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ORIGINAL ARTICLE

Lung transplant in patients with familial pulmonary fibrosis

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ABSTRACT

Objective: Familial pulmonary fibrosis (FPF) is defined as an idiopathic interstitial lung disease affecting two or more members of the same family; poor outcome with high risk of death and chronic lung allograft dysfunction (CLAD) after lung transplant has been reported in these patients. The present study aimed to compare the short- and long-term outcome of lung transplants in patients with FPF and patients transplanted because of other interstitial lung diseases. **Method:** Clinical pre- and post-transplant data from 83 consecutive patients with pulmonary fibrosis who underwent lung transplant at our centre were collected retrospectively. Patients were divided into those with familial (n=9 FPF group) and those with non-familial pulmonary fibrosis (n=74 controls). **Results:** The FPF group was composed of 4 females and 5 males; 44.5% were ex-smokers. The majority presented their CT scan and pathology evidence of usual interstitial pneumonia. Patients with FPF had significantly lower pre-transplant levels of haemoglobin and haematocrit. No other differences in pre- and post-transplant characteristics were observed concerning controls. The clinical post-operative course was similar in the two groups. No significant difference in one-year CLAD-free survival and overall survival was observed. **Conclusion:** The post-transplant course of patients with FPF was similar to patients with non-familial pulmonary fibrosis, although more patients with FPF had pre-transplant anaemia. Short- and long-term outcome was comparable in both groups. Lung transplant proved to be a valid option for patients with FPF as it was for patients with other types of pulmonary fibrosis.

Keywords: Pulmonary fibrosis; Lung transplantation; Therapeutics.

INTRODUCTION

Lung transplant (LTX) is a justified treatment option for selected patients with end-stage lung disease.[1] Although new treatments and prognostic biomarkers are available, patients with idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF) are still those who obtain the most benefit.[2-7]

Familial pulmonary fibrosis (FPF) is defined as an idiopathic interstitial lung disease affecting two or more members of the same family.[8] Since the first cases described in the 1950s, interest in FPF has increased but there are still uncertainties regarding its definition and classification.[8-12] Its age of onset is earlier than for idiopathic pulmonary fibrosis (IPF) and it can present with different radiology and pathology pictures.[13,14] Several gene variants have been associated with the onset of FPF: variants in genes encoding for the telomerase complex seem to have a major role.[15] In carriers of these variants, FPF may also have extrapulmonary manifestations, including non-specific blood disorders (anaemia and thrombocytopenia), immune alterations (ANA), liver cirrhosis, enteropathies, osteoporosis, increased risk of skin and blood tumours and early grey syndrome.[16] In carriers of variants in genes encoding the telomerase complex, LTX outcome has been reported to be poor with high rates of blood, renal and gastrointestinal complications, and increased risk of death and CLAD.[17-20]

The present study aimed to compare the short- and long-term outcomes of lung transplants in patients with familial pulmonary fibrosis, irrespective of genetic alterations, and patients undergoing LTX because of other interstitial lung diseases, at a single lung transplant centre.

METHODS

In this study, we included patients with pulmonary fibrotic disorders who underwent lung transplant from 2002 to 2019 at Siena University Hospital, Italy (Azienda Ospedaliera Universitaria Senese). Patients were divided into two groups: those with familial pulmonary fibrosis (n=9) (FPF group) and those with non-familial pulmonary

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fibrosis (n=74) (PF or control group). The research was approved by the local ethical committee (Azienda Ospedaliera Universitaria Senese, protocol OSS_REOS n° 12908). All participants gave their written informed consent to the study.

Our definition of FPF was an idiopathic diffuse parenchymal lung disease affecting two or more members of the same primary biological family.[8] The PF group was composed of patients with idiopathic interstitial pnaumonias (IIPs), hypersensitivity pneumonitis, and other forms of pulmonary fibrosis.

We collected pre- and post-operative data retrospectively from the medical records, including baseline respiratory diagnosis, comorbidities, BMI, time on a waiting list, and need for bridging extra-corporeal membrane oxygenation (ECMO) before transplantation.

