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The management of Familial Pulmonary Fibrosis in different medical settings: Where does that leave us? An Italian nationwide survey

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Abstract. *Background and aim:* Familial Pulmonary Fibrosis (FPF) is an emerging group of interstitial lung diseases (ILDs) caused by mutations mainly involving telomere-related genes (TRGs) and surfactant-related genes (SRGs). Although, in 2023, the European Respiratory Society (ERS) proposed a statement for FPF management, these still remain a burden. Our work aimed to evaluate the management and impact of FPF in three different Italian medical settings: university hospitals (UHs), non-university hospitals (n-UHs) and outpatient clinics. *Methods:* This survey was created by diffuse ILDs Study Group of Società Italiana di Pneumologia/ Italian Respiratory Society (SIP-IRS) and diffused via email to all SIP-IRS members. The descriptive statistical analysis was conducted through version 8.0 © 2023 GraphPad Software. Categorical variables were expressed as frequencies and percentages. Chi-square test was used to compare categorical variables. A p-value < 0.05 was regarded as significant. *Results:* Twenty participants replied to the survey, of which 65% (13/20) worked at UH while the remaining 25% (6/20) and 5% (1/20) worked at n-UH and outpatient clinics, respectively. Centers with, at least, 150 ILD patients visits/year followed a higher number of FPF patients, regardless of university affiliation (p=0.0046). Despite significant discrepancies in genetic testing and availability of counselling were registered, no statistically significant differences in patients' anamnesis assessment were observed between UHs and n-UHs (p=0.4192 and p=0.6525). However, there were relevant differences in the number of FPF patients undergoing genetic assessment in the centers with genetics lab or unit inside the hospital (p=0.0253). There was no consensus regarding the impact of FPF diagnosis on lung transplantation and screening of asymptomatic relatives. Similarly, no differences were reported in antifibrotic prescriptions between UHs and n-UHs. Although the typical UIP pattern was the most common radiological pattern observed in FPF patients, there were no differences in the prevalence of histopathological patterns between UHs and n-UHs. *Conclusions*: Improving pulmonologists' knowledge of the approach, diagnosis and management of FPF is a global medical topic. Scientific societies can provide significant support in raising physicians' awareness of this issue.

Key words: familial pulmonary fibrosis, interstitial lung diseases, genetic mutations, medical settings

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Introduction

The term pulmonary fibrosis embeds a growing and intriguing spectrum of chronic lung diseases characterized by a fibrotic overthrow of lung interstitium leading to a progressive respiratory failure

until the exitus. The cluster of pulmonary fibrosis encompasses several forms of the heterogeneous group of diseases known as interstitial lung diseases (ILDs) (1,2). Idiopathic pulmonary fibrosis (IPF) is the landmark of fibrotic ILDs whose 5-years prognosis remains poor without antifibrotic therapy (3). Although the knowledge in IPF pathogenesis has been increasing, the interaction between environmental factors and genetic predisposition represents one of the most reliable hypotheses responsible for triggering the pathogenetic process of pulmonary fibrosis (4,5). While many forms of fibrotic lung diseases have an unknown etiology, the emerging group of familial pulmonary fibrosis (FPF) has been gaining interest globally. FPF are defined as a subcategory of ILDs which are determined by several gene mutations or variants, that are predominantly, but not exclusively, involved in the control of telomeres length and surfactant metabolism, both alternatively known as telomere-related genes (TRGs) and surfactant-related genes (SRGs). The suspicion of FPF is based on the presence of several different findings involving different organs and districts. The presence of pulmonary fibrosis along with, at least, one between hepatic and haematological abnormalities, early grey syndrome and congenital dyskeratosis as well as lung-brain-thyroid alterations may be strongly suggestive of FPF as well as the evidence of fibrotic ILD in one or more blood relatives. Accordingly, with the growing interest and knowledge on this field, recently the European Respiratory Society (ERS) has proposed a statement assessing some specific questions on the management of FPF, including the clinical suspect, diagnostic pathway and therapeutic evidences (6).

However, the ERS paper was not designed as a clinical guideline but aimed to critically review the available evidence in literature on this topic, in order to establish the value of diagnostic tests, prognostic estimation and therapeutic effectiveness and propose a sort of "standard-of-care" for suspected and/or ascertained FPF patients.

On this field, the present survey, proposed and diffused by the Società Italiana di Pneumologia/ Italian Respiratory Society (SIP-IRS), aims to assess the management and impact of FPF in different medical settings in Italy, including university hospitals (UHs), non-university hospitals (n-UHs) and outpatient clinics, as perceived by different physicians' profiles and to compare the actual clinical practice with the statements endorsed by the ERS.

Materials and methods

Survey creation

This survey was proposed and diffused by the SIP-IRS and realized by ILD study group members in January 2023.

Survey diffusion and instructions

The survey was launched by SIP-IRS in February 2023 and remained active until June of the same year. It was disseminated to all medical doctors associated with the SIP-IRS, including the SIP-IRS study group of diffuse ILDs, via society's newsletter. Additionally, the survey was accessible on the SIP-IRS website and regular reminders were issued, via e-mail, to encourage completion, according to the weekly newsletter of society. Consent to completing the questionnaire was expressly requested before starting the online procedure.

