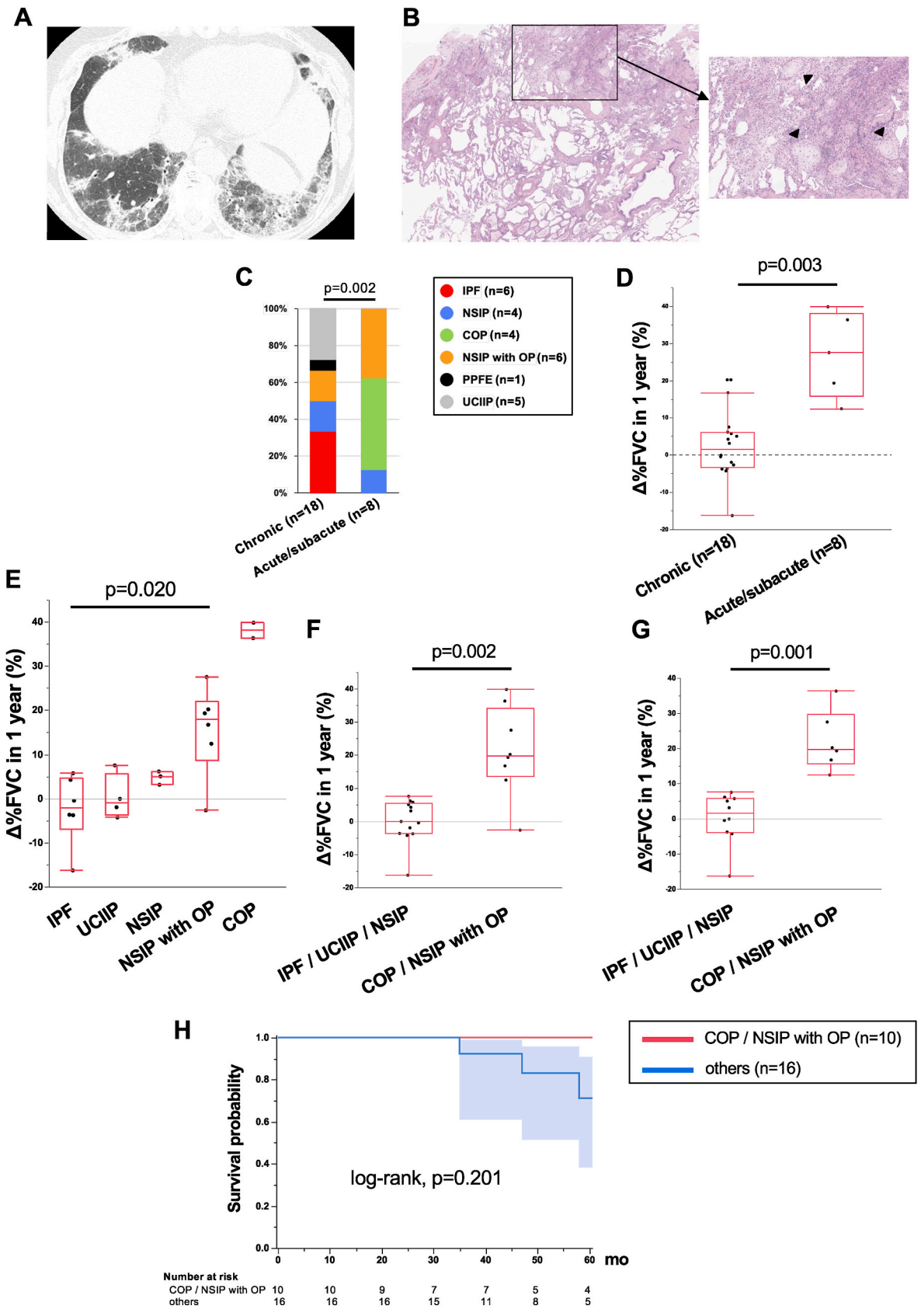

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Fig. 5. Favourable disease course in patients with IPAF and COP or NSIP with OP overlap. A representative case of NSIP with OP overlap is shown (A and B). This patient was a 67-year-old woman with subacute onset of a dry cough and dry mouth. Serum anti-ARS antibody was positive. HRCT shows GGA and patchy consolidation opacity along the BVB mixed with peripheral opacity mainly in the lower lobes (A). Haematoxylin–eosin staining of specimens by a surgical lung biopsy shows spatially and temporally homogenous mononuclear cell infiltration mixed with slight collagen deposition (lower magnification, B). In addition, many areas of patchy granulation tissue in air spaces can be seen (arrowheads in higher magnification, B). She was classified as IPAF and diagnosed with NSIP with OP overlap. Similar to in this patient, acute/subacute onset was found in 8/26 (30.8%) patients with IPAF. With regard to each type of IIP, patients who met the IPAF criteria with acute/subacute onset had higher rates of COP and NSIP with OP overlap than those with chronic onset ($p = 0.002$, C). No patients had IPF in the acute/subacute group. In patients with IPAF, the change in %FVC in 1 year was significantly greater in patients with acute/subacute onset than in those with chronic onset ($p = 0.003$, D). In patients with IPAF, changes in %FVC in each IIP are shown (E). The change in %FVC in 1 year was significantly higher in patients with NSIP with OP overlap than in those with IPF ($p = 0.020$). Furthermore, when these IIPs were divided into two groups, patients with COP or NSIP with OP overlap showed a significantly higher rate of %FVC than those with IPF, NSIP, or UCIIP ($p = 0.002$, F). When these patients were limited to those who received treatment, patients with COP or NSIP with OP overlap showed a more striking increase in %FVC than those with IPF, NSIP, or UCIIP ($p = 0.001$, G). Patients with IPAF and COP or NSIP with OP overlap tended to have a better prognosis than those with other IIPs ($p = 0.201$, H). IPAF: