Original Paper • 10.2478/pneum-2024-0010 • 72 • 2023 • 64-70

sciendo

Pneumologia

Baseline characteristics in patients with interstitial lung diseases as predictors for progression: a real life study

Ștefan Teodorescu-Drăghicescu[1], Irina Strâmbu[2,3,*]

[1]Radiology resident, Bolintin Hospital, Giurgiu county, Radiology Dept.
[2]Institute of Pneumophisiology "Marius Nasta" Bucharest, Pulmonology 5 Dept.
[3]University of Medicine and Pharmacy "Carol Davila" Bucharest, Pulmonology 1 Dept.

Abstract

English:

Interstitial lung diseases (ILDs) comprise a large number of different diseases, some of the patients having a progressive evolution toward irreversible fibrosis. The aim of this study is to identify baseline clinical, functional, and imaging characteristics at the date of the diagnosis, that could predict the evolution toward fibrosis.
This is a retrospective descriptive study that included 126 patients diagnosed and followed-up in Department 5 of the Institute of Pneumophtisiology "Marius Nasta" Bucharest between 2014 and 2022.
The authors recorded baseline demographics, symptoms, lung function tests (forced vital capacity – FVC and diffusion capacity – DLCO), high resolution CT (HRCT) imaging features. Patients were followed-up at 6 and 12 months. According to decline in lung function or imaging worsening, patients were divided in2 groups: progressors (60 patients) and non-progressors (26 patients). Baseline characteristics of the 2 groups were compared.
Results: There is an important delay since onset of symptoms to diagnosis (a mean of 17 months). Lower baseline FVC, smoking history, presence of traction bronchiectasis and/or honeycombing and male gender were associated to progressive lung fibrosis.

Keywords

progressive lung fibrosis • high resolution CT • decline in lung function • traction bronchiectasis • honeycombing

Caracteristicile inițiale ale pacienților cu pneumopatii interstițiale difuze ca predictori ai evoluției progresive: un studiu în viața reală

Rezumat

Romanian:

Pneumopatiile interstițiale difuze include un număr mare de boli diferite, o parte dintre pacienți având o evoluție progresivă spre fibroză pulmonară ireversibilă. Scopula cestui studio este de a identifica trăsăturile clinice, funcționale și imagistice de la data diagnosticului care ar putea prezice evoluția către fibroză.
Acesta este un studiu retrospectiv descriptiv care a inclus 126 de pacienți diagnosticați și urmăriți în Secția 5 a Institutului de Pneumoftiziologie Marius Nasta București între 2014 și 2020.
Autorii au înregistrat următoarele informații inițiale: date demografice, simptome, teste funcționale respiratoria (capacitate vitală forțată – FVC și capacitatea de difuziune – DLCO), caracterele imagistice pe tomografia computerizată cu înaltă rezoluție (HRCT). Pacienții au fost urmăriți la 6 și 12 luni. În funcție de declinul parametrilor funcționali sau de agravarea imagistică, au fost împărțiți în două grupuri: cu progresie (60 de pacienți) și fără progresie (26 de pacienți). Au fost comparate caracteristicile inițiale ale celor două grupuri.
Rezultate: există o întârziere importantă de la debutul simptomelor până la data diagnosticului (o medie de 17 luni). FVC inițială mai scăzută, istoricul de fumat, prezența bronșiolectaziilor de tracțiune și/sau fagurele de miere și sexul masculine au fost asociate cu evoluție fibrozantă progresivă.

Cuvinte-cheie

fibroză pulmonară progresivă • tomografie computerizată cu înaltă rezoluție • declinul funcției pulmonare • bronșiolectazii de tracțiune, fagire de miere

*Corresponding author: Irina Strambu
E-mail: irina.strambu@umfcd.ro

Introduction

Interstitial lung diseases (ILDs) are a large group of diseases sharing the diffuse involvement of lung parenchima and in some cases evolution toward pulmonary fibrosis. The classification of ILDs evolved over time, currently being classified as idiopathic, induced by external agents, lung involvement associated to systemic diseases, granulomatosis and others (1,2). Idiopathic pulmonary fibrosis (IPF) continues to be considered the most prevalent among idiopathic ILDs and, due to constant progression, bearing the worst prognosis, with a life expectancy of 3-5 years in the absence of antifibrotic treatment (3). The observation that in each group of diseases a subgroup of patients will develop pulmonary fibrosis, despite etiologic diagnosis and accurate treatment, led to the development of the concept of progressive pulmonary fibrosis (PPF) (4). This is not a distinctive disease, but a phenotype within particular ILDs, in which the initial inflammatory process is followed by a chain of events leading to development of fibrotic tissue in the lung parenchima (5). It has already been proven that patients with non-IPF ILDs with a progressive evolution benefit from antifibrotic treatment in a similar way to IPF patients (6). Nintedanib was approved for treatment of non-IPF PPF since 2020 in Europe, and since March 2022 also in Romania (7).

