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Criteria for Progressive Pulmonary Fibrosis: Getting the Horse Ready for the Cart

Progressive pulmonary fibrosis (PPF) (1), formerly progressive fibrosing interstitial lung disease (ILD) (2), designates a subset of fibrotic ILDs which share with untreated idiopathic pulmonary fibrosis (IPF) a natural course characterized by irreversible progression, causing worsening respiratory symptoms, a decline in lung function, and early mortality (3). Although each ILD is relatively rare, and a variable proportion of each develops a progressive phenotype (4), collectively, PPFs represent a devastating condition associated with a high humanistic and economic burden to patients, their caregivers, and society (5).

Generally, in medicine, potential therapy is envisaged, and clinical trials are designed long after a condition has been identified and its natural history characterized through observational studies. It is only after large trials have been conducted and experience has been acquired by specialized centers that guidelines are developed. With regard to PPF, a different and somewhat backward process was taken. In two early cohorts, including patients with both IPF or idiopathic nonspecific interstitial pneumonia, a decline in FVC over 6–12 months was associated with an increased risk of subsequent mortality, independently of the underlying ILD diagnosis (e.g., IPF vs. nonspecific interstitial pneumonia) (6, 7). A decline in lung function despite usual management, therefore, identified disease progression. An IPF-like disease behavior (8) was also identified in other non-IPF fibrotic ILDs (9, 10) and was strongly linked with mortality. The emergent concept of PPF (2) was then validated by a landmark clinical trial (INBUILD), designed and powered to provide evidence in PPF as a whole and not in specific diagnostic subgroups (11). Nintedanib decreased disease progression, as measured by FVC decline, in patients with PPF enrolled irrespective of the underlying ILD diagnosis (12).

Since then, studies have assessed the prevalence of PPF among non-IPF fibrotic ILDs and confirmed the impact of disease progression on subsequent mortality (13–16). Progression was generally defined using original or modified INBUILD criteria (11, 17). Recently, an international guideline statement proposed revised criteria for identifying PPF among fibrotic ILD (1). The criteria proposed include stand-alone measures of lung function decline and combinations of symptomatic, physiologic, and radiologic worsening, some being known to be associated with increased mortality in various fibrotic ILDs, and others being extrapolated from the IPF literature. With the exception of FVC decline, few of these criteria have been validated in non-IPF fibrotic ILDs. It was argued that clinical practice guidelines may have preceded the accumulation of evidence rather than incorporated it, "putting the cart before the horse" (18).

In this issue of the *Journal*, an article by Pugashetti and colleagues (pp. 69–76) and a letter by Khor and colleagues (pp. 102–105) explored whether different PPF criteria were associated with subsequent transplant-free survival (19, 20, respectively). Pugashetti and colleagues report the outcome of a large ($n = 1{,}341$) retrospective cohort from four centers. They confirmed that ⩾10% relative FVC decline was the strongest predictor of subsequent reduced transplant-free survival, consistent with findings from the INBUILD study (21), and was the most consistent criterion irrespective of ILD subtype. Three additional stand-alone PPF criteria in the absence of ⩾10% relative FVC decline (5–9% relative FVC decline, ⩾15% relative D_{LCO} decline, and computed tomography progression of fibrosis), and three combinations of symptomatic, physiologic, and radiologic worsening, were also associated with reduced transplant-free survival in patients with non-IPF fibrotic ILD, in both the derivation and validation cohorts (19). Results were not affected by hospital site or immunosuppressive or antifibrotic therapy; however, the underlying ILD diagnosis and the PPF criteria met had an impact on subsequent survival.

The cohort was characterized by a high rate of disease progression, as half of the patients experienced a ⩾10% relative FVC decline within 4 years. Clinicians should be aware that eventually, a majority of patients with fibrotic ILDs will experience disease progression, sometimes several years after the diagnosis; therefore, long-term follow-up is warranted. Compared with those with connective tissue disease-associated ILD, patients with fibrotic hypersensitivity pneumonitis and those with non-IPF idiopathic interstitial pneumonia more frequently experienced disease progression and had a greater risk of death after satisfying PPF criteria, paralleling previous studies (13–16). Thus, heterogeneity in disease course remains among ILD subtypes even after satisfying PPF criteria. In this study, PFF criteria were applied over a 4-year period to assess 5-year transplant-free survival (19). Disease progression was

