Secondary Pulmonary Hypertension Among Patients Qualified for Lung Transplantation: Single-Center Study

Tomasz Stącel[a], Maciej Urlik[a], Mirosław Nęcki[a], Remigiusz Antończyk[a,b], Magdalena Latos[a,b], Marta Wajda-Pokrontka[a,b,*], Zofia Tatoj[a,b], Fryderyk Zawadzki[a,b], Piotr Przybyłowski[a,c], Marian Zembala[a,b], and Marek Ochman[a,b]

[a]Silesian Centre for Heart Diseases, Zabrze, Poland; [b]Department of Cardiac, Vascular, and Endovascular Surgery and Transplantology, Medical University of Silesia, Katowice, Poland; and [c]First Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland

ABSTRACT

Introduction. Secondary pulmonary hypertension (PH) is a serious complication of end-stage lung disease and is associated with unfavorable prognosis. The aim of the study was to evaluate the incidence and severity of secondary PH among patients qualified for lung transplantation (LTx).

Material and Methods. The study population consisted of 143 patients qualified for LTx between 2004 and 2019. Analyzed medical records included results collected during the qualification process (eg, echocardiography parameters, right heart catherization [RHC]). There were 37.8% (n = 54) of patients with chronic obstructive pulmonary disease (COPD), 58.7% (n = 84) of patients with interstitial lung diseases (ILDs), and 3.5% (n = 5) of patients with combined pulmonary fibrosis and emphysema (CPFE). The inclusion criteria were ILDs, COPD or CPFE diagnosis, and the presence of RHC data preformed during qualification for LTx. The exclusion criteria were lack of RHC results and diagnosis of idiopathic pulmonary artery hypertension, pulmonary artery hypertension associated with connective tissue disease, cystic fibrosis, or bronchiectasis.

Results. PH was detected among 60.1% (n = 86) of patients qualified for LTx. The prevalence of PH was 39% (n = 18) vs 76.19% (n = 64) in the COPD vs ILDs groups, respectively. Both ILDs and COPD patients presented with similar mean artery pulmonary pressure (36.3 ± 9.61 vs 34.78 ± 11.47 mm Hg; not statistically significant). Severe PH was more frequent in the ILDs group than in the COPD group (60.94% vs 38.89%).

Conclusions. PH is commonly diagnosed in patients with chronic lung diseases qualified for LTx and more often observed among patients qualified because of ILDs. It is important to assess the pulmonary pressure because of frequent occurrence of PH among patients referred for LTx.

CHRONIC obstructive pulmonary disease (COPD), interstitial lung diseases (ILDs), and combined pulmonary fibrosis and emphysema (CPFE) are the most common diagnoses related to pulmonary hypertension (PH). Patients with co-occurrence of end-stage lung disease and PH (defined as a mean pulmonary artery pressure [mPAP] of ≥25 mm Hg at rest measured during right heart catherization [RHC]), are classified by European Society of Cardiology (ESC)/European Resuscitation Council (ERC) guidelines as group 3 of PH: "pulmonary hypertension associated with lung diseases and/or hypoxemia" [1]. The appearance of PH affects lung disease, resulting in worse prognosis and clinical manifestations [2,3]. The population

*Address correspondence to Marta Wajda-Pokrontka, Department of Cardiac, Vascular and Endovascular Surgery, and Transplantology, Silesian Center for Heart Diseases, Curie-Skłodowskiej 9, 41-800, Zabrze, Poland. E-mail: marta.wajda93@gmail.com

0041-1345/20
https://doi.org/10.1016/j.transproceed.2020.02.120

of the ESC/ERC group 3 patients presents the worst prognosis of all PH groups, although they show less elevated hemodynamic parameters mPAP and pulmonary vascular resistance (PVR) than the other ESC/ERC guideline PH groups. [4,5]. Patients with pulmonary artery hypertension related to end-stage lung diseases are a large percentage of all patients qualified for lung transplantation (LTx). Prevalence of PH in candidates for LTx with COPD and pulmonary fibrosis is a range between 23% to 84.3% and 31.4% to 46.1%, respectively [2,6–11]. Patients with end-stage CPFE commonly presented with PH, which is thought to be more frequent and severe when compared with COPD and ILDs alone [12,13]. Review of the literature indicates that patients with PH caused by ILDs should be earlier qualified for LTx because the diagnosis of ILDs, especially idiopathic pulmonary fibrosis (IPF), is associated with the worst prognosis of all indications for LTx, and the coexistence of PH is a major predictor of poor survival after LTx [14,15]. PH effect on LTx outcome is questionable [16–21]. Several studies suggest that PH does not adversely impact the survival of patients with ILDs who undergo LTx as opposed to COPD candidates for LTx [2,18–21].

The aim of the study was to assess the prevalence of secondary pulmonary artery hypertension among patients qualified for LTx (ILDs, COPD, and CPFE patients) as well as to compare medical data between ILDs, COPD, and CPFE patients with and without PH.

MATERIAL AND METHODS

Between 2004 and 2019, 381 patients were referred to Silesian Center for Heart Diseases for qualification for LTx. Patients with RHC data (n = 188, 49.34% of all qualified patients) were included in this retrospective cohort study.

