ramr
American Review of Respiratory Medicine
Revista Americana de Medicina Respiratoria

REVIEW ARTICLE

ISSN 1852-236X

Critical Analysis of the Definition of Progressive Pulmonary Fibrosis

Análisis crítico de la definición de fibrosis pulmonar progresiva

Szwarstein, Pablo[1]; Sívori, Martín[1]; Arce, Santiago C.[2]; Toibaro, Javier[3]

Received: 08/03/2023
Accepted: 12/27/2023

Correspondence
Pablo Szwarstein: E-mail: pszwarstein74@gmail.com

INTRODUCTION

Diffuse interstitial lung diseases (ILD) are a group of more than 200 diseases, many of which are rare. Idiopathic pulmonary fibrosis (IPF) is the prototype of progressive fibrosing interstitial disease.[1] There is a subgroup that shows progressive evolution, worsening of respiratory symptoms, decreased lung function, resistance to immunomodulatory treatment, and early mortality, similar to idiopathic pulmonary fibrosis (IPF).[2-3] This phenotype has been proposed as progressive- fibrosing phenotype of interstitial lung diseases (PF-ILDs), encompassing different clinical entities but with similar clinical, radiological, and functional evolution.[1] Various authors have suggested the need for early diagnosis and treatment of these diseases to attempt to alter the natural history of this progressive phenotype.[1]

In May 2022, the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) issued an updated guideline on IPF, in which they proposed definitions for progressive pulmonary fibrosis (PPF).[1] Clinical, radiological, and functional criteria were proposed to define PPF, initially termed "interstitial lung diseases with a progressive-fibrosing phenotype."[1]

Additionally, several experts have expressed their opinions on the criteria used, and various studies have employed different enrollment criteria.[2-21] Attempts have been made to validate these criteria in retrospective and prospective cohorts and patient databases, revealing initially unconsidered aspects and expressing criticism of the criteria used.[22-27]

The objective of this manuscript is to critically analyze the different definitions of PPF and support the criticism with published scientific evidence, emphasizing the clinical, functional, and radiological criteria used.

Rev Am Med Resp 2024;24:122-135
https://doi.org./10.56538/ramr.EJWK9699

[1] Pulmonology University Center, Faculty of Medicine, University of Buenos Aires. Pulmonology and Tisiology Unit, Hospital Gral. de Agudos "Dr. J. M. Ramos Mejía". Buenos Aires. Argentina.
[2] Pulmonology Service, Medical Research Institute "Alfredo Lanari", Faculty of Medicine, University of Buenos Aires. Argentina.
[3] Internal Medicine B Unit, Hospital Gral.de Agudos "Dr. J. M. Ramos Mejía". Buenos Aires. Argentina.

WHAT DEFINITION OF PPF HAS BEEN USED?

The term PPF (progressive pulmonary fibrosis) was initially proposed for various ILD associated with connective tissue disease (CTD), chronic fibrotic hypersensitivity pneumonitis (CFHP), nonspecific idiopathic interstitial pneumonia (NSIIP), unclassifiable idiopathic interstitial pneumonia (UIIP), occupational ILD, or sarcoidosis that met clinical, functional, and tomographic diagnostic criteria for a period of 24 months.[4-6]

The mentioned ATS/ERS/JRS/ALAT guidelines reduced the definition of temporal worsening from 24 to 12 months, requiring two of the three proposed criteria to be met, without another explanation for the cause of deterioration:[1]

a) Clinical: worsening of symptoms.
b) Functional: decrease in absolute values of FVC (forced vital capacity) ≥ 5% of the predicted value, or a decrease in absolute values of the diffusing capacity of the lungs for carbon dioxide (DLCO) (corrected for hemoglobin) ≥ 10% of the predicted value.
c) Imaging: clearer criteria are established to determine the worsening of fibrosis through high-resolution computed tomography (HRCT) of the chest (see further details below).

The consequence of this situation is that it has become very difficult to compare different cohort studies in their clinical characteristics and in the evolutionary variables of clinical, functional, and tomographic impact, beyond the fact that therapeutic interventions with different antifibrotic drugs in clinical studies did not precisely use similar inclusion criteria.[4,12-14,22-27]

Below, the used definition criteria for PPF will be analyzed critically in more detail.

A. Clinical criteria

The original work by Vincent Cottin considered "clinical deterioration" to be the worsening of symptoms such as cough, dyspnea, and exercise capacity as measured by a 6-minute walk test (6MWT) with a clinically significant drop value of 50 meters, and quality of life measured by the St. George's Respiratory Questionnaire (without mentioning a clinically significant value of deterioration).[6] Clinical examination signs such as Velcro-type crackles and a drop in pulse oximetry were also to be considered. "Progression" was defined as acute respiratory failure, with these signs and symptoms, without another cause that can explain them, within a 24-month evaluation period.[6]

Over time, from 2018 to the present, there has been little emphasis on the clinical criterion of PPF, at the expense of the functional and imaging criteria. However, it is important to include this criterion as part of the definition of PPF and to remember that two of the three criteria must be present.[6]

The term "fibrosing phenotype" used in some publications would not be appropriate by definition. Phenotypes are the expression of a genotype, and this would imply that the various conditions with progressive worsening share the same genetic substrate. And this has not been demonstrated so far.[1]

PPF (progressive pulmonary fibrosis) encompasses entities that are clinically different but have similar behavior and prognosis. Therefore, it is important to distinguish these entities so as to identify those in which early intervention is necessary.[8,9]

The following conditions are noted within the PPF: ILD associated with CTD, NSIP, IIP, and CFHP, caused by workplace factors, or sarcoidosis.[8,9] The last three progress despite the treatment of the specific entity (immunosuppression and antigen avoidance).[8,9]

After the COVID-19 pandemic, a potential new subgroup of patients has been added, with fibrotic sequelae and progression, who are currently being studied.[8,28]

Between 18% and 32% of patients with non-IPF interstitial lung diseases progress during follow-up at 60-80 months after diagnosis.[9] The highest risk of progression is seen in CFHPs and CTDs compared to other diseases.[9] These patients should be referred early to transplant programs, especially when they are young patients. Therefore, it is important to establish an etiological diagnosis as soon as possible to appropriately adjust the treatment.[9]

