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

Vikas K. Singh, MD,[a] M. Patricia George, MD,[b] and Cynthia J. Gries, MD, MSc[b]

From the [a]Department of Medicine, University of Pittsburgh Medical Center Mckeesport, Mckeesport, Pennsylvania; and the [b]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

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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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Reprint requests: Cynthia J. Gries, MD, MSc, PACCM, 628 NW MUH, 3459 Fifth Ave, Pittsburgh, PA 15213. Telephone: +1–412-692-2210. Fax: +1-412-692-2260.

E-mail address: griescj@upmc.edu

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

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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) $\geq$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 $\geq$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 $\geq$ 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 variance[21] 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 categoric variables are presented as percentages and counts. Univariate associations were tested using chi-square for categoric 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