Heart & Lung - The Journal of Acute and Critical Care 67 (2024) 92–99

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

The impact of time from ILD diagnosis to referral to the transplant center on the probability of inclusion in the transplant waiting list

Víctor M. Mora-Cuesta, PhD [a,*], Amaya Martínez-Meñaca, MD [b], Ángel González-Fernández, MD [c], David Iturbe-Fernández, MD [a], Sandra Tello-Mena, MD [a], Sheila Izquierdo-Cuervo, MD [a], Sonia Fernández-Rozas, MD [b], Pilar Alonso-Lecue, PhD [d], José M Cifrián-Martínez, PhD [a]

[a] Respiratory Department, Lung Transplant Unit, ERN-LUNG (European Reference Network on Rare Respiratory Diseases), Marqués de Valdecilla University Hospital, Avda. Valdecilla s/n. 39008, Santander, Spain
[b] Respiratory Department. ERN-LUNG (European Reference Network on Rare Respiratory Diseases), Marqués de Valdecilla University Hospital, Spain
[c] Schol of Medicine, University of Cantabria, Spain
[d] Valdecilla Research Institute (IDIVAL), Spain

ARTICLE INFO

Keywords:
Lung transplantation
Interstitial lung disease
Transplant center
Rehabilitation

ABSTRACT

Background: Lung transplant is a therapeutic option for patients with progressive interstitial lung disease (ILD).
Objectives: The objective of this study was to determine whether time from ILD diagnosis to referral to a transplant center influences the probability of being included in the transplant waiting list.
Methods: We performed a retrospective cohort study including all ILD patients evaluated as lung transplantation (LT) candidates at a lung transplant center between 01/01/2017 and 31/12/2022. The primary endpoint was the probability of being included in the lung transplant waiting list according to the time elapsed from diagnosis to referral to the transplant center.
Results: A total of 843 lung transplant requests were received, of which 367 (43.5%) were associated with ILD. Thirteen patients were excluded because they did not attend the first visit, whereas another 11 were excluded because some information was missing. As a result, our final sample was composed of 343 patients. The median time from diagnosis to referral was 29.4 (10.9 – 61.1) months. The overall probability of inclusion in the waiting list was 29.7%. By time from diagnosis to referral, the probability of inclusion in the waiting list was 48.1% for the patients referred ⟨ 6 months from diagnosis; 27.5% for patients referred 6 to 24 months from diagnosis; and 25.8% for patients referred ⟩ 24 months from diagnosis ($p = 0.007$).
Conclusions: Early referral to a lung transplant center seemed to increase the probability of being included in the lung transplant waiting list. Further research is needed in this topic.

Abbreviations

COPD	chronic obstructive pulmonary disease
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
ISHLT	International Society for Heart and Lung Transplantation
LT	lung transplantation
UIP	usual interstitial pneumoniae

Introduction

Interstitial lung diseases (ILDs) are a large, heterogeneous group of lung diseases with similar clinical, radiological and functional characteristics that primarily affect the interstitial space.[1–3] The estimated prevalence of ILD is 6.4–76.0 per 100,000 in Europe, and 74.3 per 100,000 in the United States.[4] However, there is great variability in the prevalence of these diseases in global terms.[5]

Of the more than 200 subtypes of ILD, idiopathic pulmonary fibrosis (IPF) is probably the most widely-known and studied disease, with an estimated survival at diagnosis of 2–5 years.[6,7] Currently, there are two approved antifibrotic treatments available for IPF (pirfenidone and nintedanib).[8–10] For other ILDs, apart from antifibrotic therapy, other treatments available include glucocorticoids, mycophenolate mofetil, tocilizumab, rituximab, azathioprine, and methotrexate, to name a few,

* Corresponding author.
E-mail address: victormanuel.mora@scsalud.es (V.M. Mora-Cuesta).

https://doi.org/10.1016/j.hrtlng.2024.04.022
Received 5 February 2024; Received in revised form 29 April 2024; Accepted 30 April 2024
Available online 11 May 2024

with different levels of evidence of efficacy for each entity.[2]

However, these treatments are not curative and they are occasionally ineffective in delaying disease progression.[11] It is estimated that 13–40% of ILD are progressive, with a prevalence of 2.2–20.0 per 100,000 inhabitants in Europe and 28.0 per 100,000 inhabitants in USA.[4] Therefore, lung transplantation (LT) should be considered as a therapeutic option for patients with progressive ILD, since it is the only treatment available for advanced disease, and the only that improves functionality significantly and increases survival.[12] Indeed, according to the International Society for Heart and Lung Transplantation (ISHLT), ILDs are the main indication for lung transplantation.[13] Additionally, due to the relentless progression of the disease, ILDs are the group with the highest waiting list mortality.[14–17] Along with cystic fibrosis, ILDs are the disease that most frequently require urgent LT.[18–20] To reduce waiting list mortality, some strategies, such as the Lung Allocation Score, have been developed to prioritize patients with interstitial diseases.[21]

Another essential strategy to guarantee transplantation in ILD patients is appropriate referral to the transplant center. The 2014 ISHLT Consensus document for the selection of LT candidates included evidence of UIP or fibrosing non-specific interstitial pneumonitis as referral criteria to LT, regardless of lung function.[22] The last update of the 2021 ISHLT Consensus document establishes as an indication for LT the availability of evidence of UIP or radiological evidence of probable or confirmed UIP, even though treatment is being initiated, in combination with other criteria (FVC $<$ 80% or DLCO $<$ 40%; need for oxygen therapy; functional decline; among others).[23] However, a significant number of ILD patients are referred with advanced-stage disease and are excluded as LT candidates.

The aim of this study was to assess whether time from ILD diagnosis to referral to the transplant center influences the probability of being listed for transplantation.

Methods

We performed a retrospective study of all ILD patients evaluated as lung transplant (LT) candidates in a lung transplant center (Hospital Universitario Marqués de Valdecilla, Santander, Spain) between 01/01/2017 and 31/12/2022. The identification of patients with interstitial diseases among the referred candidates was conducted by the medical coordinator of the hospital's lung transplant program, who has extensive experience in interstitial diseases and lung transplantation. The study was approved by the Ethics Committee (CEIm) of Cantabria under the study code 2022.202. Due to the retrospective and non-interventional nature of the study, along with loss to follow-up and mortality among some patients, the ethics committee granted exemption from informed consent.

