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Clinical Trial Paper

Adverse outcomes associated with pulmonary hypertension in chronic obstructive pulmonary disease after bilateral lung transplantation☆

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ABSTRACT

Background: The impact of pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD) on survival after lung transplantation (LTx) is not known.
Material and methods: First-time adult LTx recipients with COPD transplanted between May 2005 and September 2013 were identified in the United Network for Organ Sharing Registry database, and tracked from transplant date until death or censoring. Right heart catheterization (RHC) measurements at time of wait listing were used to predict all-cause mortality after LTx, with multivariable analyses stratified by transplant type.
Results: Of 3362 COPD LTx recipients, 3105 were included in the analytic sample, with multiple imputation used to complete missing data on covariates. Multivariable analysis found the hazard of death to increase with a 10 mmHg increase in mean pulmonary artery pressure (mPAP) among recipients of bilateral LTx (HR = 1.12; 95% CI = 1.01, 1.24; p = 0.032), but not among recipients of single LTx (HR = 0.92; 95% CI = 0.80, 1.06; p = 0.234).
Conclusion: PH prior to bilateral LTx in patients with COPD is associated with higher mortality risk.

1. Introduction

According to the World Health Organization, chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide [1]. An established comorbidity of severe end stage COPD is the development of pulmonary hypertension (PH). The prevalence of PH in the general COPD population is unknown. Routine right heart catheterization (RHC) not commonly used in the management of these patients, but small studies have reported PH occurring in 38% of patients with very advanced lung disease [2,3], and in 50% of patients awaiting lung transplantation (LTx) or lung volume reduction surgery [4].

COPD is the second most common indication for LTx in the United States [5], and the RHC is a component of the evaluation for transplant candidacy. Using data from the United Network for Organ Sharing (UNOS) Registry, our group has demonstrated the presence of PH in 48% of COPD patients listed for LTx in the United States but not transplanted due to death, removal from the list, or censoring [6]. Higher mean pulmonary artery pressure (mPAP) at the time of being listed predicted poorer waitlist survival in this population [7]. Our group has recently demonstrated that PH prior to LTx was not associated with post-transplant survival in other indications for lung transplant including cystic fibrosis (CF) and idiopathic pulmonary fibrosis (IPF) [8,9]. The impact of pre-transplant PH on waitlist outcomes in COPD raises the question of whether PH influences post-transplant survival among COPD

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Abbreviations

(BMI) body mass index
(CMV) cytomegalovirus
(COPD) chronic obstructive pulmonary disease
(ECMO) extracorporeal membrane oxygenation
(FVC) forced vital capacity
(HLA) human leukocyte antigen
(LTx) lung transplantation
(mPAP) mean pulmonary artery pressure
(PH) pulmonary hypertension
(PRA) panel reactive antibody
(RHC) right heart catheterization
(6MWD) 6-min walk distance
(TLC) total lung capacity
(UNOS) United Network for Organ Sharing

patients undergoing LTx. Recently, PH was found to negatively influence 1-year survival in patients with COPD but not CF or IPF [10]. To expand our understanding of this important issue, we completed a study involving COPD LTx recipients with the hypothesis that PH was a risk factor for post-transplant survival in the COPD population undergoing either single or bilateral LTx.

2. Methods

2.1. Data collection

A retrospective cohort study was performed of adult LTx recipients in the UNOS Registry thoracic database [11]. The study was approved by the Nationwide Children's Hospital Institutional Review Board with a waiver of the need for individual consent (IRB14-00716). All patients with COPD who underwent LTx during the modern lung allocation score era between May 2005 and September 2013 were considered for inclusion. Exclusion criteria were a history of prior LTx, age <18 years at wait listing, missing data on mPAP, and missing or zero time at risk since LTx. Survival time in days was assessed for each LTx recipient from the time of LTx until death or censoring.

The data available from the UNOS Registry database included mPAP measurements from RHC procedures for each recipient at the time of listing and at the time of LTx. Data were initially provided at the time of listing to calculate the lung allocation score, and the most recent available RHC data were entered in the registry at the time of LTx. However, RHC measurements were seldom updated for patients after they were placed on the LTx wait list. Therefore, the present analysis focused on mPAP measured at listing. The current diagnostic standard to diagnose PH is mPAP $\geq$25 mmHg on a diagnostic RHC [12,13], although the relevance of this threshold to survival after LTx in COPD has not been established. Therefore, we focus on a continuous measure of mPAP in our analysis, re-scaled to increments of 10 mmHg for regression modeling.

