Incidental discovery of interstitial lung disease: diagnostic approach, surveillance and perspectives

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Abstract

The incidental discovery of pre-clinical interstitial lung disease (ILD) has led to the designation of interstitial lung abnormalities (ILA), a radiological entity defined as the incidental finding of computed tomography (CT) abnormalities affecting more than 5% of any lung zone. Two recent documents have redefined the borders of this entity and made the recommendation to monitor patients with ILA at risk of progression. In this narrative review, we will focus on some of the limits of the current approach, underlying the potential for progression to full-blown ILD of some patients with ILA and the numerous links between subpleural fibrotic ILA and idiopathic pulmonary fibrosis (IPF). Considering the large prevalence of ILA in the general population (7%), restricting monitoring only to cases considered at risk of progression appears a reasonable approach. However, this suggestion should not prevent pulmonary physicians from pursuing an early diagnosis of ILD and timely treatment where appropriate. In cases of suspected ILD, whether found incidentally or not, the pulmonary physician is still required to make a correct ILD diagnosis according to current guidelines, and eventually treat the patient accordingly.

Introduction – the definition of ILA

The definition of interstitial lung abnormalities (ILA) is radiological. ILA have been described as nondependent abnormalities affecting more than 5% of any lung zone (upper, middle and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein) [1]. ILA refer to the presence of CT findings potentially compatible with interstitial lung disease (ILD) in patients without known or suspected ILD. Currently, the main feature that distinguishes ILA (both pre-clinical and clinically overt) from ILD is that ILA are incidental findings in patients without known or suspected ILD, therefore the definition of ILA can be summarised as the incidental finding of CT abnormalities affecting more than 5% of any lung zone [2].

ILA cohorts include patients with lung function impairment and symptoms when first detected by CT, but after clinical review these ILA are reclassified as ILD, while the remaining cases have no clinical evidence of ILD. The current distinction between ILA, pre-clinical ILD and mild ILD can be simplified and summarised as shown in table 1. In the current literature subclinical ILD, pre-clinical and early ILD are synonymous and are distinct from ILA. In the Fleischner Society document [2] a distinction was made between ILA and patients at high risk with connective tissue diseases or familial cases undergoing screening CT for ILD. The Fleischner Society argued for terming these as pre-clinical as opposed to

TABLE 1 Simplified definitions

Entity		Population	Diagnostic criteria	Definition
ILA		Only individuals without known or suspected ILD[#]	Clinical-radiological entity	Incidental finding of CT abnormalities affecting more than 5% of any lung zone
Early ILD	**Pre-clinical ILD**	Individuals at risk for ILD	Clinical-radiological-pathological entity	Any ILD in asymptomatic patients with preserved lung function
	Subclinical ILD	Individuals NOT at risk for ILD		
Mild ILD		All individuals	Clinical-radiological-pathological entity	Any clinically significant ILD with minor symptoms and/or trivial PFT abnormalities

ILA: interstitial lung abnormalities; ILD: interstitial lung disease; CT: computed tomography; PFT: pulmonary function test. [#]: abnormalities identified during screening for ILD in high-risk groups (*e.g.* those with rheumatoid arthritis, systemic sclerosis or familial ILD) are not considered as ILA because they are not incidental.

subclinical, with the latter term used in patients without known risk for ILD. Early, pre-clinical and subclinical ILD refer to asymptomatic patients with normal pulmonary function tests in whom ILD is ascertained, and eventually classified, based on current guidelines [3–7]. ILA have been incidentally detected in patients with mild symptoms and/or trivial pulmonary function impairment that were overlooked. However, when these clinically significant findings are present, ILA are likely to represent
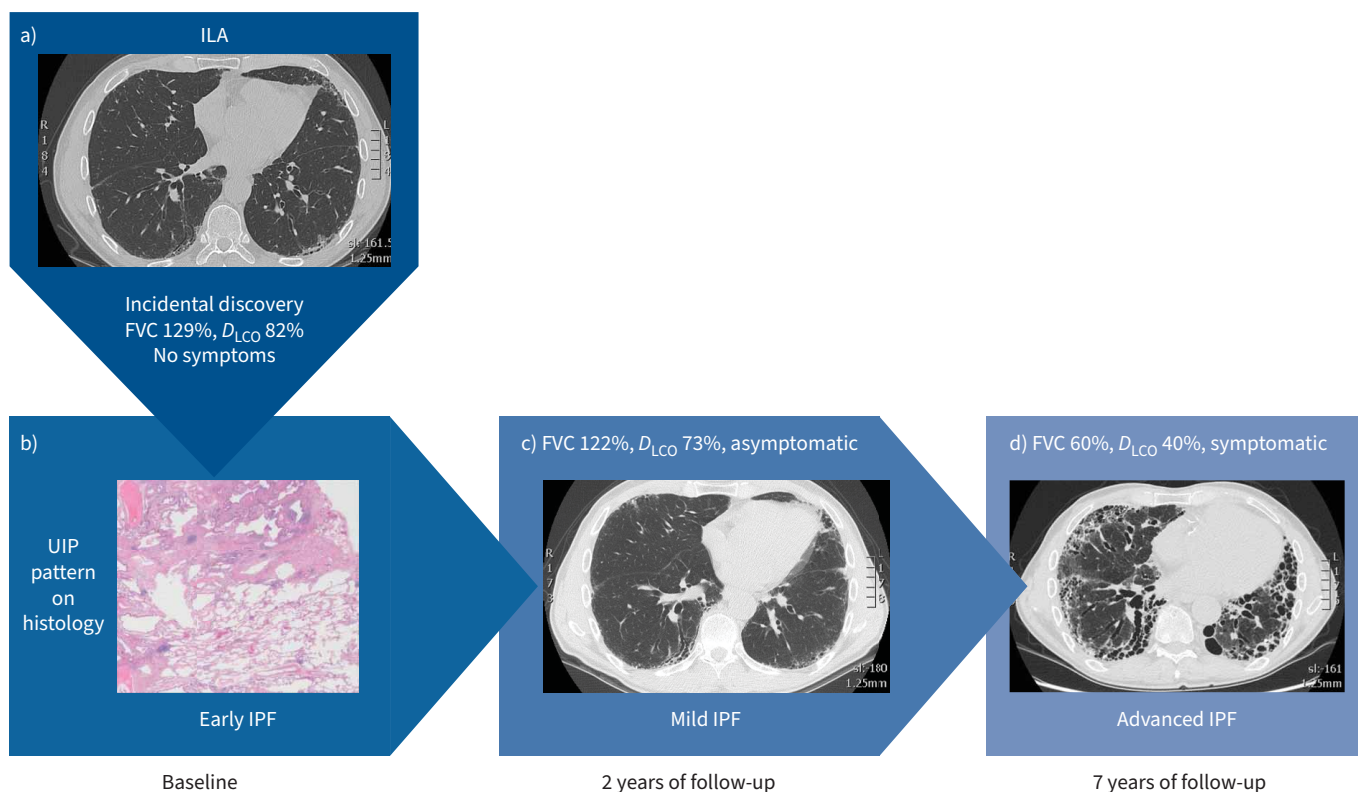
FIGURE 1 Case of clinical evolution from interstitial lung abnormalities (ILA), early idiopathic pulmonary fibrosis (IPF) (subclinical), mild IPF and to advanced IPF. A 70-year-old man without risk factors for interstitial lung disease (ILD). He presented to the Forlì ILD Clinic, V. Poletti, for the incidental finding of ILA, was reclassified to early IPF after multidisciplinary revision of radiological and pathological findings on lung biopsy and during the follow-up evolved to mild IPF, advanced IPF and ultimately died of the disease. a) ILA. Incidental finding of reticular subpleural abnormalities with traction bronchiectasis. Pulmonary function tests: forced vital capacity (FVC) 129%, diffusing capacity of the lung for carbon monoxide (D_{LCO}) 82%. No symptoms. b) Early IPF. The lung biopsy showed a definite usual interstitial pneumonia pattern and the case was reclassified as early IPF. c) Mild IPF. After 2 years of follow-up the D_{LCO} dropped to 73%. The patient remained asymptomatic, with FVC around 120%. d) Advanced IPF. After 7 years of follow-up the FVC dropped to 60%, D_{LCO} to 40% and the patient became symptomatic. The patient died after 10 years of follow-up.

