Impact of bilateral versus single lung transplantation on survival in recipients 60 years of age and older: Analysis of United Network for Organ Sharing database

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Objective: Lung transplantation has been increasingly applied to patients over the age of 60 years. Importantly, the procedure of choice, single versus bilateral lung transplantation, remains unclear. Therefore, the purpose of this study was to examine short- and midterm outcomes in this age group with particular attention to procedure type.

Methods: All first lung transplant recipients, 60 years of age or older, reported to the United Network for Organ Sharing from 1998 to 2004 were divided into two groups: bilateral and single lung transplantation. A retrospective review of pertinent baseline characteristics, clinical parameters, and outcomes was performed. Kaplan–Meier methodology was used to estimate and Cox proportional hazards regression modeling was used to compare posttransplant survival between these groups. Additionally, propensity scores analysis was performed.

Results: During the study period, 1656 lung transplant recipients were 60 years of age or older (mean 62.7 ± 2.4 years, median 62 years). Of these, 364 (28%) had bilateral and 1292 (78%) had single lung transplantation. Survival was not statistically different between the two groups. In the multivariate analysis, bilateral versus single lung transplantation was not a predictor of mortality. Idiopathic pulmonary fibrosis and a donor tobacco history of more than 20 pack-years were significantly associated with mortality ($P = .003$, CI 1.12–1.76; and $P = .006$, CI 1.09–1.63; respectively).

Conclusions: The survival of lung transplant recipients 60 years of age or older who underwent bilateral versus single lung transplantation is comparable. These data suggest that type of procedure is not a predictor of mortality in this age group. Idiopathic pulmonary fibrosis and donor cigarette use of more than 20 pack-years were independently associated with mortality.

Results of clinical lung transplantation (LTx) over the past two decades have progressively improved. Nonetheless, LTx is limited by the availability of donor organs, and a careful selection of LTx recipients is critically important. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for selection of appropriate candidates for LTx have suggested an age limit of 60 years for bilateral (BLT) and 65 years for single (SLT) lung transplantation.¹ The age limitation was based on previous reports showing that older patients have significantly higher mortality than younger patients.² However, the age distinction for BLT versus SLT has not been clearly supported by the literature. The few reports that address this issue have been limited to disease-specific database analyses^{3,4} and a single-center report with a small number of patients.⁵

As the number of older patients listed for LTx increases, the procedure of choice (BLT vs SLT) for these patients requires further scrutiny. We therefore analyzed the impact of procedure type on short- and midterm survival in recipients 60 years of age

Abbreviations and Acronyms

BLT	= bilateral lung transplantation
COPD	= chronic obstructive pulmonary disease
FVC	= forced vital capacity
IPF	= idiopathic pulmonary fibrosis
ISHLT	= International Society for Heart and Lung Transplantation
LTx	= lung transplantation
SLT	= single lung transplantation
STAR	= Standard Transplant Analysis and Research (files)
UNOS	= United Network for Organ Sharing

or older for all disease types, using data reported to the United Network for Organ Sharing (UNOS) registry in the recent era, between 1998 and 2004.

Materials and Methods**Patient Population**

Data reported to the UNOS registry for LTx performed between January 1, 1998 and December 31, 2004 were analyzed. The follow-up period was up to September 2005, which is when the files were created. This time period was chosen to represent a modern cohort of patients in light of advancements made in LTx. Among the 6785 first-time LTx recipients, we identified 1656 patients 60 years of age or older, and these were stratified by type of transplant procedure: BLT ($n = 364$) and SLT ($n = 1292$). The patient characteristics are shown in Table 1.

Statistical Analyses and Survival

All available data from the UNOS Standard Transplant Analysis and Research (STAR) files were imported into Stata version 9.0 (StataCorp. College Station, Tex), which was used for statistical computations. Continuous variables are summarized as mean $\pm$ standard deviation. Bivariate comparison of continuous variables was per-

formed with a Student t test. Associations between categorical variables were tested by the Pearson χ^2 test. Survival estimates for each procedure type were calculated by the Kaplan–Meier method, and statistical differences between survival curves were assessed by the log–rank (Mantel–Cox) test. Multivariate analyses were performed by Cox proportional hazards regression to determine whether type of procedure was an independent predictor of mortality after adjustment for potential cofounders. During the analyses for model selection, only variables with more than two thirds of available data were considered, and these are listed in Table 2. To more accurately estimate confidence intervals, we made the assumption that the missing data were missing at random and performed imputation of missing data using the single regression method. Our findings proved to be robust across models that included both imputed and nonimputed (ie, case-wise deletion of observations with missing data points) data. We therefore chose to construct a model that reflects the effect of the clinically relevant potential cofounders listed in Table 2. This model also has the lowest Akaike and Schwarz Bayesian information criterion scores, which makes it a model of choice.

