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Spectrum of interstitial lung disease from a tertiary care hospital in Karachi

Ali Bin Sarwar Zubairi
Aga Khan University, ali.zubairi@aku.edu

Maryam Hassan
Aga Khan University

Talha Shahzad
Aga Khan University, talha.shahzad@aku.edu

Sajjad Sarwar
Aga Khan University

Aamir Abbas
Aga Khan University

See next page for additional authors

Authors

Ali Bin Sarwar Zubairi, Maryam Hassan, Talha Shahzad, Sajjad Sarwar, Aamir Abbas, Huzaifa Ahmad, and Muhammad Irfan

ORIGINAL ARTICLE

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Abstract

Objective: To determine the clinical features and patterns of interstitial lung disease.

Methods: This retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised record of patients diagnosed with interstitial lung disease from January 2005 to December 2015. All patients aged 16 years and above diagnosed with interstitial lung disease on the basis of clinical features, radiological features on high-resolution computed tomography of the chest, and lung biopsies were included. SPSS 19 was used for data analysis.

Results: Of the 537 patients, 324(60.3%) of the participants were females. The overall mean age was 60.5±14.9 years. The most common co-morbid condition was diabetes mellitus in 72(13.4%) patients, followed by hypertension in 48(8.9%) and ischaemic heart disease in 21(3.9%). The most common interstitial lung disease was idiopathic pulmonary fibrosis in 217(40.4%) patients, followed by non-specific interstitial pneumonia in 106(19.7%), sarcoidosis in 82(15.3%) and connective tissue disease-related interstitial lung disease in 56(10.4%) patients.

Conclusion: Idiopathic pulmonary fibrosis was found to be the most common interstitial lung disease subtype followed by non-specific interstitial pneumonia, sarcoidosis and connective tissue disease-related-interstitial lung disease.

Keywords: Interstitial lung disease, Idiopathic pulmonary fibrosis, Pakistan. (JPMA 67: 1065; 2017)

Introduction

Interstitial lung disease (ILD) or diffuse parenchymal lung disease comprises a diverse group of more than 200 conditions that damage the lung parenchyma. These entities manifest in varying degrees of inflammation and fibrosis that result in characteristic clinical, radiological, and histopathological presentations. Two-thirds of ILD cases are idiopathic. The remainder are associated with drugs, environmental exposure, autoimmunity, infections or genetics.[1,2] The diagnosis of ILD can be challenging and requires a multidisciplinary approach involving evaluation by a pulmonologist, radiologist and histopathologist with expertise in ILD.

Epidemiological data on ILD from around the world is limited. Recently efforts have been made to establish ILD registries in several countries, to gain a better understanding of the disease. In 2013 the British Thoracic Society established an ILD registry that aimed to study clinical and diagnostic trends of idiopathic pulmonary fibrosis (IPF) and sarcoidosis in Britain.[3] Similarly in Germany, Exploring Clinical and Epidemiological Characteristics of Interstitial Lung Diseases (EXCITING-ILD) was established to determine the spectrum of ILD in the country.[4] The registries of ILD from other European countries like Belgium and Spain shows differences in incidences of various forms of ILDs as well.[5-7] A single-centre study in Romania showed IPF to be the more predominant ILD, followed by hypersensitivity pneumonia.[8]

In Asia, a few registries have published their results. Recent data published by the ILD Pakistan registry, which collected data from 2010-2016, showed IPF to be the most common ILD (32.9%), followed by sarcoidosis (18.5%).[9] In India, a prospective ILD registry found hypersensitivity pneumonitis as the most common ILD (47.35%).[10]

There is a lack of data on ILD from developing countries. The diagnosis of this condition in Pakistan is even more challenging due to higher prevalence of tuberculosis leading to fibrosis which can mimic ILD. Limited resources and poor socio-economic conditions also hinder the timely diagnosis of the disease.

The current study was planned to analyse the spectrum of ILD. This data is expected to help us understand the various spectra of this disease in our population and provide opportunities for further studies.

