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Progressive fibrotic interstitial lung disease

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ABSTRACT

Many interstitial lung diseases (ILDs) share mechanisms that result in a progressive fibrosing phenotype. In Brazil, the most common progressive fibrosing interstitial lung diseases (PF-ILDs) are chronic hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, unclassified ILD, and connective tissue diseases. PF-ILD is seen in approximately 30% of patients with ILD. Because PF-ILD is characterized by disease progression after initiation of appropriate treatment, a diagnosis of the disease resulting in fibrosis is critical. Different criteria have been proposed to define progressive disease, including worsening respiratory symptoms, lung function decline, and radiological evidence of disease progression. Although the time elapsed between diagnosis and progression varies, progression can occur at any time after diagnosis. Several factors indicate an increased risk of progression and death. In the last few years, antifibrotic drugs used in patients with idiopathic pulmonary fibrosis have been tested in patients with PF-ILD. The effects of nintedanib and placebo have been compared in patients with PF-ILD, a mean difference of 107.0 mL/year being observed, favoring nintedanib. The U.S. Food and Drug Administration and the Brazilian Health Regulatory Agency have approved the use of nintedanib in such patients on the basis of this finding. Pirfenidone has been evaluated in patients with unclassified ILD and in patients with other ILDs, the results being similar to those for nintedanib. More studies are needed in order to identify markers of increased risk of progression in patients with ILD and determine the likelihood of response to treatment with standard or new drugs.

Keywords: Alveolitis, extrinsic allergic; Idiopathic pulmonary fibrosis; Lung diseases, interstitial; Connective tissue diseases.

INTRODUCTION

Interstitial lung diseases (ILDs) are a diverse collection of illnesses defined by lung parenchymal inflammation and fibrosis. Only approximately 30% of ILD cases have a known cause. Although idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic ILDs, it only accounts for a modest proportion of patients—approximately 20% in referral centers.[1] A large multicenter cohort study in Brazil found that connective tissue disease (CTD)-associated ILD is the most common cause, in 27% of patients, closely followed by hypersensitivity pneumonitis (HP), in 23%, IPF, in 14%, and unclassified ILD, in 10%.[2] These results differ from those reported in other countries.[2]

CTD, chronic hypersensitivity pneumonitis (CHP), unclassified ILD, IPF, nonspecific interstitial pneumonia (NSIP), sarcoidosis, organizing pneumonia, and ILDs associated with occupational exposures are examples of ILDs that can progress. In a seminal study,[3] these disorders were initially grouped together under the label progressive fibrosing interstitial lung diseases (PF-ILDs). It has recently been proposed that these disorders be collectively referred to as progressive pulmonary fibrosis.[4]

Because PF-ILD is characterized by disease progression after initiation of appropriate treatment, a diagnosis of the disease resulting in pulmonary fibrosis is crucial.[5] In the case of CTD-associated ILD, this includes the use of one or more courses of immunosuppressants and, in the case of HP, removal of the offending antigen. Differentiating IPF from non-IPF is particularly important because the prognosis of IPF is worse than that of other ILDs and because of the different types of pharmacotherapy. Although IPF is the most common idiopathic fibrotic ILD, fibrosis in non-IPF ILDs is frequently preceded by or linked with inflammation. A seminal study found that treating IPF with corticosteroids and immunosuppressants leads to worse outcomes.[6] Despite major heterogeneity, ILD subtypes share morphological traits and pathogenic processes, giving birth to the concept of a progressive fibrosing phenotype, which may be applied to a wide range of fibrotic ILDs.[7]

PREVALENCE

The prevalence of PF-ILD is difficult to establish; however, 30% of ILD patients are anticipated to progress to more advanced disease despite treatment.[8] The difficulty in determining the exact prevalence of PF-ILD is most likely related to the rarity of the disease, the lack

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of a widely accepted definition, the broad spectrum of diseases, and the difficulty in establishing a diagnosis.[9,10] Clinical parameters associated with a higher likelihood of disease progression should be better defined.