In the current therapy guidelines, the criteria for starting an antifibrotic treatment in patients with fibrotic non-IPF ILDs are based on evidence of progression despite optimal therapy of the underlying condition (7). This implies a clinical observation of several months, up to 2 years, including follow-up lung function testing and high resolution CT scans, to prove that the patient is worsening (7).

As much as it is common sense that one cannot start an expensive, reimbursed treatment, that has as unique outcome the slowing of progression (and not an improvement of a measurable parameter) without having the proof of previous deterioration, it could be discussed that from an ethical point of view it may not be fair for the physician to just sit and watch the patient deteriorate before deciding to start a treatment that would prevent exactly the observed outcome. In this perspective, there is need for early markers for progression, to be searched for at the very moment of the diagnosis, allowing to start an antifibrotic treatment before the worsening of the dyspnea and quality of life.

Several markers for progression were described, the best known being the polymorphism of MUC5B promoter gene, associated to IPF, or the composite parameters including lung function measurement (8,9,10). Still, for clinical practice purposes, it would be much more useful to identify features that are currently assessed in daily routine, that could indicate early the risk for progression in ILD patients, with a special focus on HRCT findings (11,12).

The current paper addresses the identification of early markers for progression in ILDs in a real-life setting.

Objective. The current study aims to identify the clinical, functional and imaging features identified at the moment of ILD diagnosis that could be related to progression of fibrosis.

Materials and methods

This is a retrospective descriptive cohort study, analyzing the information collected in patients diagnosed with ILD in Pulmonology 5 Department of the Institute of Pneumophthysiology “Marius Nasta” Bucharest between 2014 and 2022. Sarcoidosis patients were not included. Data was collected from the patient files (medical history, lung function tests, laboratory data) and HRCT imaging, from the hospital database. The following parameters were collected:

- Demographics: gender, age;
- History: smoking status, allergen exposure, medical history.
- Signs and symptoms: dyspnea, cough, extrathoracic symptoms (fever, arthralgia, fatigue, skin changes, weight loss), and the duration of symptoms (in months).
- Lung function tests: forced vital capacity (FVC) and diffusion capacity (DLCO) at baseline and at follow-up.
- HRCT imaging: the pattern, distribution and extent of changes were evaluated at baseline and follow-up.
- Laboratory tests: angiotensin-converting enzyme, hemoglobin, antibodies.
- Initial diagnosis (at baseline) and final diagnosis (if changed during follow-up).

For the description of thoracic HRCT patterns, the following characteristics were used:

- Inflammatory pattern: predominance of ground-glass opacities, cranio-caudal distribution.
- Reticular pattern: predominance of reticular opacities.
- Probable UIP pattern: predominance of linear and reticular opacities and traction bronchiectasis, with subpleural and inferior distribution.
- Typical UIP pattern: presence of honeycombing, besides reticular opacities and traction bronchiectasis, with subpleural and inferior distribution.
- Nodular pattern: predominance of nodular opacities.

As many patients displayed several types of imaging changes, with a mixture of lesions in the same patient, we evaluated the percentage of extension of each type of lesion (ground-glass, traction bronchiectasis, honeycombing, nodules, reticulation), to assess the evolution of these changes at follow-up.

For the extension of lesions on HRCT we used 3 categories: group A – lesions occupying between 1 and 24% of lung surface, group B – between 25 and 40%, and group C – between 41 and 100%.
Data were collected at baseline (at the time of initial diagnosis) and at follow-up after 6 months and 1 year. After initial diagnosis, all patients were recommended the treatment considered optimal, according to guidelines. To note, this study was conducted before the approval of prescription of Nintedanib for non-IPF progressive pulmonary fibrosis in Romania.
Data were included in an Excel 2016 database and analyzed. For statistical analysis JASP programme was used.

