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Original Article

Evaluation of Patients with Fibrotic Interstitial Lung Disease: Preliminary results from the Turk-UIP Study

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Abstract

OBJECTIVE: Differential diagnosis of idiopathic pulmonary fibrosis (IPF) is important among fibrotic interstitial lung diseases (ILD). This study aimed to evaluate the rate of IPF in patients with fibrotic ILD and to determine the clinical-laboratory features of patients with and without IPF that would provide the differential diagnosis of IPF.

MATERIAL AND METHODS: The study included the patients with the usual interstitial pneumonia (UIP) pattern or possible UIP pattern on thorax high-resolution computed tomography, and/or UIP pattern, probable UIP or possible UIP pattern at lung biopsy according to the 2011 ATS/ERS/JRS/ALAT guidelines. Demographics and clinical and radiological data of the patients were recorded. All data recorded by researchers was evaluated by radiology and the clinical decision board.

RESULTS: A total of 336 patients (253 men, 83 women, age 65.8±9.0 years) were evaluated. Of the patients with sufficient data for diagnosis (n=300), the diagnosis was IPF in 121 (40.3%), unclassified idiopathic interstitial pneumonia in 50 (16.7%), combined pulmonary fibrosis and emphysema (CPFE) in 40 (13.3%), and lung involvement of connective tissue disease (CTD) in 16 (5.3%). When 29 patients with definite IPF features were added to the patients with CPFE, the total number of IPF patients reached 150 (50%). Rate of male sex ($p<0.001$), smoking history ($p<0.001$), and the presence of clubbing ($p=0.001$) were significantly high in patients with IPF. None of the women <50 years and none of the men <50 years of age without a smoking history were diagnosed with IPF. Presence of at least 1 of the symptoms suggestive of CTD, erythrocyte sedimentation rate (ESR), and antinuclear antibody (FANA) positivity rates were significantly higher in the non-IPF group ($p<0.001$, $p=0.029$, $p=0.009$, respectively).

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CONCLUSION: The rate of IPF among patients with fibrotic ILD was 50%. In the differential diagnosis of IPF, sex, smoking habits, and the presence of clubbing are important. The presence of symptoms related to CTD, ESR elevation, and FANA positivity reduce the likelihood of IPF.

KEYWORDS: Fibrotic interstitial lung diseases, idiopathic pulmonary fibrosis, usual interstitial pneumonia

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INTRODUCTION

Diffuse parenchymal lung disease is a category of chronic diseases encompassing approximately 200 different conditions. Incidence rates have been reported to be between 3.6 and 32 per 100,000 [1, 2]. The 2 most common diseases in this category are sarcoidosis and idiopathic pulmonary fibrosis (IPF). In a study by the Turkish Thoracic Society published in 2014, the incidence of interstitial lung diseases (ILD) in Turkey was reported as 25.8 per 100,000; and of all the patients with diffuse parenchymal lung disease, 37% was found to be sarcoidosis and 19% to be IPF [3].

The differential diagnosis of IPF is important among ILD, especially in patients with fibrosis, owing to a survival rate of 3 to 5 years and no known definitive treatment other than transplantation. Unfortunately, when evaluated according to published guidelines, only 70% of the patients with IPF could be diagnosed with certainty. In many patients who underwent lung biopsy, a definitive diagnosis could not be reached; and a multi-disciplinary approach was required for the final diagnosis. In addition, fewer lung biopsies are undertaken in this patient category worldwide because of the risk of acute exacerbation as a complication. Therefore, there is a need for methods to facilitate a diagnosis without biopsy in patients who cannot be diagnosed clinically and radiologically.

This study aimed to estimate the rate of IPF in patients with fibrotic ILD and to determine characteristics that would enable the differential diagnosis of IPF by contrasting clinical-laboratory characteristics of patients with and without IPF.

MATERIAL AND METHODS

Our study was organized by the clinical problems working group of the Turkish Thoracic Society. Ethics committee approval was obtained on March 8, 2016 (No: 2016/11). In addition, the research was recorded in clinicalTrials.gov.

