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Clinical course of suspected familial and sporadic idiopathic pulmonary fibrosis: Data from the PROOF-Next registry

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Abstract

Background and Objective: Real-life data on suspected familial fibrosis, defined as the occurrence of the disease in a patient younger than 50 and/or having at least one relative affected by pulmonary fibrosis remain scarce.

Methods: The Belgian and Luxembourg IPF registry (PROOF-Next) is a multicentric prospective longitudinal and observational study set in Belgium and Luxembourg. We compared characteristics and clinical course of patients with suspected familial pulmonary fibrosis (FPF) and sporadic IPF.

Results: We included 618 patients in the analysis, of whom 76 (12%) fulfilled criteria for FPF. They were significantly younger than sIPF (median age (range) 65 (43–87), vs. 72 (51–98), $p = 0.0001$). Male gender proportion and smoking status did not differ between groups, but the number of pack-year among current and former smokers was lower in FPF (20 vs. 25, $p = 0.02$). Besides, 87% of FPF and 76% of sIPF were treated with antifibrotic ($p = 0.047$).

Baseline pulmonary function tests were similar in both groups, as well as median time before progression and transplant-free survival. Finally, genetic testing, performed in a minority, led to the identification of 10 telomerase-related gene variants.

Conclusion: Although younger and exposed to less tobacco, patients with FPF show an equally aggressive progression as observed in sporadic IPF patients. These results warrant early referral of FPF patients to expert centres for optimal management.

KEYWORDS
clinical respiratory medicine, interstitial lung disease, pulmonary fibrosis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disease of unknown origin. Clinical course is detrimental, with a median survival of 3–5 years without treatment[1] and 6–7 years with antifibrotic treatment, according to recent registry data.[2]

Familial clustering concerns up to 10% of patients. The currently adopted clinical definition of suspected familial fibrosis relies on the two following criteria: having pulmonary fibrosis prior to the age of 50 and/or having at least one relative suffering from pulmonary fibrosis.[3–5] A common mutation in the promoter of MUC5B is currently considered the strongest risk factor for sporadic IPF.[6] A genetic trait is also usually suspected in the eventuality of idiopathic pulmonary fibrosis affecting patients younger than 50.[3] Recent advances in genetics have demonstrated an association between familial fibrosis and variants in telomere-related genes and surfactant-related genes.[7] After identifying genes conferring a risk or explaining familial clustering, the next step is to evaluate whether this would

Preliminary data from this study were previously presented at the 2021 European Respiratory Congress (ERS).

modify clinical practice, especially regarding prognosis and treatment.

Therefore, we sought to investigate the impact of the 'familial pulmonary fibrosis' (FPF) phenotype on progression and transplant-free survival in a large, multicentric and international IPF cohort. We compared patients fulfilling the criteria for FPF and patients with sporadic fibrosis within the Belgian–Luxembourg IPF registry. We studied both populations regarding their baseline characteristics, lung function decline and transplant-free survival.

SUMMARY AT A GLANCE

Familial clustering affects about 10% of idiopathic pulmonary fibrosis. This prospective multicentric study provides a reliable estimate of familial fibrosis among IPF patients and demonstrates similar dismal prognosis despite a younger age and a lighter exposure to smoking. Our results warrant early referral of familial fibrosis patients to expert centres.

METHODS

Study population

The *Prospective Observational Registry to Describe the Disease Course and Outcomes of Idiopathic Pulmonary Fibrosis Patients in a Real-world Clinical Setting* (PROOF) in Belgium and Luxembourg IPF registry, prolonged by PROOF-Next, is a prospective longitudinal study set in eight Belgian centres and one Luxembourg centre. The registry includes patients with an IPF diagnosis according to ATS-ERS guidelines used at the time of inclusion.[8,9] All patients were recruited with centres with recognized expertise in interstitial lung diseases. There was no central review of diagnosis, lung scanner and histology. Inclusion started in October 2013 and was closed in September 2020. Follow-up of patients and data entry went on until November 2021.