Inclusion criteria and follow up

We included only patients who had been on follow-up for at least 6 months from the first visit. During follow-up, we considered the following situations: inclusion in the transplant waiting list (in which case they could have been transplanted, died while on the waiting list, or be waiting for transplantation); patients on pre-transplant evaluation; or who had completed follow-up in the transplant center (in which case, the reason for follow-up discontinuation was recorded).

In relation to decision-making, the local protocol of the transplant center requires that the decision about listing for transplantation must be made by a multidisciplinary team of specialists. This team meets weekly and is composed of specialists of the units of pulmonology, thoracic surgery, anesthesiology, rehabilitation, endocrinology and intensive care medicine. In case of absolute contraindication, discontinuation of pre-transplant follow-up without prior evaluation by the multidisciplinary team is allowed. Any other decision involving follow-up discontinuation for a reason other than patient's decision, death or absolute contraindication shall be made by the multidisciplinary team.

Endpoints and study variables

The primary endpoint was the probability of being included in the LT waiting list according to the time elapsed from diagnosis to referral to the transplant center. The date of ILD diagnosis was required to be available on the medical history of the patient prior to inclusion. The referral date for all candidates was obtained from the electronic medical records for each patient compiled by the hospital's admissions department. All patients are coded upon admission using the ICD-10 classification. Patients were divided into three groups according to the time from diagnosis to referral: $<$ 6 months, 6 – 24 months and $>$ 24 months. The time from referral to first visit was also collected.

An analysis was performed before and after March 2020 to examine the potential influence of the SARS-CoV-2 pandemic on the time from diagnosis to referral of ILD patients to the transplant center.

Other variables at first visit included were related to the demographic (age, sex) and anthropometric (height, weight), characteristics of ILD patients; cardiovascular risk factors (arterial hypertension, diabetes, dyslipidemia, tobacco use); disease-related variables (type of ILD, form of diagnosis, treatments received); and functional status (functional class, previous rehabilitation, lung function test). Although the GAP index (G = gender; A = age; P = physiology variables) was originally designed for IPF patients,[24] as functional test results are similar, the GAP index was calculated in all patients in the first visit.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics 20 software package. Continuous variables were expressed as means and +/- standard deviations for normally-distributed data, and as medians and interquartile ranges for non-normally distributed data (25th and 75th P). Categorical variables were presented as frequencies and percentages.

The Kolmogorov-Smirnov test was used to assess normal distribution in continuous quantitatve variables. Student's t-test was used to assess the association between a quantitative variable with normal distribution and a qualitative variable. Non-normally distributed quantitative data were compared with qualitative data using Mann Whitney U test. Chi-squared test was used for comparison of qualitative variables. Survival was assessed using the Kaplan-Meier test.

Binary logistic regression was performed to identify factors involved in listing for LT. Results were expressed as Odds Ratio (OR) and their 95% confidence intervals. The variables to be included in univariate analysis were selected based on the literature and our clinical and research experience. Variables with a $p < 0.05$ on univariate analysis were included on multivariate analysis by backward logistic regression.

A p value ≤ 0.05 was considered statistically significant.

Results

A total of 843 transplant evaluation requests were received by the lung transplant unit, of which 367 (43.5%) were associated with ILD. A total of 332 patients were excluded for COPD (chronic obstructive pulmonary disease); 45 for bronchiectasis; 30 for pulmonary arterial hypertension; 68 for other diseases, and one retransplantation candidate. Thirteen patients were excluded because they did not attend the first visit, whereas another 11 were excluded because some information was missing. Therefore, our final sample was composed of 343 lung transplantation candidates with ILD (Fig. 1).

Table 1 summarizes the characteristics of patients at first visit. Most were men (74.6%) diagnosed of IPF (53.6%), mostly with overweight or obesity (66.8%), with MRC-m functional class 2-3 (64.5%) and stage-2 GAP (45.2%). The most remarkable finding was that the median time from diagnosis to first visit was 29.4 (10.9 – 61.1) months. The median

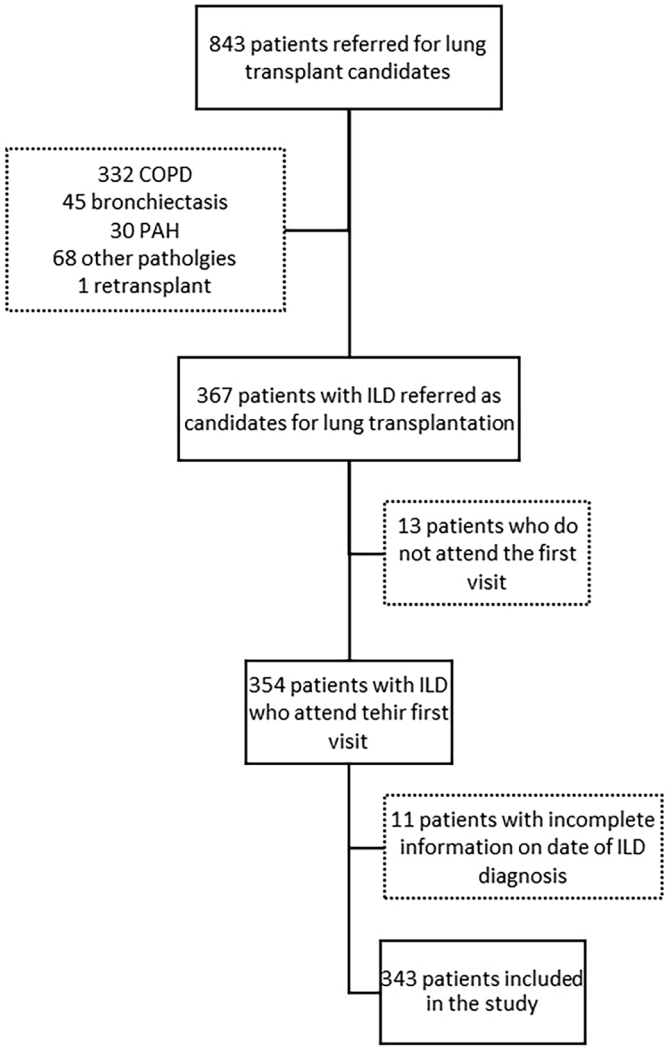

Fig. 1. Flow chart of patients referred as lung transplant candidates.

time from receipt of the evaluation request at the transplant center to first visit was 22 days[13– 35]. By type of condition, median time from diagnosis to referral to the transplant center was 21.8 (10.2 – 47.3) months for IPF patients; 57.4 (14.1 – 92.1) months for hypersensitivity pneumonitis; 23.2 months (8.3 – 53.8) for patients with other-cause pulmonary fibrosis; and 53.9 (36.4 – 99.1) months for the group of rheumatologic diseases.