In addition to the standard multivariate analysis, to reduce bias and increase precision, we generated propensity scores by developing a model that estimates the probability of a patient receiving BLT versus SLT. The factors used in this model were recipient age, donor age, body mass index, pulmonary artery mean pressure, forced vital capacity (FVC) (percent predicted), and year of transplant. Propensity scores were analyzed by the regression adjustment technique; that is, both the propensity scores and type of procedure (“treatment factor”) were included in a Cox regression model.

Results**Patient Characteristics**

Of the 1656 first LTx recipients, 364 patients received BLT and 1292 had SLT. Their ages ranged from 60 to 87 years old (mean 62.7 ± 2.4 years, median 62 years). The age distribution is shown in Figure 1. Eighty-eight percent of the patients were between 60 and 65 years old. Interestingly, there were 196 patients (12%) above the age of 65 years. Furthermore, from

TABLE 1. Clinical characteristics by type of procedure

Clinical characteristics	BLT (N = 364)	No. with data	SLT (N = 1292)	No. with data	P value
Age (y)	62.3 ± 2.1	364	62.8 ± 2.5	1292	.002
Female gender	134 (37%)	364	553 (43%)	1292	.004
Donor age (y)	32.1 ± 14.4	364	32.8 ± 13.8	1291	.4
Native disease		364		1292	<.001
COPD	224 (62%)		863 (67%)		
IPF	80 (22%)		349 (27%)		
Others	60 (16%)		80 (6%)		
BMI	24.1 ± 3.9	356	25.2 ± 6.2	1220	<.001
FEV ₁ (%)	35.5 ± 23.4		34.5 ± 20.6		.66
FVC (%)	55.5 ± 17.9	340	53.1 ± 16.3	1162	.025
Mean PAP (mm Hg)	26.2 ± 8.1	281	24.7 ± 8.5	1002	.01
Ischemia time (h)	5.3 ± 1.6	322	3.78 ± 1.3	1107	<.001
Follow-up time (mo)	21 ± 19	364	26 ± 21	1291	.001

BLT, Bilateral lung transplantation; SLT, single lung transplantation; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; BMI, body mass index; FEV₁ (%), forced expiratory volume (percent predicted); FVC, forced vital capacity; PAP, pulmonary artery pressure.

TABLE 2. Multivariate Cox proportional hazards model*

Risk factor	HR	P value	95% CI	
BLT vs SLT	0.989	.94	0.76	1.28
Age (y)	1.001	.98	0.96	1.03
Gender (F vs M)	0.885	.23	0.72	1.08
IPF (vs other native diseases)	1.405	.003	1.12	1.76
BMI (kg/m ²)	0.991	.45	.97	1.01
Donor age (y)	1.004	.29	.99	1.01
Donor > 20 pack-year cigarette use	1.333	.006	1.09	1.63
HLA mismatch level (HLA ≤ 4 vs HLA = 5.6)	1.066	.44	0.91	1.26
Transplant year	0.996	.89	.94	1.06
Ischemia time (h)	0.949	.15	.88	1.02

HR, Hazard ratio; CI, confidence limits; BLT, bilateral lung transplantation; SLT, single lung transplantation; IPF, idiopathic pulmonary fibrosis; BMI, body mass index. *Other risk factors at the time of transplant that were considered for the multivariate analyses include recipient factors: type of native disease, on ventilator, on life support (intra-aortic balloon pumping, extracorporeal membrane oxygenation), history of hypertension, history of diabetes, forced vital capacity (percent predicted), forced expiratory volume in 1 second (percent predicted), most recent pulmonary artery mean pressure, most recent panel-reactive antibody (percent) at transplant, transfusions from registration to transplant, serum creatinine, total bilirubin, and cytomegalovirus status. Other donor factors include donor cytomegalovirus status and deceased donor antihypertensive use within 24 hours before crossclamp. Recipient/donor gender and cytomegalovirus mismatch were also considered.