MAIN POINTS

- Differential diagnosis of idiopathic pulmonary fibrosis (IPF) is important among fibrotic interstitial lung diseases (ILD).
- Rate of IPF among patients with fibrotic ILD was 50%. In the differential diagnosis of IPF, sex, smoking habits, and the presence of clubbing are important factors to be considered.
- None of the women above 50 years of age was diagnosed with IPF, and none of the men above 50 years of age without a smoking history was diagnosed with IPF.
- Presence of symptoms related to connective tissue diseases, ESR elevation, and FANA positivity reduces the likelihood of IPF.

The study was announced to 4,080 members of the Turkish Thoracic Society via e-mail. Researchers who reported following 5 or more patients with IPF per year were included in the study. A total of 50 clinicians from 36 centers spanning 19 cities participated in the study. Patients who were newly diagnosed as of January 01, 2016, and whose high resolution computed tomography (HRCT) of thorax or biopsy had been performed in the previous 3 months, were included in the study. Inclusion criteria were usual interstitial pneumonia (UIP) pattern or possible UIP pattern on thorax HRCT and/or UIP pattern, probable UIP or possible UIP pattern on lung biopsy according to the 2011 ATS/ERS/JRS/ALAT guideline [4].

In this study, incidence cases that had been recorded in the first 18 months of an ongoing study were evaluated and presented. Of the 456 patients who were recruited to the database during this period, 55 patients who did not have an HRCT scan were excluded from the study. Furthermore, 65 patients who were diagnosed with inconsistent UIP by the radiology decision board and whose biopsy did not show otherwise were excluded from the study. A total of 50 researchers from 36 centers spanning 19 provinces of Turkey were included in the first part of this study (Figure 1).

An online case registration form was used in the study. At least 15 HRCT sections, taken at equal intervals from the apex to the base of the lungs, were loaded, in addition to patient data. The patients were anonymized, and a descriptive code was generated by the program to distinguish the patients. The clinicians involved in the study were not instructed/influenced regarding the diagnosis, treatment, and follow-up of their patients. Written informed consent was obtained from the patients before recording their medical data.

The HRCT scans of the patients were evaluated separately by each member of the radiology decision board, consisting of 6 thoracic radiologists; and they were asked to choose 1 of the 3 options: "UIP pattern," "possible UIP pattern," and "inconsistent UIP pattern" according to the 2011 IPF guidelines. In the evaluation of the radiology decision board, the option selected by a significant majority (at least 2 votes difference) marked the radiological evaluation of that patient. When a majority could not be reached, the evaluation was "inconclusive."

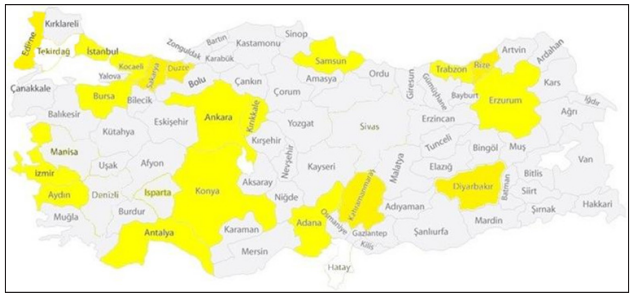

Figure 1. Cities participating in the research

After the evaluation of the radiology decision board, all data related to the patients were evaluated separately by 6 members of the clinical decision board - each board member made an independent decision as to the diagnosis according to the criteria of the 2011 ATS/ERS/JRS/ALAT guidelines. The diagnosis selected by a significant majority (at least 2 votes difference) was accepted as the diagnosis of that patient. When a majority could not be achieved, the evaluation was considered "inconclusive."

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) statistical software. Continuous variables were presented as mean ± standard deviation. Categorical variables are presented as proportions of the total population. Student t and Chi-squared tests were used to compare groups. Statistical significance of the tests was set at $p < 0.05$.

RESULTS

Of the 336 patients evaluated, 253 (75.3%) were men and 83 (24.7%) were women. The mean age at diagnosis was 65.8±9.0 years.

The decision of the radiology decision board was UIP pattern in 115 (34.2%) patients, possible UIP pattern in 40 (11.9%) patients, and inconsistent with UIP pattern in 18 (5.4%) patients. The majority of the decisions could not be reached in 160 (47.6%) patients. HRCT scans could not be evaluated in 3 patients.