Outcomes

In this analysis, we compared survival and lung function decline between patients with sporadic IPF and suspected familial IPF, defined as having at least one relative with pulmonary fibrosis and/or having IPF before the age of 50.[5] We extracted all data from the original electronic case report form (eCRF), where they had been prospectively included, with the exception of data on genetic testing, that were collected retrospectively.

Statistical analysis

We used Pearson's chi-square test of independence: to test whether two categorical variables are independent. In order to be able to interpret the results, there should not be expected frequencies lower than 5 in more than 20% of the cells of the contingency table. We used Mann–Whitney test (aka Wilcoxon rank-sum test) as a nonparametric alternative to the Student's *t*-test for two samples.

We built Kaplan–Meier curves: nonparametric estimate of the survival function, in the presence of right-censored times to event. We compared curves with Log-rank tests.

We used a Cox model (also known as Proportional hazards model), a survival model to relate some (possibly) explanatory variables to the time up to an event, in the presence of right censoring. The exponential of an estimated parameter can be interpreted as the multiplicative effect of a 1-unit increase in the covariate on the hazard rate.

To produce robust statistical comparisons, we estimated Cox models to explain the time between diagnosis and[1] the first decrease of 10% in FVC,[2] the first decrease of 15% in DLCO and[3] death or lung transplant in our population.

We built two different models: in the first ('model 1'), the explanatory variable is the 'Familial Pulmonary Fibrosis group' and we control for age, sex, body mass index (BMI), smoking status (ever smoker vs. non-smoker) and presence of emphysema at inclusion. The second model ('model 2') differs on the smoking variable, where we used the absolute number of pack-years instead of non-smoker versus ever-smoker. In the models used for time to 10% FVC decline and 15% DLCO decline, we also control for baseline FVC and DLCO, respectively. We also included interactions between the familial group and all other variables but removed one by one the interactions that were not significant.

All statistics were performed by the *Support en Méthodologie et Calcul Statistique/Statistical Methodology and Computing Service (SMCS)*, UCLouvain.

