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Interstitial lung abnormalities – current knowledge and future directions

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ABSTRACT

Efforts to grasp the significance of radiologic changes similar to interstitial lung disease (ILD) in undiagnosed individuals have intensified in the recent decade. The term interstitial lung abnormalities (ILA) is an emerging definition of such changes, defined by visual examination of computed tomography scans. Substantial insights have been made in the origins and clinical consequences of these changes, as well as automated measures of early lung fibrosis, which will likely lead to increased recognition of early fibrotic lung changes among clinicians and researchers alike.

Interstitial lung abnormalities have an estimated prevalence of 7–10% in elderly populations. They correlate with many ILD risk factors, both epidemiologic and genetic. Additionally, histopathological similarities with IPF exist in those with ILA. While no established blood biomarker of ILA exists, several have been suggested. Distinct imaging patterns indicating advanced fibrosis correlate with worse clinical outcomes. ILA are also linked with adverse clinical outcomes such as increased mortality and risk of lung cancer.

Progression of ILA has been noted in a significant portion of those with ILA and is associated with many of the same features as ILD, including advanced fibrosis. Those with ILA progression are at risk of accelerated FVC decline and increased mortality. Radiologic changes resembling ILD have also been attained by automated measures. Such measures associate with some, but not all the same factors as ILA.

ILA and similar radiologic changes are in many ways analogous to ILD and likely represent a precursor of ILD in some cases. While warranting an evaluation for ILD, they are associated with poor clinical outcomes beyond possible ILD development and thus are by themselves a significant finding. Among the present objectives of this field are the stratification of patients with regards to progression and the discovery of biomarkers with predictive value for clinical outcomes.

Introduction

The radiologic changes and physiologic changes seen in interstitial lung diseases such as idiopathic pulmonary fibrosis are extensive [1]. This has bred the theory that a pathophysiological process of pulmonary fibrosis precedes clinical symptoms or full-blown disease, which is a theory that is at least several decades old [2]. Efforts to identify people with abnormalities suggestive of early forms of interstitial lung disease (ILD) have been made possible by the advent and greatly increasing use of CT imaging. Such abnormalities were first searched for, and found in, asymptomatic relatives of patients with familial pulmonary fibrosis [3]. Later, efforts were made to identify similar abnormalities in population cohort studies [4,5]. Various terms have been used to describe these radiographic abnormalities; 'the dirty lung', 'preclinical interstitial lung disease',

and 'subclinical interstitial lung disease' are all terms that have been used in this purpose. [4,6,7] The term 'interstitial lung abnormalities' (ILA), first used in this purpose by Washko et al. in 2011 [5], has however gained a foothold in the literature in the last decade as a term for visually detected changes of this sort [8–11]. Automated measures have also been used to detect early forms of fibrotic lung changes, with the term 'high attenuation areas' (HAA), most often used for such endeavours [4,12]. An increasing number of cohort-based studies has been published in the years since that examine the significance of radiologic changes suggestive of early ILD. This has been done in a variety of cohorts, both general population-based and cohorts of smokers or lung cancer screening cohorts. This led to the Fleischner Society publishing a uniform definition of interstitial lung abnormalities

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in a Position paper by Hatabu et al. [13]. This definition and increased recognition of early forms of interstitial lung disease, in tandem with the ever-increasing use of CT scans in disease diagnosis and screening, will likely lead to more reports of such changes to clinicians and more awareness among researchers of ILD. Here, a review of the current status of knowledge of interstitial lung abnormalities and related radiologic markers of early pulmonary fibrosis is presented.

Definition and prevalence of interstitial lung abnormalities

While precise definitions of ILA have varied between studies [5,11,14–16], the definition proposed by Washko et al. [5] defined ILA as non-dependent changes that affect more than 5% of any lung zone that include ground-glass or reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, honeycombing, and traction bronchiectasis [5,8] with areas meeting criteria for emphysema not included in these estimations. Changes present in less than 5% of lung zones consisting of focal or unilateral ground-glass attenuations, focal or unilateral reticulation, and patchy ground-glass abnormalities have been defined as indeterminate for ILA [5]. The significance of these indeterminate changes is unclear since these participants are not regarded as having ILA and are most often excluded from studies of ILA. However, indeterminate changes have been found to be more common than changes meeting criteria for ILA [5,8]. Other definitions of ILA are based on similar radiologic criteria counting areas with fibrosis, honeycombing, traction bronchiectasis, ground-glass, reticular abnormalities, centrilobular nodules, and more, but precise definitions of extent and reading methods somewhat varied [11,14–16]. Many such papers also reported more minor changes with unclear significance, entitling them as 'indeterminate' or 'equivocal' [14,15]. Recently, a uniform definition for ILA has been accepted in a Fleischner Society position paper, which largely complies with the definition used by Washko et al. in 2011, with the exception that centrilobular nodules have been excluded from the term [13]. Dependent lung atelectasis, interstitial oedema, focal paraspinal fibrosis, and mild focal abnormalities such as findings of aspiration are not included in the ILA term [13].

The prevalence of interstitial lung abnormalities is variable and related to the age of the population examined as well as the frequency of smoking. In general population-based cohorts in which the mean age of participants with ILA was 70 years or older, the prevalence of ILA has been reported between 7 and 10% [8,16,17]. Among cohorts of smokers or lung cancer screening cohorts, however, the prevalence of ILA has been found to range from 4 to 20% [5,8,14,15,18–20]. While these numbers are similar to prevalence rates in the general population-based cohorts it should be noted that the mean age of participants with ILA in the cohorts of smokers ranged from 60 to 66 years, approximately 10 years younger than in the general population-based cohorts.

Epidemiological associations and parallels with interstitial lung disease

Studies of interstitial lung abnormalities have established many parallels of ILA with advanced ILD. Age is a cardinal risk factor of ILD and participants with ILA are older than participants without abnormalities [5,8]. Cigarette smoking, which is also strongly related to idiopathic pulmonary fibrosis (IPF) risk is associated with ILA, i.e. both smoking at time of examination and amount of smoking over participants' lifetimes [8], as well as reduced diffusion capacity for carbon monoxide (DL_{CO}) and reduced oxygen saturation [17]. Smokers with ILA also have increased odds of a restrictive lung deficit, decreased lung volumes, and decreased emphysema compared to their peers [5]. Still, COPD patients with ILA have higher rate of COPD exacerbations and accelerated lung function decline compared to others [21]. Measures of airway thickness are increased in both ILA and IPF [22] and CT detected vascular pruning, an indicator of decreased volume of pulmonary blood vessels, is associated with increased odds of ILA [23]. Furthermore, ILA is associated with several risk factors for IPF. Among those is obstructive sleep apnoea [24], air pollution due to elemental carbon and nitrogen oxides and occupational exposure to vapours, gas, dust, and fumes [11,25,26]. Lastly, while IPF has been associated with herpesvirus infections [27], infection with human immunodeficiency virus (HIV) has been associated with ILA [28].