Results

We analyzed 143 patients with suspected ILD. Only 126 were diagnosed with ILD.

Baseline characteristics

Fifty-eight percent were female. Mean age was 61.7 years +/- 14.3 years (between 18 and 90 years). Most patients (87%) were aged between 44 and 83 at the date of ILD diagnosis.
The initial ILD diagnosis was: IPF 18 patients (14.2%), chronic hypersensitivity pneumonitis 30 patients (23.8%), unclassifiable ILD 40 patients (31.7%), non-specific interstitial pneumonia (NSIP) 11 patients (8.7%), ILD associated to systemic diseases 16 patients (12.7%), and other diseases (lymphangioleyomyomatosis and drug induced ILD) 11 patients (8.7%) (Figure 1).
Seventy-four patients didn't have any allergen exposure, while 26 were exposed to birds, 17 to mold and 11 to other organic substances (Figure 2).
Patients had several associated diseases: 39 patients (31%) presented ischemic heart disease, 25 (20%) had diabetes mellitus, 23 (18.2%) presented gastric reflux, 16 patients (13%) associated pulmonary hypertension, 11 (8.7%) presented osteoporosis.
Fifty-eight patients (46.03%) were current or former smokers.
Symptoms at presentation were dominated by dyspnea, present in 98 patients (77.7%). It was considered moderate or severe in 69 patients. Cough was present at baseline in 75 patients (59.52%).
Various non-respiratory symptoms were present in 63 patients (49.6%): fatigue – 29 patients (22.83%), joint pain – 24 (18.89%), weight loss – 5 (3.93%), fever – 9 (7.08%), skin changes – 7 patients (5.51%).
The duration of symptoms before the initial presentation ranged between 1 and 60 months, with a mean of 17.2 months +/- 6.3 months. Six patients were asymptomatic.

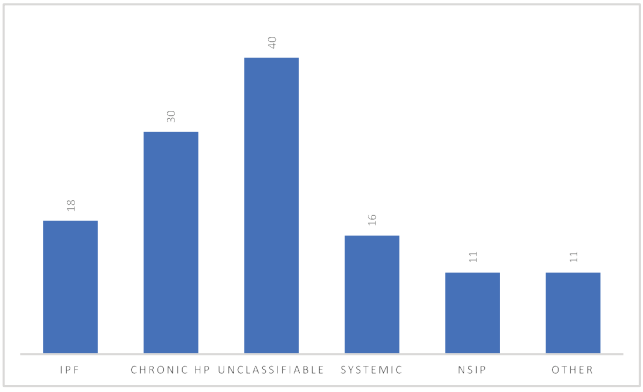

Figure 1. Distribution of ILD diagnosis (number of patients).

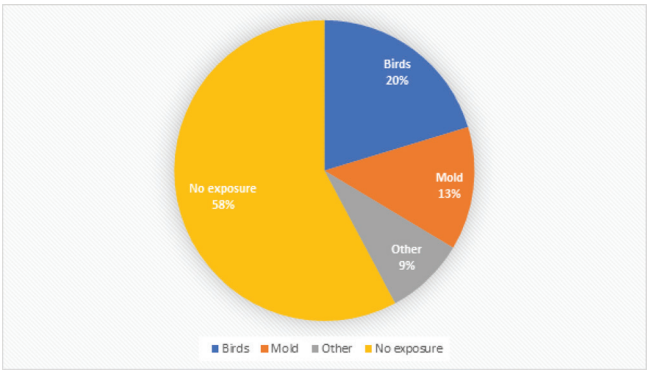

Figure 2. Exposure to allergens.

Lung function measurement showed a restrictive pattern in most patients. Mean FVC was 73.29% +/- 18.62% of predicted value. Mean DLCO was 43% +/- 21.77% of predicted.
From the 126 patients, for 82 the initial HRCT was available for analysis.
The extent of ILD lesions at baseline was mild (group A) – 8 patients, moderate (group B) – 27 patients, and severe (group C) – 47 patients.
The HRCT pattern was inflammatory (dominated by ground glass opacities) – 26 patients, 22 – probable UIP, 6 – typical UIP, 3 – reticular, 3 – combined inflammatory and fibrotic, and 4 – nodular or cystic. Patients with extensive presence of traction bronchiectasis (29 patients) were diagnosed with IPF (10 patients), chronic HP (7 patients), scleroderma (4 patients), and other diseases.

