Prognostic factors of progressive fibrotic hypersensitivity pneumonitis: a large, retrospective, multicentre, observational cohort study

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Shareable abstract (@ERSpublications)
Several prognostic factors in fibrotic hypersensitivity pneumonitis were identified. The presence of fibroblastic foci at biopsy was a predictor for increased mortality and the presence of lymphocytosis in BAL was inversely related to mortality. https://bit.ly/48EMMje

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Abstract

Background Fibrotic hypersensitivity pneumonitis (fHP) is an immune-mediated interstitial lung disease caused by sensitisation to chronic allergen inhalation. This study aimed to determine prognostic indicators of progression and mortality in fHP.

Methods This was a retrospective, multicentre, observational, cross-sectional cohort study of consecutive patients diagnosed with fHP from 1 January 2012 to 31 December 2021. Multivariate Cox regression analyses were used to calculate hazard ratios (HRs) with 95% confidence intervals for predictors of progression and survival.

Results A total of 403 patients were diagnosed with fHP: median (interquartile range) age 66.5 (14.0) years, 51.9% females and 55.1% never-smokers. The cause of fHP was mainly fungal (39.7%) or avian (41.4%). Lung biopsy was performed in 269 cases (66.7%). In the whole cohort the variables that were related to mortality or lung transplant were older age (HR 1.08; p<0.001), percentage predicted forced vital capacity (HR 0.96; p=0.001), lymphocytosis in bronchoalveolar lavage (BAL) (HR 0.93; p=0.001), presence of acute exacerbation during follow-up (HR 3.04; p=0.001) and GAP (gender, age and lung physiology) index (HR 1.96; p<0.01). In the group of biopsied patients, the presence of fibroblastic foci at biopsy (HR 8.39; p<0.001) stands out in multivariate Cox regression analyses as a highly significant predictor for increased mortality or lung transplant. GAP index (HR 1.26; p=0.009), lymphocytosis in BAL (HR 0.97; p=0.018) and age (HR 1.03; p=0.018) are also predictors of progression.

Conclusions The study identified several prognostic factors for progression and/or survival in fHP. The presence of fibroblastic foci at biopsy was a consistent predictor for increased mortality and the presence of lymphocytosis in BAL was inversely related to mortality.

Introduction

Hypersensitivity pneumonitis (HP) is a complex syndrome that occurs in genetically predisposed individuals in an inflammatory response to repeated inhalation of an antigen, usually organic. It is also a heterogeneous disease, since it can vary in the form of clinical, radiological and anatomopathological presentation, making the differential diagnosis with other interstitial lung diseases (ILDs), especially fibrosing ILDs such as idiopathic pulmonary fibrosis (IPF), a challenge for the pulmonologist [1, 2]. Recently, the publication of two international diagnostic guidelines has tried to help in the diagnosis [3, 4].

IPF is the most common fibrotic and lethal ILD of unknown cause [5]. However, other non-IPF fibrotic ILDs such as fibrotic HP (fHP) may present a similar prognosis in a subgroup of patients [6]. Patients with progressive pulmonary fibrosis (PPF) present with lung function deterioration, progressive dyspnoea, poor quality of life and poor response to conventional treatments, together with high mortality [7]. It is estimated that 30% of patients with ILD will present with this phenotype during the course of disease, although data focused on fHP report this proportion increases up to 58% [8–11]. The evolution of HP is very varied and depends on various factors, some intrinsic to the patient and others dependent on environmental exposure.

Several retrospective studies have identified different risk factors that increase the probability of progression and mortality of patients with PPF, such as male sex, advanced age, low forced vital capacity (FVC) or diffusing capacity of the lung for carbon monoxide (D_{LCO}) at the time of diagnosis and the pattern of usual interstitial pneumonia (UIP) on thoracic high-resolution computed tomography (HRCT) [10]. In addition, the presence of traction bronchiectasis or acute exacerbations during follow-up is associated with a worse prognosis [12–14]. These findings need to be specifically confirmed in cohorts of patients with fHP. A better predictive prognostic model in fHP could help clinicians to plan follow-up, prescribe specific treatments and optimise lung transplant referral timings.

This study aimed to identify prognostic markers of progression and mortality in patients with fHP and to determine the clinical, radiological and functional characteristics.

