What Is the Optimal Transplant for Older Patients With Idiopathic Pulmonary Fibrosis?

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Background. There is controversy regarding the optimal type of lung transplant—single orthotopic lung transplantation (SOLT) versus bilateral orthotopic lung transplantation (BOLT)—for patients with idiopathic pulmonary fibrosis. We performed this study to determine which type of transplant is more appropriate for older patients with this condition.

Methods. We conducted a review of the United Network for Organ Sharing database from 2005 to 2013 for patients aged 65 years or more with idiopathic pulmonary fibrosis. A 1:1 nearest-neighbor propensity match was utilized to determine differences in survival by transplant procedure type (SOLT versus BOLT). Logistic regression modeling taking into account interaction terms between prespecified variables and the type of transplant was utilized to determine variables that altered the survival outcomes associated with SOLT versus BOLT.

Results. Of 1,564 patients who met study criteria, 521 (33.3%) received BOLT. After propensity matching 498 BOLT recipients to 498 SOLT recipients, BOLT was associated with a significantly improved 5-year survival (48.7% versus 35.2%, $p < 0.01$). However, the mortality hazard associated with BOLT varied from a nonsignificant reduction in survival within 3 months after transplant (hazard ratio 1.24, 95% confidence interval: 0.80 to 1.93) to a significant survival benefit for patients who survived beyond 1 year (hazard ratio 0.64, 95% confidence interval: 0.47 to 0.86). Functional status was also found to be a significant predictor of the survival benefit associated with BOLT.

Conclusions. Bilateral orthotopic lung transplantation is associated with significantly improved survival over SOLT for older patients with idiopathic pulmonary fibrosis, driven by a late survival benefit from bilateral transplantation. However, patients with a reduced preoperative functional status do not appear to derive a similar benefit from bilateral transplantation.

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Lung transplantation has provided clinicians with a method for treating a wide spectrum of end-stage lung diseases, including chronic obstructive pulmonary disorder, cystic fibrosis, and idiopathic pulmonary fibrosis (IPF) [1–3]. For many diseases, bilateral orthotopic lung transplantation (BOLT) has been demonstrated to be associated with a significant survival benefit over single orthotopic lung transplantation (SOLT) [4, 5]. In theory, BOLT provides the recipient both the advantage of the removal of the native lungs, which decreases the risk of native lung complications, and offers substantially more allograft tissue and thus potentially higher pulmonary capacity [6, 7]. However, BOLT also requires a more extensive surgical procedure, often leading to longer intensive care unit and total hospital lengths of stay, and a higher risk of immediate postoperative complications [8, 9].

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Idiopathic pulmonary fibrosis is a progressive lung disease often associated with poor outcomes [10]. Historically, SOLT was the standard type of transplant for IPF patients, as BOLT was not shown to be associated with a significant survival benefit in this population [11, 12]. However, recent studies have demonstrated that BOLT may be associated with significantly improved survival among certain subgroups of IPF patients, including patients with a high lung allocation score (LAS) [13]. Previous work by Thabut and associates [14] demonstrated that despite no significant difference in overall survival among IPF patients treated with BOLT or SOLT, there was an increased hazard of death in the initial postoperative period associated with BOLT as compared with SOLT, followed by a survival benefit associated with BOLT in the later period.

Many etiologies have been proposed and perhaps may be responsible for the reduced early survival among BOLT patients demonstrated in the Thabut study. Nevertheless, there is concern that certain groups of patients, such as older patients, may be at an increased risk for perioperative mortality associated with BOLT versus SOLT [15, 16]. We hypothesized that older patients with IPF are at an increased risk for perioperative mortality associated with

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Abbreviations and Acronyms

AOR = adjusted odds ratio
BMI = body mass index
BOLT = bilateral orthotopic lung transplantation
CI = confidence interval
HR = hazard ratio
IPF = idiopathic pulmonary fibrosis
LAS = lung allocation score
SOLT = single orthotopic lung transplantation

BOLT as compared with SOLT. This increase in perioperative mortality may reduce the overall survival benefit associated with BOLT seen in previous studies. We, therefore, investigated the optimal type of transplant (BOLT versus SOLT) for older patients with IPF.

