Heliyon 9 (2023) e18618

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Factors associated with listing for lung transplantation in IPF patients: An analysis of the pulmonary fibrosis foundation registry

Christopher S. King [a,*], Emily White [b], Shambhu Aryal [a], Oksana A. Shlobin [a], Anju Singhal [a], A. Whitney Brown [a], Christopher Thomas [a], Vikramjit Khangoora [a], Alan Nyquist [a], Kevin R. Flaherty [c], Steven D. Nathan [a], Joshua J. Mooney [d]

[a] *Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, VA, USA*
[b] *University of Michigan, Department of Biostatistics, USA*
[c] *University of Michigan Division of Pulmonary & Critical Care Medicine, USA*
[d] *Stanford University, Division of Pulmonary and Critical Care Medicine, USA*

ARTICLE INFO

Keywords:
Pulmonary fibrosis
Idiopathic pulmonary fibrosis
Lung transplantation

ABSTRACT

Rationale and objectives: Lung transplantation is a potentially life-saving treatment option for patients with idiopathic pulmonary fibrosis (IPF); however, not all eligible candidates get referred and listed for transplantation. Amongst IPF patients within the Pulmonary Fibrosis Foundation Patient Registry (PFF-R), we sought to determine the proportion of patients who undergo lung transplant listing and the characteristics associated with transplant listing.

Methods: An analysis of IPF patients with at least six months of follow-up data was performed. Patients with well-established contraindications to lung transplantation were excluded. Two complementary analyses were performed. The "prevalent" population included all patients with IPF at time of enrollment into the registry. The "incident severe" population included all patients with IPF who progressed to GAP Stage 3.

Results: Of the 2003 patients in the PFF-R, 475 patients were included in the "prevalent" population. Of this group, only 42 (8.8%) were either listed for or underwent lung transplant. Univariable analysis of the "prevalent" population found age (per 10 year increase, OR 0.531, $p = 0.0025$), percent predicted FVC (OR 0.572, p=<0.0001), percent predicted DLCO (OR 0.606, $p < 0.0001$), 6-min walk distance (per 50 m, OR 0.831, $p = 0.019$), and oxygen use at rest (OR 5.157, $p < 0.0001$) were predictive of listing. On multivariable analysis, age (per 10 year increase, OR 0.558, $p = 0.0088$), percent predicted FVC (OR 0.728, $p = 0.0161$), and oxygen use at rest (OR 3.264, $p = 0.0029$) remained significant predictors for lung transplant listing. The "incident severe" group consisted of 176 patients (8.8%). 24 patients (13.6%) from this cohort were either listed for or received a transplant. Only age (per 10 year increase, OR 0.0286, $p = 0.0465$) was associated with transplant listing on univariable analysis in the Incident severe population.

Conclusion: Only a small proportion of potentially eligible patients with IPF are listed for lung transplantation, even when seen at pulmonary fibrosis centers of excellence. Advanced age appears to be the primary factor associated with failure to be listed. Further refinement of future registry data is required to more clearly delineate exact reasons for low rates of listing.

* Corresponding authorAdvanced Lung Disease and Transplant Program 3300 Gallows Road Falls Church, VA, 22042, USA.
E-mail address: Christopher.king@inova.org (C.S. King).

https://doi.org/10.1016/j.heliyon.2023.e18618
Received 9 December 2022; Received in revised form 27 June 2023; Accepted 24 July 2023
Available online 5 August 2023

1. Introduction

Idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic fibrotic interstitial lung diseases (ILD), is characterized by progressive pulmonary fibrosis ultimately culminating in hypoxemic respiratory failure and death [1]. The two currently approved medications for the treatment of IPF, nintedanib and pirfenidone, do not usually halt or reverse the development of fibrosis but rather only slow the disease trajectory [2]. Although recent data suggests that these anti-fibrotic medications reduce mortality in IPF, the prognosis of the disease remains poor [3]. Given the limitations of the currently available medical therapies for IPF, lung transplantation (Ltx) is frequently the only viable option to extend life and substantially improve quality of life in IPF. In fact, despite these evolving treatments ILD is the most common indication for LTx worldwide accounting for nearly a third of transplants performed worldwide [4].

The process of lung transplantation referral, evaluation and listing is guided by published recommendations from the ISHLT [5]. These include relative and absolute contraindications regarding the suitability of individual patients for listing. Absolute contraindications include: ongoing tobacco abuse, malignancy, etc. In addition, there are relative contraindications including age>70 years old, comorbid coronary artery disease, BMI>35, etc. Further, decision for lung transplantation evaluation and listing is based on shared decision making with the patient.

A recent consensus statement from the International Society of Heart and Lung Transplant (ISHLT) recommends that patients with IPF be referred for transplant evaluation at the time of diagnosis and those meeting specific clinical or physiologic criteria of progressive or advanced disease be considered for lung transplant listing [5]. Additionally, Gender-Age-Physiology (GAP) score is a validated prognostic tool in IPF with a recommendation for lung transplant listing in GAP stage 3 patients, if medically appropriate, due to a high estimated mortality of 39% at 1-year and 62% at 2-years within this patient group [6]. Despite established guidelines, many clinicians fail to refer patients with IPF for Ltx evaluation [7]. Furthermore, studies suggest that only a minority of IPF patients referred for Ltx are ultimately listed [8]. This may reflect both the co-morbidities associated with an IPF diagnosis (advanced age, deconditioning, increased risk of CAD). However, an important step in understanding the access of Ltx for IPF patients is to understand the number of patients with IPF who are ultimately listed for Ltx.

