

RESEARCH BURDEN OF INTERSTITIAL LUNG DISEASES IN TURKEY – RBILD

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ABSTRACT. *Introduction:* The aim of our study is to investigate the etiological distribution of ILD in Turkey by stratifying the epidemiological characteristics of ILD cases, and the direct cost of initial diagnosis of the diagnosed patients. *Material-Method:* The study was conducted as a multicenter, prospective, cross-sectional, clinical observation study. Patients over the age of 18 and who accepted to participate to the study were included and evaluated as considered to be ILD. The findings of diagnosis, examination and treatment carried out by the centers in accordance with routine diagnostic procedures were recorded observationally. *Results:* In total, 1070 patients were included in this study. 567 (53%) of the patients were male and 503 (47%) were female. The most frequently diagnosed disease was IPF (30.5%). Dyspnea (75.9%) was the highest incidence among the presenting symptoms. Physical examination found bibasilar inspiratory crackles in 56.2 % and radiological findings included reticular opacities and interlobular septal thickenings in 55.9 % of the cases. It was observed that clinical and radiological

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findings were used most frequently (74.9%) as a diagnostic tool. While the most common treatment approaches were the use of systemic steroids and antifibrotic drugs with a rate of 30.7% and 85.6%, respectively. The total median cost from the patient's admission to diagnosis was 540 Turkish Lira. *Conclusion:* We believe that our findings compared with data from other countries will be useful in showing the current situation of ILD in our country to discuss this problem and making plans for a solution.

KEYWORDS: Interstitial Lung Disease, Lung, Idiopathic Pulmonary Fibrosis

INTRODUCTION

Interstitial Lung Diseases (ILD) is a group of diseases with an acute or chronic course that affects the lung diffusely, causing inflammation, fibrosis and structural deterioration in the lung parenchyma (1,2). The etiology of ILD can be roughly divided into two groups as known and unknown. These detectable or undetected etiological factors cause inflammation in the lung parenchyma, which can sometimes result in fibrosis. It is known that there are more than 200 diseases under the title of ILD. In most of these diseases, clinical and radiological features are similar and this makes the differential diagnosis difficult. The gradual increase in morbidity and mortality due to interstitial lung diseases is an indication of the importance of early diagnosis and treatment. It has been reported that in the USA (United States), deaths due to IPF (Idiopathic Pulmonary Fibrosis) increased by 9.85% between 2000 and 2007(3). It was also found that mortality rates due to HP (Hypersensitivity Pneumonia) in the USA increased from 0.12/100,000 to 0.68 between 1988 and 2016 (4).

Until today, many classifications have been made for ILD according to its etiological, histopathological or radiological features. These classifications were developed and a consensus classification was created by the ATS/ERS (American Thoracic Society/European Respiratory Society) in 2002. According to the guideline, ILD (Interstitial Lung Diseases) is grouped under 4 main headings: 1) ILD associated with a known cause (drugs, connective tissue diseases and occupational/environmental factors), 2) Granulomatous ILD (Sarcoidosis,

Berylliosis, Wegener etc.), 3) Idiopathic interstitial pneumonias (IIP) and 4) Other common and rare conditions (Lymphangiomyomatosis, Pulmonary Langerhans Cell Histiocytosis, Pulmonary Alveolar Proteinosis, Eosinophilic Pneumonia etc.). In this report, Idiopathic Interstitial Pneumonias were divided into seven groups as Idiopathic Pulmonary Fibrosis (UIP), Desquamative Interstitial Pneumonia (DIP), Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD), Lymphocytic Interstitial Pneumonia (LIP), Cryptogenic Organized Pneumonia (COP), Acute Interstitial Pneumonia (AIP)), Nonspecific Interstitial Pneumonia (NSIP). In 2013, the report was revised by ATS/ERS and Idiopathic Interstitial Pneumonias; were grouped under three main headings as Major Idiopathic Interstitial Pneumonias, Rare Idiopathic Interstitial Pneumonias and Unclassified Idiopathic Interstitial Pneumonias. Major IIP is divided into 6 groups as; Idiopathic Pulmonary Fibrosis (IPF), Nonspecific Interstitial Pneumonia (NSIP), Respiratory Bronchiolitis-Interstitial Lung Disease (RBILD), Desquamative Interstitial Pneumonia (DIP), Cryptogenic Organizing Pneumonia (COP) and Acute Interstitial Pneumonia (AIP); Rare Idiopathic Interstitial Pneumonias are divided into 2 as Lymphocytic Interstitial Pneumonia (LIP) and Idiopathic Pleuroparenchymal Fibroelastosis (IPPF) (3).

The incidence of ILD is not known exactly. In a study conducted between 2001 and 2005 for the Northern European population, the incidence was reported as 31/100,000 per year (4). In a multicenter study conducted by Musellim et al. to determine the distribution of ILD in Turkey, the annual incidence was found to be 25.8/100.000 (5).

The aim of our study is to investigate the etiological distribution of ILD cases, their epidemiological characteristics such as age, gender, occupation and comorbidities, and the direct cost of the initial diagnosis of patients diagnosed in Turkey. The secondary endpoints of our study were to determine the clinical findings and lung functions according to the etiology of ILD, the diagnostic methods used in ILD cases, the time taken for diagnosis, and the treatment preferences of the physicians according to the etiology of the cases in Turkey.

Complementing the missing data on ILD in our country and creating comparable national data with the data of other countries by using the current classification and diagnostic criteria related to the distribution, etiology, treatment response and prognosis of ILD, which differs with the different genetic pools and environmental factors in different geographies will also shed light on the future scientific studies.

MATERIALS AND METHODS

The study was conducted as a multicenter, prospective, cross-sectional, clinical observation study. The researchers were volunteer physicians working in centers which were competent in diagnosis, differential diagnosis, and treatment and follow-up of patients admitted with a preliminary diagnosis of Interstitial Lung Disease (ILD). The study started on 1 January 2019 and continued until 1 August 2020.

21 centers participated in the study, and a detailed data entry form in excel format was sent to all centers by e-mail before the start of the study. The records were sent to us again by e-mail by our participants. After the data from all centers were combined, statistical analyzes were performed.

Patients over the age of 18 with consent to participate to the study were included and evaluated as considered to be ILD with clinical and radiological findings. Patients diagnosed outside the specified date range were not included in the study. No special procedures were performed on the patients within the scope of the study protocol. The findings of diagnosis, examination and treatment that are carried out by the centers in accordance with routine diagnostic procedures were recorded observationally. The final diagnosis of

the patient by the physician was taken as the basis. Patient diagnoses were grouped according to the 2013 Interstitial Lung Diseases classification of ATS/ERS. Patients other than ILD (pulmonary edema, infection, tumor and other) were also specified.

