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Survival in familial idiopathic pulmonary fibrosis and fibrotic hypersensitivity pneumonitis

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To the editor,

Familial pulmonary fibrosis (FPF) is defined as the occurrence of any interstitial lung disease (ILD) in two or more first- or second-degree relatives (1). FPF has an earlier onset than sporadic forms of ILD, with the same gender distribution and behavior as progressive pulmonary fibrosis (PPF) (1,2). Although the most frequently reported phenotype in FPF is idiopathic pulmonary fibrosis (IPF), other forms of familial ILD have been identified, such as fibrotic hypersensitivity pneumonitis (fHP), (1-3).

Recently, Cutting et al., in a cohort of 1,262 patients with various ILDs, demonstrated a shorter survival rate in those with FPF, independent of phenotype (3). However, patients with connective tissue disease (CTD), hypersensitivity pneumonitis (HP), and unclassified pulmonary disease (UPD) were included in the non-IPF group (NF-IPF) , which may have influenced the survival rates (3). There is a lack of studies of patients with FPF in low-and-middle income countries, such as Brazil, thus, this study aimed to compare the survival of patients with familial presentations of IPF and fHP to that of patients with the same sporadic ILD phenotypes. This was a retrospective study involving three reference centers for ILDs in Brazil. Patients older than 18 years diagnosed with IPF and fHP, and who were followed up from January 2007 until death or May 31, 2022, were included. Other ILD phenotypes were excluded. FPF was defined by the presence of two or more first- or second-degree relatives with an ILD of any etiology, with documentation of interstitial involvement in another family member to confirm FPF (1). High-resolution chest computed tomography (HRCT) was classified according to the ATS/ERS/JRS/ALAT guidelines (4). Clinical data on pulmonary function and imaging were collected during the first follow-up evaluation of patients. All cases were reviewed in multidisciplinary meetings. The diagnosis of IPF followed the ATS/ERS/JPS/ALAT recommendations (4).

The diagnosis of fHP was based on the following criteria (5):

- Typical HRCT findings with identified associated exposure; lymphocytosis in bronchoalveolar lavage (BAL) and/or suggestive histopathology, or;
- Typical HRCT findings without identified exposure, with suggestive histopathology, or;
- Other HRCT patterns (compatible or indeterminate) only when suggestive histopathology was present.
- In cases with UIP or probable UIP pattern, with identified associated exposure, without conclusive biopsy, the diagnosis of HP was done by multidisciplinary discussion (MDD) considering other findings as younger age, worsening with exposure, squeezes at physical examination and increase lymphocytes in BAL (> 25%).

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Only participants with definitive or high confidence diagnosis of fHP were included.[5] Multivariate Cox regression analysis was used to measure the association between variables age, gender, degree of dyspnea, pulmonary function, peripheral oxygen saturation (SpO2%), HRCT pattern, and family history and survival. Variables that showed statistical differences (p<0.05) between the familial and non-familial groups were controlled before estimating the survival curves. Kaplan-Meier survival curves were estimated and compared using the Log-Rank test. A significance level of $p < 0.05$ was adopted. A total of 198 participants were included: 88 with IPF and 110 with fHP. In the IPF group, 36 had familial forms (F-IPF), and in the fHP group, 30 had familial fHP (F-fHP) (Table 1).

The median follow-up time was 37 (3 - 1200) months. The variables age (hazard ratio [HR]: 1.03; 95% CI: 1.01 - 1.06; p = 0.01), FVC% (HR: 0.96; 95% CI: 0.94 - 0.98; p < 0.01), SpO2% (HR: 0.86; 95% CI: 0.76 - 0.97; p < 0.02), and family history of pulmonary fibrosis (HR: 1.79; 95% CI: 1.09 - 2.93; p = 0.02)

Table 1. Clinical, functional and tomography findings.