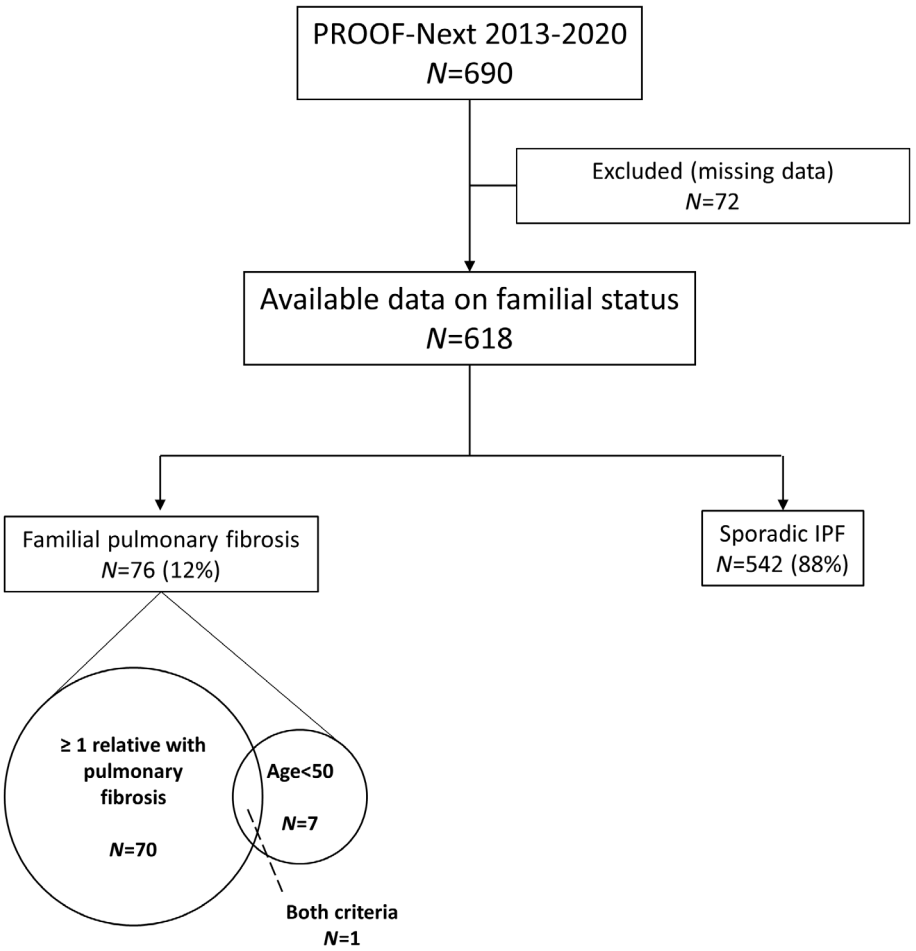
RESULTS

Study population

Six hundred ninety-one patients were included in the PROOF-Next registry and IPF diagnosis was available for 690 patients. We excluded 72 patients for whom data on familial history were missing (empty query in the eCRF). The 618 remaining patients were included in the present analysis (Figure 1).

Seventy-six patients (12%) met our criteria for familial pulmonary fibrosis (FPF): 70 had a family history of pulmonary fibrosis, with at least one relative affected. Seven patients (1%) were younger than 50-years-old at inclusion, meaning that one patient met both criteria (Figure 1). We compared those 76 patients with the 542 (88%) patients that did not fulfil criteria for FPF. We provide the main characteristics of our population in Table 1: as compared with

FIGURE 1 Study flowchart.



sporadic IPF, patient with FPF were significantly younger (65 vs. 72 years, $p < 0.001$). Although smoking status was similar in both groups, with 75% of former and active smokers, the cumulative exposure among current and former smokers, expressed by the number of pack-years, was significantly lower in the suspected familial IPF group as compared with sporadic IPF (20 pack-years vs. 25, $p = 0.02$). At 6-month follow-up, 87% of patients with suspected familial IPF and 76% of sporadic IPF were treated with an antifibrotic drug ($p = 0.047$, chi-square test).

Lung function decline is similar in suspected familial and sporadic IPF

We first compared time to first 10% relative decrease in forced vital capacity (FVC) between both groups. The curve for the familial IPF patients is based on 76 patients, with 42 events and 34 censored times. The curve for the nonfamilial IPF patients is based on 542 patients, with 297 events and 245 censored times. The estimated median time until the first decrease of 10% in FVC was 859 days (2.35 years) for the FPF patients and 1013 days (2.78 years) for the nonfamilial IPF patients (Figure 2A).

We also compared time to first 15% relative decrease in lung diffusion capacity (DLCO). The curve for the familial IPF patients is based on 76 patients, with 47 events and 29 censored times. The curve for the nonfamilial IPF patients is based on 542 patients, with 349 events and 193 censored times. The estimated median time until the first decrease of 15% in DLCO was 818 days (2.24 years) for the FPF patients and 732 days (2.01 years) for the nonfamilial IPF patients (Figure 2B).

We did not find statistically significant difference in FVC decline ($p = 0.6$, Log-Rank test) or DLCO decline ($p = 0.8$, Log-Rank test) between familial and sporadic IPF.

Mortality is similar in familial pulmonary fibrosis and sporadic IPF

We built a Kaplan-Mayer curve comparing transplant-free survival of suspected familial versus sporadic IPF (Figure 2C). The curve for the FPF patients is based on 71 patients, with 16 events and 55 censored times. The curve for the nonfamilial IPF patients is based on 527 patients, with 152 events and 375 censored times. The estimated median time until death was not defined for the FPF patients due to a lack of events and 2313 days (6.34 years) for the nonfamilial IPF patients. There was no statistical difference between curves ($p = 0.3$, Log-Rank test).

TABLE 1 Main characteristics of the study population.