In terms of genetics, the rs35705950 promoter polymorphism of the *MUC5B* gene, the best-established single genetic risk factor for IPF [29], has been shown to be strongly associated with ILA [30,31]. In addition, ILA and/or subpleural ILA have been linked with polymorphisms in *DPP9, DSP, FAM13A, MAPT,* and *IVD*, all previously associated with IPF, as well as polymorphisms near *IPO11, FCF1P3,* and *HTRE1* [31]. Supporting these genetic associations, ILA are much more common in relatives of patients with both familial pulmonary fibrosis and sporadic pulmonary fibrosis than in the general population [32]. In addition, the

histopathological appearance of lung tissue in patients with ILA has been evaluated, using tissue samples from lung nodule resections. Patients with ILA were shown to be more likely to have several types of histopathological changes commonly seen in IPF [33]; i.e. subpleural fibrosis, fibroblastic foci, honeycombing, and the usual interstitial pneumonia pattern in addition to atypical adenomatous hyperplasia [34]. In a similar study, it was demonstrated that patients with pathological abnormalities are more likely to have radiologic ILA than others [35]. Therefore, ILA have been associated with the main epidemiological and genetic risk factors of pulmonary fibrosis and share histopathological features with these conditions.

Potential IPF biomarkers have been found to be related with ILA. Matrix metalloproteases (MMPs) and Galectin-3, markers elevated in IPF patients, are elevated in cohort study participants with ILA [17,36–39]. In addition, among familial interstitial pneumonia patients, those with ILA have been found to have shorter telomeres in peripheral blood than those without ILA [40]. Among other possible biomarkers, the adhesion molecule sICAM-1 has been associated with ILA [41] as well as pro-inflammatory molecule resistin [17]. Additionally, leptin and the metabolites phosphatidylcholine, phosphatidic acid, betaine aldehyde, phosphatidylethanolamine, and 1-acylglycerophosphocholine [42–44] have been linked with ILA and certain microRNAs, in particular miR-193a-5p and miR–502–5p, have been shown to be upregulated in ILA and suggested as ILA biomarkers [45]. Rheumatoid arthritis (RA) related autoantibodies and anti-cyclic citrullinated peptide have been associated with ILA among smokers and rheumatoid factor IgA are associated with ILA regardless of smoking history [46]. Lastly, vitamin D deficiency and the use of hydrophilic HMG-CoA reductase inhibitors (statins) has been linked with ILA, while the omega-3 polyunsaturated fatty acid docosahexaenoic acid is negatively associated with ILA [44,47,48].

Imaging patterns

Participants with ILA have also been evaluated for certain imaging patterns such as the definite fibrosis pattern and the usual interstitial pneumonia (UIP) pattern, and important associations of ILA differ depending on those patterns. In these studies, the definite fibrosis pattern was defined as the presence of pulmonary parenchymal architectural distortion (such as traction bronchiectasis and/or honeycombing) that are consistent with a fibrotic lung disease. The definition used for the UIP pattern was the same as published by the Fleischner Society [49,50]. The association of ILA with the definite fibrosis pattern with the rs35705950 promoter polymorphism of the *MUC5B* gene is stronger than that of ILA without definite fibrosis. This association is also stronger among patients with ILA and possible UIP or UIP patterns than among patients with ILA that are inconsistent with the UIP pattern [51]. In a longitudinal study, both definite fibrosis and the UIP pattern were associated with increased risk of mortality. The same can be said for certain imaging features; that is non-emphysematous cysts and traction bronchiectasis [50].

Clinical outcomes

In addition to risk factors and biomarkers, ILA have been linked with poor health outcomes. First and foremost, ILA have been associated with increased risk of mortality of all causes in several research cohorts [8,10]. In one of these cohorts, ILA were related with an increased risk of death from a respiratory cause and, among those, with an increased risk of death from pulmonary fibrosis [8]. In addition to mortality, ILA have been associated with several disease processes. A lung cancer screening study has found an increased risk of ILD diagnosis among participants with ILA [19]. Patients with ILA have been found to have decreased odds of COPD and decreased COPD severity in a cohort study [5]. Still, a later case-control study among smokers failed to show a significant association with COPD and a lung cancer screening study has suggested increased risk of COPD diagnoses among participants with ILA [19,52]. Another study has associated ILA with Group B of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of COPD [53]. While associations with COPD differ, ILA have been positively associated with paraseptal emphysema, a subtype of emphysema that is not associated with airflow obstruction and is of largely unknown clinical significance [54]. What's more, an increased risk of acute respiratory distress syndrome (ARDS) among critically ill patients in the intensive care setting has been linked with ILA [55], smokers with ILA have been shown to have decreased 6-minute walking distance [56] and participants with ILA in a general-population cohort had worse performance in various tests of decreased physical function and worse self-reported health and functional status than their peers [57,58].

Lung cancer screening studies or retrospective studies of lung cancer patients have consistently found participants with ILA to be at increased risk of lung cancer and lung cancer mortality [10,19,20,59–64].

Findings from a general-population cohort support these findings [65]. While ILA and lung cancer share certain risk factors, such as age and smoking, the association between these conditions has been established even after correction for those factors. Additionally, although no definitive mechanisms connecting ILA and lung cancer have been elucidated, similarities in the pathogenesis of lung cancer and interstitial lung disease have been pointed out. Thus, the reasons for the association of ILA and lung cancer are not fully clear and future research must clarify whether it is a result of residual confounding or biological mechanisms [20,65]. On that note, ILA have been found to be a risk factor for postoperative complications after lung cancer surgery, such as ARDS, pneumonia and respiratory failure [66] as well as severe radiation pneumonitis after radiation for small cell lung cancer [67,68] and immune checkpoint inhibitor-induced interstitial lung disease among patients with lung cancer and other malignancies [69,70]. Among other outcomes associated with ILA in lung cancer screening studies are diagnoses of pneumonia, pleural empyema or lung abscesses, and respiratory failure [19]. Rheumatoid arthritis (RA) is another major disease associated with the prevalence of ILA and their progression. In this group, patients with ILA have had more respiratory symptoms, more severe RA, a restrictive pattern on pulmonary function testing and reduced exercise capacity [71–73]. These associations of ILA with various clinical outcomes are listed in Table 1 along with other known associations of ILA.