The intra-operative data concerned the type of transplant (single or bilateral), graft ischemia time, severe intra-operative arterial hypotension, need for blood transfusion, and need for intra-operative ECMO (in cases of poor hemodynamic control and low oxygenation during the operation, veno-arterial ECMO with central cannulation was performed). The post-operative data included invasive ventilation time, need for post-operative ECMO, primary graft dysfunction (PGD) at 72 hours, need for and time of inhaled nitric oxide (NO) therapy, need for tracheostomy, acute cellular rejection (ACR) episodes, duration of intensive care, total in-hospital time and one-year survival after transplant.

In a subgroup of 40 patients with PF and 6 with FPF, we measured the following blood parameters at baseline (before surgery) and post-operatively on days 7, 14, 30, 90, 180 and 365: white blood cell count (WBC), haemoglobin (HB), haematocrit (HCT), mean corpuscle volume (MCV), platelets (PLT), C-reactive protein (CRP) and lactate dehydrogenase (LDH).

All patients received corticosteroid therapy with 125 mg methylprednisolone before graft re-perfusion, followed by 375 mg on day 0 and 1 mg/kg from day 1, with subsequent 20% reductions every 2 days. Induction therapy was included in our protocol as from 2009 but was not administered to all patients, as decided by the surgeon. Therapy was based on basiliximab (20 mg at days 0 and 4) or thymoglobulin (ATG) (1.5 mg/kg/day for 2-5 days). Calcineurin inhibitors were administered between days 3 and 5: tacrolimus (trough level 10–15 ng/ml) or cyclosporine (trough level 250–300 ng/ml). Cyclosporine was used predominantly until 2007; tacrolimus subsequently. Depending on clinical condition, azathioprine 100 mg/day or mycophenolate mofetil 1 gr/day was administered between post-operative days 7 and 10. Since 2007 mycophenolate mofetil has replaced azathioprine in the base regime for all patients.

The statistical analysis was conducted with GraphPad Prism v 6.0 for Macintosh; non-parametric tests were used and differences with $p<0.05$ were considered significant. The difference between the two groups was studied by the Mann-Whitney test, analysis of the variance with the Kruskal-Wallis test, and differences in prevalence on contingency tables with the Fisher or Chi-square test. All data were expressed as mean ± standard deviation, unless otherwise stated. Survival analysis was based on Kaplan-Meyer curves and Cox regression.

RESULTS

From 2002 to 2019, 160 patients underwent lung transplant at our Transplant Centre (63 females, 97 males, age at transplant 51.4 ± 12.2 years old, 88 bilateral transplants, 72 single transplants). Basal diagnoses were: pulmonary fibrosis 52%, CF 19.3%, COPD 20%, other diagnosis 8.7%.

Patients with pulmonary fibrosis (n=83) were included in the present study; 9 had familial pulmonary fibrosis (age 54.1 ± 7.1 years, 4 females) (FPF group), and 74 non-familial pulmonary fibrosis (age 57.2 ± 7.4 years, 17 females) (PF group). Forty-nine of the 74 patients in the PF group were diagnosed with IPF, 7 with connective tissue disease-associated pulmonary fibrosis, 6 with hypersensitivity pneumonitis (HP), 4 with non-specific interstitial pneumonia (NSIP), 2 with post-GVHD (graft-versus-host-disease) pulmonary fibrosis after bone marrow transplant and 6 with unclassifiable pulmonary fibrosis.

The FPF group was composed of 4 females and 5 males; 44.5% were ex-smokers. At pre-transplant chest-high-resolution CT scan (HRCT), 6 patients had a usual interstitial pneumonia (UIP) pattern; two cases also had emphysema, with significant ground-glass pattern in one and mediastinal lymphoadenomegaly in the other. In one patient the UIP pattern was associated with pleuroparenchymal fibroelastosis in the upper lobes (case no. 6). In the remaining 3 cases, the HRCT pattern was compatible with NSIP; one also had paraseptal emphysema.

HRCT pattern corroborated pathology findings in 7/9 FPF patients. In the two discordant cases, HRCT showed an NSIP pattern while pathology revealed a UIP pattern in one, whereas in the other HRCT showed a UIP pattern combined with pulmonary emphysema, while the pathology report indicated alterations compatible with NSIP (Table 1). In one case (patient no. 9) chest HRCT showed mediastinal lymphoadenomegaly associated with UIP pattern, and the pathology report indicated a neoplastic lesion compatible with adenocarcinoma in right upper lobe in a context of dense fibrosis with UIP pattern and right hylar lymph node metastasis. This patient died of lung cancer 314 days after transplant.