interstitial pneumonia with autoimmune features, COP: cryptogenic organizing pneumonia, NSIP: nonspecific interstitial pneumonia, HRCT: high-resolution computed tomography, BVB: bronchovascular bundle, GGA: ground-glass attenuation, FVC: forced vital capacity, IPF: idiopathic pulmonary fibrosis, UCIIP: unclassifiable idiopathic interstitial pneumonia.

Availability of data and materials

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.

Funding

This research was funded by Boehringer Ingelheim Co., Ltd.

CRediT authorship contribution statement

Noriyuki Enomoto: Writing – original draft, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Shusuke Yazawa:** Data curation. **Yasutaka Mochizuka:** Data curation. **Atsuki Fukada:** Data curation. **Yuko Tanaka:** Data curation. **Hyogo Naoi:** Data curation. **Yuya Aono:** Data curation. **Yusuke Inoue:** Data curation. **Hideki Yasui:** Data curation. **Masato Karayama:** Data curation. **Yuzo Suzuki:** Data curation. **Hironao Hozumi:** Data curation. **Kazuki Furuhashi:** Data curation. **Mikio Toyoshima:** Data curation. **Masato Kono:** Data curation. **Shiro Imokawa:** Data curation. **Takehisa Sano:** Data curation. **Taisuke Akamatsu:** Data curation. **Naoki Koshimizu:** Data curation. **Koshi Yokomura:** Data curation. **Hiroyuki Matsuda:** Data curation. **Yusuke Kaida:** Data curation. **Masahiro Shirai:** Data curation. **Kazutaka Mori:** Formal analysis, Data curation. **Masafumi Masuda:** Data curation. **Tomoyuki Fujisawa:** Data curation. **Naoki Inui:** Data curation. **Yutaro Nakamura:** Writing – review & editing, Supervision, Data curation. **Hiroaki Sugiura:** Methodology, Formal analysis. **Hiromitsu Sumikawa:** Methodology, Formal analysis. **Masashi Kitani:** Methodology, Formal analysis. **Kazuhiro Tabata:** Methodology, Formal analysis. **Noriyoshi Ogawa:** Writing – review & editing, Supervision, Methodology. **Takafumi Suda:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Noriyuki Enomoto received funding from Boehringer Ingelheim Japan Co., Ltd.

All of other authors did not receive funding.