Follow-up

Patients were followed-up after 6 and 12 months, some of them had recorded follow-up visits also for longer periods (up to 3 years). From the initial group of 126 patients, 86

presented for follow-up. Follow-up consisted in evaluation of symptoms, lung function tests (spirometry and DLCO) and, when available, HRCT.
For the whole group, the mean FVC remained at the same percentage (73.29% +/- 20.56% of predicted value), while mean DLCO decreased to 35.75% +/- 18.73% (Figure 3).
For the purpose of this study, progression of the disease was defined as at least one of the following:

- Decline in FVC > 5% in 6-12 months
- Decline in DLCO > 5% in 6-12 months
- Radiological progression, defined as increase of the percentage of overall ILD involvement, or by the occurance or increase of the percentage of changes suggestive of fibrosis (traction bronchectasis or honeycombing).

From the 86 patients evaluated at follow-up 60 (69.76%) had progression (named group P, for progressors), and 26 (30.23%) showed improvement or were stable (named group NP for non-progressors). In the progressors group, 26 had decline in lung function parameters, 12 had progression on HRCT, and 22 patients had both types of progression.

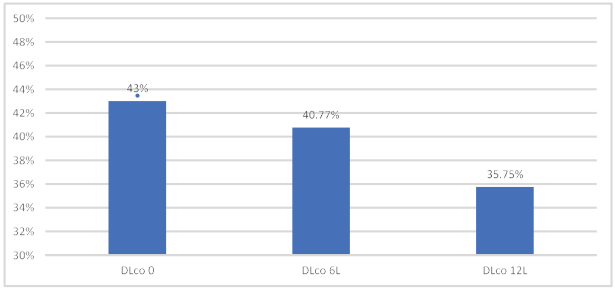

Figure 3. Evolution of mean DLCO (% predicted) at 6 and 12 months follow-up.

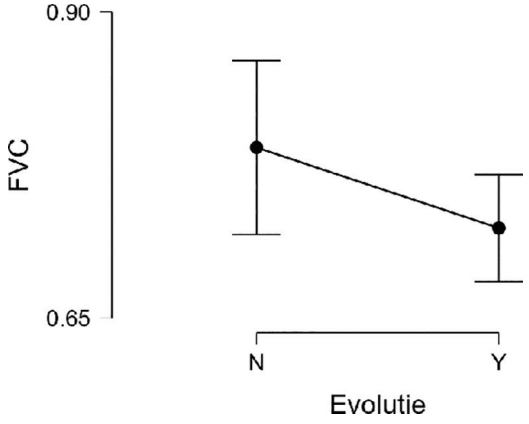

Figure 4. Comparison between baseline FVC in progressors and non-progressors groups.

The following baseline parameters were compared between the 2 groups: 1. Baseline FVC, 2. Baseline DLCO, 3. Baseline HRCT extension of lesions, 4. Baseline HRCT pattern, 5. Age, 6. Smoking status, 7. Gender.

1. FVC had a mean initial value of 73.29% +/- 18.62% of predicted value. In group P the mean FVC was 72.4%, while in group NP it was 78.9% (Figure 4 and Table 1), with a difference of 5.5% in favor of non-progressors.
2. Regarding baseline DLCO, there was no significant difference between the two groups (Table 2).
3. The extension of lesions on HRCT at baseline was quantified in 3 groups: A: between 1 and 24% of lungs surface, group B between 25 and 40%, and group C between 41 and 100%. There was no significant difference between group P (progressors) and group NP (no-progressors) regarding the initial HRCT extension of ILD lesions (Table 3).
4. The HRCT pattern at baseline didn't show significant differences between progressors and non-progressors. So, in the non-progressors group there were: 10 patients with inflammatory pattern, 6 with probable UIP, 2 with typical UIP and 2 with reticular pattern, while in the progressors group there were 16 patients with inflammatory pattern, 16 with probable UIP, 4 with typical UIP, 1 with reticulation and 4 with other changes (Figure 5).

We could note that inflammatory pattern is more frequent in the non-progressors, and probable UIP more frequent in progressors, but the small number of patients didn't allow a statistical comparison. Calculation of a relative risk of a patient with INF pattern showed that INF pattern makes 1.46 times more probable a non-progressive evolution.

