
Interstitial lung disease (ILD) in India: Insights and lessons from the prospective, landmark ILD-India registry

Interstitial lung diseases (ILDs) are a heterogeneous group of acute and chronic bilateral lung diseases of known and unknown causes and pose diagnostic and therapeutic challenges to the clinician. Clinicians and patients confronted with ILD are understandably frustrated as there is no cause or cure for most of ILDs.

While the access to computed tomography (CT) scans of chest has surfaced an increased awareness of ILD and the prevalence of ILD in several countries has increased over time,^[1-3] the incidence and prevalence of ILDs vary among studies and are likely due to differences in design as well as differential recognition and data collection, besides geographic differences in disease burden.^[2,4-6] The incidence and prevalence of ILDs in India are unknown.

The challenge in diagnosing ILDs in India is confounded by environmental and cultural factors in the midst of infections, especially tuberculosis. The lack of resources and standardized health care in India, lack of standardized approach to diagnosis of ILD, and the apparent phobia, reluctance, hesitancy, and/or uncertainty that most patients in India when confronted with the need for surgical lung biopsy (SLB) express contribute to the current conservative approach to the diagnosis of new onset of ILD in India, i.e., assumed diagnosis and reliance on the individual clinician's judgment. Thus, the treatment of ILDs is empirical in most patients.

Prospective disease registries can provide better estimates of incidence and prevalence as well as insights to etiology, associated risks, natural history, and outcomes of a disease.^[7] Most randomized controlled idiopathic pulmonary fibrosis (IPF) clinical trials and previous ILD registries have enrolled patients from Western countries; data regarding disease burden and demographics of patients from India and South Asia are scarce and may differ substantially.^[4,7-9]

The just published report by Singh *et al.* demonstrates the importance of a prospective registry for new-onset ILD; the detailed case report forms (CRFs) surfaced environmental exposures as potential causative factors for ILD and of multidisciplinary discussions (MDDs) among experts in making an accurate clinical diagnosis of ILD.^[10] The diagnosis of ILD was made on clinical grounds and validated in a prespecified and prospective manner utilizing all clinical data gathered and enrolled in the ILD-India registry: Hypersensitivity pneumonitis (HP) was

diagnosed in 47.3% ($n = 513$; exposure: 48.1% aircoolers), attributable to domestic environmental factors; connective tissue disease-associated ILD in 13.9% and IPF in 13.7%. The ILD diagnosis was made by MDD and based on the new classification of idiopathic interstitial pneumonia and the 2011 guidelines for diagnosis of IPF using high-resolution CT (HRCT) images of the chest as the main platform for diagnostic approach.^[11-13] The demographic profile of patients diagnosed with IPF is similar to the patients with IPF described in the patients of European and Asian descents living in the western and other eastern hemispheres of the world. The interobserver variation in the diagnosis of ILD between ILD experts at a center, recognized as an international authority for diagnosis and management of ILD with site principal investigators and experts familiar with ILD in India, was fair and good, respectively.

For the very first time, the data from the ILD-India registry provide the snapshot of the diagnoses of new-onset ILD in India – the true insight of the specific ILD diagnoses in patients of Indian origin living in India is an eye-opener to all concerned. To date, this is the largest and first prospective multicenter ILD registry that validated clinical diagnosis of new-onset ILD by MDD with two independent teams of ILD experts (1) a local team of national coordinating center at SMS Medical college and Asthma Bhawan, Jaipur, India (informally trained in the field of ILDs by experienced experts from the Center for ILD, UW Medicine, Seattle, WA, USA) and (2) the expert team from the experienced Center for ILD in Seattle, WA, USA.

The limitations associated with the data from the ILD-India registry while acknowledged and discussed in the report by Singh *et al.* include selection bias in the patients enrolled in the registry, not representing all geographic regions in India, the lung biopsy obtained from only 7.5% of patients, a resource-poor setting that relied exclusively on voluntary participation of investigators, and consenting patients able and self-paying for all the required essential diagnostic interventions (although in keeping with the standard of care), in accordance with the inclusion criteria. Since the main purpose of the ILD-India registry was to understand the specific diagnoses of new onset ILD, longitudinal and follow up data on treatment regimen and outcomes were not gathered. Potential variation in the quality of data acquisition from individual centers and data entry operators may have confounded the results. Given that the ILD diagnoses made entirely on clinical grounds may not be precise in a proportion of patients, and that only

7.5% of 1084 patients were subjected to SLB, IPF, and other conditions may have been underestimated; the true incidence and the proportion of individual cohorts of new-onset ILD remain unknown. The diagnosis of HP was made on unvalidated clinical features without histopathology; the association of the environmental factors, especially the exposure to the aircoolers, while a potential source for inducing the HP in susceptible persons, the study was not designed to determine the cause of HP.