The Pulmonary Fibrosis Foundation Patient Registry (PFF-R) has collected data on over 2000 patients with various forms of interstitial lung diseases, including 1230 patients with IPF, who were enrolled at 42 PFF Care Centers across the United States [9]. In order to be designated a PFF Care Center, programs must apply and be able to demonstrate the ability to provide multidisclipinary care for the full gamut of ILDs. We analyzed data on IPF patients from the PFF-R to determine the likelihood of and clinical characteristics associated with Ltx listing after excluding those patients with well recognized contraindications to transplantation.

2. Methods

We analyzed data from the PFF-R, a cohort of well-characterized patients with ILD including IPF, to identify characteristics of patients listed for LTx. Data on referral for LTx evaluation that did not result in LTx listing was not available. Data included was collected between March 2016 and July 2020.

We evaluated two separate but complementary study populations. In the first, or "prevalent population", we extracted IPF patients who were not listed for LTx at the time of enrollment to identify the proportion of IPF patients who underwent lung transplant listing within the subsequent 6-month timeframe and the characteristics associated with listing. Patients with the following established exclusion criteria were excluded: less than 6 months of follow-up data, age >75 years, BMI≥ 35, active tobacco use, known congestive heart failure, known non-skin cancer, known liver cirrhosis, missing comorbidity information, and/or missing FVC and DLCO data necessary to calculate the GAP stage [9]. In the second analysis, we evaluated IPF patients at the first time they were documented to have advanced disease, defined as GAP stage 3, to identify the proportion of these patients listed within the subsequent 6-month timeframe and to compare characteristics between listed and unlisted IPF patients with GAP stage 3 disease. We will refer to this population as the "incident severe population". The same standard exclusion criteria were applied to this population with the addition of excluding persons never reaching GAP stage 3.

Variables of interest were patient age, sex, race, ethnicity, BMI, insurance type (private/Medicare/other), miles to nearest lung transplant center (from patient's zip code center to transplant center's zip code center), and the transplant center status of the PFF care center (transplant center vs not).

We also included presence of diabetes, depression, and coronary artery disease (CAD), and the following clinical characteristics: anti-fibrotic use (yes/no), supplemental oxygen at rest (yes/no), pulmonary rehabilitation (yes/no), 6MWT distance (meters), FVC (% of predicted based on Hankinson et al. predicted values, and DLCO (% of predicted based on based on Crapo-Morris predicted values) [10,11].

Characteristics at the time of enrollment were used for the analysis using all GAP stages, and characteristics at the time of reaching GAP stage 3 were used for the GAP stage 3 analysis.

2.1. Statistical analysis

Frequencies with proportions were reported for categorical variables, and means with standard deviations for continuous variables. Generalized linear models with a logit link and a binary distribution were used for univariable associations with the outcome of lung transplant listing for both study populations. A generalized linear model with a logit link and a binary distribution was used for multivariable associations with the outcome of lung transplant listing among IPF patients of all GAP stages. Odds ratios, 95%

confidence intervals, and p-values were reported.

Variables chosen for inclusion in the multivariable analysis were based on clinical relevance to the outcome. For lung transplant listing in IPF patients, variables chosen for inclusion were the following: age, sex, % of predicted FVC, % of predicted DLCO, oxygen use at rest, and 6-min walk distance. A combination of backward and forward selection was used to determine the best fitting multivariable model, using the magnitude of the coefficient, statistical significance, and the area under the receiver-operating curve as criteria.

Missing data patterns were examined along with group means across missing data patterns. Multiple imputation was used for sensitivity analysis.

Analyses were performed using SAS version 9.4, (SAS Institute, Cary, NC, USA).

3. Results

3.1. Prevalent IPF population

There were 2003 patients in the PFF-R at the time of data analysis. 762 patients with a non-IPF diagnosis and 11 patients who had undergone single Ltx prior to enrollment were excluded. Of the remaining 1230 IPF patients, 37 patients were excluded for <6 months