A total of 184 patients (53.6%) were evaluated before March 2020 versus 159 (46.4%) after that date. The median time from diagnosis to referral to the transplant center before March 2020 was 33.2 (12.6 – 66.9 months) versus 22.4 (9.1 – 55.8) months for patients referred after March ($p = 0.033$)

Of the 343 patients, 102 (29.7%) were included on the waiting list at the date of last follow-up visit. Table 2 contains a comparison of the characteristics of patients listed and those who were not listed according to their characteristics at the first visit. Notably, the patients who were listed for a LT were slightly younger than those who were not included, were more frequently female, had higher GAP scores, cardiovascular risk factors, poorer pulmonary function tests and had taken part in a rehabilitation program more frequently.

According to the time from diagnosis to referral to the transplant center, the probability of being included on the waiting list was 48.1% for patients referred within the first six months, 27.5% for patients referred 6 to 24 months from diagnosis; and 25.8% for those referred more than 24 months after diagnosis ($p = 0.007$). (Fig. 2)

Table 3 contains logistic regression results for the variables potentially associated with a higher probability of being included in the LT waiting list. Although multiple variables reached statistical significance on univariate analysis, multivariate analysis only identified as independent variables having completed a rehabilitation program prior to referral [OR = 7.179 (3.284 – 15.694); $p < 0.001$] and DLCO [OR = 0.933 (0.898 – 0.969); $p < 0.001$]. Although the time from diagnosis to referral of less than 6 months was a significant factor for inclusion on the waiting list in the univariate analysis, it did not reach statistical significance in the multivariate analysis.

At the time of analysis, 89 (25.9%) patients underwent transplantation, 9 (2.6%) were on the LT waiting list, and 4 died while waiting for transplantation. On another note, 111 patients (32.4%) are still on pre-transplant follow-up and 130 (37.9%) discontinued follow-up. Of the 130 cases lost to follow up, reasons for discontinuation included patient's decision in 13 (10.0%) cases; disease stability in 6 (4.6%); death in 22 cases (16.9%), and absolute contraindication in 15 (11.5%) cases. Of the remaining 74 (56.9%), follow-up was discontinued by decision of the multidisciplinary transplant team due to a significant cumulative risk for a poor clinical course prior to transplantation. (Fig. 3)

Discussion

Our study examines the impact of time from ILD diagnosis to referral to the transplant center on the probability of being included in the LT waiting list. The 2014 ISHLT guidelines already recommended early referral after UIP diagnosis, due to the higher associated risk for a poor clinical course. However, these recommendations are based on expert opinions. To date, the impact of adherence to these guidelines on the probability of receiving a transplant had not been evaluated. This is of utmost importance, as UIP is the disease with the highest waiting list mortality.

Our results show that early referral of patients with ILD (<6 months from diagnosis) has an impact on the probability of being included in the LT waiting list. Hence, delayed referral to the transplant center has a strong impact on the probability of inclusion in the waiting list. Thus, the comparative study of the three groups of patients based on time from diagnosis to referral did not reveal any significant baseline differences between patients referred < 6 months and the others, except for ILD subtype and functional class. In the light of the results obtained, it is not striking that the patients referred < 6 months from diagnosis had more advanced disease than the others, which explains their higher probability of being included in the waiting list.

The fact that patients referred < 6 months from diagnosis was found to be associated with a higher probability of inclusion in the waiting list may be associated with other factors that are difficult to measure. Our lung transplantation center is the center of reference for an area that serves 6 million inhabitants. As a result, there are many professionals working at different hospitals of distinct levels of healthcare involved. In some hospitals, there are specialists of reference available for the referral and follow-up of LT candidates. These specialists often work in highly-specialized units and have extensive experience in the referral of LT candidates. In other lower-level hospitals, human and material resources are limited, and there are no professionals of reference available for the evaluation of potential LT candidates. As a result, referring physicians are not as experienced in patient selection as physicians working in higher-level hospitals. For these reasons, early referral, following ISHLT guidelines, is more probable in high-level hospitals where professionals of reference are available, with experience in candidate referral and pre-transplant preparation, including rehabilitation and vaccination, among others.

It should be taken into account that the study period includes the SARS-CoV-2 pandemic. During the pandemic, the overwhelming workload in pulmonology units may have resulted in delayed referral to the LT center. Surprisingly, time to referral was significantly shorter in

Table 1
Characteristics of patients with ILD at the time of the first consultation at the transplant center.

