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Original Research Article

Distribution of interstitial lung diseases in a tertiary care centre of South India

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ABSTRACT

Background: The term interstitial lung diseases (ILD) refer to a broad category of lung diseases rather than a specific disease entity. True prevalence of ILD is difficult to estimate and it may vary according to the geography, environment, occupation etc. Aim and objectives were to find out the distribution of interstitial lung disease (ILD) subtypes in a tertiary care centre.
Methods: A descriptive study was conducted between August 2016 and November 2018 in a tertiary care centre in Puducherry, South India. Baseline demographic details, clinical symptoms, signs, radiological findings (chest radiograph and HRCT), pathological findings, and physiological findings were taken into consideration and diagnosis of type of interstitial lung disease was made using multidisciplinary discussion. Statistical analysis was done using SPSS 19.0 version.
Results: A total of 150 patients were recruited of which 70.5% were females. Most common ILD subtype in our study was connective tissue disease associated ILD – 97 patients (65%) followed by idiopathic pulmonary fibrosis (IPF)–31 patients (22%). Most common type of CTD ILD observed in our study was progressive systemic sclerosis (46%) followed by mixed connective tissue disease (24%). The most common HRCT finding was NSIP pattern and most commonly observed physiological abnormality was moderate restriction and moderate diffusion impairment.
Conclusions: Connective tissue disease-associated ILD was the most common ILD found in our study amongst south Indian population. This suggests that the distribution of ILD would vary depending on the geographical area and the environmental exposure which was in contrast with the Indian ILD registry.

Keywords: Idiopathic diffuse interstitial pulmonary fibrosis, Pulmonary diseases, Pulmonary physiological process

INTRODUCTION

The term interstitial lung disease (ILD), in general, implies the clinical manifestation of inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells.[1] These are a group of heterogeneous disorders of known and unknown cause with varied presentation, prognosis, and treatment.[2] These disorders are grouped together because of their similar clinical, radiological, pathological, and physiological features. ILD includes more than 200 diseases that are classified together as they affect the spaces around the

alveoli called the interstitium. Sometimes they may also affect the airways, vessels, and pleura.[3]

It is difficult to estimate the true prevalence and incidence of all ILDs due to the heterogeneous nature of the disease, lack of awareness, and under-reporting of the disease. Demographic features of ILD also vary in different geographic regions. In 1978, Jindal et al published a study comprising 61 diagnosed cases of ILD among which idiopathic pulmonary fibrosis (IPF) was the most common.[2] Later on, other studies were done which showed diverse results according to the study design and geographical region. Though considered a rare entity in the Indian subcontinent, many interstitial lung diseases are misdiagnosed as infection, pulmonary edema, malignancy, etc. due to the lack of availability and the high cost of diagnostic modalities like computed tomography (CT), bronchoscopy, and video-assisted thoracoscopic surgery (VATS).

In our country, there is scarce data on interstitial lung disease caused by specific exposure factors such as immunological insult and occupational exposure. These patients require detailed work-up to identify possible etiology. In a large percentage of these patients, despite detailed work-up as per current recommendations, the etiology is unknown. In present study, we tried to find patterns in these patients that can improve our understanding of the disease and suggest ways to achieve timely and correct diagnosis.

METHODS

This was a descriptive study done in a tertiary care hospital in Puducherry, South India in the department of pulmonary medicine in collaboration with the departments of clinical immunology, radiology, pathology, and cardiothoracic vascular surgery (CTVS).

After obtaining approval from the institutional ethics committee, patients were recruited from August 2016 to November 2018 after obtaining an informed consent. Patients suspected to have ILD by history, clinical examination, and chest radiography was evaluated by high-resolution computed tomography (HRCT) thorax. The patients who had features suggestive of ILD in HRCT thorax were included in the study after taking opinion of radiologist. The demographical profile, clinical symptoms, and signs of these patients were recorded in a pre-structured proforma.

Based on radiologist opinion patients are further classified into IPF, Non IPF and ILD of unknown etiology. Routine blood investigations like complete blood count, liver function tests (LFT) and renal parameters were done for all patients to rule out infection. Inflammatory markers like erythrocyte sedimentation rate (ESR) and serum C-reactive protein (quantitative by nephelometry) were also done. Auto-antibodies ANA (anti-neutrophilic antibodies) (by immuno-fluorescence), anti-neutrophilic cytoplasmic Antibody- ANCA (by immuno-fluorescence), rheumatoid factor (RF – by nephelometry) were done for all cases. In case of a positive ANA result by Immuno-fluorescence, immunoblot for anti-nuclear antibodies was further done to characterize the auto-antibodies and subtyping of connective tissue disease associated ILD was done.

