Turk Thorac J 2022; 23(6): 395-402 DOI: 10.5152/TurkThoracJ.2022.22017

Original Article

Clinical, Functional, and Prognostic Evaluation of Idiopathic Pulmonary Fibrosis, Connective Tissue Disease-Associated Interstitial Lung Disease, Interstitial Pneumonia with Autoimmune Features: A Single-Center Prospective Study

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Cite this article as: Öz M, Erol S, Küçükşahin O, Kar İ, Çetin Atasoy K, Özdemir Kumbasar Ö. Clinical, functional, and prognostic evaluation of idiopathic pulmonary fibrosis, connective tissue disease-associated interstitial lung disease, interstitial pneumonia with autoimmune features: A single-center prospective study. *Turk Thorac J.* 2022;23(6):395-402.

Abstract

OBJECTIVE: Our study aimed to evaluate clinical, functional, and prognostic features and to determine the prognosis of idiopathic pulmonary fibrosis, connective tissue disease-associated interstitial lung diseases, and interstitial pneumonia with autoimmune features.

MATERIAL AND METHODS: Sixty-nine cases with interstitial lung diseases were recruited in this study prospectively. Demographic features, symptoms, radiological findings, functional measurements, and immunological markers were recorded twice (at the time of initial admission and in the 12th month). Twenty-four of 69 cases were idiopathic pulmonary fibrosis, 32 were connective tissue disease-associated interstitial lung diseases, and 13 were interstitial pneumonia with autoimmune features .

RESULTS: Most of the patients with idiopathic pulmonary fibrosis were male, while there were more female patients in connective tissue disease-associated interstitial lung diseases and interstitial pneumonia with autoimmune features groups. Female patients (65.0%) predominated in connective tissue disease-associated interstitial lung diseases group ($P < .001$). There was no significant difference in the mean ages of the disease groups, yet connective tissue disease-associated interstitial lung diseases patients were generally younger (min–max: 34–82 years). In the idiopathic pulmonary fibrosis group, only low titers of antinuclear antibody positivity were found. Antinuclear antibody positivity in the connective tissue disease-associated interstitial lung diseases group and interstitial pneumonia with autoimmune features group was high ($P = .001$). The long-term survival of idiopathic pulmonary fibrosis, connective tissue disease-associated interstitial lung diseases, and interstitial pneumonia with autoimmune features patients were 37%, 40 months (median) (95% CI, 5.193-74.807), 48.6%, 80 months (median) (95% CI, 57.032-102.968), 30.8%, 46 months (median) (95% CI, 26.624-65.376), respectively.

CONCLUSION: Although a consensus report describing interstitial lung diseases with autoimmune features has been published, diagnostic criteria for this group are still vague. Since the interstitial pneumonia with autoimmune features group had the worst results in terms of functional loss and survival rates, the follow-up parameters and follow-up algorithm should be established for this group. Clinical and immunological evaluation of the interstitial pneumonia with autoimmune features group should include detailed parameters because of follow-up and to estimate survival.

KEYWORDS: Interstitial lung diseases, collagen tissue diseases, IPF, IPAF
Received: *February 8, 2022* ***Accepted:*** *August 1, 2022* ***Publication Date:*** *September 12, 2022*

INTRODUCTION

Interstitial lung diseases (ILDs) share similar clinical, radiological, and functional features. There are various classifications of ILDs, so the classification of ILDs is controversial. According to the etiology and type of ILDs, treatment response and prognosis are variable. There are similar clinical, radiological, and histopathological features of idiopathic pulmonary fibrosis (IPF) and connective tissue disease (CTD)-associated ILD.[1-4] In recent years, some ILD patients without CTD but having immunological properties have been classified as interstitial pneumonia with autoimmune features (IPAF).[5] The recent definition of IPAF is a further confirmation of the close relationship between CTD and ILD.[6] It is considered that the treatment response and prognosis of the CTD-associated ILD group are different from IPF.[7] Similarly, it has been argued that the prognosis of IPAF could be different from IPF. The prognosis of ILDs is different in subgroups; besides, classification of ILDs is still controversial.[8] Multidisciplinary discussion (MDD) is currently recommended during the diagnostic process of ILD.[9] Multidisciplinary discussion is generally composed of a clinician (often a pulmonologist), a thoracic radiologist, and pathologist with experience in ILD. Other physicians as rheumatologist should be considered only in selected cases who have presence of immunological marker positivity and/or rheumatological symptoms.[10]

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Taking these points into consideration, we aimed to shed light on these patients' diagnostic criteria and prognosis estimation for ILD classification.