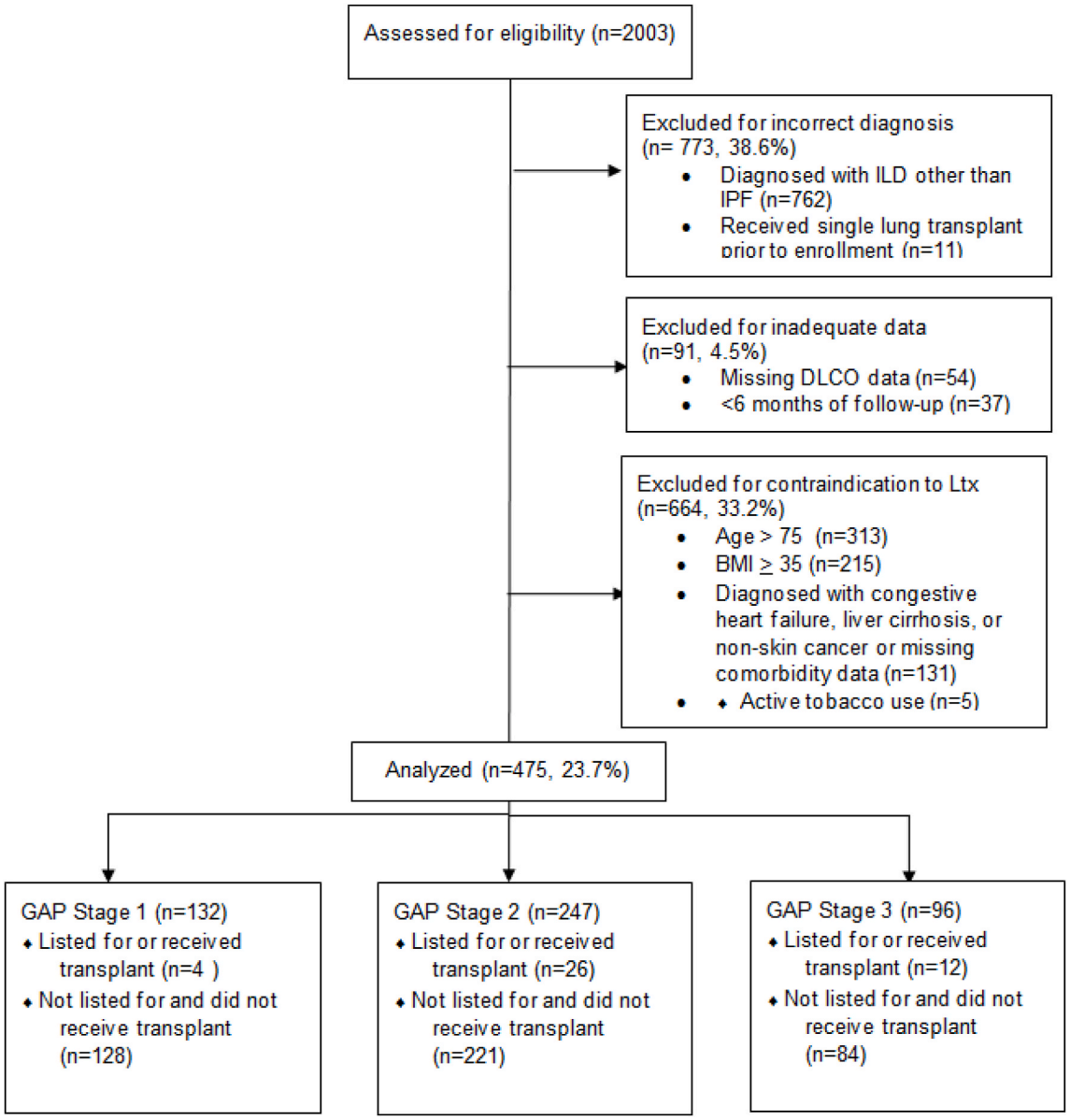

Fig. 1. CONSORT diagram shows the reasons for exclusion in the prevalent IPF population.

follow-up and 54 for missing DLCO data.

Of the remaining IPF patients, 664 (54.0%) were excluded from analysis due to established or relative contraindications to transplant including age >75 years (n = 313, 10.6%), BMI ≥35 (n = 215, 17.5%), diagnosis of congestive heart failure, liver cirrhosis, or non-skin cancer, or missing co-morbidity data (n = 131, 10.7%), or active tobacco use (n = 5, 0.4%). Fig. 1 displays the reasons for exclusion.

475 patients were included in the cohort analyzed, of which 132 (27.8%), 247 (52%) and 96 (20.2%) were categorized as GAP stage 1, 2 and 3 respectively. Only 8.8% (n = 42) of the cohort was either listed for (n = 16) or received a Ltx (n = 26). The percentage of patients listed or transplanted increased as GAP stage increased: 3% for Stage 1 (3 listed, 1 Ltx), 10.5% for stage 2 (10 listed, 16 LTx), and 12.5% for stage 3 (3 listed, 9 LTx).

3.2. Prevalent IPF population characteristics and association with lung transplant listing

Table 1 shows the characteristics of the prevalent IPF population divided into patients listed and not listed for transplant. The population was predominately male (74.3%) and predominately White (93.7%). Only 65% of patients were on anti-fibrotic therapy, with no significant difference in use of anti-fibrotics between listed (69.1%) and unlisted patients (64.9%). Age and severity of illness appeared to be the primary predictors of listing on univariate analysis. With regards to age, a decade increase in age reduced the likelihood of listing by nearly half (OR 0.531, 95% CI 0.352–0.801, p = 0.0025). Lower percent predicted FVC and DLCO, decreased 6-min walk distance, and need for supplemental oxygen were all associated with transplant listing on univariate analysis (Table 2). Sex, race, type of insurance, and proximity to a transplant center were not associated with Ltx listing. On multivariate analysis, only age, percent predicted FVC, and need for supplemental oxygen at rest remained associated with transplant listing (Table 3).

Table 1
Prevalent IPF patient population characteristics by lung transplant listing.