Acknowledgements

This study was assisted by the Japanese Respiratory Society, the Study Group on Diffuse Lung Disease, and the Scientific Research/Research on Intractable Diseases in the Ministry of Health, Labour and Welfare of Japan. We thank Ellen Knapp, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107577.

References

[1] N. Enomoto, T. Suda, M. Kato, Y. Kaida, Y. Nakamura, S. Imokawa, M. Ida, K. Chida, Quantitative analysis of fibroblastic foci in usual interstitial pneumonia, Chest 130 (1) (2006) 22–29.

[2] J.M. Oldham, A. Adegunsoye, E. Valenzi, C. Lee, L. Witt, L. Chen, A.N. Husain, S. Montner, J.H. Chung, V. Cottin, A. Fischer, I. Noth, R. Vij, M.E. Strek, Characterisation of patients with interstitial pneumonia with autoimmune features, Eur. Respir. J. 47 (6) (2016) 1767–1775.

[3] J.V. Pugashetti, A. Adegunsoye, Z. Wu, C.T. Lee, A. Srikrishnan, S. Ghodrati, V. Vo, E.A. Renzoni, A.U. Wells, C.K. Garcia, F. Chua, C.A. Newton, P.L. Molyneaux, J. M. Oldham, Validation of proposed criteria for progressive pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 207 (1) (2023) 69–76.

[4] D. Assayag, E.J. Kim, B.M. Elicker, K.D. Jones, J.A. Golden, T.E. King Jr., L.L. Koth, A.K. Shum, P.J. Wolters, H.R. Collard, J.S. Lee, Survival in interstitial pneumonia with features of autoimmune disease: a comparison of proposed criteria, Respir. Med. 109 (10) (2015) 1326–1331.

[5] A. Fischer, K.M. Antoniou, K.K. Brown, J. Cadranel, T.J. Corte, R.M. du Bois, J. S. Lee, K.O. Leslie, D.A. Lynch, E.L. Matteson, M. Mosca, I. Noth, L. Richeldi, M. E. Strek, J.J. Swigris, A.U. Wells, S.G. West, H.R. Collard, V. Cottin, An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features, Eur. Respir. J. 46 (4) (2015) 976–987.

[6] S. Chartrand, J.J. Swigris, L. Stanchev, J.S. Lee, K.K. Brown, A. Fischer, Clinical features and natural history of interstitial pneumonia with autoimmune features: a single center experience, Respir. Med. 119 (2016) 150–154.

[7] K. Ahmad, T. Barba, D. Gamondes, M. Ginoux, C. Khouatra, P. Spagnolo, M. Strek, F. Thivolet-Bejui, J. Traclet, V. Cottin, Interstitial pneumonia with autoimmune features: clinical, radiologic, and histological characteristics and outcome in a series of 57 patients, Respir. Med. 123 (2017) 56–62.

[8] K. Yoshimura, M. Kono, Y. Enomoto, K. Nishimoto, Y. Oyama, H. Yasui, H. Hozumi, M. Karayama, Y. Suzuki, K. Furuhashi, N. Enomoto, T. Fujisawa, Y. Nakamura, N. Inui, H. Sumikawa, T. Johkoh, T.V. Colby, H. Sugimura, T. Suda, Distinctive characteristics and prognostic significance of interstitial pneumonia with autoimmune features in patients with chronic fibrosing interstitial pneumonia, Respir. Med. 137 (2018) 167–175.

[9] J. Dai, L. Wang, X. Yan, H. Li, K. Zhou, J. He, F. Meng, S. Xu, G. Liang, H. Cai, Clinical features, risk factors, and outcomes of patients with interstitial pneumonia with autoimmune features: a population-based study, Clin. Rheumatol. 37 (8) (2018) 2125–2132.

[10] B.T. Kelly, T. Moua, Overlap of interstitial pneumonia with autoimmune features with undifferentiated connective tissue disease and contribution of UIP to mortality, Respirology 23 (6) (2018) 600–605.

[11] B.A. Graney, A. Fischer, Interstitial pneumonia with autoimmune features, Ann Am Thorac Soc 16 (5) (2019) 525–533.