N	343
Sex	
Male	256 (74.6%)
Female	87 (25.4%)
Age at first visit (years)	61.5 (56.1 – 64.5)
Type of ILD	
Idiopathic pulmonary fibrosis	184 (53.6%)
Hypersensitivity pneumonitis	38 (11.1%)
Rheumatological diseases	39 (11.4%)
Idiopathic NSIP	11 (3.2%)
Hermansky-Pudlak syndrome	2 (0.6%)
Pulmonary fibrosis from other cause	69 (20.1%)
Diagnosis form of ILD	
Clinical-radiological	172 (50.1%)
Histological	171 (49.9%)
Transbronchial biopsy	36 (21.2%)
Cryobipsy	57 (33.5%)
Surgical biopsy	77 (45.3%)
Time from diagnosis to referral to the transplant center (months)	29.4 (10.9 – 61.1)
Time from diagnosis to referral to the transplant center	
< 6 months	52 (15.2%)
6–24 months	109 (31.8%)
> 24 months	182 (53.1%)
Time from the evaluation request to the first visit (days)	22 (13 – 35)
Weight (kg)	77.4 ± 14.74
Height (cm)	170 (163 – 175)
BMI (kg/m^2)	27.1 (24.3 – 30.1)
WHO weight classification	
Under weight (< 18.5 kg/m^2)	3 (0.9%)
Normal weight (18.5–24.99 kg/m^2)	102 (29.7%)
Overweight (25–29.99 kg/m^2)	153 (44.6%)
Obesity grade I (30–34.99 kg/m^2)	76 (22.2%)
Obesity grade II (35–39.99 kg/m^2)	7 (2.0%)
Obesity grade III (> 40 kg/m^2)	2 (0.6%)
Arterial hypertension	82 (23.9%)
Diabetes	55 (16.0%)
Dyslipidemia	158 (46.1%)
Smoking	
Never smoker	64 (18.7%)
Former smoker	277 (80.8%)
Active smoker	2 (0.6%)
Accumulated consumption (pack-year)	30 (17 – 40)
Rehabilitation before referral	148 (43.1%)
Antifibrotic treatment	179 (52.2%)
Corticosteroids	142 (41.9%)
Mycophenolate mofetil	37 (11.1%)
Azathioprine	14 (4.2%)
Other immunosuppressants	26 (7.6%)
Functional class (m-MRC)	
0	22 (6.4%)
1	53 (15.5%)
2	118 (34.4%)
3	100 (29.2%)
4	50 (14.6%)
FVC (%)	68.4 ± 21.6
DLCO (%)	34 (26 – 46)
TLC (%)	65.1 (55 – 80)
6MWT (meters)	479.5 (378 – 540)
$PaCO_2$ (mmHg)	38.0 ± 4.6
PaO_2 (mmHg)	71.8 ± 15.4
PaO_2 classification	
< 60 mmHg	21.4%
60–80 mmHg	48.1%
> 80 mmHg	30.5%
GAP index (points)	4 (3 – 5)
GAP index	
Stage I (0–3 points)	133 (38.8%)
Stage II (4–5 points)	155 (45.2%)
Stage III (6–8 points)	55 (16.0%)

ILD = interstitial lung disease; kg = kilograms; cm = centimeters; BMI = body mass index; m^2 = square meter; WHO = World Health Organization; m-MRC = modified medical research council; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; TLC = total lung capacity; 6MWT = six minute walking test; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide.

Table 2
Characteristics of the patients at the first visit based on whether or not they were included in the waiting list for lung transplantation.

	All	Inclusion in the waiting list	Non-inclusion in the waiting list	*p*
N	343	102 (29.7%)	241 (70.3%)	–
Age (years)	61.4 (56.1 – 64.5)	60.3 (54.7 – 62.6)	61.9 (56.4 – 64.9)	0.001
Sex				0.010
Male	256 (74.6%)	67 (65.7%)	189 (78.4%)	
Female	87 (25.4%)	35 (34.3%)	52 (21.6%)	
Type of ILD				0.050
IPF	184 (53.6%)	45 (44.1%)	139 (57.7%)	
HP	38 (11.1%)	17 (16.7%)	21 (8.7%)	
Other-cause PF	82 (23.9%)	29 (28.4%)	53 (22%)	
Rheumat. diseases	39 (11.4%)	11 (10.8%)	28 (11.6%)	
GAP	4 (3 – 5)	4 (4 – 5)	4 (3 – 5)	<0.001
GAP				0.001
Stage I	132 (38.6%)	24 (23.5%)	108 (45%)	
Stage II	155 (45.3%)	58 (56.9%)	97 (40.4%)	
Stage III	55 (16.1%)	20 (19.6%)	35 (14.6%)	
Time from diagnosis to referral to the transplant center (months)	29.4 (10.9 – 61.1)	23.7 (6.9 – 58.9)	30.5 (12.5 – 67.1)	0.062
Time from diagnosis to referral to the transplant center				0.007
< 6 months	52 (15.2%)	25 (48.1%)	27 (51.9%)	
6 – 24 months	109 (31.8%)	30 (27.5%)	79 (72.5%)	
> 24 months	182 (53.1%)	47 (25.8%)	135 (74.2%)	
Diagnosis form of ILD				0.011
Clinical-Radiological	172 (50.1%)	41 (40.2%)	131 (54.4%)	
Histological	171 (49.9%)	61 (59.8%)	110 (45.6%)	
Functional class (m-MRC)				0.090
0	22 (6.4%)	3 (2.9%)	19 (7.9%)	
1	53 (15.5%)	11 (10.8%)	42 (17.4%)	
2	118 (34.4%)	35 (34.3%)	83 (34.4%)	
3	100 (29.2%)	38 (37.3%)	62 (25.7%)	
4	50 (14.6%)	15 (14.7%)	35 (14.5%)	
BMI (kg/m^2)	27.1 (23.3 – 30.0)	27.3 (24.5 – 29.3)	26.9 (24.3 – 30.7)	0.693
Arterial hypertension	82 (23.9%)	14 (13.7%)	68 (28.2%)	0.002
Diabetes	55 (16%)	8 (7.8%)	47 (19.5%)	0.004
Dyslipidemia	158 (46.1%)	53 (52.0%)	105 (43.6%)	0.096
Smoking				0.449
Never smoker	64 (18.7%)	22 (21.6%)	42 (17.4%)	
Active smoker	2 (0.6%)	0 (0%)	2 (0.8%)	
Former smoker	277 (80.8%)	80 (78.4%)	197 (81.7%)	
Accumulated consumption (pack-year)	30 (17 – 40)	30 (20 – 44.25)	29 (15 – 40)	0.632
Rehabilitation	148 (43.1%)	79 (77.5%)	69 (28.6%)	< 0.001
Antifibrotic treatment	179 (52.2%)	50 (49%)	129 (53.5%)	0.259
FVC (%)	67.0 (52.0 – 81.1)	58.3 (47.5 – 71)	71.4 (55 – 89)	<0.001
DLCO (%)	34 (26 – 46)	27 (20.9 – 34.2)	38.8 (28.5 – 50.9)	<0.001
6MWT (meters)	479.5 (378 – 540)	469 (377.2 – 525)	484 (377.5 – 545)	0.200
PaO_2 (mmHg)	72 (61 – 83)	66 (59 – 72.1)	76 (63.3 – 86.9)	<0.001
$PaCO_2$ (mmHg)	38 (35 – 41)	38 (35 – 41)	38 (34.7 – 40.8)	0.706

ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; HP = hypersensitivity pneumonitis; PF = pulmonary fibrosis; BMI = body mass index; m^2 = square meter; m-MRC = modified medical research council; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; 6MWT = six minute walking test; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide.

patients referred after March 2020, as compared to patients referred before the pandemic. This could be explained by the so-called 'era effect'. In other words, over the years, with the implementation of improvements, increased dissemination of recommendations, and better training of professionals, there is an impact on healthcare improvement.