mild ILD rather than pre-clinical ILD or ILA [2]. This categorisation has its limitations: the artificial distinction between ILA, early ILD and mild-ILD is justified by the concept that all these categories can be part of a spectrum of ILD development and progression [8]. When we are dealing with a defined ILD, the distinction between incidental and not, and between symptomatic and not, does not change our diagnostic perception. Thus, ILA, early ILD and mild ILD may simply reflect different stages of the same disease, as shown in figure 1. A notable example is idiopathic pulmonary fibrosis (IPF), a relentlessly progressive and ultimately lethal disease that, even when diagnosed while still limited, is usually actively treated [9–13]. Other trivial ILDs (*e.g.* mild, pre-clinical or incidental findings of nonspecific interstitial pneumonia, smoking-related ILD, connective tissue-related ILD, drug-related ILD, hypersensitivity pneumonitis) do not always require early treatment initiation. Removal of the cause (if known) with careful observation is often sufficient. What guides patient management in clinical practice is the ILD diagnosis, its severity and the profile of the patient (age, comorbidities, preferences), with an accurate diagnosis always preferred as a guide to treatment decisions. What is currently lacking in ILA is knowledge of a likely underlying diagnosis. The clinical profile of ILA is poorly addressed in current studies, and histology features remain largely to be investigated. We should focus our efforts toward a better clinical and histopathological definition of ILA cases. As long as ILA remain a radiological entity, their management and clinical meaning will remain uncertain, and the current literature well reflects this uncertainty.

### Why are ILA relevant? Prevalence and prognosis of ILA

High-resolution CT is highly sensitive for detecting ILA and evaluation of large cohorts of cases screened by CT (for lung cancer, COPD, cardiovascular risk factors, population longitudinal studies) has shown that these incidental abnormalities are relatively common, with a prevalence around 7% in the general elderly population (ranging from 3% for patients with ILA with a mean age of 62 years, to 17% for patients with ILA with a mean age of 78 years) [1, 2, 14–23]. The prevalence of ILA in the post-COVID-19 pandemic era remains to be determined. It is still unclear whether the majority of patients with long COVID-19, enrolled in population-based screening programmes post-COVID, with residual disease that falls in the broad extent of CT indeterminate abnormalities, should be viewed as having ILA [24, 25]. As this is an "at risk" population, post-COVID abnormalities may best be viewed as distinct from ILA, pending further data. Importantly, COVID-19 data may well be relevant to severe viral pneumonitis in general and raises the possibility that, in a subset of patients, ILA may represent post-viral damage [26–30].

ILA have been associated with adverse clinical outcomes in numerous studies, with an estimated rate of CT progression of 20% of patients over 2 years and 48% of patients over 5 years [2, 20, 31]. As detailed in table 2, subpleural and fibrotic CT appearance, increasing age and increasing copies of the MUC5B promoter variant rs35705950 are associated with ILA progression [15, 31, 32]. ARAKI *et al.* [15] showed that ILA are associated with an accelerated rate of lung function decline; ILA with progression had a mean forced vital capacity (FVC) decline of 64 mL (SD 51 mL) per year. Even considering the progressive form

TABLE 2 Interstitial lung abnormality (ILA) risk factors for progression and mortality			
	ILA progression	Mortality	First author [ref.]
Age, years	OR 1.14 (95% CI 1.11–1.17)		ARAKI [15]
MUC5B (rs35705950)	OR 2.8 (95% CI 1.7–4.4)		ARAKI [15]
Progressive ILA		HR 3.9 (95% CI 1.3–10.9)	ARAKI [15]
HRCT predictors			
Subpleural reticular markings	OR 6.6 (95% CI 2.3–19)	OR 1.6 (95% CI 1.0–2.5)	PUTMAN [31]
Traction bronchiectasis	OR 6.6 (95% CI 2.3–19)	OR 1.6 (95% CI 1.3–2.1)	PUTMAN [31]
Traction bronchiectasis score 1		HR 2.18 (median OS 8.5 years)	HIDA [32]
Traction bronchiectasis score 2		HR 2.65 (median OS 7.7 years)	HIDA [32]
Traction bronchiectasis score 3		HR 6.8 (median OS 5.4 years)	HIDA [32]
Subpleural location	OR 6.6 (95% CI 2.3–19)	OR 1.6 (95% CI 1.0–2.7)	PUTMAN [31]
Lower lobes predominant changes	OR 6.7 (95% CI 1.8–25)	NS	PUTMAN [31]
Indeterminate for UIP		NS	PUTMAN [31]
Probable UIP		OR 1.9 (95% CI 1.5–2.5)	PUTMAN [31]
Definite UIP		OR 4.5 (95% CI 2.8–7.2)	PUTMAN [31]

Traction bronchiectasis score: 0=absence; 1=bronchiolectasis only; 2=mild moderate traction bronchiectasis; 3=severe traction bronchiectasis and/or honeycombing. OR and hazard ratio (HR) on adjusted multivariable analysis. HCRT: high-resolution computed tomography; HR: hazard ratio; NS: nonsignificant when p>0.05; OS: overall survival; UIP: usual interstitial pneumonia.