Progression of ILA

Longitudinal studies exist that examine imaging progression of ILA over time. Progression of ILA has been noted in 73–76% of participants with ILA over 5 years of follow up [50,74]. Still, studies with a follow up of 2 years, albeit with younger participants and a slightly differing definition of ILA, have found that a much lower proportion of participants progress over that time [14,18]. Progression to ILD has been found to be common among relatives of familial interstitial pneumonia patients with ILA [40].

Risk of ILA progression is positively associated with several features such as age, smoking at the time of the study, and the rs35705950 promoter polymorphism of the MUC5B gene [50,74] while the directionality of the relationship of body mass index with ILA progression has varied between studies [50,74]. In addition, exposure to elemental carbon has been associated with ILA progression as well as gastroesophageal reflux [17,25]. In terms of imaging patterns, the definite fibrosis pattern, and both probable and definite UIP patterns are strongly associated with ILA progression [14,50]. In terms of imaging patterns, the definite fibrosis pattern, and both probable and definite UIP patterns are strongly associated with ILA progression [14,50]. Distinct features such as subpleural reticular markings, non-emphysematous cysts, changes predominantly in the lower lobe, and traction bronchiectasis are themselves associated with progression and progression of traction bronchiectasis is associated with poorer survival among those with ILA [50,75]. As with ILA odds in general, pruning of pulmonary vessels on CT is linked with greater odds of progression [23]. As for the possible consequences of ILA progression, participants with progression have accelerated FVC decline over time and increased mortality compared with both participants without ILA and participants with ILA but without progression [50,74]. Table 2 contains a list of the known associations of ILA progression.

Other definitions of ILD precursors

Assessment of changes on CT imaging believed to be precursors of interstitial lung disease that are defined using automated measures has also been undertaken. One such measure are high attenuation areas (HAA), defined as areas within the lung fields with a CT attenuation value between −600 and −250 Hounsfield Units (HU) [4]. Changes resembling early ILD found using this quantitative assessment have been associated with some of the same factors as the qualitatively assessed ILA. Some of the major factors associated with HAA are cigarette smoking, lower forced vital capacity, exertional dyspnoea, air pollutants in form of nitrogen oxides, shorter 6-minute walk distance and higher all cause-mortality [4,26,76,77]. In a genome-wide association study, genes related to obesity (GNPDA2, ZNF664, FAM101A, PFKP, SAMD4A), glycoproteins, carbohydrate metabolism, and glycosylation (GYPC, FUT10, GNPDA2, PFKP, SLC45A), embryonic development (FOXP4), and cell adhesion (ALCAM) have been associated with HAA [78].

HAA have been linked with proposed biomarkers of lung fibrosis as well as other biochemical measurements. The markers that have been associated with these changes are higher levels of matrix metalloprotease-7, inflammatory cytokine IL-6, and collagen biomarkers, carboxy-terminal telopeptide of collagen type I, and amino-terminal propeptide of type III procollagen in serum [76,79]. In addition, the adhesion molecules sICAM-1, sVCAM-1, and P-selectin have been associated with HAA. Moreover, RA-related autoantibodies, rheumatoid factor IgM and IgA, have also been

Table 1. The epidemiological associations of interstitial lung abnormalities.

Feature associated with interstitial lung abnormalities	Citation (s)
Risk factors of idiopathic pulmonary fibrosis	
Age	[5,8]
Pack-years of smoking	[5,8]
The rs35705950 promoter polymorphism of the MUC5B gene	[30,31]
Polymorphisms in *DPP9, DSP, FAM13A, MAPT*, and *IVD*	[31]
Family relationship with pulmonary fibrosis patients	[32]
Polymorphisms near *IPO11, FCF1P3*, and *HTRE1*	[31]
Obstructive sleep apnoea	[24]
Airway pollution from elemental carbon	[25]
Residential exposure to vapours and fumes	[26]
Exposure to vapours/gas	[11]
Biomarkers	
Galectin-3	[37]
Matrix metalloproteases	[17,39,9798]
Resistin	[17]
Soluble intracellular adhesion molecule (sICAM)-1	[41]
Phosphatidylcholine, phosphatidic acid, betaine aldehyde, phosphatidylethanolamine, and downregulated phosphatidylethanolamine	[42]
Upregulation of certain microRNAs	[45]
Rheumatoid factor IgA	[46]
Rheumatoid factor IgM and anti-CCP among smokers	[46]
Leptin among never smokers	[43]
Clinical and pathologic findings	
Histopathologic findings of fibrosis	[34,35]
Reduced total lung capacity	[5]
Lesser amount of emphysema	[5]
Decreased physical function	[56,58]
Worse functional status	[57]
Paraseptal emphysema	[54]
Increased airway wall thickness	[22]
CT vascular pruning and lower pulmonary blood vessel volume	[23]
Vitamin D deficiency	[47]
Statin use	[48]
Lower levels of docosahexaenoic acid	[44]
HIV infection	[28]
Clinical outcomes	
All-cause mortality	[8,10,19]
Death from a respiratory cause	[8]
ILD diagnosis	[19]
Acute respiratory distress syndrome	[55]
Lung cancer	[20,59,62]
Mortality due to lung cancer among smokers	[10,19,20]
Mortality from cancers other than lung cancer among smokers	[19]
Various respiratory outcomes (pneumonia, pleural empyema, lung abscesses, respiratory failure among smokers)	[10]
Increased rate of COPD exacerbations	[21]
Lung volume decline in COPD patients	[21]
Shorter survival among non-small cell lung cancer patients	[60,61,63,64]
Treatment complications among lung cancer patients	[66–69]
Rheumatoid arthritis	[71–73]
More severe arthritis and respiratory symptoms among rheumatoid arthritis patients	[71,72]

Table 2. The associations with progression of interstitial lung abnormalities.