[12] N. Enomoto, S. Homma, N. Inase, Y. Kondoh, T. Saraya, H. Takizawa, Y. Inoue, H. Ishii, Y. Taguchi, S. Izumi, Y. Yamano, Y. Tanino, Y. Nishioka, M. Toyoshima, K. Yokomura, S. Imokawa, N. Koshimizu, T. Sano, T. Akamatsu, H. Mukae, M. Kato, N. Hamada, H. Chiba, S. Akagawa, S. Muro, H. Uruga, H. Matsuda, Y. Kaida, M. Kanai, K. Mori, M. Masuda, H. Hozumi, T. Fujisawa, Y. Nakamura, N. Ogawa, T. Suda, Prospective nationwide multicentre cohort study of the clinical significance of autoimmune features in idiopathic interstitial pneumonias, Thorax 77 (2) (2022) 143–153.

[13] G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, T.V. Colby, J. F. Cordier, K.R. Flaherty, J.A. Lasky, D.A. Lynch, J.H. Ryu, J.J. Swigris, A.U. Wells, J. Ancochea, D. Bouros, C. Carvalho, U. Costabel, M. Ebina, D.M. Hansell, T. Johkoh, D.S. Kim, T.E. King, Y. Kondoh, J. Myers, N.L. Muller, A.G. Nicholson, L. Richeldi, M. Selman, R.F. Dudden, B.S. Griss, S.L. Protzko, H.J. Schunemann, An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-