Patients and Methods

Patient Population

The United Network for Organ Sharing standard transplant analysis and research files were queried for patients aged 65 years or more undergoing isolated lung transplant for a primary diagnosis of IPF (code 1604) during the years 2005 to 2013. Patients were excluded if they had a previous transplant or did not have a recorded LAS. We specifically excluded patients who underwent transplantation before the implementation of the LAS, as patients with IPF undergoing transplantation before 2005 have been demonstrated to be substantially different from those in the current era [8]. Patients were categorized on the basis of whether they underwent SOLT or BOLT. The Duke University Institutional Review Board approved the study.

Statistical Analysis

Groups were compared for baseline characteristics, transplant characteristics, and outcomes. Standardized differences were determined for each of the baseline and transplant characteristics. For outcomes, continuous variables were compared using the Kruskal-Wallis rank sum test, and categoric variables were compared using Fisher's exact test or the χ^2 test as appropriate. Kaplan-Meier analysis was utilized to determine the unadjusted association of the type of transplant (SOLT versus BOLT) and long-term survival. Patients were censored if they were lost to follow-up. Survival differences at specific follow-up timepoints of interest were compared using Kaplan-Meier estimates and standard errors.

A multivariable logistic regression model was created to determine factors associated with undergoing BOLT as compared with SOLT among this cohort. Variables incorporated in the model were determined a priori and included age, sex, race, body mass index (BMI), diabetes mellitus, hypertension, pretransplant glomerular filtration rate, oxygen requirement before transplant, LAS, steroid treatment before transplant, functional status (all activities of daily living performed independently [Karnofsky performance scale 70% to 100%], assistance needed for activities of daily living [Karnofsky performance scale 50% to 60%], or disabled/hospitalized [Karnofsky performance scale 10% to 40%]), smoking status within the past 6 months, any history of malignancy, extracorporeal membrane oxygenation (ECMO) or ventilator support at the time of transplant, and center volume over the study period. Missing variables were assumed to be missing at random. Backward stepwise variable selection was utilized to determine the final model. All variables were tested for linearity before inclusion in the model, and categorized or transformed as appropriate.

A 1:1 nearest-neighbor algorithm, propensity-matched analysis was then performed to adjust for nonrandom treatment selection among this cohort of older patients. Patients were matched on the basis of variables chosen a priori that included age, sex, race, BMI, pretransplant glomerular filtration rate, oxygen requirement before transplant, LAS, steroid treatment before transplant, functional status, smoking status within the past 6 months, time on the waiting list, any history of malignancy, ECMO or a ventilator support at the time of transplant, transplant year, and center volume over the transplant period. Standardized differences and the overlap of propensity scores between groups were compared to evaluate the success of the match. Outcomes were again compared between groups, including long-term survival using Kaplan-Meier analysis. Univariable Cox proportional hazards models were used to determine the associated hazard of BOLT versus SOLT, both in the perioperative period (within 3 months) and beyond 1 year.

Cause of death was compiled for patients who died in each of 3 time periods—within 3 months, between 3 months and 1 year, and beyond 1 year—from the overall (nonmatched) cohort. Cause of death was defined as cardiovascular (cause of death codes 2200 to 2299), cerebrovascular (cause of death codes 2400 to 2499), graft/pulmonary failure (cause of death codes 2300 to 2399), hemorrhage (cause of death codes 2500 to 2599), infection (cause of death codes 2100 to 2199), malignancy (cause of death codes 2600 to 2699), multiple organ failure (cause of death code 2705), or other/unknown (cause of death codes 998 to 999 or missing). The Fisher exact test was used to compare differences between groups.

A second multivariable logistic regression model was created among the initial cohort to determine whether there were any subpopulations for which BOLT was associated with significantly increased perioperative mortality as compared with SOLT among older patients with IPF. The outcome in this model was mortality at 90 days after transplant. Age, sex, BMI, diabetes, pretransplant glomerular filtration rate, oxygen requirement before transplant, LAS, steroid treatment, functional status, and the use of ECMO or ventilator support before transplant were initially included in the model, along with an interaction between each variable and the use of BOLT. Backward stepwise variable selection was