Data collection and analysis

The submitted answers were registered through an online format and were checked for duplication. The questionnaire could be completed using any electronic or portable device such as personal computers, iPhones, or any other device equipped with internet connectivity. Collected data was subsequently included in an electronic database guaranteeing the anonymity of every participant; descriptive statistical analysis was conducted through version 8.0 © 2023 GraphPad Software. Categorical variables were expressed as frequencies and percentages. The chi-square test was employed to investigate and identify differences between categorical variables. A p-value <0.05 was considered statistically significant.

Main topics

The survey focused on the following topics through specific closed-ended questions:

1. The number of patients with ILD and FPF followed in a definite center
2. The acquisition of the patient's personal medical history and the assessment of familial relationships.
3. The availability of a laboratory in that center and the possibility of providing a genetical

examination for checking genetic variants or mutations.
4. The number of patients who underwent genetic testing for mutations or variants at that center.
5. The presence of factors that may influence the likelihood of requiring a genetic testing.
6. The number of ILDs radiological patterns identified by chest high resolution computed tomography (HRCT).
7. The approximate number of patients, affected by FPF, who received antifibrotic therapies.
8. If FPF diagnosis can influence the possibility of performing lung transplantation (LTX).
9. The types of screening examination provided to the relatives of patients affected by FPF.
10. The timing of asymptomatic relatives periodical monitoring if screening examination tested negative.
11. The recommended age for initial chest HRCT radiological evaluation in asymptomatic patients with well-preserved lung function.

The participants had the possibility to provide free-text answers or suggestions for any of the questions. The entire questionnaire and the associated answers are reported in Table 1.

Results

Characteristics of participants

Twenty medical doctors, members of the SIP-IRS, representing 20 possible clinics, replied to the survey. The answers submitted by each participant were checked to ensure the anonymity of each participant, in accordance with standards relating to privacy and data protection. A total of 9 males (45%) and 11 females (55%) participated in the study. Of male participants, 22.2% (2/9) were aged both < 35 years-old (y/o) and among 35-45 y/o, while the most and the less representative groups were respectively composed by respondents who were over 60 y/o 44.4% (4/9) and among 45-60 y/o 11.1% (1/11). On the other hand, although the two main groups were both represented by 36.3% (4/11) female participants, aged under 35 y/o and among 45-60 y/o respectively, nevertheless the women aged from 45 to 60 y/o 18.1% (2/11) and over 60 y/o 9% (1/11) were poorly reported. Overall, there was no statistical difference in terms of sex prevalence among the age subgroups (p=0.25).

In the overall population of repliers, 95% (19/20) were either respiratory physicians or currently undergoing residency in pulmonology (16 and 3, respectively), while the remaining 5% (1/20, female) was an immunologist. In addition, pulmonologist doctors were nearly equally represented, in terms of gender, by 53% (10/19) of females and 47% (9/19) of males.

Work setting of participants

The survey participants indicated various work settings: the UH was the predominant work setting, comprising 65% (13/20) of respondents. The remaining participants, forming 25% (6/20) and 10% (2/20), worked at n-UH and outpatient clinics, respectively. Despite this, all participants declared to be qualified to prescribe antifibrotic drugs in ILD patients.

The number of patients with ILDs and FPF followed in a definite center

The survey highlighted how the major number of ILD patients were referred to and treated by UHs rather than n-UHs or other settings. All survey participants, who worked at UHs, referred at least 50 visits/year of patients with fibrotic ILD. In such a scenario, the majority of participants were divided into two main groups, with 30% (6/20) and 25% (5/20) of respondents who provided a number of patients per year from 150 to 250 and > 250. Moreover, a smaller group of participants, 10% (2/20), reported referrals of 50 to 150 patients per year. Of the survey contributors, who worked in n-UH and outpatient clinics, the latter 35% (7/20) reported a maximum of 150 patients/year. Notably, this group was made up of 20% (4/20) indicating from 50 to 150 patients, while the others settings 15% (3/20) were characterized by a number of patients fewer than 50 patients/year. Overall, UHs reported a significantly higher number of ILD patients visits/year than n-UH settings (p=0.0027).

As per ILDs, the UHs appeared to follow a higher number of patients, affected by FPF, rather than n-UHs and others settings as referred by participants, even though not reaching the statistical significance (p=0.2). For this question, FPF were defined as the evidence of two or more first or

