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Clinical profile of interstitial lung disease at a tertiary care centre, India

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ABSTRACT

BACKGROUND: Interstitial lung diseases (ILD) are a complex group of disorders. As of date, the data on ILD is mostly from the western world with scarce Indian studies. Hence, we decided to study the clinical profile of the interstitial lung disease patients at our institute. **METHODOLOGY:** A prospective observational study was conducted at a tertiary care centre over 3 years. The study was an independent subset analysis of the patients enrolled in the national ILD-India registry. Adult ILD patients diagnosed with multi-disciplinary diagnosis were included. Patients were managed as per guidelines. Follow-up was noted wherever available. Statistical analysis was done with frequency, mean, standard deviation and percentages. **RESULTS:** One hundred and forty ILD patients were included. There was a male predominance. Average age was 53.99 years. Most common symptoms were dry cough and exertional dyspnea. Examination revealed end inspiratory velcro crackles and digital clubbing. Average partial pressure of oxygen, forced vital capacity, diffusion of lung for carbon monoxide was 73.22 mmHg, 1.58 liters, 52.29%predicted respectively. Most common radiological finding was interlobular, interstitial septal thickening (79.8%). Commonest ILD was idiopathic pulmonary fibrosis (IPF). Gastroesophageal reflux disease was commonest comorbidity (76.42%). Follow-up of 67 patients was available. Therapy showed variable response as per the type of ILD. Nineteen deaths were recorded; 12 in IPF. **CONCLUSION:** IPF was the commonest ILD with poorer prognosis and higher mortality compared to non-specific interstitial pneumonia despite optimal treatment while patients of connective tissue disease associated ILD, hypersensitivity pneumonitis and sarcoidosis show excellent response to therapy.

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INTRODUCTION

Interstitial lung diseases (ILD) are a complex group of disorders involving the alveolocapillary membrane with common clinical, radiological and pathophysiological features. They are a group of highly under diagnosed and undertreated diseases. ILD involve not only the interstitium but alveolar and capillary membrane too. The most prominent feature of ILD is inflammation in the initial stages and fibrosis in the later stages of the interstitium which produces derangement of alveolar architecture and loss of functional alveolar capillary units.[1,2] More than 150 known causes of ILD have been identified. They can either be idiopathic or secondary to a known cause like drug exposure, connective tissue disorders (CTD) and familial disorders. A major share of these disorders belongs to the class of idiopathic interstitial pneumonias. Diagnosis can be made by combination of clinical, radiological features and pulmonary function tests. A histopathological diagnosis is not always necessary for the diagnosis of the disease with the advent of newer diagnostic modalities like high resolution computed tomography. Unfortunately for majority effective therapy still remains elusive, leaving patient and clinician frustrated as disease typically progresses and complications occur despite immunosuppressive therapy.

As of date, the data on ILD is mostly from the western world with scarce Indian studies. This study is being done to analyze the spectrum of ILD, their common presentations, radiological features and comorbidities so that it may help in better understanding of the disease in the Indian context. Hence we decided to study the clinical profile of the interstitial lung disease patients at our institute.