Here it is interesting to mention the terms "lumpers" and "splitters" discussed by experts in IPF. Many authors considered it important to group IPF with progressive fibrosing diseases to simplify the presentation and similar behavior ("lumpers"). However, other authors highlighted the need to separate these entities and study genetic and physiopathological differences in detail to individualize the entities and implement targeted treatments (e.g., differentiating IPF from CTD and CFHP) ("splitters").[5,16,29]

The 2022 ATS/ERS/JPS/ALAT Guidelines don't take into account if symptom worsening is evaluated by one or multiple observers, nor do they mention associated comorbidities.[1] But they emphasize the fact that the worsening should occur over 1 year and without an underlying cause. They don't clearly mention how clinical worsening is measured, although they establish clinically significant differences for the dyspnea and cough scales that are validated for this group of diseases.[1]

Finally, the European Consensus stipulates that it is necessary to differentiate PPF at the beginning of the patient evaluation with worsening symptoms and typical images from cases in which symptoms progress despite immunosuppressive treatment. This would avoid over-prescription of antifibrotics for all patients with PPF at the beginning of the evaluation since most respond to the treatment of the underlying disease (immunosuppression).[2,20]

For all these reasons, we believe that it is necessary to better agree through randomized studies on the clinical link of the PPF definition and to establish agreements to determine if there are clinical predictors of progression in the heterogeneous group of diseases that constitute the definition of PPF. A multidisciplinary clinical approach in PPF is important to make appropriate differential diagnoses of the intercurrence of the diseases that encompass PPF before defining its clinical progression (e.g., heart failure, pulmonary hypertension, lung infections, exacerbations, etc.).

Table 2 summarizes the issues that arise when establishing clinical criteria.[1]

B. Functional criteria

The initial definition by Cottin was to evaluate progression for 24 months and define it from a functional point of view by one of the two criteria:[6]

1. Relative decrease in FVC ≥ 10%, or a relative decrease in FVC between 5-10% associated with clinical or tomographic deterioration.
2. Relative decrease in DLCO over 15%.

However, other definitions have been used in various clinical studies of PPF (Table 1).[4,6,12]

B.1. FVC Decline

The force, both inspiratory and expiratory, that is necessary to achieve a vital capacity maneuver is relatively low. The accumulation of the sufficient amount of fibrous tissue that produces a significant decrease in lung distensibility for the vital capacity (VC) to start decreasing is necessary. However, this is sufficient to obliterate pulmonary capillaries and cause hypoxemia. In this context, imaging or deterioration of gas exchange manifests before the decline in VC, making these the preferred methods for early detection, although both methods have had standardization issues.[30]

Conversely, the spirometry is a highly standardized study, widely available, and with very low cost. However, as we have seen, the decline in the FVC is an associated phenomenon and not the physiopathological cause of initial respiratory failure.

The other problem lies in the dispersion in the use of prediction equations among various centers, and even within the same center.[31] Both the lack of severity in the tests and the diversity in the prediction equation pose problems when one wishes to assess functional evolution based on the percentage of the predicted value. Therefore, it would be advisable to use the same table of predictive values throughout each patient's follow-up.[31] Using an absolute FVC value would avoid being dependent on the selected prediction equation but it would make it more difficult to detect deterioration in anthropometrically small patients (female sex, short stature, elderly, or their combinations), pos-

TABLE 1. Problems in the definition of clinical criteria[15]

1. Increased prevalence of interstitial lung disease and PPF diagnosis.
2. Need for unambiguous terminology to categorize progression despite treatment.
3. Need for risk stratification for progression.
4. Restricted and, in some countries, unrestricted use of antifibrotic agents.
5. Need for alternative procedures to surgical biopsy for initial diagnosis. Advanced age of patients and multiple comorbidities.
7. Difficulty of the evaluation in ruling out intercurrent conditions.

TABLE 2. PFF Criteria according to different Studies

	ATS/ERS/JRS/ALAT	INBUILD[4]	RELIEF[12]	COTTIN[6]
Year	2022	2019	2020	2018
Definition	Two criteria in the last year without any other explanation	At least one criterion in the last two years despite standard treatment (not nintedanib/ pirfenidone)	Any criterion within the previous 6-24 months, FVC annual absolute decline in FVC ≥5% of the predicted value	Any criterion within the 24 month period
Clinical	Deterioration of clinical symptoms	Worsening of clinical symptoms		Worsening of symptoms
Functional	Absolute decline in FVC ≥5% of the predicted value or absolute decline in DLCO ≥10% of the predicted value (corrected for Hb).	Relative decline in FVC ≥10% of the predicted value. Relative decline in FVC 5-10% of the predicted value with worsening clinical symptoms or increased HRCT signs	Annual absolute decline in FVC ≥5% of the predicted value.	Relative decline in FVC ≥10%. Relative decline in DLCO ≥15%.
Imaging	Progression of at least one HRCT sign*	Increase in HRCT signs.		Worsening of HRCT signs with a relative decline of 5-10%.
*increase in severity and extent of traction bronchiectasis or bronchioloectasis; increase or appearance of new honeycomb; new ground-glass opacities with traction bronchiectasis; new fine reticulations; greater extent or irregularity of reticulations; increased lung volume loss				

sibly overlooking many cases. On the contrary, the use of absolute values would be easier to observe in anthropometrically large subjects (male sex, tall stature, young, etc.), making them susceptible to over-prescription.

Within the ILD, different rates of progression can be observed.[1,10-11] But they have also been described within the diseases encompassed by the definition of PPF.[32] It is possible that those diseases with slower progression are exposed to a higher rate of treatment adverse events that exceeds its benefits. Therefore, the rate of progression should be a universal marker, regardless of the total decline in the FVC. Of course, to be significant, it should exceed not only the variability of the method but also the natural decline that comes with age (20-30 mL/year). That is, the deterioration between two measurements must be greater than 150 mL plus 30 mL for each year within the interval between the two measurements. For example, if a patient has an interval of 3 years between measurements, there should be a decrease of more than 240 mL (150 + 30 x 3) in order to attribute it to the disease itself.

The latest recommendation for the interpretation of the spirometry considers a post-bronchodilator change with a difference ≥10% of the variable under study to be significant.[33] This differs from what was recommended in previous editions, precisely because of the reasons already mentioned. Even in the absence of longitudinal studies, logic and biostatistics would indicate that this approach should be the most reasonable, along with the use of decision and severity thresholds. For example, "if the FVC is less than a certain value, then it is advisable to start treatment, even in the absence of symptoms", based on studies that have demonstrated an important increase in mortality or a deterioration in the quality of life from that threshold.