In three patients, the pre-transplant evaluation showed mild to moderate anaemia; in two cases macrocytosis was concomitant, while none of the patients showed leukopenia or thrombocytopenia. No patients had liver disease, early grey syndrome, or other alterations compatible with short telomerase syndromes.

No other differences in pre- and post-transplant characteristics were observed between groups. The clinical post-operative course was similar in both groups (Tables 2 and 3).

Patients with FPF underwent bilateral transplants more often than patients with PF (77.7% vs. 30.1%, p=0.0081). Regarding immunosuppressant therapy, patients with FPF more frequently underwent induction therapy (basiliximab or thymoglobulin) and were more frequently treated with tacrolimus instead of cyclosporine, compared to patients with PF (77.7% vs. 36.9%, p=0.02; 88.8% vs. 45.2%, p=0.02, respectively) (Table 3).

Analysis of blood parameters showed that patients with FPF had significantly lower pre-transplant levels of HB and HTC (p=0.03 and p=0.01, respectively). Levels of HB were lower at post-operative day 180 (p=0.05), while levels of HCT were reduced at day 365 (borderline significant p=0.07). At day 180, FPF patients showed higher white blood cell counts (p=0.03) (Table 4). No difference in platelet count between groups was observed during follow-up.

Table 1. Demographic, clinical, HRCT, and pathology findings of FPF patients.

	Sex	Blood group	Age (years)	Smoking (packs/year)	HRCT pattern	Pathology pattern	Comorbidities	Number of relatives with fibrosis
Case 1	F	A-	59	NO	NSIP with micronodules	NSIP	No	4
Case 2	F	AB-	46	NO	NSIP and pulmonary emphysema	NSIP	Osteoporosis	4
Case 3	M	A+	50	20	UIP	UIP	Arterial hypertension, Osteoporosis	3
Case 4	F	A+	48	NO	UIP, intralobular ground glass and paraseptal emphysema	NSIP	Osteoporosis	3
Case 5	F	0+	44	NO	NSIP	UIP	Diabetes, Dyslipidaemia, Osteoporosis	2
Case 6	M	0+	55	20	UIP and pleuroparenchymal fibroelastosis	UIP	Arterial hypertension, Osteoporosis	2
Case 7	M	0+	60	22	UIP and pulmonary emphysema	NSIP	Arterial hypertension	2
Case 8	M	0+	65	30	UIP	UIP	Dyslipidaemia	2
Case 9	M	0+	56	20	UIP and lymph node enlargement	UIP and ADK	No	3

F: female gender; M: male gender; HRCT: high resolution computed tomography; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia; ADK: adenocarcinoma.

Table 2. Pre-operative characteristics of FPF and PF patients.

	FPF	PF	Significance
Number	9	73	
Age (years)	54.14 ± 7.116	57.23 ± 7.439	0.2409
Male sex	5 (55.55%)	56 (76.71%)	0.2243
Smoking history	6 (66.66%)	35 (47.95%)	0.4821
BMI (kg/m2)	23.39 ± 4.167	26.00 ± 4.338	0.0913
Comorbidities			
• Diabetes	1 (11.11%)	30 (41.10%)	0.1429
• Arterial hypertension	3 (33.33%)	42 (57.53%)	0.2871
• Hypercholesterolemia	2 (22.22%)	36 (48.31%)	0.1660
• Osteoporosis	5 (55.55%)	46 (63.01%)	0.7238
• Pre-LTX malignancies	0 (0%)	4 (5.4%)	>0.9999
Time on waiting list (days)	194.2 195.2	221.6 214.7	0.7171
pre-LTX ECMO (bridging)	1 (11.11%)	2 (2.74%)	0.2977

LTX: lung transplantation: FPF: familial pulmonary fibrosis; PF: pulmonary fibrosis; BMI: body mass index; ECMO: extracorporeal membrane oxygenation.

Table 3. Post-operative data of FPF and PF patients.