MATERIAL AND METHODS

The study was approved by Ankara University, Faculty of Medicine Ethics Committee and the protocol number was 01-09-14. All subjects gave their informed consent before their inclusion in the study.

Patients

We evaluated 69 cases with ILD admitted to the Department of Chest Diseases between May 1, 2013 and May 31, 2015, prospectively. We started to collect cases for our research in May 2013 and continued to May 2015. Data collection was completed in 2015, and in December 2019, we checked records of patients to evaluate long-term survival. Patients who were accepted as IPF, CTD-associated ILD, and IPAF were included in the study. All patients underwent the same diagnostic procedures. Multidisciplinary team (MDT) was composed of a rheumatologist, pulmonologists, and a radiologist specialized in thoracic imaging.

Clinical Assessment

The clinical evaluation was performed firstly by pulmonologists. Patients were queried about cough, dyspnea, Raynaud's phenomenon, arthritis, arthralgia, morning stiffness, myalgia, dry eye, dry mouth, gastroesophageal reflux, dysphagia, photosensitivity, and weight loss.

Chest x-ray, high-resolution computed tomography (HRCT), functional assessment, and immunological markers were evaluated. Demographic features, symptoms, physical examination, laboratory and radiological findings, and functional measurements were evaluated on admission and follow-up were recorded.

Instrumental Assessment

Rheumatoid factor (RF), Anti-nuclear antibody (ANA), and Anti- Cyclic Citrullinated Peptide (anti-CCP) were measured as immunological markers. Detailed immune markers (double stranded DNA antibody-antidsDNA; extractable nuclear antigens antibody-anti-ENA; Sjogren syndrome antibodies- SSA-Ro 60 and SSA-Ro 52; SSB, histidyl tRNA synthetase antibody- anti-Jo1; anti-topoisomerase I- anti-Scl 70; Autoantibodies to ribonucleoproteins -U1-RNP; anti-Ku; Smith antibody- anti-Sm) were measured in the patients who have suspicious symptoms and the positivity of RF and/or ANA. Antinuclear antibody was considered positive when the titer was 1 : 320 or higher with diffuse, speckled, homogeneous patterns, or any titer with a nucleolar or centromere pattern. When the titer of RF was ≥2× upper limit of normal, it was accepted as positivity.[11]

Spirometry and carbon monoxide diffusing capacity (DLCO) measurements, arterial blood gas analysis, and 6-min walking test (6MWT) were used as pulmonary function tests (PFTs) according to ERS/ATS recommendation.[12,13] A worsening of forced vital capacity (FVC) ≥ 10% or DLCO ≥ 15% was considered clinically significant.[14] High-resolution computed tomography was performed after chest x-ray. A Schirmer test was performed to assess dry eye due to the patients complaint of dry eye. And also patients who had complained of dry mouth, a saliva ferning test was applied to dry mouth.[15] Minor salivary gland biopsy was performed in patients having positive saliva ferning test. Nailfold video capillaroscopy and musculoskeletal ultrasonography were used to confirm the specific diagnoses by the Department of Rheumatology.[16] Nailfold capillaroscopy is now a "mainstream" investigation for rheumatologists because a "scleroderma pattern" helps to differentiate primary from secondary Raynaud's phenomenon.[17,18] For patient who had Raynaud's phenomenon, nailfold video capillaroscopy was performed to determine systemic sclerosis.

Patient Classification

The diagnosis of IPF was made according to the ERS/ATS 2011 guideline, which was used to describe IPF at that time.[19] The following criteria were evaluated for the diagnosis of IPF:

- Exclusion of other known causes of ILD, including occupational and environmental exposure, CTD, and drug toxicity,
- Entity of usual interstitial pneumonia (UIP) pattern on HRCT of patients not exposed to surgical lung biopsy,
- Specific findings of assembling of HRCT and surgical lung biopsy pattern in patients exposed to surgical lung biopsy,
- Patients were consulted by rheumatologists when there was clinical suspicion of CTD or any of the serological tests was positive.

All rheumatologic diseases would meet the classification criteria.[6,11,16,17] After rheumatological examination, the CTD-associated ILD group was created. The following criteria were evaluated for the diagnosis of CTD-associated ILD:

- Patients who had ILD and rheumatologic symptoms were examined by a rheumatologist.
- Extrathoracic specific features: Raynaud's phenomenon, arthralgia/arthritis, morning stiffness, skin manifestations (cutaneous sclerosis, distal digital fissuring or tip ulceration, telangiectasia, Gottron's sign, heliotrope rash), oral ulceration, and digital edema.
- Other nonspecific signs: nonandrogenic alopecia, dry eyes or dry mouth, photosensitivity, unintentional weight loss, dysphagia, recurrent unexplained fever, gastroeosophageal reflux, or proximal muscle weakness.

