



Pulmonary hypertension is associated with increased post-lung transplant mortality risk in patients with chronic obstructive pulmonary disease

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BACKGROUND: Pulmonary hypertension associated with lung disease (PHLD) has been shown to be a predictor of disease severity and survival in patients awaiting lung transplantation. Little is known about the relationship of PHLD and survival after lung transplantation or how this may vary by disease. This study evaluated the effect of PHLD on 1-year survival after lung transplantation for patients with the 3 most common indications for transplantation: chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and cystic fibrosis (CF).

METHODS: Organ Procurement and Transplantation Network data were obtained for all lung transplant recipients who received an allograft between May 2005 and June 2010. The relationship between PHLD and 1-year survival after lung transplantation for each diagnostic group was examined with Kaplan-Meier estimates and Cox regression. Covariates included in the model were those defined in the current Lung Allocation Score system post-transplant survival model, including age, serum creatinine, percentage predicted forced vital capacity, functional status, and mechanical ventilation use at time of transplant. The estimated relative risk was calculated using Poisson regression with robust error variance and adjustment for covariates.

RESULTS: Sample sizes for COPD, IPF, and CF patients were 2,025, 2,304, and 866, respectively. The 1-year post-transplant survival for COPD patients with PHLD was 76.9% vs 86.2% for COPD patients without PHLD ($p = 0.001$). In multivariate Cox regression analysis COPD patients with PHLD had a 1.74 (95% confidence interval, 1.3–2.3) times higher risk of 1-year post-transplant mortality ($p = 0.001$). Similar analyses for IPF and CF diagnostic groups showed no significant difference in survival between patients with and without PHLD.

CONCLUSIONS: COPD patients with PHLD have increased post-transplant 1-year mortality. No significant difference was seen in patients with IPF or CF. Further studies to evaluate the potential mechanisms for this difference between diagnoses are needed.

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Pulmonary hypertension associated with lung disease (PHLD) has been shown to be a predictor of severity of disease and mortality in patients awaiting lung transplantation.^{1–4} Although several studies have assessed the

effects of pulmonary hypertension in patients with advanced lung disease or waiting for lung transplantation,^{1–7} little is known about the relationship of PHLD and post-transplant mortality.

The implementation of the Lung Allocation Score (LAS) system has significantly reduced waiting list mortality by almost 46%.⁸ Despite this triumph, validation of the post-transplant model of the LAS has shown that it poorly predicts post-transplant mortality (area under the curve, 0.58).⁹ In an attempt to improve the predictability of the allocation model, 2 separate studies have evaluated parameters that were associated with post-transplant survival for patients with 3 specific pre-transplant diseases: chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and cystic fibrosis (CF).^{9,10} Both studies showed that the parameters included in each model were extremely different and were not always included in the post-transplant model of the LAS.^{9,10}

The diagnosis of idiopathic pulmonary arterial hypertension is a significant risk factor for post-transplant 1-year mortality, yet the effect of pre-transplant pulmonary hypertension on patients with concomitant lung disease (i.e., patients with PHLD) on post-transplant 1-year survival is not known. In this study, we investigated the association between PHLD and 1-year post-transplant mortality for the 3 most common indications for lung transplantation: COPD, IPF, and CF. Understanding the relationship between PHLD and post-transplant survival may help further refine the LAS, because pulmonary artery pressures (PAPs) are not included in the transplant benefit prediction model, and the risk of PHLD on disease-specific 1-year post-transplant mortality is not considered in the calculation of the LAS.¹¹

Methods

Institutional Review Board approval was not required for this study because the Standard Transplant Analysis and Research database from which the data were derived is a deidentified public database.

Study population

Deidentified data for all patients who received a lung transplant between May 2005 and June 2010 in the United States were obtained from the Organ Procurement and Transplantation Network (OPTN). Because transplant prioritization and pre-transplant data collection changed with the implementation of the LAS, patients who received a transplant before May 4, 2005, were excluded from our study. Patients who were aged younger than 18 years, had received a multiorgan transplant, had received a lung retransplant, or had missing survival data were also excluded from study. All remaining patients with diagnosis of COPD (exclusive of α -1 antitrypsin deficiency), IPF, or CF were included.