Statistical Method

Data were analyzed with IBM SPSS V23. Conformity to normal distribution was evaluated by Shapiro-Wilk and Kolmogorov-Smirnov tests. Chi-square test was used to compare categorical data according to diagnosis groups. One-Way Analysis of Variance was used to compare the normally distributed quantitative data according to the diagnostic groups, and the Kruskal Wallis test was used to compare the data that was not normally distributed. Analysis results were presented as mean \pm standard deviation, median (minimum- maximum) for quantitative data and frequency (percent) for categorical data. The level of significance was taken as $p < 0.05$.

RESULTS

44 health workers from 7 geographical regions, 18 different provinces and 21 centers (secondary care hospital-6.3%, tertiary care hospital-93.3%) of Turkey participated in our study. In total, 1070 patients were included in this study. 567 of the patients (53%) were male and 503 (47%) were female. The mean age of the patients was 62.05 ± 13.89 (mean \pm standard deviation). The youngest patient age was 20, and the oldest patient was 92. It was observed that most of the patients were referred from secondary care hospital (n: 446-41.7%) to the centers by specialists of chest diseases (n:553-51.7%), immunology/rheumatology (n:74-6.9%) and internal diseases (n:69-6.4%)

The result of the evaluations made for the differential diagnosis indicated that 16 patients were diagnosed with infection, 9 patients with neoplasia, 3 patients with pulmonary edema, and 36 patients with a diagnosis other than ILD. Diagnostic distribution of the remaining 1006 patients according to the 2013 classification of ATS/ERS is given in Figure 1. The distribution of these diagnoses by gender is given in Table 1.

Figure 2 shows the proportional distribution of all patients according to their diagnoses. In Table 2, the first four most diagnosed diseases of IPF (Idiopathic

Pulmonary Fibrosis), sarcoidosis, HP (Hypersensitivity Pneumonia), and CTD (Collagen Tissue Disease) are statistically compared with the demographic, clinical and radiological characteristics of the patients.

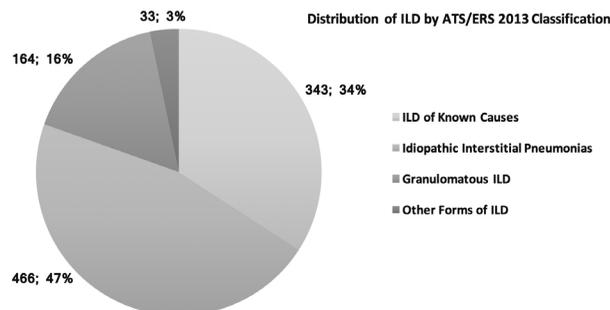


Figure 1. Distribution of Diagnosed ILD

DISCUSSION

Interstitial lung diseases are a group of diseases that concern chest diseases specialists because they cover a very wide disease group and their diagnosis and treatment are difficult. Epidemiological data of these diseases are limited in our country. In our study, the data of 1070 patients who were investigated with

Table 1. Distribution of ILD by Gender

	TOTAL n-%	MALE n-%	FEMALE n-%	P
ILD of Known Causes				
Hypersensitivity Pneumonitis	137 (13.6%)	64 (46.7%)	73 (53.3%)	.108
Connective Tissue Disease	132 (13.1%)	41 (31.1%)	91 (68.9%)	<0.001
Drug Lung	30 (3.0%)	14 (46.7%)	16 (53.3%)	.475
Pneumoconiosis	20 (2.0%)	19 (95.0%)	1 (5.0%)	<0.001
Pulmonary Involvement of Systemic Diseases (PISD)	11 (1.1%)	6 (54.5%)	5 (45.5%)	.922
Vasculitis (Wegener, ChurgStrasusetc.)	11 (1.1%)	4 (36.4%)	7 (63.6%)	.263
Radiation pneumonitis (RP)	2 (0.2%)	1 (50.0%)	1 (50.0%)	1.000
Idiopathic Interstitial Pneumonias				
Major IIP				
IPF	307 (30.5%)	229 (74.6%)	78 (25.4%)	<0.001
NSIP	45 (4.5%)	26 (57.8%)	19 (42.2%)	.545
COP	27 (2.7%)	9 (33.3%)	18 (66.7%)	.036
RB-ILD	16 (1.6%)	14 (87.5%)	2 (12.5%)	.003
DIP	5 (0.5%)	3 (60.0%)	2 (40.0%)	.508
A P	2 (0.2%)	2 (100%)	0 (0.0%)	.501
Rare IIP				
LIP	6 (0.6%)	2 (33.3%)	4 (66.7%)	.428
IPPF	2 (0.2%)	2 (100%)	0 (0.0%)	.501
Unclassifiable IIP				
CPFE	15 (1.5%)	15 (100.0%)	0 (0.0%)	<0.001
Unclassified IAH	43 (4.3%)	23 (53.5%)	20 (46.5%)	.956
Granulomatous IAH				
Sarcoidosis	164 (16.3%)	46 (28%)	118 (72%)	<0.001
Other Forms of ILD				
Histiocytosis X	16 (1.6%)	8 (50.0%)	8 (50.0%)	.804
CEP	8 (0.8%)	3 (37.5%)	5 (62.5%)	.485
AEP	2 (0.2%)	1 (50.0%)	1 (50.0%)	1.000
LAM	2 (0.2%)	0 (0.0%)	2 (100.0%)	.220
PAP, amiloidosis	2 (0.2%)	2 (100.0%)	0 (0.0%)	.501
Alveolar Microlithiasis	3 (0.3%)	2 (66.7%)	1 (33.3%)	1.000