PROGRESSION CRITERIA

The currently recommended criteria for evaluating PF-ILD are shown in Charts 1 and 2.[3,4] It should be noted that the progression criteria proposed in one of the aforementioned studies[3] are applied after 24 months of observation, and those proposed in the other study[4] are applied after 12 months of observation.[3,4] However, ILD progression should be checked on a regular basis because it can occur later in the monitoring period, resulting in certain markers of late progression being ignored.[11,12]

Dyspnea is the most significant factor influencing the quality of life of ILD patients. In IPF trials, dyspnea plays a significant and independent role in predicting survival. It is crucial to remember, however, that exertional dyspnea and lower exercise tolerance are multifactorial in patients with ILD, and their associations with functional variables are not straightforward.[13] When PF-ILD is associated with systemic disorders, a decrease in exercise capacity could indicate muscle or joint issues, anemia, pulmonary vascular disease, or left ventricular failure.

Several different outcomes have been used in order to estimate disease progression, although hospitalizations for exacerbations and the initiation of oxygen therapy have the most impact.[13] There is currently no single commonly accepted definition of acute exacerbation for all ILDs with a progressive fibrotic pattern. For IPF, specific exacerbation criteria have been proposed.[14] An acute exacerbation is defined by a sudden, severe worsening of respiratory function, with increased dyspnea and hypoxemia and new ground-glass opacities on HRCT.[14] Acute exacerbations of IPF can be idiopathic or due to infection or aspiration, but they are associated with substantial morbidity and death.[15]

Some individuals with rheumatic disease-associated ILD develop acute exacerbations, which are characterized by rapid ILD progression, substantial mortality during or soon after the exacerbation, and a very low 1-year survival rate.[16] In one study, 18 of 101 patients with biopsy-proven HP experienced acute exacerbations.[17] A reduced DL_{CO} and a radiological usual interstitial pneumonia (UIP) pattern were found to be risk factors for acute exacerbation.[17] The in-hospital mortality rate was 44.4%.[17] Patients with acute exacerbations had significantly lower median survival from diagnosis than did those without (26.0 months vs. 55.0 months; $p = 0.008$).[17] Severe dyspnea, a histological or radiological pattern of UIP, low oxygenation, low FVC, and a low baseline DL_{CO} were all risk factors for acute exacerbations in ILD patients.[17]

Acute exacerbations, on the other hand, have their own definition and do not provide a way to characterize fibrosis progression.[4] In practice, however, clinicians should reassess patients after exacerbations and use these assessments in order to determine whether progression has occurred.

Desaturation during exertion and/or at rest is a significant characteristic of fibrotic ILD, indicating poor outcomes such as pulmonary hypertension and decreased daily physical activity. When ILD patients require long-term oxygen therapy to ease dyspnea and hypoxemia, their lung function impairment has progressed to a severe degree, with a dismal

Chart 1. Criteria for evaluating progressive fibrosing interstitial lung diseases.[a]

Decline ≥ 10% predicted in FVC in the last 24 months
Decline ≥ 5% to < 10% predicted in FVC in the last 24 months with one or two of the following: Progressive worsening of symptoms Increased extent of fibrosis on HRCT
Progressive worsening of symptoms and increased extent of fibrosis on HRCT

[a]Based on Flaherty et al.[3]

Chart 2. Criteria for evaluating progressive fibrosing interstitial lung diseases.[a]

PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation:
1. Worsening respiratory symptoms
2. Physiological evidence of disease progression (either of the following): • Decline in FVC ≥ 5% predicted within 1 year of follow-up • Decline in DL_{CO} (corrected for hemoglobin) ≥ 10% predicted within 1 year of follow-up
3. Radiological evidence of disease progression (one or more of the following): • Increased extent or severity of traction bronchiectasis and bronchiolectasis • New ground-glass opacity with traction bronchiectasis • New fine reticulation • Increased extent or increased coarseness of reticular abnormality • New or increased honeycombing • Increased lobar volume loss

PPF: progressive pulmonary fibrosis. [a]Based on Raghu et al.[4]

prognosis.[13,18] In a worldwide survey,[18] 139 (17%) of 826 individuals with diverse ILDs who were either normoxic or had isolated exertional hypoxemia at baseline developed resting hypoxemia. The median transplant-free survival after the onset of resting hypoxemia was 8.2 months (IQR, 3.2-17.8 months).[18]

Because the correlation between functional trajectories and HRCT findings in patients with PF-ILD is not always direct, imaging techniques are generally noninvasive and can provide information on diagnosis and prognosis, with serial images being used for follow-up assessment, as well as to assess complications and disease progression, in conjunction with clinical and functional data. A gradual fibrosing phenotype with worsening clinical parameters but apparently stable HRCT findings (or vice versa) is therefore possible.