| FVC annual decline, mL | −35 | −40 | −64 | −83 | −187 | −224 |
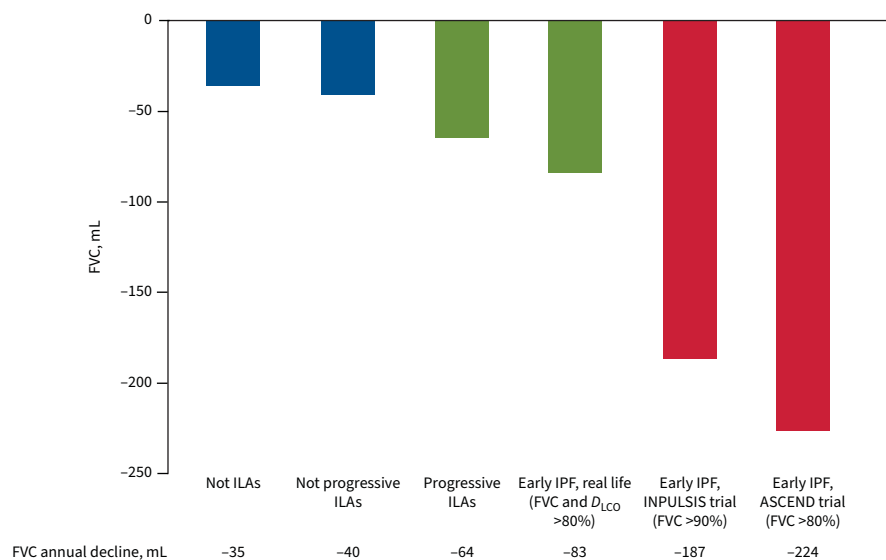
FIGURE 2 Forced vital capacity (FVC) annual trends of early idiopathic pulmonary fibrosis (IPF) and interstitial lung abnormalities (ILA). Participants without ILA had a mean decrease in FVC of 35 mL (sD 44 mL) per year, those with ILA without progression 40 mL (sD 44 mL) decrease per year, and ILA with progression had a mean decline of 64 mL (sD 51 mL) per year. Participants with ILA compared with non-ILA had a −20 mL greater loss in FVC per year and progressive ILA compared with nonprogressive ILA had a −25 mL greater loss in FVC per year [15]. Pre-clinical IPF shows a yearly FVC decline of 83 mL, compared with the 200 mL of the IPF population enrolled in clinical trials [12, 13, 33]. D_{LCO}: diffusing capacity of the lung for carbon monoxide.

of ILA, it appears that FVC progression is only 30–35 mL per year more than normal ageing and is substantially less than in IPF cohorts evaluated in clinical trials, estimated to be approximately 200 mL per year, without notable differences in IPF with or without baseline preservation of FVC [12, 13]. However, substantially slower rates of disease progression have been identified in IPF populations with preserved lung function outside clinical trials. Kondoh et al. [33] described a slow IPF progression rate in 16 patients with completely preserved lung function (both FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) >80% of predicted; CT extent 36%, range 10–88%) in which IPF was ascertained by lung biopsy. First-year decline in FVC was 83 mL and disease progression (defined by FVC 10% or D_{LCO} 15% decline) was observed in 11 of 16 patients (68.8%), over a mean period of 19.9±12.3 months. This small study needs to be replicated in larger cohorts, but it is interesting that the slow observed FVC decline in the study population differs little from that of progressive ILA (−83 mL compared with −64 mL annually), leading to the hypothesis that progressive ILA with similar FVC decline might often represent subclinical IPF. Whether the majority of progressive fibrotic ILA do, in reality, represent early IPF or whether only a minority do remains to be clarified. Functional trends of early IPF and ILA are summarised in figure 2.

One of the most consistent and relevant findings with regard to ILA is the association with increased mortality, with increased respiratory mortality and increased mortality from pulmonary fibrosis observed in the AGES-Reykjavik study [2, 16, 31]. Mortality difference between the groups of study participants with and without ILA is around 6%, with a 23% mortality (95% CI 18–28) in the AGES-Rejkyavik study. After adjustment for covariates, ILA were associated with a higher risk of death in all cohorts: the Framingham Heart Study hazard ratio (HR) 2.7 (95% CI 1.1–6.5), the AGES-Reykjavik study HR 1.3 (95% CI 1.2–1.4), the COPD-Gene study HR 1.8 (95% CI 1.1–2.8), and the ECLIPSE study HR 1.4 (95% CI 1.1–2.0). Causes of death for the AGES-Reykjavik study in the ILA population were cardiovascular in 42% of participants, cancer in 25%, and respiratory in 13%, and among those, half of deaths were related to pulmonary fibrosis [16].

ILA: the spectrum of radiological abnormalities

In chest CT analysis, the three most important tasks are: 1) to discriminate between ILA and normal/minimally abnormal appearances; 2) to discriminate between ILA and more extensive disease (pending the multidisciplinary evaluation of clinical significance); and 3) to categorise ILA based on distribution (subpleural or nonsubpleural) and presence of fibrosis (fibrotic or nonfibrotic) [34].

Distinction between ILA and normal/minimally abnormal findings

The separation of ILA from normal lung is anything but "black and white". There is a spectrum of CT abnormalities considered "indeterminate" for ILA that includes interstitial changes involving less than 5% of any lung zone: focal or unilateral ground-glass attenuation, focal or unilateral reticulation and patchy ground-glass attenuation [16]. The indeterminate pattern is more frequent than ILA in some cohorts, equalling the prevalence of normal appearances. Among 3167 participants of the AGES-Reykjavik study, 10% (n=327) had ILA, 45% (n=1435) had normal appearances and 45% (n=1405) had indeterminate high-resolution computed tomography (HRCT) findings [31]. The clinical significance of indeterminate abnormalities has not yet been clarified, but in some large cohorts, the presence of indeterminate CT changes was associated with a prognosis that falls between that of normal lung and ILA. However, the mortality difference between normal appearances and indeterminate abnormalities has been inconsistently reported, and was: 7% (95% CI 4–10, unadjusted HR 2.5, 95% CI 1.6–3.8; p<0.001) in the ECLIPSE study population; 1% (95% CI 0.4–2.0, unadjusted HR 2.5, 1.3–4.9; p=0.007) in the Framingham Heart Study population; and 10% (95% CI 7–13, unadjusted HR 1.4, 95% CI 1.3–1.6) in the AGES-Reykjavik study [16]. ILA are a radiological entity; therefore, the consistency with which radiologists define this entity and distinguish between ILA, indeterminate appearances and normality matters greatly. Despite this, no studies have reported radiologist confidence in the identification of ILA and few studies have reported observer variation, although agreement is likely to be better for the distinction between ILA and normal lung than between ILA and an indeterminate pattern. In the chest readings of the Putman study, 2836 CT were scored by at least two readers, and 57 and 66% were concordant reads in the AGES-Reykjavik study and the ECLIPSE study, respectively. Of the discordant reads, 95–98% involved indeterminate CT, while discrepancies between ILA and normal lung were far less common (2–5%) [16]. Kappa values were not reported and, thus, the actual level of agreement is very difficult to distil. Another distinct but relevant issue is to discriminate ILA from abnormalities of different nature (not ILA). HATABU *et al.* [2] in the recent Fleischner Society position paper on ILA have designated the distinction between ILA and nonspecific CT findings, identifying the conditions that are not ILA as follows: dependent lung atelectasis, focal paraspinal fibrosis in contact with osteophytes, smoking-related centrilobular nodularity in the absence of other findings, mild focal or unilateral abnormality, interstitial oedema (*e.g.* heart failure, findings of aspiration (patchy ground-glass, tree in bud).