ILD as a preliminary diagnosis were examined. After excluding 64 patients diagnosed with different diseases other than ILD, patients diagnosed with ILD were grouped according to the 2013 Interstitial Lung Diseases classification of ATS/ERS. One of the diseases in the idiopathic interstitial pneumonia group was detected in 47% of our patients. Considering the rate of individual diseases, it was observed that 306 patients (30.5%) were diagnosed with IPF. In terms of frequency, sarcoidosis was in the second rank (n:164-16.3%), and hypersensitivity pneumonia was in the third rank (n:137-13.6%). The multicenter study, in which Musellim et al. examined the epidemiological features and distribution of ILD in Turkey and published in 2013, is one of the rare studies on this subject in our country. In this study, the data of 2245 patients newly diagnosed with ILD were examined and the incidence of ILD, the general distribution of diseases in the society and the distribution rates of women and men under 50 years of age and above were examined. Considering the diagnosis rates of the patients, sarcoidosis has the

highest diagnosis rate with 37.6%. This is followed by IPF with 19.9%, pneumoconiosis with 11.8%, CVD with 9.8% and HP with 4% (7). There have been significant changes in the classification of ILD over time. In addition, the awareness and interest of physicians (chest diseases specialist, radiologist, pathologist and rheumatologist etc.) on ILD has increased. There have been improvements in the infrastructure of hospitals required for the diagnosis of ILD (PFT, DLCO, effort tests, Cardiopulmonary Exercise Tests, etc.). For this reason, the project was realized with the expectation that our study will present different data than the study of Musellim et al. As a matter of fact, many data related to ILD, which are not included in this article, were presented in our study. One of the important differences of this study is that the disease classification is made according to the 2002 ATS/ERS guideline. In our study, the 2013 classification was used. In addition to the distribution rates of ILD in the society, various factors such as the way of admission of the patients, the characteristics of the center where the diagnosis