5. The analysis of age at baseline showed no difference between group P and NP (Table 4).

Table 1. Comparison between baseline FVC in progressors and non-progressors groups

	Group	No	Mean	SD	SE	Coefficient of variation
FVC	NP	26	0.789	0.175	0.034	0.222
	P	60	0.724	0.169	0.022	0.234

SD: standard deviation, SE: standard error, P: progressors, NP: non-progressors

Independent T-test

	t	df	P	Mean difference	SE Difference	Co-hen's d	SE Cohen's d
FVC	1.635	84	0.053	0.066	0.040	0.384	0.241

Table 2. Comparison between baseline DLCO in progressors and non-progressors group

	Group	No	Mean	SD	SE	Coefficient of variation
DLCO	NP	26	0.431	0.167	0.022	0.388
	P	60	0.456	0.233	0.046	0.511

SD: standard deviation, SE: standard error, P: progressors, NP: non-progressors

Independent T-Test

	T	Df	p
DLCO	0.563	84	0.288

Table 3. Statistical comparison between group P and NP regarding baseline HRCT extension

	Extension
Pearson	0.098437
No.	86
T statistic	0.906597
DF	84
p	0.367213

Table 4. Comparison of age at baseline between P and NP groups

	Group	No	Mean	SD	SE	Coefficient of variation
Age at baseline	NP	26	62.038	13.730	2.693	0.221
	P	60	61.733	14.703	1.898	0.238

SD: standard deviation, SE: standard error

Independent samples T-Test

	t	df	p
Age at baseline	0.090	84	0.464

Table 5. Smoking exposure in the progressors vs non-progressors groups

	Group	No	Mean	SD	SE	Coefficient of variation
Packs/year	NP	26	7.308	12.667	2.484	1.733
	P	60	13.383	16.647	2.149	1.244

SD: standard deviation, SE: standard error

Independent samples T-Test

	t	df	p
Packs/year	-1.662	84	0.050

6. We analyzed the influence of the smoking status on the evolution of the disease. In the progressors group there were 29 active or former smokers (48.33%), while in the non-progressors group there were 8 active or former smokers (30.76%). Also the mean exposure, expressed as packs/year, was 13.8 +/- 16.4 in the P group, and 7.3 +/- 12.6 in the NP group. There is a significant difference in the smoking exposure, with a higher exposure in progressors (Table 5).

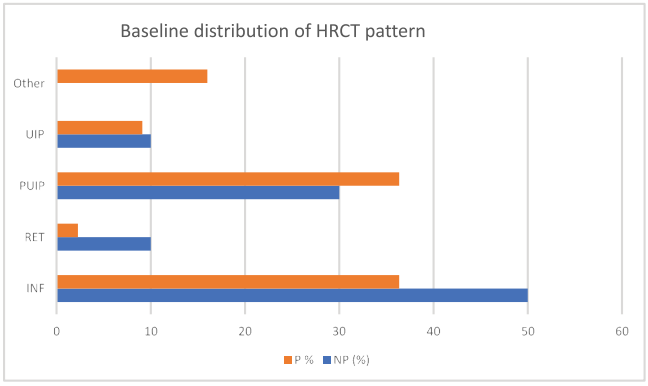

Figure 5. Baseline distribution of HRCT pattern in progressors vs non-progressors.
P: progressors, NP: non-progressors, INF: inflammatory pattern, RET: reticular pattern, PUIP: probable UIP, UIP: typical UIP.

7. We compared the evolution of the disease in male and female patients. In male patients progression was noted more frequently than in women (76.3% vs 64.5%), still there is no significant difference related to gender ($p > 0.05$).

The follow-up of ILD patients allowed the change of the initial diagnosis, as new data were becoming available. The diagnosis was changed at follow-up in 28 patients. Among them 16 had initial diagnosis of unclassifiable disease, and 7 – chronic hypersensitivity pneumonitis. New diagnosis was: IPF in 13 patients, NSIP in 6, chronic hypersensitivity pneumonitis in 5, one with systemic disease, and 3 – other diagnosis.

Discussion

This study aimed to analyze retrospectively the patients diagnosed with various ILD over 8 years in a tertiary pulmonology clinic, and to try to identify baseline features that may predict the progressive evolution toward fibrosis. There are previous reports addressing this topic (13,14,15).
In our group, we observed a high percentage of patients with unclassifiable ILD (31.7%), which is higher than the usual statistics. This may be due to the limited experience of the multidisciplinary team in our center, and to limited use of lung biopsy for diagnosis. Anyway, more than half of these patients had a change of the initial diagnosis based on the newly acquired information at follow-up, allowing a better management of the patients.