Clinical implications of ILA subcategories

The categorisation of ILA as subpleural or nonsubpleural and as fibrotic or nonfibrotic has major prognostic and clinical implications. The recent Fleischner Society position paper recognises three distinct subcategories of ILA: 1) nonsubpleural ILA that lack a predominant subpleural localisation; 2) subpleural nonfibrotic ILA that have a predominant subpleural localisation without evidence of fibrosis; 3) subpleural fibrotic ILA that have a predominant subpleural fibrosis with evidence of pulmonary fibrosis [2]. There is limited evidence that suggests acceptable agreement between radiologists in the discrimination between these categories. SVERZELLATI *et al.* [22], in a study that antedates the Fleischner consensus document, showed that the radiologists agreement was good for the diagnosis of chronic fibrotic ILA (k=0.60), for reticulation (k=0.62) and traction bronchiectasis (k=0.72) and was excellent for the recognition of honeycombing (k=1). Considering that the definition of fibrotic ILA requires honeycombing or traction bronchiectasis, we find these findings reassuring. The prevalence of the three subgroups of ILA has been variably reported in studies that antedate the Fleischner position paper and needs to be better clarified. In a recent report of 80 subjects with ILA, subpleural nonfibrotic ILA were most frequent (48% of cases), followed by subpleural fibrotic ILA (30%) and by nonsubpleural ILA (22%) [35]. However, it should be stressed that reticulation without honeycombing or traction bronchiectasis is variably regarded as fibrotic and nonfibrotic in different series.

The subcategory of nonsubpleural ILA includes ILA presenting with ground-glass opacities without a predominant subpleural localisation. ILA with a nonsubpleural distribution are usually nonprogressive and not associated with increased mortality [2]. The subpleural distribution compared with the centrilobular location increases both the likelihood of progression (adjusted odds ratio (OR) 6.7, 95% CI 1.8–25, p=0.004) and death (adjusted OR 1.6, 95% CI 1.0–2.7; p=0.05). The presence of centrilobular nodules significantly decreases the likelihood of progression (adjusted analysis for age, gender, body mass index, pack-years, smoking status and MUC-5B genotype, OR 0.2, 95% CI 0.1–0.5; p=0.0002) [31].

As shown in figure 1, fibrotic subpleural ILA are of particular clinical relevance as potential precursors to IPF or other progressive fibrotic ILDs. BUENDÍA-ROLDÁN *et al.* [35] recently reported that 4% of ILA evolve to usual interstitial pneumonia (UIP)/IPF and 6% of ILA evolve to autoimmune ILDs (n=80 ILA, 24 months of follow-up). For ILA, the CT features of fibrosis that increase the risk of progression and/or mortality have been explored in several studies and are detailed in table 2. The presence of fibrosis,

defined by HRCT as subpleural reticular markings or traction bronchiectasis, increases the odds of progression more than sixfold (OR 6.6, 95% CI 2.3–19; p=0.0004) [31]. Traction bronchiectasis and bronchiolectasis are associated with poorer survival in subjects with ILA. In the AGES-Rykjavik study, 378 CT scans of ILA were scored for bronchiolectasis and bronchiectasis severity (score 0= absence; 1=bronchiolectasis only; 2=mild moderate traction bronchiectasis; 3=severe traction bronchiectasis and/or honeycombing). ILA without bronchiectasis/bronchiolectasis (score 0) had the same prognosis as control subjects (non-ILA), median survival 11.95 years and 12.93 years, respectively. In patients with bronchiectasis/bronchiolectasis the severity of the score was predictive of a worse prognosis, median survival was 8.52 years (95% CI 7.57–9.30) for a score of 1, 7.63 years (95% CI 6.09–9.10) for a score of 2, and 5.40 years (95% CI 1.85–5.98) for a score of 3 [32].
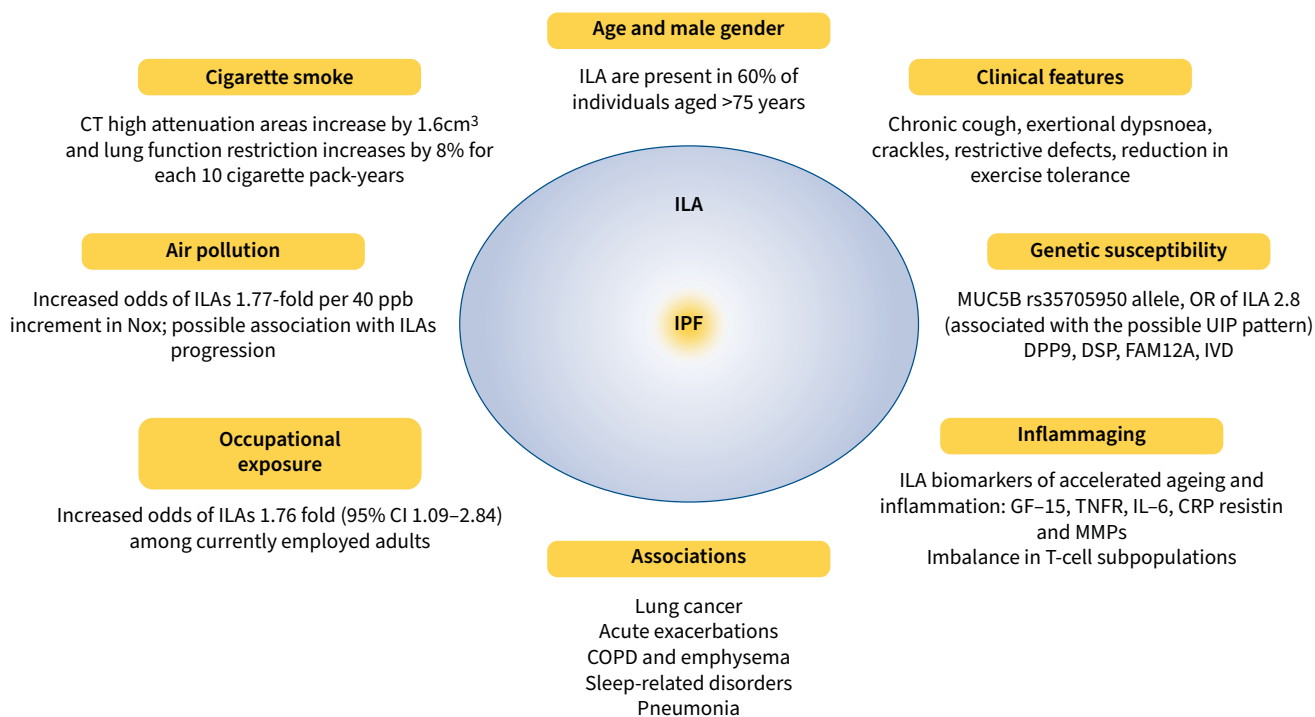
When fibrosis is present, the pattern is classified according to the 2018 Fleischner and American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Society criteria as typical, probable or indeterminate for UIP [4, 36]. All cases of ILA showing honeycombing on HRCT inexorably progress and both ILA with HRCT patterns of definite UIP and probable UIP have an increased risk of death when compared with HRCT patterns indeterminate for UIP (HR 3.9, 95% CI 2.3–6.8; p=0.0001; HR 1.7, 95% CI 1.2–2.4; p=0.001, respectively) [31].