	Familial pulmonary fibrosis ($N = 76$)	Sporadic IPF ($N = 542$)	*p*-value
Demographics			
Sex (M/F, %)	55/21 (72/28%)	416/126 (77/23%)	0.5
Age (years, IQR)	65 (59–71)	72 (67–77)	**<0.001**
Ethnicity			0.5
Caucasian	75 (99%)	518 (98%)	
African	0 (0%)	12 (2%)	
Other	1 (1%)	9 (2%)	
Smoking history	57 (75%)	407 (75%)	0.9
Pack-years (*N*, IQR)	20 (6–30)	25 (10–40)	**0.02**
Disease characteristics			
Biopsy (total, %)	24 (31%)	188 (35%)	0.7
SLB (*N*)	17	124	
TBLC (*N*)	7	54	
% baseline FVC	88 (68–100)	81 (71–95)	0.3
% baseline DLCO	55 (45–64)	51 (41–61)	0.08
HRCT pattern			0.6
UIP/probable UIP	48 (63%)	329 (61%)	
Other	28 (37%)	213 (39%)	
IPF treatment at 6 months			**0.047**
Nintedanib (*N*, %)	22 (29%)	106 (20%)	
Pirfenidone (*N*, %)	44 (58%)	301 (56%)	
None (*N*, %)	10 (13%)	128 (24%)	

Abbreviations: DLCO, lung diffusion capacity; FVC, forced vital capacity; SLB, surgical lung biopsy; TBLC, transbronchial cryobiopsy.

Cox models for selected variables comparison between suspected familial and sporadic IPF

Due to missing values, we considered 573 patients in the analyses for FVC and DLCO, and 571 in the analysis for death or lung transplant.

For the models explaining 10% FVC decline, there was no interaction between familial group and each of the other control variables. There was no difference in time to 10% FVC decline between FPF and sporadic IPF when controlling for the other explanatory variables ($p = 0.81$ for model 1, $p = 0.79$ for model 2). In both models, age and BMI were significantly related to the time between diagnosis and the first decrease of at least 10% in FVC ($p = 0.02$ and 0.01 for age, and 0.03 and 0.04 for BMI): older patients and patients with a high value of BMI have a lower hazard. In both models, the presence of emphysema was associated with a lower hazard of 10% FVC decline ($p = 0.04$ and 0.06, respectively). In the model containing the smoking status (current or former smoker vs. nonsmoker), there was a trend for association with time to first decrease of at least 10% in FVC ($p = 0.070$) (Figure 3A). In the model including smoking through pack-years (model 2), this variable was not significantly related to the time between diagnosis and the first decrease of at least 10% in FVC (Figure 3B).

Regarding time to 15% DLCO decline, our Cox models did show a trend to a significant difference between FPF and sporadic IPF ($p = 0.08$ and $p = 0.06$ for models 1 and 2, respectively). The sex was significantly related to the time between diagnosis and the first decrease of at least 15% in DLCO: women had a lower hazard ($p = 0.0172$ and 0.0077 for models 1 and 2, respectively). In the same models, BMI also correlated to the response: a higher value was associated to a lower hazard ($p = 0.033$ and 0.043 for models 1 and 2 respectively, Figure 3C,D). The effect of the presence of emphysema at inclusion was significant for model 1 ($p = 0.03$) and almost significant ($p = 0.06$) for model 2: patients with emphysema had a lower hazard. Of note, the effect of age, which was not significant in the sporadic IPF group, was significantly ($p = 0.0703$ and 0.05) different in the FPF group (higher hazard with higher age value).

Finally, our Cox models confirmed the absence of a significant difference in time to death or lung transplant between FPF and sporadic IPF ($p = 0.96$ and 0.91 for models 1 and 2, respectively). Sex was significantly related to the survival: women had a lower hazard ($p = 0.001$ and $p < 0.001$ in models 1 and 2, respectively, Figure 3E,F). The effect of age was also significant, with a higher hazard for older patients ($p = 0.008$ and 0.01). There was also a trend for an association between BMI and survival: a higher value was associated with a lower hazard ($p = 0.09$ and 0.09).