The ILD patients were also evaluated for their lung function by spirometry using Jaeger master screen pulmonary function test (PFT) machine, germany. diffusion capacity of lung with carbon monoxide (DLCO) was done by single breath diffusion technique. Spirometry results were interpreted as normal, restrictive lung disease or obstructive airway disease. Those with restriction and diffusion impairment were classified into mild, moderate, or severe based on ATS guidelines.[4,5] Those who require biopsy but had severe restriction were not taken for surgery.

In cases where HRCT findings were ambiguous but connective tissue disease markers were negative, patients were subjected to either transbronchial lung biopsy under the pulmonary medicine department or video-assisted thoracoscopic surgical lung biopsy under the CTVS department, whichever was required, after obtaining an informed consent.

Taking into consideration of clinical, radiological, physiological and pathological patterns, ILD were divided into subtypes and we tried to find out which subtype of ILD is common in our centre.

Qualitative data was expressed in terms of frequencies and percentages using SPSS 19.0 version. Various clinical aspects like age and sex distribution, sub-types of ILD, radiological patterns, pathological and physiological patterns were studied.

RESULTS

One hundred and fifty proven cases of Interstitial Lung Disease patients were included in our study. Majorities were females with 70.6% and males were 29.3%. Clinical and radiological characteristics of ILD patients were depicted in (Table 1, 2).

The mean age of presentation of ILD patients was 48 years and most of the patients belonged to the age group of 40-49 years. Smokers comprised 18.5% of the study population.

The most common symptom was dyspnea (76.2%) followed by cough (80%). The most common non-pulmonary symptom found was joint pain (41%). Symptoms of GERD were present in 38% of patients. The most common physical examination finding was raynaud's phenomenon (32.7%). The most common respiratory system examination finding found was bilateral velcro crepitations (91%) (Table 1).

Table 1: Clinical profile of interstitial lung disease patients attending a tertiary care centre, Puducherry, South India.

Characteristic	Value/frequency (%)
Age, years	48±12.95
Gender	
Female	106 (70.6)
Male	44 (29.4)
History of tuberculosis	6 (4)
Area of residence	
Rural	94 (62.67)
Urban	66 (44.0)
Occupation	
Housewife	74 (49.3)
Farmer	38 (26.0)
Private	22 (15.0)
Tailor	4 (2.7)
Student	3 (2)
Electrical	3 (2)
Borewell	3 (2)
Number of smokers	27 (18.5)
Clinical symptoms and signs	
Dyspnea	112 (76.2)
Cough	89 (60.0)
Joint pain	60 (41)
Symptoms of GERD	56 (38)
Raynaud's phenomenon	48 (32.7)
Skin tightening	41 (28)
Salt and pepper pigmentation	27 (18.4)
Crepitations	134 (91)
Pallor	19 (13)

The most common chest x-ray finding was bilateral reticular opacities (72%). The most common HRCT findings were septal thickening (85%), followed by honey-combing (54%). The most common HRCT pattern found was Non-specific interstitial pneumonia (47%). The usual interstitial pneumonia pattern was found in 38% of patients. Only 9 patients (7%) showed features of early ILD. Early ILD is the pattern in which sub-pleural ground glassing and reticular opacities are present (Table 2).

Normal spirometry was present in 18 patients (12%). Obstructive pattern was present in only one patient (0.7%). Restrictive pattern was present in 120 patients (80%). Mixed pattern was present in 5 patients (3%). Six patients were unable to perform PFT (4%) (Table 3).

Among 120 patients, mild restriction was present in 44 patients (36%), moderate restriction was present in 54 patients (45%), and severe restriction was present in 22 patients (18.3%) (Table 3).

Diffusion capacity of the lung with carbon monoxide (DLCO) was done in patients who had restrictive or mixed patterns (125 patients). Mild diffusion impairment was present in 16 patients (15%). Moderate diffusion impairment was present in 39 patients (31.2%). Severe diffusion impairment was present in 31 patients (20%). 39 patients (31.2%) were unable to perform DLCO (Table 3).