Because the entire chest must be examined subjectively, imaging approaches rely significantly on visual analysis and are limited by the use of qualitative assessment, with minor changes being difficult to identify on serial images.[19] Although computer-based quantitative HRCT evaluation is a more objective and reproducible method of measuring progression than is visual assessment, it is not extensively used and must be verified and standardized before it can be widely employed in the real world.[20]

The best interval for repeat HRCT to assess disease progression is uncertain. Limited evidence suggests that chest HRCT should be repeated within 12-24 months in patients with systemic sclerosis and stable lung function, when it may be valuable for early diagnosis of progression and might influence the outcome. This interval should be shorter (3-4 months) in conditions with a high risk of quicker progression (e.g., familial fibrosis caused by telomere mutations) or with changes in symptoms and lung function tests.

Although it may be easy to identify disease progression on HRCT in some situations, it is not always evident whether there has been fibrosis progression. This is especially true in the context of HP, in which follow-up HRCT scans can show progression of ground-glass opacity without traction bronchiolectasis but cannot determine whether this ground-glass opacity represents progressive "fine fibrosis" or an inflammatory nonfibrotic interstitial infiltrate.[21]

Deterioration in lung function is a critical requirement for PF-ILD and is most typically assessed by means of FVC and DL_{CO}. Because of their well-established connection with prognosis, changes in FVC are the most routinely used physiological parameter to monitor patients with IPF. Because this shift varies according to the criterion of interest and is heavily influenced by ILD diagnosis, it is unclear which proposed PF-ILD criteria identify those who are most likely to undergo a subsequent reduction in FVC.[22]

Decline in FVC can be calculated in three ways: an absolute change (e.g., a decline of < 100 mL in a drug vs. placebo trial); a relative decline of 10% (e.g., from 60% predicted to 54% predicted; 60% − 54% × 100/60% = 10%); and an absolute decline of 10% (e.g., from 60% predicted to 50% predicted). In the proposed decline criterion, "relative decline" refers to a percentage value in respect to the original value, whereas "absolute decline variation" refers to the predicted value.[3,4]

Absolutes (relative to predicted values) of 10% and 5% have been suggested as indicators of decline.[3,4] These metrics are simpler to calculate; however, a relative reduction of 10% in FVC may be preferable to an absolute decline of 10% in measuring disease progression because the sensitivity for detecting progression is higher.[23,24] When symptoms or imaging abnormalities deteriorate, modest changes in FVC, such as a drop of 5-10% in the predicted value, should be considered.[4,5]

A decrease in DL_{CO} (adjusted for hemoglobin) is a substantial predictor of mortality in patients with fibrotic lung disorders.[25] Previous research has shown that a 15% decrease in DL_{CO} from its initial value is clinically meaningful.[25] However, an absolute reduction of more than 10% was contemplated in a recent consensus statement.[4] Studies comparing these two techniques for predicting disease progression are required.

Before attributing any decrease in DL_{CO} to progressive fibrosis, we must rule out other reasons for a decreasing DL_{CO}. When the only other indicator that is changing is the severity of symptoms, pulmonary vascular disease should be evaluated because it can lead to an isolated reduction in DL_{CO} without any change in the degree of pulmonary fibrosis.[26] Other findings, such as increased fibrosis on HRCT and decreased FVC, are usually required in order to rule out the possibility that a decrease in DL_{CO} is due to disease progression.[4] In any case, a decrease in DL_{CO} indicates a poor prognosis.

