Survival Benefit of Lung Transplantation in the Modern Era of Lung Allocation

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Abstract

Rationale: Lung transplantation is an accepted and increasingly employed treatment for advanced lung diseases, but the anticipated survival benefit of lung transplantation is poorly understood.

Objectives: To determine whether and for which patients lung transplantation confers a survival benefit in the modern era of U.S. lung allocation.

Methods: Data on 13,040 adults listed for lung transplantation between May 2005 and September 2011 were obtained from the United Network for Organ Sharing. A structural nested accelerated failure time model was used to model the survival benefit of lung transplantation over time. The effects of patient, donor, and transplant center characteristics on the relative survival benefit of transplantation were examined.

Measurements and Main Results: Overall, 73.8% of transplant recipients were predicted to achieve a 2-year survival benefit with lung transplantation. The survival benefit of transplantation varied by native disease group ($P = 0.062$), with 2-year expected benefit in 39.2 and 98.9% of transplants occurring in those with obstructive lung disease and cystic fibrosis, respectively, and by lung allocation score at the time of transplantation ($P < 0.001$), with net 2-year benefit in only 6.8% of transplants occurring for lung allocation score less than 32.5 and in 99.9% of transplants for lung allocation score exceeding 40.

Conclusions: A majority of adults undergoing transplantation experience a survival benefit, with the greatest potential benefit in those with higher lung allocation scores or restrictive native lung disease or cystic fibrosis. These results provide novel information to assess the expected benefit of lung transplantation at an individual level and to enhance lung allocation policy.

Keywords: lung transplantation; lung allocation score; survival benefit; structural nested accelerated failure time model

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Lung transplantation is an increasingly employed treatment for adults with advanced lung disease, with the volume of transplantations doubling since 2005 to nearly 4,000 annual operations worldwide (1, 2). However, survival after lung transplantation remains poor in comparison with other solid organ transplants, with 1- and 3-year survival rates of 80 and 65%, respectively (2). The characteristics of lung transplant recipients have changed substantially, with the most robust growth found among patients more than 65 years of age (3) and a shift to interstitial lung disease as the most common indication (2). Because posttransplantation survival remains limited, determining whether and for which patients transplantation prolongs survival remains an important but controversial task.

Because of the absence of randomized trials, observational data must be used to estimate the survival benefit of lung transplantation, relative to remaining “untransplanted.” Single-center and registry-based studies (e.g., United Network for Organ Sharing [UNOS], Eurotransplant, and UK national registries) have arrived at varying and sometimes inconsistent conclusions on the efficacy of lung transplantation in adults (4–18). These studies are subject to several limitations. With the exceptions of Russo and colleagues (12) and Thabut and colleagues (15), they have used cohorts from an older era, before implementation of the lung allocation score (LAS), a composite score derived from several patient characteristics that was designed to maximize lung transplant survival benefit (19).

In addition, almost all previous studies have consistently employed a Cox model to estimate the survival benefit conferred by transplantation. However, there are inherent limitations when this statistical approach is applied to transplantation data. Because acutely ill candidates are more likely to undergo transplantation, survival times on the waiting list are informatively censored. The inclusion of time-varying covariates to address the informative censoring is also problematic for clinical interpretation. Although the lung allocation score itself incorporates an estimate of survival benefit (using inverse probability of censoring weighted estimators to account for dependent censoring from the waiting list), the estimate is limited to benefit over

only 1 year, which is insufficient for clinical usefulness.

Therefore, to understand the effect of lung transplantation on survival since implementation of the LAS, and to overcome the potential statistical limitations of the commonly employed Cox model, we leveraged UNOS registry data on 13,040 patients listed for transplantation (9,091 of whom received transplants) and employed novel statistical methods from the causal inference literature to estimate the survival benefit conferred by this procedure. We then examined the impact of patient, donor, and transplant center characteristics on the survival benefit of lung transplantation.