Feature associated with progression	Citation (s)
Age	[50,74]
The rs35705950 promoter polymorphism of the MUC5B gene	[50,74]
Smoking at the time of study	[74]
Gastroesophageal reflux	[17]
Imaging features (subpleural reticular markings, non-emphysematous cysts, traction bronchiectasis, lower lobe predominance, less centrilobular nodules)	[50]
The definite fibrosis and usual interstitial pneumonia imaging patterns	[50]
A decline in forced vital capacity (FVC)	[74]
CT vascular pruning and lower pulmonary blood vessel volume	[23]
All-cause mortality	[50,74]

have been associated with HAA while an association with ILA was not shown [81]. The associations of HAA with MMP-7, all-cause mortality, and IL-6 have been validated and found to be consistent across all lung regions [82].

Efforts have been made to assess the relationship of HAA with qualitative measures of early ILD, ILD diagnoses, and ILD-related outcomes. HAA correlate with qualitatively assessed ILA, although positive predictive values of HAA for ILA were not very high in a comparison study [9,76]. This is true for HAA independent of lung area [82]. In spite of this, HAA were not found to be associated with the rs35705950 variant in the *MUC5B* promoter polymorphism, the strongest known genetic risk factor for IPF [9]. Still, HAA have been associated with hospitalisations from ILD and ILD-specific mortality [82,83].

In addition to HAA, other attempts at automating ILA detection have been made. An automatic method involving local histogram analysis and distance from the pleura has been found to correlate decently with ILA (area under the receiver operating characteristic curve [AUROC] 0.82) and even better with ILA with definite fibrosis (AUROC 0.89) [84]. Amounts of interstitial changes measured by this method are associated with FEV_1 and FVC, quality of life, an increased risk of mortality and the rs35705950 promoter polymorphism in *MUC5B* [85]. Using yet another method, interstitial lung changes found with automated reading have been associated with worse disease-free survival in a cohort of patients that had undergone lung cancer resection [86]. In addition to measurements of lung tissue density, machine learning methods to detect early forms of pulmonary fibrosis seem to be on the horizon. A recent article has been published in which an ensemble of convolutional neural networks is used to detect ILA and does so with greater accuracy than other automated methods mentioned here. The AUROC for

associated with HAA, with associations modified by cigarette smoking. Similarly, another RA-related autoantibody, anti-cyclic citrullinated peptide, has been associated with HAA in the subgroup of smokers [46]. As with ILA, vitamin-D deficiency has been associated with HAA and HAA progression [47] and HAA have been related to lower HDL-C, ApoA-1, and serum adipokines [43,80]. Amounts of rice in diet, a proposed surrogate for arsenic exposure among urban residents,

Table 3. Epidemiological associations of automated measures of ILD precursors.

Feature associated with automated measures of ILD precursors	Citation (s)
High attenuation areas (HAAs)	
Pack-years of smoking	[4]
Lower forced vital capacity (FVC)	[76,82]
All-cause mortality	[76,82]
Hospitalisations from ILD	[83]
ILD-specific mortality	[82,83]
Interstitial lung abnormalities	[76,82]
Exertional dyspnea	[77]
Reduced exercise capacity	[76]
Matrix metalloprotease-7	[76,82]
Interleukin-6	[76,82]
Carboxy-terminal telopeptide of collagen type I and amino-terminal propeptide of type III procollagen	[79]
ICAM-1, VCAM-1, and P-selectin	[41]
Rheumatoid factor IgM and IgA and anti-CCP	[46]
Lower levels of HDL-C and ApoA-1	[80]
Lower levels of adiponectin	[43]
Higher levels of D-dimer	[89]
Pericardial and visceral adipose tissue	[90]
Resistin	[43]
Genetic markers (*GNPDA2, ZNF664, FAM101A, PFKP, SAMD4A, GYPC, FUT10, GNPDA2, PFKP, SLC45A, FOXP4, ALCAM*)	[78]
Exposure to ambient nitrogen oxides	[26]
Vitamin D deficiency	[47]
Daily rice consumption	[81]
Normal appearing areas of high attenuation	
Lower forced expiratory volume (FEV1)	[88]
Reduced exercise capacity	[88]
All-cause mortality	[88]
Higher C-reactive protein	[88]
Higher ICAM-1	[88]
Other objective assessment methods of interstitial changes	
Lower FVC, FEV1, and quality of life, increased all-cause mortality and the rs35705950 promoter polymorphism of MUC5B	[85]
ILA and worse disease-free survival among lung-cancer patients	[86]

prediction of visually assessed ILA was 0.86 using this method [87]. Another study used a K-nearest neighbour algorithm to identify areas of high attenuation that appeared normal in visual analysis. Smoking at the time of study, lower FEV1, lower FVC, shorter 6-minute walking distance, greater amounts of CRP and ICAM1, and increased mortality were associated with larger proportions of such normal-appearing high attenuation areas in the lungs of participants [88]. Known associations of HAA and other automated measures of early ILD are summarised in Table 3.

Summary and future directions

Interstitial lung abnormalities have many parallels with advanced forms of interstitial lung disease. They are associated with some of the cardinal epidemiologic, environmental, and genetic risk factors of ILD as well as some proposed biomarkers and histopathological features of ILD [5,25,31,34,37,39]. Associations have been found to differ among different imaging patterns, with stronger genetic associations and worse outcomes observed for imaging abnormalities that are extensive enough to meet criteria for ILD diagnosis among symptomatic people [5]. ILA progression has been observed and the odds of progression have been found to be increased with genetic risk factors of ILD and imaging features suggestive of more advanced fibrosis [50,74]. Aside from their relationship with ILD, ILA seem to give rise to adverse clinical outcomes, most notably lung malignancies and increased mortality [8,10,65]. So, the proposition that some or all of the changes that the ILA term encompasses represent possible precursors, or early stages, of ILD [91] are strengthened by the body of research reviewed here. In addition, the outcomes associated with ILA suggest that they can by themselves be a relevant clinical finding.

For this reason, calls have recently been made that the finding of ILA on CT in clinical practice warrants evaluation for ILD and a review of risk factors for progression of ILA. A Fleischner Society position paper recommends that patients in which ILA are identified are undergo a review of symptoms and ILD risk factors, a physical exam, and pulmonary function testing (PFT) to exclude clinically relevant ILD. Clinicians are encouraged to systematically follow-up patients with clinical or radiologic risk factors for ILA progression, re-evaluation based on symptoms is recommended for low-risk patients [13]. A recent survey among clinicians with ILD expertise adds to these recommendations. In this survey, a consensus is reached that the presence of ILA warrants evaluation with PFT and high-resolution CT imaging. Additionally, a consensus was reached that honeycombing and traction bronchiectasis were indicative of a potentially progressive ILD and warrant an assessment with a pulmonologist irrespective of PFT results. The survey recommends follow-up of patients with ILA but no PFT abnormalities, but consensus regarding the type was not reached. Additionally, a consensus was reached that radiologists reading lung cancer screening images should report honeycombing and traction bronchiectasis as a clinically significant or potentially significant finding (Lung Imaging Reporting and Data System S-modifier) and recommend a referral to a pulmonologist [92].