The inclusion criteria were diagnoses of ILDs, COPD, or CPFE and the presence of RHC data obtained during qualification for LTx.

The exclusion criteria were diagnoses of idiopathic pulmonary arterial hypertension (n = 38, 20.21%), cystic fibrosis (n = 2, 1.06%), pulmonary artery hypertension associated with connective tissue diseases (n = 3, 1.6%), or bronchiectasis (n = 2, 1.06%).

1. The study population (n = 143, 76.06%) was divided according to initial diagnosis in 3 groups: **COPD patients:** 54 (37.8%) (19 women, 35 men); **ILDs patients:** 84 (58.7%) with diagnosis of sarcoidosis (n = 7, 8.33%), IPF (n = 51, 60.72%), pneumoconiosis (n = 5, 5.95%), hypersensitivity pneumonitis (n = 19, 22.62%), and histiocytosis (n = 2, 2.38%) (35 women, 49 men); and **CPFE patients:** 5 (3.5%) (5 men).

The initial assessment consisted of the basic characteristics of patients (primary diagnosis, age at qualification for LTx, weight, height, body mass index [BMI]). The study evaluation also contained laboratory tests (level of serum creatinine, serum bilirubin, and N-terminal prohormone of brain natriuretic peptide [NT-proBNP]) and pulmonary function tests estimated by spirometry (forced expiratory volume in 1 second (FEV1%), actual FEV1 (L), forced vital capacity (FVC%), and actual FVC (L). Exercise capacity was measured by a 6-minute walk test (6MWT) (distance, Borg scale, and desaturation during test). Echocardiography data (left ventricle ejection fraction, right ventricular systolic pressure [RVSP], tricuspid annular plane systolic excursion [TAPSE], acceleration time) and RHC parameters (systolic pulmonary artery pressure, diastolic artery pulmonary pressure, mPAP, pulmonary artery wedge pressure [PCWP], cardiac index, cardiac output, PVR, and transpulmonary pressure gradient [TPG]) were used to assess general hemodynamics with special attention to pulmonary hemodynamics.

The criteria for severe PH associated with lung diseases are the following (at least 2 of these criteria must be met) [22]:

1) mPAP >35 mm Hg;
2) mPAP ≥25 mm Hg and cardiac index <2.0 L/min/m^2; and
3) PVR >6 Wood units [23].

STATISTICAL ANALYSIS

Results of collected data are presented as a mean and ± standard deviations. The Smirnov-Kolmogorov test was used to verify the type of distribution. Differences for quantitative variables between groups were measured by the Student *t* test. The χ^2test was applied for comparison of categorical variables. The survival analysis was completed according to the methods of Kaplan-Meier, and the log-rank test was used to compare survival curves. A *P* value of less than .05 was considered statistically significant. For statistical analysis, Statistica 10.0 software (StatSoft, Inc., Tulsa, Okla, United States) was used.

CPFE-PH patients were excluded from comparative analysis because of the small number of populations. Comparison of pulmonary function tests (using spirometry) between ILDs-PH and COPD-PH patients was also excluded because of the different nature of both conditions.

RESULTS

Study population consisted of 54 patients with COPD (10 patients died while on the waiting list, 31 underwent LTx: 12 single LTx, 19 double LTx, and 13 patients are on the active recipient list), 84 patients with ILDs (55 patients died while on the waiting list, 15 of them underwent LTx (10 single LTx and 5 double LTx), and 14 patients are on the active recipient list), and 4 patients with CPFE (4 candidates died while on the waiting list, 1 underwent double LTx).

Regardless of the magnitude, PH was identified among 86 (60.14%) analyzed patients: in 18 patients (33.3%) out of 54 with COPD, in 64 patients (76.2%) out of 84 with ILDs, and in 4 patients (80%) out of 5 with CPFE. Fifty-four patients from the study population (62.79%) presented with severe PH, which occurred with a frequency of 38.89%, 67.19%, and 100% in CODP, ILDs, and CPFE groups, respectively. Basic characteristics and comparative analysis of CODP and ILD patients based on the presence or absence of PH are presented in Tables 1 and 2.

Regarding echocardiographic parameters such as RVSP, there are significant differences in its magnitude between patients with an absence or presence of PH in the COPD group (RVSP of 39.36 vs 53.50 mm Hg, *P* = .008, respectively) and between patients with an absence or presence of

Table 1. Basic Patient Characteristics Based on the Presence or Absence of Pulmonary Hypertension Among Chronic Obstructive Pulmonary Disease Patients

