Interstitial lung abnormalities: do symptoms matter?

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The largest population-based cohort study on interstitial lung abnormalities adds to the evidence of an association with impaired lung function and highlights the need to systematically identify early interstitial lung disease https://bit.ly/3QizOBt

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Interstitial lung disease (ILD) continues to face diagnostic challenges in the pulmonary and wider medical communities. Delays and inaccuracies in diagnosis of ILD remain all too commonplace [1]. While there is no role for screening of the general population or even at-risk populations, as there is for lung cancer in individuals with a smoking history, the seeming ubiquity of computed tomography (CT) imaging affords an opportunity to identify patients with ILD who may not otherwise come to attention for many years. CT findings consistent with ILD in those without such a diagnosis are referred to as interstitial lung abnormalities (ILA). ILA research has grown rapidly over the last decade or so [2]. Importantly, there have been numerous studies demonstrating associations with clinically important outcomes, including mortality, lung function and progression [3–5]. With an eye towards providing guidelines and standardising ILA identification and characterisation, the Fleischner Society has recently put forward a position paper [6], where they also focus on directions of future research.

In this issue of *ERJ Open Research*, Pesonen *et al.* [7] add to this growing body of work with a population-based investigation of ILA. They employed the large national registry, the Swedish Cardiopulmonary Bioimage Study (SCAPIS) [8], which is composed of >30 000 individuals between the ages of 50 and 64 years. The current study included nearly the entire cohort, with 29 521 individuals total (excluding those without analysable CT scans), making it the largest ILA study to date. The cohort was evenly distributed between male (48.7%) and female (51.3%) subjects, with a median age of 57.4 years. Though the SCAPIS cohort consists of both never-smokers and former/current smokers, Pesonen *et al.* [7] also focused their analysis on the subset of individuals who were never-smokers, 50.8% of the cohort. The prevalence of ILA in the entire cohort of 29 521 individuals was 9.7%, while the ILA prevalence in never-smokers was 7.9%. In both groups, fibrotic ILA was found in <1% of the subjects. The overall prevalence is within the range described in a number of other large ILA studies, with estimates ranging from 4% to 9% in smokers and 2% to 7% in nonsmokers [9]. It is important to note that a higher prevalence is typically found in older populations. The current study included a middle-aged population and therefore the prevalence, particularly in nonsmokers, may be an overestimate. One reason to explain this finding may be the criteria used to delineate ILA. As the authors discussed, the ILA definition they employed varies from the Fleischner guidelines. Specifically, there was no lower threshold defined at 5% of any lung zone, which may have recategorised a portion of individuals with ILA in the current study as indeterminate.

Pesonen *et al.* [7] also found that in a multivariable regression model adjusted for age, sex, body mass index, pack-years of smoking and comorbidities, both ILA and fibrotic ILA were associated with restrictive lung physiology (defined as forced vital capacity <80% predicted or below the lower limit of normal (LLN)) and reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) (defined as below LLN) in the full cohort. In never-smokers, this association also held for D_{LCO} but only for fibrotic ILA with respect to a restrictive spirometric pattern. Importantly, there was no association of ILA or fibrotic ILA with dyspnoea based on a modified Medical Research Council score ⩾2 in either the full cohort or the

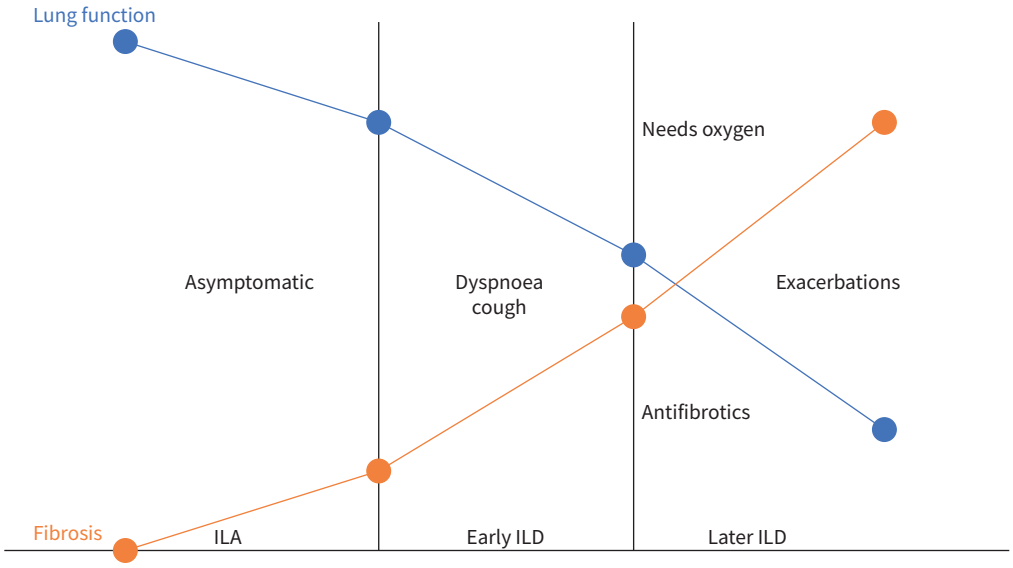

FIGURE 1 Interstitial lung disease (ILD) progression. ILA: interstitial lung abnormality.

never-smoker subset. The association between ILA and spirometric restriction or lung volume reduction has been described in a number of other studies [10–12], including the landmark study in smokers by Washko *et al.* [10]. In the present study, the link between nonsmokers and spirometric restriction was limited to the small group with fibrotic ILA. Nevertheless, as one of the few studies to demonstrate such an association in nonsmokers, it is noteworthy.

The study by Pesonen *et al.* [7] has a number of strengths. First, this is one of the largest cohorts investigated in the ILA literature. Second, all individuals included in the study were fully characterised with detailed symptom and exposure questionnaires, functional testing, and imaging. Third, this is one of the few large cohort studies to investigate ILA in never-smokers.

Due to the nature of the registry and cohort, there are some inherent limitations in the study. Most significantly, we do not have mortality data. However, given that the study included only middle-aged individuals, there may not be a significant difference in mortality with ILA in this cohort. We also cannot be sure that some of these patients with ILA did not already have an ILD diagnosis. This may have created an overestimate of ILA prevalence in this population given that ILA is defined by the lack of a pre-existing ILD diagnosis.

What is the significance of the association with lung function deficits but not with dyspnoea? First, it should be recognised that other studies on ILA have found an association with cough and dyspnoea [10, 12]. Nevertheless, the results of the current study may represent a key concept in the development of ILD. Although the course of every patient with ILD is variable, this finding supports the concept of a natural progression of disease where CT changes precede lung function decrements, which both precede the onset of symptoms (figure 1). Those who care for ILD patients know that, oftentimes, symptoms are a late manifestation of a progressive disease. These patients present when they encounter dyspnoea, by which time there is already marked fibrosis on CT imaging and a significant decline in lung function. This finding, in particular, highlights the importance of early detection of ILD. If some portion of patients with ILA already have impaired lung function, they merit early diagnosis and treatment, regardless of symptoms and even before symptoms.

In summary, this study demonstrates that ILA, as shown in many other populations, is fairly common. It further reinforces the importance of ILA, even in a general, standard-risk population, and the need to systematically identify individuals with ILA so they can receive the appropriate evaluation, diagnosis, and management.

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