Selection of predictors for post-transplant 1-year mortality

Pulmonary hypertension has been defined as a resting mean PAP (mPAP) ≥ 25 mm Hg.¹² The transpulmonary gradient (TPG), which is calculated as the difference of mPAP and pulmonary

capillary wedge pressure, is another measurement of pulmonary hypertension severity and is normally in the range of 10 to 12 mm Hg.^{13–15} TPG is the mean driving pressure in pulmonary circulation and is not affected by flow, inertia, vascular compliance, or extravascular compliance such as alveolar pressure.^{13,16–18} Therefore, TPG may be a better measurement than mPAP in this population given the significant lung disease. PHLD for our study was defined as a TPG of ≥ 20 mm Hg according to standard practice at our institution and in the literature.^{16,19}

Other variables chosen a priori for our multivariate Cox regression analysis were those used in the LAS model to calculate post-transplant 1-year survival.¹¹ These variables included age at transplant, creatinine at transplant, percentage predicted forced vital capacity (FVC %), mechanical ventilation at transplant, and functional status. Functional status had 2 levels—performs daily activities with total assistance vs performs daily activities with no or some assistance. We added PHLD as a dichotomous variable to this Cox regression model.

Primary end point and statistical analysis

Primary outcome was all-cause mortality within 1 year of transplant. Kaplan-Meier estimates of post-transplant 1-year survival for patients with PHLD (TPG ≥ 20 mm Hg) compared with normotensive (TPG < 20 mm Hg) were generated for each diagnostic group, and survival distributions between 2 groups were compared using the log-rank test. Proportional hazard assumption for Cox regression analysis was verified using scaled Schoenfeld residuals.²⁰

The relationship between TPG and all-cause 1-year mortality with estimation of relative risk per 8-mm Hg increase in TPG was also evaluated. The reference value for relative risk was 12 mm Hg, the normal value of TPG,¹³ and the rationale for choosing the 8 mm Hg interval was the difference between reference value and cutoff value of TPG used in this study. Relative risk was calculated using Poisson regression with robust error variance²¹ and was adjusted for variables selected in the Cox regression model.

Missing data

For variables used in the multivariate analysis, missing data were replaced using multiple imputations separately for each diagnostic group. For each missing value, 5 values were imputed using the imputation by chained equation package in Stata 10.1 software (StataCorp LP, College Station, TX).²² The imputed data set was analyzed using “mim” package for Stata, which generates parameter estimates and confidence intervals (CIs) computed according to Rubin’s rule for multiple imputation inference.²³ In addition, a sensitivity analysis was performed for missing data of TPG using “best” and “worst” case scenario.²⁴ Patients with calculated TPG values of < 0 were treated as missing data and were replaced using multiple imputations.

Continuous variables are reported as median and interquartile range, and categorical variables are presented as percentages and counts. Univariate associations were tested using chi-square for categorical variables, and continuous variable were tested using Student’s *t*-test. A 2-tailed level of significance of 5% was used for all analysis.

Results

For the period of May 2005 to June 2010, the OPTN database included data for 5,561 lung transplant recipients

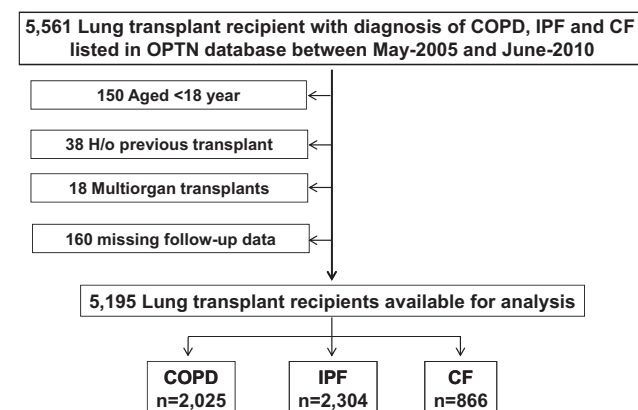


Figure 1 Flow chart of patient selection. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis. OPTN, Organ Procurement and Transplantation Network.