Another paragraph is devoted to nomenclature. The use of the percentage of the theoretical values has been shown to be subjected to bias, especially in elderly patients (precisely those most affected by interstitial diseases). The use of z-scores should also be imposed in this field for decision-making. A reanalysis of already conducted studies using z-scores instead of the percentage of the theoretical value would be advisable, while future studies exploring this topic should already include it.

Despite the bias that could influence the analysis of functional progression by FVC, it is the most

used variable in clinical follow-up studies of ILD because it is associated with prognosis.[9,27-28] The Writing Committee of the ATS/ERS/JRS/ALAT guidelines has chosen the change in absolute FVC values >5% in 1 year as a criterion for functional progression of PPF, extrapolating it from the accumulated evidence of IPF due to its predictive power on mortality.[1] However, some clinical studies have used relative changes of FVC.[34-35] Caution should be exercised regarding the definition of the change in the use of absolute vs. relative FVC values. Considering the changes in absolute values restricts the definition of progression in the new definition of PPF.[1]

It can be calculated based on the ml of the FVC or the percentage of the predicted FVC value.

For example: a patient with rheumatoid arthritis and ILD (HRCT UIP [usual interstitial pneumonia] pattern), who has started functional follow-up with FVC=70% of the predictive value and one year later has FVC=64% of the predictive value.

- By the absolute decline criterion (>5%) of the current guidelines:[1] initial 70% - 64%=6%. Therefore, it declined to be considered a functional criterion for PPF.
- By the previous relative decline criterion (>10%). For this example, the patient should have a FVC <63% after one year as the progression cut-off threshold. It is obtained by calculating 10% of 70% (7%). So, the value that should be defined as "progression" would be: 70%-7%=63%. Thus, it is clear that considering the previous "relative" decline criterion to define functional progression was less restrictive.

Different clinical studies with antifibrotics have used some definitions that are different from the criteria used for functional progression.[4,12-15]

Moreover, the minimum clinically significant difference (MCSD) for FVC in each of the ILD is not defined for this mode of progression, bearing in mind that all these progression cut-off points are extrapolations taken from the IPF for these other progressing ILD.

The natural progression of the ILD leads to hypoxemia (type I respiratory failure) due to the decrease in the area available for hematosis, caused by the progressive obliteration of the pulmonary vascular bed within the fibrotic tissue. The additional presence of hypercapnia (type II respiratory failure) is a phenomenon observed in the terminal stages of the condition. This occurs not only due to the reduction in lung size but also due to an increase in the elasticity of the parenchyma, which requires greater transpulmonary pressure that is necessary to mobilize tidal volume.[36-37] The above explains why the use of increasing doses of oxygen is the final treatment in this condition, and also why most attempts to ventilate these patients invasively or non-invasively have failed.[38-40]

Therefore, the measurement of gas exchange should be the goal for the follow-up in these patients, from a physiopathological point of view.

B.2 Decline in DLCO

Despite the fact that DLCO (corrected for hemoglobin) has proven to be a strong predictor in various ILD, it has not been used as a primary or secondary objective in the development of clinical studies.[57-58] Several factors have contributed to this: fewer centers performing the test, variability in intra-patient measurements, greater operator-dependent errors in the technique, various measurement techniques, variability between tables of predictive values, and the lack of evidence for its use as a predictor of evolution.[41-42] One of the most common errors in DLCO reporting is the absence of hemoglobin correction.

The decision to introduce this criterion, despite being less specific than FVC or HRCT and considering these technical aspects, also included ruling out other causes of DLCO worsening, such as pulmonary vascular disease, before attributing it to ILD progression. Therefore, other studies should be requested, like HRCT or Doppler echocardiogram, among others.

Greater specificity in justifying progression can be given by a simultaneous significant drop in FVC or progression in HRCT. However, the value given by the ATS/ERS/JRS/ALAT guidelines is that a decline in absolute values, with a preset threshold for DLCO greater than for FVC (>10%), alone, together with a clinical or radiographic criterion, can define progression, that is, on equal footing with the decline in FVC.[1]

Here, too, the ATS/ERS/JRS/ALAT guidelines indicate the change to define progression in absolute, not relative terms.[1]

For example: A patient with sarcoidosis and tomographic criteria of PPF who starts with 60% of the predictive value of DLCO at the initial visit, could be determined as progression:

– By absolute decline criterion: if the DLCO at one year is 50% or less (60%-50%=10 point drop) of the absolute value.
– By relative decline criterion (threshold >10%): 6% drop (10% of 60%) would be the value to use as a decline threshold, so a value of 54% or less (60%-6%=54%) would have qualified as progression.

Again, it is observed how using absolute values restricts the criterion for defining progression.

Moreover, the MCSD for DLCO in each of the DILDs is not defined for this mode of progression, bearing in mind that all these progression cut-off points are extrapolations taken from the IPF for these other progressing DILDs.

Despite the previously mentioned difficulties, this variable has been used in clinical studies as the absolute measure of DLCO without correction for alveolar ventilation (AV), which could increase collinearity with the FVC (see later) and make the conclusions in these studies less precise. One option could be to use KCO (carbon monoxide transfer coefficient) (DLCO/AV) in cases where alveolar ventilation (AV) is decreased.

Due to the variability of the method, it would be desirable to take a higher change value as a marker of progression compared to that of FVC, as it is a study with lower precision.

Finally, methodological variability has been a topic of debate for many years. Several studies have shown differences in the results between centers, particularly for DLCO, to the point that the 2005 recommendations already indicated that serial measurements should be performed at the same center (even on the same equipment) to avoid errors in decision-making.[43] This variability has driven the widespread use of the FVC in clinical studies of IPF, as this lack of precision implies the need for more costly quality controls, and larger recruitment with higher costs and longer times.[44-45]

B.3 Decline in the 6-minute walk test (6MWT)

Initially, the 6MWT was proposed as one of the criteria to define clinical deterioration (a drop of more than 50 meters from the predicted value).[6] This should not be surprising, since multiple studies have demonstrated a correlation between the 6-minute walk distance (6MWD) and the clinical status, regardless of the disease.[46-49] A decrease in the 6-minute walk distance can be due to disease progression, but it can also result from the development or progression of pulmonary hypertension, heart failure, deconditioning with muscle loss, or even the patient's own motivation. All of these are conditions associated with progressive chronic diseases.[53] Thus, while the 6MWT can be a clinical index, it is unlikely to indicate the appropriate time to use an antifibrotic treatment.