Methods

This was a retrospective, multicentre, observational, cross-sectional cohort study of consecutive patients diagnosed with fHP from 1 January 2012 to 31 December 2021. 12 centres in Spain with recognised expertise in ILD participated in the study. All of these ILD units are accredited by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).

Objectives

The primary objective was to determine the prognostic indicators of progression and mortality in fHP, including multidimensional indices. Secondary objectives were to identify the clinical, radiological and functional characteristics of patients diagnosed with fHP.

Inclusion and exclusion criteria

A definitive diagnosis of fHP was obtained in all cases after multidisciplinary discussion in the ILD committee of each centre. The final diagnosis of fHP met the American Thoracic Society/Japanese Respiratory Society/Asociación Latinoamericana del Tórax (ATS/JRS/ALAT) 2020 consensus guideline criteria for patients with definitive or a high probability of fHP in which all the information was available [3]. In the other cases included, the exposure was recognised in all of them and HRCT was suggestive of fHP but without complete information about the concrete radiological pattern (typical, compatible or indeterminate) and the diagnosis was considered certain as provided by discussion in a multidisciplinary committee, in some cases after performing a lung biopsy. The diagnostic characteristics criteria of the cohort are summarised in supplementary table S1.

All subjects were required to provide written informed consent for participation in the study.

Patients with a previous diagnosis of any type of alternative ILD or other type of associated pneumopathy were excluded from the study. Other exclusion criteria were associated diseases that would prevent the performance of the necessary tests for study and follow-up (*e.g.* dementia, disabling neurological or psychiatric pathologies, or severe hearing deficit), and the presence of any disease with a poor prognosis in the short to medium term.

Study variables

A detailed medical history was taken with special attention paid to environmental exposures. Blood was extracted for a sensitisation study using ELISA to determine the presence of specific IgG against common inciting antigens (avian and fungal). Although the type of antigen tested was variable depending on the main exposure at each region, the most common fungal types were *Aspergillus*, *Saccharopolyspora rectivirgula*, *Penicillium*, *Thermoactinomyces vulgaris* and *Trichosporon*, and pigeon and parakeet feather and droppings were the most frequently tested among the avian types. Demographics, treatments received and their duration (corticosteroids, immunosuppressants and antifibrotics) were recorded.

Spirometry was performed according to SEPAR regulations and using the reference values published by Roca *et al.* [15]. Lung volume was determined by plethysmography. The D_{LCO} test and the 6-min walk test (6MWT) were performed by established methods.

Radiology examination was performed using thoracic HRCT and the lower respiratory tract was examined by video bronchoscopy with a differential cell count in bronchoalveolar lavage (BAL) samples. A transbronchial biopsy was performed in cases where there was a firm suspicion of fHP by thoracic HRCT but antigenic sensitisation or relevant lymphocytosis (>30%) following BAL was not demonstrated. Surgical lung biopsy was performed in cases where a diagnosis of HP was not made following transbronchial biopsy.

Functional, radiological follow-up variables, exacerbations and cause/data of death or lung transplant were recorded.

Clinical definitions

Progression was defined as at least two of the following three criteria occurring in a period of 1 year with no alternative explanation: 1) worsening respiratory symptoms; 2) physiological evidence of disease progression by either absolute decline in FVC ⩾5% predicted within 1 year of follow-up or absolute decline in D_{LCO} (corrected for haemoglobin) ⩾10% predicted within 1 year of follow-up; and 3) radiological evidence of disease progression [7]. Acute exacerbation of fHP was defined as significant clinical deterioration during a period of <1 month with radiological pulmonary infiltration and without another evident causative trigger such as heart failure or pulmonary thromboembolism [16].

Positive autoimmune serologies were considered when antinuclear antibody >1:80, rheumatoid factor >2 times the upper limit of normal, or some anti-extractable nuclear antigen or antimyositis specific or associated antibodies were present. In these cases, a careful evaluation by an expert rheumatologist at diagnosis ruled out the possibility of connective tissue disease or interstitial pneumonia with autoimmune features.