2.2. Statistical methods

All analyses were performed using Stata/IC, version 13.1 (College Station, TX: StataCorp LP). All values are expressed as means ± standard deviation (SD) for continuous measures, and N's and percentages for categorical variables. Covariates were compared by the presence of PH (mPAP $\geq$ 25 mmHg) using independent t-tests for continuous variables and Chi-square tests for categorical variables. Post-transplant survival was compared according to PH category separately for single and bilateral LTx using Kaplan-Meier curves with log-rank tests. Univariate Cox proportional hazards models were used to describe the association of continuous mPAP (in increments of 10 mmHg; e.g., 10 mmHg = 1 unit, 1 mmHg = 0.1 units) and each covariate with post-transplant mortality. For the multivariable Cox proportional hazards analysis, multiple imputation by chained equations was used to fill in missing data on covariates [14]. Categorical, ordinal, and continuous variables were imputed using multinomial logistic regression, ordinal logistic regression, and least-squares regression, respectively, with imputation equations including all covariates in the analysis and the outcome variables of survival time and all-cause mortality. Ten imputed data sets were created and analyzed, with model estimates combined across data sets as previously described [14]. The multivariable analysis was adjusted for all covariates assessed over the study period, and was stratified by transplant type (single vs. bilateral LTx). For all analyses, a P value < 0.05 was considered statistically significant.

Covariates included gender matching, race matching, cytomegalovirus (CMV) matching, transplant type (single vs. bilateral LTx), age, creatinine, days on the waitlist, lung allocation score (LAS), body mass index (BMI), allograft ischemic time, the number of human leukocyte antigen (HLA) mismatches, and panel reactive antibodies (PRA). Allograft size and donor-recipient size matching were calculated using predicted total lung capacity (TLC) [15]. Forced vital capacity (FVC) and 6-min walk distance (6MWD) data were obtained from waiting list data on variables used to compute the LAS, and the earliest available measures of these two variables were included in the analysis. Additional covariates included extracorporeal membrane oxygenation (ECMO) support prior to LTx, and center volume, expressed as the total number (in 100s) of LTx performed at each transplant center over the 2005–2013 study period.

3. Results

3.1. Study population

A total of 3362 first-time LTx recipients with a COPD diagnosis who were transplanted between May 2005 and September 2013 were identified. Patients age <18 years at wait listing (1), patients with missing baseline mPAP data (230), and patients with zero or missing time at risk (26) were excluded, yielding a cohort of 3105 patients. Of this cohort, only 180 patients (6%) contributed multiple measurements of mPAP apart from the mPAP at the time of listing, which was used for analysis. The average duration from the initial RHC until transplant was 385 ± 388 days, and was strongly correlated with duration on the waitlist (Pearson's r = 0.82).

There were 1858 (60%) patients who had undergone bilateral LTx, and 1061 (34%) who had died after LTx. As recorded in the UNOS registry, the primary cause of death was similar between single LTx recipients (graft failure: 79 [17%], infection: 118 [25%], respiratory failure: 62 [13%], other: 218 [46%]) and bilateral LTx recipients (99 [17%], 119 [21%], 66 [11%], and 294 [51%], respectively; p = 0.259 by Chi-square test). Actuarial estimates of bronchiolitis obliterans syndrome-free survival were 82% and 37% at 1 and 5 years, respectively, among single LTx recipients; and 84% and 46% at 1 and 5 years, respectively, among bilateral LTx recipients.

Fifty four percent of the patients (n = 1686) met the diagnostic criterion for PH of mPAP $\geq$ 25 mmHg, including 653 (52%) of single and 1033 (56%) of bilateral LTx recipients (p = 0.072). Table 1 summarizes patient, donor, and transplant characteristics in the cohort, and compares covariates across the PH threshold of mPAP $\geq$25 mmHg. MPAP was 25.2 ± 6.8 mmHg in the single LTx group