MAIN POINTS

- Interstitial lung diseases (ILDs), also known as diffuse parenchymal lung diseases are a group of diseases sharing similar clinical, radiological, and functional features.
- It is important to diagnose idiopathic pulmonary fibrosis and connective tissue disease-associated ILD as well as interstitial pneumonia with autoimmune features (IPAF) to define clinical, radiological, functional properties and to determine prognosis.
- Since the IPAF group had the worst results in terms of functional loss and survival rates, the follow-up parameters and follow-up algorithm should be established for this group.

In our study, we did not use the criteria of ERS/ATS research statement about the IPAF group because our study had begun before this research was published.[5] In our study, patients with IPAF were determined by using the criteria published in previous studies. The following criteria were evaluated for diagnosis of IPAF:

- The presence of radiological patterns compatible with ILD,
- Exclusion of the presence of specific CTD diagnosis (or presence of unclassified CTD) was considered by rheumatologists,
    - At least 1 feature from clinical findings and at least 1 serological positivity;
    - **Clinical findings:** Raynaud's phenomenon, arthritis, arthralgia, morning stiffness that continued at least 30 minutes, myalgia, dry eye, dry mouth, gastroeosophageal reflux, dysphagia, photosensitivity, and weight loss.
    - **Serological findings:** Rheumatoid factor, ANA, anti-CCP, anti-dsDNA, anti-ENA, SSA-Ro 60, SSA-Ro 52, SSB, anti-Jo1, anti-Scl 70, U1-RNP, anti-Ku, and anti-Sm.

Statistical Analysis

Data were summarized as the mean ± standard deviation and median (minimum–maximum) for continuous variables and frequencies (percentiles) for the categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test as appropriate. Wilcoxon test or the Paired *t*-test was used to compare 2 dependent groups of continuous variables, depending on the distributional properties of the data. Survival analyses on categorical variables were performed using the Kaplan–Meier method, and significant differences between groups were identified using the log-rank test. Long-term survival time was described as from the date of diagnosis to December 31, 2019, and it was expressed as median (95% CI). Statistical significance was set at a value of $P < .05$. The data were analyzed using Statistical Package for the Social Sciences 11.5 for Windows (SPSS Inc., Chicago, Ill, USA) and R programming language. The "survival" and "survminer" packages were used to produce Kaplan–Meier curves for the 3 diagnosis groups of subjects.

RESULTS

Sixty-nine subjects classified as IPF, CTD-associated ILD, and IPAF were accepted for this study (Figure 1).

Demographic Features and Symptoms

Demographic features (gender, age, and the history of smoking) were compared; the IPF group and CTD-associated ILD group differed in terms of gender ratio. Female patients (65.0%) predominated in the CTD-associated ILD group ($P < .001$). In terms of the frequency of symptoms, cough and dyspnea were the most common symptoms in all of the groups. Rheumatologic symptoms were mostly reported in the CTD-associated ILD group. The frequency of gastroesophageal reflux was different among these groups and mostly reported in the IPF group. Dry eye, dry mouth, and arthralgia were less reported in the IPF group (Table 1).

None of the patients had an obstructive pattern on PFTs. A 6MWT was performed on 41 patients with stable general conditions. Distance of walk in the 6MWT was higher in the

