Validation of Proposed Criteria for Progressive Pulmonary Fibrosis

Progressive pulmonary fibrosis (PPF) is defined as a combination of two of the following three criteria: worsening respiratory symptoms, physiological deterioration and radiological progression. It is a potentially devastating condition, characterised by poor survival and high healthcare-utilisation. This is an important diagnosis to make as the availability of anti-fibrotic agents such as Pirfenidone and Nintedanib offer novel treatment approaches.

While it is most common in idiopathic pulmonary fibrosis (IPF), PPF is known to occur in patients with non-IPF forms of interstitial lung disease (ILD), such as fibrotic hypersensitivity pneumonitis (fHP), connective tissue disease-ILD (CTD-ILD) and non-IPF idiopathic interstitial pneumonia (IIP). Criteria have been proposed for PPF in patients with non-IPF ILD, but who were never validated, the objective of the research recently conducted by Vu Pugashetti *et al.*[1]

A relative FVC decline of ≥10% has previously been found to predict reduced survival in common ILD subtypes. Based on clinical trials and expert perspectives the authors proposed 13 additional criteria to identify PPF in this population. They performed a multicentre cohort analysis in the UK and the US, and applied these criteria retrospectively, to test the association with transplant-free survival (TFS).

The authors found that a relative FVC decline remained the strongest predictor of reduced TFS, remaining consistent across different cohorts, ILD subtypes and treatment groups. They also validated an additional six criteria associated with reduced TFS in both cohorts. These included three stand-alone criteria, namely, a 5 - 9% relative FVC decline, a ≥15% relative DLCO decline, and CT progression of fibrosis; and three combination criteria based on these stand-alone criteria.

Some heterogeneity was noted between the UK and US cohorts, with the US cohort having a higher proportion of patients with a UIP pattern (27% v. 11.5%), being slightly older, and therefore having a higher percentage of patients receiving anti-fibrotics, compared with the UK cohort where immunosuppressants were more commonly used.

Approximately 50% of patients experienced a ≥10% FVC decline within 4 years. Of the new PPF criteria satisfied in the absence of a ≥10% FVC decline, a 5 - 9% relative FVC decline was the most common, followed by a ≥15% decline in DLCO. Most patients experienced a ≥10% relative FVC decline concurrently with fulfilling other criteria, and it remained the strongest predictor of reduced TFS. Among patients who did not have a ≥10% FVC decline, TFS was highly variable depending on the ILD subtype, with CTD-ILD and fHP having the best prognosis. In patients with a ≥10% FVC decline, TFS closely approximated that of IPF, in linevwith the progressive nature of severe lung fibrosis. Notably, CT progression of fibrosis was found to be the best predictor of subsequent FVC decline, whereas a ≥10% relative FVC decline poorly predicted additional FVC decline.

A puzzling aspect of the study is the use of the criterion of a relative decline in FVC of ≥10%, which is in contrast with the most recent practice guideline from the international respiratory societies regarding IPF and PPF, who use an absolute reduction in FVC of ≥5%.[2] This discrepancy not only affects the definition of PPF with FVC criteria, but also the other results as an absolute decline of 5% is significantly more sensitive for patients with an FVC above 50% predicted, and becomes more so the higher the starting FVC. It is therefore unclear how many of the patients newly identified with the additional criteria from this study would have been identified with the use of the ATS/ERS/JRS/ALAT criteria. Moreover, a ≥15% DLCO decline could at times identify patients with worsening pulmonary vasculopathy rather than ILD progression. Finally, the authors noted that a 5-year TFS is only rarely used as an outcome in ILD clinical trials. Therefore PPF criteria that predict survival may fail to optimally identify patients suited for intervention with anti-fibrotics. CT progression of fibrosis could potentially be used to identify patients for intervention with anti-fibrotics, as this criterion was best at predicting future FVC decline.

This study succeeded in validating new criteria for the diagnosis of PPF and provided further evidence of the progressive nature of advanced lung fibrosis. This will be of significant value to clinicians in identifying patients with the PPF phenotype. However, the contrast in criteria with recent guidelines may create confusion, and it is also not clear whether the patients identified with these criteria are those most suitable for intervention. Hopefully, further research and analysis will guide us in optimising our treatment of these patients.

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2. Raghu G, Remy-Jardin M, Richeldi L et al. Idiopathic pulmonary fibrosis (an Update) and progressive pulmonary fibrosis in adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022; 205(9):e18-e47. https://doi.org/10.1164/rccm.202202-0399st