MATERIAL AND METHODS

This prospective observational study was conducted at a tertiary care centre after ethics committee approval. The study was an independent subset analysis of the patients enrolled in the national ILD-India registry from our centre. Adult patients willing to give consent with diagnosis of ILD were included in the study. Recruitment for this prospective registry was from 3/2012 to 4/2015 with 27 investigators in 19 cities. Patients ≥18 years old were included. Patients with malignant diseases and active tuberculosis were excluded. The patients, who were referred to the pulmonary medicine department, were evaluated as per guidelines[1,2] with multidisciplinary modality diagnosis of interstitial lung diseases. Data regarding the patient's demography, history, clinical details and investigation reports was recorded through a case record form. A detailed medical history was taken and clinical examination done. Reports of investigations like complete haemogram, blood sugar, renal function tests, arterial blood gas (ABG) analysis with alveolo-arterial (A-a) gradient calculation, spirometry with measurement of diffusion capacity of carbon monoxide(DLCO), six-minute walk distance (6MWD), post-exercise desaturation, radiological investigations like chest roentgenogram (CXR) and high resolution computerized tomography (HRCT) thorax were noted. Two-dimensional echocardiography (2D-ECHO) for indirect estimate of pulmonary artery systolic pressures by tricuspid regurgitation jet method and polysomnography were done to rule out pulmonary hypertension and obstructive sleep apnoea syndrome respectively. As per guidelines[1,2] selected patients willing for surgical lung biopsy were evaluated with the same. The patients were classified into various types of interstitial lung diseases according to the British thoracic Society (BTS) 2008 guidelines[1] into those due to known causes, idiopathic interstitial pneumonias, granulomatous lung diseases and unique entities. Idiopathic interstitial pneumonias were further classified as per revised American Thoracic Society (ATS)/European Respiratory Society (ERS) 2013 classification of idiopathic interstitial pneumonias.[2] Patients were managed as per guidelines with pharmacotherapy and pulmonary rehabilitation. Six month follow-up was noted wherever available.

Qualitative data was analysed with frequencies and percentages. Various clinical aspects of interstitial lung diseases were analysed in the form of age and sex distribution, frequencies of various types of ILD's, frequencies of various clinical and radiological factors and incidence of pulmonary artery hypertension.

RESULTS

One hundred and forty patients of ILD were enrolled in our study. Seventy six (54%) of them were men and 64 (46%) were women. The age distribution of patients ranged from 18 years to 82 years. Majority of patients (52%) belonged to the age group 50-69 years. Average age was 53.99 (13.68) years (Table 1). Thirty one (22.14%) patients were smokers. Cough and progressive breathlessness were the most common symptoms seen in 97.14% and 98.57% while other symptoms like fever and chest pain were rare findings. Average duration of symptoms in patients was 48.64 (5.2) months. End-inspiratory velcro

TABLE 1. Characteristics of ILD patients.

Characteristic	No. of patients
Age group	
18-29 years	8
30-49 years	40
50-69 years	73
70-90 years	19
Sex	
Men	76 (54%)
Women	64 (46%)
Clinical symptoms	
Breathlessness	138 (98.57%)
Cough	136 (97.14%)
Fever	4 (2.86%)
Chest pain	8 (5.71%)
Clinical Signs	
Clubbing	78 (55.7%)
Crackles	138 (98.57%)
Post exercise desaturation	126 (90%)
Radiological abnormalities on computed tomography of thorax	
Septal thickening	111 (79.8%)
Ground glass opacities	21 (15%)
Honeycombing	56 (40%)
Centrilobular nodules	24 (17.14%)
Mediastinal Lymphadenopathy	10 (7.14%)
Emphysema	7 (5%)
Co-morbidities	
GERD	107 (76.42%)
Osteoporosis	31 (22.14%)
Metabolic syndrome	18 (12.85%)
Psychiatric	13 (9.28%)
Obstructive sleep apnoea	22 (15.71%)
Ischemic heart disease	10 (7.14%)
Hypothyroidism	11 (7.86%)