	COPD Patients				
	n (%)	mPAP <25 mm Hg	n (%)	mPAP ≥ 25 mm Hg	*P* Value
Patients died on waiting list, %	6	(16.66)	4	(22.22)	.6203*
Patients on waiting list, %	11	(30.56)	2	(11.11)	.1151*
Patients underwent LTx, %	19	(52.78)	12	(66.67)	.3306*
SLT, %	**10**	**(52.63)**	**2**	**(16.67)**	**.0452***
DLT, %	**9**	**(47.37)**	**10**	**(83.33)**	
Sex, women, %	13	(36.11)	6	(33.33)	.8403*
Age at qualification for LTx, y	19	55.21±6.50	18	49.72±9.75	.0507†
Age at LTx, y	19	55.79±6.51	12	50.17±9.09	.0541†
Time on waiting list, days	36	349.00±367.24	18	249.61±288.00	.3206†
Height, m	36	168.60±10.12	18	167.36±8.57	.6586†
Weight, kg	36	61.00±12.74	18	63.15±11.74	.5513†
BMI, kg/m^2	36	21.36±3.42	18	22.45±3.36	.2736†
NT-proBNP, pg/mL	**31**	87.47±50.56	**16**	413.12±681.90	**.0104†**
Serum creatinine, mg/dL	35	0.74±0.17	17	0.74±0.18	.9843†
Albumins, g/L	21	42.29±8.68	10	41.80±6.12	.8752†
Total protein, g/dL	23	7.01±0.61	12	6.99±0.83	.9548†
Serum bilirubin, μmol/L	36	8.94±4.40	18	8.09±5.21	.5286†
EFLV, %	35	53.66±4.92	18	53.67±4.33	.9945†
RVSP, mm Hg	**28**	39.36±10.12	**14**	53.50±22.96	**.0081†**
TAPSE, mm	**28**	22.04±4.70	**15**	18.93±4.38	**.0410†**
AcT, ms	28	91.71±22.57	14	93.07±22.52	.8551†
FEV1, L	**19**	0.64±0.16	**13**	1.11±0.91	**.0343†**
FEV1, %	**19**	20.86±4.69	**13**	33.18±19.17	**.0112†**
FVC, L	18	1.99±0.94	13	2.21±0.85	.5012†
FVC, %	18	51.20±17.53	13	58.39±16.87	.2616†
Pseudo-Tiffenau index	18	35.55±9.89	13	49.08±31.71	.0982†
6MWT distance, m	36	152.03±111.55	18	190.56±138.69	.2755†
Borg scale	33	4.42±1.66	18	4.89±2.03	.3813†
Desaturation after 6MWT	36	6.97±4.82	18	9.11±6.87	.1894†

Values are given as the mean ± standard deviation.
Bold values are statistically significant.
Abbreviations: 6MWT, 6-minute walk test; AcT, acceleration time; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLT, double lung transplantation; EFLV, left ventricle ejection fraction; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; LTx, lung transplantation; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RVSP, right ventricular systolic pressure; SLT, single lung transplantation; TAPSE, tricuspid annular plane systolic excursion.
*P value: χ^2 test.
†P value: t test.

PH in the ILD group (RVSP of 38.55 vs 57.95 mm Hg, $P = .025$, respectively).

Additionally, patients with co-occurrence of COPD and PH (COPD-PH) in comparison to patients with COPD but without PH presented significantly lower value of TAPSE (22.04 ± 4.7 vs 18.93 ± 4.38 mm, $P < .05$). The same goes in patients with co-occurrence of ILDs and PH (ILDs-PH) in comparison to patients with ILDs but without PH: TAPSE was also lower, almost reaching statistical importance ($P = .0527$) (Tables 1 and 2).

NT-proBNP was about 5 times higher in the population of COPD-PH compared with patients with COPD but without PH, and this difference was statistically important ($P = .0104$), while in the population of ILDs-PH compared to patients with ILDs but without PH, NT-proBNP was about 13 times higher and did not reach statistical importance ($P = .0758$) (Tables 1 and 2).

FEV1 (L) and FEV1% parameters were distinctly reduced in the COPD population with the absence of PH. Similarly, pulmonary function parameters, FEV1 (L) and FVC (L) were lower in ILDs candidates without PH. Patients with ILDs-PH had statistically significant higher body weight and BMIs than ILD patients without PH ($P = .0036$ and $P = .004$, respectively), and we did not observe the same relationship for COPD-PH vs COPD patients (Tables 1 and 2).

Severe PH was observed more often among patients with ILDs-PH than COPD-PH (60.94% vs 38.89%, not statistically significant, respectively). Candidates with COPD-PH diagnosis have lower body weight and presented smaller desaturation during 6MWT than ILDs-PH patients (all statistically important), but their hemodynamic parameters as PCWP and acceleration time were importantly increased in comparison to ILDs-PH patients (18.2 ± 10.5 mm Hg vs 12.1 ± 6.9 mm Hg; $P = .007$; 93.0 ± 2.5 ms vs 79.0 ± 21.0 ms; $P = .0303$, respectively; Table 3).

COPD patients with the presence of PH more often died while on the waiting list without receiving a lung transplant than COPD candidates without PH; however, this

Table 2. Patient's Basic Characteristics Based on the Presence or Absence of Pulmonary Hypertension Among Interstitial Lung Disease Patients