Patients and Methods

This retrospective, observational study was conducted at the Aga Khan University Hospital (AKUH), Karachi, and comprised records of patients diagnosed with ILD from January 2005 till December 2015. The AKUH is a tertiary

Aga Khan University, Karachi.

Correspondence: Ali Bin Sarwar Zubairi. Email: ali.zubairi@aku.edu

care hospital with a total of 640 beds.All adult patients with suspected ILD on the basis of clinical history and radiological features on high-resolution computed tomography (HRCT) scan of the chest were reviewed by a multidisciplinary team consisting of a senior pulmonologist and radiologist with expertise in diagnosis of ILD. The files were retrieved using International Classification of Diseases-9 (ICD-9) coding. The definite diagnosis of ILD was based on histopathology if available. Other cases were labelled as ILD on the basis of clinical and HRCT findings. Patients with post-infectious fibrosis or bronchiectasis were excluded (Figure).

The study was reviewed and approved by the institutional ethical review committee. The data was collected through medical records. The information about demographic variables, occupation, environmental exposures, smoking, medications, co-morbid conditions, radiological and pathological pattern, severity and treatment of the disease were collected in a predesigned questionnaire.

The American Thoracic Society/European Respiratory Society Statement on Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias 2013 was used in the diagnosis and classification of ILD.[11] Interstitial lung diseases were classified into different categories including IPF, non-specific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis (HP), cryptogenic organising pneumonia (COP), sarcoidosis, connective tissue disease-associated interstitial lung disease (CTD-ILD) and other rare interstitial lung diseases depending upon the patient's clinical presentation, laboratory investigations, lung function tests, environmental exposures, radiological findings and pathological diagnosis if available.

The following HRCT descriptive findings were used to classify ILDs:

IPF: The presence of bilateral honeycombing, reticular opacities, traction bronchiectasis, sub pleural cysts with minimal or no ground glass opacities and predominant basal involvementwith exclusion of other causes of ILD.[11]

NSIP: The presence of ground glass opacities, irregular linear or reticular infiltrates and associated with traction bronchiectasis with most commonly bilateral and symmetrical distribution.

HP: poorly defined centrilobularmicronodules, widespread ground-glass opacities, mosaic attenuation and air trapping with a predominance of disease in upper and middle lung zones under appropriate clinical setting.[12]

COP: Presence of multiple patchy alveolar opacities with a peripheral and bilateral distribution, ground glass opacities and peribronchiolar nodules extending into the lung parenchyma.[11]

Sarcoidosis: The presence of mediastinal lymphadenopathy, nodular opacities and micronodules along bronchovascular bundles, central bronchovascular thickening and nodularity, confluent nodular opacities with air bronchograms, ground glass opacities, crowding and central retraction of bronchi and vessels near the hilae, and pleural or subpleural nodules.[13]

Pulmonary langerhans cell histiocytosis (PLCH): the combination of multiple cysts and nodules, with mid to upper zone predominance, and