Column1	All	Listed for Lung Transplant	Not Listed for Lung Transplant
	N = 475	N = 42	N = 433
Age, years	67.2 (±6.4)	64.0 (±8.2)	67.5 (±6.1)
Age			
<65	132 (27.8%)	16 (38.1%)	116 (26.8%)
65–69	140 (29.5%)	15 (35.7%)	125 (28.9%)
70–72	105 (22.1%)	7 (16.7%)	98 (22.6%)
73–75	98 (20.6%)	4 (9.5%)	94 (21.7%)
Male Gender	353 (74.3%)	30 (71.4%)	323 (74.6%)
Race			
White	445 (93.7%)	36 (85.7%)	409 (94.5%)
Black	8 (1.7%)	2 (4.8%)	6 (1.4%)
Other	22 (4.6%)	4 (9.5%)	18 (4.2%)
Ethnicity			
Hispanic	13 (2.7%)	1 (2.4%)	12 (2.8%)
Non-Hispanic	448 (94.3%)	39 (92.9%)	409 (94.5%)
Unknown	14 (3.0%)	2 (4.8%)	12 (2.8%)
Body Mass Index	28.1 (±3.9)	27.6 (±3.9)	28.1 (±3.8)
Percent Predicted FVC	67.4 (±16.2)	55.9 (±13.5)	68.5 (±16.0)
Percent Predicted DLCO	42.6 (±18.0)	32.7 (±16.5)	43.5 (±17.9)
GAP Score			
1	132 (27.8%)	4 (9.5%)	128 (29.6%)
2	247 (52.0%)	26 (61.9%)	221 (51.0%)
3	96 (20.2%)	12 (28.6%)	84 (19.4%)
Anti-fibrotic Use	310 (65.3%)	29 (69.1%)	281 (64.9%)
Pulmonary Rehab Enrollment	123 (25.9%)	21 (50.0%)	102 (23.6%)
Oxygen Use at Rest.	184 (38.7%)	31 (73.8%)	153 (35.3%)
Six Minute Walk Distance, meters (N = 281)	391.0 (±122.7)	338.7 (±120.5)	396.8 (±121.8)
Medical Comorbidities			
Diabetes	89 (18.7%)	7 (16.7%)	82 (18.9%)
Depression	82 (17.3%)	12 (28.6%)	70 (16.2%)
Coronary Artery Disease	115 (24.2%)	14 (33.3%)	101 (23.3%)
Insurance			
Private	146 (30.7%)	14 (33.3%)	132 (30.5%)
Medicare	287 (60.4%)	24 (57.1%)	263 (60.7%)
Other	42 (8.8%)	4 (9.5%)	38 (8.8%)
Distance to Nearest. Lung Transplant Center, miles (N = 472)	57.4 (±60.0)	52.3 (±58.6)	57.8 (±60.2)
PFF Care Center Status			
Lung Transplant Center	376 (79.2%)	33 (78.6%)	343 (79.2%)
Not a Lung Transplant Center	99 (20.8%)	9 (21.4%)	90 (20.8%)

*Categorical variables reported as number (%), Continuous variables reported as mean (standard deviation).
Abbreviations: DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; FVC = Forced Vital Capacity; IPF= Idiopathic pulmonary fibrosis; GAP= Gender, Age, and Physiology Score; PFF= Pulmonary Fibrosis Foundation.

3.3. Incident severe population

In the second analysis performed, patients enrolled in the PFF-R were followed longitudinally and only those patients who progressed to GAP stage 3 were included. Of the 2003 patients in the PFF-R, 715 (35.7%) were excluded for incorrect diagnosis or having had a single transplant prior to enrollment. Of note, the number of patients with a non-IPF diagnosis increased from 658 to 704. This occurred because PFF Care Centers were allowed to update the diagnosis over time if new clinical information became available or a clinical change occurred. 234 patients (11.7%) were excluded for inadequate data. 497 patients (24.8%) were excluded due to a well-established contraindication to Ltx. After excluding these groups, 557 patients (27.8%) remained. Of these 557 patients, only 176 (31.6%) progressed to GAP stage 3. Fig. 2 delineates the excluded patients for the Incident Severe population.

3.4. Incident severe population patient characteristics and their association with transplant listing

Of the 176 patients who progressed to Gap Stage 3, only 24 (13.6%) were listed for or received a transplant. Table 4 summarizes the patient characteristics of the incident severe population overall, as well as divided by those listed for or not listed for Ltx. Like the prevalent IPF cohort, the incident severe IPF cohort was predominately male (90.3%) and White (90.3%). The incident severe cohort was older (70.1 $\pm$ 3.4 years) than the prevalent cohort (67.2 $\pm$ 6.4 years). A higher percentage of patients were on anti-fibrotic treatment (72.7% versus 65.3%) in the incident severe population versus the prevalent population. Interestingly, within the incident cohort the percentage of patients on anti-fibrotics was higher in the "not listed" group than in the "listed" group (82.4% versus 66.7%). The percentage of patients enrolled in pulmonary rehabilitation was low in both the incident and prevalent populations at 31.3% and 25.9% respectively. Univariate analysis of patient characteristics associated with transplant listing in the Incident severe cohort found only age as a predictor. Sex, race, insurance type, and proximity to a transplant center were not found to be associated with transplant listing. Furthermore, in contrast to the prevalent population, none of the markers of disease severity, to include percent predicted FVC and DLCO, 6-MWT distance, and need for supplemental oxygen were associated with LTx listing. Table 5 summarizes the univariable analysis of the Incident severe cohort.