ILA and IPF: links, similarities and differences

Aside from the evident radiological similarities between the progressive subpleural fibrotic forms of ILA and IPF, there are several other features that these two entities have in common: the epidemiological profile and risk factors, clinical and functional features, common clinical associations, shared pathogenetic mechanisms and predisposing genetic factors. Similarities between ILA and IPF are summarised in figure 3.

Age, gender, cigarette smoke and exposures

ILA are more frequent in advanced age and male gender subjects [16, 20, 23, 37, 38]. Each 10 years increase in age is associated with a 2.2 times increase in the odds of having ILA [2, 37]. COPLEY et al. [39, 40], also including cases with minimal changes, identified interstitial abnormalities in 60% of individuals

Cigarette smoke

CT high attenuation areas increase by 1.6cm³ and lung function restriction increases by 8% for each 10 cigarette pack-years

Air pollution

Increased odds of ILAs 1.77-fold per 40 ppb increment in Nox; possible association with ILAs progression

Occupational exposure

Increased odds of ILAs 1.76 fold (95% CI 1.09–2.84) among currently employed adults

Age and male gender

ILA are present in 60% of individuals aged >75 years

Clinical features

Chronic cough, exertional dypsnoea, crackles, restrictive defects, reduction in exercise tolerance

Genetic susceptibility

MUC5B rs35705950 allele, OR of ILA 2.8 (associated with the possible UIP pattern) DPP9, DSP, FAM12A, IVD

Inflammaging

ILA biomarkers of accelerated ageing and inflammation: GF–15, TNFR, IL–6, CRP resistin and MMPs
Imbalance in T-cell subpopulations

Associations

Lung cancer
Acute exacerbations
COPD and emphysema
Sleep-related disorders
Pneumonia

ILA

IPF

FIGURE 3 Summary of shared features between interstitial lung abnormalities (ILA) and idiopathic pulmonary fibrosis (IPF). CRP: C-reactive protein; CT: computed tomography; GF-15: growth differentiation factor 15; IL: interleukin; MMP: matrix metalloproteinase; Nox: nitric oxide; OR: odds ratio; TNFR: tumour necrosis factor α receptor II; UIP: usual interstitial pneumonia.

aged more than 75 years, although this estimate includes abnormalities that would now be categorised as indeterminant. Given that ILA in the elderly are relatively common, there is a need to identify distinctive elements that can help physicians to discriminate between "ageing lung" and the progressive form of ILA [40]. This distinction is critical to avoid both the risk of over-monitoring of elderly patients and the risk of delayed treatment for progressive ILD. Male gender is also a known demographic risk factor described for both ILA and IPF [16, 41] and, in smokers with ILA, male gender is associated with a 1.7 fold increase in ILA prevalence [37]. Smoking is an independent risk factor for IPF [42, 43] and is also the most well replicated risk factor for ILA [1, 14, 16, 22]. Among participants of the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study, both parenchymal lung abnormalities and spirometric restriction were associated with a greater number of pack-years of cigarette smoked independent of body size, current smoking status and other potential confounders [17]. SACK et al. [18] have recently shown that ambient air pollution exposure is associated with ILA. The odds of ILA increased 1.62 fold per 40 ppb increment in nitrogen oxide (95% CI 0.97–2.71; p=0.06). RICE et al. [44] have recently found that an elemental carbon (a constituent of traffic-related fine particulate matter PM 2.5) 5-year exposure interquartile range (IQR) difference of 0.14 $\mu g \cdot m^{-3}$ was associated with both a 1.27 times (95% CI 1.04–1.55) greater odds of ILA, and a 1.33 times (95% CI 1.00–1.76) greater odds of ILA progression. Occupational exposure has been recently linked to the risk of ILA. Self-reported occupational exposures to vapours, gas, dust and fumes was associated with the presence of subclinical ILD in community-dwelling adults, with an increased likelihood of ILA among those currently employed (1.76-fold, 95% CI 1.09–2.84) and those less than 65 years old (1.97-fold, 95% CI 1.16–3.35) [45]. Data from 485 ILA cases extracted from the Asbestos Review Programme registry show a relatively low asbestos exposure of 0.7 fibre·mL-year^{-1} (95% CI 0.09–2.32) in cases with a mild chronic stable phenotype of asbestos-associated ILA. In contrast with the traditionally accepted view that asbestosis requires high exposures, ILA that fit criteria for asbestosis are common in cases with low asbestos exposure, and a minority experience lung function decline (8.2% had an FVC decline of ⩾10% and 6.2% D_{LCO} decline of ⩾15% per year) [46].

Clinical features of ILA

Although symptoms are far less common in ILA than in more advanced ILD and IPF, when present the spectrum of respiratory symptoms is indistinguishable from IPF and is characterised by the presence of chronic cough (12–41% in ILA compared with 73–86% in IPF), and exertional dyspnoea (15–60% in ILA, almost universal in IPF) [1, 14, 19, 47]. Bi-basal crackles have been described in a subgroup of patients with ILA (up to 26% of cases) [19, 47]. Reductions in total lung capacity, diffusion capacity, exercise tolerance and restrictive defects have been described in some ILA cases [1, 14, 19, 47]. To avoid confusion in the terminology the recent Fleischner Society position paper discourage the use of the term ILA in patients that have overt clinical features of ILD, favouring the term "mild ILD" (table 1) [2].