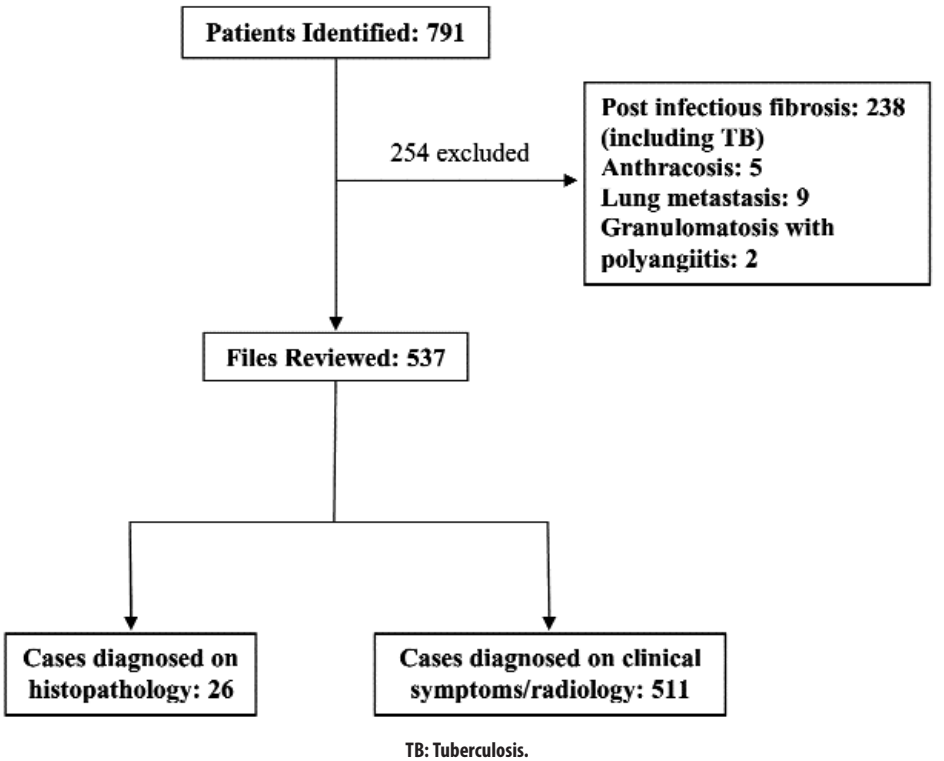

Figure: Flow Chart of the Study.

interstitial thickening.[14]

Pulmonary lymphangioleiomyomatosis (LAM): the presence of numerous thin-walled cysts, ranging in size from a few millimetres to six centimetres, scattered throughout both lungs with normal intervening lung parenchyma.[15]

Pulmonary alveolar proteinosis (PAP): the presence of ground glass and/or consolidative infiltrates in patchy or diffuse distributions, reticular opacities or interlobular septal thickening present within the airspace infiltrates, creating a "crazy-paving" pattern on HRCT.[16]

CTD-ILD: The ILD pattern on HRCT along with the clinical and serologic evidence of connective tissue disease.

The data was analysed using the SPSS 19. Means and standard deviations were reported for quantitative variables and frequencies with percentages were reported for qualitative variables. Variables such as gender, age, smoking status, clinical presentation and pulmonary function tests (PFT) were analysed to determine their distribution across ILD subtypes. Independent sample t-test was used to compare the mean age of IPF and non-IPF ILD. Depending on the minimum expected cell count, chi-square or Fisher's exact test was used to check the association between types of ILD and different qualitative variables. Logistic regression was used to calculate crude and adjusted odds ratio for the factors associated with IPF versus non-IPF ILDs.

Results

Of the 791 files reviewed, 537(67.8%) met the inclusion criteria. The overall mean age was 60.5±14.9 years and 324(60.3%) of the participants were females. Diabetes mellitus was found to be the most common co-morbid condition, seen in 72(13.4%) patients, followed by hypertension in 48(8.9%) patients and ischaemic heart disease in 21(3.9%) patients (Table-1).

Table-1: Distribution of ILD subtypes.

Clinical Types	N (%)
Idiopathic Pulmonary Fibrosis (IPF)	217 (40.4)
Non Specific Interstitial Pneumonia (NSIP)	106 (19.7)
Connective Tissue Disease ILD (CTD-ILD)	56 (10.4)
Rheumatoid Arthritis (RA)	30 (53.5)
Systemic Lupus Erythematosus (SLE)	8 (14.2)
Systemic Sclerosis (SS)	11 (19.6)
Mixed Connective Tissue Disease (MCTD)	7 (12.5)
Sarcoidosis	82 (15.3)
Hypersensitivity Pneumonitis (HP)	30 (5.6)
Cryptogenic organizing pneumonia (COP)	15 (2.8)
Desquamative Interstitial Pneumonia (DIP)	11 (2.0)
Pulmonary Langerhans Cell Histiocytosis (PLCH)	3 (0.6)
Drug Induced	6 (1.1)
Protein Alveolar Proteinosis (PAP)	3 (0.6)
Lymphangioleiomyomatosis (LAM)	3 (0.6)
Autoimmune-associated ILD	2 (0.4)

ILD: Interstitial lung disease.

Table-2: Characteristics of patients with common ILDs.

