Pulmonary Artery Pressure and Benefit of Lung Transplantation in Adult Cystic Fibrosis Patients

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Background. **The effect of lung transplantation (LTx) in patients afflicted with cystic fibrosis (CF) and pulmonary hypertension (PH) at placement on the waiting list is not well studied.**

Methods. **To predict the relationship between initial mean pulmonary artery pressure (MPAP) and hazard ratio (HR) of death after listing associated with LTx in adult patients with CF, the United Network for Organ Sharing database was queried for the years 2005 to 2013. Survival was assessed from waiting list entry until death on the waiting list, death after LTx, or censoring. A multivariate Cox model was performed to estimate the HR of LTx conditional on MPAP at listing.**

Results. **Of 1,841 patients with CF, 10% (177) died on the waiting list, 18% (325) were censored without undergoing LTx, and 73% (1,339) underwent transplantation, 361 of whom died after transplantation. A multivariate Cox model of survival since list entry including 1,336 patients found a protective but statistically insignificant benefit of LTx for patients whose MPAP at listing was 25 mm Hg (HR, 0.879; 95% confidence interval [CI], 0.657–1.177; $p = 0.388$), yet LTx was predicted to be more protective at higher initial MPAP levels, as indicated by the significant interaction term between LTx and MPAP (HR, 0.953; 95% CI, 0.928–0.978; $p < 0.001$). The predicted LTx HR and 95% CI were protective (HR < 1) at $p < 0.05$ for patients with MPAP greater than or equal to 30 mm Hg at listing.**

Conclusions. **Survival benefit of LTx in CF was increasingly protective at higher MPAP levels, with a severity level of PH established above which a survival advantage of LTx was found.**

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Cystic fibrosis (CF) is a common genetic disease predominately afflicting the white population [1, 2]. Progressive respiratory failure is the primary cause of mortality in CF [3]. Consequently, lung transplantation (LTx) is widely accepted as a treatment option that can improve quality of life and provide a potential survival benefit to the CF population [4, 5]. Investigators have attempted to identify predictors for optimal timing of LTx in the CF population, with the majority of experts using pulmonary function as a risk factor for shortened survival and a threshold for referral for LTx. The landmark publication by Kerem and colleagues [6] identified a forced expiratory volume in 1 second (FEV_1) less than 30% as a predictive indicator for mortality. Subsequent research demonstrated that an annual rate of decline in the FEV_1 appears to be a more reliable predictor of death [7]. Furthermore, the FEV_1 threshold is influenced by hypercapnia ($Paco_2 \geq 50$ mm Hg) with FEV_1 greater than 30% associated with higher mortality, whereas an FEV_1 less than or equal to 30% was not [8]. Consequently, investigators have strongly suspected that using FEV_1 less than 30% as the benchmark for referral for LTx is likely associated with a high rate of premature referrals [9], but this conjecture has not been formally tested.

The international guidelines [10] for patient referral for LTx in the CF population use the criterion of an FEV_1 less than 30% for referral along with other clinical factors, including the development of pulmonary hypertension (PH) in the absence of hypoxic exacerbation, defined as a systolic pulmonary arterial pressure (PAP) greater than 35 mm Hg on echocardiography or mean PAP (MPAP) greater than 25 mm Hg measured by right heart catheterization. For placement on the waiting list, these same guidelines [10] recommend the diagnosis of PH with no specific measurements regarding PAP. Although PH is a part of these widely accepted guidelines for referral and placement on the waiting list for LTx in CF, no data exist regarding clinical outcomes and expected benefit of LTx associated with PH at the time of the initial listing. Therefore we sought to identify the role of MPAP at the time of placement on the waiting list in moderating the survival benefit of LTx in patients with CF, using an available database in the United States. With diagnostic criteria for PH increasingly including pulmonary vascular resistance (PVR), we examined whether PVR similarly moderated the survival benefit of LTx [11].

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Patients and Methods

Data Collection

We retrospectively evaluated data from patients with CF who were registered in the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) Registry database [12]. The study was approved with a waiver for the need for individual consent (IRB14-00716) by the Institutional Review Board at Nationwide Children's Hospital. The UNOS/OPTN thoracic database was queried for adult patients with CF listed for LTx from May 1, 2005 to September 6, 2013, representing the cohort listed since the inception of the lung allocation score. Survival was assessed from waiting list entry until death on the waiting list or death after LTx, with censoring on the waiting list or after transplantation, if applicable.