Methods

Data Sources, Setting, and Participants

Data were provided by the UNOS registry on all candidates in the United States on the waiting list for lung transplantation between May 4, 2005 (LAS implementation) and September 30, 2011 ($n = 15,686$). Excluded were those who had received a prior lung or heart–lung transplant ($n = 381$), were listed for simultaneous organ transplants ($n = 288$), received an LAS of 0 (indicative of having been listed before May 4, 2005 but with no clinical information provided to compute the LAS after its implementation, and therefore suspended from the waiting list; $n = 1,188$), were less than 18 years of age at listing ($n = 561$), or received a noncadaveric transplant ($n = 3$). We also excluded non-U.S. citizens ($n = 224$) because the Social Security Death Master File (SSDMF) contains limited data on non-U.S. citizens (see the online supplement) and was used to ascertain the death dates for candidates removed from the waiting list while alive. A total of 13,040 individuals were included in this analysis. A CONSORT diagram is included in the online supplement (Table E1). This study was declared exempt by the Duke University Institutional Review Board.

Statistical Methods

Characteristics of the candidates, at registration and at transplantation, and donor characteristics were summarized as medians (25th–75th percentiles) for continuous covariates and frequency (percent) for categorical characteristics. The cumulative incidence of death or of being

transplanted while off the waiting list, and graft survival after transplantation, were estimated with a product limit estimator.

To model the survival benefit of lung transplantation, we fit a “structural nested accelerated failure time model” (SNAFTM) (20–23), an approach that has been previously applied in a variety of other clinical applications (24–31) but not, to our knowledge, in lung transplantation. A “structural nested model” is a model to compare the distribution of counterfactual residual survival if a patient were to receive a transplanted organ with the survival distribution if the patient did not receive that organ and never received one subsequently.

The structural nested model assumes that if a candidate is on the waiting list, then the probability of this patient dying within t_{trans} days after receiving a transplant is the same as that person dying within $h(t_{\text{trans}}) = t_{\text{wl}}$ days had the candidate remained on the waiting list and never received a transplant. The ratio between t_{trans} and t_{wl} represents the relative increase or decrease in survival time if a candidate were transplanted compared with the residual survival had the candidate never received a transplant, given recipient and donor characteristics. We refer to this ratio as the *relative survival benefit* of transplantation at time t_{trans} . If this ratio is greater than 1, then the transplant results in a survival benefit t_{trans} days after transplantation relative to remaining on the waiting list. The derivative of the function $h(t_{\text{trans}})$ is commonly referred to as the *acceleration factor*, which describes the relative rate at which an untransplanted patient “ages” compared with a transplanted patient.

An accelerated failure time model describes or parameterizes how the acceleration factor varies with different covariates. We assumed that the log acceleration factor was linearly related to current LAS, LAS squared, native disease grouping, center volume over the preceding 2 years, recipient age, donor age greater than 55 years, donor smoking status, and difference in height greater than 0 between recipient and donor (4–18, 32–35). That is, these factors may moderate the effect of transplantation and increase or decrease the relative survival benefit on the multiplicative scale. LAS squared was included because Russo and colleagues suggested that the net benefit of

transplantation may increase until a certain LAS and then decline (12).

Most accelerated failure time models assume that an intervention, for example, transplantation, proportionally increases or decreases the residual lifetime of a subject, that is, the relative survival benefit and acceleration factor are constant across time (20–31). However, transplantation may incur a survival loss shortly after transplantation due to peri- and early postoperative complications but confer a survival benefit in the longer term (5, 10, 13, 17). As described in the online supplement, to address this possibility, we allowed the acceleration factor to change at 180, 365, and 730 days posttransplantation,

which allows for a different early and long-term relative survival benefit.

Follow-up for each subject continued until death, retransplantation, or the study censor date of September 30, 2011. Because we use the SSDMF to ascertain death dates, living participants were not censored when removed from the waiting list.

Parameters in the SNAFTM were estimated by G-estimation (20–31), which has been described in the context of lung transplantation by Vock and colleagues (36). G-estimation appropriately accounts for confounders and, therefore, estimates the causal, as opposed to associational, effect of lung transplantation. As described in the online supplement, this model and

estimation approach offers advantages over the Cox proportional hazards model with a time-dependent indicator for transplantation, which leads to a biased estimator of the causal effect of transplantation (37, 38).

After fitting the model, we computed the relative survival benefit conferred by transplantation at 1, 2, and 3 years for each participant who was transplanted, based on the recipient's and donor's characteristics. The percentage of participants for whom transplantation is expected to result in a survival benefit (i.e., an estimated relative survival benefit greater than 1) at 1, 2, and 3 years was reported overall and by strata of recipient and donor characteristics.