RISK ELEMENTS

Several data points in the first evaluation of patients with fibrotic ILD lead to a higher chance of progression (Chart 3).[8,26,27,42] In scleroderma, some specific abnormalities are linked to increased ILD progression and a poor prognosis, including smoking, being Black, diffuse cutaneous involvement, and concurrent myopathy, as well as autoantibodies such as anti-topoisomerase I/anti-Th/To and anti-U11/U12 ribonucleoprotein antibodies.[35,38,40,43]

PF-ILD MANAGEMENT

Pharmacological and nonpharmacological treatments are used in the management of PF-ILD. Nonpharmacological management techniques such as oxygen therapy, rehabilitation, lung transplantation, and palliative care are critical but will not be covered here.[44] In patients with IPF, treatment with an

Chart 3. Major risk factors for interstitial lung disease progression.[a]

- Advanced age
- Male sex
- Family history (short telomeres)
- Clubbing of the fingers
- Need for oxygen therapy
- > 20% extent of fibrosis on HRCT
- Extensive traction bronchiectasis on HRCT
- FVC of < 50-65% predicted
- DL_{CO} of < 50% predicted
- An SpO_2 of < 85% during exercise
- No identification or avoidance of antigens in CHP
- Pulmonary hypertension

CHP: chronic hypersensitivity pneumonitis. [a]Based on Valenzuela & Cottin,[8] as well as on other references.[15-42]

antifibrotic drug should begin as soon as the diagnosis is made.

Antifibrotic drugs used in patients with IPF have recently been studied in patients with PF-ILD. In a study published in 2019,[3] the efficacy of nintedanib vs. placebo was investigated in 663 patients with fibrosing lung diseases that had progressed after two years of surveillance. Of the 663 patients, 173 (26%) had CHP, 170 (26%) had CTD, 125 (19%) had NSIP, 114 (17%) had unclassified ILD, and 81 (12%) had other ILDs.[3] The adjusted rate of FVC reduction with nintedanib was 80.8 mL/year vs. 187.8 mL/year with placebo, with a mean difference of 107.0 mL/year (95% CI, 65.4-148.5; p = 0.001).[3] The adjusted rate of FVC deterioration in patients with an IPF-like fibrotic pattern was 82.9 mL/year with nintedanib and 211.1 mL/year with placebo, a difference of 128.2 mL/year (95% CI, 70.8-185.6; p = 0.001).[3] In the absence of unusual findings, an IPF-like pattern was defined as the presence of a UIP pattern on HRCT but no diagnosis of IPF or probable IPF on CT.[3]

The effect of nintedanib vs. placebo in reducing the rate of FVC decline (mL/year) was consistent across the five ILD subgroups included in the study: CHP (73.1 mL/year; 95% CI, −8.6 to 154.8), autoimmune diseases (104.0 mL/year; 95% CI, 21.1-186.9), NSIP (141.5 mL/year; 95% CI, 46.0-237.2), unclassified ILD (68.3 mL/year; 95% CI, −31.4 to 168.1), and other ILDs (197.1 mL/year; 95% CI, 77.6-316.7).[45] The study was not designed to have enough power to determine whether certain subgroups benefited. Nonetheless, the findings show that nintedanib reduces the progression of ILD in individuals with chronic fibrosing disease and a progressive phenotype. This is true regardless of the cause of the disease. In a separate data analysis, 134 patients (40.4%) in the nintedanib group and 181 (54.7%) in the placebo group experienced disease progression or died (hazard ratio, 0.66; 95% CI, 0.53-0.83; p = 0.001). Exacerbations were less common in the nintedanib group (hazard ratio, 0.67; 95% CI, 0.46-0.98; p = 0.04).[46] As expected, the most prevalent side effect of nintedanib was diarrhea. The U.S. Food and Drug Administration and the Brazilian Health Regulatory Agency have approved the use of nintedanib in such cases on the basis of the findings of the aforementioned study.[3]

Antigen identification is associated with improved survival in patients with CHP.[47] Even in patients with fibrosis, complete antigen clearance, especially when paired with clinical improvement, is associated with extended survival in a considerable proportion of patients.[27,48] Complete elimination of exposure is required for disease control. In Brazil, however, exposure to mold in the home is prevalent, complicating disease management. Immunosuppressants can be used in these patients in order to minimize the inflammatory response and fibrosis development.[49] The use of antifibrotics in this situation is debatable.

There have been no prospective trials of CHP patients using immunosuppressants. Azathioprine and mycophenolate are the most commonly used drugs.[49] Treatment with corticosteroids alone should be considered in acute cases or during episodes of aggravation in chronic situations. In some circumstances, immunosuppressants allow the use of lower corticosteroid doses or even corticosteroid discontinuation.