The current literature regarding ILA brings up several possible applications of the ILA term. The potential for early detection or prevention of ILD is an obvious and compelling possibility that is a longstanding focus among researchers of early radiologic changes resembling pulmonary fibrosis [91,93]. The dire prognosis of the most common of interstitial lung diseases such as idiopathic pulmonary fibrosis highlights the

potential impact of this possibility [91] and adding weight to this is the relatively recent development of therapies that modify the disease progression of idiopathic pulmonary fibrosis [94,95]. However, the previously mentioned difference in incidence of ILA and ILD is a predictable obstacle to this approach, since it likely is not cost-effective or beneficial to treat, or aim preventive measures at, everyone with ILA. Therefore, finding factors that predict the progression of ILA to ILD will be vital for this approach. Although some work has been done in this respect, especially regarding radiographic features and patterns [50], the identification of more epidemiological, genetic, and biochemical risk factors of ILA progression should prove essential. A blood-based biomarker of ILA progression would be especially valuable due to the ubiquity of biochemical measurements of blood samples in clinical work. Such work could pave the way for stratification or subtyping of people with ILA based on their risk of progression.

Another possible application is acquiring insights into the pathobiology and risk factors of the rare idiopathic interstitial pneumonias by exploring the relatively common changes that are ILA. The rarity of diseases such as IPF, with estimates of prevalence ranging from 14 to 63 per 100,000 [96,97], makes it difficult to study risk factors of these diseases in cohort studies. In comparison, ILA and other measures of preclinical ILD have been found to have a prevalence that is orders of magnitude greater than that of IPF [8,10]. Participants in major cohort studies, for which extensive genotypic and phenotypic information have been made available, have been characterized with regards to the presence of ILA or other measures of subclinical ILD [4,8]. This, in addition to a growing number of computed tomography-based lung cancer screening studies that have added ILA to their study of pulmonary nodules [10,14,18,20] allows for the study of genetic and epidemiological risk factors of fibrotic pulmonary disease in more research settings with more research subjects than previously possible.

There are several challenges in future research of ILA. The universal adoption of the definition of interstitial lung abnormalities proposed recently by the Fleischner Society [13] is necessary for useful comparison of different studies of ILA, not only ILA in general but also for different subtypes and imaging patterns. Research of different subtypes and patterns using such a classification is needed since ILA encompasses a non-uniform set of changes that are likely to confer risks of different endpoints. Because of this heterogeneity, reproduced studies that provide robust information on which epidemiological and radiographic

characteristics confer increased risk of progression should prove vital in determining which patient populations are likely to progress. Clinical studies on how to best assess and follow-up patients with ILA, complementing a recent expert survey [92], are also necessary. Biomarkers that could provide insight into which patients are at risk should be a priority of these studies, especially blood-based biomarkers due to the accessibility of such markers and their ubiquitous use in clinical practice. It is possible that the usefulness of biomarker studies of ILA could, in addition to predicting ILA progression and ILD-related mortality, extend to predicting other serious clinical outcomes associated with ILA, such as malignancies and all-cause mortality. This is important because the increased mortality risk among those with ILA is too great to be only explained by undiagnosed progressive ILD, urging the need for further research of clinical endpoints associated with ILA. An evaluation of the possible endpoints of automated measures of ILA precursors with regards to progression could also prove valuable as automated measures are easier to screen for en masse than ILA. On that note, machine learning could prove pivotal in automating both the diagnosis of radiologic signs such as ILA as well as the identification and risk stratification of patients at risk of ILA progression, other morbidities, or mortality.

In conclusion, ILA and related terms encompass a set of changes that are similar to ILD but have a much greater prevalence. They share risk factors of ILD and likely represent a precursor of ILD in some cases but by themselves they confer increased risk of mortality, malignant disease, and other morbidities as well as complications of medical treatment.

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Dr. Axelsson is an internal medicine resident at Landspitali University Hospital, Iceland and a PhD student at the University of Iceland and the Icelandic Heart Association. The focus of his studies has been interstitial lung abnormalities, about which he has published several studies.

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Contributorship

GTA and GG both contributed to the design and concept of the paper and the writing and revision of the manuscript.

References

[1] Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–11.

[2] Bitterman PB, Rennard SI, Keogh BA, et al. Familial idiopathic pulmonary fibrosis. evidence of lung inflammation in unaffected family members. N Engl J Med. 1986;314(21):1343–1347. published Online First: 1986/05/22.

[3] Rosas IO, Ren P, Avila NA, et al. Early interstitial lung disease in familial pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176(7):698–705.

[4] Lederer DJ, Enright PL, Kawut SM, 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(5):407–414.

[5] Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011;364 (10):897–906. published Online First: 2011/03/11.

[6] Guckel C, Hansell DM. Imaging the 'dirty lung'–has high resolution computed tomography cleared the smoke? Clin Radiol. 1998;53(10):717–722. published Online First: 1998/11/17.

[7] Gochuico BR, Avila, NA, and Chow, CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med. 2008;168(2):159–166. published Online First: 2008/01/30.

[8] Putman RK, Hatabu H, Araki T, et al. Association between interstitial lung abnormalities and all-cause mortality. JAMA. 2016;315(7):672–681. published Online First: 2016/02/18.

[9] Kliment CR, Araki T, Doyle TJ, et al. A comparison of visual and quantitative methods to identify interstitial lung abnormalities. BMC Pulm Med. 2015;15(1):134.

[10] Hoyer N, Wille MMW, Thomsen LH, et al. Interstitial lung abnormalities are associated with increased mortality in smokers. Respir Med. 2018;136:77–82. published Online First: 2018/03/05.

[11] Sack CS, Doney BC, Podolanczuk AJ, et al. Occupational exposures and subclinical interstitial lung disease. the mesa (multi-ethnic study of atherosclerosis) air and lung studies. Am J Respir Crit Care Med. 2017;196(8):1031–1039.

