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Comparison of wait times and mortality for idiopathic pulmonary fibrosis patients listed for single or bilateral lung transplantation

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BACKGROUND: Lung transplantation is the one form of solid-organ transplantation in which there is the option for patients to receive one or two organs. Idiopathic pulmonary fibrosis (IPF) candidates can be accommodated by either procedure but the decision about these two options remains controversial. Therefore, we sought to determine whether IPF patients listed for bilateral lung transplantation only had longer wait times and higher mortality on the waiting list than those listed for single lungs only. Patients with chronic obstructive pulmonary disease (COPD) were also analyzed as a comparison group.

METHODS: This study was a retrospective analysis of the Organ Procurement and Transplantation Network database of patients with IPF and COPD listed for lung transplantation between May 2005 and December 2007. An analysis of wait times and mortality in this era as well as the pre–lung allocation score (pre-LAS) era of 2002 to 2004 was performed.

RESULTS: Of the 1,339 patients with IPF listed for lung transplantation, 31.7% were listed for bilateral lung transplantation only, 41% for single-lung transplantation only and 27.3% for either procedure. Patients listed for the bilateral procedure only were at greater risk of dying on the transplant list ($p < 0.003$), and were less likely to receive a lung transplant ($p < 0.012$). No difference in outcomes was seen in the COPD patients. Comparatively, in the pre-LAS era, wait times and mortality on the list for IPF patients were significantly greater for all forms of transplantation.

CONCLUSIONS: There has been a significant improvement in wait times and mortality for IPF patients since the inception of the LAS system. Nonetheless, despite the goal of transplant equity, IPF patients listed for bilateral lung transplantation might have a clinically meaningful increased risk of pre-transplant mortality. The choice of procedures therefore needs to be made with careful consideration of patients' survival both pre- and post-transplantation. Evaluation of transplant outcomes should not only be based on post-transplant survival, but should also account for the impact of the choice of procedure.

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Lung transplantation is the only viable therapeutic option for select patients with idiopathic pulmonary fibrosis (IPF) that might improve their survival. It remains controversial as to whether patients with IPF are better served with a single (SLTx) or bilateral lung transplant (BLTx). Based on data from the International Society for Heart and Lung Transplantion (ISHLT), approximately 15.1% of lung transplants for IPF in 1991 were BLTxs compared with 49.2% in 2006.[1] This shift in the choice of procedures appears to be predicated by the general perception that patients have better long-term outcomes with BLTx than with SLTx. Indeed,

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the ISHLT data does demonstrate a 5-year survival of 55.01% for all BLTx recipients, compared with 47.08% for SLTx recipients for the time period of January 1994 through June 2006.[1] However, this is cumulative data for all primary disease groups and BLTx might not be superior in all instances. It has been demonstrated previously that patients with IPF might paradoxically have worse short-term outcomes with BLTx compared with SLTx.[2] On the other hand, there are more recent data suggestive of superior outcomes with the bilateral procedure among patients with IPF.[1,3] Therefore, the issue of the best procedure in IPF remains unresolved and somewhat controversial.

Another area of interest in the decision-making process regarding which procedure to perform involves the differences in waiting time for BLTx compared with SLTx. This "front end" component that may impact candidate survival has mostly been overlooked previously. We hypothesized that those patients listed for BLTx only would have to wait longer to receive their transplants than those listed for SLTx only. We further sought to determine whether this might impact outcomes and mortality on the waiting list. This issue is especially salient for IPF patients who are at the highest risk of mortality on the waiting list and who can also be served by either procedure. Preliminary results of this study have been reported in abstract form.[4]

Methods

We performed a retrospective analysis of the Organ Procurement and Transplantation Network (OPTN) database for patients with IPF listed for lung transplantation between May 4, 2005 and December 31, 2007 (the LAS period). We chose this time-frame to include only those patients listed under the new lung allocation score (LAS) system and to provide adequate follow-up of all listed patients. As a comparison, we performed a similar analysis of patients with chronic obstructive pulmonary disease (COPD), since these patients can also be accommodated and listed for SLTx only, for BLTx only or for either procedure.

The primary outcome measure of the study was patient disposition at 12 months after listing for SLTx vs BLTx. Patients could have one of four possible outcomes on the list: transplanted; died while waiting; removal from the list for other reasons; or still waiting. Patient outcomes after transplantation were not evaluated or included in this analysis.

A subgroup analysis was performed with patients stratified by their LAS at the time of listing into one of four groups: LAS 30 to <35 (Group 1); LAS 35 to <40 (Group 2); LAS 40 to <50 (Group 3); and LAS ≥50 (Group 4). Patients were further categorized as to whether they were listed for SLTx only, for BLTx only or for either procedure. Patients could therefore fall into one of 12 groups for this analysis. Median time on the waiting list and mortality for all transplanted patients were calculated for each group based on listing for SLTx and BLTx. Patients listed for either SLTx or BLTx were excluded from this analysis.

A comparison was performed of wait times for IPF patients from the LAS era to the pre-LAS period from 2002 to 2004. In addition, mortality on the list for IPF patients from the pre-LAS era was also evaluated. For all comparative analyses, patients listed for SLTx only or for BLTx only were included, whereas patients listed for either SLTx or BLTx were excluded.

Statistical analysis

Since a waiting list candidate can have more than one type of event (death, transplant, removal from the waiting list for other reasons), standard survival analysis techniques for censored data for binary outcomes (e.g., Kaplan–Meier) were not appropriate. For this reason, a competing risks approach was the primary analysis employed to estimate the probability of pre-transplant outcomes. The cumulative incidence technique proposed by Kalbfleisch and Prentice[5] was used to obtain probability estimates, and confidence intervals about the probability estimates were based on variance estimates derived by Aalen.[6] Non-parametric time to event percentile estimates (e.g., median) were based on the competing risk probability distributions for each event calculated as described previously. A comparison of the cumulative incidence of death and transplant between groups was based on the method of Gray.[7]

To further assess the risk of death while waiting, a multivariate competing risks model was utilized, focusing specifically on the outcome of mortality following listing for the two IPF groups: candidates waiting for BLTx vs those waiting for SLTx. This competing risks model was based on the method of Fine and Gray.[8] Factors in the model included candidate age at listing, pulmonary artery systolic pressure, need for continuous mechanical ventilation, body mass index, oxygen requirement at rest, 6-minute walk distance, forced vital capacity percent predicted (FVC), presence or absence of diabetes, New York Heart Association functional class and center waiting list volume. All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC) or R for Windows (version 2.5.1) software. Statistical significance was assumed at $p < 0.05$. All p-values were 2-sided.

Results

LAS era analysis

During the LAS study period, 1,350 patients with COPD and 1,339 patients with IPF were listed for lung transplantation. Comparison of the patients listed for SLTx only, BLTx and either SLTx or BLTx is shown in Table 1. Of the IPF patients, 31.7% were listed for BLTx only (425 of 1,339). IPF patients listed for BLTx had more pulmonary hypertension, shorter 6-minute walk distances and higher LASs than those listed for SLTx only. In addition, more of the SLTx-only patients were >65 years of age.