In patients diagnosed with hypersensitivity pneumonitis, only 74% had identified exposures. For the others, the diagnosis was based on HRCT pattern and broncho-alveolar lavage findings.
The duration of symptoms before having a diagnosis is high, with a mean of 17.2 months +/- 6.3 months. This is in accordance with other published data, reflecting the general delay of diagnosis in ILDs (16). In our group, 61.9% of patients presented with moderate or severe dyspnea at baseline, indicating an already severe disease. This is supported also by the high percentage of patients having extensive lesions on HRCT, over 40% of the lung surface (57.3% of all patients). Only 8 patients presented with limited extension of the disease (less than 24% of lung surface). These findings suggest that typically patients have a late diagnosis of ILD after the onset of symptoms.
The comparison of baseline characteristics of the patients who progressed at follow-up, versus the patients who were stable or improved showed some interesting findings. The baseline forced vital capacity was lower in the progressors group (a difference of 5.5%, $p = 0.053$), at the limit of statistical significance. No difference was noted between the two groups in the mean baseline DLCO value. This should suggest that FVC is a more reliable parameter to predict the evolution than initial DLCO. The DLCO measurement is influenced by many factors, making it a “noisy” parameter.
We couldn’t find a correlation between the extent of HRCT ILD involvement and the progression of the disease, with a difference between groups with $p = 0.36$. This could be explained by the fact that inflammatory pattern consists mainly of extensive ground glass opacities, that counts to an important percentage of lung surface involvement, but also may reside and improve with treatment. On the other hand, fibrotic lesions can occupy smaller surfaces of the lung, but will have the tendency to progress.
Regarding the HRCT pattern, there was a higher prevalence of typical UIP pattern and probable UIP pattern in patient with progression as compared to the non-progressors. It seems that the presence of traction bronchiectasis at baseline, no matter the underlying diagnosis, may be associated to a future progression and further development of fibrosis. We can consider that not the extension of the lesions, but the type of lesions seen on HRCT are more important for predicting the future evolution.
Anyway, due to the small number of cases analyzed, it is not possible to quantify a specific pattern that predicts this evolution. We only calculated the relative risk (RR), as the ratio between the probability of a patient with inflammatory pattern to have a progression. RR was 1.46, meaning that a patient with an inflammatory pattern on HRCT will have a 1.46 times higher probability to have a favorable outcome.
There was no significant difference in age between the progressors and non-progressors. The evolution towards fibrosis was more frequently encountered in male patients.
Smoking history seems to be a risk factor for progression, as it was significantly more associated to the progression, in percentage of patients with smoking history, and in the amplitude of exposure, expressed in pack/years.
There are several limits of this study. Being conducted in a single department of the Institution, it included only a limited number of patients. The real life and retrospective setting of the observation added more biases: some patients never presented for a follow-up, the intervals between the follow-up visits were irregular, the investigations performed on the visits were incomplete in some patients, some data were lost. Also, the evaluation of the HRCT images was made by a single observer, using a subjective appreciation of the extent of the lesions and type of lesions present.
Despite these limitations, the study manages to indicate some of the baseline features identifiable in regular practice, that could suggest a future progression to fibrosis: initial low FVC, active or former smoking, male gender, UIP and probable UIP patterns on baseline HRCT, and presence of traction bronchiectasis at the baseline HRCT. As “protective” features we noted: normal values of lung function testing, inflammatory imaging pattern, female gender.

Conclusions

The study suggests that male, former smoking patients, with a low FVC, and imaging patterns including traction bronchiectasis and honeycombing are more prone to have a progressive disease and develop fibrosis, no matter the initial ILD diagnosis.
Also, the study showed there is a major delay since the onset of symptoms to the moment of the diagnosis, with severe impact on the long-term prognosis of these patients. The efficient treatment will be started late, in advanced stages of the disease, with important consequences on the quality of life and survival.
Changing the diagnosis at follow-up doesn’t signify a limited capacity to make a diagnosis, but reflects the flexibility of the physicians, who incorporate the new data and the evolution of the patient in the diagnostic algorithm, to the benefit of the patient.
A prospective study, including a larger number of patients, would be necessary to confirm the findings of the current study.