based guidelines for diagnosis and management, Am. J. Respir. Crit. Care Med. 183 (6) (2011) 788–824.
[14] W.D. Travis, U. Costabel, D.M. Hansell, T.E. King, D.A. Lynch, A.G. Nicholson, C. J. Ryerson, J.H. Ryu, M. Selman, A.U. Wells, J. Behr, D. Bouros, K.K. Brown, T. V. Colby, H.R. Collard, C.R. Cordeiro, V. Cottin, B. Crestani, M. Drent, R.F. Dudden, J. Egan, K. Flaherty, C. Hogaboam, Y. Inoue, T. Johkoh, D.S. Kim, M. Kitaichi, J. Loyd, F.J. Martinez, J. Myers, S. Protzko, G. Raghu, L. Richeldi, N. Sverzellati, J. Swigris, D. Valeyre, An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, Am. J. Respir. Crit. Care Med. 188 (6) (2013) 733–748.
[15] N. Enomoto, H. Sumikawa, H. Sugiura, M. Kitani, T. Tanaka, H. Hozumi, T. Fujisawa, T. Suda, Clinical, radiological, and pathological evaluation of "NSIP with OP overlap" pattern compared with NSIP in patients with idiopathic interstitial pneumonias, Respir. Med. 174 (2020) 106201.
[16] D. Aletaha, T. Neogi, A.J. Silman, J. Funovits, D.T. Felson, C.O. Bingham 3rd, N. S. Birnbaum, G.R. Burmester, V.P. Bykerk, M.D. Cohen, B. Combe, K. H. Costenbader, M. Dougados, P. Emery, G. Ferraccioli, J.M. Hazes, K. Hobbs, T. W. Huizinga, A. Kavanaugh, J. Kay, T.K. Kvien, T. Laing, P. Mease, H.A. Menard, L. W. Moreland, R.L. Naden, T. Pincus, J.S. Smolen, E. Stanislawska-Biernat, D. Symmons, P.P. Tak, K.S. Upchurch, J. Vencovsky, F. Wolfe, G. Hawker, Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League against Rheumatism collaborative initiative, Arthritis Rheum. 62 (9) (2010) 2569–2581, 2010.
[17] S.C. Shiboski, C.H. Shiboski, L. Criswell, A. Baer, S. Challacombe, H. Lanfranchi, M. Schiodt, H. Umehara, F. Vivino, Y. Zhao, Y. Dong, D. Greenspan, A. M. Heidenreich, P. Helin, B. Kirkham, K. Kitagawa, G. Larkin, M. Li, T. Lietman, J. Lindegaard, N. McNamara, K. Sack, P. Shirlaw, S. Sugai, C. Vollenweider, J. Whitcher, A. Wu, S. Zhang, W. Zhang, J. Greenspan, T. Daniels, G. Sjogren's International Collaborative Clinical Alliance Research, American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort, Arthritis Care Res. 64 (4) (2012) 475–487.
[18] A. Bohan, J.B. Peter, Polymyositis and dermatomyositis (first of two parts), N. Engl. J. Med. 292 (7) (1975) 344–347.
[19] F. van den Hoogen, D. Khanna, J. Fransen, S.R. Johnson, M. Baron, A. Tyndall, M. Matucci-Cerinic, R.P. Naden, T.A. Medsger Jr., P.E. Carreira, G. Riemekasten, P. J. Clements, C.P. Denton, O. Distler, Y. Allanore, D.E. Furst, A. Gabrielli, M. D. Mayes, J.M. van Laar, J.R. Seibold, L. Czirjak, V.D. Steen, M. Inanc, O. Kowal-Bielecka, U. Muller-Ladner, G. Valentini, D.J. Veale, M.C. Vonk, U.A. Walker, L. Chung, D.H. Collier, M.E. Csuka, B.J. Fessler, S. Guiducci, A. Herrick, V.M. Hsu, S. Jimenez, B. Kahaleh, P.A. Merkel, S. Sierakowski, R.M. Silver, R.W. Simms, J. Varga, J.E. Pope, Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative, Arthritis Rheum. 65 (11) (2013) 2737–2747, 2013.
[20] M.C. Hochberg, Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum. 40 (9) (1997) 1725.
[21] M. Petri, A.M. Orbai, G.S. Alarcon, C. Gordon, J.T. Merrill, P.R. Fortin, I.N. Bruce, D. Isenberg, D.J. Wallace, O. Nived, G. Sturfelt, R. Ramsey-Goldman, S.C. Bae, J. G. Hanly, J. Sanchez-Guerrero, A. Clarke, C. Aranow, S. Manzi, M. Urowitz, D. Gladman, K. Kalunian, M. Costner, V.P. Werth, A. Zoma, S. Bernatsky, G. Ruiz-Irastorza, M.A. Khamashta, S. Jacobsen, J.P. Buyon, P. Maddison, M.A. Dooley, R. F. van Vollenhoven, E. Ginzler, T. Stoll, C. Peschken, J.L. Jorizzo, J.P. Callen, S. S. Lim, B.J. Fessler, M. Inanc, D.L. Kamen, A. Rahman, K. Steinsson, A. G. Franks Jr., L. Sigler, S. Hameed, H. Fang, N. Pham, R. Brey, M.H. Weisman, G. McGwin Jr., L.S. Magder, Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum. 64 (8) (2012) 2677–2686.
[22] D. Alarcon-Segovia, M.H. Cardiel, Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients, J. Rheumatol. 16 (3) (1989) 328–334.
