Mortality Risk and Pulmonary Function in Adults With Cystic Fibrosis at Time of Wait Listing for Lung Transplantation

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Background. **Lung transplantation (LTx) benefit for survival in cystic fibrosis (CF) patients placed on the wait list is not well studied.**

Methods. **To predict the relationship between initial forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) and the hazard ratio (HR) associated with LTx in CF patients, the United Network for Organ Sharing database was queried from 2005 to 2006 for adult patients with CF. Survival was assessed from wait list entry time until death on wait list, death after LTx, or censoring. Multivariate Cox proportional hazards models were used to assess the effect of LTx. The first model estimated the HR of LTx with adjustment for FEV_1 or FVC and other covariates, and the second model estimated the HR of LTx conditional on FEV_1 or FVC at listing.**

Results. **Two hundred seventy-eight patients with CF were included in the cohort, and 277 were used for survival analysis. Lung transplantation reduced the risk for death controlling for FEV_1 (HR, 0.601; 95% confidence interval, 0.375 to 0.964; $p = 0.035$) or controlling for FVC (HR, 0.547; 95% confidence interval, 0.336 to 0.889; $p = 0.015$). Interaction models found that the HR of LTx varied significantly across initial FEV_1 and FVC, with the predicted LTx HR and 95% confidence interval being protective (HR < 1) at FEV_1 of 25% or less and FVC of 40% or less, respectively.**

Conclusions. **The benefit of LTx in adults with CF was significant at a lower baseline FEV_1 than expected. A threshold for baseline FVC was established below which LTx was protective.**

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Cystic fibrosis (CF) is the most common lethal genetic disease in the white population [1]. The respiratory and gastrointestinal tracts are primarily involved in CF, with progressive respiratory failure being the most common cause of death [2]. Lung transplantation (LTx) has become a conventional option to not only improve quality of life but also provide a survival benefit to patients with CF, especially adults with the disease [3].

As a result of death occurring at a young age, numerous investigators have attempted to identify predictors for optimal timing of LTx. The landmark case published by Kerem and colleagues [4] in 1992 involving 673 CF patients found the single best predictive indicator of mortality was forced expiratory volume in 1 second (FEV_1). The authors reported that an FEV_1 less than 30% predicted was associated with a 2-year mortality of 50%, whereas in patients 10 years or younger with the same FEV_1, the relative risk of death was 2.0 (95% confidence interval [CI], 1.5 to 2.6; $p < 0.001$) [4]. International guidelines for CF patient selection for LTx include an FEV_1 less than 30% predicted threshold for placement on the wait list (WL), with consideration for earlier referral of female and younger patients [5]. Subsequent versions of these selection guidelines [6, 7] have upheld an FEV_1 of 30% predicted as the threshold for referral for LTx.

In contrast, other investigators reported that a cutoff of FEV_1 less than 30% predicted is not necessarily a reliable predictor of high risk for death within 2 years in single-center studies [8–11]. Rather than a specific FEV_1 value, a decline in the FEV_1 percent predicted was a more significant predictor of the risk of death [8–11]. Data from the Cystic Fibrosis Foundation National Patient Registry were used to develop multivariate logistic regression models to define clinical predictors of 2-year mortality among patients with CF to assist in selection for LTx, but this analysis provided no better diagnostic accuracy than the widely used criterion of FEV_1 less than 30% predicted [12]. In contrast to this work predicting risk factors for death before LTx, we sought to identify variation in the hazard ratio (HR) of LTx associated with pulmonary function at time of placement on the WL using an available database in the United States.

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Material and Methods

Data Collection

We retrospectively evaluated data from patients with CF who were registered in the Organ Procurement and Transplant Network (OPTN) Standard Transplant Analysis and Research Database administered by United Network for Organ Sharing (UNOS) [13]. The study was approved by the Nationwide Children's Hospital Institutional Review Board with a waiver of the need for individual consent (IRB14-00716). The UNOS/OPTN thoracic database was queried for patients with CF listed during the contemporary era of LTx from January 1, 2005, to December 31, 2006, representing the earliest cohort of lung transplant candidates since the inception of the lung allocation score. Data on specific pulmonary function measures at listing were not available for lung transplant candidates listed in 2007 or later because of changes in data reporting to UNOS. The analytic sample of 278 transplant candidates was compared with 2,497 patients with CF listed for LTx in 2007 or later. Deaths on the WL were less frequent in the later cohort (5.4%) as compared with the analytic sample (16%; $p < 0.001$), but there were no statistically significant differences between the two samples in mean WL time, transplantation events, post-transplant deaths, or any of the covariates included in the multivariate regression analysis, described in more detail subsequently.