In our study, 125 patients (83%) were diagnosed with history, high-resolution computed tomography (HRCT), and serology. Invasive diagnostic procedures like trans-bronchial lung biopsy (TBLB), open surgical lung biopsy for histopathological confirmation were done in 25 patients (17%).

The most common type of ILD was connective tissue disease-associated ILD (CTD ILD) (64.6%), followed by IPF (20.7%). NSIP pattern was present in 5.4%. Lymphangioleiomyomatosis and Pulmonary alveolar microlithiasis were present each in 1.4%, Sarcoidosis in 2.7%, and silicosis in 2% of the patients. All the patients with silicosis presented with progressive massive fibrosis. Four patients of sarcoidosis were present among which 3 patients presented at stage I disease and one patient presented at stage II disease (Table 4).

Table 2: Radiological profile of interstitial lung disease patients in a tertiary care centre, Puducherry, South India

Radiological findings in chest X-ray	Frequency (percentage)
Bilateral reticular and reticulonodular opacities	124 (82)
Normal	16 (11)
Distribution of abnormality in HRCT	
Upper lobe predominant	10 (6.8)
Lower lobe predominant	108 (72)
Diffuse involvement	32 (21.3)
HRCT findings (Septal thickening)	124 (85)
Intra lobular septal thickening	39 (26)
Intra and interlobular septal thickening	79 (52.6)
Interlobular septal thickening	5 (3.3)
Honey-combing	79 (54)
Ground glassing	56 (38.4)
Traction bronchiectasis	51 (35)
HRCT pattern	

Continued.

Radiological findings in chest X-ray	Frequency (percentage)
Early ILD	9 (7)
Usual interstitial pneumonia pattern	49 (38)
Non-specific interstitial pneumonia pattern	62 (47)

Table 3: Physiological profile of Interstitial Lung disease patients attending a tertiary care centre, Puducherry, SouthIndia

Spirometry abnormality	Frequency (percentage)
Normal	18 (12)
Obstructive pattern	1 (0.7)
Restrictive pattern	120 (80)
Mixed pattern	5 (3)
Not able to perform	6 (4)
Grading of the severity of restriction	Frequency (percentage)
Mild restriction	44 (29)
Moderate restriction	54 (36)
Severe restriction	22 (15)
Grading of DLCO	Frequency (percentage)
Mild diffusion impairment	16 (15.0)
Moderate diffusion impairment	39 (31.2)
Severe diffusion impairment	31 (20)
Not able to perform DLCO	39 (31.2)

Table 4: Type of interstitial lung disease patients attending a tertiary care centre, Puducherry, South India.

Type of ILD	Frequency (percentage)
CTD ILD (connective tissue disease-associated interstitial lung disease)	97 (64.6)
Progressive systemic sclerosis	42(46)
Mixed connective tissue disease	23 (24)
Rheumatoid arthritis	14 (14.4)
Dermatomyositis/Polymyositis	2 (2)
Systemic lupus erythematosus	2 (2)
Sjogren's syndrome	2 (2)
Undifferentiated connective tissue disease	4(4)
Overlap CTD ILD	6 (6)
IPF(Idiopathic Pulmonary Fibrosis)	31 (20.7)
NSIP(Non-Specific Interstitial Pneumonia)	8 (5.4)
Sarcoidosis	4 (2.7)
Silicosis	3 (2.0)
Unclassified ILD	3 (2.0)
PAM (Pulmonary Alveolar Microlithiasis)	2 (1.4)
LAM (Lymphangioleiomyomatosis)	2 (1.4)
Total	150

The most common type of CTD ILD was Progressive Systemic Sclerosis (46%), followed by mixed connective tissue disease-associated ILD (24%). Rheumatoid arthritis-associated ILD was present in 14 patients (14.4%). Polymyositis and Dermatomyositis associated ILD was present in 2% of the patients (Table 4).

DISCUSSION

This was a descriptive study done in a tertiary care hospital in Puducherry, South India to find out the distribution of different ILD subtypes and most common type of ILD in our centre.

The mean age of ILD patients in our study was 48 years. This was similar to the studies done by Adesh et al (Uttar Pradesh), Raj Kumar et al (New Delhi). Ashok K et al (Ahmedabad), and Sen et al (Mumbai).[6-9] The mean age was less than 10 years when compared to the Indian ILD registry. This may be due to the presence of more CTD ILD cases which will present at a younger age group.