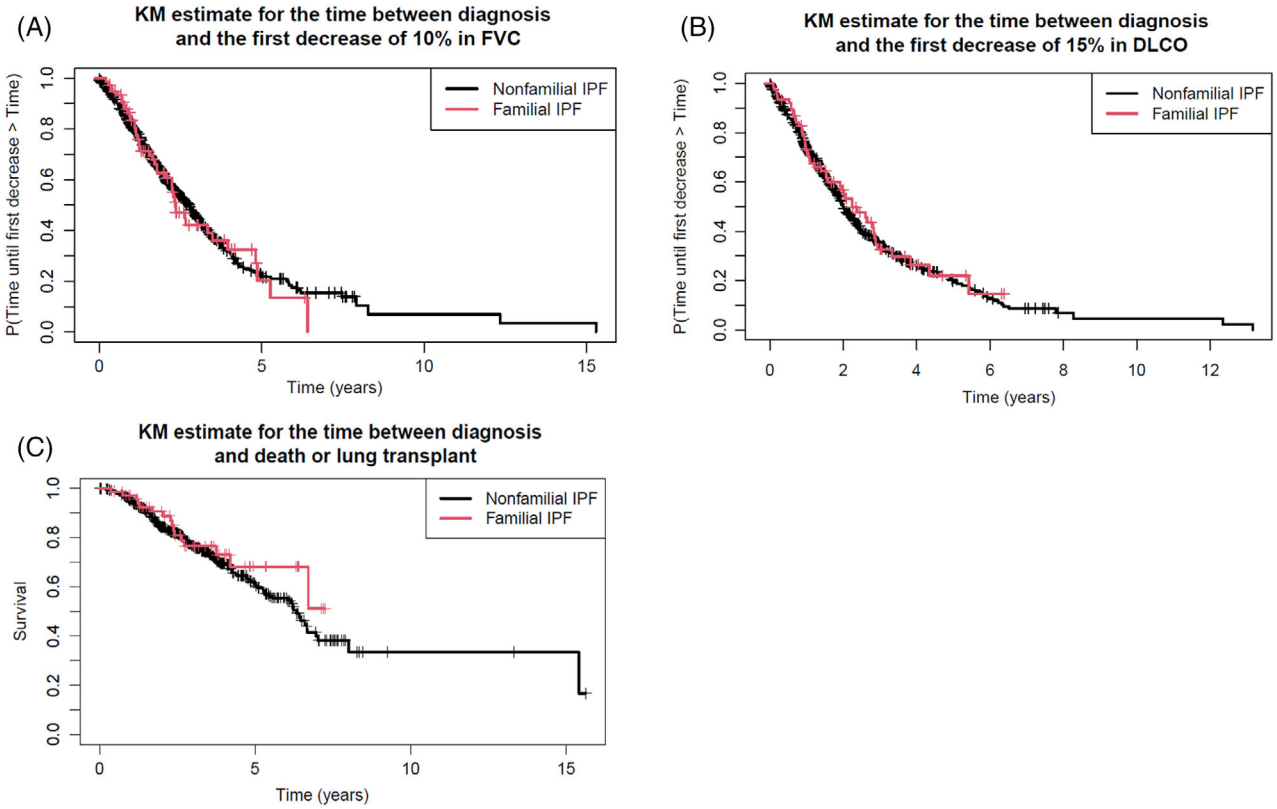


FIGURE 2 Kaplan–Mayer curves for forced vital capacity decline (1A), lung diffusion decline (1B) and transplant-free survival (1C).

The Cox models did not show significant differences between suspected familial and sporadic IPF with regards to time to 10% decline in FVC or time to death or lung transplant when adjusting for age, smoking status, BMI, emphysema (and baseline FVC in the model for FVC decline).

Genetic testing among FPF population

We retrospectively collected available data on genetic testing of our FPF populations (Figure 4). Tests were performed in 33 patients (43%) and led to the identification of 10 telomere-related gene variants affecting TERT (reverse transcriptase of telomerase, $N = 5$); PARN (poly(A)-specific ribonuclease, $N = 3$) and RTEL1 (regulator of telomere elongation helicase 1, $N = 2$). Three FPF patients were heterozygous carriers of the *rs35705950* variant of MUC5B promoter. Of note, three patients (2 TERT and 1 RTEL1) had extrapulmonary signs potentially associated with telomere syndrome at baseline (thrombopenia $N = 2$, elevated liver enzymes $N = 1$).

DISCUSSION

With this study, we provide real-life data comparing clinical and functional characteristics of patients with either sporadic or familial IPF, according to the currently accepted definition. To the best of our knowledge, the PROOF-Next registry is one of the largest studies allowing a prospective comparison of sporadic IPF and FPF.