1998 to 2004, there was an increase from 19% to 27% in the number of first LTx recipients 60 years of age and older. Likewise, the number of BLTs performed among these patients increased from 14% in 1998 to 34% in 2004 (Figure 2). Table 1 compares the details of patient preoperative clinical characteristics between the two groups. Patients who received BLT versus SLT were statistically younger (62.3 ± 2.1 years vs 62.8 ± 2.5 years; $P = .002$). There were fewer female patients in the BLT group (37% vs 43%; $P = .04$), lower body mass index (24.1 ± 3.9 vs 25.2 ± 6.2 ; $P = .001$), higher percent predicted FVC ($55.5\% \pm 17.9\%$ vs $53.1\% \pm 16.3\%$; $P = .025$), and mean pulmonary artery pressure (26.2 ± 8.1 mm Hg vs 24.7 ± 8.5 mm Hg; $P = .01$). Graft ischemia time, recorded as the time from recovery to implantation of the second lung in BLT, was longer in the BLT group (5.3 ± 1.6 hours vs 3.8 ± 1.3 hours; $P < .001$). Furthermore, the BLT group had shorter mean follow-up time than the SLT group (21 ± 19 months vs 26 ± 21 months; $P = .001$).

Patient Survival

As shown in Figure 3, 30-day survival was 94.9% for BLT and 95.2% for SLT and 1-year survival was also comparable: 78% for BLT and 77.2% for SLT. Although there appeared to be a favorable survival trend with BLT (45.3% vs 38% for SLT) at 5 years, there was no statistically significant difference in the overall survival experiences between these groups ($P = .33$).

Figure 1. Age distribution.

Likewise, no statistical survival advantage of either procedure type was noted when patients were further analyzed by diagnosis. For patients with chronic obstructive pulmonary disease (COPD), 1-, 3-, and 5-year survivals were 81.2%, 62.9%, and 50.7% for BLT and 81.5%, 61.5%, and 42.5% for SLT, respectively ($P = .56$) (Figure 4). Similarly, patients who received LTx for idiopathic pulmonary fibrosis (IPF) had 1-, 3-, and 5-year survivals of 72.4%, 54.3%, and 54.3% for BLT and 69.4%, 51.7%, and 33.1% for SLT, respectively ($P = .51$) (Figure 5). Independent of procedure type, 30-day mortality was less than 7% for IPF, COPD, and the entire cohort. Additionally, when only patients who are 61 years of age or older are considered in all the above survival analyses ($P = .39$ for the entire cohort), the results are similar.

Multivariate Analysis of Patient Survival

In a multivariate Cox proportional hazards model that was adjusted for recipient age, gender, body mass index, and native disease and for donor age, cigarette use, transplant year, and HLA mismatch; IPF and donor cigarette use for more than 20 pack-years emerged as significant predictors of mortality. Type of procedure was not a significant predictor of mortality (Table 2). Other variables that were considered for the model were not statistically significant and are shown in the appendix to Table 2.

Furthermore, propensity scores analysis by the regression adjustment technique was performed, whereby both the propensity scores and type of procedure, as well as other potential risk factors, were included as predictors of outcome. BLT versus SLT still did not emerge as predictors of mortality, whereas donor cigarette use for more than 20 pack-years and IPF remained independent predictors.

Discussion

This study of a large cohort of elderly patients (60 years of age and older) who received LTx from 1998 to 2004 did not show

Figure 2. Distribution of type of procedure. BLT, Bilateral lung transplantation; SLT, single lung transplantation.

significant differences in short- and midterm survival between BLT and SLT. In addition, IPF and heavy donor tobacco use were independently associated with mortality. Moreover, operative mortality was less than 10%, which is better than previous reports.