Table 1. Survey's Questionnaire

Questions	Answers (n=20)	%
Q1: How many patients, affected by ILDs, does in ILD center see every year?		
> 250	6	30%
150-250	5	25%
50-150	6	30%
>50	3	15%
Q2: Was the patient's personal anamnesis included in the standard pathway for ILD? If yes, up to which degree of kinship?		
Yes, up to the first degree of kinship	6	30%
Yes, up to the second degree of kinship	10	50%
No	1	5%
Yes, but only if suspicion criteria (age < 60 y/o, early grey syndrome, haematological alterations, congenital dyskeratosis, liver alterations) were present	3	15%
Q3: What is the approximate number of patients that are visited annually at your ILD center, according to the FPF definition?		
< 10	9	45%
10-50	10	50%
50-100	1	5%
> 100	0	0
Q4: Does your ILD center have a genetic laboratory? If so, is the laboratory capable of conducting genetic diagnostic tests for patients with FPF?		
Yes, but FPF genetic tests were not available	7	35%
Yes, and it performed FPF genetic tests	3	15%
No, it was absent	10	50%
Q5: What percentage of patients with FPF underwent genetic testing at your center?		
< 20%	16	80%
20-50%	1	5%
50-75%	1	5%
>75%	2	10%
Q6: Which of the following criteria influence your decision to request a genetic evaluation in a patient with ILD?		
Diagnosis of FPF defined as the presence of at least two first- or second-degree relatives affected by ILDs, age < 50 y/o, early grey syndrome, haematological alterations, congenital dyskeratosis, liver alterations, never smoker	18	90%
Age < 50 y/o	2	10%
Q7: Radiological pattern of FPF	**Mean ± SD**	
UIP definite	32.9 ± 25.5	
Probable UIP	26.5 ± 11.6	
Indeterminate for UIP	26.8 ± 17.9	
Other diagnosis	13.5 ± 15.6	
Q8: Histopathologic pattern of FPF	**Mean ± SD**	
UIP definite	41.45 ± 28.16	
Probable UIP	28.75 ± 12.30	
Indeterminate for UIP	18.95 ± 17.22	
Other diagnosis	11.75 ± 16.46	

Questions	Answers (n=20)	%
Q9: Which is the approximative percentage of patients, affected by FPF, who has received antifibrotic treatment?		
< 10%	4	20%
10-50%	3	15%
50-75%	7	35%
> 75%	6	30%
Q10: Does FPF diagnosis affect the decision to list a patient for lung transplantation?		
Yes, it does	11	55%
No, it does not	9	45%
Q11: Screening assessment of asymptomatic relatives of FPF patients		
Physical examination, spirometry and DLCO	20	100%
Physical examination, spirometry, DLCO and 6MWT	11	55%
Physical examination, spirometry, DLCO and 6MWT, liver and full blood count assessment	10	50%
Physical examination, spirometry, DLCO and 6MWT, liver and full blood count assessment, genetic counseling	4	20%
Q12: Monitoring of asymptomatic relatives of FPF patients		
Never	1	5%
6 months follow-up	2	10%
1-year follow-up	12	60%
2-year follow-up	5	25%
Q13: When do you recommend a chest HRCT in asymptomatic relatives with a well-preserved lung function?		
> 30 y/o	3	15%
> 40 y/o	10	50%
> 50 y/o	6	30%
> 60 y/o	1	5%

Abbreviations: ILDs, interstitial lung diseases; FPF, familial pulmonary fibrosis; UIP, usual interstitial pneumonia; SD, standard deviation; DLCO, diffusing capacity of the lung for monoxide carbon; 6MWT, 6 minute-walk-test; HRCT, high resolution computed tomography.

second-degree family members affected by a fibrotic ILD, as stated by the ERS statement (5). The 40% of responders (8/20), working at UH, declared to visit from 10 to 50 patients/year. At the same time, both the remaining 25% (4/20) and 5% (1/20) referred < 10 and among 50-100 subjects per year.

The findings from participants at n-UH revealed that 25% (4/20) of them responded with a number <10 patients as most frequent answer, while another 5% (1/20) stated that they followed 10-50 patients. In addition, 5% (1/20) of respondents from outpatient clinics reported a relevant number of patients between 10 and 50. This differs from the other 5% (1/20) who indicated less than 10 patients. However, centers with at least 150 ILD patients visits/year reported a higher number of FPF patients followed, regardless the affiliation with the university (p=0.0046). (Figure 1).

Assessment of patients' personal anamnesis

The assessment of the patient's family history was a crucial topic in this survey. Overall, only one participant (5%) reported that the assessment of family history for ILD is not a standard question of the medical evaluation of ILD patients. Three participants (15%) declared that family history is investigated only in case of clinical features suspected for FPF (such as age < 60 y/o, haematological or hepatological alteration at lab tests, early grey syndrome or congenital dyskeratosis), while in all the other centers (80%), all ILD patients are systematically asked about the presence of ILD in their family.