	ILD Patients				
	n (%)	mPAP <25 mm Hg	n (%)	mPAP ≥25 mm Hg	*P* Value
Patients died on waiting list, %	13	(65.00)	42	(65.63)	.9591*
Patients on waiting list, %	**0**	**(0.00)**	**14**	**(21.88)**	**.0219***
Patients underwent LTx, %	**7**	**(35.00)**	**8**	**(12.50)**	**.0218***
SLT, %	**2**	**(28.57)**	**8**	**(100.00)**	**.0034***
DLT, %	**5**	**(71.43)**	**0**	**(0.00)**	
Sex, women, %	12	(60.00)	23	(35.94)	.0567*
Age at qualification for LTx, y	20	50.95±9.23	64	51.28±7.83	.8748†
Age at LTx, y	7	49.71±10.09	64	51.28±7.83	.6267†
Time on waiting list, days	20	344.00±356.02	64	462.84±523.03	.3460†
Height, m	20	165.85±10.23	64	168.14±9.24	.3482†
Weight, kg	**20**	**62.66±10.48**	**64**	**71.52±11.85**	**.0036†**
BMI, kg/m^2	**20**	**22.76±3.05**	**64**	**25.25±3.35**	**.0040†**
NT-proBNP, pg/mL	**13**	**113.55±172.07**	**55**	**1452.76±2659.86**	**.0758†**
Serum creatinine, mg/dL	17	0.72±0.17	60	0.82±0.22	.0858†
Albumins, g/L	13	39.78±5.08	42	41.47±5.39	.3211†
Total protein, g/dL	16	7.41±0.84	45	8.62±9.99	.6300†
Serum bilirubin, μmol/L	17	9.66±4.39	62	13.40±11.51	.1947†
EFLV, %	19	56.16±7.41	62	54.21±5.25	.2049†
RVSP, mm Hg	**11**	**38.55±9.26**	**42**	**57.95±19.57**	**.0025†**
TAPSE, mm	17	20.82±4.48	58	18.53±4.14	.0527†
AcT, ms	17	90.35±20.06	57	79.02±21.01	.0525†
FEV1, L	**12**	**1.18±0.58**	**40**	**1.56±0.55**	**.0431†**
FEV1, %	14	40.81±12.52	41	48.55±14.60	.0822†
FVC, L	**11**	**1.31±0.46**	**37**	**1.86±0.81**	**.0352†**
FVC, %	11	42.75±14.98	37	47.14±15.10	.4009†
Pseudo-Tiffenau index	11	83.69±19.61	37	85.10±11.72	.7665†
6MWT distance, m	15	236.83±169.37	61	207.88±144.17	.5030†
Borg scale	13	4.15±1.57	57	4.91±2.05	.2162†
Desaturation after 6MWT	15	14.03±10.56	60	15.65±7.64	.4993†

Values are given as the mean ± standard deiation.
Bold values are statistically significant.
Abbreviations: 6MWT, 6-minute walk test; AcT, acceleration time; BMI, body mass index; DLT, double lung transplantation; EFLV, left ventricle ejection fraction; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; ILDs, interstitial lung diseases; LTx, lung transplantation; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide, RVSP, right ventricular systolic pressure; SLT, single lung transplantation; TAPS,E tricuspid annular plane systolic excursion.
*P value: χ^2 test.
†P value: t test.

observation was not statistically important. The COPD-PH patients compared to COPD patients without PH spent 100 days fewer on the waiting list, on average. Analogous comparison of ILDs patients also showed no statistical difference in survival between patients with and without PH waiting for transplantation (Fig 1).

The evaluation of survival was also performed with regard to the presence or absence of severe PH during qualification for LTx for each group, and no statistically important difference was found between the survival of patients with COPD and ILDs with this aspect (log-rank test $P = .3203$ and $P = .3507$) (Fig 2).

We also analyzed survival after LTx among COPD and ILDs patients, which revealed no statistical differences regardless of presence or absence of PH (as estimated by Kaplan-Meier curves) (Fig 3). There was no difference in survival post-LTx based on the severity of PH in both COPD and ILDs recipients (log-rank test $P = .1017$ and $P = .2885$, respectively) (Fig 4).

Comparison analysis of survival of COPD-PH and ILDs-PH patients during qualification and after LTx revealed better survival among ILDs-PH group with no statistical significance (Fig 5).

DISCUSSION

This retrospective cohort study identified PH in 60.14% of patients with end-stage COPD, ILDs, and CPFE who were evaluated for LTx in Silesian Center for Heart Diseases in Zabrze, Poland, between 2004 and 2019.

There are several dozens of studies describing the incidence of PH among candidates with ILDs (mostly IPF), COPD, and CPFE separately. In our analysis, 76.19% patients with ILDs referred to LTx have PH diagnosis. With comparison to work of Shorr et al [9] (large retrospective cohort study), PH was reported only in 46.1% of IPF patients. Also, Solidoro et al [6] revealed PH in only 31.4% of candidates for LTx, and these results are consistent with

Table 3. Clinical Characteristics of Candidates for Lung Transplantation With Pulmonary Hypertension by Interstitial Lung Disease or Chronic Obstructive Pulmonary Disease Diagnosis

