Interstitial Lung Abnormalities: An Evolving Entity

The entity of subclinical interstitial lung abnormalities (ILAs) has been explored in large cohort computed tomography (CT) screening studies. However, the identification of individuals with ILAs that are more likely to evolve to clinical significance has been challenging (1–3). ILAs, present on CT in 5–10% of elderly subjects, have two main radiologic phenotypes, fibrotic and nonfibrotic, but the criteria used to separate these two subtypes has varied between studies. In this issue of the *Journal*, Zhang and coworkers (pp. 178–185) report two intriguing sets of observations (4). The authors explore the prevalence and subtypes of ILAs across a much wider age range than before, extending to much younger ages than reported in previous large cohorts. They also identify CT features predictive of progression on serial CT, with potentially important implications for future ILA classification.

The profile of ILAs in the study of Zhang and coworkers is unique because the population is a "health check-up" population, with low-dose screening CT scans performed in a huge cohort of 155,539 individuals with a mean age of 46.1 years. The study population is hugely removed from past cohorts, selected as elderly subjects or in screening for cardiac disease or lung cancer (5–8). The study shows that ILAs are not merely an incidental finding in the aged population but exist in much younger subjects with a prevalence of 1.2% in the 40–49 age band, increasingly linearly to 9.6% in subjects aged over 70. Importantly, fibrotic ILAs made up only 21 of 1,511 ILAs (1.4%) seen in those aged less than 60, underlining the uncertainty on whether ILAs in this age group have the same biological significance as in elderly subjects.

Real-world studies of huge patient cohorts have the advantage of allowing "big-picture" conclusions to be drawn despite the data imprecisions that inevitably exist in the real world. Nonetheless, uncertainties must be acknowledged, if only to be avoided in future work. Once identified, ILAs were scored meticulously by experienced radiologists, but the selection of ILAs was on the basis of imaging reports, and details of medical conditions were extracted from electronic medical records, with the exclusion of patients with preexisting interstitial lung disease or connective tissue disease, as identified by the data extraction process. Without an audit of this process, comparing extracted data with a more detailed evaluation in a small subcohort (and thus excluding underreporting of excluded disorders), some readers may have reservations with regard to exact statements of prevalence. However, we do not believe this caveat detracts materially from the conclusions discussed below.

Fibrotic ILAs, as defined by the recent FS (Fleischner Society) ILA classification, made up only 5.5% of the 3,300 CT scans exhibiting ILAs, scored by experienced radiologists, although reticulation was present in 42.2% (3, 4). This study represents the first application of the FS criteria to a large ILA cohort, and the low prevalence of fibrotic ILAs contrasts strikingly with their much higher prevalence in past cohorts, including a prevalence of 34% in the landmark cohort of Putman and coworkers (1). This striking discordance was not an artifact of the low prevalence of fibrotic ILAs in younger subjects in the study of Zhang and coworkers: in subjects aged over 70, fibrotic ILAs made up only 73 of 1,077 ILAs (6.8%).

This discrepancy reflects the distinction between the tight classification criteria proposed by the FS and the much looser criteria used to designate fibrotic ILAs in past studies. The FS criteria for fibrotic ILAs include the presence of honeycombing, traction bronchiectasis, and anatomic distortion. However, reticulation is not, in isolation, a criterion for fibrotic ILA designation in the FS classification (3). This may seem counterintuitive to some readers as traction bronchiectasis may be difficult to identify using low-dose CT protocols when reticulation is limited in extent. However, the FS approach is tailored to the confident identification of underlying fibrotic abnormalities, with a view to selective monitoring of patients at higher risk of progression. The danger lies in the overly rigorous application of tight criteria and the possibility that underlying fibrotic disease will be missed in many patients.

This problem was explored in the study of Zhang and coworkers with a substudy of change on serial CT in 536 individuals, a minority subgroup with a bias toward older age and a larger number of comorbidities. The authors examined the rate of progression at a mean time interval of 4.2 years against baseline ILA characteristics, broken down into subgroups on the basis of the presence of individual patterns, the distinction between fibrotic and nonfibrotic ILAs, the distribution of disease, and the extent of reticulation. Among a large number of reported comparisons, there were two notable observations. Progression occurred in 35.2% of individuals with subpleural nonfibrotic ILAs with reticulation, which was an independent risk factor for progression on multivariable analysis. Furthermore, subpleural nonfibrotic ILAs with more extensive reticulation and fibrotic ILAs were equally likely to progress ($n = 54$ [73.0%] and $n = 11$ [68.8%], respectively). Overall, only 11 of 234 individuals (4.7%) with progressive ILAs had fibrotic ILAs at baseline.

The higher risk of ILA progression on serial CT in individuals with subpleural reticular changes was first reported by Putman and coworkers and was highlighted in the FS statement, in which "evidence of fibrosis and subpleural basal predominant distribution" were both identified as risk factors (1–3). The novelty in the current study lies in the very low prevalence of fibrotic ILAs in a very large cohort and the strikingly higher yield in predicting progression when the two high-risk groups were amalgamated.