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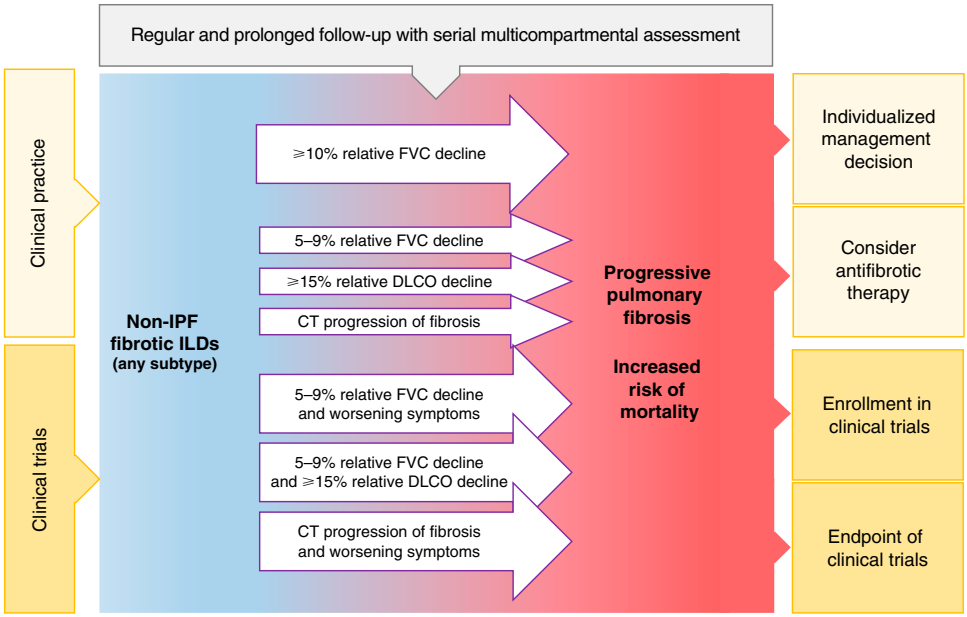

Figure 1. Algorithm was derived from the study by Pugashetti and colleagues (19). In clinical practice and clinical trials, regular follow-up of patients with any non-IPF fibrotic ILD is warranted, using multicompartmental assessment. Criteria associated with reduced transplant-free survival were ⩾10% relative FVC decline, three stand-alone features (5–9% relative FVC decline, ⩾15% relative D_{LCO} decline, and CT progression of fibrosis), and three criteria requiring a combination of physiologic, radiologic, and symptomatic worsening. Identification of progressive pulmonary fibrosis leads to reconsidering current management, including initiation of antifibrotic therapy, which may lead to enrollment into clinical trials or may serve as an endpoint in clinical trials. CT = computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.

assessed as a time-dependent covariate (e.g., time to ⩾10% relative FVC) that may occur over 4 years and not as a categorical criterion (e.g., the proportion of patients satisfying PPF criteria within 1 year of follow-up) (1).

In another cohort of 753 patients with non-IPF fibrotic ILD, Khor and colleagues (20) compared the prevalence of PPF and transplant-free survival using PPF criteria from guidelines (1) and three different trials (11, 22, 23). Only a small proportion of patients met all four definitions for PPF, demonstrating the major impact of apparently minor differences between different sets of criteria, with implications for patient care and research (20). In both studies, multicompartmental criteria were less sensitive than single-domain criteria and captured a lower percentage of patients with PFF (19, 20) while being similarly associated with an increased risk of mortality.

Although providing invaluable information on PPF criteria, both studies were limited by their retrospective design, which may have particularly affected the assessment of symptomatic worsening (yet used only in combination with physiologic or radiologic worsening), and heterogeneity across participating centers. As Pugashetti and colleagues did not evaluate the combined set of guideline PPF criteria (1), further studies are warranted to investigate its value and implementation in the target population of non-IPF fibrotic ILDs.

In conclusion, in clinical practice, as in clinical trials, ⩾10% relative FVC decline is certainly the best stand-alone criterion to define disease progression. When this criterion is not met, 5–9% relative FVC decline, ⩾15% relative D_{LCO} decline, or computed tomography progression of fibrosis also indicate disease progression that should lead to a reevaluation of current management, often including the institution of antifibrotic therapy (Figure 1). Management decisions, however, must be individualized and should take into account the underlying ILD diagnosis, comorbidities, disease severity, and timelines of disease progression. These observations reiterate the need for regular and prolonged follow-up of patients with fibrotic ILD using multicompartmental assessment, including pulmonary function tests, and set the stage for refining the PPF criteria on the basis of evidence. ■

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Vincent Cottin, M.D., Ph.D.
National Reference Centre for Rare Pulmonary Diseases
Louis Pradel Hospital, Hospices Civils de Lyon
Lyon, France
and
UMR 754, Institut national de recherche agronomique et environnement
Claude Bernard University Lyon 1
Lyon, France

ORCID ID: 0000-0002-5591-0955 (V.C.).

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Expanding the Reach of Lung Cancer Screening: Risk Models for Individuals Who Never Smoked

Lung cancer represents a substantial portion of the overall burden of cancer and resulted in an estimated 2.2 million new cases and 1.8 million deaths worldwide in 2020, representing approximately 1 in 10 (11.4%) cancers diagnosed and one in five (18.0%) deaths (1).

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In 2011, the U.S. National Lung Screening Trial demonstrated a 20% relative reduction in lung cancer mortality with annual low-dose computed tomography (LDCT) among individuals at high risk based on age and tobacco use criteria (2). The NELSON trial (Dutch-Belgian lung cancer screening trial) recently confirmed a mortality benefit to annual LDCT screening among high-risk populations (3).

However, current screening criteria exclude a substantial proportion of individuals who will go on to be diagnosed with lung cancer. The proportion of lung cancers diagnosed in individuals who have never smoked is increasing over time, accounting for 25% of all lung cancers. If considered as a distinct disease entity, non–smoking-related lung cancer would rank as the seventh most common cause of cancer-related death worldwide (4). In Asia, 30–40% of all lung cancers and 60–80% of lung cancers in women occur in never-smokers, considerably higher than the proportion observed in the United States and Europe (5, 6). The observed increase in lung