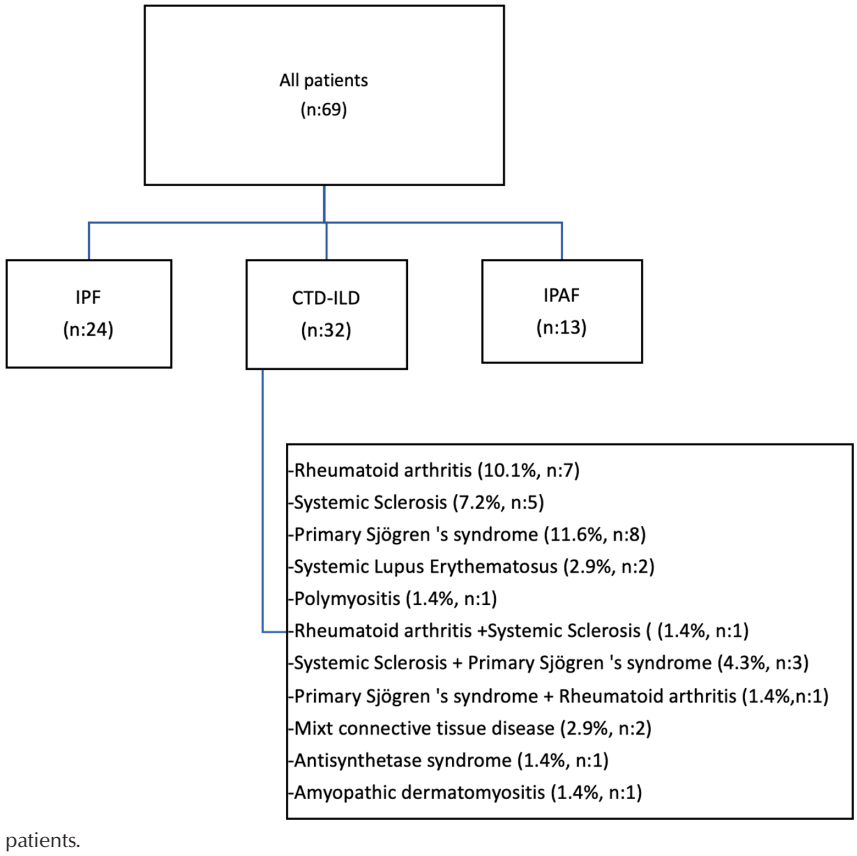

Figure 1. Flowchart of patients.

Table 1. Characteristics, Symptomatic, and Functional Features. PFTs was performed in 23 patients with IPF, 29 patients with CTD-associated ILD, and 9 patients with IPAF groups. PFTs could not be performed in 7 patients because of poor general condition. FVC and DLCO are reported in the percentage of the predicted

Characteristics		IPF n = 24	CTD-Associated ILD n = 32	IPAF n = 13	*P*
Female, n (%)		7 (29.2%)[a]	26 (81.2%)[b]	7 (53.8%)[a,b]	<.001
Age years, mean ± SD		62 ± 10.8	60.9 ± 11.7	60.4 ± 12.1	.912
Smoker (former or current), n (%)		15 (62.5%)	12 (37.5%)	7 (53.8%)	.228
Symptoms, n (%)					
Pulmonary	Cough	20 (83.3%)	18 (56.2%)	10 (76.9%)	.076
	Dyspnea	18 (75%)	30 (93.8%)	11 (84.6%)	.119
Musculoskeletal	Raynaud's phenomenon	0 (0)	6 (18.8%)	1 (7.7%)	.056
	Arthritis	0 (0)	3 (9.4%)	2 (15.4%)	.156
	Arthralgia	1 (4.2%)[a]	12 (37.5%)[b]	3 (23.1%)[a,b]	.014
	Myalgia	3 (12.5%)	2 (6.2%)	1 (7.7%)	.852
	Morning stiffness	1 (7.2%)	7 (21.9%)	3 (23.1%)	.140
	Proximal muscle weakness	0	4 (13.8%)	0	.130
Dermatologial	Skin manifestations	0	4 (13.8%)	0	.130
	Oral ulceration	0	1 (3.6%)	0	.476
	Digital edema	0	1 (3.6%)	0	.476
	Nonandrogenic alopesia	0	1 (3.6%)	0	.476
	Dry eye	1 (4.2%)[a]	15 (46.9%)[b]	4 (30.8%)[a,b]	.002
	Dry mouth	5 (20.8%)[a]	18 (56.2%)[b]	5 (38.5%)[a,b]	.028
Gastrointestinal	GER	7 (29.2%)[a]	1 (3.1%)[b]	2 (15.4%)[a,b]	.017
	Dysphagia	0 (0)	4 (12.5%)	0 (0)	.129
	Photosensitivity	4 (16.7%)	1 (3.1%)	2 (15.4%)	.168
	Weight loss	2 (8.3%)	5 (15.6%)	1 (7.7%)	.701
Other	Recurrent unexplained fever	0	2 (6.9%)	1 (7.7%)	.433
Functional parameters					
	Baseline FVC, mean ± SD	70.1 ± 15.7 n = 23	71.8 ± 19.8 n = 29	67.6 ± 16.2 n = 9	.937
	Baseline DLCO, mean ± SD	40.4 (15.7) n = 17	43.4 (14.6) n = 25	49.8 (23.9) n = 6	.484
6MWT	Walking distance (m), mean ± SD	472.73 ± 116.93[a]	362.06 ± 92.25[b]	356.63 ± 202.27[a,b]	.026
Presence of UIP pattern, n (%)		22 (91.7%)[a]	5 (15.6%)[b]	2 (15.4%)[b]	<.001
Immune markers positivity, n (%)					
	ANA	6 (26.1%)[a]	21 (65.6%)[b]	10 (76.9%)[b]	.001
	RF	2 (9.1%)	8 (25.8%)	2 (15.4%)	.282
	Anti-CCP	0 (0)	4 (13.8%)	0 (0)	.130
	Anti-dsDNA	0 (0)	2 (6.9%)	1 (7.7%)	.433
	SSA-Ro-60	0 (0)[a]	6 (20.7%) [a]	0 (0) [a]	.044
	SSA-Ro-52	0 (0) [a]	8 (28.6%)[b]	0 (0)[a,b]	.005
	SSB	0 (0)	4 (13.8%)	0 (0)	.130
	Anti-Jo-1	0 (0)	2 (6.9%)	1 (7.7%)	.587
	Anti-Scl-70	0 (0)	4 (13.8%)	0 (0)	.130
	U1nRNP	0 (0)	1 (3.6%)	0 (0)	.476
	Anti-Ku	0 (0)	2 (7.4%)	1 (7.7)	.448
	Anti-Sm	0 (0)	2 (6.9%)	1 (7.7%)	.587