Steady improvements in the management of LTx patients have led to better outcomes. This has emboldened programs to offer LTx to older patients. The ISHLT/UNOS registry has shown a steady increase in the proportion of LTx recipients 60 years of age and older.⁶ This raises the important and persistently controversial question of which procedure type (BLT vs SLT) is optimal in patients over the age of 60. Meyer and associates³ analyzed the ISHLT/UNOS registry for all recipients who received LTx for COPD between 1991 and 1997. They concluded that SLT offered acceptable early survival, but long-term survival data favored BLT except in patients over the age of 60. Likewise, a single-center study of 126 LTx recipients from 1991 to 1996 demonstrated survival advantages of BLT over SLT in patients with COPD, but increased morbidity in BLT patients over the age of 55 years. The authors therefore discouraged the use of BLT in patients above this age.⁷ A more recent analysis of 1994-2000 UNOS data for patients with IPF found no difference in survival between SLT and BLT in the subanalysis of patients 60 to 69 years of age.⁴

Nonetheless, we hypothesized that modern improvements in LTx have led to better outcomes in elderly patients. Our analysis of first LTx recipients 60 years of age or older reported to UNOS from 1998 to 2004 showed that procedure type was not a predictor of mortality by unadjusted or adjusted analysis. In contrast to older studies, survival was markedly better in this study. According to the report by Meyer and colleagues,³ patients older than 60 years with COPD who received LTx between 1991 and 1997 had 30-day and 1-year survivals of 93.5% and 72.9%, respectively, for SLT versus 77.8% and 66%, respectively, for BLT. In our study, 30-day survival was about 95% for both the BLT and SLT groups and 1-year survival was 77.2% for SLT and 78% for BLT for the entire cohort. Furthermore, when only patients with COPD are

Figure 3. Kaplan-Meier estimates of survival for all patients, stratified by type of procedure. BLT, Bilateral lung transplantation; SLT, single lung transplantation.

analyzed, the 30-day and 1-year survivals are 95.8% and 81.5% respectively, for SLT and 95% and 81.2%, respectively, for BLT. This suggests that concerns over increased perioperative mortality for BLT owing to a more complex operation are unfounded in the recent cohort. The favorable survival trend observed by 5 years with BLT did not achieve statistical significance in our study. However, since we chose a recent time period, the number of patients who could be analyzed at 5 years was small. The 5-year survival of 45% for BLT and 39% for SLT for this cohort of elderly patients is lower than the 49% overall 5-year survival for LTx reported by the 2005 ISHLT registry.⁶

The multivariate analysis identified IPF and donor cigarette use of more than 20 pack-years as independent predictors of mortality. Donor tobacco use has been previously reported in the ISHLT data set as a risk factor for long-term mortality, but it is interesting that IPF remains a risk in the elderly cohort. Although this study does not allow further exploration of this phenomenon, it suggests that one should exercise caution when using a donor with more than 20 pack-years of cigarette use in elderly patients with IPF.

The decision to perform BLT or SLT in elderly patients is somewhat entrenched in institutions. Although, guidelines exist with age cutoffs (BLT in patients > 60 and SLT in patients > 65), several centers perform BLT in all patients preferentially. Overall, proponents of SLT in LTx have argued that SLT is an easier procedure to perform, has less morbidity and mortality associated with it than BLT, and results in less ischemic time; therefore, an SLT has better early graft function, has improved early survival, and will allow more patients to receive LTx. Proponents of BLT have argued that BLTs result in fewer ventilation/perfusion mismatches, are easier to care for in the perioperative period, will provide better overall

Figure 4. Kaplan–Meier estimates of survival for patients with chronic obstructive pulmonary disease, stratified by type of procedure. *BLT*, Bilateral lung transplantation; *SLT*, single lung transplantation.

Figure 5. Kaplan–Meier estimates of survival for patients with idiopathic pulmonary fibrosis, stratified by type of procedure. *BLT*, Bilateral lung transplantation; *SLT*, single lung transplantation.

lung function, are protective against the physiologic manifestations of obliterative bronchiolitis, and offer a better long-term survival.⁸ Furthermore, although BLT does entail longer donor ischemic times for the second lung implanted, this has not translated into measurable adverse sequelae.^{9,10}