Regardless, there are several learning points and implications from this study that need immediate actions by all stakeholders and concerned. These include the following:

1. The accomplishments of the ILD-India registry is a milestone, especially considering the challenges confronted with lack of resources, needed support, and complete reliance of dedicated investigators who volunteered to initiate and fulfill the set magnanimous task
2. The data provide true insights and shed light to the field of ILD in India and contribute to the overall knowledge evolving worldwide; the results may, however, not be extrapolated to the rest of the world because of unique environmental, cultural, and genetic factors in India
3. The essentials and importance of eliciting a detailed, prompted history for diagnostic evaluation of ILD: leading/prompted questions capture the environmental exposures, medical and family history, current and past medications comprehensively
4. The eye-opening awareness of the diagnosis of HP as the leading ILD in India, associated with domestic environmental factors in the vast majority of patients with HP in India, and it being a preventable disease need to be widely dispersed to the general public. Coupled with the necessary actions that will hopefully be implemented by regulating authorities to address environmental factors, as well as patients/unaffected people attending to their own domestic environmental factors that includes proper and regular maintenance of their ventilation systems, guided by manufacturers of units such as air coolers, air conditioners etc, the onset and progression of HP can hopefully be prevented by facilitating people to breathe "cleaner air" at their home and work places
5. Prompted CRFs including environmental exposures in prospective registries will likely provide further insight into the etiology and management of ILD worldwide
6. An immediate need to alert and educate the general public and medical community that the vast majority of Indian patients living in India with new-onset ILD have a preventable disease and if not diagnosed and treated early, progresses to manifest irreversible pulmonary fibrosis and death
7. Need for better education and training medical students, postgraduates, and clinicians in the diagnosis and management of ILD -for thorough evaluation of patients with ILD include bronchoalveolar lavage cellular analyses and histopathological diagnosis in ILD cases who do not meet the HRCT criteria for usual interstitial pneumonia and clinical setting of IPF
8. The importance of ascertaining the accurate diagnosis by MDD among a team of experts for optimum treatment and better management
9. The need to bridge the knowledge gap between the general pulmonologist and experts in ILD in making an accurate diagnosis is evident by the kappa value for inter observer agreement on ILD diagnosis of only 0.351 (a poor agreement) between site investigators and MDD at the Center for ILD, USA
10. Centers of excellence for diagnosis and management of ILD, with expertise in pulmonary rheumatology, radiology, thoracic surgery, and pathology are needed in community and academic environment are needed to enhance the accuracy of diagnosis of ILD that will lead to better management and outcomes for patients.

FUTURE DIRECTIONS

- There is an imperative need to maintain a prospective ILD registry active and interactive, gather longitudinal data prospectively, and understand treatment response and outcomes that are meaningful to patients
- Investigate cause-effect relationship in patients with HP presumed to be induced by environmental factors, especially unkempt aircoolers
- Enhance training programs and clinical and basic science fellowships in ILD in India
- Foster prospective clinical studies through multicenter sites and investigators in India through an expanded ILD network and a designated Data Coordinating Center
- Seek funding resources for the absolute need for maintenance of ILD-India registry, much-needed clinical research in India, and collaborate with investigators through this and similar network beyond India
- Expand the scope of the initiated ILD-India registry and develop an infrastructure for a large ILD network among multiple centers and site investigators dedicated to ILD in India: further contribute to the clinical and basic science in the field of ILD such as obtaining biosamples from patients enrolled in this registry that will lead to pharmacogenomics, genetic studies, and precision medicine taking the environmental, cultural, social, and geographical factors into consideration.

Notwithstanding the above facts, the results of the ILD-India registry prospectively created, initiated, and maintained through an ILD net in India is indeed a milestone and a testimony to the hard work, passion, patience, and perseverance of the joint efforts and collaborations of the few dedicated investigators. Accomplishing this with no resources is an unparalleled feat and represents the results of the collective work of all the investigators/authors and centers in India with a nodal center in India and the Center for ILD at the University of Washington, Seattle, USA.^[10]

In essence, the ILD-India registry has opened the eyes and minds of all concerned regarding the current landscape of ILD in India, especially the high proportion of ILDs manifesting HP – a disease associated with attributable domestic environmental factors and thus preventable if exposures are avoided.

It is hoped that this initiative will spring forward, provoke the interest of young investigators, will open the floodgates for high-quality research in India, and foster collaborations with other leading investigators beyond India in this field. It augurs well for our patients and for ILD in India – the beginnings of a new template!

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