Given the fact that the deterioration of gas exchange is a cardinal marker of these conditions, and that SpO_2 is affected (both basal and during exercise), its monitoring has been proposed.[53] But the use of SpO_2 in any of its variables (basal, final, nadir, delta, etc.) has the main limitation of its poor sensitivity to early changes in the disease, being evident only with progression towards marked severity.[53] Some studies have proposed the drop in oxygen saturation (SpO_2) during the 6-minute walk test (6MWT), and this has been used as a follow-up parameter.[50] However, there are various problems that limit its utility and reliability. On one hand, there is significant diversity in the quality of pulse oximeters. This depends not only on the quality of the sensor but also on the reading and averaging algorithm. At the same moment and in the same patient, two oximeters can show differences of up to seven percentage points in their measurements. Another factor is that due to the morphology of the hemoglobin dissociation curve, gas exchange can decrease by up to 30% before this translates into significant desaturation.[51] In this context, it is more reasonable to measure the PaO_2 at rest or the DLCO. The problem is that the former is relatively invasive and subject to bias due to pre-analytical issues (sample oxygenation, processing delays, mixing with venous blood).[52] On the other hand, the DLCO has proven to be a reliable and reproducible test in controlled studies and guidelines, but its reliability is relative when comparing results from different centers. For this reason, several clinical studies have attempted to do without it in an effort to simplify detection, broaden recruitment of research centers, and reduce costs.

Thus, like the 6MWT, the SpO_2 can be of great clinical utility, but has limited resolution for making decisions on its own.

B.4.Compound endpoints

Compound endpoints could be a valid alternative to explore in future studies on PPF considering the events as the main objective, since the diseases involved cause damage in various forms.[54] The results could represent the global effects of the treatment and, in some cases, might reduce the sample size needed to reach the desired number of events. However, the components of the endpoint should have certain characteristics. Each of the events that make up the endpoint must have similar weight (if the proportion of one event is greater than others, it could lead to misinterpretation), and any collinearity should be minimal.[54] Collinearity occurs when there is a relationship between the measured variables (in regression models, this represents a significant problem). In this case, if the endpoints are related, there is a risk of assessing the same parameter in two different ways, which could lead to inappropriate results.[54] The components could link different physiological factors and show different domains of the disease, for example, changes in FVC and 6MWD. The first primarily reflects the progression of fibrosis, while the second indicates changes in various components (pulmonary, pulmonary vasculature, skeletal muscle, cardiovascular, etc.). Both measurements could worsen independently, but due to the relationship between the two tests, there could be minimal collinearity. On the other hand, between FVC and DLCO, collinearity is more pronounced, as they represent similar events in the development of interstitial disease.

Therefore, significant problems are established when assessing functional deterioration, which should be taken into account (Table 3).

B.5 General considerations

Other factors to consider regarding functional decline in real life

Real life is not a clinical study, and other factors must be considered. In our country, there are accredited differences in the management of pulmonary function laboratories, and patients often bring tests from different places over time to the clinic, and we should determine whether there has been progression or not.[56]

- Center accreditation: trained operator, biosafety standards, validated equipment, daily calibration.
- Use of the same predictive values throughout the follow-up of each patient.
- Differences in the tables of predictive values for the pulmonary function indicators in question (up to 10 % in FVC).[43,56-57]

Interesting retrospective and prospective studies don't consider these important factors that alone could explain differences in the indicators of the different participating centers, neither in the methodology nor in the analysis.[22-23,26]

Given the few prospective studies and the heterogeneity of the included population, it is prob-

TABLE 3. Problems in the definition of functional criteria[15]

1. Variability between pulmonary function laboratories (technical training and quality of maneuvers, calibration, various measurement methods).
2. Use of different tables of predictive values.
3. Different FVC decline rates in each of the diseases included in the PPF, and even within the same disease.
4. Different FVC behaviors in phase III studies and real-life studies.
5. No definition of MCSD for FVC and DLCO in the diseases included in PPF.
6. Phenomenon of regression to the mean.
7. Difficulty of the DLCO maneuver.
8. Interpretation of DLCO deterioration.
9. Frequent lack of correction for hemoglobin in DLCO.
10. 6MWT: limited validation in PPF clinical studies.
11. 6MWT: multicausal deterioration in distance walked.
12. Decrease in arterial oxygen saturation in 6MWT: variability in measurement accuracy between pulse oximeters, algorithm equipment and inter-device averaging.

6MWT: 6-minute walk test

ably still very premature to establish the pulmonary function values suggested by the guidelines as definitive.

Our suggestion is that pulmonary function tests be performed in duly accredited centers that meet quality standards, with trained and certified operators, and that evolution and follow-up always be done with the same team and in the same location so as to reduce the already described bias.

Meanwhile, more prospective research should be carried out to determine which thresholds of decline in pulmonary function indicators (FVC and DLCO) are decisive for defining progression, whether alone or in conjunction with other clinical and/or tomographic criteria, and the appropriate time window for evaluation. It is also necessary to assess whether a "one size fits all" approach can be applied, or not.

Mortality, surrogate markers, and FVC variability

Mortality is considered one of the most robust variables for evaluating the efficacy of drugs in clinical trials of IPF.[58] So far, few studies have demonstrated a benefit in mortality in this population. However, it should be considered that due to the eligibility criteria, recruited patients have mild to moderate disease with a 1-year and 2-year mortality rate of 6.6% and 13.7%, respectively.[59] For this reason, the use of this endpoint requires longer clinical trials, something that seems complex due to study costs, loss to follow-up, and the emergence of new therapies, among other difficulties. The lower mortality rate of patients with IPF who participate in clinical trials (23%) compared to those who don't (44%) can reflect the type of population included in the studies (with fewer comorbidities) and affect the external validity of study conclusions, including pivotal trials. FVC is considered a predictor of mortality, and therefore its measurement could indicate whether a patient who is receiving certain treatment can improve their survival in the medium and long term. It is necessary to consider what is represented by this variable: the level of fibrosis, mortality, or both. If it represents mortality, there may be some difficulties with its application, both in daily practice and in research.