with diagnosis of COPD, IPF, or CF (Figure 1). The study excluded 150 patients who were aged younger than 18 years, 38 with a history of previous transplant, and 18 who had received multiple organ transplants. Also excluded were 160 patients with missing follow-up data for survival time. Our analysis included 2,025 patients with COPD, 2,304 with IPF, and 866 with CF (Figure 1).

There were notable differences in baseline characteristics of patients in these 3 diagnostic groups (Table 1). CF patients were relatively younger than those with COPD and IPF, and the IPF group was predominantly male. Prevalence of diabetes was highest among CF patients (47%), followed by IPF (19%) and COPD (9%). Double-lung transplantation was performed in 56% of COPD patients, 50% of IPF patients, and 100% of CF patients. TPG values were missing for 6.7% of COPD patients, 7.1% of IPF patients, and 26.7% of CF patients.

The percentage of patients with PHLD (defined as TPG \geq 20 mm Hg) was 13.4% ($n = 248$) for COPD, 26.5%

($n = 560$) for IPF, and 29.4% ($n = 185$) for CF patients (Table 1). Compared with normotensive COPD patients, an increased number of patients with COPD and PHLD were supported with mechanical ventilation at the time of lung transplant (3.7% vs 6.8%, $p < 0.05$). This difference was not present in the IPF and CF diagnostic groups.

COPD patients with PHLD had significantly decreased 1-year survival compared with normotensive patients (75.9% vs 86.1%, $p = 0.001$; Figure 2). This association did not reach statistical significance for the IPF and CF diagnostic groups.

Adjusted estimated relative risk (eRR) for all-cause 1-year mortality increased with an incremental rise in TPG for COPD patients and was statistically significant (Table 2 and Figure 3). Compared with COPD patients with a TPG < 12 mm Hg, those with a TPG in the range of 20 to 27.9 mm Hg and TPG ≥ 28 mm Hg had a eRR of 1.51 (95% CI, 1.06–2.15) and 2.0 (95% CI, 1.38–2.9), respectively (Table 2 and Figure 3). This was not true for patients with IPF and CF. Also, there was no significant difference in cause of death by TPG for any diagnosis (data not shown).

Multivariate Cox regression analysis showed patients with COPD and PHLD (TPG ≥ 20 mm Hg) had a 74% higher risk of 1-year mortality (Table 3) compared with COPD patients without PHLD ($p < 0.001$). This did not reach statistical significance for the IPF and CF groups. In sensitivity analysis, PHLD remained a significant risk factor for post-transplant 1-year mortality in the COPD diagnostic group but not for IPF and CF.

The same multivariate Cox regression analysis was repeated using mPAP (cutoff of 25 mm Hg) and did not yield significant results. The hazard ratios were 1.1 ($p = 0.3$), 0.95 ($p = 0.6$), and 0.82 ($p = 0.4$), respectively, for the COPD, IPF, and CF diagnostic groups. In a repeat of multivariate Cox regression analysis with pulmonary vascular resistance (cutoff of 3 Woods units), the hazard