Groups with the same superscript letters do not differ from each other.
GER, gastroesophageal reflux; DLCO, diffusion lung for carbon monoxide;, FVC, forced vital capacity; UIP, usual interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung diseases; CTD, connective tissue disease; IPAF, interstitial pneumonia with autoimmune features; ANA, antinuclear antibody; RF, rheumatiod factor; 6MWT, six-minute walking test.

Table 2. Functional Parameters on Follow-Up

Patient Groups		Baseline*	Follow-Up	*P* Value
IPF	FVC, mean ± SD (n = 11)	76.1 ± 11	74.1 ± 11.5	.688
	DLCO, mean ± SD, (n = 7)	52 ± 12.5	49.5 ± 12.9	.242
CTD-associated ILD	FVC, mean ± SD (n = 11)	80.9 ± 20.1	77.1 ± 25.5	.477
	DLCO, mean ± SD (n = 10)	46.2 ± 12.3	45.2 ± 20.2	.838
IPAF	FVC, mean ± SD (n = 3)	80.5 ± 20.1	49 ± 36.8	.180
	DLCO, mean ± SD (n = 3)	47.3 ± 44.3	34.6 ± 31.3	.180

*Baseline PFT parameters include only patients who had follow-up parameters.Abbreviations: IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung diseases; CTD, connective tissue disease; DLCO, diffusion lung for carbon monoxide;, FVC, forced vital capacity.

IPF group than in the others, and this was significant statistically (Table 1).

There was no significant difference among the 3 groups regarding RF positivity. Low titers of RF and ANA positivity were found in the IPF group. Antinuclear antibody positivity was found in 10 patients of the IPAF group, and the presence of CTD was excluded in these patients. Antinuclear antibody positivity in the CTD-associated ILD group and IPAF group was high ($P = .001$) (Table 1).

Saliva ferning test was reported positive in 2 patients (8.3%) with IPF, 14 patients (43.8%) with CTD-associated ILD, and 4 patients (30.8%) with IPAF. Minor salivary gland biopsy was performed in 9 of 14 patients with positive saliva test in the CTD-associated ILD group and was determined positive for Sjogren's syndrome on pathological examination in 4 patients. Schirmer test was applied to only 2 patients with IPF and it was found negative. However, in CTD-associated ILD group, it was applied to 12 patients and positivity was found in 7 patients.

Radiological Features

idiopathic Pulmonary Fibrosis Group

In the IPF group, 22 patients had a UIP pattern on HRCT, but only 2 patients had a possible UIP pattern. The UIP pattern was demonstrated in these 2 patients with surgical biopsy.

onnective Tissue Disease-Associated Interstitial Lung Diseases Group

All patients in CTD-associated ILD group had non-specific interstitial pneumonia (NSIP) pattern on HRCT.

IPAF Group

In the IPAF group, 8 patients had NSIP pattern, 3 patients had organized pneumonia pattern, and 2 patients had subpleural reticulations on HRCT.