Females (70.6%) were more in our study; which may be due to the predominance of CTD ILD (64.6%) in our study. A study done by Valappil et al found connective tissue disease-associated ILD to be more common and they showed a predominantly female population which is in concordance with our study.[10] Indian ILD registry (by Singh et al) also showed female preponderance but hypersensitivity pneumonitis was the most common ILD reported.[11] In a study done by Sen et al (Mumbai), male predominance was reported probably due to more number of cases of IPF in their study.[9]

In our study, smokers were only 18.5%, such low proportions may be due to less number of IPF patients in our study population.

The most common symptom found in our study was dyspnea (76.2%) followed by cough (60%). Bilateral velcro crepitations were heard in 90% of patients. These findings were comparable to other studies. Findings of nonpulmonary symptoms like joint pain, skin thickening, Raynaud's phenomenon, hand ulcers, dry mouth, and dry eyes were present in connective tissue disease- associated ILD patients. In our study, symptoms of GERD were present in 38% which was similar to a study conducted by Valappil et al in Kerala (34%).[10]

Though the most common chest radiograph finding was bilateral reticular opacities (72%), a normal chest radiograph was found in 11% of the study population. This shows that the presence of a normal chest radiograph cannot rule out ILD and HRCT is imperative for proper diagnosis of ILD.

The most common HRCT findings in our study were septal thickening (85%), followed by bilateral reticular opacities (66%), honeycombing (54%), and ground glassing (38.4%). Similar findings were observed in the studies done by Ashok K et al (Ahmedabad in 2012), Raj Kumar et al (New Delhi in 2014), Mitra et al (West Bengal in 2014), Adesh et al (Uttar Pradesh in 2016), Varun Das et al (Mumbai in 2017), Dhooria et al (PGIMER in 2018) and Valappil et al (Kerala in 2018).[6-10,13,14]

In our study, NSIP pattern was observed in 47.6% of patients and UIP pattern in 38% of patients. the predominance of NSIP pattern in our study is probably due to the greater number of CTD ILD patients, whereas the Indian ILD registry reported more of hypersensitivity pneumonitis and other ILDs. Therefore, geographical and environmental factors may play a significant role in the occurrence of different subtypes of ILD.

Major PFT abnormality present in our study was the restrictive pattern which was in concordance with other studies.[6-14]

In our study, 83% of the patients were diagnosed by clinical history, HRCT, and serological investigations. After excluding known causes of ILD, patients with uncertain diagnosis were further evaluated for other causes of ILD and if patient is fit for biopsy then they were considered for open surgical lung biopsy or transbronchial lung biopsy. Out of 17% of the cases subjected to various biopsies, 20 patients underwent transbronchial lung biopsy, 1 patient had surgical lung biopsy, ultrasound-guided biopsy done in 1 patient while 1 patient for postmortem biopsy after being clinically declared dead. Two cases of sarcoidosis were confirmed through alternative method of diagnosis by salivary gland and liver biopsy which showed non- necrotizing granulomas and other additive diagnostic tests for sarcoidosis. In a study done by Zubairi et al (Karachi study), 5% of the patients had a pathological diagnosis.[15] Surprisingly, in the Indian ILD registry, only 7.5% had pathological diagnosis, indicating that many ILDs might have been misdiagnosed or wrongly grouped in Indian ILD registry.[11] Though diagnosis for sub-typing of most of ILD was done by clinical history, HRCT and serological examination but still pathological diagnosis by biopsy is required to avoid any discrepancy so that correct sub-typing of ILD can be done.

Table 5: Comparison of different types of ILD from our study with other international studies.

Type of ILD	Our study N=150	China study[16] 2018 N=2615	Indian ild registry[11] (2017) N=1084	Paris study[17] 2016 N=1170	Turkey study[18] 2013 N=2245	Greek study[19] 2009 N=967
CTD associated ILD	97 (64.6%)	631 (24.1%)	151 (13.9%)	145 (12.3%)	201 (9.8%)	120 (12.4%)
IPF	31 (20.7%)	692 (26.5%)	148 (13.7%)	98 (8.3%)	408 (19.9%)	189 (19.5%)
HP	0	62 (2.4%)	513 (47.3%)	28 (2.3%)	82 (4.0%)	25 (2.6%)
Pneumoconiosis	3 (2%)	58 (2.2%)	33 (3%)	42 (3.5%)	241 (11.8%)	20 (2.0%)
LAM	2 (1.3%)	-	2 (0.2%)	9 (0.76%)	6 (0.3%)	6 (0.6%)
Sarcoidosis	4 (2.7%)	147 (5.6%)	85 (7.8%)	361 (30.8%)	771 (37.6%)	330 (34.1%)
PAM	2 (1.4%)	-	1 (0.1%)	-	7 (0.3%)	-
NSIP	8 (5.4%)	55 (2.1%)	92 (8.5%)	20 (1.7%)	21 (1%)	27 (2.8%)