	Patients With Pulmonary Hypertension mPAP ≥25 mm Hg				
	n (%)	COPD	n (%)	ILDs	*P* Value
Patients who died on waiting list, %	**4**	**(22.22)**	**42**	**(65.63)**	**.0010***
Patients on waiting list, %	2	(11.11)	14	(21.88)	.3087*
Patients who underwent LTx, %	**12**	**(66.67)**	**8**	**(12.50)**	**<.0001***
SLT, %	**2**	**(16.67)**	**8**	**(100.00)**	**.0003***
DLT, %	**10**	**(83.33)**	**0**	**(0.00)**	
Severe PH, %	7	(38.89)	39	(60.94)	.0959*
Sex, women, %	6	(33.33)	23	(35.94)	.8382*
Age at qualification for LTx, y	18	49.72±9.75	64	51.28±7.83	.4824†
Age at LTx, y	12	50.17±9.09	8	50.63±10.91	.9199†
Height, m	18	167.36±8.57	64	168.14±9.24	.7489†
Weight, kg	**18**	**63.15±11.74**	**64**	**71.52±11.85**	**.0097†**
BMI, kg/m^2	**18**	**22.45±3.36**	**64**	**25.25±3.35**	**.0024†**
NT-proBNP, pg/mL	16	413.12±681.90	55	1452.76±2659.86	.1278†
Serum creatinine, mg/dL	17	0.74±0.18	60	0.82±0.22	.1710†
Albumins, g/L	10	41.80±6.12	42	41.47±5.39	.8676†
Total protein, g/dL	12	6.99±0.83	45	8.62±9.99	.5768†
Serum bilirubin, μmol/L	18	8.09±5.21	62	13.40±11.51	.0619†
EFLV, %	18	53.67±4.33	62	54.21±5.25	.6897†
RVSP, mm Hg	14	53.50±22.96	42	57.95±19.57	.4832†
TAPSE, mm	15	18.93±4.38	58	18.53±4.14	.7433†
AcT, ms	**14**	**93.07±22.52**	**57**	**79.02±21.01**	**.0303†**
sPAP, mm Hg	17	50.06±17.36	64	57.22±18.27	.1508†
dPAP, mm Hg	17	24.47±8.49	64	22.83±8.19	.7950†
mPAP, mm Hg	18	34.78±11.47	64	36.30±9.61	.5719†
PCWP, mm Hg	**16**	**18.19±10.51**	**57**	**12.12±6.89**	**.0076†**
CI	13	3.07±0.70	49	3.06±0.76	.9660†
CO	13	5.01±1.46	21	5.64±1.31	.1999†
PVR	10	4.17±2.23	52	4.71±2.17	.4756†
TPG	11	20.90±10.56	45	23.44±9.37	.4342†
6MWT distance, m	18	190.56±138.69	61	207.88±144.17	.6528†
Borg scale	18	4.89±2.03	57	4.91±2.05	.9664†
Desaturation after 6MWT	**18**	**9.11±6.87**	**60**	**15.65±7.64**	**.0017†**

Values are given as the mean ± standard deviation.
Bold values are statistically significant.
Abbreviations: 6MWT, 6-minute walk test; AcT, acceleration time; BMI, body mass index; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; DLT, double lung transplantation; dPAP, diastolic pulmonary artery pressure; EFLV, left ventricle ejection fraction; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; ILDs, interstitial lung diseases; LTx, lung transplantation; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure; SLT, single lung transplantation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary pressure gradient.
*P value: χ^2 test.
†P value: t test.

that presented by Nathan et al [10], where PH diagnosis at primary evaluation for LTx in IPF patients was found in 38.6%. However, the incidence of PH progresses with time and reaches 86.4% at the time of LTx [10].

PH is also commonly observed in end-stage COPD. Observations from our transplantology center showed that COPD-PH is present in 33.33% of potential lung recipients. The comparable frequency was also noticed in study by Cuttica et al and Andersen et al [2,8]. They detected COPD with the presence of PH in 30.4% and 36%, respectively [2,8]. Some authors revealed a higher incidence of PH in COPD candidates for LTx. Solidoro et al [6] reported an almost 84.3% prevalence of PH in end-stage COPD.

This study suggests that occurrence of PH is more often noticed in patients with a diagnosis of CPFE than in patients with ILDs or COPD. Mejía et al [12] observed higher systolic pulmonary artery pressure in patients who had CPFE than in patients with an IPF diagnosis (82 mm Hg vs 57 mm Hg, respectively). Additionally, Cottin et al [13] reported in a retrospective multicenter study that CPFE-PH patients have severe PH (mPAP = 40 mm Hg). Unfortunately, these publications did not relate to patients in the end-stage CPFE or qualified for LTx because of CPFE. Our analysis showed an 80% incidence of PH among patients with CPFE. Additionally, all patients presented severe PH. Our work is limited by a small population of candidates qualified for LTx because of CPFE.

Unfortunately, only 2 papers undertake a comparative analysis of frequency of PH involving ILDs and COPD lung transplant candidates [6,24]. Solidoro et al [6] evaluated 73 patients qualified for LTx: 35 with pulmonary fibrosis and 38