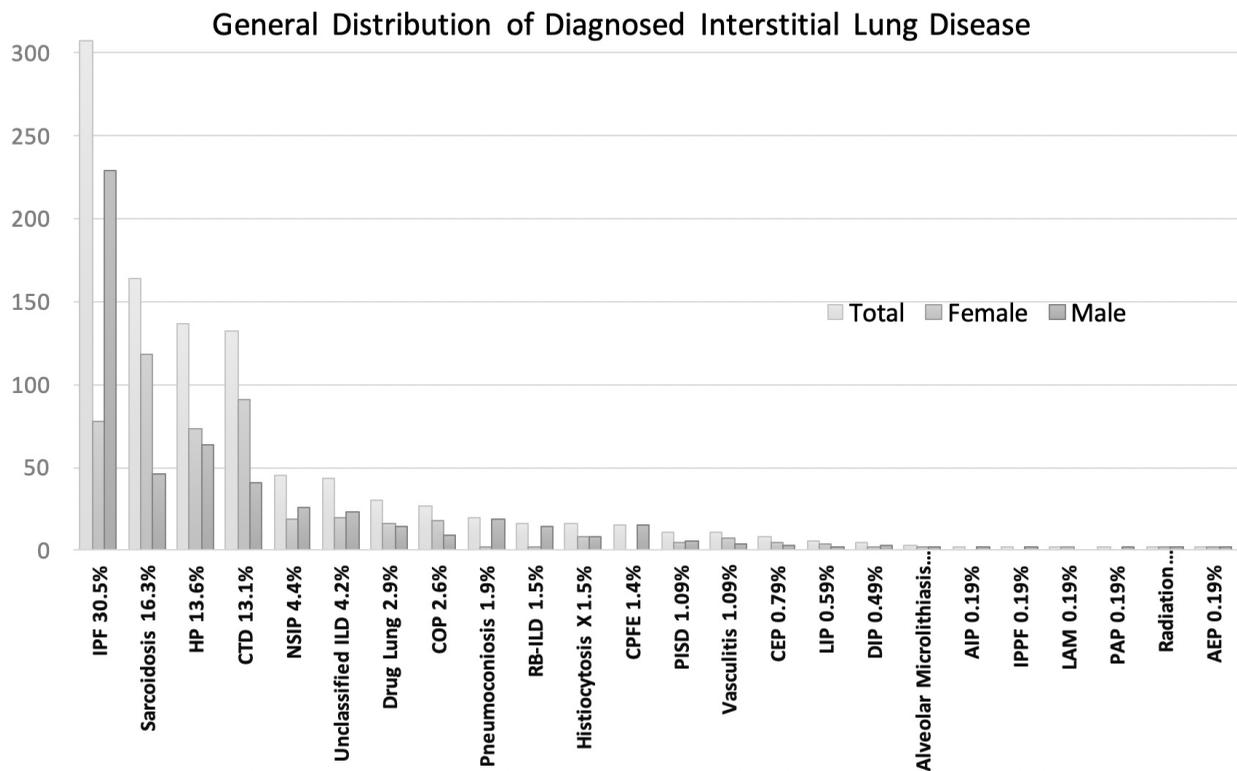


Figure 2. General Distribution of Diagnosed ILD

Table 2. Demographic, Clinical and Radiological Characteristics of ILD

	SARCOIDOSIS <i>n:164-16.3%</i>	IPF <i>n:306-30.5%</i>	HP <i>n:137-13.6%</i>	CTD <i>n:132-13.1%</i>	TOTAL <i>n:1006-100%</i>	<i>p</i>
Gender						
Male	46 (28.0%)a	229 (74.8%)b	64 (46.7%)c	40 (30.3%)a	532 (53.0%)	<0,001
Female	118 (72.0%)a	77 (25.2%)b	73(53.3%)c	92 (69.7%)a	472 (47.0%)	
Age						
Mean±SD	50.45±12.959	69.97±8.502	59.71±14.297	62.30±10.759	62.22±13.560	<0,001
Median (Min-Max)	49 (22-85)	71 (27-90)	62 (20-92)	63 (30-83)	64.50 (20-92)	
Center of Diagnosis						
Secondary hospital	7 (4.3%)a	31 (10.1%)b	5 (3.6%)a	6 (4.5%)a, b	70 (7.0%)	<0.106
Tertiary hospital	156 (95.1%)a	274 (89.5%)b	132 (96.4%)a	126 (95.5%)a	932 (92.8%)	
Others	1 (0.6%)a	1 (0.3%)a	0 (0.0%)a	0 (0.0%)a	2 (0.2%)	
Environment						
Urban area	142 (86.6%)a	223 (72.9%)b	83 (60.6%)c	111 (84.1%)a	761 (75.8%)	<0,001
Ruralarea	22 (13.4%)a	83 (27.1%)b	54 (39.4%)c	21 (15.9%)a	243 (24.2%)	
How to Apply to Hospital						
Self reference	51 (31.1%)a	101 (33.0%)b	39 (28.5%)a, b	29 (22.0%)a	311 (31.0%)	<0,001
Referred from primary care hospital	9 (5.5%)a	38 (12.4%)b	4 (2.9%)a	2 (1.5%)a	57 (5.7%)	
Referred from secondary care hospital	58 (35.4%)a	140 (45.8%)b	61 (44.5%)a, b	49 (37.1%)a, b	421 (42.0%)	
Referred from tertiary care hospital	46(28.0%)a	27 (8.8%)b	33 (24.1%)a	52 (39.4%)c	214 (21.3%)	
ReferringPhysician						
Family Doctor/Medical practitioner	8 (6.6%)a	6 (2.4%)b	3 (3.0%)a,b	1 (0.9%)b	19 (2.5%)	<0,001
Pulmonologist	67 (54.9%)a	212 (85.8%)b	83 (83.0%)b	35 (32.4%)c	531 (70.1%)	
Internal Medicine	14 (11.5%)a	10 (4.0%)b	8 (8.0%)a, b	10 (9.3%)a	59 (7.8%)	
Immunology/Rheumatology	6 (4.9%)a	3 (1.2%)b	2 (2.0%)a, b	52 (48.1%)c	70 (9.2%)	
Ophthalmologist	3 (2.5%)a	0 (0.0%)b	1 (1.0%)a, b	0 (0.0%)a, b	4 (0.5%)	
Dermatologist	4 (3.3%)a	0 (0.0%)b	0 (0.0%)a, b	1 (0.9%)a, b	5 (0.7%)	
Others	20 (16.4%)a	16 (6.5%)b	3 (3.0%)b	9 (8.3%)b	70 (9.2%)	
Comorbidity						
Hypertension	26 (15.9%)c	105 (34.3%)b	32 (23.4%)a, c	34 (25.8%)a, b	279 (27.8%)	<0,001
Diabetes Mellitus	17 (10.4%)c	57 (18.6%)b	14 (10.2%)a, c	20 (15.2%)a,b,c	146 (14.5%)	.070
Coronary Artery Disease	8 (4.9%)b	57 (18.6%)a	16 (11.7%)a, c	12 (9.1%)b, c	139 (13.8%)	<0,001
COPD	2 (1.2%)b	44 (14.4%)c	3 (2.2%)b	5 (3.8%)a, b	73 (7.3%)	<0,001
Asthma	11 (6.7%)a	7 (2.3%)b	9 (6.6%)a	12 (9.1%)a	60 (6.0%)	.009
Hyper/hypothyroidism	8 (4.9%)a	6 (2.0%)a	2 (1.5%)a	6 (4.5%)a	28 (2.8%)	.193
HeartFailure	1 (0.6%)b	10 (3.3%)a, b	1 (0.7%)a, b	1(0.8%)a, b	24 (2.4%)	.042
Reflux, Sliding Hernia	2 (1.2%)a	12 (3.9%)a	4 (2.9%)a	4 (3.0%)a	27 (2.7%)	.424
Extrapulmonary Solid Organ Malignancy	6 (3.7%)a, b	1 (0.3%)c	1 (0.7%)b, c	2 (1.5%)a, b, c	24 (2.4%)	.001
Arrhythmia	2 (1.2%)a	6 (2.0%)a	4 (2.9%)a	2(1.5%)a	22 (2.2%)	.687
Chronic Renal Failure	0 (0.0%)b	2 (0.7%)b	2 (1.5%)a, b	1 (0.8%)a, b	15 (1.5%)	.008
Heart Valve Disease	2 (1.2%)a	4 (1.3%)a	1 (0.7%)a	1 (0.8%)a	13 (1.3%)	.849
Hematological Malignancy	0 (0.0%)a	1 (0.3%)a	0 (0.0%)a	1 (0.8%)a	5 (0.5%)	.404
Cerebrovascular Disease, Alzheimer's	1 (0.6%)a	4 (1.3%)a	0 (0.0%)a	0 (0.0%)a	6 (0.6%)	.351
Neuromuscular Disease	1 (0.6%)a, b	0 (0.0%)b	0 (0.0%)a, b	2 (1.5%)a	4 (0.4%)	.191
Epilepsy	3 (1.8%)b	1 (0.3%)a, b	0 (0.0%)a, b	1 (0.8%)a, b	5 (0.5%)	.083
Lung Malignancy	0 (0.0%)a	1 (0.3%)a	0 (0.0%)a	0 (0.0%)a	3 (0.3%)	.532
Cirrhosis/ChronicLiver Disease	0 (0.0%)a	0 (0.0%)a	0 (0.0%)a	0 (0.0%)a	2 (0.2%)	.232
Symptoms						
Dyspnea, exercise intolerance	86 (52.4%)b	254 (83.0%)a	111 (81.0%)a	103 (78.0%)a	762 (75.9%)	<0,001
Cough	83 (50.6%)b	187 (61.1%)a	88 (64.2%)a	78 (59.1%)a, b	587 (58.5%)	.126

