

Laying the ground for research of interstitial lung disease in our country: ILD India registry

India is a country with great diversity where dresses, dialects and diets vary drastically from place to place. But, above all there is a vast universality in thinking and emotions throughout India. Likewise, many chronic diseases have identical presentations, but with subtle and yet important regional differences.

Interstitial lung disease (ILD) represents a group of about 200 distinct disorders involving lung parenchyma. ILDs are often referred to as diffuse parenchymal lung disease (DPLD). We have used both these terms in this editorial. Uniform approach to diagnosis and treatment of ILD is buttressed from time to time with the help of standard guidelines. In 2002, the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines classified idiopathic interstitial pneumonias (IIPs) into seven specific entities and offered standardized terminology and diagnostic criteria. The “gold standard” need of a histological diagnosis was changed to a multidisciplinary approach.^[1]

New information about ILD is regularly available after 2002 guidelines. The 2013 update is a supplement to the previous 2002 guidelines.^[2] There was a need to provide a better clinical algorithm for diagnosis and management of IIPs. Idiopathic nonspecific interstitial pneumonia (NSIP) is now accepted as a specific disease entity and in smokers respiratory bronchiolitis-ILD (RB-ILD) is increasingly diagnosed without surgical lung biopsy. Pleuroparenchymal fibroelastosis as well as bronchiolocentric inflammation and fibrosis are recognized as specific rare entities.

According to 2013 update, there are three broad categories: First, *major* idiopathic interstitial pneumonias comprising of idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia, RB-ILD, desquamative interstitial pneumonia, cryptogenic organizing pneumonia and acute interstitial pneumonia. Second, *rare* idiopathic interstitial pneumonias are pleuroparenchymal fibroelastosis and lymphoid interstitial pneumonia. The third and

final category is *unclassifiable* idiopathic interstitial pneumonias.^[2]

Incorporation of genetic and molecular studies may revolutionize the approach to diagnosis and classification of the IIPs. Some potential biomarkers useful in the differential diagnosis and prognosis of ILD are chemokine ligand (CCL); intercellular adhesion molecule (ICAM); Krebs von den Lungen-6 (KL-6); matrix metalloproteinase (MMP); protein encoded by S100-A12 gene (S100-A12); surfactant protein (SP); vascular cell adhesion protein (VCAM).^[2,3]

Usually, there are multiple sources of data collection for ILD or any other similar disease of great public health importance.^[4] Studies based on questionnaires for pulmonary physicians, use of pre-existing databases, such as hospital database and death register, or small case-series are usual source of data. In these studies, there are major methodological limitations and heterogeneity which make the comparison of epidemiological parameters virtually impossible. The data available from national registries, on the other hand, can provide more homogeneous information.

The pioneer ILD registry by Coultas *et al.* was from a county of New Mexico in the United States.^[5] According to this registry, the prevalence of IPF was about 20 per lakh in males as against about 13 per lakh in females. According to Thomeer *et al.* a lower proportion of IPF was reported from Belgium.^[6] On the other hand, an Italian registry reported IPF in 27% of cases.^[7]

According to a recent review of 15 studies, prevalence of IPF in the United States is between 14 and 63 cases per lakh population and an incidence of 7% to 17% as against European incidence of 0.2% to 7%.^[8] It can be assumed that with introduction of better diagnostic amenities and superior overall life expectancy, the incidence of ILD will further increase. Some newer IPF registries are being set up which are likely to yield important data on IPF after the revision of diagnostic criteria in 2002.^[9,10]

There is a paucity of literature on the pattern, determinants, distribution and response of treatment of ILD in India. Small regional studies have contributed a lot in our understanding of the disease. Though no true epidemiological study on prevalence of ILDs and its different subgroups from India is available; according to the studies available proportion

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of IPF may vary between approximately 30% and 45% [Table 1]. In all Indian studies, CTD associated ILD, hypersensitivity pneumonitis and sarcoidosis are present in significant proportions.

In 1979, Jindal *et al.* published their data on cases of DPLD seen over a period of five years and among them 46% of cases were having IPF.^[11] In 1984, Sharma *et al.* reported IPF to be present in 28.6% of their patients with DPLD.^[12] In 2004, Maheshwari *et al.* showed female preponderance of IPF and mean age of presentation about 50 years.^[13] In the same year a group of investigators from south India supported the fact that secondary DPLD (55%) was more common than IPF.^[14] In addition subjective improvement with steroids was more in secondary DPLD as compared to IPF. In 2010, Sen *et al.* in their retrospective analysis reported that besides IPF, sarcoidosis, ILDs secondary to CTD and hypersensitivity pneumonitis were the main diagnoses.^[15] After 2011 ATS/ERS guidelines, there is a drastic change in our algorithm to approach to IIPs. Unfortunately, no large Indian study worth reporting is available in more recent period.