ILA share common clinical associations with lung cancer, increased risk of acute exacerbations and respiratory failure, sleep-related breathing disorders, COPD, emphysema and pneumonia [48]. Similarly to IPF, people with ILA are at increased risk of lung cancer and lung cancer mortality, but not of other cancers [49, 50]. Data from the AGES-Reykjavik study show a greater cumulative incidence of lung cancer diagnoses and lung cancer mortality in participants with ILA (lung cancer diagnosis HR 2.77 and lung cancer mortality HR 2.89) [49]. ILA have been associated with higher post-operative pulmonary complications (overall post-operative complications, adjusted OR 1.91 95% CI 1.02–2.13; p=0.004; severe post-operative complications, adjusted OR 1.09, 95% CI 1.03–1.16; p=0.002) [51], immune checkpoint inhibitor-induced pulmonary toxicity (OR 6.29, 95% CI 2.34–16.92; p<0.001) [52, 53], radiation pneumonitis (OR 1.86, 95% CI 0.48–7.20; p=0.37) [54], and chemotherapy complications [54–56]. ILA are present in 9.5% of patients with stage I nonsmall cell lung cancer and are associated with shorter overall survival (median 3.85 years, 95% CI 3.36–not reached; compared with median survival in non-ILA 10.16 years, 95% CI 8.65–not reached). In Cox proportional hazards model, ILA significantly increased the risk for death in stage I nonsmall cell lung cancer (adjusted HR=2.88; p=0.005) [57].

Patients with ILA are at increased risk of acute exacerbations (acute respiratory distress syndrome (ARDS)) [58]. PUTMAN et al. [31] retrospectively reviewed 227 CT scans of patients with ARDS performed before admission to the intensive care unit (ICU) (at least 7 days before), and found 19 cases (8%) with pre-existing ILA (the remaining 95 (42%) were indeterminate for ILA and 113 (50%) had normal appearances). After adjusting for age and Acute Physiology and Chronic Health Evaluation (APACHE) scores, patients with ILA had a four-fold increased risk of ARDS (OR 4.2, 95% CI 2.1–8.2; p<0.0001) and a two-fold increase of 28 days mortality (OR 2.3, 95% CI 1.2–4.2; p=0.01) [58].

The association of ILA with COPD has yet to be confirmed. Data collected from the Danish National Health Registries show that the 332 (16.7%) participants with ILA were more likely to be diagnosed with

COPD (HR 1.7, 95% CI 1.2–2.3; p=0.01) among other respiratory conditions [48]. However, a study designed specifically to address the association between COPD and ILA did not show any linkage. In COPD cases from Multicentric Italian Lung Detection trial (n=457) analysed with a nested matching case: control of 1:2 according to age, gender and smoking history, a similar frequency of definite ILA between cases and controls was shown (p=0.20), independent of the presence of signs of lung fibrosis (p=0.07) [59]. By contrast, LEE et al. [60] evaluated 363 patients with COPD, 44 and 103 having respectively equivocal and definite ILA, and showed an association between ILA and the annual incidence of moderate to severe acute exacerbations (adjusted OR 2.03; p=0.45). In summary, low-dose CT signs of lung fibrosis can also be observed in COPD, but their clinical relevance remains to be determined and recent data on associations between COPD exacerbations and the presence of ILA are conflicting [59–61].

Moderate to severe obstructive sleep apnoea syndrome (OSAS) has been associated with ILA. A cross-sectional analysis of 1690 community-dwelling adults from the MESA study revealed that an obstructive apnoea/hypopnoea index (oAHI) greater than 15 was associated with 35% increased odds of ILA (95% CI 13–61%; p=0.001). The association of oAHI greater than 15 and ILA varied slightly in relation to BMI (BMI <25 kg·m^{-2}, 2.3-fold increased odds of ILA, 95% CI 1.3–4.1; p=0.005; BMI >30 kg·m^{-2}, 1.8-fold greater odds of ILA, 95% CI 1.1–2.9; p=0.01) [62].

ILA: predisposing genetic factors and pathogenetic mechanisms

ILA and IPF share genetic features and a similar ageing-related pathogenetic disease profile. A common promoter polymorphism (rs35705950) in MUC5B, the gene encoding mucin 5B, is associated with IPF, fibrotic HP, RA-ILD and asbestosis [63–67]. In 2013, HUNNINGHAKE et al. [14] found that the same MUC5B promoter variant rs35705950 increases the odds of ILA 2.8 fold (95% CI 2.0–3.9; p<0.001), and the odds of definite CT evidence of pulmonary fibrosis 6.3 fold (95% CI 3.1–12.7; p<0.001). When narrowed to specific radiological subtypes of ILA, the MUC5B genotype remained strongly associated with a possible UIP pattern (OR 2.7, 95% CI 2.3–3.2; p=1×10^{-30}, I^2=1%), while there was no evidence for an association with the MUC5B promoter variant rs35705950 when ILA was limited to those with a centrilobular pattern (OR 0.91, 95% CI 0.63–1.3; p=1.0, I^2=15%) [68]. Recently HOBBS et al. [69]showed that among 12 previously reported IPF GWAS loci, five (DPP9, DSP, FAM13A, IVD and MUC5B) were significantly associated (p<0.05) with ILA. Moreover, novel ILA associations were not associated with IPF, IPO11 (rs6886640; p=3.8×10^{-8}) and FCF1P3 (rs73199442; p=4.8×10^{-8}) were associated with ILA, and near HTRE1 (rs7744971; p=4.2×10^{-8}) with subpleural-predominant ILA. These findings highlight both genetically driven biologic pathways common to ILA and IPF, and also suggest distinct pathways that might be linked to other fibrotic ILDs.

Recently, SANDERS and colleagues [70] addressed the link between ILA and plasma biomarkers of accelerated ageing. They showed that increasing plasma concentration of growth differentiation factor 15 (GF-15) was strongly associated with the presence of ILA (OR 3.4, 95% CI 1.8–6.4; p=0.0002) and mortality (HR 2.0, 95% CI 1.1–3.5; p=0.02), along with other less robust but still significant ageing biomarkers: tumour necrosis factor α receptor II (TNFR), interleukin-6 (IL-6) and C-reactive protein (CRP). Inflammation and ageing may contribute to the development of ILA, and the putative contribution of the immune response has been recently investigated by MACHAHUA et al. [71]. The authors showed that CD4+T-cells from ILA subjects are highly proliferative with an excessive functional activity, likely to be related to loss of KLRG1 expression, which may contribute to an inflammatory state and the development of ILA [71]. Finally, BUENDÍA-ROLDÁN et al. [35] recently reported increased serum concentrations of matrix metalloproteinases (MMPs) and resistin in ILA, with resistin significantly associated with ILA after adjustment for age, gender and D_{LCO} (AUC 0.74, OR 1.12, CI 95% 1.0–1.2; p=0.01), thus hypothesising that pro-inflammatory molecules may play a pathogenic role and may help to identify individuals who may be at higher risk of developing ILA. In this study, TERT (telomerase reverse transcriptase) and telomere shortening were not significantly associated with ILA and none of the genetic or molecular markers (MMPs, IL-6 and resistin) showed an association with progression. Whether these biomarkers are linked to ILA in general or to pre-clinical IPF ILA remains to be addressed. Given that only a minority of ILA develop IPF, these recent findings highlight the need of a future biomarker that will identify those ILA that will evolve to IPF (the so-called pre-clinical IPF ILA). The future identification of therapeutic targets and theragnostic biomarkers may be helpful in guiding treatment choices.