Table 1. Characteristics of participants at first registration and at transplantation

	At Listing (<i>n</i> = 13,040)*		At Transplantation (<i>n</i> = 9,091)	
	Median (25th–75th Centiles) or <i>n</i> (%)	% Missing [†]	Median (25th–75th Centiles) or <i>n</i> (%)	% Missing [†]
Age, yr	57 (48–63)	0.0	58 (49–63)	0.0
Sex		0.0		0.0
Female	6,054 (46.4)		3,739 (41.1)	
Male	6,986 (53.6)		5,352 (58.9)	
Race and ethnicity		0.0		0.0
White	10,854 (83.2)		7,704 (84.7)	
Black	1,246 (9.6)		797 (8.8)	
Hispanic	661 (5.1)		413 (4.5)	
Asian	183 (1.4)		113 (1.2)	
Other	96 (0.7)		64 (0.7)	
Native disease grouping		0.0		0.0
Obstructive	4,963 (38.1)		3,334 (36.7)	
Pulmonary vascular	677 (5.2)		333 (3.7)	
Cystic fibrosis	1,567 (12.0)		1,144 (12.6)	
Restrictive	5,833 (44.7)		4,280 (47.1)	
Lung allocation score	35.4 (32.6–41.5)	0.0	38.7 (34.3–47.5)	0.0
6-min walk distance, m	258 (165–343)	6.4	240 (137–330)	3.0
O ₂ required, L/d	3 (2–5)	6.9	4 (3–6)	3.3
Functional class		0.0		1.0
No assistance	2,243 (17.2)		800 (8.9)	
Some assistance	9,616 (73.7)		7,360 (81.8)	
Total assistance	1,181 (9.1)		841 (9.3)	
Ventilator use		0.0		1.0
Continuous mechanical	296 (2.3)		323 (3.6)	
Intermittent mechanical	76 (0.6)		43 (0.5)	
BiPAP	650 (5.0)		715 (7.9)	
CPAP	310 (2.4)		244 (2.7)	
No assisted ventilation	11,708 (89.8)		7,677 (85.3)	
Diabetes		2.2		1.8
Insulin dependent	1,123 (8.8)		864 (9.7)	
Non-insulin-dependent or dependence unknown	1,213 (9.5)		918 (10.3)	
Nondiabetic	10,416 (81.7)		7,142 (80.0)	
Body mass index, kg/m ²	25.5 (21.5–29.0)	0.4	25.3 (21.4–28.8)	1.1
Center volume in preceding 2 yr	65 (39–104)	0.0	69 (41–110)	0.0

Definition of abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

*For patients listed before lung allocation score (LAS) era, covariates are measured at the time of first nonzero LAS.

[†]Missing includes observations categorized as unknown or test not performed.

Results

Cohort Characteristics

Of 13,040 listed patients, 9,091 (69.7%) were transplanted. The percentage of candidates transplanted or (dying before transplantation) was estimated to be 51.7 (8.0), 63.0 (10.5), and 70.8 (13.2) within 6, 12, and 24 months after initial listing, respectively. The 1- and 3-year posttransplantation graft survival rates were estimated to be 83.4 and 66.3%, respectively.

Characteristics of the candidates, donors, and surgery are summarized in Tables 1 and 2 (additional characteristics are given in Table E2). The majority of those listed and undergoing transplantation had restrictive lung disease, primarily interstitial lung disease. The median LAS at listing was 35.4 (25th–75th percentiles, 32.6–41.5) and was 38.9 (34.3–47.5) at transplantation. Approximately two-thirds of transplantation procedures were bilateral.

Overall Results

The estimated relative survival benefit of transplantation and the effect of donor and recipient characteristics on the survival benefit are given in Table 3 and Figure 1. Because we assume that the survival benefit is modified by recipient and donor characteristics, we first report the effect of transplantation at the median (continuous variables) or most frequent (categorical variables) recipient and donor characteristics. At the average value of the recipient and donor characteristics, the relative survival benefit of transplantation within the first 180 days after surgery was 1.11 (95% confidence interval [CI], 0.90–1.38), indicating no survival benefit conferred over the first 6 months posttransplantation.

Long term, the relative survival benefit was 1.59 (95% CI, 1.43–1.78), 1.93 (95% CI, 1.82–2.05), and 2.23 (95% CI, 2.13–2.33) at 1, 2, and 3 years posttransplantation. These results indicate that a candidate undergoing lung transplantation in the United States with typical characteristics would have the same probability of dying within 1, 2, and 3 years after transplantation as in 0.63 (i.e., 1/1.59), 1.03 (i.e., 2/1.93), and 1.34 (i.e., 3/2.23) years, respectively, if he or she had never received a transplant.