ILD India registry is step toward knowing these facts about these diseases especially the IPF.^[16]

ILD India registry was started in 2011. Inclusion criteria are respiratory symptoms such as shortness of breath and cough and bilateral abnormalities in x-ray/high-resolution computed tomography (HRCT) scan of thorax. History, physical examination, spirometry, and HRCT chest are essential. Six-minute walk test is optional. If patient has symptoms consistent with a collagen vascular disease then rheumatoid factor and ANA are done. If either test is positive a full panel is done. If a patient with an initial diagnosis of ILD develops pulmonary tuberculosis over the course of treatment, he/she is included in the ILD India registry. A patient having history of AFB smear positive tuberculosis without prior ILD is not included. However, patients with no history of AFB positivity and a doubtful radiographic pattern are included as this may be due to sarcoidosis or other similar ILDs. In patients with no clear cut pattern of ILD bronchoalveolar lavage, transbronchial lung biopsy and open lung biopsy are required in order to

try to establish a diagnosis. Any infectious or malignant diseases are criteria of exclusion in the registry. Detailed history of exposure and past medications is incorporated in registry to include all possible factors linked to the disease. We recently encountered a series of cases of hypersensitivity pneumonitis after very unusual exposure to dug-well which was not previously reported from India or rest of the world.^[17] The environmental assessment of dug-well as well as detailed work-up of patients suggested toward *Aspergillus* species as the main culprit.

There is a simple procedure for submitting data of individual patients. After taking informed consent the investigator fills the proforma. Relevant investigations are done (spirometry and HRCT scan thorax are mandatory). Investigator makes a diagnosis and submits the proforma online. Investigator then sends the following data in electronic format to the National Co-ordinator: Spirometry tracings with report (scanned or good photocopy), X-ray chest report and photo, HRCT scan (preferably a DICOM CD) and histopathology slides along with a copy of biopsy report. Both inspiratory/expiratory and supine/prone films are preferable. A slice thickness of 1 to 1.5 mm is required. If clinical features and chest radiograph suggest hilar enlargement, then contrast is required to delineate mediastinal structures. Confirmation of diagnoses is done by expert panel (two radiologists, two physicians and two histopathologists) at national and international levels as a two-step process. There is a facility of data entry on follow up visits and any unforeseen event (e.g. death) is informed to the registry.

This issue of Lung India contains an article on the pattern of ILD in eastern India.^[18] Kundu *et al.* have studied clinical, laboratory and imaging parameters of patients with ILD and compared the presentations of IPF with Connective Tissue Disease Associated ILD (CTD-ILD). They found IPF to be present in 38.04% of their study participants and CTD-ILD in 31.5%. In western literature, the incidence of IPF exceeds far beyond the other groups. As far as the frequency of individual ILD is concerned, hypersensitivity pneumonitis and sarcoidosis are close competitors with CTD-ILD throughout world. They also found that IPF and CTD-ILD vary considerably with respect to certain

Table 1: Studies reporting pattern of ILD in India

Study team	Study population	Main findings
Jindal, <i>et al.</i>	61 patients with DPLD seen over a five year period	CTD related ILD in 50.8% and IPF in 46% cases
Sharma, <i>et al.</i>	133 patients with DPLD	IPF was seen in 28.6%
Maheshwari, <i>et al.</i>	76 patients with IPF	Female preponderance of IPF with a ratio of 41:35 and mean age of about 50 years
Subhash, <i>et al.</i>	97 patients with the diagnosis of DPLD	Secondary DPLD in 40 (55%) and IPF in 33 (45%) patients. Secondary DPLD-SS in 12, RA in 11, overlap synd. in 8, sarcoidosis in 7 and SLE in 2
Sen, <i>et al.</i>	Retrospective analysis of 274 patients with ILD seen during the period 1994-2001	IPF (43%), sarcoidosis (22%), ILDs secondary to CTD (18%) and extrinsic allergic alveolitis (6%)
Kundu, <i>et al.</i>	A prospective study of 92 patients with DPLD	Proportion of IPF ($n=35$, 38.04%) was more than that of CTD-DPLD ($n=29$, 31.5%) CTD-DPLD patients belong to a younger age group, with longer duration of symptoms, more extrapulmonary features, better physiological parameters

DPLD: Diffuse parenchymal lung disease, CTD: Connective tissue disorders, ILD: Interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, RA: Rheumatoid arthritis

demographical, clinical, physiological and radiographic parameters. In this study, comparison of serum markers of CTD between IPF and CTD-ILD, in our opinion, is superfluous. Comparisons of biomarkers between these would have been more informative. Another variance in this study was exclusion of many cases that could have been included. As stated above, we include upper lobe fibrotic patterns where there is no history of AFB positivity. NSIP patterns are also included in the registry as an isolated group of IIP other than that associated with CTD-ILD even if no biopsy is available. A confident diagnosis of NSIP can be made based on clearly defined HRCT features.^[19-21] The follow-up of the cases shown in the study is too short to be of significant importance for a disease with a variable long term course such as ILD.^[22] Nevertheless, this study documents pattern of ILD from eastern part of India and is a commendable effort directed toward workup of patients with ILD in their region.

All the premium Indian journals of pulmonary diseases are regularly publishing scientific material on ILD but it is much less as compared to the fast growing body of word literature on ILD. Moreover, most of the Indian literature on ILD is in the form of interesting case reports or case series on individual ILDs. We advocate for more focused research on this disease especially on IPF by our own indigenous people.

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