It is remarkable that time from diagnosis to referral was > 2 years, despite the fact that half the patients had IPF. These patients are the paradigm of patients with a radiological and histological pattern of UIP; therefore, these patients should have been referred to the transplant center at diagnosis, as established in ISHLT guidelines. However, IPF patients were referred earlier than patients with hypersensitivity pneumonitis (4 year-delay), and the high delay in referral (53.9 months, i.e. > 4 years) of patients with connective tissue disorders is also surprising. The ISHLT recommends earlier referral of this subgroup of patients to evaluate extrapulmonary manifestations.

The decision to refer a patient as a LT candidate is challenging and involves a thorough evaluation of the patient. Factors to be considered are disease-related; along with socioeconomic, functional, emotional, anatomical, immunological, and microbiological factors, to name a few. Therefore, referral to the transplant center should be performed with enough time to be able to perform a condition prior to transplantation. Time to referral is of special relevance for patients with interstitial diseases, as they are most frequently progressive. To facilitate decision-making, the ISHLT developed a set of referral criteria for lung transplantation. However, in the light of the results obtained, adherence to ISHLT recommendations is poor.

As mentioned above, the evaluation of candidates to transplantation is complex and includes very relevant factors, some of which may be modifiable. For example, there is evidence that patients with a low socioeconomic status have more limited access to pulmonary transplant[25] or may even have poorer post-transplant outcomes.[26] With enough time, adequate social support can be provided to these candidates. In addition, low body weight and obesity at the moment of transplantation have been associated with poorer post-transplant survival.[27,28] In contrast, loss of weight in obese candidates is associated with improved outcomes.[29,30] It is worth mentioning that only 29.7% of patients in our study had a normal body weight at the first visit. However, improving the nutritional status of candidates prior to transplantation also requires time. Mental disorders are highly prevalent among candidates to LT due to the emotional impact of facing a transplant.[31] Again, a correct approach also requires time. Coronary arterial disease is not infrequent among LT candidates. When adequately treated, patients with

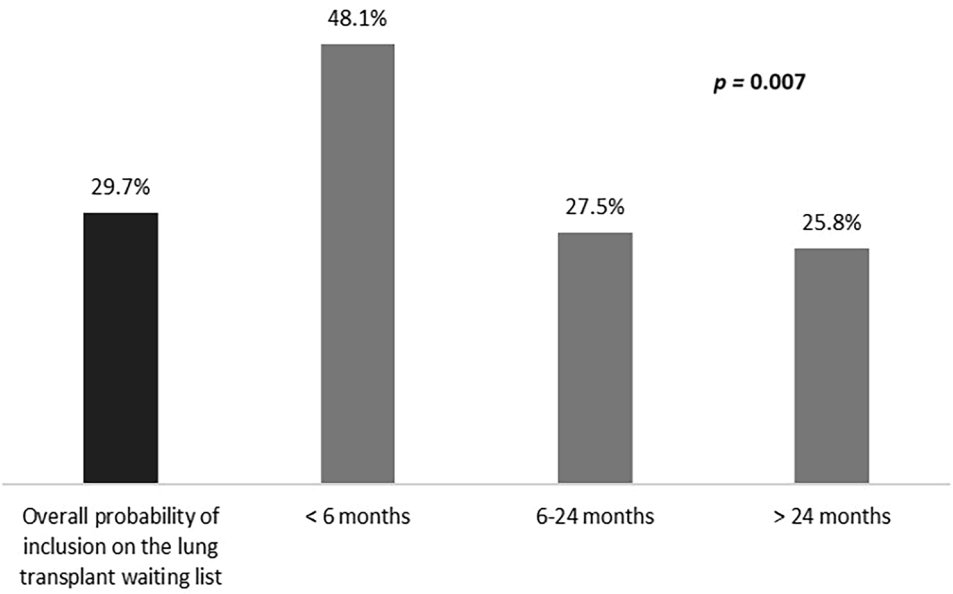

Fig. 2. Probability of inclusion in the waiting list according to the time from diagnosis of ILD to referral to the transplant center.

pre-transplant coronary arterial disease have similar outcomes as other candidates.[32–36] However, both, the revascularization process and duration of dual anti-platelet therapy are time-consuming, and time is crucial in LT.

One of the most important pre-transplant interventions is rehabilitation. Thus, there is evidence that rehabilitation improves patient's quality of life, tolerance to physical exercise and clinical outcomes after the procedure.[37–39] At referral, only 43.1% of patients had been referred to a respiratory rehabilitation program. It is striking that we did not find any differences across the three groups of time to referral, in terms of previous rehabilitation. Up to 40.4% of patients referred < 6 months from diagnosis had already been evaluated for rehabilitation. Indeed, having completed a rehabilitation program prior to referral was the independent factor that best predicted the probability of inclusion in the LT waiting list. This factor had a higher predictive value than the characteristics of the disease, pharmacological treatments, cardiovascular risk factors, or functional status.

Inter-hospital coordination is essential, given the geographic dispersion of pulmonary transplant centers. The timing of listing by the transplant center is as relevant as appropriate referral by the referring center. To increase adherence to ISHLT referral criteria, several online sessions have been held in our center in the last two years between the

Table 3
Logistic regression analysis of variables related to inclusion in the waiting list for lung transplantation.