Individual recipient and donor characteristics significantly moderated the

Table 2. Characteristics of donor, surgery, and transplantation type for the 9,091 transplantations

	Median (25th–75th Centiles) or n (%)	% Missing
Donor age, yr	32 (21–46)	0.0
Donor sex		0.0
Female	3,598 (39.6)	
Male	5,493 (60.4)	
Race and ethnicity		0.0
White	5,696 (62.7)	
Black	1,715 (18.9)	
Hispanic	1,351 (14.9)	
Asian	210 (2.3)	
Other	119 (1.3)	
Donor cause of death		0.0
Anoxia	1,110 (12.2)	
Cerebrovascular/stroke	3,299 (36.3)	
Head trauma	4,385 (48.2)	
Central nervous system tumor	74 (0.8)	
Other	222 (2.4)	
Donor diabetes		1.8
Insulin dependent	864 (9.7)	
Non–insulin-dependent or dependence unknown	918 (10.3)	
Nondiabetic	7,142 (80.0)	
Extended criterion donor		0.0
No	8,107 (89.2)	
Yes	984 (10.8)	
Donor cytomegalovirus serology		0.2
Indeterminate	21 (0.2)	
Negative	3,408 (37.6)	
Positive	5,644 (62.2)	
Donor cigarette history		0.8
<20 pack-years	7,872 (87.3)	
≥20 pack-years and recent use	1,144 (12.7)	
Donor Po ₂	422 (246–494)	1.0
Donor body mass index, kg/m ²	24.8 (22.1–28.1)	0.0
Ischemic time, h	5.0 (3.9–6.0)	5.8
Distance for graft retrieval, km	204 (34–534)	0.0
Difference in height, recipient – donor, cm	–2.5 (–7.6 to 5.0)	0.0
Sex mismatch		0.0
No mismatch	6,288 (69.2)	
Mismatch	2,803 (30.8)	
Transplant type		0.0
Bilateral	5,923 (65.2)	
Single	3,168 (34.8)	

relative survival benefit of transplantation (P for group test, <0.001). Indeed, among all participants undergoing transplantation, 35.6, 26.2, and 18.1% did not have an expected a 1-, 2-, and 3-year survival benefit. We, therefore, sought to estimate the degree to which specific recipient, donor, and transplant center characteristics lead to individual differences in the relative survival benefit (Figure 1).

LAS at Transplantation

The LAS at transplantation (LAS-T) significantly modified the survival benefit of transplantation ($P < 0.001$ for both LAS-T and LAS-T squared) (Table 3). After

controlling for other characteristics, the relative survival benefit of transplantation increased by 59.4% (95% CI, 50.2–69.1%) and 45.1% (95% CI, 41.0–49.2%) as LAS-T increases from 30 to 35 and from 50 to 55, respectively. Although the effect of a 1-unit change in LAS-T on the relative survival benefit did attenuate with increasing LAS-T (P for quadratic term < 0.001), over the range of LAS-T values, increasing LAS-T conferred an increasing relative survival benefit; that is, there was no threshold score above which increasing LAS-T was associated with decreased relative survival benefit (Figures 1 and 2). Figure 1 demonstrates that holding other

Table 3. Parameter estimates for structural nested accelerated failure time model

	Estimate	SE	exp(Estimate)	Lower CI	Upper CI	P Value
Intercept*						
0–180 d	0.11	0.11	1.11	0.90	1.38	0.34
181–360 d	1.03	0.29	2.81	1.58	5.00	<0.001
361–720 d	0.90	0.12	2.45	1.93	3.12	<0.001
721 d+	1.17	0.12	3.23	2.55	4.09	<0.001
Single lung transplant (ref: bilateral)	–0.13	0.037	0.88	0.82	0.95	0.001
LAS [†]	0.087	0.0046	1.09	1.08	1.10	<0.001
LAS squared [†]	–0.00047	0.00014	1.00	1.00	1.00	0.001
Obstructive lung disease (ref: restrictive lung disease) [†]	–0.22	0.13	0.81	0.62	1.04	0.10
Pulmonary vascular disease (ref: restrictive lung disease) [†]	–0.35	0.37	0.70	0.34	1.46	0.35
Cystic fibrosis (ref: restrictive lung disease) [†]	0.37	0.28	1.45	0.83	2.53	0.19
Recipient age	0.029	0.051	1.03	0.93	1.14	0.57
Donor age, ≥55 yr (ref: <55 yr) [†]	–0.16	0.064	0.85	0.75	0.96	0.010
Donor, ≥20 pack-years (ref: <20 pack-years) [†]	–0.10	0.047	0.90	0.82	0.99	0.035
Two-year center volume (per 30 increase) [†]	0.18	0.058	1.20	1.07	1.34	0.002
Size difference (per 5-cm increase) [†]	–0.074	0.021	0.93	0.89	0.97	0.001