	FPF	PF	Significance
LTX procedure			
• Single LTX	2 (22.22%)	51 (69.86%)	0.0081*
• Bilateral LTX	7 (77.77%)	22 (30.14%)	
Ischemia Time			
• 1st Lung (minutes)	246.8±52.69	270.7± 111.9	0.5548
• 2nd Lung (for bilateral LTX) (minutes)	374.9±85.43	437.3±220.1	0.4773
Induction therapy (basiliximab or thymoglobulin)	7 (77.77%)	27 (36.99%)	0.0296*
CNI therapy			
• Cyclosporine	1 (11.11%)	40 (54.79%)	0.0291*
• Tacrolimus	8 (88.88%)	33 (45.21%)	
Azathioprine/mycophenolate mophetil	7 (77.77%)	47 (64.38%)	0.7113
Severe hypotension/hemodynamic decompensation	2 (22.22%)	14 (19.18%)	>0.9999
Vasoactive amines (hours)	64.00±41.57	93.74±144.6	0.5431
Blood transfusion	4 (44.44%)	29 (39.73%)	>0.9999
IMV > 96 hours	4 (44.44%)	36 (49.31%)	>0.9999
Tracheostomy	1 (11.11%)	18	0.6772
NO inhalation (hours)	42.00±34.47	78.25±92.20	0.2480
Intra-operative ECMO	2 (22.22%)	13	0.6662
Post-operative ECMO	0	7	>0.9999
PGD at 72 hours			
• All Grades	7 (77.77%)	55	>0.9999
• Grade 1	1 (11.11%)	13	>0.9999
• Grade 2	4 (44.44%)	24	0.6950
• Grade 3	2 (22.22%)	16	>0.9999
ACR			
• 1 episode of ACR	5 (55.5%)	36 (49.3%)	0.3868
• ≥ 2 episodes of ACR	0 (0%)	11 (15%)	0.6006
ICU stay (days)	16.89±10.65	19.48±19.62	0.6993
Total in-hospital stay (days)	42.22±18.16	42.68±26.21	0.9596
Overall survival			
• 1 year	66.6%	58.4%	0.7067
• 3 years	41.6%	45.4%	
• 5 years	41.6%	43.4%	
Overall survival according to LTX type (single/bilateral)			
• 1 year	37.5% / 50%	58.6% / 69.2%	0.2689 / 0.6774
• 3 years	12.5% / 50%	36.0% / 65.1%	
• 5 years	12.5% / 50%	36.0% / 65.1%	
CLAD-free survival			
• 1 year	87.5%	73.8%	0.1883
• 3 years	72.9%	44.3%	
• 5 years	72.9%	39.4%	
CLAD-free survival according to LTX type (single/bilateral)			
• 1 year	100% / 62.5%	83.3% / 68.2%	0.5326 / 0.1837
• 3 years	100% / 62.5%	42.5% / 48.3%	
• 5 years	100% / 62.5%	34.7% / 41.5%	

LTX: lung transplantation; FPF: familial pulmonary fibrosis; PF: pulmonary fibrosis; CNI: calcineurin inhibitor; NO: nitric oxide; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation; ACR: acute cellular rejection; PGD: primary graft dysfunction; ICU: intensive care unit; CLAD: chronic lung allograft dysfunction. *statistically significant.

Table 4. Pre- and post-transplant blood parameters and acute-phase proteins in FPF and PF patients.