crackles were the most common examination finding in 138 (98.57%) followed by clubbing in 78 (55.7%). Post exercise desaturation was found in 126 patients (90%). The mean BMI was 23.25 (4.6) kg/m^2. The mean haemoglobin level was 12.68 (1.92) gm/dl and mean fasting blood sugar level was 106.79 (30.89) mg/dl. The average 6MWD was 320.64 (98.68) meters. On ABG, the average PaO_2 was 73.22 (12.16) mmHg, $PaCO_2$ was 37.445 (SD) mmHg and A-a gradient was 29.25 (13.16). On spirometry, the mean forced vital capacity (FVC) was 1.58 (0.76) litres and FEV1 was 1.35 (0.57) litres. DLCO could be performed by 45 patients, mean DLCO was 52.29 (24.55) % predicted. CXR abnormality in the form of bilateral reticulonodular opacities were seen in all. The most common HRCT thorax findings were interlobular, intralobular, septal thickening in 111 (79.8%) followed by honey combing in 56 (40%), centrilobular nodules in 24 (17.14%), ground glass opacities in 21 (15%) and mediastinal adenopathy in 10 (7.14%). Associated centrilobular emphysema was seen in 7 patients of IPF (Table 1). As indicated by guidelines, 11 patients consented and underwent open lung biopsy. The histopathological diagnosis was IPF in 2, hypersensitivity pneumonitis in 7 and sarcoidosis in 2 patients. These concurred with the clinical and radiological diagnosis of these patients. Most of the patients belonged to the group of Idiopathic interstitial pneumonias (IIP) i.e. 83 (59.28%) while other common aetiologies were granulomatous diseases like sarcoidosis in 12 (8.57%), hypersensitivity pneumonitis (HP) in 12 (8.57%) and connective tissue disease (CTD) associated ILD in 22 (15.71%). Rest 11 (7.87%) patients were constituted by occupational ILD (5), drug induced ILD (2), tropical pulmonary eosinophilia (3) and unclassified ILD (1). Amongst the IIP, idiopathic pulmonary fibrosis (IPF) was the most common diagnosis in this study observed in 41(29.29%) followed by non specific interstitial pneumonia (NSIP) in 38 (27.14%) and respiratory bronchiolitis associated ILD (RBILD) in 4 (2.85%). None of our patients had the diagnoses of desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP). The connective tissue disease associated ILD comprised of 22 patients of whom 11 had rheumatoid arthritis, 9 had systemic sclerosis and 2 had mixed connective tissue disease. Occupational lung disease was diagnosed in 5; of whom 2 had talcosis, 1 had cadmium dust associated ILD, 1 had rayon lung disease and 1 had mixed dust fibrosis. Drug induced ILD was found in 2 patients; 1 due to bleomycin therapy in a case of treated testicular cancer and 1 due to methotrexate use in rheumatoid arthritis. Table 2 gives the distribution of various ILD.

Comorbidities play an important role in the quality of life of ILD patients. In this study, the most common co-morbidity encountered was gastroesophageal reflux disease (GERD) in 107 patients (76.42%) followed by osteoporosis - 31 (22.14%), obstructive sleep apnea (OSA) - 22

TABLE 2. Distribution of various types of interstitial lung diseases.

Type of interstitial lung disease (ILD)	No. of patients (percentages)
Idiopathic Pulmonary Fibrosis	41 (29.29%)
Non-Specific Interstitial Pneumonia	38 (27.14%)
Sarcoidosis	12 (8.57%)
CTD associated ILD	22 (15.71%)
Hypersensitivity pneumonitis	12 (8.57%)
Respiratory Bronchiolitis ILD	4 (2.85%)
Occupational ILD	5 (3.57%)
Drug induced ILD	2 (1.42%)
Tropical pulmonary eosinophilia	3 (2.14%)
Unclassified ILD	1 (0.71%)

(15.71%), metabolic syndrome - 18 (12.85%), psychiatric disorders - 13(9.28%), ischemic heart disease - 10 (7.14%) and hypothyroidism - 11 (7.86%). Table 1 enlists the various co-morbid conditions in ILD. Pulmonary hypertension (PH) which is an important sequalae of ILD was seen in 52 patients (37.14%). Treatment of ILD is still a matter of debate in view of unpredictable response and high incidence of adverse effects. Hence, significant section of our patients with stable lung functions or who refused treatment were kept under observation with regular follow up. Of those who opted for treatment, 14 (10%) patients received pirfenidone therapy, 32 (22.85%) received triple drug therapy consisting of prednisolone, azathioprine/cyclophosphamide and N-acetyl cysteine, 24 (17.14%) received oral corticosteroids. Four patients of RBILD were managed with smoking cessation only. Of the 41 IPF patients, 14 patients were treated with pirfenidone therapy and the rest were kept under observation. Of the 38 NSIP patients, 18 were treated with triple drug therapy, 3 with oral corticosteroids, while 17 were kept under observation. Among the patients with connective tissue disease associated ILD, 14 patients were treated with triple drug therapy, 3 with oral corticosteroids, 5 observed. Of the patients with hypersensitivity pneumonitis, 10 patients were treated with oral corticosteroids while 2 were kept under observation. Of the 12 sarcoidosis patients, 8 received oral corticosteroids and 4 were observed.