A total of 70 (20.8%) patients underwent tissue lung biopsy, either surgically or by video-assisted thoracoscopic surgery (VATS), and 2 patients were diagnosed via cryobiopsy. Of the patients who underwent these biopsies, 50% were diagnosed with IPF. The final diagnosis rate of IPF was 32.3% in those without a biopsy. In terms of radiology decision board judgement, the biopsy was performed in 8.7% of patients with UIP pattern, 15% of patients with probable UIP pattern, and 21.9% of patients with inconclusive pattern (Table 1). Transbronchial biopsies were performed in 10 patients (3%), and no specific diagnosis could be reached in any of these patients.

At the final evaluation, data were insufficient for diagnosis in 36 patients (10.7%). In the remaining 300 patients, the diagnosis was IPF in 121 (40.3%), unclassified idiopathic interstitial pneumonia (IIP) in 50 (16.7%), combined pulmonary fibrosis and emphysema (CPFE) in 40 (13.3%), lung involvement of connective tissue disease CTD in 16 (5.3%), hypersensitivity pneumonia (HP) in 6 (2%), autoimmune interstitial pneumonia in 3 (1%), drug induced disease in 2 (0.7%), nonspecific interstitial pneumonia (NSIP) in 2 (0.7%), and pneumoconiosis in 2 (0.7%). The diagnosis in 58 patients was inconclusive (19.3%).

Table 1. Biopsy results of the patients included in the study

Radiology (n)		No biopsy	Surgical biopsy or cryobiopsy (n)	UIP	Probable UIP	Possible UIP	Inconsistent with UIP	No diagnosis	HP
UIP pattern	115	105	10	6	3	1			
Possible UIP	40	34	6	4		1		1	
Inconsistent with UIP	18		18	14	2	2			
No majority	160	125	35	23	7	2	1	1	1
HRCT not able to be evaluated	3		3	3					
Total	336	264	72	50	12	6	1	2	1

HP; hypersensitivity pneumonia, HRCT; high resolution computed tomography, UIP; usual interstitial pneumonia

Table 2. Demographic characteristics of the patients according to their diagnosis

	IPF (n=150)	HP (n=6)	CTD (n=16)	Unclassified IIP (n=50)	CPFE (n=40)	Total (n=336)
Sex (male/female)	133/17	4/2	8/8	34/16	40/0	253/83
Age (years)	65.6±8.3	65.8±10.4	66.3±13.1	66.5±8.9	65.1±7.6	65.8±9.0
Over 50 years (n)	143	6	15	49	39	318
Smokers, %	84.7	66.7	46.7	52.1	94.7	68.2
Active smokers, %	10.0	0	18.7	6.3	26.3	8.3
Pack-years	36.0±24.2	38.7±15.5	56.0±26.9	31.7±10.6	45.8±22.7	38.1±23.9
Alcohol, %	13.3	0	12.5	10.4	23.7	9.8
Height (cm)	168±8	161±13	164±10	16.4±10.0	19.0±6.4	166±9
Weight (kg)	77.9±12.4	77.8±12.2	76.2±16.9	76.4±12.4	75.6±11.7	77.9±13.0
BMI	27.5±4.2	30.0±3.9	28.7±5.2	28.3±4.0	26.5±1.2	28.3±4.2

CPFE; Combined pulmonary fibrosis and emphysema, BMI; body mass index, HP; hypersensitivity pneumonia, IPF; idiopathic pulmonary fibrosis, IIP; idiopathic interstitial pneumonia, CTD; connective tissue disease

When 29 patients with definite IPF features were added to the patients with CPFE, the total number of IPF patients reached 150 (50%). Of the 16 patients diagnosed with CTD, 7 had rheumatoid arthritis, 5 had scleroderma, and 4 had Sjogren's syndrome.

IPF was diagnosed in 69.6% of the patients whose radiological evaluation was a definite UIP pattern. Possible UIP pattern was diagnosed as IPF in 15% of cases. These ratios are 73.4% and 19.4%, respectively, when patients with insufficient data for diagnosis are excluded. The general characteristics of the patients according to their diagnosis are shown in Table 2. The percentages of symptoms according to the diagnoses are shown in Table 3, and physical examination findings are shown in Table 4.