These findings pose the provocative question: how useful is the strict separation between fibrotic and nonfibrotic ILAs as a cardinal ILA distinction if it is an insensitive guide to future progression? The current study needs to be confirmed and does not, in any case, provide a robust answer as CT subgroups at higher risk of CT progression were not examined against significant lung function decline or mortality. However, given the need for more accurate prognostication, the individual CT risk factors described by Zhang

Originally Published in Press as DOI: 10.1164/rccm.202204-0676ED on May 10, 2022

and coworkers should be examined forensically against clinically important outcomes in future studies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Sara Tomassetti, M.D.
Department of Experimental and Clinical Medicine
Careggi University Hospital and University of Florence
Florence, Italy

Athol Wells
Royal Brompton Hospital & Imperial College
London, United Kingdom

ORCID ID: 0000-0002-4781-6539 (S.T.).

References

1. Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, *et al.*; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators; COPDGene Investigators. Association between interstitial lung abnormalities and all-cause mortality. *JAMA* 2016;315:672–681.
2. Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, *et al.* Development and progression of interstitial lung abnormalities in the Framingham heart study. *Am J Respir Crit Care Med* 2016;194: 1514–1522.
3. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, *et al.* Interstitial lung abnormalities detected incidentally on CT: a position paper from the Fleischner Society. *Lancet Respir Med* 2020;8:726–737.
4. Zhang Y, Wan H, Richeldi L, Zhu M, Huang Y, Xiong X, *et al.* Reticulation is a risk factor of progressive subpleural nonfibrotic interstitial lung abnormalities. *Am J Respir Crit Care Med* 2022;206: 178–185.
5. Lederer DJ, Enright PL, Kawut SM, Hoffman EA, Hunninghake G, van Beek EJ, *et al.* Cigarette smoking is associated with subclinical parenchymal lung disease: the multi-ethnic study of atherosclerosis (MESA)-lung study. *Am J Respir Crit Care Med* 2009;180: 407–414.
6. Sack C, Vedal S, Sheppard L, Raghu G, Barr RG, Podolanczuk A, *et al.* Air pollution and subclinical interstitial lung disease: the multi-ethnic study of atherosclerosis (MESA) air-lung study. *Eur Respir J* 2017;50: 1700559.
7. Jin GY, Lynch D, Chawla A, Garg K, Tammemagi MC, Sahin H, *et al.* Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology* 2013;268:563–571.
8. Sverzellati N, Guerci L, Randi G, Calabrò E, La Vecchia C, Marchianò A, *et al.* Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J* 2011;38:392–400.

A dUTY to Protect: Addressing "Y" We See Sex Differences in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a progressive disease, characterized by elevated pulmonary arterial pressure and subsequent right heart failure. These changes result from pulmonary vasculature wall thickening and remodeling. Pathogenic vascular remodeling stems in part from endothelial cell dysfunction and vascular smooth muscle cell proliferation (1). Pulmonary vascular disease progression is also driven by increased inflammatory cells and mediators, such as macrophages and cytokines, which promote further pathologic remodeling (2). Interestingly, the epidemiology of PAH reveals a fourfold greater disease prevalence in females than males, accompanied by a reciprocal increase of disease severity in males versus females (3). Insights into the sexual dimorphism observed in PAH may lead to the development of better therapeutics, as current therapies are not curative (4). But, the mechanism(s) underlying these gender differences remain poorly understood (5).

Guided by a historical focus on the role of sex hormones in PAH, a puzzling yet crucial finding has emerged: estrogen prevents disease experimentally, while clinically, females have higher disease incidence (3). Thus, sex hormone differences alone may not adequately explain the female predominance of PAH development. Accordingly, Umar and colleagues looked to chromosomal differences between the two sexes instead. Previously, they found a protective role of the Y chromosome (ChrY) in PAH, independent of gonadal hormones (6). At the same time, Yan and colleagues described pathogenic activity of the ChrY gene *sry* in PAH via regulation of BMPR2 gene expression in fibroblasts—findings that also suggested a role of *sry* in PAH gender differences (7). But, *sry* alone could not alone explain ChrY-dependent protection, because XY *female* mice lacking *Sry* were still protected against PAH when compared with XX females (6).

In this issue of the *Journal* (pp. 186–196), this group delved deeper to understand how the ChrY confers protection against the development of PAH (8). The authors concluded that the ChrY gene, *uty* (ubiquitously transcribed tetratricopeptide repeat containing, y-linked), is responsible for this protective role, and identified downstream inflammatory mediators as important therapeutic targets. The group first found ChrY genes that were expressed in mouse lung tissue and individually knocked down each gene in the lungs of gonadectomized hypoxic mice. Of the four genes they investigated, only knockdown of *uty* resulted in PAH development.

Supported by NIH grants R01 HL124021 and HL 122596 and the American Heart Association grant 18EIA33900027 (S.Y.C.).

Originally Published in Press as DOI: 10.1164/rccm.202204-0653ED on May 11, 2022