Table 1 Characteristics of Study Patients Before Transplant

Recipient characteristics	COPD	IPF	CF	Missing data
	($n = 2,025$)	($n = 2,304$)	($n = 866$)	(%)
Age, median (IQR) years	60 (56, 64)	61 (55, 65)	29 (24, 37)	0
Female, % (n)	48.4 (979)	28.6 (658)	46.7 (404)	0
Creatinine, median (IQR) mg/dl	0.8 (0.7, 1)	0.9 (0.7, 1)	0.7 (0.56, 0.9)	0.33
BMI, median (IQR) kg/m ²	24.3 (21.3, 27.3)	27.7 (24.9, 30.1)	19.0 (17.7, 20.8)	0.02
FEV ₁ %, median (IQR)	20 (16, 26)	50 (40, 63)	22 (18, 27)	1.9
FVC%, median (IQR)	51 (40, 64)	46 (37, 58)	37 (30, 45)	1.7
On ventilator support, % (n)	4.3 (85)	5.2 (117)	10.6 (90)	1.6
Functional status-needs total assistance, % (n)	9.9 (193)	12.5 (271)	14.2 (116)	5.4
TPG, median (IQR) mm Hg	13 (10, 17)	14 (10, 20)	16 (12, 20)	11.5
TPG ≥ 20 mmHg, % (n)	13.4 (248)	26.5 (560)	29.4 (185)	11.5
mPAP, median (IQR) mm Hg	25 (21, 30)	24 (19, 30)	25 (21, 30)	8.2
PCWP, median (IQR) mm Hg	12 (8, 15)	9 (6, 13)	9 (6, 12)	8.2
Diabetes, % (n)	9.2 (187)	18.8 (434)	47.5 (411)	0.04
Double-lung transplant, % (n)	55.6 (1,127)	49.4 (1,139)	99.8 (864)	0

BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FEV₁%, forced expiratory volume in 1 second percentage; FVC%, forced vital capacity percentage predicted; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient.

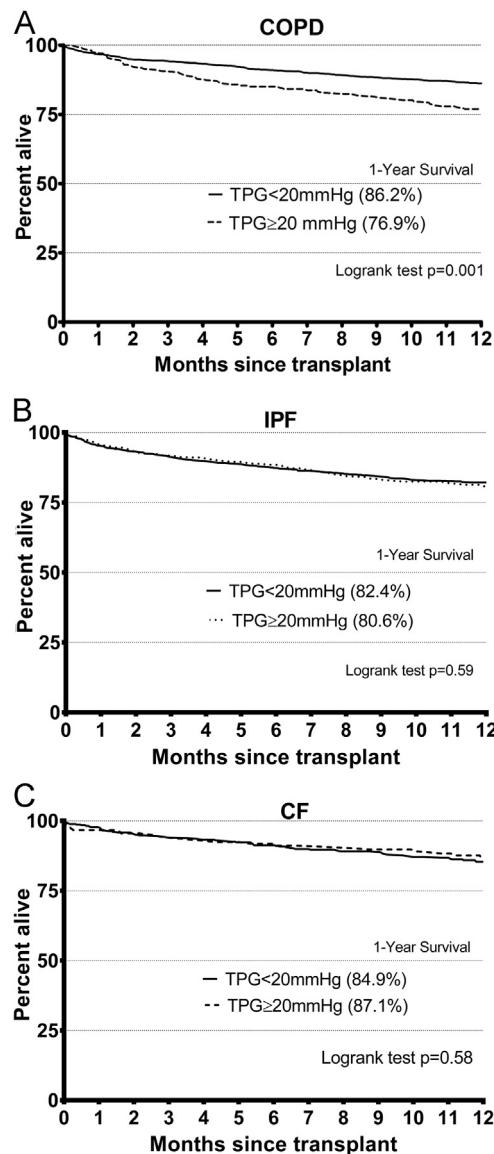


Figure 2 Effect of transpulmonary gradient (TPG) on Kaplan-Meier 1-year survival (values in parenthesis) for patients with (A) chronic obstructive pulmonary disease (COPD), (B) idiopathic pulmonary fibrosis (IPF), and (C) cystic fibrosis (CF).

ratios were 1.5 ($p = 0.002$), 0.96 ($p = 0.7$), and 0.9 ($p = 0.6$), respectively, for the COPD, IPF, and CF diagnostic groups. Inclusion of the variable lung transplant (single vs double) in multivariate Cox regression analysis had no major effect on the final results for any diagnostic group. The same multivariate Cox regression analysis for 90-day all-cause mortality showed similar results as 1-year all-cause mortality (data not shown).