[23] R. Watts, S. Lane, T. Hanslik, T. Hauser, B. Hellmich, W. Koldingsnes, A. Mahr, M. Segelmark, J.W. Cohen-Tervaert, D. Scott, Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies, Ann. Rheum. Dis. 66 (2) (2007) 222–227.
[24] Y. Kanda, Investigation of the freely available easy-to-use software 'EZR' for medical statistics, Bone Marrow Transplant. 48 (3) (2013) 452–458.
[25] G. Raghu, M. Remy-Jardin, J.L. Myers, L. Richeldi, C.J. Ryerson, D.J. Lederer, J. Behr, V. Cottin, S.K. Danoff, F. Morell, K.R. Flaherty, A. Wells, F.J. Martinez, A. Azuma, T.J. Bice, D. Bouros, K.K. Brown, H.R. Collard, A. Duggal, L. Galvin, Y. Inoue, R.G. Jenkins, T. Johkoh, E.A. Kazerooni, M. Kitaichi, S.L. Knight, G. Mansour, A.G. Nicholson, S.N.J. Pipavath, I. Buendia-Roldan, M. Selman, W. D. Travis, S. Walsh, K.C. Wilson, E.R.S.J.R.S. American Thoracic Society, S. Latin American Thoracic, Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ ERS/JRS/ALAT clinical practice guideline, Am. J. Respir. Crit. Care Med. 198 (5) (2018) e44–e68.
[26] G. Raghu, M. Remy-Jardin, L. Richeldi, C.C. Thomson, Y. Inoue, T. Johkoh, M. Kreuter, D.A. Lynch, T.M. Maher, F.J. Martinez, M. Molina-Molina, J.L. Myers, A.G. Nicholson, C.J. Ryerson, M.E. Strek, L.K. Troy, M. Wijsenbeek, M.J. Mammen, T. Hossain, B.D. Bissell, D.D. Herman, S.M. Hon, F. Kheir, Y.H. Khor, M. Macrea, K. M. Antoniou, D. Bouros, I. Buendia-Roldan, F. Caro, B. Crestani, L. Ho, J. Morisset, A.L. Olson, A. Podolanczuk, V. Poletti, M. Selman, T. Ewing, S. Jones, S.L. Knight, M. Ghazipura, K.C. Wilson, Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline, Am. J. Respir. Crit. Care Med. 205 (9) (2022) e18–e47.
[27] N. Jiwrajka, G. Loizidis, K.C. Patterson, M.E. Kreider, C.R. Johnson, W.T. Miller Jr., E.J.M. Barbosa Jr., N. Patel, M.F. Beers, L.A. Litzky, M.D. George, M.K. Porteous, Identification and prognosis of patients with interstitial pneumonia with autoimmune features, J. Clin. Rheumatol. 28 (5) (2022) 257–264.
[28] G. Sambataro, D. Sambataro, L. Spicuzza, F. Meloni, G. Lorini, L. Malatino, M. Colaci, G. Sebastiani, A. Iuliano, C. Canofari, F. Luppi, G. Franco, U. Zanini, A. Manfredi, F. Gozzi, M. Sebastiani, S. Palmucci, L. Cavagna, C. Vancheri, Progression and prognosis of interstitial pneumonia with autoimmune features: a longitudinal, prospective, multi-centre study, Clin. Exp. Rheumatol. 41 (5) (2023) 1140–1148.
[29] S. Palmucci, A. Di Mari, G. Cancemi, I. Pennisi, L.A. Mauro, G. Sambataro, D. Sambataro, F. Galioto, G. Fazio, A. Ferlito, F. Pino, A. Basile, C. Vancheri, Clinical and radiological features of interstitial lung diseases associated with polymyositis and dermatomyositis, Medicina-Lithuania 58 (12) (2022).
[30] J. Graham, I.B. Ventura, C.A. Newton, C. Lee, N. Boctor, J.V. Pugashetti, C. Cutting, E. Joerns, H. Sandhu, J.H. Chung, C.K. Garcia, M. Kadoch, I. Noth, A. Adegunsoye, M.E. Strek, J.M. Oldham, Myositis-specific antibodies identify a distinct interstitial pneumonia with autoimmune features phenotype, Eur. Respir. J. 56 (6) (2020).
[31] G.R. Connors, L. Christopher-Stine, C.V. Oddis, S.K. Danoff, Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest 138 (6) (2010) 1464–1474.
[32] J.C. Lega, Q. Reynaud, A. Belot, N. Fabien, I. Durieu, V. Cottin, Idiopathic inflammatory myopathies and the lung, Eur. Respir. Rev. 24 (136) (2015) 216–238.
[33] J. Solomon, J.J. Swigris, K.K. Brown, Myositis-related interstitial lung disease and antisynthetase syndrome, J. Bras. Pneumol. 37 (1) (2011) 100–109.
[34] G. Zanframundo, S. Faghihi-Kashani, C.A. Scire, F. Bonella, T.J. Corte, T.J. Doyle, D. Fiorentino, M.A. Gonzalez-Gay, M. Hudson, M. Kuwana, I.E. Lundberg, A. Mammen, N. McHugh, F.W. Miller, C. Monteccucco, C.V. Oddis, J. Rojas-Serrano, J. Schmidt, A. Selva-O'Callaghan, V.P. Werth, G. Sakellariou, R. Aggarwal, L. Cavagna, Defining anti-synthetase syndrome: a systematic literature review, Clin. Exp. Rheumatol. 40 (2) (2022) 309–319.