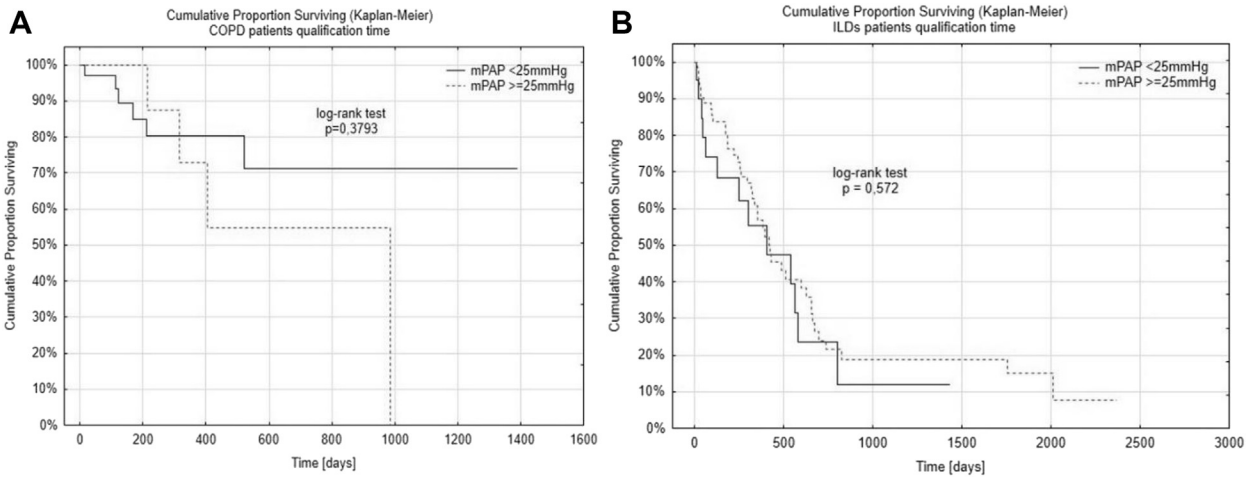

Fig 1. Kaplan-Meier survival curves of chronic obstructive pulmonary disease (COPD) **(A)** and interstitial lung disease (ILD) **(B)** candidates depending on the presence or absence of pulmonary hypertension (PH) at the time of qualification for lung transplantation

with COPD diagnosis, where frequency of PH among these candidates were as follows: 84.3% and 33.33%, respectively; those results were opposite to our study findings. It is impossible to compare PH severity in these studies because of the different classifications of severe PH. Organ Procurement and Transplantation Network data were discussed by Singh et al [24] in large retrospective study, which contained 2025 patients with COPD, 2304 patients with IPF, and 866 patients with cystic fibrosis. [24] This analysis revealed occurrence of PH in 13.4% of COPD and in 26.5% of IPF candidates for LTx (PH defined due to lung diseases as TPG $\geq$ 20 mm Hg). Unfortunately, comparison of the study results with our study population results is also impossible owing to the different division of the patients selected for analysis.

The literature review shows that less body weight positively influences pulmonary function tests [23,25,26]. However, in our study, ILD-PH patients had a higher BMI (25.25 $\pm$ 3.35 kg/m^2 vs 22.76 $\pm$ 3.05 kg/m^2; $P = .004$) and body weight (71.52 $\pm$ 11.85 kg vs 62.66 kg $\pm$10.48 kg ; $P = .0036$) than ILD patients with an absence of PH and achieved statistically better results in spirometry FEV1 (L) (1.56 $\pm$ 0.55 L vs 1.18 $\pm$ 0.58 L; $P = .0431$) and FVC (L) (1.86 $\pm$ 0.81 L vs 1.31 $\pm$ 0.46 L; $P = .0352$). BMIs in ILD-PH patients are slightly above the norm. The possible explanation is that patients with ILD-PH are qualified for LTx earlier than patients without PH and therefore spend about 120 days longer on the waiting list (344 $\pm$ 356.02 days vs 462.84 $\pm$ 523.03 days, respectively.) Therefore, they are characterized by better parameters of lung function and nutritional status. Nevertheless, the literature review showed that BMI is not an excellent parameter, and body composition indices measured by bioelectrical impedance analysis and WH-ratio would be better indicators for the analysis [27–30].

Survival of COPD or ILD candidates in our population at the time of qualification for LTx estimated by Kaplan-Meier

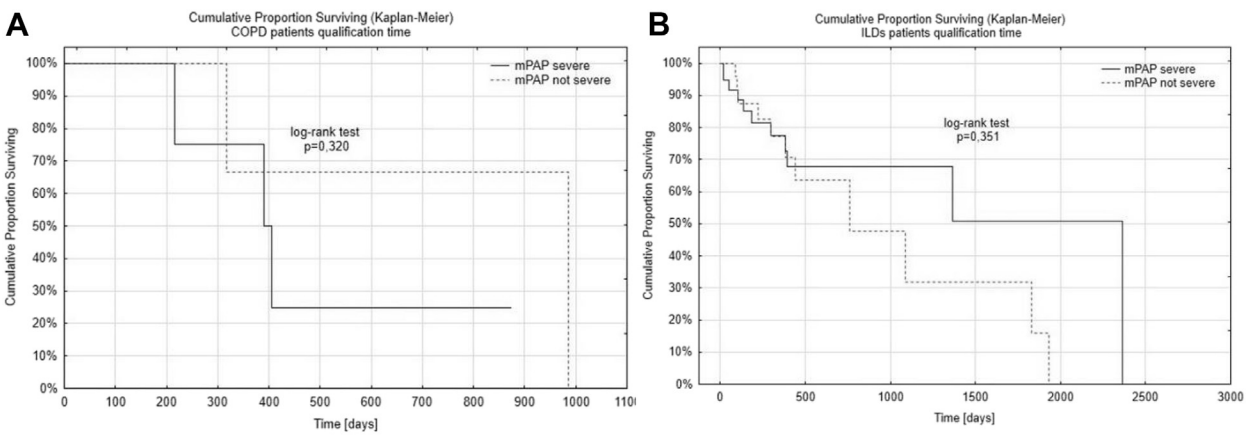

Fig 2. Kaplan-Meier survival curves of chronic obstructive pulmonary disease (COPD) **(A)** and interstitial lung disease (ILD) **(B)** candidates depending on severity of pulmonary hypertension (PH) at the time of qualification for lung transplantation