Discussion

Our study demonstrates that PHLD is associated with increased post-transplant all-cause 1-year mortality in patients with a pre-transplant diagnosis of COPD. This association was not found in patients with IPF or CF. This finding supports the concept that not all pre-transplant characteristics have the same effect on post-transplant

survival and that disease-specific allocation modeling may be important to improve the predictive ability of the LAS. Further research is needed to determine why TPG may have effects on post-transplant survival for patients with a history of COPD rather than IPF or CF.

We hypothesize that this finding may have several potential explanations. One consideration is that COPD patients with pulmonary hypertension may have a higher severity of disease and/or have a higher burden of comorbidities than IPF or CF patients who have pulmonary hypertension. This theory is supported by the concept that the rate of pulmonary hypertension progression is much slower in patients with COPD (at 0.2 mm Hg/month) compared with that of IPF (3.8 mm Hg/month).^{25,26} Therefore, patients with COPD who develop pulmonary hypertension may have been ill for a prolonged period and developed multiple comorbidities that would predispose them for worse outcomes after transplant. Furthermore, the use of mechanical ventilation at time of transplant is also a marker of severity of pre-transplant disease. Our study found the use of mechanical ventilation at the time of transplant was significantly higher in COPD patients with pulmonary hypertension than in those without. This difference was not identified in patients with IPF or CF.

Furthermore, pulmonary hypertension in COPD has been classically attributed to pulmonary arterial vasoconstriction in response to hypoxia. In recent years, studies have provided evidence that development of pulmonary hypertension in COPD has a more complex pathogenesis. Pulmonary vasculature changes indicative of pulmonary hypertension have been shown to be independent of hypoxia and airflow obstruction.²⁷ Seimetz et al²⁸ used a mice model of emphysema to show that pulmonary vascular dysfunction, vascular remodeling, and pulmonary hypertension were independent of hypoxia. Different mechanism of pulmonary hypertension may lead to different phenotypes and outcomes among various diseases.

In addition, mortality may be different between patients with different diagnoses because of confounders that are not

Table 2 Adjusted Estimated Relative Risk for All-Cause 1-Year Mortality for Patients with Chronic Obstructive Pulmonary Disease, Idiopathic Pulmonary Fibrosis, or Cystic Fibrosis

Variable	COPD	IPF	CF
	eRR (95% CI)	eRR (95% CI)	eRR (95% CI)
TPG, mm Hg ^a			
12–19.9	1.05 (0.81–1.35)	0.99 (0.8–1.2)	0.76 (0.5–1.2)
20–27.9	1.51 (1.06–2.15)	0.94 (0.71–1.2)	0.86 (0.5–1.7)
> 28	2.0 (1.38–2.9)	1.2 (0.8–1.5)	0.4 (0.12–1.5)

CF, cystic fibrosis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; eRR, estimated relative risk; TPG, transpulmonary gradient.

^aReference is TPG < 12 mm Hg.

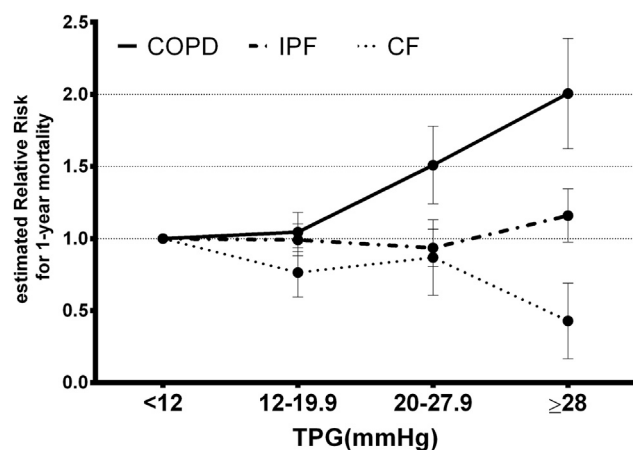


Figure 3 Effect of transpulmonary gradient (TPG) on adjusted estimated relative risk (eRR) for all cause 1-year mortality patients with chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and cystic fibrosis (CF).