The follow up of 67 patients was available. Of the 24 IPF patients for whom follow up was available 10 were treated. Of these patients; the lung functions of only 2 patients improved, 3 remained stable while 5 died. Of the rest 14 patients kept under observation; 5 remained stable, 2 worsened and 7 died. Thus, mortality was observed in 50% (12 patients) of IPF cases irrespective of therapy. In the NSIP group, the follow up data for 13 treated patients reflected 4 patients had improved, 6 were stable and 3 died and of the 7 patients kept under observation 1 improved, 2 remained stable, 1 worsened and 3 died. Thus therapy more or less stabilized the disease with improvement in some. None of the CTD associated ILD, hypersensitivity pneumonitis and sarcoidosis patients deteriorated/died irrespective of therapy and most improved with therapy. In the 67 patients were follow up was available; 19 deaths were recorded; 12 in IPF, 6 in NSIP and 1 in chemotherapy induced ILD.

DISCUSSION

Our study was aimed to study the clinical and radiological profile of interstitial lung disease patients. Interstitial lung disease (ILD) is a heterogenous group of disease with a variety of clinical and radiological presentation[1,2]. Hence a high induction of suspicion is to be kept for diagnosing this condition. It is not uncommon to see ILD patients being treated with multiple courses of anti-tuberculosis therapy including that for multidrug resistant tuberculosis. Many western studies have shown that the incidence of ILD is on the rise.[3] So it is understood that it was previously highly misdiagnosed and underdiagnosed disease. It is important to make awareness about this disease among the physicians and the general public. Very few studies have been undertaken to study this disease, especially in India[4-11]. Hence we undertook this study.

One hundred and forty consecutive patients of ILD diagnosed with multi-disciplinary discussion were included in the study. We observed a peak incidence in the age group 50-69 years, average age of presentation being 53.98 years. This data matched various Indian[4-11] and western[12,13] studies. Slight male predominance was seen in our study in agreement with previous studies by Mahasur et al[5], Sharma SK et al[8] and Turner et al[14]. Thirty-one (22.14%) of the patients were smokers. Smoking is a known risk for many ILD like IPF, RBILD, DIP, CPFE etc. Patients enrolled in our study were allotted specific ILD diagnosis keeping in mind their specific clinical and radiological features. Majority of our patients belonged to the idiopathic interstitial pneumonia group - 83 (59.28%). IPF was the most common subtype seen in 41 (29.29%) followed by NSIP in 38 (27.14%), CTD associated ILD in 22 (15.71%), sarcoidosis in 12 (8.57%) and HP in 12

(8.57%). This was similar to some of the Indian studies like those by Kalra et al[9], Subhash et al[10], Udwadia et al[11] and western study by Coulltas et al[15]. This is however discordant with the current ILD – India registry results published online ahead of print[16] recently of which our centre was a significant contributor and the only one from western India, Mumbai. The registry reported HP as the commonest ILD in 47.3% (attributing to air-cooler exposure in Northern India in 48.1%), CTD associated ILD in 13.9% and IPF only in 13.7%. Mumbai being a humid city in western India, use of air-coolers is negligible. Ours is a tertiary care cosmopolitan referral centre in west India. Though we had cases from all parts of India most of our patients hailed from Maharashtra, Gujarat, Goa and some from South India. Negligible patients were referred from the Northern states on India. These could be the possible reasons for less HP in our patients.