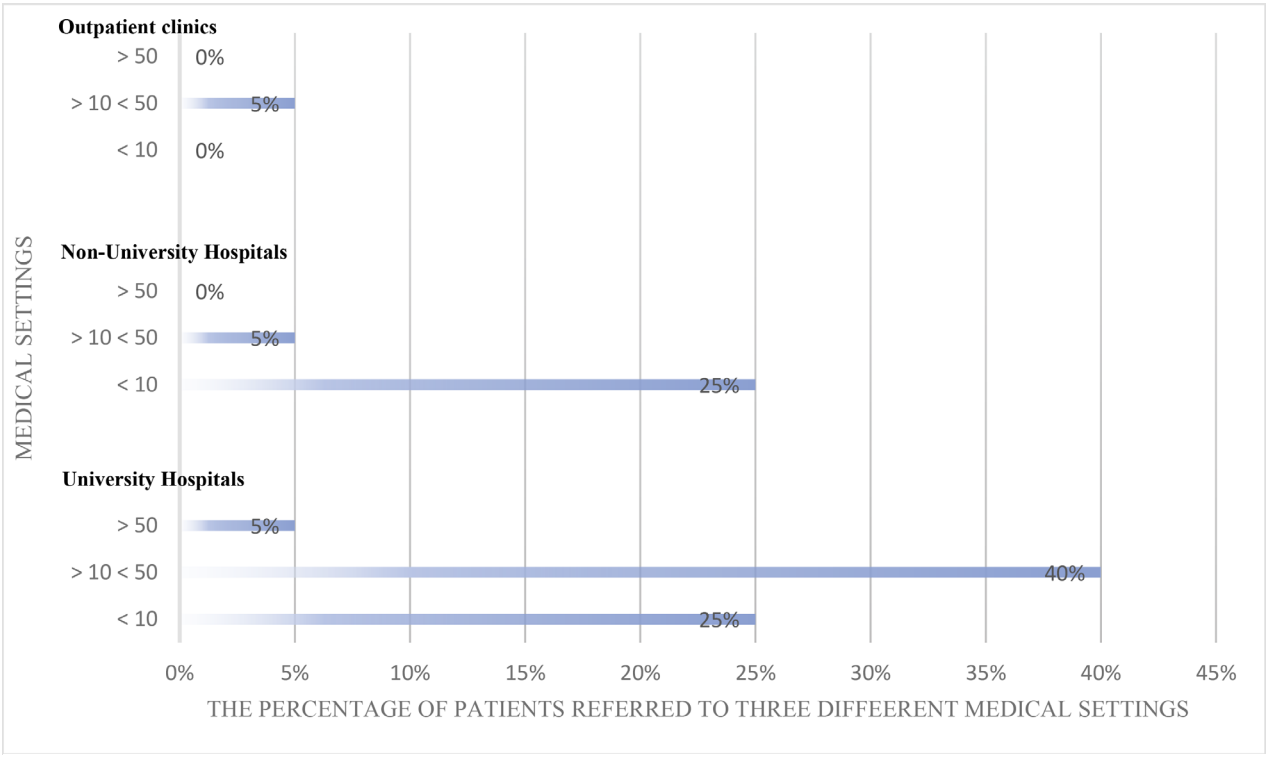

Figure 1. Distribution of the FPF patients: the figure shows the distribution of patients, affected by FPF, referred to three different medical settings: UH, n-UH, and outpatient clinic.
Abbreviations: UHs, university hospital; n-UHs, non-university hospital.

A higher heterogeneity was observed concerning the degree of relatives investigated during the medical visits: the majority of centers (12/19, 63%) performed the inquiry until, at least, the second degree of kinship, while the remnant 7 (37%) investigated only the first degree. We didn't observe any differences between UH and n-UH settings and/or high (> 150) or low amount of patients visits/year on this parameter (p=0.4192 and p=0.6525, respectively).

Availability of genetic assessment and counselling

The genetic assessment plays a pivotal role in the diagnosis of FPF in presence of a high suspicion of disease. There was a significant variability in the answers of survey participants. Only 15% (3/20) of respondents, all working at UH, reported that a genetics lab, certified for genetic sequencing in ILD patients, is available in their settings. In contrast, 40% of participants (8/20) declared that they do not have the possibility to refer suspected FPF patients for a targeted genetic assessment even though a genetics lab or ambulatory is present in their hospital. This may be determined by the inability of genetic laboratories to sequence and analyze certain genetic mutations associated with rare diseases, encompassing TRGs and SRGs mutations. The latest part of participants (9/20, 45%) reported that a genetics lab or unit is not available in their setting and acknowledged the inability to conduct genetic evaluations. Likewise, the lack of a laboratory was similarly reported by 15% (3/20) and 10% (2/20) of participants, who worked at hospitals not affiliated with a university, as well as at outpatient clinics.

More discrepancies were observed regarding the prescription and availability of genetic counselling in FPF patients: the majority of the centers (16/20, 80%) showed that less than 20% of FPF patients underwent a genetic visit, even though 6 among them declared the availability of genetics lab/unit in their hospital. The remaining four participants reported that more than 75% of FPF patients have performed genetic counselling throughout the follow-up, while the remaining two acknowledged a percentage between 50% and 75%. Stratifying the cohort of participants according to the accessibility to genetics,

we observed a significantly higher percentage of FPF patients undergoing genetic counselling or sequencing in the centers with genetics lab or unit inside the hospital (p=0.0253).

Criteria for FPF genetic testing

In this category, the obtained answers were rather homogeneous and in accordance with ERS statement on FPF (5). The 90% (18/20) of respondents confirmed that the major suspicion of FPF was related to the presence of definite criteria such as: diagnosis of FPF defined as the presence of at least 2 patients with ILD with first- or second-degree relatives, number of family members with ILDs, age of onset < 50 y/o, haematological alterations, early grey syndrome, impairment of liver function and the presence of congenital dyskeratosis. Conversely, the remaining 10% (2/10) reported that the presence of age of onset < 50 y/o and one or more family members affected by ILD were enough for asking a genetic evaluation.