	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	0.964	0.934 – 0.994	0.020	–	–	–
Sex (male)	0.014	0.316 – 0.878	0.014	–	–	–
GAP						
Stage I	0.389	0.192 – 0.787	0.009	–	–	–
Stage II	0.889	0.553 – 1.981	0.889	–	–	–
Stage III	Ref.	–	–	–	–	–
Functional class						
0	Ref.	–	–	–	–	–
1	1.659	0.414 – 6.639	0.474	–	–	–
2	2.671	0.742 – 9.607	0.133	–	–	–
3	3.882	1.076 – 14.001	0.038	–	–	–
4	2.714	0.697 – 10.571	0.150	–	–	–
BMI	1.010	0.984 – 1.038	0.446			
Arterial hypertension	0.405	0.216 – 0.760	0.005	–	–	–
Diabetes	0.351	0.160 – 0.773	0.009	–	–	–
Dyslipidemia	1.401	0.880 – 2.229	0.155			
Rehabilitation	8.562	4.980 – 14.720	<0.001	7.179	3.284 – 15.694	< 0.001
Antifibrotic therapy	0.445	0.525 – 1.327	0.445			
Corticosteroids	1.740	1.084 – 2.791	0.022	–	–	–
FVC (%)	0.966	0.953 – 0.979	< 0.001	0.980	0.959 – 1.002	0.077
DLCO (%)	0.934	0.911 – 0.957	< 0.001	0.933	0.898 – 0.969	< 0.001
6MWT	0.999	0.997 – 1.001	0.549			
PaO_2	0.960	0.941 – 0.979	< 0.001	–	–	–
$PaCO_2$	1.011	0.954 – 1.071	0.711			
Time from diagnosis to referral to the transplant center						
< 6 months	2.660	1.406 – 5.030	0.003	–	–	–
6 – 24 months	1.091	0.638 – 1.864	0.751			
> 24 months	Ref.	–	–			

BMI = body mass index; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; 6MWT = six minute walking test; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide.

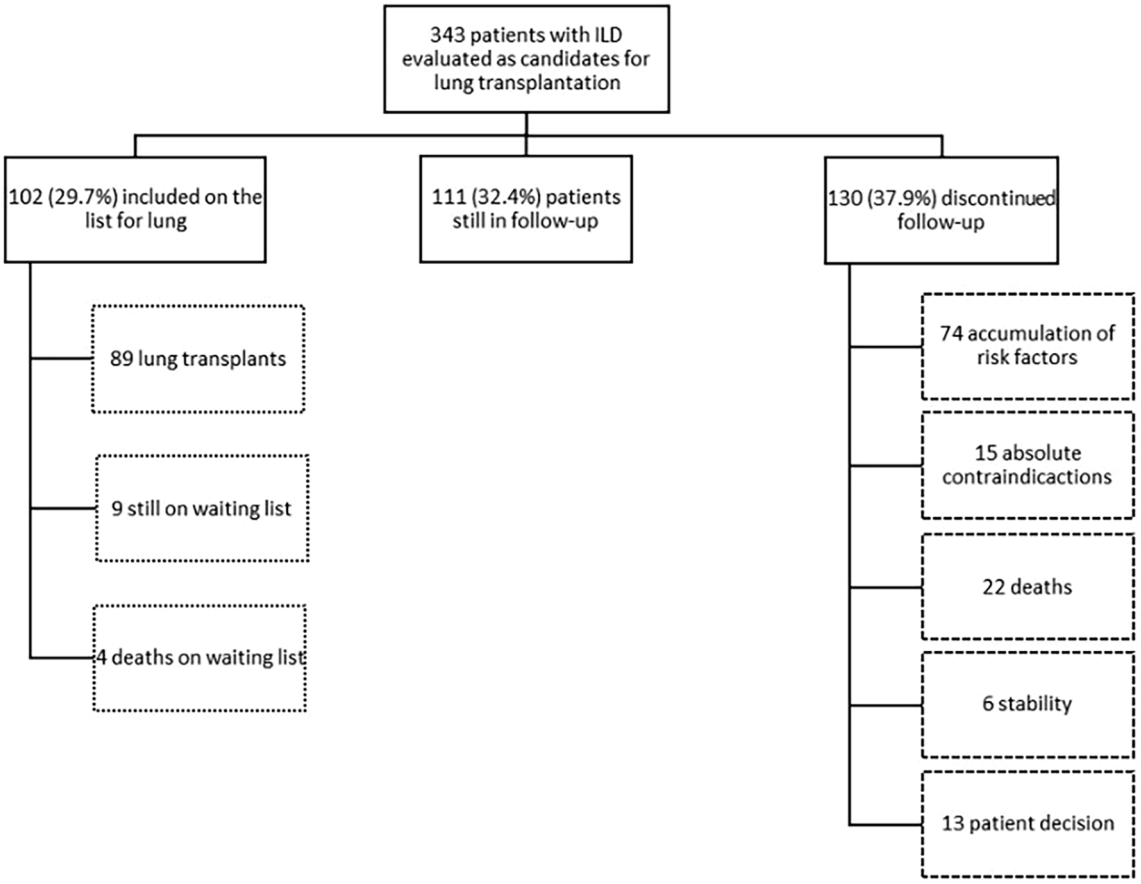

Fig. 3. Follow-up of patients with ILD evaluated as candidates for lung transplantation.

transplant center and referring centers to raise awareness about the referral criteria for the most frequent entities. In addition, apart from the ISHLT consensus document, other clinical guidelines and consensus documents should make emphasis on these criteria. For example, the latest ATS/ERS/JRS/ALAT clinical guidelines for the management of IPF consider referral to the transplant center at diagnosis among treatment options, but only in cases of "increased risk of mortality".[40] This specification is not included in ISHLT recommendations, and IPF is a severe disease with a poor 5-year prognosis where LT should be considered. The Spanish guidelines for the pharmacological management of IPF do not include this requirement either. Thus, its treatment algorithm suggests that referral to the transplant center is performed in advanced stages of the disease.[41]

Limitations and strengths

Although our results are of special relevance, they should be considered cautiously due to the limitations of the study. Firstly, it is a single-center study. Therefore, decision-making about listing is made by a sole transplant team. Although this team has 25-year experience, decisions are based on its experience and resources available. Additionally, it is a retrospective study, and some information was missing in relation to the study variables. In this study, we examined referral to the transplant center. The LT team has room for maneuver beyond the dissemination of information, as the final decision about referral falls on the referring physician; therefore, there was broad variability in referrals. Socioeconomic factors were not evaluated. However, the Spanish healthcare system is public, and all citizens, regardless of their socioeconomic status, have access to lung transplantation. On the other hand, the study has several strengths: it was conducted in a center with over 25 years of experience in lung transplantation, with a high transplant volume (over 40 per year), and in one of the world's leading countries in terms of the number of donors and transplant procedures performed. Additionally, a large number of variables have been included, enabling robust conclusions to be drawn.

