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Single Versus Bilateral Lung Transplantation for Idiopathic Pulmonary Fibrosis in the Lung Allocation Score Era

John R. Spratt, MD, MA,[a,*,1] Rade Tomic, MD,[b,1] Roland Z. Brown, BS,[c] Kyle Rudser, PhD,[c] Gabriel Loor, MD,[d] Marshall Hertz, MD,[b] Sara Shumway, MD,[d] and Rosemary F. Kelly, MD[d]

[a] Department of Surgery, University of Minnesota, Minneapolis, Minnesota
[b] Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, University of Minnesota, Minneapolis, Minnesota
[c] Division of Biostatistics, University of Minnesota, Minneapolis, Minnesota
[d] Division of Cardiothoracic Surgery, Department of Surgery, University of Minnesota, Minneapolis, Minnesota

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease. Lung transplantation is the only therapy associated with prolonged survival. The ideal transplant procedure for IPF is unclear. Outcomes after single transplantation (SLTx) versus bilateral lung transplantation (BLTx) in IPF patients after introduction of the Lung Allocation Score were examined.

Methods: Records of patients undergoing lung transplantation for IPF at our institution between May 2005 and March 2017 were reviewed to examine the effect of transplant laterality. Primary outcomes were overall, rejection-free, and bronchiolitis obliterans (BOS)-free survival at 1 and 5 years post-transplant.

Results: Lung transplantation was performed in 151 IPF patients post-Lung Allocation Score. Most recipients were male with average age 59 ± 8 years. SLTx was performed in 94 patients (62%). In the overall cohort, comparative survival between SLTx and BLTx was similar at 1 and 5 years before and after adjusting for age and pulmonary hypertension (PH). SLTx was associated with shorter ventilator time and intensive care unit stay and trended toward improved survival over BLTx in patients without PH.

Conclusions: The use of SLTx versus BLTx in IPF did not correspond to significantly different survival adjusting for age and PH. BLTx was associated with prolonged postoperative ventilation and length of stay compared with SLTx. Patients without PH, all older patients, and patients with PH and advanced disease should be considered for SLTx for IPF.

* *Corresponding author*. Department of Surgery, University of Minnesota, 420 Delaware St SE Mayo Mail Code 195, Minneapolis, MN 55455, USA. Tel.: +843 324-2218; fax: +612 625-1683.
E-mail address: sprat020@umn.edu (J.R. Spratt).

[1] J.R.S. and R.T. have contributed equally to the preparation of this manuscript.

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Introduction

Lung transplantation is a lifesaving therapy for patients with idiopathic pulmonary fibrosis (IPF). Among all potential lung recipients, patients with IPF have the highest waiting list mortality. Waiting time is prolonged if the patient is listed for bilateral lung transplantation (BLTx).[1,2] Whether single lung transplantation (SLTx) or BLTx is optimal for IPF is controversial. Although many early lung transplants were unilateral, BLTx has eclipsed this over the last 2 decades.[3] International Society for Heart and Lung Transplantation registry data demonstrate that, among all recipients, 63% of all lung transplants are bilateral, and survival is better in BLTx than that in SLTx (median survival 7 vs 4.5 years, $P < 0.0001$).[3] However, this association is confounded by the large differences between these recipient populations.[3] In IPF patients, only about 42% of lung transplants are bilateral, and the long-term outcome advantage is less clear.[1,3]

The implementation of the Lung Allocation Score (LAS) has shifted the demographics of SLTx and BLTx recipients by favoring expected survival benefit over simply accrued wait list time when selecting recipients. This change in allocation practices has made lung transplant available to more patients with IPF and patients with greater disease severity compared with pre-LAS.[4] The effect of this paradigm shift on post-transplant survival has not yet been fully characterized. At our center, we have observed that many patients with IPF who undergo transplantation present either in a state of acute clinical decline or in extremis. These patients suffered exacerbation of their disease, which is often accompanied by new or acute on chronic pulmonary hypertension. This is consistent with national trends and represents a significant shift in IPF disease severity compared with pre-LAS, when very few severely ill IPF patients were able to wait successfully on the list for transplantation.[4]

Many of the existing reports examining procedure type (SLTx vs BLTx) and survival after lung transplantation for IPF are now more difficult to interpret because of their inclusion of pre-LAS patients.[1,3,5-10] Patient age and pulmonary hypertension (PH) may impact post-transplant outcomes in IPF. PH has also been demonstrated to be a risk factor for mortality and primary graft dysfunction (PGD) in patients with IPF post-transplant, although again, much of this data was also obtained from SLTx recipients before LAS implementation.[11-13] More recent studies of post-LAS cohorts challenge these conclusions, partly because IPF patients may either be transplanted earlier in their disease course or subject to decreased waiting list mortality post-LAS.[14-17] Finally, compared with single-center studies, large database analyses may not be as effective in providing granular insight into patient-level decision-making reflective of provider expertise and program experience as patient care evolves over time. For these reasons, we retrospectively reviewed our prospectively collected, single-center database for patients who underwent lung transplantation for IPF post-LAS with the goal of real-time examination of differences in transplant outcomes between SLTx and BLTx and the extent to which this may be affected by recipient age or PH which we believe is reflective of real-world clinical practice.

Materials and methods

We reviewed our database for all patients who underwent SLTx or BLTx for IPF between May 2005 (start of LAS era) and March 2017. Our institutional review board granted approval for the study (IRB #1006M83333).

Institutional practice for single vs. bilateral lung transplant in IPF

At our institution, patients with IPF without or with only mild/moderate PH, significant perfusion imbalance or prior unilateral surgery and/or pleurodesis are generally offered SLTx. Patients with severe PH and/or superimposed chronic infection (e.g., *Mycobacterium* spp., *Aspergillus* spp.) are offered BLTx. Post-LAS, a greater proportion of IPF patients have presented in exacerbation with PH; these patients are generally offered BLTx. We do not have strict age cutoffs for offering SLTx vs BLTx. Patients with higher LAS tend to receive BLTx instead of SLTx.

Patient characteristics and outcomes

Primary survival outcomes were overall, rejection-free, and bronchiolitis obliterans (BOS)-free survival at 1- and 5-year after transplant, with secondary outcomes of PGD grade 3 in the first 72 h, postoperative ventilation time >48 h, intensive care unit (ICU) length of stay (LOS) > 7 days, inpatient LOS >14 days, and >30 days hospitalized in the first year after transplant. In addition to laterality (BLTx vs. SLTx) and PH, recipient characteristics included sex, age, smoking status, time on waiting list, LAS, graft ischemia time, and cytomegalovirus (CMV) status. Donor characteristics included sex, age, and CMV status. Patients with resting mean pulmonary artery pressures (PAPs) ≥25 mmHg were considered to have PH.

Statistical analysis

We tabulated descriptive statistics for the overall cohort, by laterality, and by combinations of laterality and PH, including the mean and standard deviation for continuous variables and frequency with percentage for categorical variables. *P*-values corresponding to differences in descriptive statistics between groups were calculated using t-tests for quantitative variables and chi-square tests for categorical variables. We used Kaplan–Meier estimates for unadjusted survival curves and performed adjusted survival analyses using Cox proportional hazards regression models with robust variance estimates for confidence intervals (CIs) and *P*-values for estimated hazard ratios (HRs). Time at risk for survival analyses started at the time of transplantation until death or censoring (lost to follow-up or administratively censored at data extraction). We also evaluated rejection- and BOS-free survival as composite endpoints. Adjusted odds ratios (ORs) were estimated for secondary outcomes using logistic regression with robust variance estimation for CIs and *P*-values. All regression analyses included terms for