Statistics

Differences between groups in progression and survival were assessed using Cox regression analyses to calculate hazard ratios (HRs) with 95% confidence intervals. Multivariate Cox regression models were performed by adjusting for all confounding variables. We included all the variables that could be clinically relevant to predict progression or mortality. Two multivariate models were carried out: Model 1, excluding the GAP (gender, age and lung physiology) index (and including those variables that are in this multidimensional index: age, sex, FVC and D_{LCO}), and Model 2, including the GAP index (and excluding those variables that are in this multidimensional index: age, sex, FVC and D_{LCO}). Time to death was obtained from medical records and data were censored at the last medical visit or end of follow-up as of 31 November 2020.

Continuous data were summarised by mean with standard deviation or median (interquartile range (IQR)), and categorical data by number (percentage). Annual rates of change in FVC and D_{LCO} following treatment with antifibrotics were evaluated with multiple linear regression with mixed effects, using random intercept and slopes for modelling longitudinal measures. Using this model, pairwise comparisons were performed between three temporal times (baseline, start of treatment and end of follow-up), adjusting the p-values by the false discovery rate method [17]. A p-value <0.05 was considered statistically significant.

Statistical analyses were performed using MedCalc version 14.8.1 (MedCalc Software, Ostend, Belgium) and SPSS version 25 for Mac (IBM, Armonk, NY, USA). The mixed model analyses were performed with the R package (www.R-project.org).

Ethics

The study was conducted in accordance with the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects developed by the World Medical Association. All participants provided written informed consent. The study was approved by the Galician Research Ethics Committee (register number 2018/203) and the ethics committee of each participating centre.

Results

The study included 403 patients diagnosed with fHP. Patients were subdivided into two groups: those surviving at follow-up (n=291) and those who died or underwent lung transplantation (n=112). The demographics and clinical characteristics of patients are summarised in table 1. Overall, patients had a median (IQR) age of 66.5 (14.0) years, 51.9% (n=209) were females and 55.1% (n=222) were never-smokers. The mean±SD time of follow-up after fHP diagnosis was 43.8±26.8 months. The causal exposure was identified in 81.4% (n=328) of cases and was mainly fungal (39.7% (n=160)) or avian (41.4% (n=167)). The mean±SD lifetime antigen exposure was 29.1±18.9 years. In most cases (61.5% (n=248)), sensitisation was confirmed by determination of plasma precipitins/IgG.

BAL and cellular count were carried out in 324 patients (80.4%), and HRCT identified honeycomb lung in 109 patients (27.0%).

Lung biopsy was performed in 269 cases (66.7%) to aid diagnosis. In biopsied patients, the most common procedure was transbronchial biopsy with a cryoprobe (54.6% (n=147)), then surgical biopsy (29.7%; n=80) and conventional transbronchial biopsy (14.9% (n=40)). The most relevant findings in the biopsy group were the presence of a UIP-like pattern (41.3%) and peribronchial fibrosis (25.7%). The presence of fibroblastic foci was evident in 27.5% of biopsied cases (n=74).

Most patients received corticosteroids (79.4%). The rest of the treatments are summarised in table 2.

Predictors of disease progression

Of 403 patients, 225 (55.8%) showed disease progression. Multivariate Cox analysis showed, in Model 1, that older age (HR 1.03, 95% CI 1.005–1.056; p=0.018), presence of nail clubbing (HR 2.10, 95% CI 1.26–3.48; p=0.004), lymphocyte percentage in BAL (HR 0.97, 95% CI 0.95–0.99; p=0.018) and, in Model 2, GAP index (HR 1.26, 95% CI 1.05–1.50; p=0.009) were significantly associated with disease progression (table 3).

Predictors of overall survival

In the whole cohort (n=403), 93 (23%) patients died. In the Model 1 multivariate Cox analysis, older age (HR 1.08, 95% CI 1.04–1.12; p<0.001), lymphocyte percentage in BAL (HR 0.93, 95% CI 0.90–0.97; p=0.001), presence of acute exacerbations during follow-up (HR 3.04, 95% CI 1.53–6.04; p=0.001) and FVC at diagnosis (HR 0.96, 95% CI 0.94–0.98; p=0.001) were significantly associated with overall survival. In Model 2, GAP index (HR 1.96, 95% CI 1.49–2.57; p<0.001) was also associated with overall survival (table 4).