Follow-Up

Patients were controlled at 3-6 months intervals. We compared the PFT results at the beginning of the study and at the 12th month control (Table 2). Although there was deterioration in FVC and DLCO in the 12th month, no significant difference was found statistically.

Survival

The survival rates were compared between the groups for the evaluation of prognosis. Sixteen patients (66.7%) with IPF, 20 patients (62.5%) with CTD-associated ILD, and 10 patients (76.9%) with IPAF died during the follow-up. Although the mortality was high in the IPAF group, no statistically significant difference was found among these groups because the number of patients in the groups was different. In the first 2 years of our study, the survival percent of IPF,

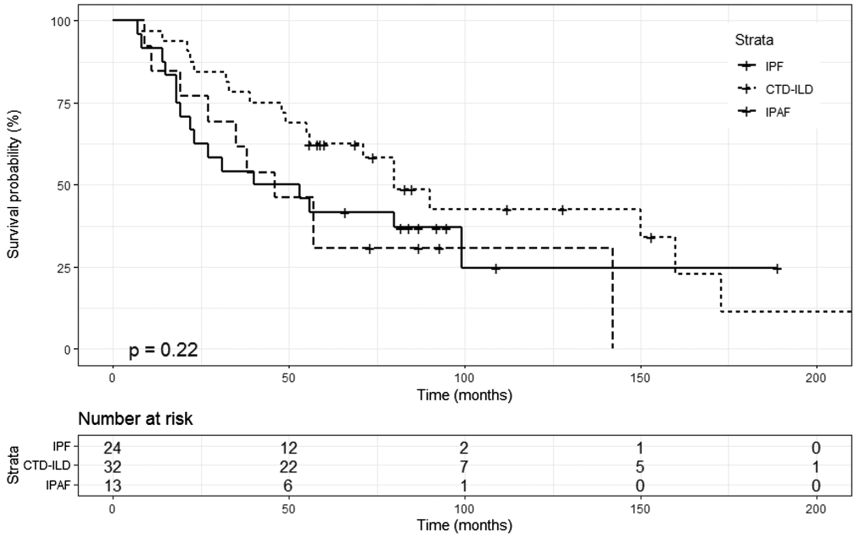

Figure 2. Total survival curves of patients with IPF, CTD-associated ILD, and IPAF groups. Kaplan–Meier survival comparison between IPF, CTD-associated ILD, and IPAF at long term (log-rank, $P = 0.22$) (small dash: IPF, medium dash: CTD-associated ILD, solid line: IPAF). IPF, idiopathic pulmonary fibrosis; CTD-associated ILD, connective tissue disease-associated interstitial lung disease; IPAF, interstitial pneumonia with autoimmune feature.

CTD-associated ILD, and IPAF patients was 62.5%, 84.4%, and 76.9%, respectively. We investigated these patients to evaluate the long-term survival. So we recorded these patients' survival time from the date of diagnosis to December 31, 2019. The long-term survival of IPF, CTD-associated ILD, and IPAF patients was 37% and 40 months (median) (95% CI, 5.193-74.807); 48.6% and 80 months (median) (95% CI, 57.032-102.968); and 30.8% and 46 months (median) (95% CI, 26.624-65.376), respectively (Figure 2).

Prognostic Factors in Idiopathic Pulmonary Fibrosis, Connective Tissue Disease-Associated Interstitial Lung Diseases, and Interstitial Pneumonia with Autoimmune Feature Groups

This study did not detect any factors associated to death at univariate analysis. No difference was observed regarding age, male sex, being a current smoker, DLCO and FVC worsening, and the presence of radiological UIP pattern of the patients.

DISCUSSION

Interstitial lung diseases are diffuse lung diseases with varying appearances in the interstitial region of the lung.[20] In our study, IPF, CTD-associated ILD, and IPAF groups were evaluated for clinical, functional, and prognostic features.

Connective tissue disease–ILD can display a varied clinical course ranging from an incidental sign radiologically to a rapidly progressive disease causing respiratory failure or death. In terms of prognosis and treatment, there were different clinical findings for CTD–ILD and IPF. Patients with CTD–ILD had better results than IPF patients.[21] Prognosis of the IPAF group is not clear yet.

