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Post-transplant survival in idiopathic pulmonary fibrosis patients concurrently listed for single and double lung transplantation

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BACKGROUND: Lung transplantation is a widely accepted treatment for patients with end-stage lung disease related to idiopathic pulmonary fibrosis (IPF). However, there are conflicting data on whether double lung transplant (DLT) or single lung transplant (SLT) is the superior therapy in these patients. The purpose of this study was to determine whether actuarial post-transplant graft survival among IPF patients concurrently listed for DLT and SLT is greater for recipients undergoing the former or the latter.
METHODS: The United Network for Organ Sharing provided de-identified patient-level data. Analysis included lung transplant candidates with IPF listed between January 1, 2001 and December 31, 2009 ($n = 3,411$). The study population included 1,001 (29.3%) lung transplant recipients concurrently listed for DLT and SLT, all ≥ 18 years of age. The primary outcome measure was actuarial post-transplant graft survival, expressed in years.
RESULTS: Among the study population, 433 (43.26%) recipients underwent SLT and 568 (56.74%) recipients underwent DLT. The analysis included 2,722.5 years at risk, with median graft survival of 5.31 years. On univariate ($p = 0.317$) and multivariate ($p = 0.415$) regression analyses, there was no difference in graft survival between DLT and SLT.
CONCLUSIONS: Among IPF recipients concurrently listed for DLT and SLT, there is no statistical difference in actuarial graft survival between recipients undergoing DLT vs SLT. This analysis suggests that increased use of SLT for IPF patients may increase the availability of organs to other candidates, and thus increase the net benefit of these organs, without measurably compromising outcomes.
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Lung transplantation is a widely accepted treatment for patients with end-stage lung disease, including lung disease related to idiopathic pulmonary fibrosis (IPF). IPF is the second most frequent indication for lung transplantation[1,2]; however, there are conflicting data on whether double lung transplant (DLT) or single lung transplant (SLT) is the superior strategy for IPF patients.[3]

The purpose of this analysis was to determine whether actuarial post-transplant graft survival among IPF recipients, concurrently listed for DLT and SLT, is greater for recipients undergoing the former or the latter type of transplant. Although many IPF candidates are concurrently

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Table 1 Study Population Characteristics

	DLT		SLT		
Variable	Frequency (%)	Mean (SD)	Frequency (%)	Mean (SD)	*p*-value
Recipient pulmonary artery diastolic pressure (mm Hg)	NA	16.31 (7.55)	NA	14.71 (7.67)	0.0018
Donor had diabetes mellitus	31 (5.46)	NA	22 (5.08)	NA	0.7920
Male donor	178 (31.34)	NA	141 (32.56)	NA	0.6800
Donor positive for hepatitis C	0 (0)	NA	0 (0)	NA	NA
Donor age (years)	NA	34.02 (15.08)	NA	32.40 (14.14)	0.0846
Poor functional status (dichotomized)	225 (39.61)	NA	210 (48.50%)	NA	0.027
FEV_1 % predicted at transplant	NA	49.84 (17.08)	NA	52.57 (16.59)	0.0132
FVC % predicted at transplant	NA	47.13 (16.58)	NA	48.16 (15.20)	0.3198

The *p*-values for frequencies were calculated with Pearson's chi-square; *p*-values for means were calculated with 2-sample *t*-test ($\alpha = 0.05$). DLT, double lung transplant; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not available; SLT, single lung transplant.

listed for both DLT and SLT, it remains unclear which is the better approach. The present study design comparing patients considered eligible for both DLT and SLT is important because there is no, and likely will never be, a randomized trial exploring the superiority of one therapy over the other. Therefore, our analysis presents results that, although not obtained from a randomized trial, offer the best available evidence to compare DLT with SLT in IPF patients.

Methods

Data collection

Study approval was granted by our institution's institutional review board (IRB No. 2013.77) and is in accordance with the United Network for Organ Sharing (UNOS) Data Use Agreement. The individual consent requirement was waived due to the retroactive and de-identified nature of the data. The Standard Transplant Analysis and Research data set was provided by UNOS (Data Source #061809-6). This data set contains information collected from the UNet[sm] forms, including the Transplant Candidate Registration Form, the Transplant Recipient Registration Form and the Transplant Recipient Follow-up Form. These data are the basis of the UNOS Thoracic Registry.