ILA and IPF main differences

The main difference between these two entities rests in their definition. IPF is a disease characterised by the presence of a UIP pattern in the absence of a known cause, whereas ILA is a radiological entity defined by the incidental finding of CT changes. The second most notable difference is that the prevalence of ILA is strikingly higher than the prevalence of IPF (7% versus 0.063%), a difference of over 100 fold. This

suggests that the various links to IPF may be driven by a minority of ILA cases. Thirdly, whereas IPF is always fibrotic and progressive and is defined by the presence of bibasilar honeycombing (*i.e.* radiological or pathological UIP), ILA are a heterogeneous radiological entity that can present with different CT features and distributions (subpleural or not and fibrotic or not) and variable prognosis. Unlike IPF, the histopathology of ILA remains largely unknown, with the few published studies mainly consisting of lung cancer resection specimens that might not be representative of the subpleural form of ILA. Most cases are reviewed as smoking-related changes, with fibrosis in the vast majority of cases of ILA (73%). UIP is less frequently encountered in 7–8% of ILA cases (0.5–0.7% of the total cohort) [72, 73]. Studies focusing on the histopathology of subpleural fibrotic ILA and progressive ILA are urgently needed.

Diagnostic approach and surveillance of ILA

The management plan for ILA is currently based on expert opinions and is supported by minimal evidence. The Fleischner Society document and the recently published Delphi consensus document elicited broadly similar conclusions [2, 74]. The experts of the Fleischner Society position paper suggest that the follow-up of ILA should be based on the presence of risk factors for progression. Risk factors for progression were clearly identified and grouped into clinical factors (cigarette smoking, inhalation exposure), drugs (*e.g.* chemotherapy, immune checkpoint inhibitors, radiation therapy, surgery, physiological or gas exchange findings at lower limits of normal) and radiological factors (nonfibrotic ILA with basal subpleural predominance, fibrotic ILA with a probable UIP radiological pattern, and ILA with a UIP radiological pattern). Individuals with subpleural fibrotic ILA should be further categorised according to the recently published diagnostic categories for UIP, typical UIP, probable UIP, indeterminate, and is suggestive of an alternative diagnosis [4, 75]. The uncertain relationship between ILA and subsequent development of IPF applies especially to ILA that are limited in extent (*e.g.* subpleural reticulation without overt signs of lung fibrosis). However, typical UIP or a probable UIP pattern may be found in patients with ILA without symptoms, and have a much higher IPF diagnostic likelihood [75].
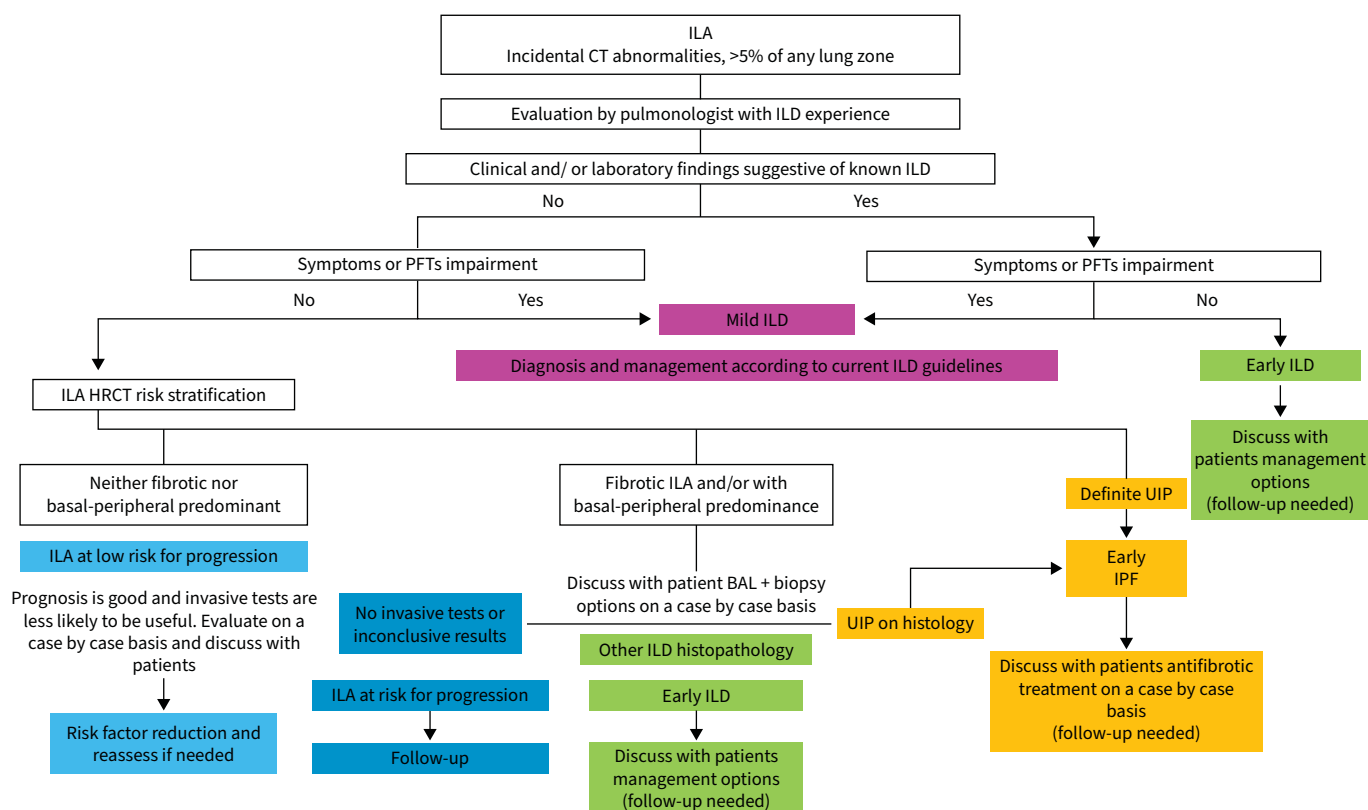
FIGURE 4 Proposed algorithm for diagnosis and management of interstitial lung abnormalities (ILA), early interstitial lung disease (ILD) (both subclinical and pre-clinical) and mild ILD. BAL: bronchoalveolar lavage; CT: computed tomography; HRCT: high-resolution computed tomography; IPF: idiopathic pulmonary fibrosis; PFT: pulmonary function test; UIP: usual interstitial pneumonia.