	Basal (pre-LTX)			Day 7			Day 14			Day 30		
	PF (n 6)	FPF (n 40)	p	PF (n 6)	FPF (n 39)	p	PF (n 6)	FPF (n 36)	p	PF (n 6)	FPF (n 34)	p
WBC	12.66 ± 4.19	13.09 ± 4.35	0.81	11.73 ± 4.11	10.09 ± 2.61	0.37	13.58 ± 7.42	11.15 ± 6.54	0.32	8.26 ± 3.95	9.90 ± 8.00	0.95
HB	14.3 ± 1.7	11.8 ± 2.9	0.03*	9.6 ± 1.2	9.7 ± 0.8	0.77	10.0 ± 1.2	9.9 ± 1.2	0.73	10.5 ± 1.4	10.7 ± 1.3	0.63
HCT	43.3 ± 4.9	35.6 ± 7.7	00.1*	29.6 ± 3.6	30.3 ± 1.8	0.55	29.8 ± 4.6	30.3 ± 3.9	0.97	31.8 ± 3.9	32.5 ± 4.0	0.64
MCV	90.8 ± 3.9	93.5 ± 9.7	0.86	91.2 ± 4.6	93.1 ± 4.8	0.42	90.3 ± 4.0	91.0 ± 4.0	0.79	91.5 ± 3.6	91.6 ± 4.2	0.882
PLT	212.0 ± 64.4	272.2 ± 84.6	0.09	127.7 ± 70.4	132.2 ± 57.7	0.72	171.4 ± 98.2	239.5 ± 110.7	0.19	192.5 ± 87.1	277.0 ± 214.4	0.62
CRP	1.07 ± 1.25	2.01 ± 1.87	0.54	4.12 ± 4.91	12.33 ± 9.29	0.17	6.09 ± 10.03	3.11 ± 2.69	0.76	2.49 ± 3.86	1.04 ± 1.42	0.17
LDH	376.7 ± 150.3	340.6 ± 140.0	0.60	836.9 ± 165.7	344.5 ± 42.2	0.23	686.0 ± 640.7	541.3 ± 227.5	0.90	371.0 ± 171.8	323.6 ± 140.4	0.53
	Day 90			Day 180			Day 365					
	PF (n 6)	FPF (n 29)	p	PF (n 4)	FPF (n 27)	p	PF (n 4)	FPF (n 25)	p			
WBC	7.87 ± 3.24	9.14 ± 3.16	0.21	7.29 ± 2.10	11.00 ± 2.07	0.03*	7.03 ± 2.36	10.11 ± 5.96	0.42			
HB	11.4 ± 1.4	11.6 ± 0.7	0.88	12.1 ± 1.2	10.5 ± 0.9	0.05*	11.9 ± 1.4	9.9 ± 1.8	0.14			
HCT	34.9 ± 4.2	35.3 ± 2.4	0.91	37.2 ± 3.5	33.2 ± 2.9	0.07	36.8 ± 3.9	31.3 ± 5.3	0.07*			
MCV	93.3 ± 5.0	97.3 ± 7.5	0.24	93.5 ± 5.9	94.9 ± 4.8	0.98	91.2 ± 9.1	90.8 ± 10.9	0.99			
PLT	199.8 ± 57.1	224.6 ± 94.5	0.81	209.5 ± 58.2	226.7 ± 105.0	0.99	188.3 ± 65.4	321.0 ± 183.8	0.41			
PCR	1.04 ± 1.42	1.19 ± 1.40	0.83	0.67 ± 1.28	0.87 ± 118	0.93	2.4 ± 8.2	0.07 ± 0.03	0.25			
LDH	289.1 ± 124.3	280.5 ± 113.1	0.97	282.1 ± 89.5	340.7 ± 294.0	0.41	243.3± 62.6	232.5 ± 40.3	0.94			

FPF: familial pulmonary fibrosis; PF: pulmonary fibrosis; WBC: white blood cells; HB: haemoglobin; HCT: haematocrit; MCV: mean corpuscle volume; PLT: platelet; CRP: C reactive protein; LDH: lactate dehydrogenase; n: number; p: statistical significance; * statistically significant.

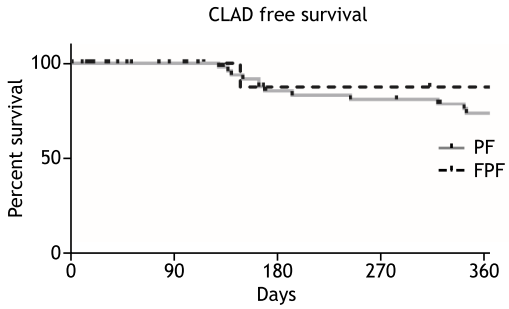

Figure 1. CLAD-free survival at 1 year based on Kaplan-Meyer curves in FPF and PF patients.

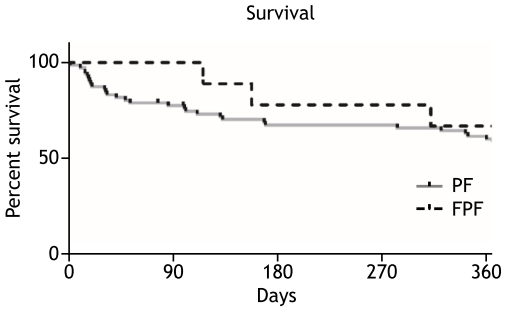

Figure 2. 1-year survival analysis based on Kaplan-Meyer curves FPF and PF patients.