Table 2. Demographic, Clinical and Radiological Characteristics of ILD

		SARCOIDOSIS <i>n:164-16.3%</i>	IPF <i>n:306-30.5%</i>	HP <i>n:137-13.6%</i>	CTD <i>n:132-13.1%</i>	TOTAL <i>n:1006-100%</i>	<i>p</i>
Weightloss		12 (7.3%)a	20 (6.5%)a	10 (7.3%)a	7 (5.3%)a	65 (6.5%)	.947
Weakness		32 (19.5%)b, c	37 (12.1%)a	18 (13.1%)a, b	33 (25.0%)c	164 (16.3%)	.009
Others		47 (28.7%)c	15 (4.9%)d	9 (6.6%)b, d	19 (14.4%)a	116 (11.6%)	<0,001
DyspneaDuration (Days)	Mean±SD	3397.22±702.811	699.24±823.889	775.05±1223.668	717.35±1051.608	671.05±944.957	<0,001
	Median (Min-Max)	120.00 (3-3650)	365.00 (7-7000)	365.00 (7-6500)	365.00 (15-5475)	365.00 (3-7000)	
CoughDuration (Days)	Mean±SD	308.01±521.074	597.62±762.520	669.42±1037.162	571.88±992.084	554.53±834.491	<0,001
	Median (Min-Max)	90.00 (3-3650)	365.00 (7-7000)	180.00 (7-3650)	180.00 (3-5475)	225.00 (3-7000)	
Physical Examination Findings							
Bibasilar Inspiratory Crackles		20 (12.2%)b	258 (84.3%)c	80 (58.4%)a	67 (50.8%)a	564 (56.2%)	<0,001
Clubbing finger		8 (4.9%)b	91 (29.7%)c	23 (16.8%)a	19 (14.4%)a	189 (18.8%)	<0,001
Arthritis		7 (4.3%)b	2 (0.7%)a	0 (0.0%)a	31 (23.5%)c	42 (4.2%)	<0,001
Edema		4 (2.4%)a, b	3 (1.0%)b	2 (1.5%)a, b	7 (5.3%)a	26 (2.6%)	.057
Erythema Nodosum		15 (9.1%)b	0 (0.0%)a	0 (0.0%)a	0 (0.0%)a	17 (1.7%)	<0,001
Cyanosis		0 (0.0%)b	3 (1.0%)a, b	2 (1.5%)a, b	1 (0.8%)a, b	13 (1.3%)	.166
Peripheral Lymphadenomegaly		5 (3.0%)c	0 (0.0%)b	0 (0.0%)a, b	3 (2.3%)a, c	9 (0.9%)	.003
Raynaud's Phenomenon		1 (0.6%)a	2 (0.7%)a	0 (0.0%)a	6 (4.5%)b	9 (0.9%)	<0,001
Rash		2 (1.2%)a, b	1 (0.3%)a	0 (0.0%)a	4 (3.0%)b	7 (0.7%)	.006
Alopesi		0 (0.0%)a	1 (0.3%)a	1 (0.7%)a	1 (0.8%)a	6 (0.6%)	.603
Other		48 (29.3%)b	9 (2.9%)c	7 (5.1%)a, c	10 (7.6%)a	103 (10.3%)	<0,001
Previous Diagnosis							
COPD/Chronic Bronchitis		4 (2.4%)b	137 (44.8%)c	16 (11.7%)d	16 (12.1%)a, d	226 (22.5%)	<0,001
Asthma/Allergic Bronchitis		36 (22.0%)a	38b (12.4%)	34 (24.8%)a	32 (24.2%)a	196 (19.5%)	.004
Non-ILD other diagnosis		36 (22.0%)c	23 (7.5%)b	8 (5.8%)b	20 (15.2%)a, c	117 (11.7%)	<0,001
Heartdisease		2 (1.2%)b	14 (4.6%)a, b	5 (3.6%)a, b	6 (4.5%)a, b	41 (4.1%)	.206
Previous Treatment							
Bronchodilators		42 (25.6%)b	191 (62.4%)c	44 (32.4%)b, d	48 (36.4%)a, d	441 (44.0%)	<0,001
Inhaled Corticosteroid		26 (15.9%)b	87 (28.4%)a	35 (25.7%)a	29 (22.0%)a, b	250 (24.9%)	.028
Diuretic		0 (0.0%)b	16 (5.2%)a	3 (2.2%)a, b	4 (3.0%)a	30 (3.0%)	.030
Other		27 (16.5%)b	31 (10.1%)a	13 (9.6%)a, b	20 (15.2%)a, b	124 (12.4%)	.216
Radiological Finding							
Reticular, interlobular septal thickenings		38 (23.2%)b	221 (72.2%)c	73 (53.3%)a	84 (63.6%)a, c	561 (55.9%)	<0,001
Tractionbronchiectasis		8 (4.9%)b	178 (58.2%)c	35 (25.5%)a	45 (34.1%)a	334 (33.3%)	<0,001
Ground glass opacities		47 (28.7%)b	75 (24.5%)b	104 (75.9%)c	63 (47.7%)d	460 (45.8%)	<0,001
Honeycomb		3 (1.8%)b	211 (69.0%)c	16 (11.7%)a	34 (25.8%)d	299 (29.8%)	<0,001
Subpleural location		6 (3.7%)b	130 (42.5%)c	17 (12.4%)a	52 (39.4%)c	247 (24.6%)	<0,001
Central location		14 (8.5%)b	0 (0.0%)c	3 (2.2%)a	1 (0.8%)a, c	23 (2.3%)	<0,001
Peripherallocation		5 (3.0%)b	63 (20.6%)c	8 (5.8%)a, b	21 (15.9%)c	121 (12.1%)	<0,001
Peribronchial, perivascular location		23 (14.0%)b	1 (0.3%)c	7 (5.1%)a	3 (2.3%)a	48 (4.8%)	<0,001
Basal predominant involvement		7 (4.3%)b	177 (57.8%)c	42 (30.7%)a	64 (48.5%)c	382 (38.0%)	<0,001
Apical predominant involvement		16 (9.8%)a, b	9 (2.9%)c	22 (16.1%)a	8 (6.1%)b, c	91 (9.1%)	<0,001
Diffus involvement		7 (4.3%)b, c	7 (2.3%)c	29 (21.2%)a	10 (7.6%)b	106 (10.6%)	<0,001
Centrilobular nodules		14 (8.5%)a	0 (0.0%)b	13 (9.5%)a	6 (4.5%)a	51 (5.1%)	<0,001
Micronodules		50 (30.5%)b	4 (1.3%)c	12 (8.8%)a	13 (9.8%)a	112 (11.2%)	<0,001
Consolidation		18 (11.0%)a	0 (0.0%)b	1 (0.7%)b, c	2 (1.5%)c	58 (5.8%)	<0,001
Transient, mobile infiltrates		2 (1.2%)a	0 (0.0%)a	1 (0.7%)a	0 (0.0%)a	6 (0.6%)	.286
Mosaic perfusion		9 (5.5%)a, b	9 (2.9%)b	43 (31.4%)c	9 (6.8%)a, b	89 (8.9%)	<0,001
Mediastinal LAP		113 (68.9%)b	8 (2.6%)c	4 (2.9%)c, d	9 (6.8%)a, d	156 (15.5%)	<0,001
Pleural involvement		1 (0.6%)b	3 (1.0%)b	2 (1.5%)a, b	6 (4.5%)a	18 (1.8%)	.073