4. Discussion

The value of any registry lies in its ability to provide a broad real world overview of various aspects of disease and disease management. In this regard, our analysis of IPF patients from the PFF Patient Registry regarding Ltx listing of potential candidates provides insight that there may be more patients potentially eligible for this potential life-saving treatment option. Specifically, the primary finding of the study was that only a small percentage (8.8% of the prevalent IPF cohort) were either listed for or underwent Ltx. Even when the population was narrowed to only those who had progressed to GAP Stage 3, which is associated with a 1-year mortality rate of 39.2%, only 13.6% of the patients were listed for transplant despite eliminating those with obvious contraindications [6]. The low percentage of IPF patients achieving listed status is notable given these patients are managed at PFF care centers, many of which have Ltx programs within their institution. The decision for lung tx referral is a complex decision that involves both patient level and system level challenges. While this study cannot address the rate of Ltx referral, the low rate of listing is indicative of important gaps in knowledge regarding what barriers exist to listing.

Table 2
Univariable associations between patient characteristics and lung transplant listing in prevalent IPF patient population.

	Odds Ratio	95% Confidence Interval	p-value
Age			
Age, per 10 year increase	0.531	(0.352, 0.801)	0.0025**
Age, per 5 year increase	0.729	(0.593, 0.895)	0.0025**
Sex			
Male	Reference		
Female	1.175	(0.581, 2.374)	0.6540
Race			
White	Reference		
Black	3.787	(0.737, 19.448)	0.3161
Other	2.525	(0.811, 7.860)	0.7070
Insurance			
Medicare	Reference		
Private	1.162	(0.582, 2.321)	0.8433
Other	1.154	(0.379, 3.507)	0.9029
Percent Predicted FVC, per 10%	0.572	(0.453, 0.723)	<0.0001**
Percent Predicted DLCO, per 10%	0.606	(0.472, 0.779)	<0.0001**
6-min Walk Distance, per 50 m	0.831	(0.712, 0.970)	0.0188**
Oxygen Use at Rest.	5.157	(2.522, 10.548)	<0.0001**
Distance to Nearest. Transplant Center, per 10 miles	0.984	(0.930, 1.041)	0.5688
Transplant Center at PFF Care Center	0.962	(0.444, 2.083)	0.9212

**denotes statistical significance for an alpha <0.05.
Abbreviations: DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; FVC = Forced Vital Capacity; PFF = Pulmonary Fibrosis Foundation.

Table 3
Final multivariable associations between patient characteristics and lung transplant listing in prevalent IPF patient population.

	Odds Ratio	95% Confidence Interval	p-value
Age, per 10 year increase	0.558	(0.360, 0.863)	0.0088**
Percent Predicted FVC, per 10%	0.728	(0.562, 0.943)	0.0161**
Percent Predicted DLCO, per 10%	0.793	(0.611, 1.029)	0.0811
Oxygen Use at Rest.	3.264	(1.497, 7.116)	0.0029**

**denotes statistical significance for an alpha <0.05.
Abbreviations: DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; FVC = Forced Vital Capacity.

IPF patients with a corresponding GAP stage of 3 are recommended to be considered for lung transplant evaluation, given the associated mortality of 39% at 1-year and 62% at 2-years [6]. Additionally, a recent ISHLT consensus statement details criteria for listing for Ltx which include the following: absolute decline in forced vital capacity (FVC) > 10%, absolute decline in diffusing capacity of the lung for carbon monoxide (DLCO) > 10%, decline in FVC >5% plus radiographic progression, desaturation to < 88% on a 6-min walk test (6MWT), a decline of >50 m on a 6MWT in 6 month period, pulmonary hypertension (PH) by right heart catheterization or echocardiography, or hospitalization due to respiratory decline, pneumothorax, or acute exacerbation [5]. Further analysis of progressive decline in the FVC, DLCO, and 6-MWT distance was felt to be outside the scope of this analysis as the number of included patients would have been too small to draw meaningful conclusions. However, the available data does shed some light on the failure to achieve listing. For instance, over a third of the prevalent cohort and more than half of the incident severe cohort who were not listed required supplemental oxygen at rest. Based on the ISHLT consensus, these patients should be regarded as candidates for Ltx listing.

Age was the primary variable that was associated with LTX listing. For every 10 year increase in age, the likelihood of being listed for Ltx dropped by nearly half (OR 0.531) in the prevalent population and almost 75% in the incident severe IPF population (OR 0.286). Advanced age certainly represents a relative contraindication to Ltx, although no upper limit of age has been endorsed as an absolute contraindication to transplant [5]. Elderly patients are at risk of physical frailty, sarcopenia, cognitive issues, and increased risk of co-morbidities [12]. Despite these concerns, Ltx centers have developed increasing experience in selecting and transplanting candidates of advanced age and carefully selected candidates can achieve outcomes similar to those of younger recipients [13]. In fact, patients age 65 or greater comprise over 30% of the waiting list and are the age group with the highest transplant rate [14]. It is noteworthy that the age cutoff we used for this analysis was 75, therefore it was not patients who were clearly beyond the accepted transplant upper age range that drove age as a limiting factor to transplant listing. It should be acknowledged though that 75 years might be higher than some Ltx centers are comfortable with. Also, relative contraindications might weigh more heavily in elderly transplant candidates regarding their transplant candidacy. Importantly, it was not age alone that factored into the low listing rate since over 50% of the "not listed" patients in the prevalent population and ~40% of the "not listed" patients in the incident severe population were under age 70. While this data does not capture referral for Ltx evaluation, it is not clear whether other patient level factors impacted the decision for referral and ultimately listing.