After we had started the research, the task force was published by ERS/ATS in 2015, and the IPAF group was defined. The task force offers the term "interstitial pneumonia with autoimmune features (IPAF)" for cases with some features that recommend an underlying autoimmune duration disease but without a definite diagnosis of CTD (Table 3 in the supplementary document).[5] We first used the term "immune-mediated ILD," but after the publication of the task force, we renamed this group as IPAF. We benefited in line with previous studies and we prefered the term IPAF to describe this group.[4,22,23]

The clinical and serological criteria were found in most of the patients in the previous 3 published cohorts, and there was at least 1 clinical criterion in 47%-63% of IPAF patients.[24-26] The most common clinical sign was Raynaud's phenomenon, and the second most common was distal digital fissuring (mechanic hands); these were followed by arthritis or morning stiffness and unexplained fixed rash on the digital extensor surfaces (Gottron's sign).[27] In a study by Ahmad et al. Gottron's sign, mechanic hand, and distal digital tip ulceration were less commonly seen in IPAF patients (11%, 7%, and 0%, respectively).[24] Ahmad et al suggested that these findings were usually recognized and seen in CTD when the presence of these symptoms caused a diagnosis of dermatomyositis or systemic sclerosis rather than of IPAF.[24] In our study, we did not use Gottron's

Table 3. Classification Criteria for "Interstitial Pneumonia with Autoimmune Features"[5]

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and,
2. Exclusion of alternative etiologies and,
3. Does not meet criteria of a defined connective tissue disease and,
4. At least 1 feature from at least 2 of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

A. Clinical domain
   1. Distal digital fissuring (i.e. "mechanic hands")
   2. Distal digital tip ulceration
   3. Inflammatory arthritis or polyarticular morning joint stiffness ⩾60 min
   4. Palmar telangiectasia
   5. Raynaud's phenomenon
   6. Unexplained digital edema
   7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain
   1. ANA ⩾ 1:320 titer, diffuse, speckled, homogeneous patterns or a. ANA nucleolar pattern (any titer) or b. ANA centromere pattern (any titer)
   2. Rheumatoid factor ⩾ 2 upper limit of normal
   3. Anti-CCP
   4. Anti-dsDNA
   5. Anti-Ro (SS-A)
   6. Anti-La (SS-B)
   7. Anti-ribonucleoprotein
   8. Anti-Smith
   9. Anti-topoisomerase (Scl-70)
   10. Anti-tRNA synthetase (e.g. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
   11. Anti-PM-Scl
   12. Anti-MDA-5

C. Morphologic domain
   1. Suggestive radiology patterns by HRCT (see text for descriptions):
      a. NSIP
      b. OP
      c. NSIP with OP overlap
      d. LIP
   2. Histopathology patterns or features by surgical lung biopsy:
      a. NSIP
      b. OP
      c. NSIP with OP overlap
      d. LIP
      e. Interstitial lymphoid aggregates with germinal centers
      f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
   3. Multi-compartment involvement (in addition to interstitial pneumonia):
      a. Unexplained pleural effusion or thickening
      b. Unexplained pericardial effusion or thickening
      c. Unexplained intrinsic airways disease# (by PFT, imaging or pathology)
      d. Unexplained pulmonary vasculopathy

HRCT, high-resolution computed tomography; ANA, antinuclear antibody; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; LIP, lymphoid interstitial pneumonia; PFT, pulmonary function testing. #Includes airflow obstruction, bronchiolitis, or bronchiectasis.

sign and mechanic hand as the clinical criterion for IPAF because these findings usually have been seen in CTD, and we think that the task force's clinical criteria are arguable and updatable.

Anti-nuclear antibody positivity was higher in CTD-associated ILD and IPAF group. This difference was statistically significant. Although the groups considered as CTD-associated ILD and IPAF were not statistically different from each other, ANA titers in the CTD-associated ILD group were higher than those admitted as IPAF.