When patients initially diagnosed as IPF but subsequently categorized otherwise were compared (excluding unclassified IIP), a significant difference was found in terms of sex ($p < 0.001$) (IPF group male:female=7.8, non-IPF group male:female=1.4). There was no statistical difference in age. Smoking was significantly more prevalent in patients with IPF ($p<0.001$). Among those who smoked, no significant difference was found in terms of the number of smoking years, packet-years, and years after cessation. None of the female patients under the age of 50 was diagnosed with IPF. None of the male patients under 50 years of age and without a smoking history was diagnosed with IPF. There was no statistical difference in body mass index between patients with and without IPF.

Table 3. Symptoms according to diagnoses

	IPF (n=150) (%)	HP (n=6) (%)	CTD (n=16) (%)	Unclassified IIP (n=50) (%)	CPFE (n=40) (%)	Total (n=336) (%)
Dyspnea	85.3	100	93.8	84.0	82.5	86.3
Cough	80.0	83.3	75.0	78.0	80.0	79.5
Sputum	32.7	50	31.3	24.0	35.0	32.4
Hemoptysis	4.0	0	0	2.0	7.5	3.6
Chest pain	10.0	16.7	0	0	10.0	9.5
Fatigue	26.0	16.7	37.5	18.0	27.5	26.5
Fever	4.7	16.7	12.5	0	2.5	5.7
Clubbing	26.7	16.7	0	16.0	27.5	22.3
Weight loss	14.7	33.3	12.5	4.0	7.5	10.1
Night sweating	4.7	0	6.3	4.0	2.5	5.1
Joint pain	4.7	50	68.8	6.0	0	13.4
Swelling in the joints	0.7	0	43.8	2.0	0	4.8
Nausea	2.0	0	6.3	2.0	0	2.4
Vomiting	0	0	6.3	2.0	2.5	0.6
Diarrhea	0.7	0	12.5	0	2.5	1.2
Abdominal pain	2.0	0	0	0	2.5	1.2
Difficulty swallowing	0.7	0	18.8	0	0	2.1
Signs of GERD	8.0	0	18.8	8.0	7.5	10.1
Raynaud's	0	0	18.8	0	2.5	2.1
Skin thickening	0	0	25.0	0	0	1.8
Superficial ulcer in fingers	0	0	6.3	0	0	0.3
Calcinosis cutis	0	0	6.3	0	0	0.3
Telangiectasia	0	0	6.3	0	0	0.3
Muscle weakness	0.7	0	0	0	0	0.9
Hair loss	0	0	0	0	0	0.9
Skin rash	1.3	0	0	0	2.5	0.9
Dry mouth	6.0	0	12.5	10.0	7.5	9.8
Dry eye	2.0	0	31.3	4.0	5.0	4.2
Headache	2.7	0	6.3	2.0	0	3.3
General symptoms	19.3	50	18.8	6.0	12.5	17.3
CTD complaints	10.0	50	87.5	18.0	7.5	22.3

CPFE; Combined pulmonary fibrosis and emphysema, GERD; gastroesophageal reflux disease, HP; hypersensitivity pneumonia, IPF; idiopathic pulmonary fibrosis, IIP; idiopathic interstitial pneumonia, CTD; connective tissue disease

Table 4. Physical examination findings according to diagnoses

	IPF (n=150) (%)	HP (n=6) (%)	CTD (n=16) (%)	Unclassified IIP (n=50) (%)	CPFE (n=40) (%)	Total (n=336) (%)
Velcro-type crackles	92.0	100	93.8	94.0	82.5	90.5
Squawk	4.7	0	6.3	2.0	2.5	4.2
Clubbing	38.7	16.7	6.3	20.0	42.5	31.0
Edema	3.3	0	0	2.0	2.5	3.0
Mechanic's hand	0.7	0	6.3	0	2.5	0.6
Distal digital ulcer	0	0	0	0	0	0
Morning stiffness	1.3	0	18.8	0	2.5	2.4
Palmar telangiectasia	0	0	0	0	0	0

CPFE; Combined pulmonary fibrosis and emphysema, HP; hypersensitivity pneumonia, IIP; idiopathic interstitial pneumonia, IPF; idiopathic pulmonary fibrosis, CTD; connective tissue disease