Table 2. Demographic, Clinical and Radiological Characteristics of ILD

	SARCOIDOSIS <i>n:164-16.3%</i>	IPF <i>n:306-30.5%</i>	HP <i>n:137-13.6%</i>	CTD <i>n:132-13.1%</i>	TOTAL <i>n:1006-100%</i>	<i>p</i>	
Discrete air cysts	0 (0.0%)b	4(1.3%)b	6 (4.4%)c	2 (1.5%)b, c	45 (4.5%)	<0,001	
Halo sign	1 (0.6%)a	0 (0.0%)a	0 (0.0%)a	0 (0.0%)a	1 (0.1%)	.275	
Inverted halo sign	0 (0.0%)a, b	0 (0.0%)b	0 (0.0%)a, b	0 (0.0%)a, b	6 (0.6%)	.002	
Diagnostic Tool							
Clinic and radiology	82 (50.0%)b	232 (75.8%)a	105 (76.6%)a	122 (92.4%)c	752 (74.9%)	<0,001	
Bronchoalveolar lavage	19 (11.6%)a, b	8 (2.6%)c	47 (34.3%)d	8 (6.1%)b, c	115 (11.5%)	<0,001	
Transbronchial lung biopsy	20 (12.2%)a	6 (2.0%)b	20 (14.6%)a	4 (3.0%)b	72 (7.2%)	<0,001	
Transthoracic needle biopsy	4 (2.4%)a	5 (1.6%)a	1 (0.7%)a	0 (0.0%)a	17 (1.7%)	.285	
EBUS	76 (46.3%)b	1 (0.3%)a	0 (0.0%)a	0 (0.0%)a	77 (7.7%)	<0,001	
VATS	10 (6.1%)b, c	29 (9.5%)a, b	19 (13.9%)a	4 (3.0%)c	85 (8.5%)	.013	
Thoracotomy	10 (6.1%)b	8 (2.6%)a, b	0 (0.0%)a	0 (0.0%)a	20 (2.0%)	.001	
Multidisciplinary council decision	13 (7.9%)a, b, c	34 (11.1%)c	7 (5.1%)a	19 (14.4%)b, c	89 (8.9%)	.018	
Differential diagnosis could not be made	0 (0.0%)b	0 (0.0%)b	0 (0.0%)b	0 (0.0%)b	9 (0.9%)	<0,001	
Consulted Departments							
Immunology, rheumatology	25 (15.2%)b	198 (64.7%)c	49 (35.8%)a	94 (71.8%)c	464 (46.3%)	<0,001	
Cardiology	40 (24.4%)a	82 (26.8%)a	32 (23.4%)a	41 (31.3%)a	275 (27.4%)	.411	
Ophthalmatology	82 (50.0%)b	20 (6.5%)c	24 (17.5%)a	17 (13.0%)a	184 (18.3%)	<0,001	
Nephrology	6 (3.7%)a	3 (1.0%)b	1 (0.7%)a, b	3 (2.3%)a, b	22 (2.2%)	.141	
Other	37 (22.6%)b	15 (4.9%)c	11 (8.0%)a, c	8 (6.1%)a, c	104 (10.4%)	<0,001	
Consultation not requested	32 (19.5%)b	53 (17.3%)b	49 (35.8%)a	19 (14.5%)b	239 (23.8%)	<0,001	
Initiated Treatment							
Untreated Follow-up	76 (46.3%)b	6 (2.0%)c	35 (25.5%)a	11 (8.4%)d	203 (20.2%)	<0,001	
Symptomatic Treatment	29 (17.7%)b	30 (9.8%)c	16 (11.7%)b, c	17 (13.0%)b, c	163 (16.3%)	<0,001	
Antifibrosing Drug	1 (0.6%)a	262 (85.6%)b	4 (2.9%)a	1 (0.8%)a	276 (27.5%)	<0,001	
Systemic Steroid	57 (34.8%)a	4 (1.3%)b	86 (62.8%)c	68 (51.9%)c	308 (30.7%)	<0,001	
Cytostatic Drugs	3 (1.8%)a, b	1 (0.3%)b	3 (2.2%)a, b	59 (45.0%)c	77 (7.7%)	<0,001	
immunological therapy	1 (0.6%)a	1 (0.3%)a	0 (0.0%)a	12 (9.2%)b	16 (1.6%)	<0,001	
Oxygenotherapy at home	1 (0.6%)b	24 (7.8%)c	7 (5.1%)a, c	5 (3.8%)a, b, c	44 (4.4%)	.001	
Reflux treatment	0 (0.0%)b	18 (5.9%)c	4 (2.9%)a, c	7 (5.3%)c	32 (3.2%)	.001	
Referral to othercenter	0 (0.0%)a	1 (0.3%)a	0 (0.0%)a	4 (3.1%)b	6 (0.6%)	.003	
Preparation for transplantation	0 (0.0%)a	2 (0.7%)a	0 (0.0%)a	0 (0.0%)a	3 (0.3%)	.620	
Other	3 (1.8%)b, c	4 (1.3%)c	2 (1.5%)c	12 (9.2%)a	36 (3.6%)	<0,001	
Pulmonary Function Tests							
FVC (%)	Mean±SD	87.12 ±20.764	74.61±20.820	77.68±23.092	81.18±20.945	79.03±22.674	<0,001
	Median (Min-Max)	87.00 (32-134)	74.00 (28-134)	74.00 (33-140)	82.00 (35-127)	78.00 (22-176)	
FEV1 (%)	Mean±SD	84.22±20.507	80.52±20.272	80.23±24.040	82.35±20.374	81.32±22.014	.159
	Median (Min-Max)	85.00 (34-142)	80.00 (33-143)	78.50 (35-162)	82.00 (35-1409)	81.00 (22-162)	
FEV1/FVC	Mean±SD	82.80±11.410	85.38±9.631	85.59±10.761	83.82±9.882	84.01±10.823	.057
	Median (Min-Max)	83.00 (50-126)	85.00 (45-124)	86.00 (42-132)	84.00 (57-119)	84.00 (42-1389)	
DLCO %	Mean±SD	80.37±26.358	57.67±22.136	64.25±29.519	70.22±41.060	66.53±35.912	<0,001
	Median (Min-Max)	79.50 (9-175)	56.00 (17-176)	58.00 (10-164)	65.00 (22-305)	63.00 (9-541)	
DLCO/VA %	Mean±SD	97.29±26.364	81.93±25.613	81.00±24.639	88.89±30.477	84.49±27.292	<0,001
	Median (Min-Max)	99.00 (22-177)	81.00 (18-212)	82.00 (14-147)	90.00 (25-154)	84.00 (14-212)	
6 Minute Walk Test	Mean±SD	433.78±137.244	352.75±128.820	350.33±153.169	334.32±129.693	355.52±133.531	.003
	Median (Min-Max)	450.00 (80-696)	368.00 (25-636)	367.00 (30-800)	360.00 (30-560)	372.50 (25-800)	
PaO2 with pulseoximetry	Mean±SD	95.99±2.590	93.22±2.90	93.46±4.64	94.72±3.85	94.20±1.68	<0,001
	Median (Min-Max)	97.00 (80-99)	95.00 (69-99)	95.00 (75-99)	96.00 (78-99)	95.00 (69-99)	