Final Diagnosis				
Variables	**IPF (n=88)**		**fHP (n=110)**	
	NF-IPF n=52	**F-IPF n=36**	**NF-fHP n=80**	**F-fHP n=30**
Age, years (± SD) #	70 ± 8	70 ± 8	63 ± 12	64 ± 9
Female, n (%) #	12 (23.0%)	11 (31.0%)	39 (49.0%)	16 (53.0%)
Smokers/former smokers, n (%) #	34 (65.0%)	24 (67.0%)	45 (56.0%)	17 (57.0%)
Dyspnea (mMRC), n (%) #				
O mMRC	4 (7.7%)	11 (30.5%)	6 (7.6%)	4 (13.4%)
I mMRC	27 (51.9%)	19 (52.7%)	28 (35.0%)	15 (50.0%)
II mMRC	15 (28.9%)	6 (16.8%)	37 (46.2%)	9 (30.0%)
III mMRC	6 (11.5%)	0 (0%)	8 (10.0%)	1 (3.3%)
IV mMRC	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (3.3%)
Velcro crackles#	45 (87.0%)	26 (72.0%)	51 (64.0%)	20 (67.0%)
FVC% (x ± SD), n=196#	75 ± 15	82 ± 19	70 ± 15	72 ± 16
DLCO% (x ± SD), n=103	58 ± 15	61 ± 19	55 ± 17	61 ± 16
SpO_2 (x ± SD), n=194	94.7 ± 1,8	94.7 ± 2,2	94.8 ± 2,1	95.0 ± 1.8
HRCT pattern, n (%) #				
UIP	38 (73.1%)	16 (44.4%)	10 (12.5%)	7 (23.3%)
Probable UIP	11 (21.2%)	19 (52.8%)	30 (37.5%)	9 (30.0%)
Alternative diagnosis	3 (5.8%)	1 (2.8%)	40 (50.0%)	14 (46.7%)
Conclusive biopsies Ɨ	10 (19.2%)	5 (13.9%)	33 (41.2%)	11 (36.7%)
Treatment, n (%)				
Corticosteroids	**14 (26.9%)**	**2 (5.6%)**	**51 (63.8%)**	**15 (50.0%)**
Immunosuppressors	**7 (13.5%)**	**2 (5.6%)**	**22 (61.1%)**	**4 (13.3%)**
Antifibrotics treatment#	**20 (38.5%)**	23 (65.7%)	7 (8.9%)*	7 (24.1%)

Ɨ Surgical lung and transbronchial biopsies (these in cases of HP); #: p < 0.05 between the four groups (t- student test or ANOVA); *: p <0.05 between the groups with and without family history

Abbreviations: F-IPF: familial idiopathic pulmonary fibrosis; NF-IPF: non familial idiopathic pulmonary fibrosis; F-fHP: familial fibrotic hypersensitivity pneumonitis; NF-fHP: non familial fibrotic hypersensitivity pneumonitis; SD: standard deviation; mMRC: modified medical research council dyspnea scale; FVC%: forced vital capacity percent predicted; DLCO%: lung diffusion capacity for carbon monoxide percent predicted; SpO_2: peripheral oxygen saturation; HRCT: high resolution computed tomography; UIP: usual interstitial pneumonia. *Note:* No patient was classified with an indeterminate HRCT pattern.

were associated with mortality and were controlled before performing the survival curves. After adjusting for these four covariates, patients with F-IPF and F-fHP had similar survival curves, but worse than the corresponding sporadic forms. Survival was significantly worse for patients with F-IPF (log-rank=3.94, p=0.046) and F-fHP (log rank=4.81, p=0.028). When merged cases of familial IPF and fHP were compared to the remaining, considering age, FVC% and SpO2 at rest, by Cox analysis, the HR for mortality was 2.00 (CI95% 1.19-3.33), in familial cases. The median survival for the FPF group was 46 months compared to 75 months for the non-familial group (p = 0.009), (Figure 1).