The expected rate of decline in the analysis of the placebo groups of IPF clinical trials has proven that the deterioration of the lung function in patients with mild to moderate disease who received a placebo was approximately 150-200 ml/year.[60-62] However, the behavior varied greatly among the individuals. Some progressed rapidly, while others remained stable during the trial, suggesting that the proposed models are poor disease predictors. Data from the CAPACITY and ASCEND studies demonstrated that the change in FVC was highly variable and did not predict 6-month outcomes.[60-62] In the INPULSIS trials, patients treated with placebo and with an FVC >90% or <90% at baseline had a very similar decrease in FVC at 52 weeks, which could suggest that patients with preserved FVC should not be considered at low risk of progression.[62]

In other autoimmune diseases such as systemic sclerosis, different behaviors in the clinical evolution of the disease have been documented (depending on the tomographic pattern and the presence of risk factors for progression). For example, in studies of systemic sclerosis, there are other primary endpoints; tocilizumab was approved by the Food and Drug Administration for interstitial pulmonary disease in systemic sclerosis based on the FOCUSSED and FASSCINATE studies (using tests for hierarchical hypotheses).[63-64] The primary objective was the improvement of the skin evaluated with the Rodnan score (not achieved). However, upon observing a stabilization of the FVC (secondary objective) in the open-label period, despite the study not being designed for this objective, the drug was approved for that indication.[64] In rheumatoid arthritis, where the inflammatory component and the course of the disease can influence evaluations.[10-11,25-26]

For these reasons, the following methodological issues can arise: 1) The rate of lung function decline can differ in patients with the same etiology or in patients with different diagnoses. 2) The drug must demonstrate that it improves functionality, taking into account the expected rate of decline. However, this measurement is highly variable even within a group of patients with the same disease. 3) The timing of the lung function measurement may need to be extended in some cases for the effect to be more pronounced, whether due to the drug's mechanism of action or the underlying disease and its concomitant treatments. This does not imply a worse or better evolution. Therefore, if measured at an inappropriate time,

it can result in a misinterpretation of the results. Not all the drugs act in the same way. While the observational data and recommendations state that the decline is measured at 12 or 24 weeks, these times do not necessarily replicate in the context of treatment, especially with therapeutic targets that are different from those already used.

Can a predictor variable of death be used as a parameter for monitoring pharmacological treatment? If the variable, (like for example, the FVC) is intended to be used as a surrogate endpoint, certain characteristics that these types of variables must meet should be considered. The progression of lung damage can be slow and its assessment may require at least 12 months of follow-up. In the INPULSIS studies (patients with IPF, 52-week follow-up, evaluating nintedanib) and INBUILD studies (patients with PF-ILD), around 15% of patients receiving placebo maintained their FVC.[14,62] The progression pattern will depend on the etiology and phenotype of each individual, among other variables. Therefore, differentiating those with slow progression from those at higher risk of rapid progression is important, both for daily practice and for clinical trials.

Can the FVC be considered a good surrogate marker of mortality? The FDA accepted the FVC as a surrogate marker of mortality based on findings of the correlation between mortality and FVC in the review of clinical trial data for nintedanib and pirfenidone and information from observational studies.[28] Surrogate markers are generally biomarkers capable of reflecting a clinical endpoint before it is produced. Ideally, the markers should have certain characteristics that make them reliable; first, they should be related to the physiopathological process of the disease under study, so that before damage occurs, the marker changes as an expression of the process. Secondly, its value changes in two directions, meaning it can improve if the clinical endpoint improves, or worsen if the clinical event worsens. In some cases, they are confused with risk or protective factors that always vary in one direction only. For example, if the patient has the risk factor, it is associated with worse clinical evolution, but the absence of the risk factor does not mean better evolution. Thirdly, they should be reproducible and easy to interpret, among other characteristics. Some of the biomarkers suggested for IPF, such as genetic markers, plasma soluble factors, metabolomics, clinical, or imaging markers, have not been validated and, in some cases, they are not available for daily practice. It is also important to consider that different therapeutic targets should be reflected in the biomarker measurement. If the therapeutic target occurs later in the physiopathological pathway of the damage, probably it will not be reflected in the measurements. Therefore, a good surrogate marker may not be useful for all strategies and treatment monitoring in daily practice. FVC or DLCO can behave as good measures of lung impairment degree, but as a surrogate marker of mortality, they can pose some questions. In fact, candidates are still being investigated to provide a more accurate measure for each disease.

Phenomenon of regression to the mean

In chronic diseases that have exacerbations but also show a progressive decline, such as the PPF, regression to the mean could represent an improvement in the clinical condition as part of the natural history of the disease (an inherent property of each disease without intervention).[65] Therefore, we must make every effort to differentiate improvement caused by pharmacological intervention from regression to the mean. It is expected that in randomized clinical trials this difficulty will be resolved, since both the group receiving the drug under study and the comparator have the same component of regression to the mean when all participants have the same etiology. It is complex to extrapolate regression to the mean from one disease to another. When patients with different diseases are enrolled in a study, regression to the mean can act as a bias/confounding factor if the etiologies are not evenly distributed through the comparative groups. This applies to the different diseases that could fall under the definition of PPF. Acute exacerbations of IPF have been observed in 2-16% of patients treated with placebo over a period of 24 to 60 weeks, and mortality ranged from 2.5 to 13.3% over a period of 28 to 96 weeks.[60-62]

C. Imaging criteria

The ATS/ERS/JRS/ALAT 2022 guidelines establish the following tomographic criteria for the progression of PPF[1]:

– Increased severity and extent of traction bronchiectasis or bronchiolectasis.

– Increase or appearance of new honeycomb pattern.
– New ground-glass opacity with traction bronchiectasis.
– New fine reticulations.
– Greater extent or irregularity of reticulations.
– Greater loss of lung volume.