At the 12-month follow-up, PFT values were recorded. When the initial and follow-up data of the patients were compared, no statistically significant difference was found. During the data collection period, between May 2013 and May 2015, FVC values decreased by 3% in the IPF group, 5% in the CTD-associated ILD group, and 8% in the IPAF group. Diffusion capacity decreased by 5% in the IPF group, 3% in the CTD-associated ILD group, and 27% in the IPAF group. Although there was no statistically significant decrease in the diffusion capacity assessment, there was a considerable decrease in diffusion capacity in the IPAF group. FVC and DLCO parameters were compared for the progression of illness, and it was seen that the course of the IPAF group was worse than the CTD-associated ILD group, but we could not find statistically significant results for FVC worsening in IPAF (HR: 1.000 [95% CI, 0.801-1.248]) and DLCO worsening in IPAF (HR: 1.298 [95% CI, 0.475-3.547]). Vij et al reported that the progression of the autoimmune ILD group was not different from that of the IPF group, but it had a worse prognosis than the CTD-related ILD group.[4] In our study, although the number of patients considered as IPAF was not statistically significant due to the small number of patients, the course of this group was found to be worse. The course of CTD–ILD group is generally considered to be better than that of IPF. From this perspective, it can be expected that ILD with immune features has a better prognosis than IPF. In our study, the mortality rate of the patients was compared among the groups. Although the mortality rate was higher in the IPF group, no statistically significant difference was found. This was due to the low number of patients and unequal distribution of groups. When we compared groups regarding long-term survival, the survival of patients with IPAF was poorer than the other groups. There was no statistically significant difference in overall survival among groups. Similarly, in the study by Vij et al. the exitus rates of the autoimmune ILD group were not different from IPF. Still, the disease course was worse, and the exitus rate was higher compared to the CTD-associated ILD group. In the IPAF cohort study by Oldham et al. the ERS/ATS criteria to classify patients with autoimmune ILD were retrospectively applied to the patients, survival analysis was evaluated, and the course of IPAF was found to be better than IPF and worse than those with CTD-associated ILD. In a meta-analaysis performed by Kimaya et al. it was mentioned that all-cause mortality of IPAF was significantly better than that of IPF in 2 studies. In the same meta-analysis, mortality of IPAF with UIP pattern was not significantly different from that of IPF, but old age was significantly associated with worse mortality of IPAF.[28] In our study, we did not find statistical significance affecting survival in prognostic parameters such as age, male sex, current smoker, DLCO and FVC worsening, and presence of radiological UIP pattern. These parameters were not observed as effective on prognosis. Contrary to our findings, the presence of UIP pattern and lower DLCO were associated with poorer survival in patients with IPAF.[29]

The main strength of our study is that, since the IPAF group had the worst results in terms of functional loss and survival rates, the follow-up parameters and follow-up algorithm should be established for this group. Although the long-term results of the IPF group were found to be worse in previous studies, it was observed that the IPAF group did not progress better in our study.

Our study provides a different perspective when compared to previous studies in terms of determining the diagnosis and follow-up criteria of the IPAF group.

We think that our study contributes to previous studies about the diagnostic criteria of these 3 groups; IPF, CTD-associated ILD, and IPAF. Especially, creating diagnostic criteria for the IPAF group is very important because of the treatment and prognosis of this group. Survival rates in the IPAF group are not better than IPF or CTD-associated ILD group in our study as different from other studies. We suggest that the diagnostic criteria of the IPAF group should be revised to classify this group and our study offers supportive suggestions.

There are several limitations of our study. Firstly, the number of patients among the groups was low and not equal in each group. Secondly, diseases and the number of patients in the CTD-associated ILD group were heterogeneous. Thirdly, the follow-up could not be performed at the desired intervals in each case. We could assess the patients' 12th-month follow-ups only. Fourthly, we selected IPAF patients according to the previous criteria because ERS/ATS task force criteria were published after our research. The task force has suggested using an agreed description of the IPAF group. Although we were unable to use the criteria of the task force for patient definition, we discussed our consequences by using these criteria. Recommendations of the task force are arguable. Finally, this research provided a short follow-up to investigate prognostic factors. Therefore, at the 12-month follow-up, no statistically significant prognostic factors were found. This duration appears to be too short to assess the prognosis of these groups.

CONCLUSION

In our study, the functional and prognostic features of the 3 groups were similar. Although a consensus report describing IPAF has been published, diagnostic criteria for this group are still problematic. In our study, although the number of patients in the groups was not equal and was low, there was no statistically significant difference between the survival rates. However, the long-time prognosis of the IPAF group described with our criteria was not better than that of the IPF group. It is important to determine patients with different prognosis and those who need different treatment protocols. Studies with more cases are necessary to determine the characteristics of this group.

Ethics Committee Approval: This study was approved by Ehtics committee of Ankara University Faculty of Medicine, (Approval No: 01-09-14, Date: Jan 13, 2014).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Ö., Ö.Ö.K.; Design – M.Ö., Ö.Ö.K.; Supervision – Ö.Ö.K; Materials – M.Ö., Ö.Ö.K.; Data Collection and/or Processing – M.Ö., Ö.Ö.K.; Amalysis and/or Interpretation – İ.K.; Literature Review – M.Ö., S.E., O.K., K.Ç.A., Ö.Ö.K.; Critical Review – M.Ö., S.E, O.K, K.Ç.A., Ö.Ö.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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