Radiological and histopathological pattern of FPF

Concerning the radiological assessment of ILDs, through chest HRCT, a typical usual interstitial pneumonia (UIP) pattern was reported in 32.9 ± 25.5 of FPF patients, resulting the most common phenotype, followed by the indeterminate for UIP (26.8 ± 17.9), probable UIP (26.5 ± 11.6) and not-UIP pattern (13.5 ± 15.6). (Figure 2) Radiological UIP pattern appeared to be more commonly reported in university setting (p<0.05) while no differences were observed between centers with more or less than 150 ILD patients' visits per year. This could be mainly explained by the high expertise in ILDs of radiologists working in UHs even in the presence of a relatively low number of ILD patients. Despite the lack of centralized evaluation of chest HRCT images and tissue samples from patients with ILD, the availability of ILD multidisciplinary meeting (MDM), a team consisting of radiologists, pulmonologists, rheumatologists and pathologists provides an accurate diagnosis and increases the detection rate of ILD radiological and histopathological patterns. The histopathological assessment, whenever available, substantially confirmed the typical UIP as the most common pattern observed in FPF patients, while the occurrence of indeterminate and alternative UIP patterns was found to be less common at chest HRCT analysis, even though not significantly. No differences were observed in terms of prevalence of histopathological pattern between UHs and n-UHs

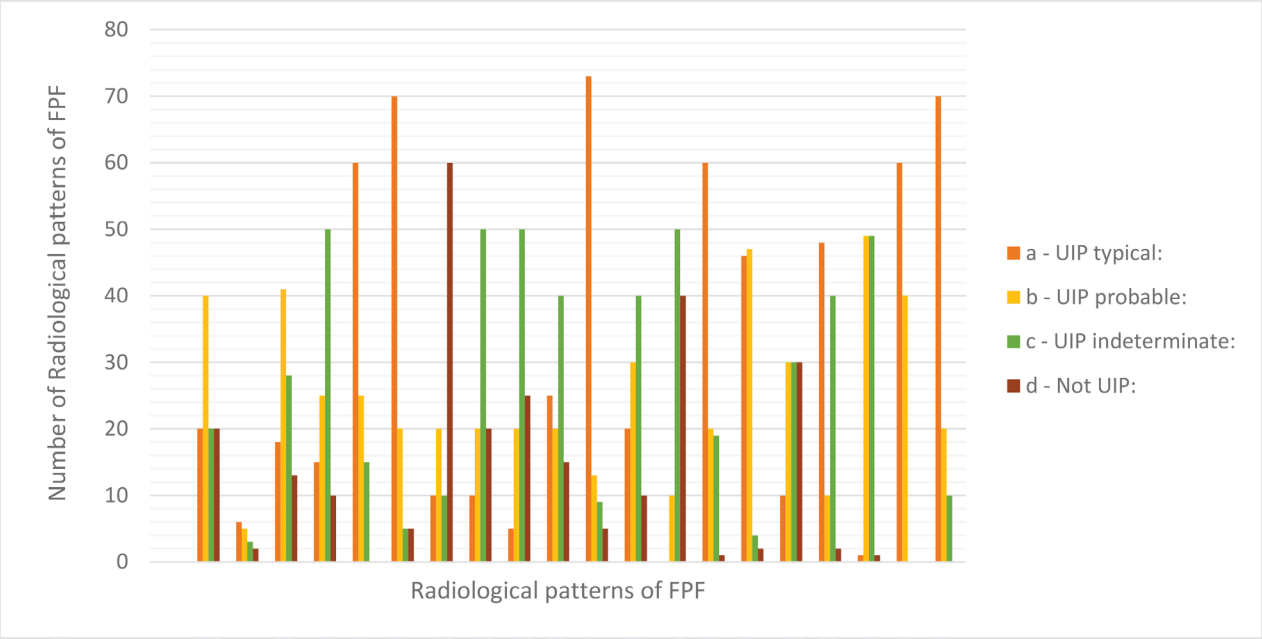

Figure 2. Distribution of FPF radiological patterns: The graph illustrates the total number of FPF radiological patterns detected through chest HRCT scans conducted in three distinct medical settings: UH, n-UH, and outpatient clinic.