Cross-sectional, coronal, and sagittal sections of the upper, middle, and lower lung fields should be evaluated. In the INBUILD study, progression occurs when the observer defines a 10% or higher increase in interstitial involvement. However, this concept requires further evaluation in other clinical studies.[4] The main drawback of the imaging definition is the interobserver variability and lack of agreement among imaging specialists, especially in non-UIP patterns. This is why a multidisciplinary approach and discussion are suggested to improve agreement.[5,66] Over the years, technological advances have increased interobserver agreement and improved the kappa index and the ability of both specialized and non-specialized radiologists and pulmonologists to identify tomographic patterns.[67] There is diagnostic correlation among ILD (interstitial lung disease) expert radiologists (kappa 0.86), with lower agreement in the extent of fibrosis and presence of reticulations than in the presence of honeycombing, traction bronchiectasis, and presence of fibrosis (kappa range between 0.63-0.84).[68]

The UIP pattern in CFHP is correlated with significant functional decline as in IPF, and is also a strong progression factor in rheumatoid arthritis-associated UIP.[69-70]

It is crucial to rule out alternative diagnoses such as lung infections, heart failure, and pulmonary thromboembolism when considering tomographic progression. With regard to the timing of the tomography, no specific periodicity is established. Clinical evaluation and functional deterioration should be assessed, but it is generally agreed that at least one annual tomography would be advisable.[1,2]

In 2008, Goh et al developed a quantitative method to evaluate the extent of fibrosis on HRCT in scleroderma-related interstitial lung disease, defining limited disease as <10% and extensive disease as >30%, also involving the FVC for the classification.[71] The extent of the disease is measured in five cuts: large vessels, carina, pulmonary vein confluence, halfway between the third and fifth cut, and above the right hemidiaphragm.[71]

New advances in tomographic diagnoses are emerging with the advent of artificial intelligence.[66] The CALIPER program allows the differentiation between IPF and connective tissue disease-related fibrosis (CTD-F), observing differences in peripheral reticulation volumes—greater in IPF than in CTD-F—and the volume of pulmonary vascular structures.[72-73] In IPF, these two quantitative markers are related to functional deterioration.[72] New scales are emerging for PPF that combine indices of traction bronchiectasis and reticulation, which are related to prognosis and evolution.[20,6] Additionally, the loss of volume in the lower lobe has been added as a prognostic parameter.[74] All artificial intelligence projects and their interaction with radiologists would require validation following the learning curve.

A notable advancement has been driven by a group of radiologists led by Simon Walsh, promoting the use of AI to evaluate the prognostic accuracy of a deep learning algorithm (SOFIA, Systematic Objective Fibrotic Imaging Analysis algorithm).[6] Trained and validated in UIP identification in a cohort of IPF patients from the British national registry, SOFIA has been used to identify the extent and different patterns of UIP, comparing the evaluations to those of expert radiologists.[75] Another technique being evaluated for interstitial lung disease progression is the nuclear magnetic resonance (NMR).[1,76] The conventional NMR has limited utility, but research is ongoing into the potential use of pulmonary perfusion NMR with angiography.[76]

It is important to use both quantitative and qualitative methods in the evaluation of the HRCT in PPF to diagnose and assess the progression of fibrosis in the various conditions that make up the PPF.[72]

Over the years, quantitative and qualitative methods for tomographic quantification of PPF have been used, both in contrast with each other and also complementing each other (with no method predominating over the other). It is recommended to use both methods together as complementary approaches.

In our region, in reality, there is significant variation in the criteria for characterizing each tomographic sign, adding another problem to the existing problems of tomographic equipment

TABLE 4. Problems in the definition of imaging criteria[15]

1. Inter-observer variability in assessing progression.
2. Variability in the quality of high-resolution CT scans between different machines.
3. Lack of training for radiologists in defining interstitial CT patterns.
4. Subjective definition of progression by the observer.
5. Validation of >10% of the progression as an index.
6. Low availability of software programs for assessing tomographic progression.

heterogeneity and updates, as well as the lack of training among radiologists in defining interstitial tomographic patterns. Continuous medical education programs by relevant scientific societies will undoubtedly be the most immediate and effective contribution in evaluating tomographic progression as an imaging criterion to define PPF. These programs will also help identify imaging centers with appropriate equipment.

Table 4 outlines the difficulties in assessing deterioration through imaging to define PPF current criteria.

To conclude, the criteria for defining progressive fibrosing pulmonary diseases are constantly evolving. A critical analysis was conducted to determine the assessments needed to define disease progression with clinical, functional, and imaging criteria. Many aspects detailed in this manuscript will surely require validation in future prospective and controlled clinical studies of the analyzed indices. Therefore, current interpretations must be analyzed in the context of the factors affecting them.

REFERENCES

1. 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:e18-e47. https://doi.org/10.1164/rccm.202202-0399ST
2. Rajan SK, Cottin V, Dhar R, et al. Progressive Pulmonary Fibrosis: an expert group consensus statement. Eur Respir J 2023;61:2103187. https://doi.org/10.1183/13993003.03187-2021
3. Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J 2013;42:750–7. https://doi.org/10.1183/09031936.00131912
4. Flaherty KR, Brown KK, Wells AU, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respir Res 2017; 4:e000212. https://doi.org/10.1136/bmjresp-2017-000212
5. Wells AU, Brown KK, Flaherty KR, et al. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J 2018;51:1800692. https://doi.org/10.1183/13993003.00692-2018
6. Cottin V, Hirani NA, Hotchkin DL et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27:180076. https://doi.org/10.1183/16000617.0076-2018
7. Cottin V, Wollin L, Fischer A, et al. Fibrosing interstitial lung diseases:knows and unknows. Eur Respir Rev 2019:28:180100. https://doi.org/10.1183/16000617.0100-2018
8. Cottin V. Treatment of progressive fibrosis interstitial lung diseases: a milestone in the management of interstitial lung diseases. Eur Respir Rev 2019;28:190109. https://doi.org/10.1183/16000617.0109-2019
9. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med 2020;383:958–68. https://doi.org/10.1056/NEJMra2005230
10. Brown KK, Martinez FJ, Walsh SL, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020;55:2000085. https://doi.org/10.1183/13993003.00085-2020
11. Kolb M, Vasákova. The natural history of progressive fibrosing interstitial lung diseases. Respir Res. 2019;20:57. https://doi.org/10.1186/s12931-019-1022-1
12. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020;8:147–57. https://doi.org/10.1016/S2213-2600(19)30341-8
13. Behr J, Prasse A, Kreuter M, et al. RELIEF Investigators. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9:476–86. https://doi.org/10.1016/S2213-2600(20)30554-3
14. Flaherty KR, Wells AU, Cottin V, et al. INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27. https://doi.org/10.1056/NEJMoa1908681