FPF can present with different phenotypes, even within the same family. The incidence of fHP in Brazil is high and probable UIP is more commonly seen in fHP, in comparison to IPF (6). Cutting et al. showed a shorter survival rate in FPF patients, regardless of the etiology (3). In their results, F-IPF participants had an 80% higher risk of death or lung transplant compared to those with sporadic IPF (HR: 1.8; 95% CI: 1.37 - 2.37; p < 0.001) (3). In a smaller cohort, Newton et al., evaluating 115 patients with genes related to telomere biology alterations and ILD with a family history, found a median survival of 2.75 years (95% CI: 1.64 - 4.61) for IPF and 3.11 years (95% CI: 2.56 - 4.82) for non-IPF ILD. However, only 12% of the 77 non-IPF ILD cases were diagnosed with fHP.[2] In contrast to our findings, the two studies mentioned above included various etiologies in the non-IPF ILD group, which may have influenced the final results. We only evaluated IPF and fHP due to the high prevalence of these conditions in Brazil (6) and to avoid biases related to other diagnoses, such as CTD that have better response to immunosuppressive treatments. In our results, the median survival was less than four years for familial diseases, and there was no difference between F-fHP and F-IPF, suggesting that an interaction between genetics and environmental exposure may contribute to greater severity and shorter survival in F-fHP. This study has some limitations that should be noted. First, it is an observational retrospective study, potentially with the biases associated with this type of study. However, a significant number of patients were followed for an extended period, supporting the robustness of the findings. Second, not all patients were using antifibrotic drugs, which were approved in Brazil in 2014 and remain limited in availability due to the lack of public access. In conclusion, patients with familial presentations of IPF and fHP have significantly shorter survival compared to patients with non-familial disease of the same diseases. In clinical practice across many countries, genetic testing is not widely available, so family history should always be investigated.

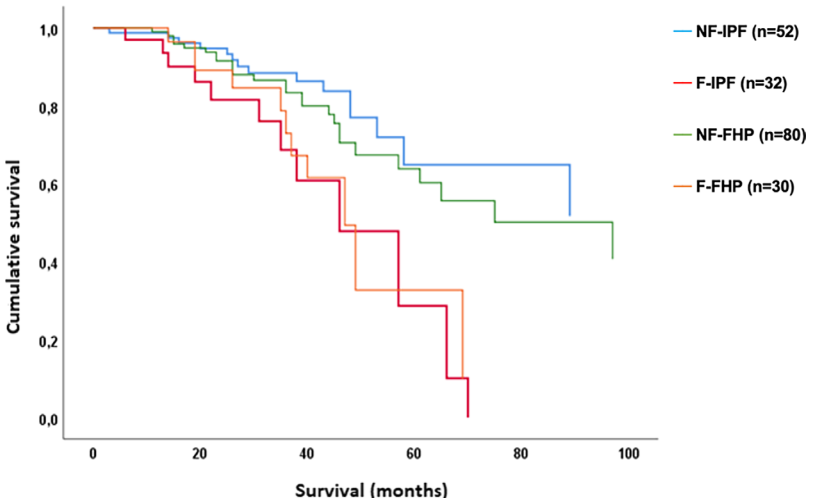

Figure 1. Survival in the idiopathic pulmonary fibrosis (IPF) and fibrotic hypersensitivity pneumonitis (fHP) groups, separated by diagnosis and family history, considering covariates. Survival was significantly worse for patients with F-IPF (log-rank=3.94, p=0.046) and F-fHP (log-rank=4.81, p=0.028). The median survival for the FPF group was 46 months compared to 75 months for the non-familial group (p = 0.009). *Abbreviations:* NF-IPF: non-familial idiopathic pulmonary fibrosis; F-IPF= familial idiopathic pulmonary fibrosis; NF-fHP: non-familial fibrotic hypersensitivity pneumonitis; F-fHP: familial fibrotic hypersensitivity pneumonitis

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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