Study population

The analysis included lung transplant candidates with IPF listed for transplantation between January 1, 2001 and December 31, 2009 ($n = 3{,}411$). The study population included 1,001 (29.3%) lung transplant recipients, concurrently listed for DLT and SLT, all ≥ 18 years of age. Of these patients, 1,437 (42.1%) and 972 (28.5%) were excluded from the analysis because they were listed for only SLT and only DLT, respectively.

Outcome measures

The primary outcome measure was actuarial post-transplant graft survival, expressed in years.

Data analysis

Kaplan-Meier curves and a log-rank test were used to assess the relationship between DLT and actuarial graft survival. We created a backward stepwise estimation model using Cox multivariate regression analysis with exclusion criteria at $p > 0.2$. Candidate variables were selected based on the author's previously published risk score model for 1-year post-transplant survival.[4] Recipient age, donor age, ischemia time, body mass index (BMI), functional status and pulmonary function tests at the time of transplant, recipient gender and donor gender were included in list of candidate variables. Recipient functional status at time of transplant was dichotomized into 2 groups from functional status data provided by UNOS. Table 1 includes a complete list of variables considered in the stepwise estimation Cox regression analysis model.

Results

Study population

The study population included 1,001 lung transplant recipients concurrently listed for DLT and SLT. Four hundred thirty-four (43.36%) recipients underwent SLT and 568 (56.74%) recipients underwent DLT. The DLT and SLT groups did have statistically significant baseline differences, specifically: recipient in the hospital or in the intensive care unit (ICU); recipient on extracorporeal membrane oxygenation (ECMO) or ventilator; recipient receiving steroids; recipient age; ischemic time; functional status; pulmonary function tests; and pulmonary artery diastolic pressure (Table 1).

Survival analysis

The survival analysis consisted of a total of 2,722.5 years at risk, and median graft survival was 5.31 years. On univariate Cox regression analysis, there was no statistically significant difference in graft survival between patients getting SLT vs DLT ($p = 0.317$). After stepwise estimation, the variables included in final Cox proportional hazards model were ICU admission at transplant, estimated glomerular filtration rate (eGFR), history of stroke, donor age, pulmonary artery diastolic pressure, ischemia time, recipient hepatitis C status and low recipient BMI. There was no interaction between the candidate variables. Results for variables derived by the stepwise estimation model are presented in Table 2. In the stepwise estimation model, there

Table 2 Risk Factor Model Variables Included in Stepwise Estimation

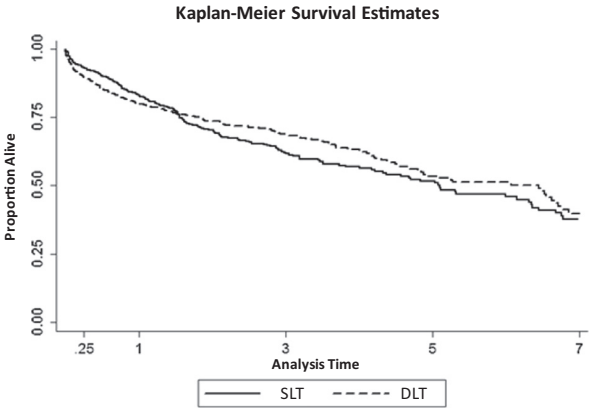
Variable	Hazards ratio	SE	95% CI (LL-UL)	p-value
Recipient with stroke	3.840	1.598	1.698–8.682	0.001
Recipient in ICU	1.964	0.418	1.294–2.981	0.002
Donor age	1.013	0.004	1.005–1.021	0.002
Recipient GFR	0.970	0.010	0.949–0.990	0.004
Recipient peripheral artery diastolic pressure	1.017	0.007	1.003–1.031	0.017
BMI underweight	1.722	0.533	0.938–3.160	0.079
Ischemia time	0.941	0.036	0.872–1.015	0.114
Recipient hepatitis C	1.574	0.515	0.829–2.989	0.166

BMI, body mass index; GFR, glomerular filtration rate; ICU, intensive care unit; LL, lower limit; SE, standard error; UL, upper limit.

was no statistically significant difference in graft survival between patients getting SLT vs DLT ($p = 0.415$). The Kaplan-Meier curve for DLT vs SLT recipients shows that, at 3 months, 93.30% of SLT patients were alive and 89.91% of DLT patients were alive; at 1 year, 83.27% of SLT patients were alive and 80.26% of DLT patients were alive; and, at 5 years, 51.68% of SLT patients were alive and 53.43% of DLT patients were alive (Figure 1).