No significant difference in one-year CLAD-free survival was observed. While FPF patients showed a better outcome, the difference was not significant (CLAD one-year survival FPF group 87.5%, PF 73.8%) (Figure 1). Likewise, survival analysis at 1 year did not show significant differences between groups (66.7% FPF, 58.4% PF) (Figure 2). 1, 3, and 5-years survival and CLAD-free survival data, also stratified for single/bilateral LTX, are reported in Table 3.

DISCUSSION

Lung transplant is a viable therapeutic option in patients with end-stage lung disease and vascular lung disease unresponsive to medical or surgical therapy or in patients for whom no therapy is available.[1] Patients with pulmonary fibrosis, CF, and COPD are those most likely to benefit, although the long-term outcome in cases of IPF is reportedly poorer than in cases with other indications.[21] In the USA, since the advent of the Lung Allocation Score (a composite score based on various clinical and physiological parameters predicting life expectancy in the waiting list), IPF has become the first indication for transplant.[22] However, mortality on the waiting list is still a major issue for these patients.[23]

Some patients with pulmonary fibrosis may have one or more family members with interstitial lung disease. In these cases, the definition of familial pulmonary fibrosis (FPF) has been proposed.[8] Radiological and clinical manifestations vary widely, as do evolution and prognosis.[8-14] FPF has a vertical transmission, suggesting autosomal dominant inheritance with incomplete penetrance (i.e. not everyone with the genetic variant develops the disease).[15] Several genetic variants have been documented, but nearly 80% of cases are unknown. Most of the known variants of concern genes encoding the telomerase complex.[15,16] Here we compared clinical features and short- and long-term outcomes of patients with FPF and of patients with other interstitial lung diseases (PF or control group) who underwent lung transplants at our centre.

The baseline demographic and clinical features of our populations were homogeneous. Our cohort did not show the demographic differences commonly reported between patients with FPF and patients with sporadic IPF (younger age, the same prevalence in males and females, less exposure to smoking).[8-14] This was probably because the group of patients with sporadic pulmonary fibrosis was selected for transplant, where age below 65 years old, for example, is a fundamental prerequisite for the waiting list. As regards gender, the PF group also included diseases other than IPF (e.g. connective tissue disease, hypersensitivity pneumonitis) where gender distribution is not always in favour of males.

Several pathologies and HRCT presentation patterns have been reported in FPF patients, the UIP pattern being the most frequent.[13] However, aspects of NSIP, COP, centrilobular nodulation, and unclassified pulmonary fibrosis are not uncommon.[8-14] In our cases, HRCT scans showed a UIP pattern in most patients (66.7%) and pathology data were congruous, showing UIP alterations in 55.5% of patients. Radiology and pathology findings were discordant in two cases; similar data of CT and pathology accordance have been reported.[24,25]

One patient was diagnosed with lung cancer from the pathology report on the native lungs and made a very poor post-operative course. Despite chemotherapy, the patient died about a year later. Diagnosis of lung cancer after transplant has been reported by others and evolution in these cases can be very aggressive.[26] Accurate pre-transplant screening for chest cancer is important, especially in patients with pulmonary fibrosis. There is a strong association between PF and lung cancer and a higher incidence than in the general population and other lung diseases.[21] Nevertheless, post-transplant solid-organ malignancies in lung transplant recipients is a major issue; in particular, skin and lung cancers demonstrated a higher incidence rate.[27]

About pre-LTX malignancies, our centre requires 5 years disease-free interval before listing for LTX. In the

present study, the incidence of pre-LTX malignancies was not different between groups. In the FPF group, no patients had pre-LTX tumors, while in the PF two patients had a history of a haematological disease for which underwent bone marrow transplantation and subsequently developed chronic pulmonary graft-versus-host-disease (GVHD) and so got to LTX, one patient had colorectal cancer (pT1, N0, M0) 6 years before LTX and another undergone abdominal surgery for a gastrointestinal stromal tumor (GIST) that was considered a benign lesion.