Onset of symptoms is usually gradual, with dyspnoea as the most prominent and disabling symptom. A non-productive cough is usual and may be paroxysmal. It is often refractory to antitussive agents. In a retrospective analysis of biopsy-proven IPF patients in a tertiary care centre in Mumbai, 93% of patients had breathlessness and 88% of patients had persistent cough as their presenting symptoms.[17] Constitutional symptoms are unusual. In our study too, dry cough and breathlessness were the most common symptoms present in more than 95%. Constitutional symptoms like fever and chest pain were seen in less than 10%. The most characteristic examination findings in ILD are clubbing, fine end inspiratory Velcro crackles and post-exercise desaturation. Studies have shown that clubbing may be seen in 25%-50% patients[18,19] and 'velcro' crackles may be present in more than 80% patients.[18,19] Our study had similar results with clubbing and crackles reported in 55.7% and 98.57% respectively. These findings also correlate well with studies by Mahasur et al[5] and Jindal et al[4]. Significant post exercise desaturation (desaturation by more than 4%) is an important prognostic factor in ILD was observed in 90% of our patients.

Multidisciplinary diagnosis involving clinical and radiological correlation is able to diagnose and classify most of the ILD. Radiology is an important tool for diagnosis. Newer advances in imaging modalities have obviated the need for surgical lung biopsy. Chest radiograph can be normal in some patients. The most common CXR abnormality are reticulonodular opacities, which were seen in all the patients in our study. The most important HRCT findings were interlobular and intralobular septal thickening – 111 (79.8%), honeycombing – 56 (40%), centrilobular nodules – 24 (17.14%), ground glass opacities – 21 (15%), mediastinal lymphadenopathy and emphysema. A study done by Venkata Ramana et al[7] showed septal thickening in 42%, honey combing in 38% and ground glass opacities in 20%, results which were comparable to our study. Another study by Gagiya et al[6] also revealed similar findings. Emphysema was seen in a group of patients with combined pulmonary fibrosis and emphysema. As reported by studies of Cottin et al[20], these patients present with severe hypoxemia, low DLCO, well preserved FVC, severe pulmonary hypertension and have a high mortality. The most characteristic spirometry abnormality in ILD is a restrictive abnormality with decreased DLCO. Due to easy availability, spirometry can be a very useful aid in the diagnosis, prognostication and assessing response to therapy. In our study, all the patients showed restrictive abnormality. The average FVC was 1.58 (53%) litres. Only 45 patients could perform DLCO and average DLCO percentage was 52.29% predicted. As per the old guidelines, surgical lung biopsy was mandatory for the diagnosis of ILD. According to the 2013 ATS-ERS update on the classification of IIP[2], a multidisciplinary approach has to be followed for diagnosis of ILD with a proper collaboration between the physician, radiologist and the pathologist. It also emphasizes this approach does not negate the importance of lung biopsy but gives special situations where it has to be performed. This can be explained in the context of IPF. If in a patient of ILD, no identifiable cause is identified and HRCT demonstrate typical UIP pattern, a diagnosis of IPF can be made. But if typical features are not there (possible UIP and inconsistent with UIP pattern), surgical biopsy can be helpful in the diagnosis. It helps in distinguishing from other types of ILD like sarcoidosis, fibrotic NSIP and chronic HP. Studies have shown that surgical lung biopsy could distinguish IPF from other differential diagnoses in about 50%.In our study, 11 patients underwent open lung biopsy. In 2 patients, the diagnosis was IPF, HP in 7 and sarcoidosis in 2.These histological diagnoses concurred with the clinical and radiological diagnosis of these patients.

ILD is a chronic progressive disease in which comorbidities further hamper the quality of life of patients, although many of these are treatable and preventable. Even though the search for effective treatment for interstitial lung disease is still on, proper treatment of these comorbidities can play an important role in improving the quality of life in these patients. These include gastroesophageal reflux disease, sleep disordered breathing, coronary artery disease, psychiatric manifestations like depression and