Funding

None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

No informed consent was necessary.

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. W. D. Travis *et al.*, "An official American Thoracic Society/ European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias," *Am J Respir Crit Care Med*, vol. 188, no. 6, pp. 733–748, Sep. 2013, doi: 10.1164/rccm.201308-1483ST.
2. B. Kaul, V. Cottin, H. R. Collard, and C. Valenzuela, "Variability in Global Prevalence of Interstitial Lung Disease," *Frontiers in Medicine*, vol. 8. Frontiers Media S.A., Nov. 04, 2021. doi: 10.3389/fmed.2021.751181.
3. G. Raghu *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*, vol. 205, no. 9, pp. E18–E47, May 2022, doi: 10.1164/ rccm.202202-0399ST.
4. M. Wijsenbeek and V. Cottin, "Spectrum of Fibrotic Lung Diseases," *New England Journal of Medicine*, vol. 383, no. 10, pp. 958–968, Sep. 2020, doi: 10.1056/nejmra2005230.
5. M. Kolb and M. Vašáková, "The natural history of progressive fibrosing interstitial lung diseases," *Respiratory Research*, vol. 20, no. 1. BioMed Central Ltd., Mar. 14, 2019. doi: 10.1186/s12931-019-1022-1.
6. L. Richeldi *et al.*, "Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis," *New England Journal of Medicine*, vol. 370, no. 22, pp. 2071–2082, May 2014, doi: 10.1056/nejmoa1402584.
7. Monitorul Oficial al Romaniei – Anul 190 (XXXIV) – Nr 242 Bis, 2022, pp. 69–72.
8. Yang IV, Fingerlin TE, Evans CM, Schwarz MI, Schwartz DA. MUC5B and Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc. 2015 Nov;12 Suppl 2(Suppl 2):S193-9. doi: 10.1513/AnnalsATS.201503-110AW. PMID: 26595739; PMCID: PMC4722833.
9. C. J. Ryerson *et al.*, "Predicting survival across chronic interstitial lung disease: The ILD-GAP model," *Chest*, vol. 145, no. 4, pp. 723–728, 2014, doi: 10.1378/chest.13-1474.
10. A. W. Wong, C. J. Ryerson, and S. A. Guler, "Progression of fibrosing interstitial lung disease," *Respiratory Research*, vol. 21, no. 1. BioMed Central Ltd., Jan. 29, 2020. doi: 10.1186/ s12931-020-1296-3.
11. S. L. F. Walsh *et al.*, "Role of imaging in progressive-fibrosing interstitial lung diseases," *European Respiratory Review*, vol. 27, no. 150. European Respiratory Society, 2018. doi: 10.1183/16000617.0073-2018.
12. Irina Strambu, Ionela Belaconi, and Voicu Tudorache, "TOMOGRAFIA COMPUTERIZATĂ CU ÎNALTĂ REZOLUTIE (HRCT)," in *GHID DE DIAGNOSTIC SI TRATAMENT AL PNEUMOPATIILOR INTERSTITIALE DIFUZE*, 2015.
13. J. H. Fisher *et al.*, "Baseline characteristics and comorbidities in the CAnadian Registry for Pulmonary Fibrosis," *BMC Pulm Med*, vol. 19, no. 1, Nov. 2019, doi: 10.1186/ s12890-019-0986-4.
14. Kawano-Dourado L, Doyle TJ, Bonfiglioli K, et al. Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. Chest 2020, 158(4), pp. 1546–1554, doi.org/10.1016/j.chest.2020.04.061
15. Langford B, Diamantopoulos A, Maher TM et al. Using data on survival with idiopathic pulmonary fibrosis to estimate survival with other types of progressive fibrosis interstitial lung disease: a Bayesian framework. Adv Therap 2021. 39(151). DOI: 10.1007/ s12325-021-02014-z.
16. van de Sar I, Jones S, Clarke DL, Bonella F, Fourrier JM, Lewandowska K, Bermudo G, Simidchiev A, Strambu IR, Wijsenbeek MS, Parfrey H. Patient reported experiences and delays during the diagnostic pathway for pulmonary fibrosis: a multinational European survey. Front Med 2021. 8:711194. DOI: 10.3389/fmed.2021.711194