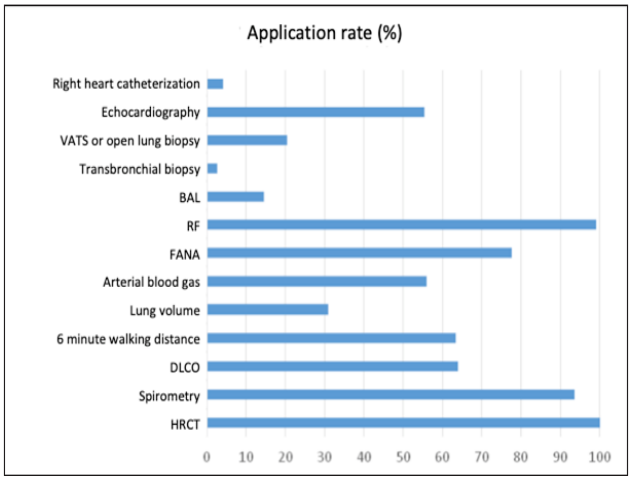

Figure 2. Rate of application of diagnostic methods

The first respiratory complaints of the patients started 27.1±47.8 months prior to diagnosis (median=12 months). The difference between patients with and without IPF was not significant. Respiratory symptoms started at a mean age of 63.4±9.9 years (median=65 years). The first complaint was dyspnea in 26.4% and cough in 14.9% of the patients. In 56.6% of the patients, the 2 symptoms commenced simultaneously. The duration of the respiratory symptoms, the age at which the respiratory symptoms started, and the type of the first respiratory symptom were not statistically different between patients with and without IPF. A total of 29 (19.3%) patients with IPF had at least 1 symptom such as fever, night sweats, or weight loss. However, there was no statistical difference for patients without IPF. The number of patients with IPF with any of the symptoms suggesting CTD was 15 (10.0%). Joint pain and joint swelling (p<0.001), difficulty in swallowing (p=0.007), Raynaud's phenomenon (p=0.001), skin thickening (p<0.001), and dry eyes (p=0.002) were significantly higher in the presence of a non-IPF diagnosis. Complaints suggesting any CTD were associated with non-IPF disease (p<0.001). The presence of Velcro-type crackles was not distinctive for the diagnosis of IPF. The presence of clubbing was associated with IPF (p=0.001).

A total of 98 (29.2%) patients had occupational exposure. Exposure history was asbestos in 13 (3.9%) patients, silica in 9 (2.7%), coal dust in 8 (2.4%), metal dust in 16 (4.8%), wood dust in 13 (3.9%), dye in 18 (5.4%), birds in 5 (1.5%), mold in 7 (2.1%), other plants in 31 (9.2%), and others in 23 (6.8%). A total of 120 (35.7%) patients reported occupational or domestic exposure.

Of the 150 patients diagnosed with IPF, 49 (30.8%) had domestic or occupational exposure. Exposure was present in all 6 (100%) patients with HP. Exposure was seen in 2 (12.5%) of the 16 patients with CTD, in 13 (26.0%) of the 50 patients with unclassified IIP, in 17 (42.5%) of the 40 patients with CPFE, and in 2 patients with NSIP. No relationship was found between the presence of occupational or domestic exposure and the diagnosis of IPF.

A total of 45 (13.4%) patients had a gastroesophageal reflux disease (GERD) diagnosis. In 49 (14.6%), no clinical enquiry was made as to the GERD; 18 (12.0%) patients with IPF, 4 (25%) with CTD, 5 (10.0%) with unclassified IIP, and 5 (12.5%) with CPFE had GERD. When patients diagnosed with GERD and/or GERD symptoms were evaluated together, 56 (16.7%) of the patients were positive. A total of 22 (14.7%) of patients with IPF, 6 (37.5%) with CTD, 6 (12.0%) with unclassified IIPs, and 6 (15.0%) with CPFE was positive. None of the patients with HP had a diagnosis or complaint of GERD. The probability of IPF was not higher in patients who were diagnosed with GERD or had GERD symptoms.

Of the 2 (0.6%) patients diagnosed with obstructive sleep apnea syndrome, 1 had IPF and the other had insufficient data for diagnosis. The tests performed in patients is shown in Figure 2.