15. Kreuter M, Kahn N, Sambataro FM, et al. To be or not to be-the uncertainty of PF-ILD. Eur Respir J. 2020;56:3713. https://doi.org/10.1183/13993003.congress-2020.3713
16. Cottin V, Teague R, Nicholson L, Langham S, Baldwin M. The burden of progressive-fibrosing interstitial lung diseases. Front Med (Lausanne). 2022;9:799912. https://doi.org/10.3389/fmed.2022.799912
17. Cottin V, Brown KK, Flaherty K, Wells AU. Progressive pulmonary fibrosis: should the timelines be taken out of the definition? Am J Respir Crit Care Med. 2022;206:1293–4. https://doi.org/10.1164/rccm.202206-1143LE
18. Johannson KA, Kolb M, Fisher JH, Walsh SL. Progressive pulmonary fibrosis: putting the cart before the horse. Am J Respir Crit Care Med. 2022;206:1294–5. https://doi.org/10.1164/rccm.202206-1166LE
19. Cottin V. Criteria for Progressive Pulmonary Fibrosis: getting the horse ready for the cart. Am J Respir Crit Care Med 2023;207:11-2. https://doi.org/10.1164/rccm.202208-1639ED
20. Molina Molina M, Buendia Roldan I, Castillo D, Caro F, Valenzuela C, Selman M. Diagnostic and therapeutic developments in Progressive Pulmonary Fibrosis. Arch Bronchoneumol. 2022;58:418-24. https://doi.org/10.1016/j.arbres.2021.12.006
21. Stanel SC, Rivera-Ortega P. Present and future perspectives in early diagnosis and monitoring for progressive fibrosing interstitial lung diseases. Front Med. 2023;10.1114722. https://doi.org/10.3389/fmed.2023.1114722
22. Khor YH, Farooqi M, Ryerson CJ. Patients characteristics and survival for progressive pulmonary fibrosis using different definitions. Am J Respir Crit Care Med. 2023;207:102-5. https://doi.org/10.1164/rccm.202205-0910LE
23. Pugashetti JV, Adegunsoye A, Wu Z, et al. Validation of proposed criteria for progressive pulmonary fibrosis. Am J Respir Crit Care Med. 2023;207:69–76. https://doi.org/10.1164/rccm.202201-0124OC
24. Nasser M, Larrieu S, Si-Mohamed S, et al. Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). Eur Respir J. 2021;57:2002718. https://doi.org/10.1183/13993003.02718-2020
25. Takei R, Brown KK, Yamano Y, et al. Prevalence and prognosis of chronic fibrosing interstitial lung diseases with a progressive phenotype. Respirology. 2022;27:333–40. https://doi.org/10.1111/resp.14245
26. Hambly N, Farooqi MM, Dvorkin-Gheva A, et al. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. Eur Respir J 2022;60:2102571. https://doi.org/10.1183/13993003.02571-2021
27. Torrisi SE, Kahn N, Wälscher J, et al. Outcomes and incidence of PF-ILD according to different definitions in a real world setting. Front Pharmacol. 2021;12:790204. https://doi.org/10.3389/fphar.2021.790204
28. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis–FDA review of pirfenidone and nintedanib. N Engl J Med. 2015;372:1189–91. https://doi.org/10.1056/NEJMp1500526
29. Gil B, Usandivaras M, Enghelmayer J, et al. Enfermedades pulmonares intersticiales fibrosantes con fenotipo progresivo (EPID-FP). Acceso e 1 de Julio de 2023 en http://www.aamr.org.ar/lagaceta/enfermedades-pulmonares-intersticiales-fibrosantes-con-fenotipo-progresivo-epid-fp/
30. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J. 2017;49:1601011. https://doi.org/10.1183/13993003.01011-2016
31. Arce SC, DE Vito EL. Ecuaciones espirométricas utilizadas en la Argentina y su implicancia diagnóstica. Abstract ALAT 2012.
32. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011;184:1382–9. https://doi.org/10.1164/rccm.201105-0840OC
33. Oldham JM, Lee CT, Wu Z, Bowman WS, Vu Pugashetti J, Dao N, et al. Lung function trajectory in progressive fibrosing interstitial lung disease. Eur Respir J. 2021;59:2101396. https://doi.org/10.1183/13993003.01396-2021
34. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. ATS/ERS Task Force: Standartization of Lung Function Testing. Eur Respir J. 2005;26:48-68.
35. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168:538–42. https://doi.org/10.1164/rccm.200211-1311OC
36. West JB. West's Pulmonary Pathophysiology, 8th edition 2012, Editors Wolters Kluwer.
37. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378:1949-61. https://doi.org/10.1016/S0140-6736(11)60052-4
38. Copeland CR, Lancaster LH. Management of Progressive Fibrosing Interstitial Lung Diseases (PF-ILD). Front Med (Lausanne). 2021;8:743977. https://doi.org/10.3389/fmed.2021.743977
39. Fernández-Pérez ER, Yilmaz M, Jenad H, et al. Ventilator settings and outcome of 12qc xrespiratory failure in chronic interstitial lung disease. Chest. 2008;133:1113-9. https://doi.org/10.1378/chest.07-1481
40. Mooney JJ, Raimundo K, Chang E, Broder MS. Mechanical ventilation in idiopathic pulmonary fibrosis: a nationwide analysis of ventilator use, outcomes, and resource burden. BMC Pulm Med. 2017;17:84. https://doi.org/10.1186/s12890-017-0426-2
41. Collard HR, King TE jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168:538-42. https://doi.org/10.1164/rccm.200211-1311OC
42. Ryerson Cj, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphy-