Twelve percent of our patients met criteria for FPF. This proportion is somewhat in line with previous findings: Hodgson and colleagues were the first to estimate the proportion of familial IPF in the Finnish population at a nationwide scale and determined that 3.7% of IPF patients had a familial history of IPF.[10] Recently, Terwiel and colleagues, from the Netherlands, reported a 20% proportion of familial IPF among their IPF population.[11] The difference between those two studies could relate to (1): different populations, (2) methodological aspects (i.e., underreporting of cases in the Finnish study and the use of different definitions). The high prevalence of FPF in the study by Terwiel could also result from a selection bias as the study took place in an expert centre in familial interstitial lung diseases. Finally, an American study published in 2020 showed that 25% of IPF patients reported a familial history of pulmonary fibrosis in at least one first or second-degree relative and that self-reported familial IPF was associated with worse outcome.[12] Altogether, considering these methodological differences, we feel that our study provides a reliable estimate of the prevalence of familial fibrosis among IPF patients.

Of note, we also confirmed that IPF, even in a familial context, mostly affects elderly, as only 1% of our patients were younger than 50. Our FPF patients were younger, significantly less exposed to tobacco and significantly more treated with antifibrotics as compared to IPF patients. Sex

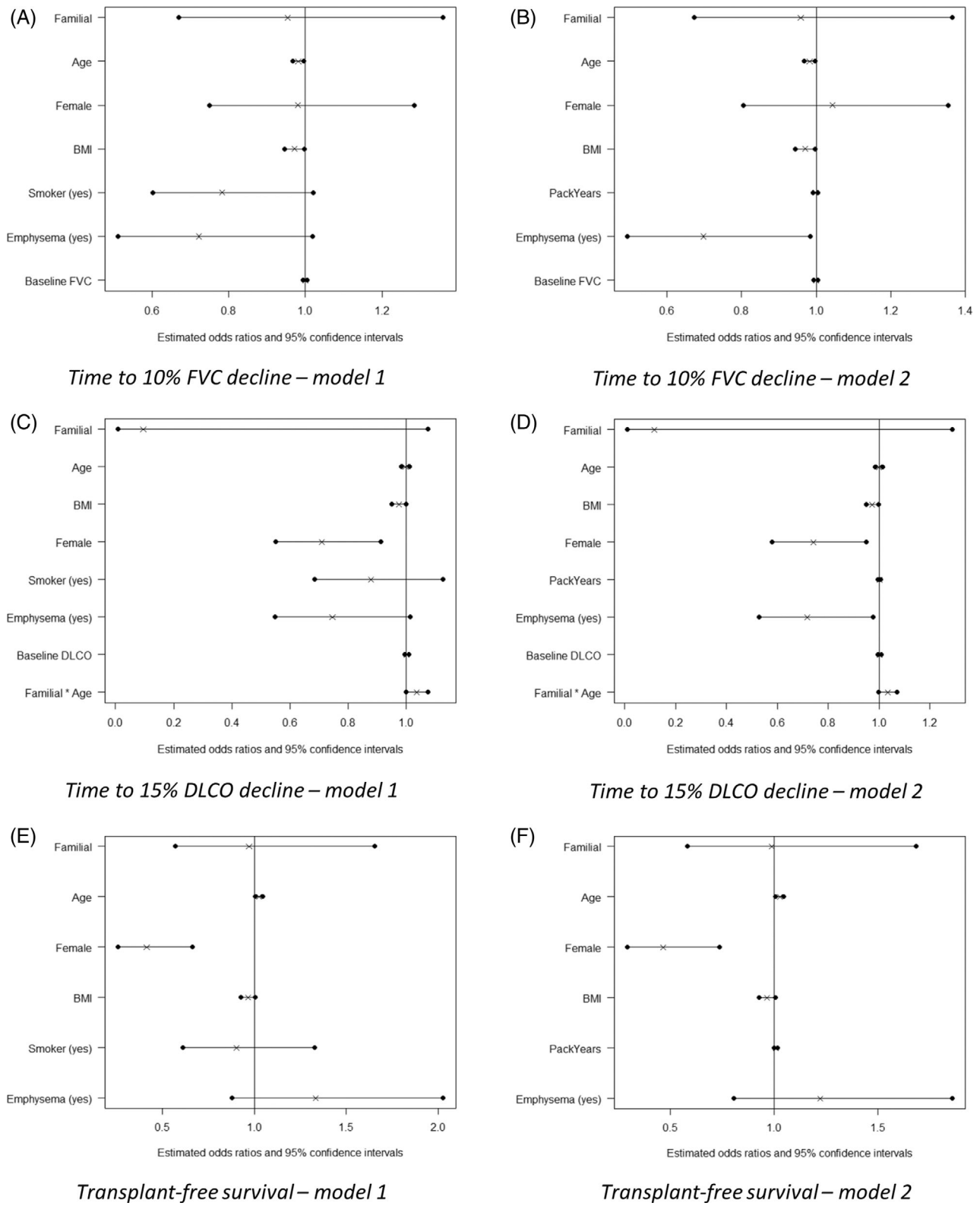


FIGURE 3 Cox models for time to 10% forced vital capacity decline, 15% DLCO decline and time to death or lung transplantation. Panels A, C and E represent the influence of control variables including smoking expressed in pack-years (model 1). Panels B, D and F represent the influence of control variables including smoking as a dichotomist variable (model 2).

ratio was similar in both groups. An Italian study described a higher proportion of women in FPF as compared to sporadic IPF, but the sample size was relatively small (19 FPF and 53 IPF).[13] In our study, the proportion of patients treated with an antifibrotic was higher in FPF than in IPF group (87% vs. 76%). This likely reflects the propensity of

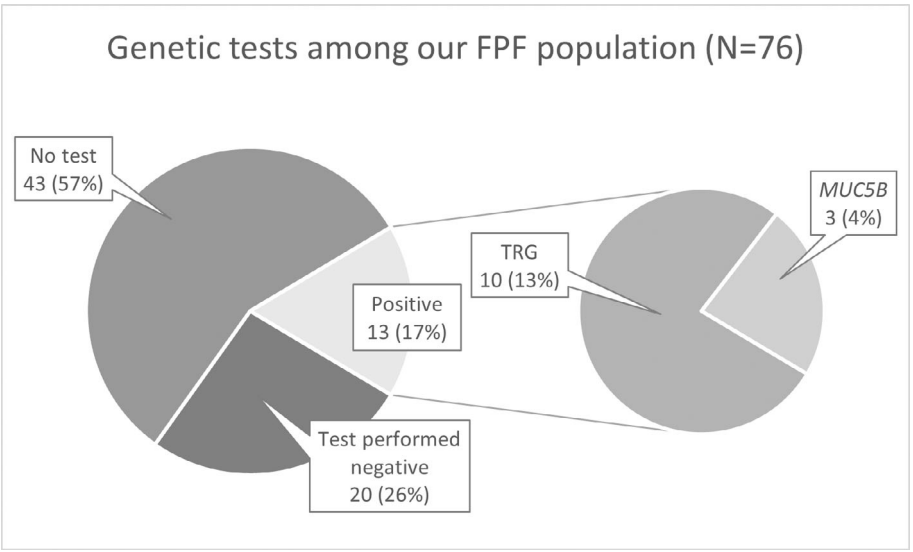


FIGURE 4 Overview of genetic testing within our FPF cohort. FPF, familial pulmonary fibrosis; MUC5B, mucine 5B; TRG, telomere-related genes.

caregivers to treat younger patients more precociously. Several studies evaluated the effect of antifibrotics in FPF: Justet et al., in a multicentric study, demonstrated the safety and efficacy of pirfenidone and nintedanib in FPF patients with a telomerase-related gene mutation.[14,15] Lung function decline was similar between patients treated with pirfenidone and nintedanib.

The burden of smoking, expressed in pack-years, was lower in FPF as compared to IPF, likely reflecting the younger age of FPF patients.