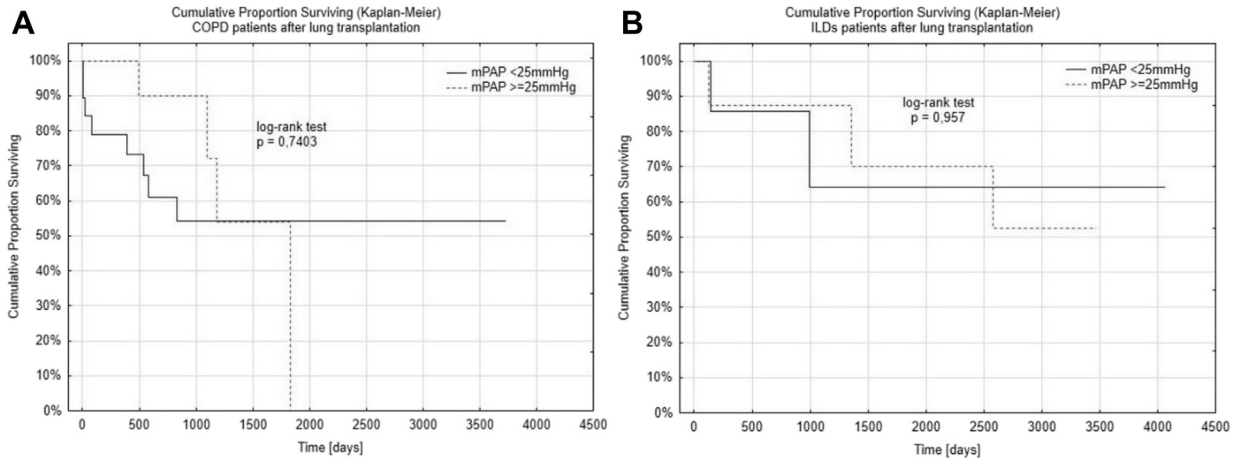

Fig 3. Kaplan-Meier survival curves after lung transplantation of chronic obstructive pulmonary disease (COPD) **(A)** and interstitial lung disease (ILD) **(B)** patients depending on presence or not of pulmonary hypertension (PH).

curves revealed no statistical differences regardless of the presence or absence of PH (log-rank test $P = .3793$ vs $P = .5717$, respectively).

The study published by Kimura et al [3] showed statistically significant worse survival among potential recipients with IPF-PH with mPAP >20 mm Hg, (log-rank test $P = .001$). The median survival estimates for those patients was 20.8 months, where in our analysis it was 22.33 months, but a different cut-off point for mPAP was chosen for selected patients with PH.

In 2013, Andersen et al [2] in an retrospective study involving 355 COPD-PH patients (PH classified by mPAP ≥25 mm Hg and PCWP ≤15 mm Hg) revealed the significant effect of PH on survival. The 5-year survival of patients in the PH group was worse compared with the non-PH group: 37% vs 63% survival rate (log-rank test $P = .016$). Because of the limited time of survival analysis in our COPD candidate's population, comparison of 2-year survival can be assessed. Survival rates are 85% vs 71% and 76% vs 55% in patients with the presence and absence of PH, respectively. Hayes et al [11] also reported significant differences (log-rank test $P < .0001$) of survival among COPD patients with and without PH. Additionally, they revealed statistical importance of the influence of PH severity (defined as mPAP ≥35 mm Hg) in the COPD population on pretransplant outcome (log-rank test $P < .0001$).

Our study showed no statistically significant differences in the Kaplan-Meier estimates of the survival after LTx depending on presence or absence of PH in both COPD and ILD groups (log-rank test $P = .7403$ vs $P = .9572$, respectively.) We also reported no influence of PH severity at the time of qualification on post-transplant outcome in COPD and ILD recipients (log-rank test $P = .1017$ and $P = .2885$, respectively).

In the review of literature, there can be found similar results to ours with respect to ILDs group. Hayes et al [17]