The diffusing capacity of the lungs for carbon monoxide (DLCO) % values at the time of diagnosis of patients with IPF were lower than those in patients without IPF (p=0.01); however, there was no difference in forced vital capacity percent values. The proportion of patients with FVC below 50% in the whole patient group was 11.3%. This rate was 13.1% in patients with IPF, 0% in patients with HP, 12.5% in patients with CTD, 10.2% in patients with unclassified IIP, and 8.1% in patients with CPFE. Of all the patients, 6.8% had DLCO below 30%. This rate was 14% in patients with IPF, 12.5% in patients with CTD, 6.7% in patients with unclassified IIP, and

27.6% in patients with CPFE. All the patients with HP had DLCO above 30%.

When GAP indices were evaluated, the mean score of all the patients was 3.9±1.6 (median=3.0); 39.7% of the patients were in group I, 43.7% were in group II, and 16.6% were in group III. The mean GAP score in patients with IPF was 4.1±1.4 (median=4); 33.6% of patients with IPF were in group I, 47.8% were in group II, and 18.6% were in group III. GAP scores did not differ significantly between the IPF and other groups (p=0.06).

Mean erythrocyte sedimentation rate (ESR) was 30.3±27.3 mm/h (median=24 mm/h) in the total population, 25.7±22.5 (median=20mm/h) in patients with IPF, 39.1±23.7mm/h (median=40mm/h) in patients with CTD, 30.8±22.5 mm/h (median=24.5mm/h) in patients with unclassified IIP, and 21.8±19.7 mm/h (median=12.5 mm/h) in patients with CPFE. Antinuclear antibody (FANA) was positive at a level of at least 1/100 in 18 (5.4%) patients; 4 (2.7%) patients with IPF, 0 (0%) patients with HP, 2 (4.0%) patients with unclassified IIP, 3 (18.8%) patients with CTD, 0 (0%) patients with CPFE. FANA positivity rate was found to be 7.4% for undiagnosed patients. ESR (p=0.029) and FANA positivity rates were higher in patients without IPF (p=0.009).

Bronchoalveolar lavage (BAL) was performed in 50 (14.9%) patients. In 18 patients with IPF who had BAL, 21.2±14.9% neutrophils (median=20%), 8.8±6.1% lymphocytes (median=8%), and 0.4±0.9% eosinophils (median=0%) were detected on average.

Researchers reported that 61% of the patients were initially monitored without treatment. The rate of patients who received continuous oxygen therapy was 13.5%, and 7.1% of patients received steroids. The rate of patients using N-acetylcysteine (NAC) was 2.4% and azathioprine was 0.5%. Warfarin was not initiated. Pirfenidone was started in 29.5% and nintedanib in 1.4%. The researchers were able to perform rehabilitation in only 3.3% of the patients diagnosed with IPF. Of all the patients, 3.3% of patients received the influenza vaccine and 2.9% received a pneumococcal vaccine. The rate of patients referred for lung transplantation was 11%.

DISCUSSION

This study showed that the final diagnosis of patients with fibrotic ILD was IPF in 40.3% and CPFE in 13.3%. When 29 patients with definite IPF features were added to the patients with CPFE, the total number of IPF patients reached 150 (50%). IPF was diagnosed in 69.6% of the patients whose radiological evaluation was a definite UIP pattern. A possible UIP pattern was diagnosed as IPF in 15% of the patients. The rate of male sex, smoking history, and presence of clubbing were significantly higher in patients with IPF than in those without IPF.