Antifibrotic therapy should be considered for patients who continue to deteriorate despite antigen avoidance or when there is a high likelihood that they will not respond (no evidence of inflammation on HRCT; bronchoalveolar lavage fluid without lymphocytosis; FVC of < 50% of predicted; UIP findings on HRCT or in lung biopsy material; and extensive traction bronchiectasis).[50-53] In a study evaluating patients with CHP, the mean difference in functional decline between the placebo and treated groups was 73.1 mL, but the range was considerable (95% CI, −8.6 to 154.8).[3] No information was provided regarding the diagnostic criteria used or the eventual removal of antigen exposure. Patients with CHP and UIP (particularly fibroblastic foci) in lung biopsies have poorer results.[54] Antifibrotic drugs may be more effective in these cases. The results of CHP treatment with pirfenidone have recently been published.[55] The COVID-19 pandemic halted enrollment after 40 patients had been randomly assigned. At week 52, there was no significant difference in percent predicted FVC across groups (mean difference, −0.76%; 95% CI, −6.34 to 4.82). The experiment was insufficiently powered to detect a change in the major endpoint, rendering it inconclusive.

Two studies examined the use of pirfenidone in individuals with unclassified ILD as well as other types of ILD.[56,57] Following a multidisciplinary debate, one phase 2 study explored the efficacy and safety of pirfenidone in patients with ILD of uncertain etiology.[56] Up to 6 months prior to participation, patients had a > 5% decline in FVC or worsening of symptoms, linked to deteriorating ILD. The primary goal was a change in FVC evaluated by home spirometry; however, because of outliers, FVC measured at trial visits, a secondary endpoint, was analyzed, indicating less decline in the treated group than in the placebo group

(−17.8 mL vs. −113 mL). The other study examined patients with an FVC decline of 5% or more in the previous 24 months despite standard treatment.[57] The primary outcome was the change in percent predicted FVC at week 48. A total of 127 patients were randomly assigned to receive treatment with pirfenidone or placebo. CHP was the most common ILD (in 45% of the study participants). The study was terminated prematurely after 127 individuals had been randomized, because of low recruitment. Pirfenidone had a slight advantage; however, some data points were missing.

A meta-analysis[56-58] included the two aforementioned studies. The median difference in FVC was 100 mL (95% CI, 98.1-101.9), and the six-minute walk distance (25.2 m; 95% CI, 8.3-42.1) favored pirfenidone over placebo. Changes in DL_{CO} also favored pirfenidone (median difference, 3.0 mL/min/mmHg; 95% CI, 0.75-5.25), and the risk of DL_{CO} decreasing by more than 15% favored pirfenidone (relative risk, 0.27; 95% CI, 0.08-0.95).

In summary, a diagnosis of fibrotic ILD is required for appropriate initial management. Antifibrotics constitute a treatment option for patients with increasing deterioration. More research is needed in order to identify markers of increased risk of progression in patients with ILD and determine the likelihood of response to therapy with standard or novel medications.