Both procedures have been accepted by practitioners and likely will be acceptable for the foreseeable future, and the percentage of BLTs performed in elderly patients has been increasing. Our current report refutes the concerns about higher perioperative mortality for BLT in this patient population, and although a statistical survival advantage was not demonstrated, other single-center reports suggest that BLT is overall associated with better long-term survival and freedom from bronchiolitis obliterans.¹¹ Our findings also agree with a recently published report of 107 consecutive LTx recipients 61 years of age and older that demonstrated comparable short- and midterm outcomes achieved with BLT and SLT.¹² In their study, Palmer and associates¹² also reported 1-, 2-, and 5-year survival estimates of 82%, 75%, and 68%, respectively, for BLT and 78%, 70%, and 44%, respectively, for SLT. The survival advantage of BLT also did not achieve statistical significance. Even if use of BLT for the elderly population has a positive impact on patient survival, concerns remain about whether this strategy may decrease the availability of donor organs.

Our institution prefers the use of BLT for all patients because we believe that there are short- and long-term advantages. However, owing to the limited number of organs available, we recognize that SLT is a reasonable option for older patients with COPD and IPF as compared with the alternative, which is death. In general, it appears that BLT has already been empirically accepted by many in the transplant community inasmuch as the percentage of patients over 60 receiving BLT continuously increased between 1998 and 2004. Ultimately, more studies and the analysis of long-term results from this database will be necessary to determine an advantage of one procedure type over another.

The current study has the inherent limitations of the review of a multi-institutional voluntary registry. Analysis of survival data may be compromised by lack of uniformity of reporting and nonstandardized organ preservation and surgical techniques, as well as postoperative and immunosuppressive management. Only first LTx recipients were included to help achieve a more uniform cohort of patients. The 1998 to 2004 era was also selected to reflect the advancements that have recently evolved in LTx. There may have been selection bias in favor of BLT because our data did show that the BLT patients were statistically younger. The clinical significance of 6 months' difference is, however, questionable. This difference is most likely a reflection of the tendency to perform transplantation in patients who are relatively younger and to use BLT. However, age is one of the clinical cofounders that was controlled for in the Cox proportional hazards model. There were fewer female recipients, lower body mass index, and higher percent predicted FVC in the BLT group, although these patients also had higher mean pulmonary artery pressure. On the other

hand, the differences in these parameters between the two groups do not appear to have significant clinical implications. When these parameters are controlled for in a multivariate model as well as propensity scores analysis, the same results were obtained. Evaluation of other secondary end points such as bronchiolitis obliterans may also provide important insights into the advantage of one procedure over another.

Conclusions

Our analysis of the UNOS database from a recent era showed comparable short- and midterm survival for BLT versus SLT in patients 60 years of age or older. These data suggest that recipients older than 60 years should not be excluded from the use of BLT based on concerns of higher early mortality. Long-term outcomes will better define any survival advantage of BLT over SLT, and future studies will help to determine the best use of BLT versus SLT in the older population.

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Discussion

Dr G. Alexander Patterson (*St Louis, Mo*). This study was undertaken primarily to determine whether there was any difference in outcome between SLT and BLT recipients of older age. The authors have noted the expected preoperative differences between BLT and SLT recipients with respect to age, preoperative FVC, and pulmonary artery pressure, all of which you would expect to be different, but I would argue those differences are clinically irrelevant.

There are a number of observations in this report that I think are important. First, perioperative mortality was surprisingly low in this age group. Our own experience at Washington University is similar, actually. Among 168 patients over the age of 60, our operative mortality rate was only 2.4%. I think low mortality rates are achievable in these patients. Mortality did not differ between SLT and BLT recipients. One-year and 5-year survivals are similar for both of these procedures in older patients but lower than we would expect and lower than previously has been reported for younger recipients. In addition, the study provides important confirmation of previously reported data suggesting poorer outcome with older donors and donors with a significant smoking history. I know we are going to be talking about that in a subsequent presentation. However, there are some limitations in this study that I think are relevant. First of all, it does suffer from the defects of a multicenter, multiprotocol registry with limited data fields. Dr Nwakanma, you did acknowledge that in your slides, but I think of more importance is that this information was accumulated in an era predating the current allocation scheme, which allocates priority for donor lungs by severity of disease rather than by waiting time. The former system of priority by waiting time favored the patients with emphysema on the waiting list. The current system of priority by severity of disease favors the patients with fibrosis. As you might expect, 65% of the recipients reported from this previous era in the current report had emphysema and only 26% had fibrosis. We should be very careful in extrapolating these results in elderly patients to the current era. It is likely that in future years older patients with fibrosis will predominate on our waiting list. The authors have clearly demonstrated what is already known, that patients with fibrosis have poorer immediate and long-term outcome than patients with obstructive lung disease after LTx.