anxiety, chronic obstructive lung disease, venous thromboembolism and lung cancer. In our study, the most common comorbidity was gastroesophageal reflux disease seen in 76.42%. Raghu et al[21] conducted a prospective study GERD in IPF including sixty-five patients. A significantly higher prevalence was seen, but there was no correlation between the severity of IPF and the percentage of proximal and distal oesophageal acid reflux time. Only 47% of the IPF patients had typical reflux symptoms of heartburn or regurgitation. In a prospective study of 17 consecutive IPF patients, Tobin and colleagues[22] found a significantly higher prevalence of oesophageal acid reflux (detected by ambulatory pH monitoring) in the IPF group. In our study, patients were screened for evidence of OSA with overnight polysomnography which diagnosed 22 cases. Of the 21 IPF patients, 9 had OSA. Findings from a recent study in which nocturnal polysomnography was performed in 50 patients with IPF suggested that up to 88% had OSA.[23] In such chronic illness, it is not uncommon for patients to become anxious or depressed. A study of 41 IPF patients found that approximately 25% had significant depressive symptoms.[24] Patients with depression are 3 times more likely than non-depressed patients to be nonadherent with medical treatment. In our study, psychiatric illnesses were noted in 13 (9.28%) of which 10 had depression, 2 had anxiety and 1 had psychosis. Other comorbidities seen in our patients were osteoporosis/osteopenia in 31 (22.14%), metabolic syndrome in 18 (12.85%), ischemic heart disease in 10 (7.14%)and hypothyroidism in 11 (7.86%). PH is associated with reduced exercise capacity and worse survival. It is most likely due to destruction of the pulmonary vasculature from lung fibrosis and honeycomb change.[25] In our study, PH was seen in 52 (37.14%) patients consistent with previous reports.[25]

Management of ILD starts with counselling about this chronic disease. Our patients and relatives were counselled for the same. Pharmacotherapy in ILD is aimed not to cure the disease but to arrest the progression. One of most frequently used treatment in ILD was triple drug therapy-a combination of oral corticosteroid, immunosuppressive agent like azathioprine or cyclophosphamide and N-acetylcysteine. However, with newer studies this therapy is obsolete in IPF.[2] Pirfenidone, an antifibrotic agent is one of the newer drugs used in the treatment of IPF. In non-IPF ILD, treatment with oral corticosteroids with immunosuppressive agents has been effective in conditions like NSIP and CTD associated ILD. Oral corticosteroids alone are used in sarcoidosis and HP. In case scenarios like stable lung functions and where therapy risks outweigh the benefits; patients can be counselled and offered to be kept under observation with regular follow up three monthly. However, pulmonary rehabilitation, GERD treatment and optimal therapy of comorbidities is beneficial in improving the quality of life. Of our patients who opted for the therapy; 14 (10%) received pirfenidone therapy, 32 (22.85%) received triple drug therapy, 24 (17.14%) received oral corticosteroids and 4 (2.85%) patients of RBILD were managed with smoking cessation only. Our patients were offered pulmonary rehabilitation in form of chest physiotherapy, vaccination with pneumococcal and influenza vaccines, dietary advice and management for their comorbidities in form of proton pump inhibitors for GERD, calcium & vitamin D supplementation and bisphosphonates for osteoporosis, CPAP therapy in patients with OSA and so on. The follow up of 67 patients was available. IPF was associated with poor prognosis and high mortality despite optimal treatment. Compared to IPF, NSIP had better prognosis and response to therapy. Other groups like CTD associated ILD, sarcoidosis, hypersensitivity pneumonitis had excellent response to the therapy. There were 19 deaths during the study, 12 IPF, 6 NSIP and 1 chemotherapy induced ILD. This is therapy response and clinical course is already known in IPF and non-IPF ILD literature.[1,2]

Currently there is deficiency in awareness about the various ILD, their profile and management in India. Being a chronic respiratory disease, it requires a thorough counselling by explaining the natural course, the available treatment options, their adverse effects and optimal management of associated treatable comorbidities. A confident diagnosis can be achieved with multidisciplinary approach obviating the need for lung biopsy. IPF has poorer prognosis and higher mortality compared to NSIP despite optimal treatment while patients of CTD associated ILD, hypersensitivity pneumonitis and sarcoidosis show excellent response to therapy. We have tried to study the clinical profile of ILD. But the study is far from complete. Our patient database consisted of referrals to a tertiary care centre with limited follow up data. Hence a population/registry based study of ILD would be ideal and need of the day.

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