well characterized in the OPTN database. COPD with severe pulmonary hypertension is known to be associated with cardiovascular comorbid conditions, such as left ventricular disease, pulmonary embolism, and other conditions associated with COPD, that could affect a patient’s post-transplant survival.²⁹ In contrast, a study of more than 1,000 patients with IPF showed that cardiovascular disease was not a risk factor for death in unadjusted or adjusted models.³⁰

Another potential factor explaining the varying effect of PHLD on post-transplant survival could be the difference in treatment of PHLD in COPD and IPF patients.

Poor short-term post-transplant survival with elevated mPAP has been reported in IPF patients by Whelan et al,³¹ but their study cohort was from the pre-LAS era and 44% lung of IPF lung transplant recipients were missing mPAP data. Missing data of this magnitude can introduce bias in results.³² Compared with the study by Whelan et al,³¹ our study had missing data on TPG only for 7.1% of IPF patients. Another important factor is that their study was from pre-LAS era, which may have affected transplant timing and PHLD effect on post-transplant survival. In addition we had a significantly larger sample size of 2,304 IPF patients compared with 830 in the Whelan et al³¹ study.

One of the major limitations of our study is its retrospective design; however, this is the largest available database to answer questions of this magnitude. Another limitation was missing TPG data, and we tried to minimize this effect by using multiple imputations. Also, the right heart catheterization (RHC) data available in the OPTN database are not intraoperative data. Significant time may have passed between RHC and lung transplant, and the available TPG may be underestimating the true TPG. Finally, TPG is not measured on all CF patients, which may result in a healthy bias. This may result in an unexpected eRR of 0.4 (Table 2) for a TPG > 28 mm Hg. Although post-transplant events likely factor into post-transplant survival, our goal was to evaluate pre-transplant characteristics with the possibility of ultimately improving optimization of the patient before transplant (i.e., screening patients with COPD earlier in their disease course for PHLD, before transplant evaluation). Results of our study will need to be validated in a prospective study.

Also, because this is a retrospective data collection, we are unable to accurately determine the cause of death. Prospective studies that collect information about cause of death are needed. Another limitation is that we did not collect center-specific data; therefore, we do not know if lung transplant volumes were a factor affecting the cause of death.

From the results of our study, we conclude that PHLD is associated with increased 1-year post-transplant mortality for patients with a diagnosis of COPD. This information may help pre-transplant counseling regarding the risks and benefits of lung transplantation of patients with COPD and PHLD. Furthermore, given the survival difference seen between COPD patients with and without PHLD in our study, we advocate for a consideration of an adjustment for this variable in the calculation of the LAS post-transplant model.

Disclosure statement

This study was supported by Health Resources and Services Administration contract No. 231-00-0115. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services.

Table 3 Univariate and Multivariate Cox Proportional Hazard Regression for Transplant Recipients with Chronic Obstructive Pulmonary Disease, Idiopathic Pulmonary Fibrosis, or Cystic Fibrosis^a

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
COPD with TPG ≥ 20mm Hg ^b	1.88 (1.4–2.5)	0.001 ^c	1.74 (1.3–2.3)	0.001 ^c
IPF with TPG ≥ 20 mm Hg ^b	1.07 (0.84–1.35)	0.76	1.03 (0.8–1.3)	0.9
CF with TPG ≥ 20 mm Hg ^b	0.88 (0.54–1.45)	0.86	0.95 (0.57–1.6)	0.6

CF, cystic fibrosis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; TPG, transpulmonary gradient.

^aCovariates used in multivariate analysis were age, serum creatinine, forced vital capacity percentage predicted, mechanical ventilation at transplant, and functional status.

^bReference variable is TPG < 20 mm Hg.

^cStatistically significant.

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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