Table 2. Demographic, Clinical and Radiological Characteristics of ILD

		SARCOIDOSIS <i>n:164-16.3%</i>	IPF <i>n:306-30.5%</i>	HP <i>n:137-13.6%</i>	CTD <i>n:132-13.1%</i>	TOTAL <i>n:1006-100%</i>	<i>p</i>
A-a O2 Gradiyent.	Mean±SD	26.40±11.900	34.57±17.258	36.53±14.415	29.33±14.394	34.67±16.896	.331
	Median (Min-Max)	26.00 (13-46)	34.00 (5-68)	37.00 (9-59)	23.70 (10-52)	36.50 (5-83)	
ECHO PAB	Mean±SD	24.30±9.225	36.77±17.503	35.19±12.298	31.25±12.872	32.22±14.391	<0,001
	Median (Min-Max)	23.00 (12-65)	31.00 (11-104)	30.50 (15-77)	28.00 (15-85)	30.00 (11-104)	
Cost (TL)	Mean±SD	1053.44±896.576	759.47±1012.659	1157.24±884.576	811.97±942.431	977.06±1117.276	<0,001
	Median (Min-Max)	920.50 (65-4637)	300.00 (80-6893)	850.76 (64-4133)	450.00 (64-5450)	540.00 (62-8000)	
Time to Diagnosis (Days)	Mean±SD	88.80±164.720	93.77±163.126	60.39±96.269	54.35±100.281	78.84±142.855	.071
	Median (Min-Max)	34.00 (3-943)	35.00 (2-917)	31.00 (1-735)	28.00 (1-777)	33.00 (1-943)	

was made, the symptoms at presentation, physical examination and radiological findings, which diagnostic methods were used most, which branches were mostly studied during diagnosis, and preferred treatments were evaluated. In addition, when the data of the two studies were examined, it was observed that the distribution of ILD in our country changed over time, and it was noted that the rates of IPF diagnosis increased. In a study regarding the epidemiology of interstitial lung diseases conducted in Greece in 2009, it was observed that among 259 newly diagnosed patients, 60 patients (23.2%) with sarcoidosis, 84 patients (32.4%) with IPF, and 30 patients (11.6%) with collagen tissue were diagnosed in a 1-year period(8). In our study, the diagnosis rates of IPF were higher than all other diseases. This may be attributed to the fact that the diagnosis of IPF has been clarified with the latest guidelines, the usual pattern of interstitial pneumonia in HRCT in clinically compatible patients, and the fact that it is sufficient to exclude CTD with serological tests, making the diagnosis of IPF easier(9).

Furthermore, the large, randomized studies have shown that antifibrotic drugs such as pirfenidone and nintedanib slow down the worsening of lung functions in IPF, unlike other ILD, and these drugs were approved by the FDI in 2014 (10,11,12). We believe that all these developments increased the awareness of clinicians about IPF and make them more willing to diagnose.

As regards the distribution of ILD by gender and age, sarcoidosis was mostly detected in women and under 50 years of age. In the study conducted by Baughman et al., in which the clinical characteristics of sarcoidosis were investigated, it was shown that 63.6% of the cases were women and while female patients were

mostly diagnosed at the age of 40 years and above, male patients were under 40 years of age with a higher rate (13). In our study, 72% of sarcoidosis patients were female, and the mean age, regardless of gender was 50.45±12,959. It is known that IPF is more common in men and seen mostly above the age of 75 (14). In our study, also consistent with the literature, the male sex ratio in the IPF group was 74.8% and the mean age was 69.97±8,502. Collagen tissue diseases were observed at a higher rate in women than as reported in the literature. In a study conducted in China, in which the clinical features of 1044 patients diagnosed with CVD were analyzed, the male/female ratio was 1:1.8 in patients with lung involvement, and the mean age was found as 59.7 years±13.2(15). In our study, the male/female ratio was determined 1:2.25 and the mean age was 62.30±10,759.

The ratio of female patients in the hypersensitivity pneumonia group was 53.3%, and the mean age was 59.71±14,297. In the study conducted by Perez et al. in the United States, the rate of women in patients diagnosed with hypersensitivity pneumonia was found to be 57.6 % and the mean age was 52.4±20.1 (16).

It was observed that all groups received diagnosis and treatment in tertiary hospitals at a very high rate. This situation can be explained by the difficulty of diagnosis and differential diagnosis of ILD in primary and secondary care facilities. The group with the highest rate of living in the rural area was the HP group with 39.4%. The most observed form of HP is farmer's lung which is defined by Ramazzani in grain workers and is more common in rural areas (17).

The way our patients applied was mostly from secondary care centers and with the routing of chest diseases specialists with high frequency (Respectively, $p<0.001$, $p<0.001$).

In the study of Schwarzkop et al., Chronic Obstructive Pulmonary Disease (COPD), arterial hypertension, and ischemic heart disease (HRD) were found to be the most common comorbidities in 36,821 interstitial lung patients (18). In our study among the accompanying comorbidities, hypertension, diabetes mellitus and coronary artery disease were in the first three ranks. While there was a statistically significant difference between the groups in terms of hypertension and coronary artery disease, no significant difference was found in terms of diabetes mellitus (p values, respectively <0.001 , 0.070 , <0.001). IPF was the most common diagnostic group for all three diseases.

Dyspnea is the most common symptom in ILD, especially in IPF. In a study conducted by Guenther et al. examining the clinical features of IPF patients in Europe, dyspnea was found to be the most common symptom with a rate of 90.1% (19). In our patients, the dyspnea was detected in diagnosis groups at a high percentage in IPF (% 83.0). In addition, dyspnea had the highest rate among the symptoms seen in IPF. The disease with the least incidence of dyspnea was sarcoidosis (52.4%). Another common symptom in ILD is cough. The prevalence of cough has been reported to be as 84% (20) in patients with IPF (20), 56% in sarcoidosis (21), 83% in patients with chronic hypersensitivity pneumonia (22), and 73% in patients with scleroderma associated ILD (23). In our study, the rate of cough was determined as 50.6% in sarcoidosis, 61.1% in IPF, 64.2% in HP and 59.1% in CTD. In general, the rate of cough in our patients was lower than the rates reported in the literature and there was no statistically significant difference between the groups in terms of incidence ($p=0.126$).