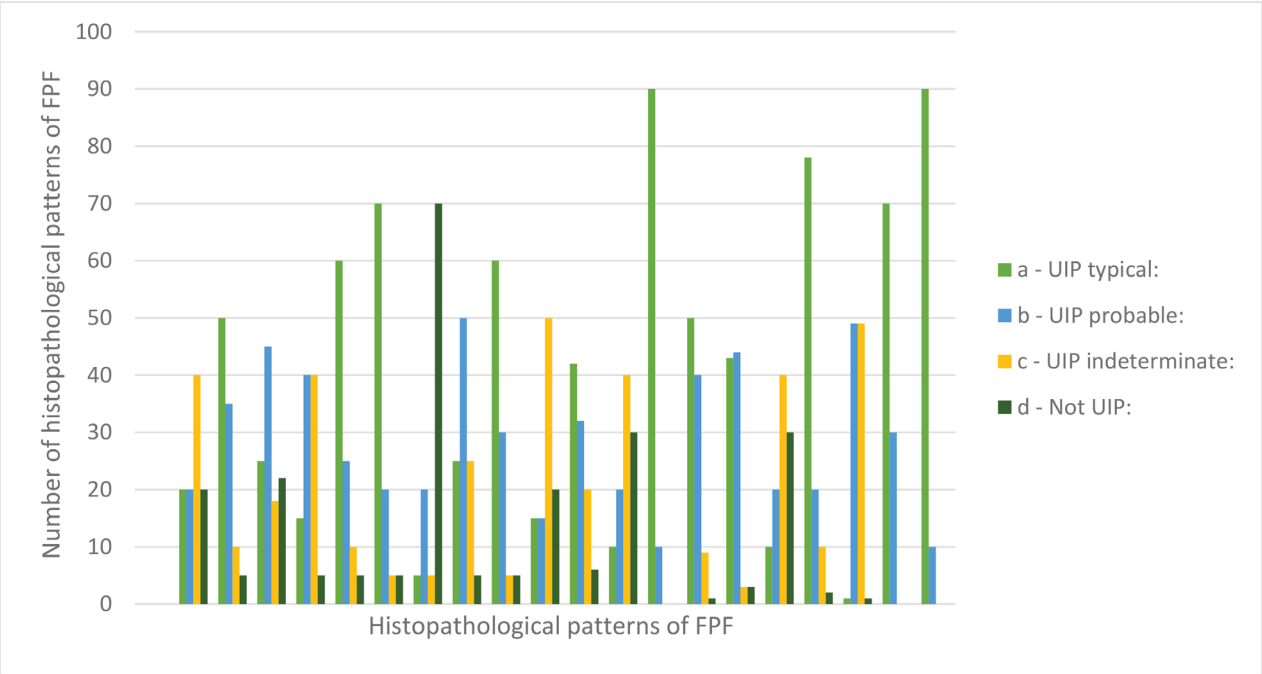

Figure 3. Distribution of FPF histopathological patterns: the graph shows the total number of FPF histopathological patterns identified in the three different medical settings: UHs, n-UHs, and outpatient clinics.

or between centers with more or less than 150 ILD patients' visits per year. (Figure 3)

Antifibrotic treatment in FPF patients

An approximate number of patients, who has received antifibrotic treatment, was also assessed among the respondents. The first aim of this research was to understand the availability of antifibrotic prescriptions for FPF patients in different centers. Thirteen centers (65%) referred a percentage of FPF patients treated with antifibrotic therapy superior to 50% (7/20 among 50-75% and 6/20 >75%). Three participants (15%) reported having between 10 and 50% of FPF patients under treatment, while in the remaining professionals declared that less of 10% of FPF patients in their center are or have been treated with antifibrotics. No differences were observed in terms of antifibrotic prescriptions between UHs and n-UHs or between centers with more or less 150 ILD visits/year.

FPF diagnosis in lung transplantation

To date, lung transplantation remains an important option for patients with progressive lung diseases such as ILDs and fibrotic lung disease. The authors also investigated whether a diagnosis of FPF could influence the eligibility of the patient for LTX. In response to this question, there was not a remarkable consensus regarding this issue. Fifty-five percent (11/20) of respondents agreed that FPF diagnosis could significantly influence the referral for LTX, while the remaining 45% (9/20) believed that FPF diagnosis should not have any impact on this issue.

Screening assessment of asymptomatic relatives of FPF patients

Screening assessment has a pivotal role in the management of the patients with FPF and their at-risk asymptomatic relatives. Overall, on this topic, we did not observe any significant differences of results between UHs and n-UHs or between centers declaring more or less than 150 patients/year at ILD clinic. There was a unanimous global consensus (20/20) on performing physical examination, along with spirometry and diffusing capacity of the lung for monoxide carbon (DLCO) tests to assess lung function to first- and second-degree blood relatives of FPF patients as first-line screening tool. Additionally, 55% (11/20) of repliers suggest including in the basal clinical assessment also an exertional respiratory function test such as 6-minute-walk-test (6MWT). Fifty percent

(10/20) of respondents added the full blood count and liver function assessment through liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl-transferase (GGT) to previous examinations. Genetic counselling was proposed at screening only by four centers (20%).

The monitoring of asymptomatic relatives with previous negative screening is still a topic, which did not have a universal consensus. In this survey, this point has been examined providing different points of view. The repetition of patients' screening after 1 year resulted the most common answer provided by 60% (12/20) of respondents. Secondly, the other 25% (5/20) supported a 2-year follow up screening examinations. Lastly, the 10% of participants (2/20) supported a stricter follow-up protocol, with medical evaluations and respiratory functional assessments scheduled every 6 months whereas only one professional declared to not repeat the screening analysis after the first had tested negative.

As per biochemical examinations and lung function tests, the radiological assessment in asymptomatic relatives with no biochemical and pulmonary functions alterations has been representing an intriguing issue, which is still under discussion. Concerning imaging, none of the participants voted for chest X-ray as a screening tool. All professionals recommended chest HRCT as the most proper imaging exam to detect the presence of ILD but only half of the participants suggested to prescribe it as a first-line screening exam (10/20). Indeed, some different proposals emerged from this survey also for the timing of chest HRCT. Notably, the half of participants (50%, 10/20) shared an age > 40 y/o as cut-off value for chest HRCT screening, instead the further 35% supported an age > 50 years. Lastly, a chest HRCT screening > 30 or > 60 y/o was only recommended by the 15% (3/20) and 5% (1/20) of respondents, respectively.