AUTHOR CONTRIBUTIONS

CACP: conceptualization; and drafting, reviewing, and editing of the manuscript. SC and ACR: drafting of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018;378(19):1811-1823. https://doi.org/10.1056/NEJMra1705751
2. Matias SLK. Relative frequency of incidental interstitial lung diseases in six centers in Brazil (thesis in Portuguese). São Paulo: Universidade Federal de São Paulo; 2022.
3. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-1727. https://doi.org/10.1056/NEJMoa1908681
4. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, 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
5. Rajan SK, Cottin V, Dhar R, Danoff S, Flaherty KR, Brown KK, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J. 2023;61(3):2103187. https://doi.org/10.1183/13993003.03187-2021
6. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968-1977. https://doi.org/10.1056/NEJMoa1113354
7. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020;383(10):958-968. https://doi.org/10.1056/NEJMra2005230
8. Valenzuela C, Cottin V. Epidemiology and real-life experience in progressive pulmonary fibrosis. Curr Opin Pulm Med. 2022;28(5):407-413. https://doi.org/10.1097/MCP.0000000000000908
9. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med. 2020;8(9):925-934. https://doi.org/10.1016/S2213-2600(20)30355-6
10. Ryerson CJ, Corte TJ, Lee JS, Richeldi L, Walsh SLF, Myers JL, et al. A Standardized Diagnostic Ontology for Fibrotic Interstitial Lung Disease. An International Working Group Perspective. Am J Respir Crit Care Med. 2017;196(10):1249-1254. https://doi.org/10.1164/rccm.201702-0400PP
11. Simpson T, Barratt SL, Beirne P, Chaudhuri N, Crawshaw A, Crowley LE, et al. The burden of progressive fibrotic interstitial lung disease across the UK. Eur Respir J. 2021;58(1):2100221. https://doi.org/10.1183/13993003.00221-2021
12. Kolb MR, Flaherty KR. The justification for the progressive fibrotic phenotype. Curr Opin Pulm Med. 2021;27(5):363-367. https://doi.org/10.1097/MCP.0000000000000803
13. Fukuda CY, Soares MR, de Castro Pereira CA. A score without diffusion capacity of the lung for carbon monoxide for estimating survival in idiopathic pulmonary fibrosis. Medicine (Baltimore). 2020;99(25):e20739. https://doi.org/10.1097/MD.0000000000020739
14. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016;194(3):265-275. https://doi.org/10.1164/rccm.201604-0801CI
15. Ryerson CJ, Cottin V, Brown KK, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm. Eur Respir J. 2015;46(2):512-520. https://doi.org/10.1183/13993003.00419-2015
16. Luppi F, Sebastiani M, Salvarani C, Bendstrup E, Manfredi A. Acute exacerbation of interstitial lung disease associated with rheumatic disease. Nat Rev Rheumatol. 2022;18(2):85-96. https://doi.org/10.1038/s41584-021-00721-z
17. Kang J, Kim YJ, Choe J, Chae EJ, Song JW. Acute exacerbation of fibrotic hypersensitivity pneumonitis: incidence and outcomes. Respir Res. 2021;22(1):152. https://doi.org/10.1186/s12931-021-01748-2
18. Khor YH, Gutman L, Abu Hussein N, Johannson KA, Glaspole IN, Guler SA, et al. Incidence and Prognostic Significance of Hypoxemia in Fibrotic Interstitial Lung Disease: An International Cohort Study. Chest. 2021;160(3):994-1005. https://doi.org/10.1016/j.chest.2021.04.037
19. Walsh SLF, Devaraj A, Enghelmayer JI, Kishi K, Silva RS, Patel N, et al. Role of imaging in progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27(150):180073. https://doi.org/10.1183/16000617.0073-2018
20. Egashira R, Raghu G. Quantitative computed tomography of the chest for fibrotic lung diseases: Prime time for its use in routine clinical practice?. Respirology. 2022;27(12):1008-1011. https://doi.org/10.1111/resp.14351
21. Devaraj A, Milanese G, Sverzellati N. Thoracic computed tomography in the progressive fibrotic phenotype. Curr Opin Pulm Med. 2021;27(5):350-354. https://doi.org/10.1097/MCP.0000000000000804
22. Oldham JM, Lee CT, Wu Z, Bowman WS, Pugashetti JV, Dao N, et al. Lung function trajectory in progressive fibrosing interstitial lung disease. Eur Respir J. 2022;59(6):2101396. https://doi.org/10.1183/13993003.01396-2021
23. 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(5):407-411. https://doi.org/10.1136/thoraxjnl-2011-201184
24. Pugashetti JV, Adegunsoye A, Wu Z, Lee CT, Srikrishnan A, Ghodrati S, et al. Validation of Proposed Criteria for Progressive Pulmonary Fibrosis. Am J Respir Crit Care Med. 2023;207(1):69-76. https://doi.org/10.1164/rccm.202201-0124OC

25. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc. 2006;3(4):315-321. https://doi.org/10.1513/pats.200602-022TK
26. Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res. 2019;20(1):57. https://doi.org/10.1186/s12931-019-1022-1
27. Petnak T, Thongprayoon C, Baqir M, Ryu JH, Moua T. Antigen identification and avoidance on outcomes in fibrotic hypersensitivity pneumonitis. Eur Respir J. 2022;60(4):2101336. https://doi.org/10.1183/13993003.01336-2021
28. Oh JH, Kang J, Song JW. Fibrosis score predicts mortality in patients with fibrotic hypersensitivity pneumonitis. Front Med (Lausanne). 2023;10:1131070. https://doi.org/10.3389/fmed.2023.1131070
29. Salisbury ML, Gu T, Murray S, Gross BH, Chughtai A, Sayyouh M, et al. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest. 2019;155(4):699-711. https://doi.org/10.1016/j.chest.2018.08.1076
30. Oliveira RK, Pereira CA, Ramos RP, Ferreira EV, Messina CM, Kuranishi LT, et al. A haemodynamic study of pulmonary hypertension in chronic hypersensitivity pneumonitis. Eur Respir J. 2014;44(2):415-424. https://doi.org/10.1183/09031936.00010414
31. Creamer AW, Barratt SL. Prognostic factors in chronic hypersensitivity pneumonitis. Eur Respir Rev. 2020;29(156):190167. https://doi.org/10.1183/16000617.0167-2019
32. Trushenko NV, Suvorova OA, Pershina ES, Nekludova GV, Chikina SY, Levina IA, et al. Predictors of Progression and Mortality in Patients with Chronic Hypersensitivity Pneumonitis: Retrospective Analysis of Registry of Fibrosing Interstitial Lung Diseases. Life (Basel). 2023;13(2):467. https://doi.org/10.3390/life13020467
33. Chiu YH, Koops MFM, Voortman M, van Es HW, Langezaal LCM, Welsing PMJ, et al. Prognostication of progressive pulmonary fibrosis in connective tissue disease-associated interstitial lung diseases: A cohort study. Front Med (Lausanne). 2023;10:1106560.
34. Chen X, Guo J, Yu D, Jie B, Zhou Y. Predictors of Mortality in Progressive Fibrosing Interstitial Lung Diseases. Front Pharmacol. 2021;12:754851. https://doi.org/10.3389/fphar.2021.754851
35. Qiu M, Jiang J, Nian X, Wang Y, Yu P, Song J, et al. Factors associated with mortality in rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. Respir Res. 2021;22(1):264. https://doi.org/10.1186/s12931-021-01856-z
36. Le Gall A, Hoang-Thi TN, Porcher R, Dunogué B, Berezné A, Guillevin L, et al. Prognostic value of automated assessment of interstitial lung disease on CT in systemic sclerosis [published online ahead of print, 2023 Apr 19]. Rheumatology (Oxford). 2023;kead164. https://doi.org/10.1093/rheumatology/kead164
37. Campochiaro C, Hoffmann-Vold AM, Avouac J, Henes J, de Vries-Bouwstra J, Smith V, et al. Sex influence on outcomes of patients with systemic sclerosis-associated interstitial lung disease: a EUSTAR database analysis. Rheumatology (Oxford). 2023;62(7):2483-2491. https://doi.org/10.1093/rheumatology/keac660
38. Cacciapaglia F, Airò P, Fornaro M, Trerotoli P, De Lorenzis E, Corrado A, et al. Survival and prognostic factors from a multicentre large cohort of unselected Italian systemic sclerosis patients. Rheumatology (Oxford). 2023;62(4):1552-1558. https://doi.org/10.1093/rheumatology/keac512
39. de Oliveira Martins LV, Oliveira SM, Silvatti J, de Amorim FG, Agapito Tito CV, Kayser C. Mortality in Systemic Sclerosis-Associated Interstitial Lung Disease in Brazil: A Real-Life, Long-Term Follow-up Observational Study. J Clin Rheumatol. 2022;28(2):e532-e538. https://doi.org/10.1097/RHU.0000000000001792
40. Zhou M, Jiang L, Nie L, Chen T, Zhang T, Sun W, et al. Myopathy is a Risk Factor for Poor Prognosis of Patients with Systemic Sclerosis: A retrospective cohort study. Medicine (Baltimore). 2020;99(33):e21734. https://doi.org/10.1097/MD.0000000000021734