According to our previous study, we know that IPF is seen in approximately 20% of all patients with ILD in Turkey. Nevertheless, we did not know the rate among fibrotic ILD with a radiologically definite or probable UIP pattern [3]. Given that these patients are the most difficult group for differential diagnosis, it is very important to know the answer to this question. We have not come across any study in the international literature on the rate of IPF in this patient group. Current guidelines do not recommend biopsy in this patient group as more than 90% of the patients with radiological UIP patterns also have UIP patterns in surgical biopsies [5, 6]. Yet, only approximately 50% of patients with IPF present with a clear UIP pattern. Diagnostic guidelines recommend surgical biopsy in patients with no definite UIP pattern. In our study, patients with findings incompatible with UIP on HRCT and biopsy were excluded. The radiology decision board decided on the UIP pattern in 34.2%, possible UIP in 11.9%, and non-UIP pattern in 5.4% of the patients. In 47.6% of the patients, a majority decision could not be reached. The ratio of patients with a radiological UIP pattern was lower than what was reported in the literature. Furthermore, the radiology board was not able to reach a decision in a large number of patients as our protocol required a significant majority of votes (at least 2 differences). This may be the root cause of this difference. The concordance of UIP pattern assessment among radiologists is low in all studies [7]. As a result, in clinical practice, 50%–65% of patients are shown to be candidates for biopsy for differential diagnosis of IPF. However, in the literature, the results obtained by surgical biopsy in patients with radiologically probable UIP are contradictory. Although some studies show that 90% of these patients have definite UIP pathology results, other studies have not confirmed these results [6, 8]. In our study, in patients with radiologically definite or probable UIP and/or demonstrated to be other than non-UIP by biopsy with the multidisciplinary approach, the IPF diagnosis rate was found to be 50% when the patients with insufficient data for diagnosis were excluded. In this patient group, the second most common diagnosis was unclassified IIP (16.7%) and the third most common diagnosis was CTD (5.3%). Other diagnoses were HP 2%, autoimmune interstitial pneumonia 1%, drug induced disease 0.7%, NSIP 0.7%, and pneumoconiosis 0.7%. The decision for an exact diagnosis could not be made in 19.3% of the patients. Of the 16 patients diagnosed with CTD; 7 had rheumatoid arthritis, 5 had scleroderma, and 4 had Sjogren's syndrome. In recent years, although HP is reported at a high rate in this patient group, the rate in our study was low [9, 10]. However, only patients with fibrotic ILD who were radiologically definitive UIP or probable UIP and/or non-UIP with confirmed biopsy were included in our study. This could be the main reason for the low rate. Another reason could be the lack of diagnostic procedures in more than 10% of the patients. BAL, which is especially important in the diagnosis of HP, was performed in only 14.9% of the patients. In addition, the rate of HP may be much higher considering the fact that 20% of the patients had an inconclusive diagnosis. It is reported in the literature that 10%–25% of the patients with fibrotic ILD cannot be diagnosed with a multidisciplinary approach [11]. This ratio increases in the elderly population. Considering the mean age of our patient group was 65 years, it can be said that the rate of 19.3% is in line with what is reported in the literature.

The diagnosis of IPF was made in 73.4% of the patients with a radiological UIP pattern and 19.4% of the patients with a radiologically possible UIP pattern. Although 41.9% of this patient group was diagnosed as unclassified idiopathic ILD, the diagnosis of 16.1% was inconclusive.

In our study, the rate of surgical biopsy (thoracotomy or VATS) was 20.5%. This rate is similar to that of many previous registries [12]. As the IPF diagnostic guideline suggests, when the biopsy was performed in patients with a probable UIP, 66.7% of patients had pathologically definite UIP results. Probable UIP results were seen in 16.7% of the patients. According to the algorithm proposed by the 2011 diagnosis and treatment guideline, 83.4% of these patients can be diagnosed as IPF. However, only 6 of the patients underwent biopsy in this group. When 36 patients who underwent biopsy because of inconclusive radiological decision, were included (in the total 42 patients), 64.3% had pathologically definite UIP, 16.7% probable UIP, and 7.1% possible UIP. In the INSIGHTS-IPF study, when a surgical biopsy was performed in patients other than those with a radiological UIP pattern, 73.6% had definite UIP, and 8.8% had possible UIP (82.4% totally) [13]. These results are very similar to our findings. These results suggest that in the group that should have gotten a biopsy, the rate of diagnosis is far below what is expected even with a multidisciplinary approach.

Most of our study population was male with a mean age of 65.8 years. The rates of male sex and smoking habit were significantly higher in patients with IPF. No significant difference was found between patients with and without IPF when age alone was evaluated. When sex and smoking habits were evaluated, none of the female patients under the age of 50 was diagnosed with IPF. The probability of IPF was 0 in male patients under the age of 50 without a history of smoking. These data indicate the importance of age, sex, and smoking in the differential diagnosis of IPF.