[12] Podolanczuk AJ, Oelsner EC, Barr RG, et al. High attenuation areas on chest computed tomography in community-dwelling adults: The mesa study. Eur Respir J. 2016;48(5):1442–1452. published Online First: 2016/11/02.

[13] Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: A Position Paper from the Fleischner society. Lancet Respir Med. 2020;8(7):726–737.

[14] Jin GY, Lynch D, Chawla A, et al. Interstitial lung abnormalities in a CT lung cancer screening population: Prevalence and progression rate. Radiology. 2013;268 (2):563–571. published Online First: 2013/03/21.

[15] Sverzellati N, Guerci L, Randi G, et al. Interstitial lung diseases in a lung cancer screening trial. Eur Respir J. 2011;38(2):392–400. published Online First: 2011/01/15.

[16] Tsushima K, Sone S, Yoshikawa S, et al. The radiological patterns of interstitial change at an early phase: Over a 4-year follow-up. Respir Med. 2010;104(11):1712–1721. published Online First: 2010/06/12.

[17] Buendía-Roldán I, Fernandez R, Mejía M, et al. Risk factors associated with the development of interstitial lung abnormalities. Eur Respir J. 2021;58(2):2003005.

[18] Mackintosh JA, Marshall HM, and Slaughter R, et al. Interstitial lung abnormalities in the Queensland lung cancer screening study: Prevalence and progression over 2 years of surveillance Intern Med J . 2019;49(7):843–849.

[19] Hoyer N, Thomsen LH, Wille MMW, et al. Increased respiratory morbidity in individuals with interstitial lung abnormalities. BMC Pulm Med. 2020;20(1):67.

[20] Whittaker Brown S-A, Padilla M, Mhango G, et al. Interstitial lung abnormalities and lung cancer risk in the national lung screening trial. Chest. 2019; DOI:10.1016/j.chest.2019.06.041.

[21] Lee TS, Jin KN, Lee HW, et al. Interstitial lung abnormalities and the clinical course in patients with COPD. Chest. 2021;159(1):128–137.

[22] Miller ER, Putman RK, Diaz AA, et al. Increased airway wall thickness in interstitial lung abnormalities and idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2019;16(4):447–454. published Online First: 2018/12/14.

[23] Synn AJ, Li W, Hunninghake GM, et al. Vascular Pruning on CT and interstitial lung abnormalities in the Framingham heart study. Chest. 2021;159(2):663–672.

[24] Kim JS, Podolanczuk AJ, Borker P, et al. Obstructive sleep apnea and subclinical interstitial lung disease in the multi-ethnic study of atherosclerosis (mesa). Ann Am Thorac Soc. 2017;14(12):1786–1795. published Online First: 2017/06/15.

[25] Rice MB, Li W, Schwartz J, et al. Ambient air pollution exposure and risk and progression of interstitial lung abnormalities: The Framingham heart Study. Thorax. 2019;74(11): published Online First: 2019/08/09. DOI:10.1136/thoraxjnl-2018-212877

[26] Sack C, Vedal S, Sheppard L, et al. Air pollution and subclinical interstitial lung disease: The multi-ethnic study of atherosclerosis (mesa) air-lung study. Eur Respir J. 2017;50(6):1700559.

[27] Lawson WE, Crossno PF, Polosukhin VV, et al. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: Association with altered surfactant protein processing and herpesvirus infection. Am J Physiol Lung Cell Mol Physiol. 2008;294(6):L1119–L26.

[28] Ronit A, Benfield T, Lundgren J, et al. Interstitial lung abnormalities in people with HIV infection and uninfected controls. J Infect Dis. 2020;221(12):1973–1977. published Online First: 2020/02/01.

[29] Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364(16):1503–1512. published Online First: 2011/04/22.

[30] Hunninghake GM, Hatabu H, Okajima Y, et al. MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013;368(23):2192–2200. published Online First: 2013/05/23.

[31] Hobbs BD, Putman RK, Araki T, et al. Overlap of genetic risk between interstitial lung abnormalities and idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2019;200(11):1402–1413. published Online First: 2019/07/25.

[32] Hunninghake GM, Quesada-Arias LD, Carmichael NE, et al. Interstitial lung disease in relatives of patients with pulmonary fibrosis. Am J Respir Crit Care Med. 2020;201(10):1240–1248. published Online First: 2020/02/06.

[33] Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824. published Online First: 2011/04/08.

[34] Miller ER, Putman RK, Vivero M, et al. Histopathology of interstitial lung abnormalities in the context of lung nodule resections. Am J Respir Crit Care Med. 2018;197(7):955–958. published Online First: 2017/09/22.

[35] Hung YP, Hunninghake GM, Miller ER, et al. Incidental nonneoplastic parenchymal findings in patients undergoing lung resection for mass lesions. Hum Pathol. 2019;86:93–101.

[36] Mackinnon AC, Gibbons MA, Farnworth SL, et al. Regulation of transforming growth factor-beta1-driven lung fibrosis by galectin-3. Am J Respir Crit Care Med. 2012;185(5):537–546. published Online First: 2011/11/19.

[37] Ho JE, Gao W, Levy D, et al. Galectin-3 Is associated with restrictive lung disease and interstitial lung abnormalities. Am J Respir Crit Care Med. 2016;194(1):77–83. published Online First: 2016/01/16.

[38] Song JW, Do KH, Jang SJ, et al. Blood Biomarkers MMP-7 and SP-A: Predictors of outcome in idiopathic pulmonary fibrosis. Chest. 2013;143(5):1422–1429.

[39] Armstrong HF, Podolanczuk AJ, Barr RG, et al. Serum Matrix Metalloproteinase-7, respiratory symptoms, and mortality in community-dwelling adults. mesa (multi-ethnic study of atherosclerosis). Am J Respir Crit Care Med. 2017;196(10):1311–1317.

[40] Salisbury ML, Hewlett JC, Ding G, et al. Development and progression of radiologic abnormalities in individuals at risk for familial ILD. Am J Respir Crit Care Med. 2020;201(10):1230–1239.

[41] McGroder CF, Aaron CP, Bielinski SJ, et al. Circulating adhesion molecules and subclinical interstitial lung disease: The multi-ethnic study of atherosclerosis. Eur Respir J. 2019;54(3):1900295. published Online First: 2019/08/03.