In the biopsy-confirmed fHP subgroup (n=269), 67 patients (24.9%) died. In this subgroup, in the Model 1 multivariate Cox analysis, presence of fibroblastic foci was a highly significant risk factor for mortality (HR 8.39, 95% CI 3.47–20.31; p<0.001). Other predictors of survival identified by Model 1 in this subgroup were lymphocyte percentage in BAL (HR 0.95, 95% CI 0.91–0.99; p=0.02) and FVC (HR 0.96, 95% CI 0.94–0.99; p=0.018). In Model 2, GAP index (HR 1.62, 95% CI 1.1–2.38; p=0.013) was also a predictor of survival (table 5).

Functional attributes of patients treated with antifibrotic drugs

Overall, 10% of patients (40 out of 403) were treated with antifibrotics (nintedanib and pirfenidone): 18 (4.5%) with pirfenidone and 22 (5.5%) with nintedanib. There were no significant differences in demographics and clinical characteristics between the two subgroups except for D_{LCO} values at follow-up: mean±SD D_{LCO} was lower in patients treated with pirfenidone (33.9±8.1) compared with nintedanib (46.5±15.7) (p=0.006). Adjusted mixed models results are presented in table 6 and figure 1.

Discussion

In this study of a large cohort of patients with fHP, multivariate Cox analyses identified a series of prognostic factors that were significantly associated with disease progression and survival. Analysis of the whole cohort showed that multidimensional GAP staging and older age are associated with both disease progression and survival. Another relevant finding is that lymphocytosis in BAL is inversely related to

TABLE 1 Demographics and clinical characteristics of the cohort (n=403)

Gender	
Male	194 (48.1)
Female	209 (51.9)
Age (years), median (IQR)	66.5 (14)
Smoking status	
Current smoker	14 (3.5)
Ex-smoker	160 (39.7)
Never-smoker	222 (55.1)
Not recorded	7 (1.7)
Tobacco consumption (pack-years), median (IQR)	16 (38.8)
Respiratory symptoms until ILD diagnosis (months)	18.6±14.6
Follow-up (months)	43.8±26.8
Family history of ILD	24 (6.0)
Charlson Comorbidity Index, median (IQR)	3 (2)
Gastro-oesophageal reflux	67 (16.6)
Pulmonary hypertension	81 (20.1)
Positive autoimmunity test	109 (27.0)
Recognised antigen exposure	328 (81.4)
Lifetime antigen exposure (years)	29.1±18.9
Type of antigen exposure	
Fungal	160 (39.7)
Avian	167 (41.4)
Other	1 (0.2)
Unknown	75 (18.6)
Sensitisation confirmed	
Precipitin/IgG test	248 (61.5)
Exposure test	4 (1.0)
Unconfirmed	72 (17.9)
Oxygen saturation (%)	95.2±3.2
Nail clubbing	49 (12.9)
Pulmonary crackles	316 (78.4)
PFT at diagnosis	
FVC (mL)	2434±837
FVC (% pred)	77.2±19.9
D_{LCO} (% pred)	57.6±16.1
FEV_1 (mL), median (IQR)	1910 (840)
FEV_1 (% pred)	82.9±22.4
TLC (mL)	4428±1112
TLC (% pred)	78.7±14.5
PFT at end of follow-up	
FVC (% pred)	71.5±21.7
D_{LCO} (% pred)	47.3±17.2
Thoracic HRCT[#]	
Traction bronchiectasis	240 (59.6)
Honeycomb	109 (27.0)
Emphysema	85 (21.1)
Radiological pattern	
Typical HP	120 (29.8)
Compatible HP	150 (37.2)
Indeterminate pattern	34 (8.4)
Not recorded	99 (24.6)
Biopsied	269 (66.7)
Type of biopsy[¶]	
Surgical	80 (29.7)
Conventional transbronchial	40 (14.9)
Cryobiopsy	147 (54.6)
Not recorded	2 (0.07)
Biopsy findings	
Fibroblastic foci[¶]	74 (27.5)
Pathological pattern[¶]	
Peribronchial fibrosis	69 (25.7)