The first respiratory complaints of the patients started on average 12 months prior to diagnosis. This indicates a significant delay in diagnosis. This period is especially important in IPF where survival is between 3 and 5 years. However, in the eurIPFreg study, this period was 21.8 months, and it was 3.9±4.4 years in the INSIGHTS-IPF study [9, 13]. Therefore, the diagnostic delay in our country is not more than the other countries. The first complaint was dyspnea in 26.4% and cough in 14.9% of the patients. In 56.6% of the patients, the 2 symptoms started together. There was no difference between patients with and without IPF in terms of these symptoms. However, joint pain and swelling, difficulty swallowing, Raynaud's, skin thickening, and dry eyes were significantly higher in the presence of a non-IPF diagnosis. Complaints suggesting any CTD are associated with the non-IPF disease. ESR and FANA positivity rates were also higher in patients without IPF.

The presence of Velcro-type crackles on physical examination is not differential for the diagnosis of IPF. Detection of clubbing was associated with IPF. Although there is evidence that clubbing is detected in approximately 50% of patients with IPF, there is little information on this issue. Besides, the clubbing rate can vary greatly according to the assessment method [14]. However, clubbing should be considered in the differential diagnosis of IPF.

When patients with GERD symptoms and/or diagnosis were evaluated together, the rate in patients with IPF was 14.7%. There was no significant difference between patients with and without IPF in this regard. Although GERD rates of 0%–94% have been reported in patients with IPF, recent meta-analyses have shown that the relationship is not significant [15, 16]. Our data support this finding.

Even in the centers where physicians are particularly interested in this disease group, there are limitations in the diagnostic possibilities in Turkey. The rate of surgical lung biopsy in this patient group was found to be 20.5% in our study. Although 34.2% of our patients had radiological UIP patterns, the biopsy rates were low, suggesting that the recommendations of the diagnosis and treatment guidelines could not be applied in Turkey as in the world [9]. BAL, which is important for differential diagnosis of HP, was performed only in 14.6% of the patients. The most basic serological examinations for CTD were performed in 70% of the patients. DLCO and 6-minute walk test, which are important in follow-up, were performed in 60% of the patients. The DLCO% values at the time of diagnosis of patients with IPF were lower than in those without IPF (44.9±17.0 vs. 56.8±18.5, p=0.01). However, there was no difference in FVC%. The rate of patients diagnosed with IPF with FVC below 50% was 13.1%. The rate of patients with DLCO below 30% in the IPF group was 14%. These data indicate that approximately 85% of the patients consult a physician before they reach an advanced stage.

When IPF therapies, which the researchers started according to their own decisions, were evaluated, 61% of the patients were initially monitored without treatment. The rate of patients who received continuous oxygen therapy was 13.5%, and 7.1% of the patients received steroids. The rates of patients using NAC and azathioprine were 2.4% and 0.5%, respectively. Warfarin was not initiated. Pirfenidone was started in 29.5% and nintedanib in 1.4% of the patients. However, it should be taken into consideration that nintedanib was not licensed in Turkey during the first half of our study period. This may be the reason for the low rate of nintedanib usage.

The rates of rehabilitation, influenza and pneumococcal vaccines, referral to lung transplantation were far from ideal. Therefore, activities emphasizing the importance of non-pharmacological methods in this patient group are important in Turkey.

This study was a preliminary evaluation of the Turk-UIP survey, in which data of 1,500 patients were recorded. Cases that have been recorded in the first 18 months of an ongoing study were evaluated and presented. A more detailed statistical analysis will be performed when evaluation of all the data of the Turk-UIP study is completed. It would not be appropriate to make definitive inferences before then.

In conclusion, the rate of IPF among patients with fibrotic ILD was 50%. Despite the multidisciplinary approach, diagnosis in approximately one-fifth of the patients was inconclusive. Although the diagnostic rate in patients who had surgical biopsy is very high, the rate of referral to biopsy in Turkey remains low. In the differential diagnosis of

IPF, sex, smoking habits, and the presence of clubbing are important. None of the female patients under the age of 50 and none of the male patients under 50 years of age and without a smoking history were diagnosed with IPF. The presence of at least 1 of the symptoms suggestive of CTD, ESR elevation, and FANA positivity decreases the likelihood of IPF.

Ethics Committee Approval: This study was approved by Ethics committee of Yedikule Training and Research Hospital, (Approval No: 2016/11, 8 March 2016).

Informed Consent: Written informed consent was obtained from the patients before recording their medical data.

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