Discussion

The existence of familial clusters of ILD has been long established: this epidemiological evidence has subsequently paved the way to the demonstration of many genetic mutations or specific single nucleotide polymorphisms (SNPs) expression associated not only with the susceptibility to develop a lung fibrotic disorder, but also with a higher or lower probability to develop a more aggressive clinical course or to show a different response to the treatment (7). Large recently-published genome-wide association studies have further enlarged the list of mutations or SNPs associated with a higher risk of pulmonary fibrosis. In the field of personalized medicine, next generation sequencing (NGS) techniques able to provide quick and reliable genetic evaluation are expected to be increasingly implemented in the management of ILDs, considering how potential unidentified mutations may significantly impact in the response to treatment or in the safety of specific procedures, such as LTX (8,9). Moreover, the availability of a rapid and affordable genetic assessment could be crucial as a screening tool for asymptomatic and younger relatives of FPF patients, also in an optic of early diagnosis and radiation sparing approach (2).

Standing the recent international statement published by the ERS, whose objective was to define the main milestones for the diagnostic and therapeutic management of FPF patients, the main aim of the present survey was to provide a comprehensive overview of the Italian centers, focusing on those with an established experience in the management and treatment of fibrotic ILDs. In order to detect potential discrepancies or differential approaches, we decided to stratify the responding centers according to their affiliation to university and to their annual amount of ILD patients, as previously reported (6).

As expected, considering the estimated percentage of FPF among the ILD population reported in literature, centers declaring larger ILD cohorts reported a higher number of FPF patients, identified through the epidemiological criteria of at least two first or second-degree blood relatives with ILD (10). This finding may be explained not only by the numerousness of centers' cohorts, but also by a variability in conducting the medical examination of ILD patients. Indeed, although the familial history is collected by almost all the participating centers, a substantial heterogeneity was observed concerning the degrees of kinship usually explored, as 37% of the sample declared to investigate only the first degree. Even though crucial, familial history assessment may be difficult or even misleading, standing that the majority of ILDs are unknown to general population and may also not be diagnosed in the older generations of index case. Still, considering the proposed definition of FPF by the ERS, the development of a standardized approach for familial history collection is pivotal and will need to be implemented in the clinical practice.

Further, a prompt referral to a genetic unit appears to be a crucial point: as expected, UHs reported an easier accessibility to genetic sequencing and counselling and, consequently, a significantly larger percentage of patients with suspected FPF is referred to a specialist assessment for confirmation or identification of the specific genetic mutation. Considering that the clinical or epidemiological criteria to ask for genetic testing were homogeneous for all centers and complied to the ERS statement, to guarantee a prompt, equal and easy access to these services is a critical issue to deal with and to ameliorate in the next years (6).

Concerning the radiological and histopathological features, our results were substantially comparable to literature data: in fact, quite a half of patients were classified as indeterminate or not-UIP pattern, confirming how also not-IPF ILDs may show a familial distribution. Interestingly, our results suggest a good agreement between chest HRCT and lung tissue analysis, despite the relevant percentage of atypical patterns that have been described to impair the concordance between radiological and histopathological assessment (11,12). However, our study was absolutely not focused and powered for this issue.

Overall, the therapeutic management of FPF appeared to reflect the radiological and histopathological features, in line with international guidelines for the treatment of IPF and progressive pulmonary fibrosis (PPF) (12). The percentage of FPF treated with antifibrotics appeared to be quite similar to the prevalence of typical or probable UIP pattern, for which antifibrotic treatment is recommended prior to MDM. However, data on the effectiveness of pirfenidone and nintedanib in FPF setting is few and conflicting: some reports suggest a faster forced vital capacity (FVC) decline rate during antifibrotic treatment in FPF patients in respect with sporadic IPF and PPF as well as a discontinuing treatment with nintedanib in patients affected by IPF (13). Conversely, the only one study inquiring the effectiveness of nintedanib in FPF patients with a specific mutation showed no differences in terms of functional disease progression (14). Even though beyond the scope of this paper, in the landscape of a personalized approach for ILD patients, we believe that the assessment of antifibrotic treatment in subpopulations with specific SNPs or genetic mutations will be crucial for a proper management of these patients.

Concerning the LTX, we observed that a diagnosis of FPF is considered a concern for 55% of the participants: the dichotomization of the results on this specific topic may be related to the evidence that patients, affected by TRGs mutations, are clearly associated to a higher risk of bone marrow failure, osteoporosis, gastrointestinal diseases (i.e. enteropathy, liver cirrhosis), haematological and skin tumors (15). In such a scenario, a number of complications were observed in patients with TRG mutations who had undergone LTX. These included haematological, renal, gastrointestinal and pulmonary complications. The observed complications included thrombocytopenia, anaemia and haemolytic anaemia, neutropenia, myelodysplastic syndrome, bone marrow failure, as well as acute renal failure, gastrointestinal bleeding and pulmonary infections (15,16). Additionally, drug toxicity induced by azathioprine, dapsone and pentamidine was noted (15). Furthermore, this subgroup of FPF patients often shows typical clinical and laboratory alterations (e.g. early grey syndrome) and, therefore, may be quite easier to detect. Moreover, considering that FPF patients are usually younger than sporadic ILD patients, LTX represents a fundamental therapeutic option, especially in non-responder or fast-progressor patients: thus, to consider a diagnosis of FPF as an obstacle or even a contraindication for LTX eligibility may have been judged as ethically unacceptable by some of the participants (17).