41. Jeganathan N, Sathananthan M. Connective Tissue Disease-Related Interstitial Lung Disease: Prevalence, Patterns, Predictors, Prognosis, and Treatment. Lung. 2020;198(5):735-759. https://doi.org/10.1007/s00408-020-00383-w
42. Wang Y, Guo Z, Ma R, Wang J, Wu N, Fan Y, et al. Prognostic Predictive Prognostic Predictive Characteristics in Patients With Fibrosing Interstitial Lung Disease: A Retrospective Cohort Study. Front Pharmacol. 2022;13:924754. https://doi.org/10.3389/fphar.2022.924754
43. Kuwana M, Gil-Vila A, Selva-O'Callaghan A. Role of autoantibodies in the diagnosis and prognosis of interstitial lung disease in autoimmune rheumatic disorders. Ther Adv Musculoskelet Dis. 2021;13:1759720X211032457. https://doi.org/10.1177/1759720X211032457
44. Kreuter M, Bendstrup E, Russell AM, Bajwah S, Lindell K, Adir Y, et al. Palliative care in interstitial lung disease: living well. Lancet Respir Med. 2017;5(12):968-980. https://doi.org/10.1016/S2213-2600(17)30383-1
45. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020;8(5):453-460. https://doi.org/10.1016/S2213-2600(20)30036-9
46. Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. Eur Respir J. 2022;59(3):2004538. https://doi.org/10.1183/13993003.04538-2020
47. Fernández Pérez ER, Swigris JJ, Forssén AV, Tourin O, Solomon JJ, Huie TJ, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. Chest. 2013;144(5):1644-1651. https://doi.org/10.1378/chest.12-2685
48. Gimenez A, Storrer K, Kuranishi L, Soares MR, Ferreira RG, Pereira CAC. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. Thorax. 2018;73(4):391-392. https://doi.org/10.1136/thoraxjnl-2017-210035
49. Mullin ML, Churg A, Ryerson CJ. Management of fibrotic hypersensitivity pneumonitis. Curr Opin Pulm Med. 2022;28(5):421-431. https://doi.org/10.1097/MCP.0000000000000904
50. Ejima M, Okamoto T, Suzuki T, Anzai T, Takahashi K, Miyazaki Y. Efficacy of treatment with corticosteroids for fibrotic hypersensitivity pneumonitis: a propensity score-matched cohort analysis. BMC Pulm Med. 2021;21(1):243. https://doi.org/10.1186/s12890-021-01608-1
51. De Sadeleer LJ, Hermans F, De Dycker E, Yserbyt J, Verschakelen JA, Verbeken EK, et al. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study. Eur Respir J. 2020;55(4):1901983. https://doi.org/10.1183/13993003.01983-2019
52. Raimundo S, Pimenta AC, Cruz-Martins N, Rodrigues MC, Melo N, Mota PC, et al. Insights on chronic hypersensitivity pneumonitis' treatment: Factors associated with a favourable response to azathioprine. Life Sci. 2021;272:119274. https://doi.org/10.1016/j.lfs.2021.119274
53. Walsh SL, Sverzellati N, Devaraj A, Wells AU, Hansell DM. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. Eur Radiol. 2012;22(8):1672-1679. https://doi.org/10.1007/s00330-012-2427-0
54. Wang P, Jones KD, Urisman A, Elicker BM, Urbania T, Johannson KA, et al. Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis. Chest. 2017;152(3):502-509. https://doi.org/10.1016/j.chest.2017.02.011
55. Fernández Pérez ER, Crooks JL, Lynch DA, Humphries SM, Koelsch TL, Swigris JJ, et al. Pirfenidone in fibrotic hypersensitivity pneumonitis: a double-blind, randomised clinical trial of efficacy and safety [published online ahead of print, 2023 Apr 7]. Thorax. 2023;thorax-2022-219795. https://doi.org/10.1136/thorax-2022-219795
56. 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(2):147-157. https://doi.org/10.1016/S2213-2600(19)30341-8
57. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, et al 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(5):476-486. https://doi.org/10.1016/S2213-2600(20)30554-3
58. Ghazipura M, Mammen MJ, Bissell BD, Macrea M, Herman DD, Hon SM, et al. Pirfenidone in Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2022;19(6):1030-1039. https://doi.org/10.1513/AnnalsATS.202103-342OC