One issue open for debate is whether semi-invasive or invasive procedures such as bronchoalveolar lavage (BAL), transbronchial biopsy, cryobiopsy and surgical lung biopsy have clinical utility. Discussing the safety and diagnostic yield of these techniques is outside the scope of this manuscript. Based on the literature and on our experience, transbronchial lung cryobiopsy can be safely used in expert hands to ascertain the histology type of ILD. As shown in figures 1 and 4, asymptomatic individuals, with apparently normal pulmonary function and no clinical or laboratory signs suggestive of a specific ILD, can have subclinical IPF or other ILDs. The decision to perform BAL or lung biopsy should be carefully balanced and discussed with patients on a case by case basis. In those cases, the ILA HRCT appearance is most helpful to guide the clinical suspicion and eventually the choice of invasive test. ILA lacking both fibrosis and subpleural distribution have a good prognosis and invasive tests are less likely to give useful information. Patients with fibrotic ILA and with basal and peripheral distribution are at higher risk of progression and may have subclinical IPF or ILD: in this setting lung biopsy is most useful to properly diagnose IPF or specific ILDs, and BAL can add useful information in the context of the multidisciplinary team (MDT) discussion. Finally ILA patients with HRCT UIP pattern that are reclassified by the MDT as subclinical IPF can be managed accordingly without the need for invasive tests. In those patients that do not undergo invasive tests, or in whom biopsy and BAL results are inconclusive, the physician can follow the Fleischner Society ILA recommendations. Individuals without risk factors do not require follow-up and are advised to return for evaluation if they develop symptoms. Individuals with one or more risk factors should be followed, but the appropriate evaluation (pulmonary physiology, symptoms, HRCT) and timing are currently unknown. Both the Fleischner Society paper and the recent Delphi Survey suggest performing the first follow-up at 12 months at least (3–12 months for the Fleischner and 6–12 months for the Delphi consensus) [2, 74]. The majority of Delphi participants recommended full pulmonary function tests with split opinions on repeating HRCT. The Fleischner Society statement recommends repeating CT at 12–24 months or sooner in case of symptomatic or pulmonary function test (PFT) progression. The Fleischner Society paper defines ILA progression as the development of respiratory symptoms and signs (*e.g.* exercise limitation, crackles on auscultation), the development of abnormal pulmonary physiology or gas exchange or an increase in the extent of CT abnormalities, particularly with the development of specific fibrotic features. ILA should be regarded as an important comorbidity particularly in those individuals exposed to a risk of pulmonary toxicity (*e.g.* radiotherapy, chemotherapy, immune checkpoint inhibitors) [2]. The Delphi panel agreed on the need for radiologists to standardise the reporting of ILA on lung cancer screening scans (Lung-RADS "S-modifier") and to recommend pulmonologist referral in cases with honeycombing [74]. For individuals known to be at risk, that are not considered to have ILA but pre-clinical ILD based on current Fleischner Soc definition, the Delphi group reached a consensus regarding the need for screening for ILD in patients aged >50 years in the setting of systemic sclerosis and in patients with more than one relative affected by ILD [74]. All individuals with symptoms or pulmonary physiological abnormalities ascribable to ILD or extensive CT abnormalities (*i.e.* disease involving three or more of the six lung zones) should be referred for pulmonologist evaluation and managed as ILD following standard guidelines [2].

The caution of current expert recommendations reflects the uncertainty on the trajectory of ILA progression that needs to be clarified by large prospective studies. However, based on current data, it appears likely that a subgroup of patients with subpleural and/or fibrotic ILA develop IPF, progressive fibrotic ILDs or autoimmune diseases. If so, restricting follow-up to patients believed to be at higher risk might delay the early diagnosis of ILD in some cases, losing a window of opportunity for timely treatment. As previously shown in IPF [12, 13], it is possible that early treatment of fibrotic/subpleural ILA could reduce the rate of disease progression and mortality. One limit for the practical application of the current documents is inherent to ILA definition: a radiological entity is difficult to manage [76, 77]. When subjects with ILA are evaluated by the ILD pulmonologist (or by the multidisciplinary team), the radiological findings are integrated with the dynamic clinical scenario and subsequent decisions are be based on diagnostic conclusions. In the mind of the clinician, the subject is always, even if only potentially, a patient. Below we offer some food for thought comparing the focus of current documents with a pragmatic clinical approach.

First, in the correct clinical scenario a case of incidental CT findings of basal subpleural honeycombing (*i.e.* radiological definite UIP pattern) can be diagnosed as subclinical IPF and treated accordingly [4, 5]. Second, in the correct clinical scenario, cases with subpleural fibrotic changes could represent IPF with early HRCT findings (*i.e.* probable UIP or indeterminate for UIP): in this setting, other investigations and, particularly, lung biopsy, might help to refine the diagnosis and the subsequent management of cases [4, 5, 78]. Third, irrespective of the radiological feature of ILA, any case with an autoimmune flavour should be promptly evaluated by a rheumatologist [79]. All other cases with nonfibrotic nonsubpleural lesions and a completely silent clinical and laboratory evaluation can be discharged from follow-up and seen again in case of worsening. The algorithm we currently use in our clinical practice is shown in figure 4. The algorithm and our thoughts should not be viewed as recommendations, they simply arise from our clinical

experience, and lack validation. We acknowledge that there are resource limitations in many settings, limiting the access of patients with ILA to expert ILD evaluation. Moreover, it is important to underline that early initiation of medication in subclinical ILDs has not been explored in robust trials, has potential adverse events and costs that should be carefully balanced.

The clinical meaning of ILA has yet to be fully disclosed. We need to understand whether fibrotic ILA have a poor prognosis only in a minority of cases or in a large proportion of cases in the longer term. Moreover, it remains unclear whether the mortality of fibrotic ILA is linked mainly to evolution to IPF or to other age-related diseases. In any case, the links between ILA and IPF suggest strongly that early IPF makes up a significant proportion of fibrotic ILA and, hence, there is an urgent need for a biomarker that accurately predicts evolution to IPF. One current biomarker that may identify early IPF, as opposed to other fibrotic ILA, is the presence of a UIP pattern. In cases that lack UIP on HRCT, UIP can be documented histologically. Mini-invasive biopsy techniques such as transbronchial lung cryobiopsy (TBLC) can be helpful in discriminating early IPF from ILA. The safety and feasibility of TBLC have been reported in several studies that included early ILD cases mixed with more advanced cases: thus, studies designed to evaluate the accuracy of TBLC in early ILDs and ILA are needed [30, 80–87]. Innovative guidance systems for TBLC are currently under investigation and may open new scenarios for a safer and more accurate diagnosis of cases with limited disease extent on HRCT [88].

In conclusion, the currently recommended management of ILA consists of following-up at risk patients. However, this wait-and-see approach is based on weak evidence. Better characterisation of ILA, leading to a timely diagnosis of ILD, is needed to predict the functional trajectory and choose early optimal treatment. Perhaps precision medicine will help in the future, if it transpires that clinical decisions are eventually based mainly on genetic and molecular signature of diseases. In the meanwhile, to better inform our management decisions, instead of marking time waiting for the "big leap forward" that is precision medicine, we might usefully attempt to translate the nondiagnosis of an ILA label into an established diagnosis of pre-clinical ILD using the tools that we currently have, including mini-invasive lung biopsies in selected cases.

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