Discussion

Based on the data analysis, there is no significant difference in actuarial graft survival between recipients undergoing DLT vs SLT for IPF patients concurrently listed for DLT and SLT. There have been conflicting results in other studies regarding the benefit of DLT over SLT in IPF patients. The majority of studies aiming to address this question have been limited by either small sample sizes or short follow-up intervals. Some have argued that DLT may provide a survival advantage by reducing the damage to pulmonary function in cases of early complications or by providing better functional respiratory mechanics and pulmonary reserve.[5] Recently, Mason et al analyzed institutional outcomes of 82 IPF patients who underwent transplantation over a 15-year time interval, and reported that DLT offers a survival advantage for high-risk patients.[6] Likewise, in their analysis of the UNOS database from 2005 to 2007, Weiss et al demonstrated that DLT appears to offer a survival advantage over SLT for a similar group of high-risk patients.[7] In addition, Force et al demonstrated that, among 3,860 patients in the UNOS registry, DLT offers better long-term survival for younger patients.[8] In keeping with these results, recent International Society for Heart and Lung Transplantation (ISHLT) annual reports showed that the annual ratio of DLT to SLT is increasing.[9]



Time (yrs)	0.25	1	3	5	7
SLT	0.9330	0.8327	0.6205	0.5168	0.3779
DLT	0.8991	0.8026	0.6870	0.5343	0.3983

Figure 1 Kaplan-Meier curve for single lung transplant vs double lung transplant.

However, the superiority of DLT in IPF patients has not been observed by all investigators. Thabut et al analyzed UNOS data of 3,327 IPF patients who underwent transplantation between 1987 and 2009.[3] Using several methods of risk adjustment, including multivariable regression and propensity-based matching, they found that there was no difference in long-term survival between SLT and DLT patients. In addition, Meyers et al found no differences in functional status between SLT and DLT recipients based on forced expiratory volume in 1 second (FEV_1) and 6-minute walk distance.[10] Furthermore, they demonstrated that, among patients <60 years of age, there was a survival benefit for SLT over DLT.[11] Therefore, there are currently mixed opinions in the literature on, first, whether DLT is associated with greater survival than SLT and, second, how to best identify recipients that may benefit from one therapy over the other.

In this analysis, there was no statistical difference in actuarial survival between IPF recipients undergoing DLT vs SLT. We compared survival in IPF patients who were cross-listed for SLT and DLT, instead of using propensity analysis to compare patients listed solely for either SLT or DLT, as in most of the literature to date. Therefore, we have presented results that, although not obtained from a randomized trial, offer the best available evidence to compare DLT with SLT in IPF patients. Our analysis suggests that use of SLT instead of DLT in IPF patients may increase the availability of organs to other candidates, and thus increase the net benefit of these organs without measurably compromising individual patient survival.

Limitations

By comparing SLT and DLT cross-listed IPF patients, our study has addressed survival advantages of DLT over SLT. This type of analysis assumes that organ matching was

random and based solely on the donor organs. Although this assumption may be true in many cases, whether a patient received a SLT or DLT may not have been a completely random event in all cases analyzed. For example, some sites may cross-list their IPF patients for both SLT and DLT, but preferentially perform one type of operation on those patients. Furthermore, our analysis has shown that patients undergoing SLT and DLT differed with regard to some pre-transplant characteristics. Although multivariate regression models were used to control for differences in the 2 groups, there may have been other recipient-related factors that impacted the decision to perform SLT or DLT that were not present in the data set or obvious in the statistical analysis. Despite these limitations and some experimental imperfections, this study does offer a good approximation to a randomized trial.

In addition, as with most large patient registries, bias may be introduced from incompleteness of data entry. However, in general, most data fields within the UNOS registry are well populated, with a 90% to 99% data entry rate. Further, although UNOS provides definitions for clinical variables, there exists the potential for center-to-center reporting variability. Nonetheless, the major outcome of our survival analysis (post-transplant survival, expressed in years) is unlikely to be affected by variations in center reporting.

In conclusion, compared with SLT, DLT showed no statistically significant difference in actuarial survival for IPF patients. This suggests that increased use of SLT in this population may increase the availability of organs to other candidates and thus increase the net benefit of transplantation, without compromising outcomes.

Disclosure statement

The authors have no conflicts of interest to disclose.

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