Table 6: comparison of different types of ILD from our study with other Indian studies:

Type of ILD	Our study	Study by Valappil et al (Kerala)[10] N=129	Study by SahajalDooria et al (PGIMER)[14] N=803	Study by Adesh et al (Uttar Pradesh)[6] N=289	Study by Mitra et al (West Bengal)[12] N=92	Study by Sen et al (Mumbai)[9] N=274
CTD associated ILD	97 (64.6%)	45 (34.9%)	102 (12.2%)	13 (12.34%)	29 (31.5%)	51 (18%)
IPF	31 (20.7%)	30 (23.25%)	170 (21.2%)	80 (27.68%)	35 (38.04%)	117 (43%)
HP	-	7 (5.42%)	86 (10.7%)	7	10 (10.09%)	15 (6%)
Pneumoconiosis	3 (2%)	-	7 (0.9%)	-	5 (5.4%)	2
LAM	2 (1.3%)	3 (2.32%)	1 (0.1%)	-	0	-
Sarcoidosis	4 (2.7%)	22 (17.1%)	339 (42.2%)	108 (37.37%)	5 (5.4%)	12 (10.34%)
PAM	2 (1.4%)	-	1 (0.1%)	-	1 (1.1%)	-
NSIP	8 (5.4%)	10 (7.8%)	63 (7.8%)	74 (25.6%)	-	18 (15.51%)

In our study, we found that connective tissue disease ILD was the most common ILD, whereas in the Indian ILD registry, Hypersensitivity Pneumonitis was the most common type of ILD reported followed by CTD associated ILD and IPF.[11] In Greek, Paris, and Turkey, sarcoidosis was the most common type of ILD prevalent.[17-19] In China, IPF was found to be the most common type of ILD.[19] This disparity may be due to the geographical diversity and the environmental factors that may also influence the type of ILD (Table 5).

In our study, CTD ILD was the most common type of ILD found. It was similar to that of the study done by Valappil et al (Kerala) in which CTD ILD constitutes about 34.9% of patients.[10] In PGIMER and New Delhi study, sarcoidosis was the most common ILD reported.[5,14] In Mumbai, UP, and West Bengal studies, IPF was the most common type of ILD observed.[6,9,12] (Table 6).

No case of HP was reported in our study. On the contrary, HP was the most common ILD described in the Indian ILD registry which may be due to lesser number of centres included from South India. Contaminated air coolers were attributed to be the common cause for HP in Indian ILD registry but usage of air coolers are less in southern part of India due to the climate difference. So based on the Indian ILD registry we cannot generalize HP to be the most common ILD. Instead, there are a few regions in India where other types of ILDs are common. This can be further confirmed by the study done by Valappil et al in Kerala.[10]

However, the diagnosis of interstitial lung disease was made by taking into account the clinical profile, radiological profile, pathological profile, and physiological profile. Therefore, the diagnosis of ILD needs multidisciplinary discussion and decision.

Our study is bound by some limitations. Being a single centre study, the data cannot be generalized to whole of India. Hence, multicentric studies are the need of the hour. Also, most patients presented at an advanced stage, so physiological parameters could not be evaluated for all the patients and a six-minute walk test could not be done. Also further researches on various biomarkers are necessary for confirming the diagnosis.

CONCLUSION

Connective tissue disease-associated ILD was more common in our study followed by IPF. Among CTD ILD, progressive systemic sclerosis was the most common ILD observed. The HRCT pattern most found in our study was fibrotic NSIP (30%) followed by a definite UIP pattern. Physiologically, moderate restriction and moderate diffusion impairment was often noted. Lack of recognition of disease at an early stage leads to delayed diagnosis in most of the patients. This emphasizes the importance of taking a detailed history and clinical evaluation with appropriate imaging modalities to make an early diagnosis of ILD.

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