Continued

TABLE 1 Continued

Fibrotic NSIP-like pattern	25 (9.3)
UIP-like pattern	111 (41.3)
Other	33 (12.3)
Not recorded	31 (11.5)
Diagnostic GAP index, median (IQR)	3 (2)
Diagnostic GAP stage	
1	230 (57.1)
2	114 (28.3)
3	20 (5.0)
Not recorded	39 (9.7)
Lymphocytes in BAL (%)	19.5±12.8
Exacerbation	52 (12.9)
Disease progression	225 (55.8)
Death	93 (23)
Lung transplant	19 (4.7)
Lost to follow-up	33 (8.2)

Data are presented as n (%) or mean±SD, unless otherwise stated. IQR: interquartile range; ILD: interstitial lung disease; PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; HRCT: high-resolution computed tomography; HP: hypersensitivity pneumonitis; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; GAP: gender, age and lung physiology; BAL: bronchoalveolar lavage. #: patients may have displayed more than one pathological change; ¶: percentages as a proportion of patients biopsied.

mortality and progression. In addition, the presence of fibroblastic foci in those patients who underwent a lung biopsy for their diagnostic process is proportionally related to an increase in mortality or lung transplantation.

The proportion of fHP patients that presented with PPF in our cohort was 55.8%, similar to recent data from a Canadian cohort and higher than the mean percentage of non-IPF fibrotic ILDs [11]. BAL lymphocytosis is commonly used in the diagnostic setting to discriminate fHP from other fibrotic ILDs, such as IPF. A systematic review reported that an optimised BAL lymphocytosis value of 21.3% gave a sensitivity of 66.5% and specificity of 65.9% for this purpose [18]. However, studies that have evaluated the relationship between a higher lymphocyte count in BAL of patients with HP to a longer survival are scarce. Ojanguren *et al.* [19] demonstrated this in 160 patients with fHP. The low percentage of lymphocytes in BAL was an independent predictor of mortality, along with age, D_{LCO} and a UIP pattern [19]. However, since histological confirmation is not required as the "gold standard", evaluating the prognostic factor for lymphocytosis when it is included in the variables used in the diagnostic algorithm (as in the latest ATS/JRS/ALAT guideline) may imply a bias [3]. Taking this into account, Hill *et al.* [20] designed a study where they selected patients without including BAL among the diagnostic criteria for fHP. Despite eliminating this inclusion bias, lymphocytosis in BAL was similarly related to survival in patients with fHP [20]. Our results are consistent with the scarce prior evidence. We observed that the percentage of lymphocytes in BAL is inversely related to survival and progression in fHP, even in the cohort of biopsied patients.

TABLE 2 Treatments of the whole cohort (n=403)

Corticosteroids	320 (79.4)
Corticosteroid dose ($mg \cdot day^{-1}$)	19.8±12.5
Immunosuppression	
Mycophenolate	91 (22.6)
Rituximab	2 (0.5)
Azathioprine	38 (9.4)
Other	2 (0.5)
Antifibrotic treatment	
Pirfenidone	18 (4.5)
Nintedanib	22 (5.5)
Antigen avoidance	188 (46.7)
Oxygen therapy	112 (27.8)

Data are presented as n (%) or mean±SD.

TABLE 3 Cox analysis of progression predictors: multivariate analysis (n=403)

	Model 1		Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.030 (1.005–1.056)	0.018		
Male sex	1.195 (0.665–2.148)	0.551		
Ever-smoker	1.346 (0.754–2.402)	0.316	1.2056 (0.758–1.915)	0.430
ILD family history	0.705 (0.346–1.435)	0.338	0.758 (0.376–1.528)	0.441
Charlson Comorbidity Index[#]	0.920 (0.781–1.083)	0.321	0.951 (0.816–1.108)	0.526
Pulmonary hypertension	0.934 (0.520–1.678)	0.821	0.975 (0.542–1.754)	0.933
Nail clubbing	2.101 (1.266–3.485)	0.004	2.029 (1.248–3.289)	0.0045
Duration of respiratory symptoms until ILD diagnosis	1.004 (0.989–1.018)	0.576	1.006 (0.992–1.019)	0.367
FVC % pred	0.985 (0.968–1.002)	0.102		
D_{LCO} % pred	0.990 (0.967–1.013)	0.408		
HRCT honeycomb at diagnosis	0.874 (0.519–1.472)	0.616	0.840 (0.509–1.383)	0.459
Associated autoimmunity	0.830 (0.494–1.394)	0.484	0.794 (0.473–1.332)	0.385
Recognised antigen exposure	1.232 (0.619–2.450)	0.554	1.110 (0.572–2.151)	0.758
Lymphocyte percentage in BAL	0.976 (0.958–0.9959)	0.018	0.974 (0.956–0.993)	0.0079
Acute exacerbation	1.107 (0.681–1.801)	0.681	0.941 (0.577–1.534)	0.808
Antigen avoidance	0.779 (0.450–1.347)	0.374	0.857 (0.512–1.434)	0.559
GAP index			1.261 (1.059–1.502)	0.009