Regarding intra- and post-operative variables, patients with FPF and PF received similar treatment and we did not observe different short- and long-term outcomes. The only differences were the type of transplant and immunosuppressant therapy. Patients with FPF underwent bilateral LTX, received induction therapy, and first-line immunosuppressant therapy was based on tacrolimus more frequently than in PF patients. These differences reflect the different eras in which patients underwent a transplant in our centre. Indeed, induction therapy, tacrolimus instead of cyclosporine, and bilateral transplant are in line with our more recent clinical activity, in parallel with the literature and with experience acquired by our team.[28,29] In our PF cohort, the use of basiliximab showed to be associated with a better outcome in terms of overall survival and CLAD-free survival (p=0.05, HR=0.503 (0.247-1.027) and p=0.003, HR=0.165 (0.050-0.543), respectively). Most patients with FPF were transplanted since 2009 when our protocol had already undergone substantial changes (only one patient was transplanted previously, in 2006), so 7 of the 9 FPF patients were treated with basiliximab and received bilateral LTX. Cox regression analysis did not demonstrate a significant association of gender, age, LTX type procedure (single/bilateral), use of basiliximab, and tacrolimus instead of cyclosporine with overall survival and CLAD-free survival in this group (data not shown). ACR is a recognized risk factor for CLAD development however, in our cohorts, we could not demonstrate this association (p=0.123, HR=2.158 in PF patients, and p=0.848, HR=1.266 in FPF patients respectively).

Blood and liver anomalies have been reported in patients with FPF. In particular, anaemia, thrombocytopenia, and in some cases, leukopenia have been observed in patients with short telomere syndrome, mainly linked to variants in genes encoding the telomerase complex.[15,16] A negative effect of immunosuppressant therapies has been reported in IPF patients with short telomere. In 2018, patients with this syndrome from the PANTHER-IPF and ACE-IPF studies and an independent observational cohort study from the University of Texas Southwestern Medical Center (UTSW), exposed to triple prednisone/azathioprine/N-acetylcysteine therapy, showed an increased risk of mortality, post-transplant complications, hospitalization and a greater reduction in forced vital capacity (FVC).[29] Lung transplant patients with short telomere are also reported to have a poorer outcome with high rates of blood, renal and gastrointestinal complications, impaired immunity to CMV, and increased risk of death and CLAD.[17-20,30,31] In 2018, the Leuven group reported positive outcomes in a case series of multiple solid organ transplants in patients with telomeropathy.[32]

In our cohort, three patients showed mild-moderate anaemia before transplant, with macrocytosis in two cases, while no patient showed leukopenia, thrombocytopenia, liver anomalies, or other manifestations of short telomere syndromes, including early grey syndrome. Unfortunately, we did not consider genetic variants because the genetic analysis was only available for three patients and was found negative in all three (genes for surfact C and A2, ABCA3, TERT, and TERC were tested).

Compared to the PF group, our FPF patients showed a significant reduction in pre-transplant values of haemoglobin and haematocrit. These differences were no longer significant in the early post-transplant phase but reappeared 6 and 12 months later. This is probably due to the effect of post-operative blood and platelet transfusions, which while not significantly different between groups, could have mitigated blood parameter differences. The hypothesis that these patients could be a carrier of some genetic mutations resulting in telomere abnormalities is interesting; however, since no genetic analysis was available, no definite conclusion can be made.

The long-term outcome of our PF patients was in line with the literature[21] and no differences between FPF and PF groups were found. Time to CLAD development did not differ between groups and one, three and five-year survival was similar. Literature is controversial on long term outcome in FPF and patients with genetic mutations; some studies reported lung transplant may still be viable and offer reasonable survival to patients with FPF, despite major complications,[17,18] while some other studies observed worse survival and shorter time to onset of chronic lung allograft dysfunction in patients with telomere abnormalities.[19,20]

The present study has several limitations, notably the small statistical sample, the fact that the study was retrospective, concerned a single institution and genetic analysis was not available. The number of patients enrolled is small because FPF is rare, even if our centre has earned a name for particular attention to these patients.

In conclusion, our study offers further evidence that lung transplant is just as valid a therapeutic option for patients with familial pulmonary fibrosis as it is for patients with sporadic pulmonary fibrosis. Baseline characteristics were similar and the risk of blood complications was not different, although more patients with FPF may have pre-transplant anaemia.

Short- and long-term outcomes were comparable in patients with familial and non-familial pulmonary fibrosis, confirming that despite major complications, a lung transplant may still be viable and offer reasonable survival to patients with FPF.

Further studies, considering specific genetic variants and involving multicentre cohorts, are needed for better evaluation of lung transplant candidates with familial pulmonary fibrosis and a better appreciation of long-term outcomes.

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ERRATUM

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