As illustrated by our survival curve, despite being younger, less exposed to tobacco and more frequently treated with antifibrotics, FPF patients had a similar survival and lung function decline as compared to sporadic IPF. These results are unexpected, as most studies reported a worse prognosis of patients with familial fibrosis: Cameli et al. compared the effectiveness of nintedanib in IPF, FPF, and progressive and fibrosing ILD (PF-ILD). They showed that patients with FPF had a worse lung function decline despite treatment.[16] However, this was a retrospective study on a relatively small number of patients. Furthermore, as stated above, a greater proportion of FPF patients in our cohort received antifibrotics. Another difference is the fact that our study only included patients fulfilling international criteria for IPF, meaning that patients with FPF displaying another pattern (i.e., pleuroparenchymal fibroelastosis, fibrotic NSIP or fibrotic hypersensitivity pneumonitis) were not included. Of note, Newton and colleagues showed in 2016 that discordant interstitial lung disease diagnoses did not influence the rate of progression in patients affected with telomere-related gene mutations.[17]

Finally, we show that genetic testing was only performed in a minority (43%) of FPF patients. This may be due to (1) lower awareness on FPF in the first years of the registry, (2) differences in access to genetic testing and (3) the absence of statements from scientific societies on genetic testing until 2023. We hope that the recently published statements by the *European Respiratory Society*[5] and the *Pulmonary Fibrosis Foundation Genetic Testing Work Group* will lead to an increased rate of genetic tests among FPF patients.[18]

Our study has some limitations: first, we only included patients with a clinical diagnosis of IPF, excluding de facto other patterns of FPF. Second, we did not prospectively collect DNA samples from patients, so we were only able to retrospectively collect genetic data from participating centres. Similarly, we do not have any information on telomere length and lack clinical information on telomere-related clinical features like bone marrow failure, early hair greying or liver failure.

Altogether, our study shows that sporadic IPF and FPF have a similar prognosis, although FPF patients are younger, more frequently treated with antifibrotics and less exposed to smoking. Our findings highlight the need for early referral of those patients to specialized centres to provide optimal management.

AUTHOR CONTRIBUTIONS

Antoine Froidure: Conceptualization (lead); formal analysis (equal); investigation (equal); project administration (equal); validation (equal); writing – original draft (lead); writing – review and editing (equal). **Benjamin Bondue:** Investigation (equal); validation (equal); writing – review and editing (equal). **Caroline Dahlqvist:** Investigation (equal); validation (equal); writing – review and editing (equal). **Julien Guiot:** Investigation (equal); validation (equal); writing – review and editing (equal). **Natacha Gusbin:** Investigation (equal); validation (equal); writing – review and editing (equal). **Gil Wirtz:** Conceptualization (supporting); investigation (equal); validation (supporting); writing – original draft (supporting); writing – review and editing (equal). **Guy Brusselle:** Investigation (equal); validation (equal); writing – review and editing (equal). **Danielle Strens:** Project administration (equal);

validation (equal); writing – review and editing (equal). **Hans Slabbynck:** Investigation (equal); project administration (equal); validation (equal); writing – review and editing (equal). **Wim A. Wuyts:** Investigation (equal); project administration (equal); validation (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

Antoine Froidure reports speaker and consultancy fees from Roche, Boehringer Ingelheim and GlaxoSmithKline and unrestricted research grants from Roche and Boehringer Ingelheim, outside the submitted work. Benjamin Bondue reports speaker and consultancy fees from Roche, Boehringer Ingelheim and unrestricted research grants from Roche and Boehringer Ingelheim, outside the submitted work. Caroline Dahlqvist reports speaker and consultancy fees from Roche, Boehringer Ingelheim and unrestricted research grants from Roche and Boehringer Ingelheim, outside the submitted work. Guy Brusselle reports speaker fees and advisory board fees from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, MSD, Novartis and Sanofi. Hans Slabbynck reports speaker and consultancy fees from Roche and Boehringer Ingelheim outside the submitted work. Wim A. Wuyts reports travel and research grants from Boehringer-Ingelheim, Roche, Galapagos, FWO flanders and NIH.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

HUMAN ETHICS APPROVAL DECLARATION

Central and local review boards of participating centres approved the study the PROOF-Next registry. All patients provided informed consent prior to inclusion.

Clinical trial registration: NCT03732859 at https://ichgcp.net/clinical-trials-registry

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