HR: hazard ratio; ILD: interstitial lung disease; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage; GAP: gender, age and lung physiology. [#]: Charlson Comorbidity Index without age score.

In the current study, multivariate Cox analysis showed that the presence of fibroblastic foci was the strongest predictor for mortality in those patients who underwent biopsy. The relationship between the presence of fibroblastic foci in the lung biopsy of various fibrotic ILDs and the severity of the fibrotic findings in thoracic HRCT is known [21]. In the case of fHP, the fibroblastic foci profusion score has been correlated above all with the presence of traction bronchiectasis (r^2=0.45, p<0.0001) [21]. Our results are also consistent with other data published to date [13]. Wang *et al*. [22] observed in a cohort of 190 patients with fHP that the histological patterns of cellular nonspecific interstitial pneumonia (NSIP) and the

TABLE 4 Cox analysis of mortality or lung transplant predictors: multivariate analysis (n=403)

	Model 1		Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.080 (1.041–1.120)	<0.001		
Male sex	0.552 (0.210–1.448)	0.229		
Ever-smoker	0.444 (0.156–1.266)	0.131	0.657 (0.331–1.302)	0.231
ILD family history	0.430 (0.117–1.132)	0.137	0.451 (0.182–1.117)	0.087
Charlson Comorbidity Index[#]	0.866 (0.688–1.090)	0.225	0.963 (0.775–1.197)	0.739
Pulmonary hypertension	0.648 (0.291–1.442)	0.290	0.765 (0.347–1.686)	0.509
Nail clubbing	1.848 (0.918–3.719)	0.086	1.867 (0.970–3.596)	0.062
Duration of respiratory symptoms until ILD diagnosis	1.006 (0.987–1.026)	0.487	1.016 (0.998–1.034)	0.080
FVC % pred	0.963 (0.941–0.986)	0.001		
D_{LCO} % pred	0.973 (0.945–1.002)	0.074		
HRCT honeycomb at diagnosis	1.119 (0.564–2.220)	0.748	1.392 (0.708–2.737)	0.340
Associated autoimmunity	0.917 (0.439–1.913)	0.818	0.610 (0.292–1275)	0.191
Recognised antigen exposure	1.903 (0.718–5.043)	0.197	1.436 (0.572–3.605)	0.443
Lymphocyte percentage in BAL	0.938 (0.904–0.973)	0.001	0.945 (0.914–0.977)	0.001
Acute exacerbation	3.040 (1.530–6.041)	0.001	1.954 (1.051–3.634)	0.035
Antigen avoidance	0.819 (0.392–1.708)	0.596	0.741 (0.363–1.513)	0.413
GAP index			1.964 (1.496–2.579)	<0.001

HR: hazard ratio; ILD: interstitial lung disease; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage; GAP: gender, age and lung physiology. [#]: Charlson Comorbidity Index without age score.

TABLE 5 Cox analysis of mortality or lung transplant predictors in biopsied patients: multivariate analysis (n=269)