Socioeconomic factors including gender, race, insurance type, proximity to a transplant center, and being seen at a PFF Care Center with an affiliated LTx center within their institution were not factors associated with failure to achieve listed status. These results should be interpreted with caution, as the vast majority of the included patients were Caucasian men, which may have limited the ability of the study to detect differences in listing amongst races and genders. Racial disparity in access to Ltx has been noted in other studies and the failure to demonstrate this might have resulted from the demographics of patients referred and seen at PFF Centers or those who consented for inclusion in the PFF-R [14].

Our analysis does have a number of limitations which should be noted. One issue is that we only have data on Ltx listing but cannot comment on Ltx referral. It is possible that patients were appropriately referred for Ltx evaluation and were in the process of completing an evaluation, declined due to the presence of an identified contraindication to transplant, or deferred pending further disease progression. We also do not have information on the patient's attitude to Ltx, as well as other factors that might have impacted their transplant candidacy. It is possible that many patients, particularly those of advanced age, may have elected not to pursue Ltx as a therapeutic option. Finally, it was impossible to account for frailty and other medical contraindications that may preclude Ltx in individual patients, particularly those with advanced age.

This analysis underscores that there are not only learnings from the PFF-R, but also learnings for the PFF. Specifically, can the PFF be engaged in trying to understand and address this apparent shortfall in the utilization of LTx. Since there might be other factors that precluded transplant candidacy, consideration could be given to the addition of other data capture fields, particularly capture of lung transplant referral in the PFF-R. In addition to providing information on whether patients were being appropriately referred, this data may also lend insight into why referrals are not happening or why patients who are referred never achieve listing. As the PFF gears up to start enrollment in version 2.0 of the PFF-R, it is our sincere hope that this data will be captured, enabling improved understanding of the barriers to Ltx as a therapeutic option for IPF. Perhaps the PFF can also engage in education for both providers and patients on timely referral for Ltx.

Despite the limitations of the study, the data does seem to indicate that Ltx remains an underutilized treatment option for IPF. Improved patient education may better inform patients of their potential candidacy for Ltx prompting them to self-advocate for referral. Additionally, improved clinician education may help ILD physicians better understand whom and when to refer for Ltx evaluation. The GAP index was utilized in this analysis as it is the most commonly employed risk stratification calculator in IPF [6]. While the GAP index is easy to use and can provide risk stratification to presenting patients, given the limited variables incorporated, it