The presence of many diseases under the title of ILD and their similar clinical and radiological features make it difficult for clinicians in differential diagnosis. In addition to their similarities, some symptoms and signs can be confused with other diseases of the lung, and patients are tried to be treated under misdiagnoses for a long time. In a survey of 600 people diagnosed with ILD on this subject, Cosgrove et al. found that 55% of the patients had ≥ 1 misdiagnosis and 38% had ≥ 2 misdiagnoses before the current diagnosis. The most common misdiagnoses are asthma (13.5%), pneumonia (13.0%) and bronchitis (12.3%). While the median

time from the onset of symptoms to diagnosis was 7 months (0-252), it was observed that it took 1 year for 43% of the patients to be diagnosed and more than 3 years for 19% to be diagnosed (24). In our study, the median dyspnea duration until diagnosis was determined as 360 days (0-7000), and the duration of cough was 180 days (0-7200). It was observed that there was a significant difference between the diagnosis groups in terms of duration of dyspnea and cough ($p<0.001$). It was determined that a total of 580 (57%) of the patients applied to the hospital with these complaints and received different diagnoses and related treatments. Of these patients, 226 (22.5%) of them had COPD, 196 (19.5%) had asthma, 41 (4.1%) had heart disease, and 117 (11.7%) had a diagnosis other than ILD. When the distribution of previously diagnosed diagnoses by groups is examined, the highest proportion of patients diagnosed with COPD/chronic bronchitis (44.8%) is in the IPF group, those diagnosed with asthma/allergic bronchitis (24.8%) are in the HP group, and those diagnosed with other diseases other than ILD (22%) are in the sarcoidosis group. Those diagnosed with heart disease were also in the IPF group (4.6%). When the examination findings of the patients were evaluated, as expected, rales (84.3%) and clubbing (29.7%) were most common in the IPF group, arthritis (23.5%) was most common in the CVD group, and erythema nodosum (9.1%) was observed in the sarcoidosis group.

The most common chest tomography findings were reticular, interlobular septal thickening (55.9%), ground glass opacities (45.8%), traction bronchiectasis (33.3%), honeycomb (29.8%). Basal predominant involvement was present in 38% of the patients.

When the distribution of radiological findings according to the diagnosis groups was examined reticular opacities and interlobular septal thickenings were observed in 72% of the IPF group, traction bronchiectasis in 58.2%, honeycomb in 69%, basal-weighted involvement in 57.8%, while ground glass opacities were presented in only 24.5%. The most common finding in the sarcoidosis group was mediastinal lymphadenopathy (68.9%), ground glass opacities (75.9%) in the HP group, and reticular opacities and interlobular septal thickenings in the CTD group.

It was seen that consultation was requested from the immunology/rheumatology department most

frequently in the CTD group (71.8%), and from the ophthalmology department most frequently in the sarcoidosis group (50%). The rate of not asking for consultation was 35.8% in the HP group ($p < 0.001$). Cardiology and nephrology consultations had similar rates in all patients. A multidisciplinary approach is essential in the diagnosis of ILD, and this approach is becoming more and more applicable by clinicians day by day. We believe that the increase in the number and experience of rheumatology, radiology and chest specialists contributes to this process.

Untreated follow-up was in sarcoidosis group with the highest rate of 46.3%. The second most common treatment approach in this group was systemic steroids (34.8%). It was observed that antifibrotic drugs were administered at a rate of 85.6% in the IPF group. The diagnosis group in which systemic steroid was most frequently applied was the HP group with 62.8%. This was followed by the CTD group with 51.9%. Cytostatic drugs were detected at the highest rate (45%) in the CTD group. The biggest development in the treatment of IPF in recent years is the introduction of antifibrotic drugs that prevent the progression of lung fibrosis. Studies showing the efficacy and reliability of these drugs in IPF (25,26) motivate clinicians to use them much more. Indeed, it is used at a high rate in patients diagnosed with IPF in our country.

ILD is a disease group that is difficult to diagnose and treat, and it causes increasing costs for countries with increasing diagnosis rates. There are various studies investigating the economic burden caused by ILD. Frank et al. investigated the total cost of ILD within the scope of hospitalization, medication and doctor visits and calculated the annual cost per patient for IIPs as 4,036 € and for sarcoidosis as 2,938 €, excluding health-care costs for other reasons (27). Niewiadomska et al. calculated the average annual cost of treatment for sarcoidosis in the Silesian Voivodeship of €538.21 per patient. In this study, it was observed that the costs varied according to the clinical forms of the disease, and the hospitalization cost of pulmonary sarcoidosis was found to be the highest (1,205.49 €)(28). In a retrospective study conducted by Raimundo et al., investigating the clinical and economic burden of IPF, it was determined that non-drug health care costs were \$52,716 per patient, of which \$14,684 consisted of outpatient services

and \$38,032 inpatient services. In all these studies, diagnostic costs were not given in isolation (29). Davidsen et al. It investigated the economic burden of systemic sclerosis in 8 European countries and examined overall costs as well as diagnostic costs. Among all countries, the highest cost of diagnosis was found in Switzerland with 2376 € and the lowest in Greece with 122.17 € (30). In our study, we examined the hospital costs of the patients from the time of admission to the diagnosis, and their median values were 540.00 (62-8000) in TL (Turkish Lira), 920.50 (65-4637) in the sarcoidosis group, 300.00 (80-6893) in the IPF group, and 300.00 (80-6893) in the HP group. We found it to be 850.76 (64-4133) TL in the CTD group and 450.00 (64-5450) TL in the CTD group.

There was no significant difference between the disease groups in terms of the time from the patient's admission to the hospital to the diagnosis ($p: 0.071$). The minimum time to diagnosis was observed as 1 day in all groups. This situation can be explained by the fact that some patients were previously investigated in different centers for diagnosis and applied to the center where the diagnosis was made with tests performed in other centers, and these patients were diagnosed clinically and radiologically without any invasive procedure.

Overall our findings indicate that the most frequently diagnosed group in ILD is IPF followed by sarcoidosis, HP and CTD, and that the cases assumed to be ILD are frequently referred by chest diseases specialists. The most common presenting symptoms were dyspnea and coughlasting with more than one year of complaints. The diagnosis is mostly made in tertiary hospitals as COPD, asthma, and heart failure; the most common chronic diseases accompanying these patients are hypertension and DM. The branches whose consultation is requested in the diagnostic process are immunology/rheumatology, ophthalmology, cardiology, and nephrology; in the vast majority of cases, clinical and radiological findings and the decision of the multidisciplinary council are sufficient and invasive sampling is not required. Furthermore, while corticosteroid treatment is most frequently used in patients with CTD, HP and sarcoidosis, it shows that the use of antifibrotic drugs in the IPF group is quite high. In conclusion, we believe that our findings will

be useful to show the current situation of ILD in our country in comparison with data from other countries, as well as discussing the issue to make future plans for clarification.

CONFLICTS OF INTEREST: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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