[42] Tan Y, Jia D, Lin Z, et al. Potential metabolic biomarkers to identify interstitial lung abnormalities. Int J Mol Sci. 2016;17(7):1148.

[43] Kim JS, Anderson MR, Podolanczuk AJ, et al. Associations of serum adipokines with subclinical interstitial lung disease among community-dwelling adults: The multi-ethnic study of atherosclerosis (mesa). Chest. 2020;157(3):580–589.

[44] Kim JS, Steffen BT, Podolanczuk AJ, et al. Associations of ω-3 fatty acids with interstitial lung disease and lung imaging abnormalities among adults. Am J Epidemiol. 2021;190(1):95–108. published Online First: 2020/08/18.

[45] Ortiz-Quintero B, Buendía-Roldán I, Ramírez-Salazar EG, et al. Circulating microRNA signature associated to interstitial lung abnormalities in respiratory asymptomatic subjects. Cells. 2020;9(6):1556.

[46] Bernstein EJ, Barr RG, Austin JH, et al. Rheumatoid arthritis-associated autoantibodies and subclinical interstitial lung disease: The multi-ethnic study of atherosclerosis. Thorax. 2016;71(12):1082–1090. published Online First: 2016/09/10.

[47] Kim SM, Zhao D, Podolanczuk AJ, et al. Serum 25-Hydroxyvitamin D concentrations are associated with computed tomography markers of subclinical interstitial lung disease among community-dwelling adults in the multi-ethnic study of atherosclerosis (mesa). J Nutr. 2018;148(7):1126–1134. published Online First: 2018/06/23.

[48] Xu JF, Washko GR, Nakahira K, et al. Statins and pulmonary fibrosis: The potential role of NLRP3 inflammasome activation. Am J Respir Crit Care Med. 2012;185(5):547–556. published Online First: 2012/01/17.

[49] Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: A Fleischner society white paper. Lancet Respir Med. 2018;6(2):138–153.

[50] Putman RK, Gudmundsson G, Axelsson GT, et al. Imaging patterns are associated with interstitial lung abnormality progression and mortality. Am J Respir Crit Care Med. 2019;200(2):175–183. published Online First: 2019/01/24.

[51] Putman RK, Gudmundsson G, Araki T, et al. The MUC5B promoter polymorphism is associated with specific interstitial lung abnormality subtypes. Eur Respir J. 2017;50:3.

[52] Bozzetti F, Paladini I, Rabaiotti E, et al. Are interstitial lung abnormalities associated with COPD? A nested case-control study. Int J Chron Obstruct Pulmon Dis. 2016;11:1087–1096.

[53] Ohgiya M, Matsui H, Tamura A, et al. The evaluation of interstitial abnormalities in group B of the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Classification of Chronic Obstructive Pulmonary Disease (COPD). Intern Med. 2017;56(20):2711–2717. published Online First: 2017/09/15.

[54] Araki T, Nishino M, Zazueta OE, et al. Paraseptal emphysema: Prevalence and distribution on CT and association with interstitial lung abnormalities. Eur J Radiol. 2015;84(7):1413–1418. published Online First: 2015/04/15.

[55] Putman RK, Hunninghake GM, Dieffenbach PB, et al. Interstitial lung abnormalities are associated with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195(1):138–141. published Online First: 2016/12/31.

[56] Doyle TJ, Washko GR, Fernandez IE, et al. Interstitial lung abnormalities and reduced exercise capacity. Am J Respir Crit Care Med. 2012;185(7):756–762. published Online First: 2012/01/24.

[57] Axelsson GT, Putman RK, Araki T, et al. Interstitial lung abnormalities and self-reported health and functional status. Thorax. 2018;73(9):884–886. published Online First: 2018/01/11.

[58] Axelsson GT, Putman RK, Miller ER, et al. Interstitial lung abnormalities and physical function. ERJ Open Res. 2018;4(3):3. published Online First: 2018/09/07.

[59] Wille MM, Thomsen LH, Petersen J, et al. Visual assessment of early emphysema and interstitial abnormalities on CT is useful in lung cancer risk analysis. Eur Radiol. 2016;26(2):487–494. published Online First: 2015/05/10.

[60] Nishino M, Cardarella S, Dahlberg SE, et al. Interstitial lung abnormalities in treatment-naïve advanced non-small-cell lung cancer patients are associated with shorter survival. Eur J Radiol. 2015;84(5):998–1004. published Online First: 2015/02/07.

[61] Araki T, Dahlberg SE, Hida T, et al. Interstitial lung abnormality in stage IV non-small cell lung cancer: A validation study for the association with poor clinical outcome. Eur J Radiol Open. 2019;6:1082–1090. published Online First: 2019/04/16.

[62] Chubachi S, Takahashi S, Tsutsumi A, et al. Radiologic features of precancerous areas of the lungs in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2017;12:1613–1624.

[63] Gu K, Lee HY, Lee K, et al. Integrated evaluation of clinical, pathological and radiological prognostic factors in squamous cell carcinoma of the lung. PLoS One. 2019;14(10):e0223298–e98.

[64] Hida T, Hata A, Lu J, et al. Interstitial lung abnormalities in patients with stage I non-small cell lung cancer are associated with shorter overall survival: The Boston lung cancer study. Cancer Imaging. 2021;21(1):14. [published Online First: 2021/01/21.

[65] Axelsson GT, Putman RK, Aspelund T, et al. The associations of interstitial lung abnormalities with cancer diagnoses and mortality. Eur Respir J. 2020;73 (9):1902154.

[66] Im Y, Park HY, Shin S, et al. Prevalence of and risk factors for pulmonary complications after curative resection in otherwise healthy elderly patients with early stage lung cancer. Respir Res. 2019;20(1):36–136.

[67] Li F, Zhou Z, Wu A, et al. Preexisting radiological interstitial lung abnormalities are a risk factor for severe radiation pneumonitis in patients with small-cell lung cancer after thoracic radiation therapy. Radiat Oncol. 2018;13(1):82.

[68] Kobayashi H, Wakuda K, Naito T, et al. Chemoradiotherapy for limited-stage small-cell lung cancer and interstitial lung abnormalities. Radiat Oncol. 2021;16(1):52. published Online First: 2021/03/19.

[69] Nakanishi Y, Masuda T, Yamaguchi K, et al. Pre-existing interstitial lung abnormalities are risk factors for immune checkpoint inhibitor-induced interstitial lung disease in non-small cell lung cancer. Respir Investig. 2019;57(5):451–459.