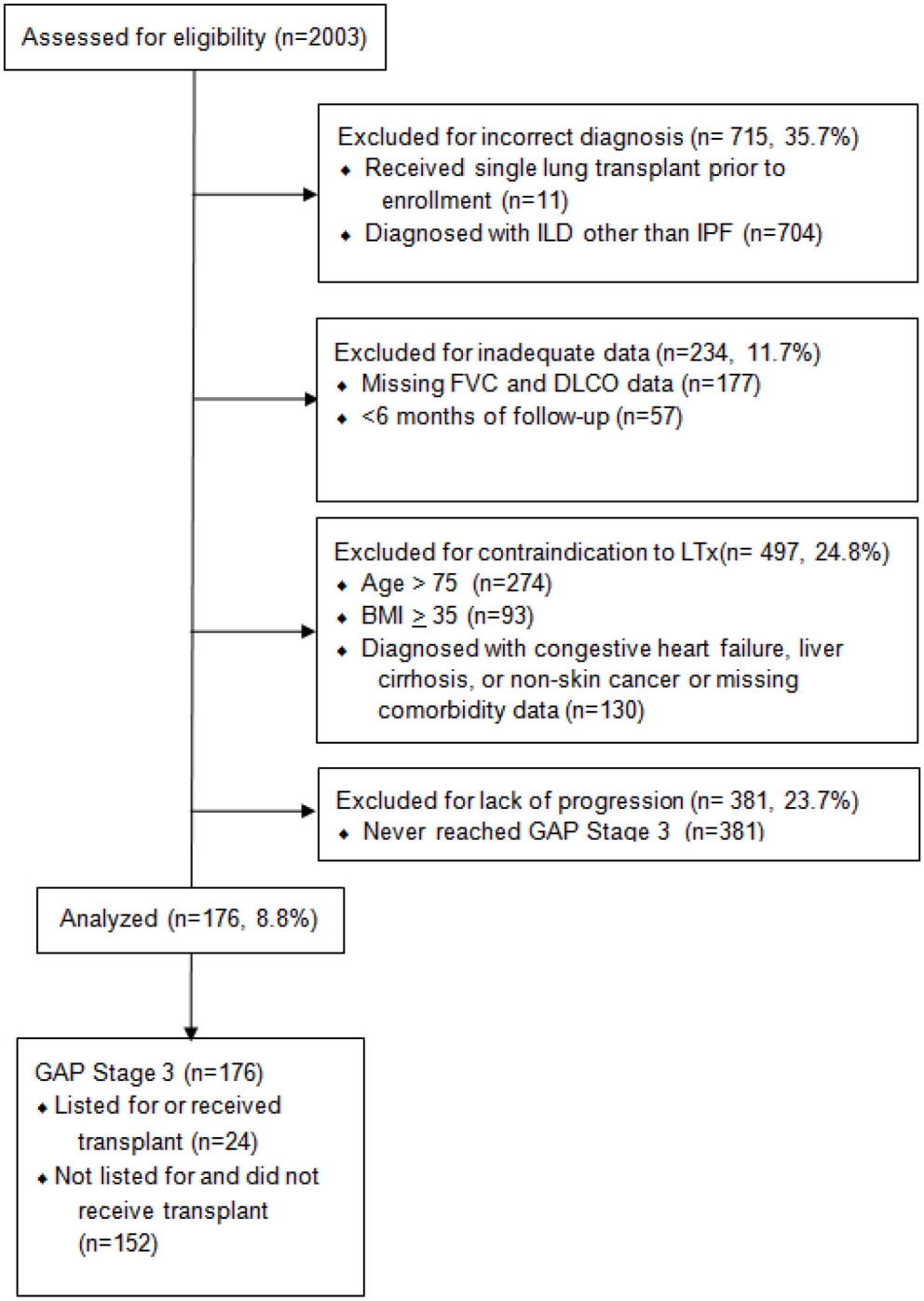

Fig. 2. CONSORT diagram showing the reasons for exclusion in the incident severe IPF population.

cannot adequately account for disease progression. Novel and facile risk stratification tools that more accurately reflect disease progression might enable providers to optimize timing of Ltx listing. While beyond the scope of this study, it would also be relevant to understand the factors that impact the progression from lung tx referral to listing in the IPF population to see if modifiable factors can be addressed systematically.

In conclusion, a minority of IPF patients included in the PFF-R who were seen at PFF Care Centers are listed for Ltx. Advanced age accounts for part of the underutilization of this potentially life-saving procedure. However, it is clear that there are other factors involved, some of which the PFF Patient Registry might not be equipped to capture. We suggest that there should be modifications to the PFF-R and further research in the PFF CCN to ensure that this management option is adequately explained and explored with

Table 4
Incident severe IPF population patient characteristics by lung transplant listing.

Column1	All	Listed for Lung Transplant	Not Listed for Lung Transplant
	N = 176	N = 24	N = 152
Age, years	70.1 (±3.4)	68.8 (±3.9)	70.3 (±3.3)
Age			
<65	10 (5.7%)	3 (12.5%)	7 (4.6%)
65–69	63(35.8%)	11 (45.8%)	52 (34.2%)
70–72	49 (27.8%)	5 (20.8%)	44 (29.0%)
73–75	54 (30.7%)	5 (20.8%)	49 (32.2%)
Male Gender	159 (90.3%)	23 (95.8%)	136 (89.5%)
Race			
White	159 (90.3%)	21 (87.5%)	138 (90.8%)
Black	5 (2.8%)	0 (0.0%)	5 (3.3%)
Other	12 (6.8%)	3 (12.5%)	9 (5.9%)
Ethnicity			
Hispanic	6 (3.4%)	0 (0.0%)	6 (4.0%)
Non-Hispanic	165 (93.8%)	23 (95.8%)	142 (93.4%)
Unknown	5 (2.8%)	1 (4.2%)	4 (2.6%)
Body Mass Index	27.4 (±3.9)	26.6 (±4.3)	27.5 (±3.9)
Percent Predicted FVC	53.2 (±11.2)	50.9 (±10.9)	53.5 (±11.3)
Percent Predicted DLCO	28.6 (±7.3)	28.3 (±6.1)	28.7 (±7.5)
Anti-fibrotic Use	128 (72.7%)	16 (66.7%)	112 (82.4%)
Pulmonary Rehab Enrollment	55 (31.3%)	7 (29.2%)	48 (31.6%)
Oxygen Use at Rest.	99 (56.3%)	15 (62.5%)	84 (55.3%)
Six Minute Walk Distance, meters (N = 110)	342.2 (±136.4)	392.7 (±131.4)	335.4 (±136.3)
Medical Comorbidities			
Diabetes	45 (25.6%)	2 (8.3%)	43 (28.3%)
Depression	22 (12.5%)	3 (12.5%)	19 (12.5%)
Coronary Artery Disease	64 (36.4%)	10 (41.7%)	54 (35.5%)
Insurance			
Private	26 (14.8%)	5 (20.8%)	21 (13.8%)
Medicare	134 (76.1%)	17 (70.8%)	117 (77.0%)
Other	16 (9.1%)	2 (8.4%)	14 (9.2%)
Distance to Nearest. Lung Transplant Center, miles (N = 175)	61.3 (±64.1)	65.0 (±81.1)	60.8 (±61.3)
PFF Care Center Status			
Lung Transplant Center	138 (78.4%)	19 (79.2%)	119 (78.3%)
Not a Lung Transplant Center	38 (21.6%)	5 (20.8%)	33 (21.7%)

*Categorical variables reported as number (%), Continuous variables reported as mean (standard deviation).
Abbreviations: DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; FVC = Forced Vital Capacity; IPF= Idiopathic pulmonary fibrosis; GAP= Gender, Age, and Physiology Score; PFF= Pulmonary Fibrosis Foundation.

Table 5
Univariable Associations Between Patient Characteristics and Lung Transplant Listing in Incident Severe IPF patients.