	IPF n=217	NSIP n=106	Sarcoidosis n=82	CTD-ILD n=56
Mean Age	67.2±12.1	58.4±15.6	55.5±11.6	54.1±15.6
Male/Female	112/105	28/78	34/48	7/49
Smoking Status n(%)				
Current Smoker	50(23.04)	9(8.4)	1(1.2)	3 (5.3)
Ex-smoker	53(24.4)	16(15.09)	10(12.19)	6(10.7)
Never Smoked	114(52.5)	81(76.4)	71(86.5)	45(80.3)
Symptoms n(%)				
Cough	193(88.9)	97(91.5)	76(92.6)	52(92.8)
Dyspnoea	205(94.4)	102(96.2)	70(85.3)	54(96.4)
Clubbing	32(14.7)	9(8.4)	2(2.4)	7(12.5)
Crackles	205(94.4)	91(85.8)	53(64.6	51(91.07)
Clinical Onset n(%)				
Acute	4(1.8)	1(0.9)	5(6.09)	1(1.7)
Sub-acute	5(2.3)	6(5.6)	6(7.3)	3(5.3)
Chronic	208(95.8)	99(93.3)	71(86.5)	52(9.2)
PFT (n=195) n(%)				
Non Specific	89 (93.7)	32 (82.1)	28 (70.0)	16 (76.2)
Obstructive	0 (0.0)	5 (12.8)	6 (15.0)	2 (9.5)
Mixed	3 (3.2)	2 (5.1)	4 (10.0)	3 (14.3)
Normal	3 (3.2)	0 (0.0)	2 (5.0)	0 (0.0)

ILD: Interstitial lung disease
IPF: Idiopathic pulmonary fibrosis
NSIP: Non-specific interstitial pneumonitis (
CTD-ILD: Connective tissue disease-associated interstitial lung disease
SD: Standard deviation
PFT: Pulmonary function test.

IPF was the most common ILD which occurred in 217(40.4%) individuals, followed by NSIP in 106(19.6%) patients, sarcoidosis in 82(15.3%) and CTD-ILD in 56(10.4%) patients (Table-2).

All of the ILD types were found to be more predominant in the female population except IPF. The mean age was different across the various types of ILD ($p<0.01$); patients with NSIP, CTD-ILD and sarcoidosis presented at a younger age in contrast to IPF.

As IPF was the most common pattern in our study, we also compared the characteristics of IPF with other types of ILD (Table-3).

On logistic regression analysis, age greater than 60 years (odds ratio [OR] 3.4; 95% confidence interval [CI] 2.3 to 5.0) and male gender (OR 2.1; 95% CI 1.4 to 3.2) were significantly associated with IPF as compared to non-IPF

Table-3: Comparison of Characteristics of IPF and other ILDs.

	IPF	Others	p value
Age Mean	67.24±12.13	55.97±14.95	<0.01
Gender n (%)			
Male	112 (51.6)	101 (31.6)	<0.01
Female	105 (48.4)	219 (68.4)	
Smoking n (%)			
Non-smoker	167 (77)	290 (90.6)	<0.01
Smoker	50 (23)	30 (9.4)	
Cough n (%)			
Yes	194 (89.4)	296 (92.5)	0.21
No	23 (10.6)	24 (7.5)	
Dyspnoea n (%)			
Yes	205 (94.5)	302 (94.4)	0.96
No	12 (5.5)	18 (5.6)	
Crackles n (%)			
Yes	205 (94.5)	265 (82.8)	<0.01
No	12 (5.5)	55 (17.2)	
Clubbing n (%)			
Yes	32 (14.7)	22 (6.9)	<0.01
No	185 (85.3)	298 (93.1)	
Onset n (%)			
Acute	4 (1.8)	15 (4.7)	
Subacute	5 (2.3)	23 (7.2)	0.01
Chronic	208 (95.9)	282 (88.1)	
PFTs n (%)			
Non-specific	89 (93.7)	101 (78.9)	
Obstructive	0 (0)	15 (11.7)	<0.01
Mixed	3 (3.2)	10 (7.8)	
Normal	3 (3.2)	2 (1.6)	

IPF: Idiopathic pulmonary fibrosis. ILD:Interstitial lung disease. PFT:Pulmonary function test. SD: Standard deviation.