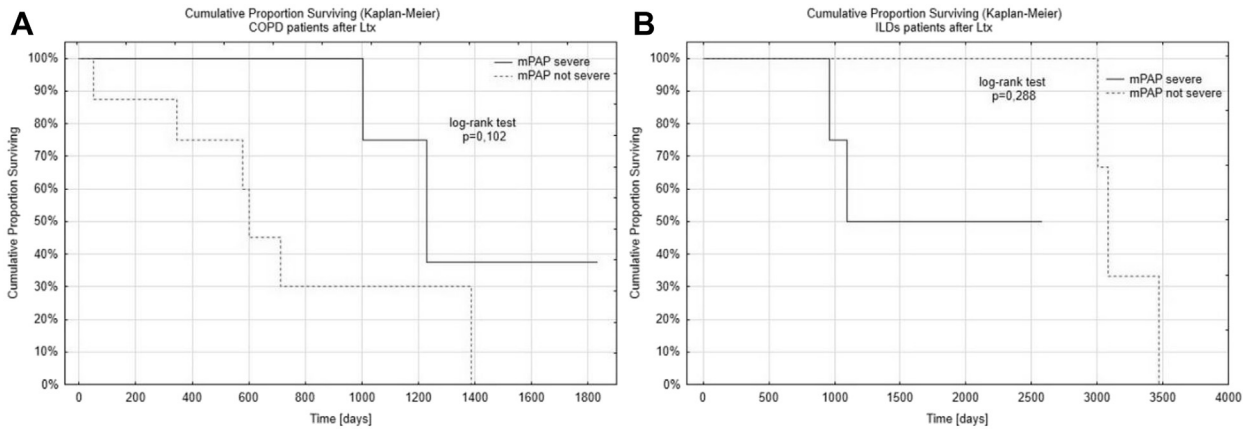

Fig 4. Post-transplant survival based on severity of pulmonary hypertension (PH) at the time of qualification for lung transplantation in chronic obstructive pulmonary disease (COPD) **(A)** and interstitial lung disease (ILD) **(B)** patients.

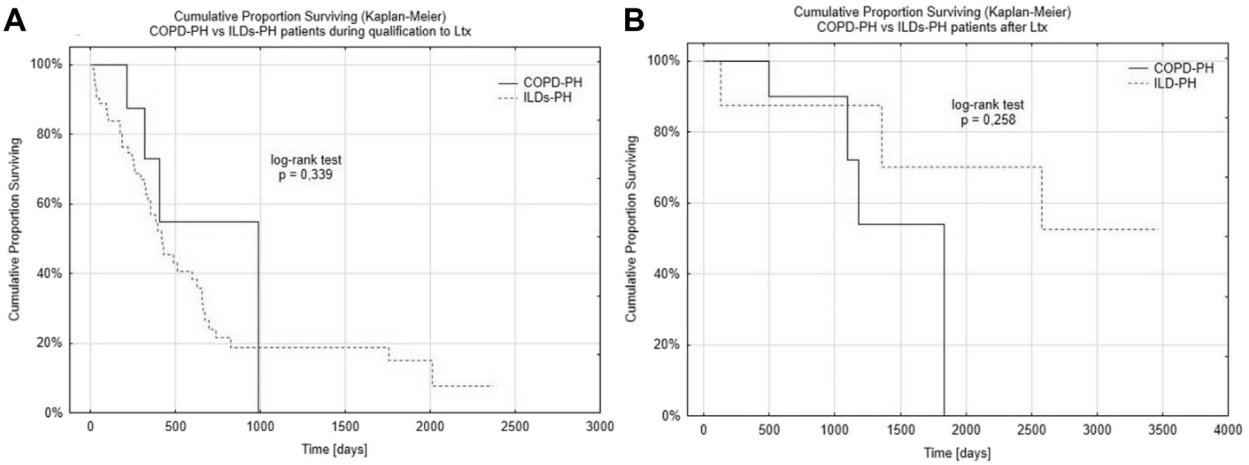

Fig 5. Kaplan-Meier survival curves of chronic obstructive pulmonary disease pulmonary hypertension (COPD-PH) and interstitial lung disease pulmonary hypertension (ILD-PH) candidates at the time of qualification for lung transplantation **(A)** and after lung transplantation **(B)**.

conducted a large retrospective study, evaluating data from 2542 LTx recipients with IPF from the United Network for Organ Sharing (UNOS). The study reported no significant differences in the survival as estimated by the Kaplan-Meier curves with regard to the presence or absence of PH (log-rank $P = .876$). They also showed no effect of the presence of severe PH (defined as a mPAP $\geq$35 mm Hg) on survival after LTx (log-rank test $P = .247$). Nathan et al [10] defined severe PH as a mPAP of $\geq$31mm Hg and also reported no influence of severity of PH on outcome for ILDs after LTx (log-rank test $P = .745$).

Andersen et al [2] evaluated post-transplant survival of COPD recipients regardless of PH status and did not notice a statistically significant difference (log-rank test $P = .37$). In contrast, Singh et al [24] used a different definition of PH (TPG $\geq$20 mm Hg) and showed that COPD patients with PH had a significantly decreased 1-year survival compared with normotensive patients (75.9% vs 86.1%, log-rank test $P = .001$).

In our study population, no statistical differences were found in comparison analyses of survival of COPD-PH and ILD-PH patients during qualification as well as after LTx, although patients with ILD-PH diagnosis presented with better survival. Unfortunately, to the best of our knowledge, no literature discusses the topic of comparison survival among those groups.

The authors of this study are aware of the following limitations: small, disproportionate study population and lack of multivariate analysis of possible predictors associated with the presence of PH [6]. These limitations will be eliminated in the next study planned by the authors.

CONCLUSIONS

Assessing PH is an integral part of examining patients with end-stage lung diseases while qualifying patients for LTx. PH can influence, as based on literature review and our findings survival on waiting list and after transplantation. Presence or absence of PH also affect the pre- and post-operative management of lung transplant recipient.

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