[70] Shimoji K, Masuda T, Yamaguchi K, et al. Association of preexisting interstitial lung abnormalities with immune checkpoint inhibitor-induced interstitial lung disease among patients with nonlung cancers. JAMA Network Open. 2020;3(11):e2022906–e06.

[71] Dong H, Julien PJ, Demoruelle MK, et al. Interstitial lung abnormalities in patients with early rheumatoid arthritis: A pilot study evaluating prevalence and progression. Eur J Rheumatol. 2018;6(4):193–198.

[72] Doyle TJ, Dellaripa PF, Batra K, et al. Functional impact of a spectrum of interstitial lung abnormalities in rheumatoid arthritis. Chest. 2014;146(1):41–50. published Online First: 2013/12/07.

[73] Kawano-Dourado L, Doyle TJ, Bonfiglioli K, et al. Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. Chest. 2020;158(4):1546–1554.

[74] Araki T, Putman RK, Hatabu H, et al. Development and progression of interstitial lung abnormalities in the Framingham heart study. Am J Respir Crit Care Med. 2016;194(12):1514–1522. published Online First: 2016/06/18.

[75] Hino T, Hida T, Nishino M, et al. Progression of traction bronchiectasis/bronchiolectasis in interstitial lung abnormalities is associated with increased all-cause mortality: Age gene/environment susceptibility-Reykjavik study. Eur J Radiol Open. 2021;8:100334. published Online First: 2021/03/23.

[76] Podolanczuk AJ, Oelsner EC, Barr RG, et al. High attenuation areas on chest computed tomography in community-dwelling adults: The Mesa study. Eur Respir J. 2016;48(5):1442.

[77] Easthausen I, Podolanczuk A, Hoffman E, et al. Reference values for high attenuation areas on chest CT in a healthy, never-smoker, multi-ethnic sample: The mesa study. Respirology. 2020;25(8):855–862.

[78] Manichaikul A, Wang X-Q, Sun L, et al. Genome-wide association study of subclinical interstitial lung disease in mesa. Respir Res. 2017;18(1):97.

[79] Madahar P, Duprez DA, Podolanczuk AJ, et al. Collagen biomarkers and subclinical interstitial lung disease: The multi-ethnic study of atherosclerosis. Respir Med. 2018;140:108–114. published Online First: 2018/06/30.

[80] Podolanczuk AJ, Raghu G, Tsai MY, et al. Cholesterol, lipoproteins and subclinical interstitial lung disease: The mesa study. Thorax. 2017;72(5):472–474. published Online First: 2017/01/29.

[81] Sanchez TR, Oelsner EC, Lederer DJ, et al. Rice consumption and subclinical lung disease in us adults: Observational evidence from the multi-ethnic study of atherosclerosis. Am J Epidemiol. 2019;188(9):1655–1665.

[82] Choi B, Kawut SM, Raghu G, et al. Regional distribution of high-attenuation areas on chest computed tomography in the multi-ethnic study of atherosclerosis. ERJ Open Res. 2020;6(1):00115–2019.

[83] Podolanczuk AJ, Oelsner EC, Barr RG, et al. High-attenuation areas on chest computed tomography and clinical respiratory outcomes in community-dwelling adults. Am J Respir Crit Care Med. 2017;196 (11):1434–1442.

[84] Ash SY, Harmouche R, Ross JC, et al. The objective identification and quantification of interstitial lung abnormalities in smokers. Acad Radiol. 2017;24 (8):941–946. published Online First: 2016/12/15.

[85] Ash SY, Harmouche R, Putman RK, et al. Clinical and genetic associations of objectively identified interstitial changes in smokers. Chest. 2017;152(4):780–791. published Online First: 2017/05/12.

[86] Iwasawa T, Okudela K, Takemura T, et al. Computer-aided quantification of pulmonary fibrosis in patients with lung cancer: Relationship to disease-free survival. Radiology. 2019;292(2):489–498. published Online First: 2019/06/05.

[87] Bermejo-Peláez D, Ash SY, Washko GR, et al. Classification of interstitial lung abnormality patterns with an ensemble of deep convolutional neural networks. Sci Rep. 2020;10(1):38–338.

[88] Harmouche R, Ash SY, Putman RK, et al. Objectively measured chronic lung injury on chest CT. Chest. 2019;156(6):1149–1159.

[89] Kim JS, Anderson MR, and Bernstein EJ, et al. Associations of D-dimer with CT lung abnormalities, serum biomarkers of lung injury, and forced vital capacity: Mesa lung study. Ann Am Thorac Soc 2021 . (ja): null. 10.1513/AnnalsATS.202012-1557OC.

[90] Anderson MR, Kim JS, Allison M, et al. Adiposity and interstitial lung abnormalities in community dwelling adults: The mesa cohort study. Chest. 2021;160(2):582–594. published Online First: 2021/04/13.

[91] Hunninghake GM. Interstitial lung abnormalities: Erecting fences in the path towards advanced pulmonary fibrosis. Thorax. 2019 ;thoraxjnl–2018–212446. DOI:10.1136/thoraxjnl-2018-212446

[92] Hunninghake GM, Goldin JG, Kadoch MA, et al. Detection and early referral of patients with interstitial lung abnormalities: An expert survey initiative. Chest. DOI:10.1016/j.chest.2021.06.035.

[93] Doyle TJ, Hunninghake GM, Rosas IO. Subclinical interstitial lung disease: Why you should care. Am J Respir Crit Care Med. 2012;185(11):1147–1153. published Online First: 2012/03/01.

[94] Richeldi L, Du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–2082.

[95] King TE, Bradford WZ, Castro-Bernardini S, et al. A Phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–2092.

[96] Nalysnyk L, Cid-Ruzafa J, Rotella P, et al. Incidence and prevalence of idiopathic pulmonary fibrosis: Review of the literature. Eur Respir Rev. 2012;21(126):355–361. published Online First: 2012/12/04.

[97] Esposito DB, Lanes S, Donneyong M, et al. Idiopathic pulmonary fibrosis in USA automated claims. incidence, prevalence, and algorithm validation. Am J Respir Crit Care Med. 2015;192(10):1200–1207.

[98] Buendia-Roldan I, Machuca N, Mejía M, et al. Lower levels of α-Klotho in serum are associated with decreased lung function in individuals with interstitial lung abnormalities. Sci Rep. 2019;9(1):01–10801.