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Functional Criteria to Define Progressive Pulmonary Fibrosis: Searching for the Holy Grail

To the Editor:

We have reviewed with great interest the article "Validation of Proposed Criteria for Progressive Pulmonary Fibrosis" by Pugashetti and colleagues (1). The authors have assessed progressive pulmonary fibrosis (PPF) criteria proposed in different studies and their association with transplant-free survival in patients with nonidiopathic pulmonary fibrosis (non-IPF). After different analyses, the authors conclude that an FVC decline of ⩾10% and six additional PPF criteria in the absence of such decline identify patients with non-IPF interstitial lung disease (ILD) at increased risk of death or lung transplant (1).

When we assess the progression of ILD, we consider absolute or relative changes in FVC and D_{LCO} over a period of time. The absolute decrease is calculated as the initial measurement minus the final measurement, and the relative decrease is calculated as the difference between the initial and final measurements divided by the initial measurement (2). This differentiation is important. In IPF, the incidence of progression could be different using relative or absolute values (3). The use of a relative FVC decline of ⩾10% is preferred when assessing progression (4) compared with the absolute method. However, for example, the absolute 5% drop in FVC in 1 year (but not relative change) is associated with an increased risk of death and transplantation at 2 years in IPF (3).

The study by Pugashetti and colleagues (1) assessed a relative FVC decline of ⩾10%. The absolute change was not included in the study. However, they included absolute changes for other values and for D_{LCO} (1). In the discussion, they also mentioned the recently published guidelines for PPF (2). However, in these guidelines, they recommended an absolute decrease in FVC of >5% or absolute decrease in D_{LCO} (corrected for Hb) of >10% within 1 year of follow-up to define functional progression. From the data of the authors, FVC decline of ⩾10% was a better prognostic factor than those proposed by guidelines (although FVC decline >5% was not assessed, only FVC decline 5–9%). In addition, the study period extends to 4 years, in contrast with 1 year in the PPF guidelines.

From our perspective, it is important to clarify which values, methods (relative or absolute), and study periods are suitable for PPF criteria. Early identification of PPF and proper early treatment are overarching objectives. To avoid confusion in the ILD community, scientific research and guideline groups need to work together to decide which criteria are better for the early identification of PPF. ■

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

Acknowledgment: The authors thank the entire team that makes up the interstitial lung diseases unit.

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Supported by Instituto de Salud Carlos III (ISCIII) through the project PI19/01152, Sociedad Española de Neumología (SEPAR), Societat Catalana de Pneumologia (SOCAP), Fundació Catalana de Pneumologia (FUCAP), and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS).

Author Contributions: Study conception and design: J.S., M.N.-S., F.H.-G., X.A.-R., and N.P.-R. Draft manuscript preparation: J.S. and M.N.-S. All authors reviewed the results and approved the final version of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202209-1772LE on September 29, 2022

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Reply to Noboa-Sevilla *et al.*

From the Authors:

We thank Noboa-Sevilla and colleagues for their letter in response to our manuscript (1). We agree the methodology used to ascertain progression status in patients with fibrotic interstitial lung disease (ILD) is of critical importance. In our study, we sought to validate the proposed criteria for progressive pulmonary fibrosis (PPF), including those comprising the recent international PPF guideline (2), by ascertaining whether each criterion was associated with transplant-free survival. Given the strong link between 10% or higher relative FVC decline and subsequent mortality (3–10), we focused on proposed PPF criteria satisfied in the absence of such decline. Our rationale is that only criteria providing prognostic information independent of this well-established marker of ILD progression are likely to be of clinical value. We elected to model a 10% or higher relative FVC decline as this approach has been shown to capture more patients than an absolute decline threshold in patients with IPF without sacrificing prognostic value (5).

As Noboa-Sevilla and colleagues correctly highlight, our approach resulted in differences in the criteria modeled in our investigation and those proposed by the PPF guideline. We fully acknowledge that different sets of patients are captured using 5–9% FVC decline (relative and absolute) and 5% or higher absolute FVC decline thresholds, as the former excludes those with concurrent 10% or higher relative FVC decline, whereas the latter does not. We maintain that separating those with 5–9% FVC decline (relative and absolute) from those with 10% or higher relative FVC is preferred to modeling 5% or higher FVC (relative and absolute), as our data suggest these groups are inherently different with regard to outcome risk. We share the concern outlined by others that the PPF guideline may have been premature given the paucity of data to inform these criteria in the target population (11), with our data suggesting that substantial heterogeneity exists within the PPF phenotype (1).

Noboa-Sevilla and colleagues also call important attention to the timeframe over which PPF criteria may be satisfied, nicely contrasting our approach to the one proposed in the PPF guideline. In a prior study assessing lung function trajectory after satisfying PPF criteria, we found that progression can occur up to 10 years after diagnosis (12). Accordingly, we support others who have called for the dissociation of progression criteria from rigid timelines (13). The use of established timelines is understandable when applying composite criteria, but our data suggest that standalone PPF criteria, namely 5–9% relative FVC decline, computed tomography progression of fibrosis, and 15% or higher relative D_{LCO} decline, perform as well, and sometimes better, than composite criteria that include these features (1). In conclusion, we agree with Noboa-Sevilla and colleagues that the international community must come together to collaboratively study, define, and evolve the phenotype we have labeled PPF. The era of single-center ILD studies is over. It took decades to establish consensus surrounding IPF, and our patients with progressive disease must not wait that long. ■

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

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Originally Published in Press as DOI: 10.1164/rccm.202209-1807LE on September 29, 2022