I have two questions. Dr Nwakanma, could you comment on what you think the current algorithm or the current lung allocation scoring system might do to these results looking forward? Also, I think it would be helpful if you could tell us where that 87-year-old patient received the LTx, because I think the program directors of that program need psychiatric help.

Dr Nwakanma. Thank you, Dr. Patterson, for your time and for commenting on our paper.

To answer your first question, as you mentioned, the new lung allocation system actually bases on severity of disease. We believe that what we have been able to show with these data is that the patients who are older than 60 do not have a worse outcome with BLT in a recent cohort. Therefore, if the organ is available and the elderly patient has a high lung allocation system score, then the patient should not be deprived of receiving bilateral lungs. The new system was only implemented in, I believe, the spring of 2005, so time will tell the actual effect of the new allocation system on the choice of SLT versus BLT in elderly patients.

As regards your second question, we had the same question in our minds when we saw that there was an 87-year-old patient. We triple-checked by the transplant identification and by the donor

identification, and we contacted UNOS several times. They confirmed verbally and in writing that there was an 87-year-old recipient according to their data. Whether that was a mistake or not, they could not clarify, but they told us it was an actual recipient, and the patient actually received the LTx in July 1998, but the location of the program where the transplantation was performed is confidential information, as you might imagine. It was not done at Johns Hopkins.

Dr Thomas C. Wozniak (*Indianapolis, Ind*). I like this trial because it shows that the mortality really is not any different for BLT. Like probably most programs, we are listing more and more people over the age of 60. In the past we had traditionally favored SLT in those patients if they could tolerate that. However, what we are beginning to see now are more patients whom we really wish we had treated with BLT rather than SLT. They have survived, but I do not believe they have recovered and reached a functional quality of life that they could have, and they have struggled. Do you have any way to look at the functional outcome as opposed to the actual survival in these patients?

Dr Nwakanma. Thank you for your question. That's a nice comment. We really wish we could, but the data do not provide reliable information to make a good conclusion in terms of functional outcomes.

Dr Robert Shen (*Charlottesville, Va*). I was quite interested by the findings of your multivariate analysis, which showed that the only two factors that were predictive of increased mortality were smoking greater than 20 years in the donor and the diagnosis of IPF. The most recent annual report of the ISHLT data shows that body mass index and advanced age of the recipient were the only two factors in that registry that were predictive of increased mortality. Do you have a hypothesis or an explanation for the difference in the two outcomes based on the two different registries?

Dr Nwakanma. Thank you for your questions. The 2005 ISHLT registry report by Trulock and colleagues was looking at patients mainly from 1994 to 2003. Our patient cohort includes patients from 1998 to 2004, and, as I mentioned, we chose this period to represent mainly the modern cohort and reflect the modern improvements in LTx. It is possible that a difference in the predictors of mortality is based on the different time era. Moreover, the registry report looks at all patients, but our analysis looked at only those who are older than 60 years. Those differences might explain the different results.

Dr Bryan F. Meyers (*St Louis, Mo*). I am interested in your results with regard to IPF and the absence of an effect of SLT versus BLT in these older patients. Your results are particularly interesting in light of the fact that Meyer and colleagues, last year, came to an opposite conclusion—that older patients did worse with the BLT for fibrosis than with SLT—and I think it was probably based on much the same data. I wondered if you are aware of that report and if you have any estimate of why the two reports come to different conclusions.

Dr Nwakanma. Thank you for that question. The answer also lies in the answers I gave for the previous question. The report from Meyer and colleagues, reported in 2005, was looking, again, at all patients regardless of age who had native disease of IPF. However, when they did a subanalysis that looked at only patients who were 60 to 69 years old, they actually found no difference between SLT and BLT in that subgroup of patients according to that particular paper. Although we have about the same time period, they actually also found no difference for the subgroup between 60 to 69 years old.