	Odds Ratio	95% Confidence Interval	p-value
Age			
Age, per 10 year increase	0.286	(0.083, 0.981)	0.0465**
Age, per 5 year increase	0.535	(0.288, 0.990)	0.0465**
Sex			
Male	Reference		
Female	0.370	(0.047, 2.923)	0.3456
Race			
White	Reference		
Black	N/A		
Other	2.190	(0.548, 8.750)	0.9671
Insurance			
Medicare	Reference		
Private	1.639	(0.545, 4.923)	0.4312
Other	0.983	(0.205, 4.709)	0.7435
Percent Predicted FVC, per 10%	0.809	(0.548, 1.194)	0.2853
Percent Predicted DLCO, per 10%	0.930	(0.515, 1.677)	0.8081
6-min Walk Distance, per 50 m	1.178	(0.938, 1.480)	0.1586
Oxygen Use at Rest.	1.349	(0.556, 3.273)	0.5077
Distance to Nearest. Transplant Center, per 10 miles	1.010	(0.946, 1.078)	0.7663
Transplant Center at PFF Care Center	1.054	(0.366, 3.035)	0.9227

**denotes statistical significance for an alpha <0.05.
Abbreviations: DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; FVC = Forced Vital Capacity; PFF = Pulmonary Fibrosis Foundation.

appropriate documentation of non-candidacy when Ltx is ruled out. Future registry studies should attempt to capture data on Ltx referral patterns and patient perspectives of Ltx, specifically to identify gaps in the access to lung transplant.

Author contribution statement

Christopher S. King – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Emily White – Conceived and designed the experiments, Performed the experiments, Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Alan Nyquist – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

A. Whitney Brown – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Joshua J Mooney – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Shambhu Aryal – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Oksana A. Shlobin – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Anju Singhal – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Christopher Thomas – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Vikramjit Khangoora – Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Kevin R. Flaherty – Conceived and designed the experiments, Performed the experiments, Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Steven D. Nathan - Conceived and designed the experiments, Performed the experiments, Conceived and designed the experiments, Analyzed and interpreted the data, Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank all patients who participated in the PFF Patient Registry. We also thank the investigators and other staff at participating PFF Care Centers for providing clinical data, the Pulmonary Fibrosis Foundation, which established and has maintained the PFF Registry since 2016, and lastly, the many generous donors to the PFF Registry.

References

[1] V. Cottin, Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases, Eur Respir Rev. 28 (2019), 190109.

[2] J.P. Finnerty, A. Ponnuswamy, P. Dutta, A. Abdelaziz, H. Kamil, Efficacy of antifibrotic drugs, nintedanib and pirfenidone, in treatment of progressive pulmonary fibrosis in both idiopathic pulmonary fibrosis (IPF) and non-IPF: a systematic review and meta-analysis, BMC Pulm. Med. 21 (2021) 411.

[3] T. Petnak, P. Lertjitbanjong, C. Thongprayoon, T. Moua, Impact of antifibrotic therapy on mortality and acute exacerbation in idiopathic pulmonary fibrosis A systematic review and meta-analysis, Chest 160 (5) (2021) 1751–1763.

[4] D.C. Chambers, W.S. Cherikh, M.O. Harhay, et al., The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult lung and heart–lung transplantation report – 2019; focus theme: donor and recipient size match, J. Heart Lung Transplant. 38 (2019) 1042–1055.

[5] L.E. Leard, A.M. Holm, M. Valapour, et al., Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation, J. Heart Lung Transplant. 40 (11) (2021) 1349–1379.

[6] B. Ley, C.J. Ryerson, E. Vittinghoff, et al., A multidimensional index and staging system for idiopathic pulmonary fibrosis, Ann. Intern. Med. 156 (10) (2012) 684–691.

[7] L. Paoletti, S. Palmer, E. Yow, et al., Underutilization of lung transplant referral among patients with newly diagnosed idiopathic pulmonary fibrosis (IPF), J. Heart Lung Transplant. 36 (4) (2017) S115 (Abstract only).

[8] Y. Liu, M. Vela, T. Rudakevych, et al., Patient factors associated with lung transplant referral and waitlist for patients with cystic fibrosis and pulmonary fibrosis, J. Heart Lung Transplant. 36 (2017) 264–271.

[9] https://www.pulmonaryfibrosis.org/pff-registry/pff-patient-registry. (Accessed 12 May 2023).

[10] J.L. Hankinson, J.R. Odencrantz, K.B. Fedan, Spirometric reference values from a sample of the general U.S. population, Am. J. Respir. Crit. Care Med. 159 (1) (1999 Jan) 179–187.

[11] R.O. Crapo, A.H. Morris, Standardized single breath normal values for carbon monoxide diffusing capacity, Am. Rev. Respir. Dis. 123 (2) (1981 Feb) 185–189.

[12] J.M. Schaenman, J.M. Diamond, J.R. Greenland, et al., Frailty and aging-associated syndrome in lung transplant candidates and recipients, Am. J. Transplant. 21 (2021) 2018–2024.

[13] A.J. Hayanga, J.K. Aboagye, H.E. Hayanga, et al., Contemporary analysis of early outcomes after lung transplantation in the elderly using a national registry, J. Heart Lung Transplant. 34 (2015) 182–188.

[14] M. Valapour, C.J. Lehr, M.A. Skeans, et al., OPTN/SRTR 2019 annual data report: lung, Am. J. Transplant. 21 (2021) 441–520.