Table-4: Logistic regression model showing factors associated with IPF versus non-IPF ILDs.

Variable	Univariate		Multivariate	
	Unadjusted OR	95% CI	Adjusted OR	95% CI
Age				
>60	3.6	2.5 to 5.3	3.4	2.3 to 5.0
≤ 60	1		1	
Gender				
Male	2.3	1.6 to 3.3	2.1	1.4 to 3.2
Female	1		1	
Crackles				
Yes	3.6	1.9 to 6.8	2.8	1.4 to 5.6
No	1		1	
Clubbing				
Yes	2.3	1.3 to 4.2	2.6	1.3 to 5.0
No	1		1	
Smoking				
Current Smoker	2.9	1.8 to 4.7	1.4	0.8 to 2.5
Non Smoker	1		1	
Clinical Onset				
Chronic	2.8	0.9 to 8.5	2.2	0.7 to 7.0
Sub-acute	0.8	0.2 to 3.5	0.7	0.1 to 3.0
Acute	1		1	

IPF: Idiopathic pulmonary fibrosis
ILD: Interstitial lung disease.

ILDs when adjusted for smoking status and clinical onset of disease (Table-4).

Discussion

We identified IPF, NSIP, sarcoidosis and CTD-ILD as the four most common ILD subtypes in our population. Our data is consistent with findings reported from the ILD Pakistan (ILDPAK) registry and from Greece.[17] ILD was more common in females in our study population. This finding is in accordance with the results of the ILDPAK and Indian registry, while in contrast to those from New Mexico and Belgium which found that ILD is more common among males due to occupational exposure.[6,18] The majority of females in our study were housewives.

In our study population, IPF was found to be the most common type of ILD. The higher prevalence of IPF (40.4%) in our region is important to note when compared with data from Greece (20.1%) and Saudi Arabia (23.3%).[13,19] However, our data differs from the results of the prospective ILD registry in India in which hypersensitivity pneumonitis was found to be the most common ILD (47.35%).[10] Data from a single-centre study from India showed similar findings with IPF present in 45% patients in the study.[20] The results of logistic regression analysis showed that age more than 60 was significantly associated with IPF in our population. Previous studies have suggested that aging increases susceptibility to developing IPF, however, the link between the two remains unclear.[21]

Sarcoidosis was the third most prevalent type of ILD in our study. In contrast, sarcoidosis was found to be the predominant ILD in studies from Greece, Belgium and Spain.[17,22] These differences can be attributed to racial and regional differences. The incidence of sarcoidosis in the Pakistani population is underestimated, as the disease is commonly undiagnosed because it can be asymptomatic and patients are often mistreated as having tuberculosis.

CTD-ILD was the fourth-most common ILD among our patient population. Among the CTD-ILD, rheumatoid arthritis (RA) was found to be the most common subtype in our female population. The mean age of the patients presenting with CTD-ILD (54.1 years) was less than the other ILDs. This earlier presentation might be due to the nature of the disease, which commonly occurs in younger patients.

The current study was one of the largest studies on spectrum of ILD from Pakistan.

It is unclear what the true burden of the disease is in the region. ILD is often unrecognised and unreported due to

a lack of knowledge about the diagnostic criteria and resources available to recognise the disease pattern.

The current study had its limitations as well. As a single-centre study, our data was not generalisable. The risk factors for ILD were difficult to assess from the retrospective data. In Pakistan, where most of the healthcare expenditure is paid out of pocket, cost is a major obstacle for evaluation of ILD. Pulmonary function tests were not performed in a majority of patients due to cost implications. Inability to perform histopathology for definitive diagnosis was another limitation of our study.

Conclusion

IPF was found to be the most common ILD, followed by NSIP, sarcoidosis and CTD-ILD. Larger multi-centre studies are required nationwide to establish the true prevalence of ILD in Pakistan.

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Competing Interests: None.

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