	Model 1		Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.044 (1.001–1.091)	0.05		
Male sex	0.837 (0.270–2.589)	0.759		
Ever-smoker	0.778 (0.262–2.313)	0.654	0.898 (0.432–1.867)	0.776
ILD family history	0.831 (0.278–2.481)	0.742	0.965 (0.354–2.629)	0.945
Charlson Comorbidity Index[#]	0.834 (0.621–1.120)	0.232	0.898 (0.683–1.181)	0.447
Pulmonary hypertension	0.614 (0.241–1.558)	0.307	0.808 (0.330–1.976)	0.642
Nail clubbing	1.787 (0.802–3.980)	0.157	1.710 (0.817–3.577)	0.156
Duration of respiratory symptoms until ILD diagnosis	1.006 (0.981–1.031)	0.628	1.013 (0.991–1.036)	0.231
FVC % pred	0.968 (0.943–0.994)	0.018		
D_{LCO} % pred	0.986 (0.949–1.024)	0.472		
HRCT honeycomb at diagnosis	0.665 (0.258–1.717)	0.402	0.740 (0.293–1.866)	0.526
Associated autoimmunity	1.465 (0.605–3.546)	0.398	1.372 (0.572–3.288)	0.480
Recognised antigen exposure	1.501 (0.490–4.593)	0.478	0.976 (0.344–2.764)	0.964
Lymphocyte percentage in BAL	0.952 (0.914–0.992)	0.020	0.962 (0.928–0.998)	0.041
Acute exacerbation	2.201 (0.942–5.138)	0.069	1.553 (0.701–3.441)	0.279
Antigen avoidance	1.094 (0.455–2.628)	0.841	1.349 (0.576–3.156)	0.492
GAP index			1.626 (1.108–2.387)	0.013
Fibroblastic foci	8.399 (3.472–20.318)	<0.001	9.131 (3.871–21.536)	<0.001

HR: hazard ratio; ILD: interstitial lung disease; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage; GAP: gender, age and lung physiology. [#]: Charlson Comorbidity Index without age score.

presence of peribronchial inflammation with poorly formed granulomas were associated with greater survival than the histological patterns of UIP or fibrotic NSIP. Moreover, the presence of fibroblastic foci or dense collagenous fibrosis was associated with higher mortality [22].

In our cohort, the presence of acute exacerbations during follow-up was an independent factor associated with higher mortality in the multivariate analysis despite correcting by avoiding the exposure to the possible causative antigen. Acute exacerbations in fHP, as in any ILD, are life-threatening episodes. Preventing acute exacerbations should be one of the main objectives of any clinician during the follow-up of these patients. The hospital mortality is ∼44% [12]. Miyazaki *et al.* [23] described various predictors of acute exacerbation at the time of fHP diagnosis, such as low total lung capacity and D_{LCO}, low levels of lymphocytes in BAL or a histological pattern of UIP.

The GAP model was initially designed and validated in IPF [24] and its use was later extended to other ILDs after the publication of the ILD-GAP index, by adding a new variable to the GAP index that depends on the type of PPF and thus makes it possible to correct the theoretical higher survival of these diseases with respect to IPF [6]. Few studies have evaluated its role exclusively in patients with fHP. One of them

TABLE 6 Rates of change in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) in patients with fibrotic hypersensitivity pneumonitis treated with antifibrotics

	Nintedanib (n=22)		Pirfenidone (n=18)	
	Absolute change (% pred) (95% CI)	p-value	Absolute change (% pred) (95% CI)	p-value
$FVC_b - FVC_s$	−0.1 (−16.7–16.5)	0.837	−1.33 (−17.5–20.2)	0.902
$FVC_s - FVC_f$	−5.04 (−11.8–21.9)	0.495	−16.3 (4.4–34.3)	0.004
$D_{LCOb} - D_{LCOs}$	1.33 (−13.7–11.0)	0.834	−6.02 (−5.6–17.6)	0.122
$D_{LCOs} - D_{LCOf}$	−10.76 (3.8–22.3)	0.012	−17.02 (3.6–30.3)	0.031

FVC_b: FVC at baseline; FVC_s: FVC at start of treatment; FVC_f: final FVC (at end of follow-up); D_{LCOb}: D_{LCO} at baseline; D_{LCOs}: D_{LCO} at start of treatment; D_{LCOf}: final D_{LCO} (at end of follow-up). Mixed models adjusted for sex, age, smoking status, immunosuppressor and/or corticosteroids. p-value adjusted by the false discovery rate method.