Statistical Methods

All analyses were performed using Stata/MP, version 13.1 (StataCorp LP, College Station, TX). For all analyses, a probability value of less than 0.05 was considered statistically significant. The characteristics of CF patients who received a lung transplant and those who remained or died on the WL were compared using unpaired Student's t tests (for continuous variables) and χ^2 tests (for categorical variables). Descriptive statistics for continuous variables were presented as mean and standard deviations, and descriptive statistics for categorical variables were presented as proportions.

Survival was assessed from WL entry time until death on WL or death after LTx, with censoring occurring at the most recent follow-up in 2013 or the date a patient was lost to follow-up, if applicable. Two multivariate Cox proportional hazards models were fitted to estimate the effect of LTx on patients' mortality hazard. Patients who did not undergo transplantation contributed one time segment, from listing until death or censoring on the WL. Patients who did undergo transplantation contributed two time segments—one from listing until LTx, and one from LTx until death or censoring after LTx. Therefore, LTx was treated as a time-varying covariate equaling 0 up to the date of transplantation (or until death or censoring, if the patient did not receive a transplant), and equaling 1 afterward.

Model 1 estimated the hazard ratio (HR) of LTx for mortality after listing, adjusting for potential confounders, including patient sex, patient race, patient age, creatinine level, and body mass index at WL entry. Model 2 added an interaction term between the LTx time-varying covariate and baseline FEV_1 or FVC, respectively. Two variables in this model were of particular interest: the main effect of LTx, or the HR shown for LTx alone, and the interaction term (eg, LTx $\times$ FEV_1). The significance test on the interaction term reflected whether there was a statistically significant linear relationship between the log HR of LTx and each initial pulmonary function measure, with the linear slope of this relationship estimated as the log HR of the interaction term [14]. In contrast to model 1, the main effect of LTx represented the estimated HR of LTx for patients scoring a 0 on each pulmonary function covariate, and no longer represented the effect of LTx for all patients.

Because values of 0 on FEV_1 or FVC were implausible, these variables were centered at approximately their means to simplify interpretation of results from model 2. Centering a variable subtracts a certain constant from all values, resulting in a different—and substantively more informative—meaning of 0 for the centered variables [15]. The FEV_1 was centered at 25% predicted, and the FVC was centered at 40% predicted, meaning that in the regression models, FEV_1 of 0 referred to 25% predicted, with FEV_1 of 5 referring to 30% predicted, and so on. Centering FEV_1 and FVC did not change the estimated interaction between each of these variables and LTx, but meant that the main effect of LTx (ie, the HR shown in the LTx row of the regression tables) referred to the estimated HR of LTx when FEV_1 was 25% predicted, or FVC was 40% predicted, respectively. The confidence interval (CI) around the main effect of LTx described the 95% CI of the HR of LTx at those baseline levels of pulmonary function, respectively.

As a result of the interaction term in model 2, the estimated HR of LTx varied according to FEV_1 or FVC levels. To illustrate that variation, FEV_1 was recentered at 5% increments from 15% to 40%, and HRs and CIs of the main effect of LTx were plotted. The same procedure was performed with FVC, recentering this variable at 5% increments from 25% to 65%.

Results

Study Population

A total of 278 adult (age, $\geq$18 years) patients with a CF diagnosis at WL entry who entered the WL between January 1, 2005, and December 31, 2006, and contributed data on FEV_1 and FVC at the time of listing were selected for analysis. This sample included patients who died on the WL, patients who remained on the WL and did not receive a lung transplant, and patients who received a single or double lung transplant. One patient died less than a day after entering the WL and was excluded from survival analysis. Thus, multivariate Cox proportional hazards models had a sample size of 277 patients contributing 475 time segments.

In the analytic sample, 45 of 278 patients (16%) died on the WL, 198 (71%) received transplants, and 35 (13%) were censored without receiving a lung transplant.