Last but not least, also the screening and follow-up protocols for asymptomatic relatives of FPF patients provided some discrepancies in our survey. Despite a 100% agreement in performing pulmonary function tests (PFTs) with DLCO in these subjects as a screening tool, probably due to their non-invasive and repeatable nature, a relevant heterogeneity was observed concerning 6MWT, genetic counselling and chest HRCT (18). Although the 6MWT has been demonstrated to be a useful and reliable test for the assessment of disease status and prognosis in IPF patients, there are currently no data on its use and applicability in asymptomatic relatives of patients affected by FPF (19). Additionally, the necessity for standardized conditions represents a significant limitation to the performance of this test in an outpatient clinic setting (19,20). This data is quite similar to the evidence available in literature and is presumably related to the different penetrance and anticipation among the genetic mutations, as well as the clinical indication to expose asymptomatic subjects to ionizing radiations and/or genetic counselling. Concerning the timing of follow-up, the majority of participants agreed to repeat medical examination and PFTs after 1 year from

the first visit in asymptomatic subjects. These results are in line with the majority of ERS Task Force members, even if there is a significant lack of evidence in this area and regarding follow-up of asymptomatic relatives of FPF patients after 1-2 years and 5 years of systematic screening, respectively. Further data are required to gain a deeper understanding of the course and natural history of the asymptomatic relatives of FPF patients.

Conclusions

In conclusion, to promote the knowledge and the sensitivity of pulmonologists towards the diagnosis and treatment of the emerging group of FPF is a relevant scientific and clinical aim. To diffuse the correct genetic approach to the diagnosis of FPF throughout the National territory also outside the UH is a fundamental scope. The scientific societies of respiratory medicine could make their contribution.

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References

1. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. Drazen JM, editor. N Engl J Med. 2020 Sep 3;383(10):958–68.
2. Zhang D, Newton CA. Familial Pulmonary Fibrosis. Chest. 2021 Nov;160(5):1764–73.
3. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. The Lancet. 2017 May;389(10082):1941–52.
4. Baratella E, Ruaro B, Giudici F, et al. Evaluation of Correlations between Genetic Variants and High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis. Diagnostics. 2021 Apr 23;11(5):762.
5. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. Longo DL, editor. N Engl J Med. 2018 May 10;378(19):1811–23.
6. Borie R, Kannengiesser C, Antoniou K, et al. European Respiratory Society statement on familial pulmonary fibrosis. Eur Respir J. 2023 Mar;61(3):2201383.
7. Oldham JM, Ma SF, Martinez FJ, et al. TOLLIP, MUC5B, and the Response to N -Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2015 Dec 15; 192(12):1475–82.
8. Allen RJ, Stockwell A, Oldham JM, et al. Genome-wide association study across five cohorts identifies five novel loci associated with idiopathic pulmonary fibrosis. Thorax. 2022 Aug;77(8):829–33.
9. Allen RJ, Guillen-Guio B, Oldham JM, et al. Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2020 Mar 1;201(5):564–74.
10. Liu Q, Zhou Y, Cogan JD, et al. The Genetic Landscape of Familial Pulmonary Fibrosis. Am J Respir Crit Care Med. 2023 May 15; 207(10):1345–57.
11. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. The Lancet Respiratory Medicine. 2018 Feb;6(2):138–53.
12. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022 May 1;205(9):e18–47.
13. Ruaro B, Salotti A, Reccardini N, et al. Functional Progression after Dose Suspension or Discontinuation of Nintedanib in Idiopathic Pulmonary Fibrosis: A Real-Life Multicentre Study. Pharmaceuticals. 2024 Jan 17;17(1):119.
14. Cameli P, Alonzi V, d'Alessandro M, et al. The Effectiveness of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis, Familial Pulmonary Fibrosis and Progressive Fibrosing Interstitial Lung Diseases: A Real-World Study. Biomedicines. 2022 Aug 15;10(8):1973.
15. Silhan LL, Shah PD, Chambers DC, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. European Respiratory Journal. 2014 Jul 1;44(1):178–87.
16. Borie R, Kannengiesser C, Hirschi S, et al. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. The Journal of Heart and Lung Transplantation. 2015 Apr;34(4):538–46.
17. Bennett D, Fossi A, Lanzarone N, et al. Lung transplant in patients with familial pulmonary fibrosis. J Bras Pneumol. 2020 Jul 27;46(6):e20200032–e20200032.
18. Bennett D, Mazzei MA, Squitieri NC, et al. Familial pulmonary fibrosis: Clinical and radiological characteristics and progression analysis in different high resolution-CT patterns. Respiratory Medicine. 2017 May;126:75–83.
19. Bois RMD, Weycker D, Albera C, et al. Six-Minute-Walk Test in Idiopathic Pulmonary Fibrosis: Test Validation and Minimal Clinically Important Difference. Am J Respir Crit Care Med. 2011 May 1; 183(9):1231–7.
20. Nathan SD, Du Bois RM, Albera C, et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respiratory Medicine. 2015 Jul;109(7):914–22.