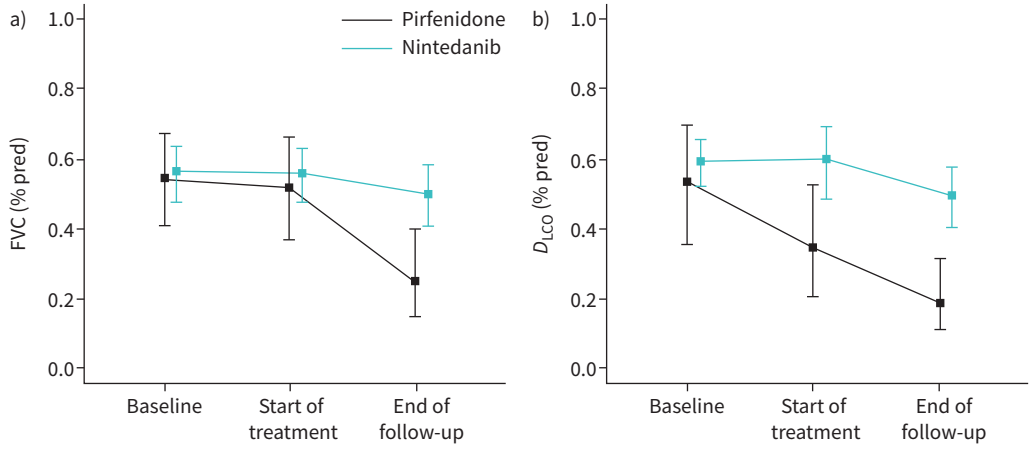

FIGURE 1 Lung function trajectory in patients with fibrotic hypersensitivity pneumonitis from baseline to the start of antifibrotic treatment and from the start of treatment to the end of follow-up: a) forced vital capacity (FVC) and b) diffusing capacity of the lung for carbon monoxide (D_{LCO}). Mixed models adjusted for sex, age, smoking status, immunosuppressor and/or corticosteroids.

was by Almeida *et al.* [25] who analysed 141 patients with fHP, of whom 37.6% (n=53) died during follow-up. They found that patients with an ILD-GAP score >3 were proportionally associated with higher mortality (HR 6.48, 95% CI 3.03–13.96) despite adjusting for the presence of acute exacerbations [25]. In our analysis of the whole cohort we showed that multidimensional GAP staging was associated with both disease progression and survival. Our publication is the largest fHP cohort published to date that corroborates these results, also performing a multivariate analysis not only taking into account the presence of acute exacerbations, but also other possible confounding variables.

Regarding other predictors of progression or mortality at the time of diagnosis, older age or respiratory functional variables at diagnosis, such as low FVC, have already been described and are consistent with previous studies. However, the main limitations of some of those studies are the methodology used (univariate analysis), without correction for possible confounding factors [19, 26–29].

In the present study, nintedanib seems to slow the decline in FVC but not in D_{LCO} from baseline to end of treatment compared with pirfenidone. The modest results obtained may be related to the low number of patients evaluated. This low number is probably related to the fact that nintedanib was approved for the indication of PPF late in the study period. In any case, these results are in line with previous scientific evidence, such as the INBUILD study, a placebo-controlled clinical trial that showed that nintedanib slowed the rate of FVC decline in progressive fibrosing ILDs [30, 31].

The retrospective nature of the study represents a limitation. By design, the study may be biased due to the loss of essential data to enable correct prognostic analyses. For example, not all patients underwent BAL and this may be a bias in their analysis as a predictive factor. It is possible that those who did not undergo BAL (~20%) did not do so because they presented an impaired lung function and it was considered a contraindication.

Plasma precipitin determination panels are not standard for each of the centres and many of them have adapted the panels to the antigens that are usually found in their environment. For this reason, not all the IgG determinations were collected in the database and, by protocol, they were only divided into the main types, which were fungal and avian.

Nevertheless, for minority diseases, it is common practice to use a retrospective approach to validate prognostic and mortality criteria. A strength of the study is that it was conducted across multiple participating expert centres with a relatively large patient sample size over a 10-year period, thus helping to mitigate (within limits) any design bias.

In conclusion, multivariate Cox regression analyses identified several prognostic factors for progression and/or survival in fHP. The presence of histological fibroblastic foci, acute exacerbations and low FVC at

diagnosis were highly significant predictors for increased mortality; and GAP staging, low lymphocyte percentage in BAL and older age were associated with both disease progression and survival. These factors need to be validated in large prospective studies.

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