sema in idiopathic pulmonary fibrosis. Chest. 2013;144:234-40. https://doi.org/10.1378/chest.12-2403
43. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir. J 2022;60:2101499. https://doi.org/10.1183/13993003.01499-2021
44. Jensen RL, Teeter JG, England RD, White HJ, Pickering EH, Crapo RO. Instrument accuracy and reproducibility in measurements of pulmonary function. Chest. 2007;132:388-95. https://doi.org/10.1378/chest.06-1998
45. Jensen RL, Teeter JG, England RD, Howell HM, White HJ, Pickering EH, Crapo RO. Sources of long-term variability in measurements of lung function: implications for interpretation and clinical trial design. Chest. 2007;132:396-402. https://doi.org/10.1378/chest.06-1999
46. Martens P, Augusto SN Jr, Finet JE, Tang WHW. Distinct Impact of Noncardiac Comorbidities on Exercise Capacity and Functional Status in Chronic Heart Failure. JACC Heart Fail. 2023;17:S2213-1779(23)00254-8.
47. Szarvas Z, Fekete M, Horvath R, et al. Cardiopulmonary rehabilitation programme improves physical health and quality of life in post-COVID syndrome. Ann Palliat Med. 2023;12:548-60. https://doi.org/10.21037/apm-22-1143
48. Ferreira MB, Saraiva FA, Fonseca T, et al. Clinical associations and prognostic implications of 6-minute walk test in rheumatoid arthritis. Sci Rep. 2022;12:18672. https://doi.org/10.1038/s41598-022-21547-z
49. Khor YH, Farooqi M, Hambly N, et al. Austin ILD Registry and CARE-PF Investigators. Trajectories and Prognostic Significance of 6-Minute Walk Test Parameters in Fibrotic Interstitial Lung Disease: A Multicenter Study. Chest. 2023;163:345-57. https://doi.org/10.1016/j.chest.2022.08.2233
50. Lancaster LH. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2018;13:45. https://doi.org/10.1186/s40248-018-0158-z
51. Hsia CC. Respiratory function of hemoglobin. N Engl J Med. 1998;338:239-47. https://doi.org/10.1056/NEJM199801223380407
52. Baird G. Preanalytical considerations in blood gas analysis. Biochem Med (Zagreb). 2013;23:19-27. https://doi.org/10.11613/BM.2013.005
53. Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, et al. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax. 2012;67:407–11. https://doi.org/10.1136/thoraxjnl-2011-201184
54. European Network for Health Technology Assessment. Guideline of Endpoints used for relative effectiveness assessment of pharmaceuticals Composite endpoints: Final Version.Febrero 2023. Acceso el 7 de Junio de 2023 en https://www.eunethta.eu/wp-content/uploads/2018/01/Composite-endpoints.pdf
55. Holland A, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428-46. https://doi.org/10.1136/thoraxjnl-2011-201184
56. Arce S, De Vito E. Caracteristicas de los laboratorios de función pulmonar en Argentina. Rev Am Med Respir. 2011;4:167-75.
57. Galindez F, Sivori M, Garcia O, et al. Valores espirométricos normales para la ciudad de Buenos Aires. Medicina Buenos Aires 1998;58:141-6.
58. Nathana SD, Meyerb KC. IPF clinical trial design and endpoints,. Curr Opin Pulm Med. 2014;20:463–71. https://doi.org/10.1097/MCP.0000000000000091
59. King TE Jr, Albera C, Bradford WZ, et al. All-cause mortality rate in patients with idiopathic pulmonary fibrosis: implications for the design and execution of clinical trials. Am J Respir Crit Care Med. 2014; 189:825–31. https://doi.org/10.1164/rccm.201311-1951OC
60. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. Lancet. 2011;377:1760-9. https://doi.org/10.1016/S0140-6736(11)60405-4
61. 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;370:2083-2. https://doi.org/10.1056/NEJMoa1402582
62. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in Idiopathic Pulmonary Fibrosis. N Engl J Med. 2014;370:2071-82. https://doi.org/10.1056/NEJMoa1402584
63. Roofeh D, Lin CF, Goldin J, et al. Tocilizumab prevents progression of early systemic Sclerosis- associated interstitial lung disease. Arthritis Rheumatol. 2021;73:1301-10. https://doi.org/10.1002/art.41668
64. Khanna D, Denton CP, Lin CJ, et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of phase II randomized controlled trial (fascinate. Ann Rheum Dis. 2018;77:212-20. https://doi.org/10.1136/annrheumdis-2017-211682
65. Stigler SM, Regression towards the mean, historically considered. Stat Meth Med Res. 1997;6:103-14. https://doi.org/10.1177/096228029700600202
66. Aziz ZA, Wells AU, Hansell DM, et al. HRCT diagnosis of diffuse parenchymal lung disease: inter-observer variation. Thorax. 2004; 59: 506–511. https://doi.org/10.1136/thx.2003.020396
67. Lynch D, Godwin JD, Safrin S, et al. High resolution computed tomography in idiophatic pulmonary fibrosis: diagnosis and prognostic. Am J Respir Crit Care Med. 2005;172:488-93. https://doi.org/10.1164/rccm.200412-1756OC
68. Gagliardi M, Berg DV, Heylen CE, et al. Real-life prevalence of progressive fibrosing interstitial lung diseases. Sci Rep. 2021;11:23988. https://doi.org/10.1038/s41598-021-03481-8
69. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010;35:1322–8. https://doi.org/10.1183/09031936.00092309
70. Kim HC, Lee JS, Lee EY, et al. Risk prediction model in rheumatoid arthritis-associated interstitial lung disease. Respirology. 2020;25:1257–64. https://doi.org/10.1111/resp.13848

71. Goh N, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system Am J Respir Crit Care Med. 2008;177:1248-54. https://doi.org/10.1164/rccm.200706-877OC
72. Walsh SLF, Devaraj A, Enghelmayer JI, et al. Role of imaging in progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018; 27: 180073. https://doi.org/10.1183/16000617.0073-2018
73. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: a patient outcome study. BMC Med. 2016;14:190. https://doi.org/10.1186/s12916-016-0739-7
74. Clukers J, Lanclus M, Belmans D, et al. Interstitial lung disease in systemic sclerosis quantification of disease classification and progression with high-resolution computed tomography: An observational study. Scleroderma Relat Disord. 2021;6:154-64. https://doi.org/10.1177/2397198320985377
75. Walsh SLF, Mackintosh JA, Callandriello L, et al. Deep learning-based outcome prediction in progressive fibrotic lung disease using high resolution computed tomography. Am J Respir Crit Care Med. 2022;206:883-91. https://doi.org/10.1164/rccm.202112-2684OC
76. Lonzetti L, Zanon M, Sartori Pacini G, et al. Magnetic resonance imaging of interstitial lung diseases: A state-of-the-art review. Respir Med. 2019;155:79–85. https://doi.org/10.1016/j.rmed.2019.07.006