Statistical Methods

All analyses were performed using Stata/MP, version 13.1 (StataCorp LP, College Station, TX). A p value less than 0.05 was considered statistically significant for all analyses. The characteristics of patients with CF who underwent LTx and those who remained or died on the waiting list were compared using unpaired t tests (continuous variables) and χ^2 tests (categorical variables).

A Cox proportional hazards model was fitted to estimate effects of LTx and other variables in the analysis on survival after listing. LTx was treated as a time-varying covariate equaling 0 up to the date of transplantation and equaling 1 afterward. The inclusion of LTx as a time-varying covariate in a Cox proportional hazards model of death after waiting list entry has been used previously to estimate the survival benefit of LTx [13, 14].

To examine variation in the hazard ratio (HR) of LTx (ie, variation in the survival benefit of LTx) across initial MPAP levels, the final multivariate model included LTx as a time-varying covariate, MPAP and its quadratic transformation, an interaction between MPAP and LTx, and controls for candidate age, race, creatinine levels, and body mass index (BMI). The interaction between the quadratic transformation of MPAP and the LTx covariate was not statistically significant and therefore was not included in the final model. MPAP was centered at 25 mm Hg, which is the diagnostic threshold for PH, by subtracting 25 from each patient's MPAP value. This allowed the HR of the LTx term to represent the survival benefit associated with LTx when the initial MPAP equaled 25 mm Hg. To interpret variation in the HR of LTx across levels of the initial MPAP, predicted HRs of LTx and 95% confidence intervals (CIs) were graphed for selected values of MPAP at waiting list entry.

PVR was considered as an alternative moderator of LTx benefit. PVR was not reported directly in the UNOS registry data but was calculated from available PAP, pulmonary capillary wedge, and cardiac output data. The use of additional variables with incomplete data reduced the analytic sample size by 82 cases. The final multivariate model for PVR was the same as for MPAP but excluding the quadratic PVR term, which was not a statistically significant predictor of survival.

After a threshold of MPAP was identified at which LTx was protective (HR of death after list entry associated with LTx <1 and $p < 0.05$), a multivariate logistic regression model was fitted to examine how other risk factors included in the analysis were related to the odds of MPAP exceeding this threshold.

Results

Study Population

A total of 1,841 adult (aged $\geq$18 years) patients with a CF diagnosis who were listed for LTx since the inception of the lung allocation score in 2005 were selected for analysis. A total of 1,819 of these patients had a known death or censoring date that was preceded by the date of waiting list entry. Among these patients, a total of 1,336 had data on MPAP and all covariates at waiting list entry and were eligible to be included in the multivariate survival analysis.

Table 1 summarizes the patient demographics and characteristics of the respective cohort used for the analysis. A total of 73% (1,339 of 1,841) underwent LTx during the study period. Of the 502 patients who did not undergo LTx, 177 died on the waiting list (10% of total sample), and the remaining 325 were censored while on the waiting list. Among patients who underwent transplantation, 361 died and 974 survived and were censored. Patients with CF who underwent LTx were more likely to be men and more likely to have a pan-resistant bacterial lung infection at the time of listing.

The proportions of patients who underwent transplantation in each subgroup defined by the categorical covariates are shown in Table 2. A comparison of survival after listing (inclusive of survival on the waiting list and survival after transplantation) by MPAP ($<$25 mm Hg compared with $\geq$25 mm Hg) at the time of list entry found no statistically significant differences in the survival functions (Fig 1) (log-rank $p = 0.161$), although this analysis did not capture the survival consequences of undergoing LTx, which are estimated using Cox proportional hazards regression further on.

Deaths on the Waiting List

Among 502 patients who did not undergo transplantation, 177 died on the waiting list. Data regarding MPAP were available for 77% (386 of 502) of patients who did not undergo transplantation. MPAP was higher among patients who died on the waiting list (mean, 27.55 ± 9.88) and patients who survived but did not undergo transplantation (mean, 25.68 ± 6.72; $p = 0.031$). However, using a threshold of 25 mm Hg to define PH, the proportion of patients with PH was not significantly higher among those who died on the waiting list (60.34%) versus those who survived but did not undergo transplantation (52.59%; $p = 0.160$).

Multivariate Survival Analysis

In a Cox proportional hazards model (Table 3), higher MPAP was associated with significant risk of death