Conclusion

It seems that an early referral of patients with advanced ILD to transplant units could impact the probability of being listed for lung transplantation.

Statement of ethics

This study was approved by the Drug Research Ethics Committee of Cantabria (Spain) and coordinated by the Valdecilla Research Institute (IDIVAL, Instituto de Investigación Valdecilla), with protocol code 2022.202.

Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Víctor M. Mora-Cuesta: Conceptualization, Methodology, Formal

analysis, Investigation, Writing – original draft. **Amaya Martínez-Meñaca:** Writing – original draft, Methodology, Investigation. **Ángel González-Fernández:** Writing – original draft, Methodology, Investigation. **David Iturbe-Fernández:** Writing – review & editing, Investigation. **Sandra Tello-Mena:** Writing – review & editing, Investigation. **Sheila Izquierdo-Cuervo:** Writing – review & editing, Investigation. **Sonia Fernández-Rozas:** Investigation. **Pilar Alonso-Lecue:** Project administration. **José M Cifrián-Martínez:** Supervision, Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

References

1. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev*. 2018;27(150), 180076. https://doi.org/10.1183/16000617.0076-2018 [Internet].
2. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med*. 2020;383(10):958–968.
3. Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. *Lancet*. 2022;400(10354):769–786.
4. Olson A, Hartmann N, Patnaik P, et al. Estimation of the prevalence of progressive fibrosing interstitial lung diseases: systematic literature review and data from a physician survey. *Adv Ther*. 2021;38(2):854–867.
5. Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in global prevalence of interstitial lung disease. *Front Med*. 2021;8 (Lausanne).
6. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med*. 2014;2(7):566–572. https://doi.org/10.1016/S2213-2600(14)-70101-8 [Internet].
7. Kaunisto J, Salomaa ER, Hodgson U, Kaarteenaho R, Myllärniemi M. Idiopathic pulmonary fibrosis–a systematic review on methodology for the collection of epidemiological data. *BMC Pulm Med*. 2013;13:53. https://doi.org/10.1186/1471-2466-13-53.
8. Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. *Adv Ther*. 2018;35(5):724–736. https://doi.org/10.1007/s12325-018-0693-1 [Internet].
9. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071–2082.
10. King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083–2092.
11. George PM, Spagnolo P, Kreuter M, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. *Lancet Respir Med*. 2020;8(9):925–934.
12. George PM, Patterson CM, Reed AK, Thillai M. Lung transplantation for idiopathic pulmonary fibrosis. *Lancet Respir Med*. 2019;7(3):271–282. https://doi.org/10.1016/S2213-2600(18)30502-2 [Internet].
13. Perch M, Hayes Jr D, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-ninth adult lung transplantation report-2022; focus on lung transplant recipients with chronic obstructive pulmonary disease. *J Heart Lung Transplant*. 2022;41(10):1335–1347. https://doi.org/10.1016/j.healun.2022.08.007. Epub 2022 Aug 20. PMID: 36050206; PMCID: PMC10257980.
14. Valapour M, Lehr CJ, Schladt DP, et al. OPTN/SRTR 2021 annual data report: lung. *Am J Transplant*. 2023;23(2):S379–S442. https://doi.org/10.1016/j.ajt.2023.02.009. Suppl 1PMID: 37132345; PMCID: PMC9970343.
15. Hirama T, Akiba M, Watanabe T, et al. Waiting time and mortality rate on lung transplant candidates in Japan: a single-center retrospective cohort study. *BMC Pulm Med*. 2021;21:390. https://doi.org/10.1186/s12890-021-01760-8.
16. Deitz RL, Emerel L, Chan EG, et al. Waitlist mortality and extracorporeal membrane oxygenation bridge to lung transplant. *Ann Thorac Surg*. 2023;116(1):156–162. https://doi.org/10.1016/j.athoracsur.2023.02.062. Epub 2023 Mar 31. PMID: 37004804.
17. Bennett D, Fossi A, Bargagli E, et al. Mortality on the waiting list for lung transplantation in patients with idiopathic pulmonary fibrosis: a single-centre experience. *Lung*. 2015;193(5):677–681. https://doi.org/10.1007/s00408-015-9767-x. Epub 2015 Jul 28. PMID: 26216722.
18. Tang A, Thuita L, Siddiqui HU, et al. Urgently listed lung transplant patients have outcomes similar to those of electively listed patients. *J Thorac Cardiovasc Surg*. 2020;S0022-5223(20). https://doi.org/10.1016/j.jtcvs.2020.02.140, 30997-1Epub ahead of print. PMID: 32622567.
19. Orsini B, Sage E, Olland A, et al. High-emergency waiting list for lung transplantation: early results of a nation-based study. *Eur J Cardiothorac Surg*. 2014;46(3):e41–e47. https://doi.org/10.1093/ejcts/ezu259. discussion e47.Epub 2014 Jul 3. PMID: 24994754.
20. Schiavon M, Faggi G, Rosso L, et al. Outcomes and risk factors identification in urgent lung transplantation: a multicentric study. *J Thorac Dis*. 2019;11(11):4746–4754. https://doi.org/10.21037/jtd.2019.10.55. PMID: 31903264; PMCID: PMC6940257.
21. Gottlieb J. Lung allocation. *J Thorac Dis*. 2017;9(8):2670–2674. https://doi.org/10.21037/jtd.2017.07.83. PMID: 28932574; PMCID: PMC5594149.
22. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34(1):1–15. https://doi.org/10.1016/j.healun.2014.06.014. Epub 2014 Jun 26. PMID: 25085497.
23. Leard LE, Holm AM, Valapour M, 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*. 2021;40(11):1349–1379. https://doi.org/10.1016/j.healun.2021.07.005. Epub 2021 Jul 24. PMID: 34419372; PMCID: PMC8979471.
24. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med*. 2012;156(10):684–691. https://doi.org/10.7326/0003-4819-156-10-201205150-00004. PMID: 22586007.
25. Lehr CJ, Fink AK, Skeans M, et al. Impact of Socioeconomic position on access to the U.S. lung transplant waiting list in a matched cystic fibrosis cohort. *Ann Am Thorac Soc*. 2020;17(11):1384–1392. https://doi.org/10.1513/AnnalsATS.202001-030OC. PMID: 32649218; PMCID: PMC7787007.
26. Malas J, Chen Q, Megna D, et al. Lung transplantation outcomes in patients from socioeconomically distressed communities. *J Heart Lung Transplant*. 2023;S1053-2498(23). https://doi.org/10.1016/j.healun.2023.07.007, 01938-1Epub ahead of print. PMID: 37481047.
27. Lederer DJ, Wilt JS, D'Ovidio F, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med*. 2009;180(9):887–895. https://doi.org/10.1164/rccm.200903-0425OC. Epub 2009 Jul 16. PMID: 19608717; PMCID: PMC2773915.
28. Singer JP, Peterson ER, Snyder ME, et al. Body composition and mortality after adult lung transplantation in the United States. *Am J Respir Crit Care Med*. 2014;190(9):1012–1021. https://doi.org/10.1164/rccm.201405-0973OC. PMID: 25233138; PMCID: PMC4299586.
29. Chandrashekaran S, Keller CA, Kremers WK, Peters SG, Hathcock MA, Kennedy CC. Weight loss prior to lung transplantation is associated with improved survival. *J Heart Lung Transplant*. 2015;34(5):651–657. https://doi.org/10.1016/j.healun.2014.11.018. Epub 2014 Nov 17. PMID: 25578626; PMCID: PMC4417392.
30. Clausen ES, Frankel C, Palmer SM, Snyder LD, Smith PJ. Pre-transplant weight loss and clinical outcomes after lung transplantation. *J Heart Lung Transplant*. 2018;37(12):1443–1447. https://doi.org/10.1016/j.healun.2018.07.015. Epub 2018 Jul 29. PMID: 30228085; PMCID: PMC6653635.
31. Søyseth TS, Lund MB, Bjørtuft Ø, et al. Psychiatric disorders and psychological distress in patients undergoing evaluation for lung transplantation: a national cohort study. *Gen Hosp Psychiatry*. 2016;42:67–73. https://doi.org/10.1016/j.genhosppsych.2016.07.001. Epub 2016 Jul 8. PMID: 27638975.
32. Makey IA, Sui JW, Huynh C, Das NA, Thomas M, Johnson S. Lung transplant patients with coronary artery disease rarely die of cardiac causes. *Clin Transplant*. 2018;32(9):e13354. https://doi.org/10.1111/ctr.13354. Epub 2018 Aug 30. PMID: 30022532.
33. Sinha N, Balayla G, Braghiroli J. Coronary artery disease in lung transplant patients. *Clin Transplant*. 2020;34(11):e14078. https://doi.org/10.1111/ctr.14078. Epub 2020 Oct 4. PMID: 32940380.
34. Franz M, Siemeni T, Aburahma K, et al. Lung transplant and severe coronary artery disease: results from a single-centre experience. *Eur J Cardiothorac Surg*. 2022;62(2):ezac348. https://doi.org/10.1093/ejcts/ezac348. PMID: 35703921.
35. Aggarwal R, Jackson S, Lemke NT, et al. Lung Transplant Recipients With Prior Coronary Artery Bypass Grafting Are At Increased Risk Of Death And Early Perioperative Hemorrhage. *Semin Thorac Cardiovasc Surg*. 2022;34(2):763–770. https://doi.org/10.1053/j.semtcvs.2021.03.048. Epub 2021 May 21. PMID: 34023526.
36. McKellar SH, Bowen ME, Baird BC, Raman S, Cahill BC, Selzman CH. Lung transplantation following coronary artery bypass surgery-improved outcomes following single-lung transplant. *J Heart Lung Transplant*. 2016;35(11):1289–1294. https://doi.org/10.1016/j.healun.2016.05.029. Epub 2016 Jun 14. PMID: 27381675.
37. Hoffman M, Chaves G, Ribeiro-Samora GA, Britto RR, Parreira VF. Effects of pulmonary rehabilitation in lung transplant candidates: a systematic review. *BMJ Open*. 2017;7(2), e013445. https://doi.org/10.1136/bmjopen-2016-013445. PMID: 28159852; PMCID: PMC5294003.
38. Hume E, Ward L, Wilkinson M, Manifield J, Clark S, Vogiatzis I. Exercise training for lung transplant candidates and recipients: a systematic review. *Eur Respir Rev*. 2020;29(158), 200053. https://doi.org/10.1183/16000617.0053-2020. PMID: 33115788; PMCID: PMC9488968.
39. Polastri M, Dell'Amore A, Eden A, Pehlivan E. Does preoperative rehabilitation influence the quality of life in patients who are candidates for lung transplant? *Exp Clin Transplant*. 2022;20(6):543–548. https://doi.org/10.6002/ect.2022.0039. PMID: 35791828.
40. 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;205(9):e18–e47. https://doi.org/10.1164/rccm.202202-0399ST. PMID: 35486072; PMCID: PMC9851481.
41. Xaubet A, Molina-Molina M, Acosta O, et al. Guidelines for the medical treatment of idiopathic pulmonary fibrosis. *Arch Bronconeumol*. 2017;53(5):263–269. https://doi.org/10.1016/j.arbres.2016.12.011. English, SpanishEpub 2017 Mar 11. Erratum in: Arch Bronconeumol. 2017 Nov;53(11):657-658. PMID: 28292522.