Definition of abbreviations: CI = confidence interval; LAS = lung allocation score.

*We centered or set the reference level for the continuous covariates at the median levels and the categorical covariates at the most frequent level given in Tables 1 and 2. Therefore, the intercept terms are the logarithm of the acceleration factor for this reference level of the covariates. Note that the acceleration factor (and, hence, the relative survival benefit of transplantation) is allowed to vary over time. The relative survival benefit at 6 months, 1 year, 2 years, and 3 years is given by $1/\exp(-\beta_{01})$, $1/[0.5 \exp(-\beta_{01}) + 0.5 \exp(-\beta_{02})]$, $1/[0.25 \exp(-\beta_{01}) + 0.25 \exp(-\beta_{02}) + 0.5 \exp(-\beta_{03})]$, and $1/[0.166 \exp(-\beta_{01}) + 0.166 \exp(-\beta_{02}) + 0.333 \exp(-\beta_{03}) + 0.333 \exp(-\beta_{04})]$, respectively.

[†]Each of these covariates is the modifying effect of that covariate on the relative survival benefit of transplantation. The interpretation of the parameter estimates for these covariates is that a 1-unit increase in the covariates changes the relative survival benefit by a factor of $\exp(\text{Estimate})$.

characteristics constant, the 2-year relative survival benefit of transplantation changes dramatically over the range of typical LAS-T, especially in comparison with the change in relative survival benefit due to other factors.

Table 4 shows the percentage of transplant recipients who were estimated to have a 1-, 2-, and 3-year expected survival benefit, stratified by recipient and donor characteristics. Among those with an LAS-T less than 32.5 and between 32.5 and 34.9, only 6.8 and 36.7% of patients, respectively, could be expected to have a 2-year relative survival benefit. With increasing LAS strata, the proportion of transplant recipients with no expected survival benefit over the first 3 years decreases, and for almost all transplant recipients with an LAS-T greater than 40, transplantation confers an expected survival benefit.

Figure 2 plots the estimated cumulative incidence of death for transplanted study participants after transplantation, and for patients who had never been transplanted, separated by LAS strata. There was a strong relationship between LAS-T and survival benefit: patients with an LAS-T of 32.5 or less were more likely to die if transplanted than if not transplanted, even over the long term.

Patients with an LAS-T between 32.5 and 35 were more likely to die if transplanted, at least over the first 2 years of follow-up. In contrast, patients with an LAS-T of at least 35 were less likely to die if transplanted at any point during long-term follow-up, a pattern that held even for patients with very high LAS-T scores, between 50 and 100.

Native Lung Disease

The difference in the relative survival benefit among the various native disease groupings (at the mean age for recipients in those groupings but holding other factors constant) was borderline significant ($P = 0.062$ for group test), with those with obstructive lung disease (such as chronic obstructive pulmonary disease) showing the worst and those with cystic fibrosis demonstrating the greatest relative survival benefit ($P = 0.014$ for pairwise comparison). Specifically, the relative survival benefit of transplantation was estimated to be 54.4% greater (95% CI, 9.6–117.6%) for those with cystic fibrosis compared with those with obstructive lung disease. The proportion of transplant recipients with a 2-year expected survival benefit varied between 39.2% for those with obstructive lung disease and 98.9% for those with cystic native diseases.

These differences were due not only to the independent effect of native disease, but also to differences in average LAS-T among the native disease groupings (Table 4). Tables E4a–E4c give the percentage of transplant recipients who were estimated to have a 1-, 2-, and 3-year expected survival benefit, stratified by recipient and donor characteristics among native disease grouping.

Other Characteristics

There were small but statistically significant differences in relative survival benefit by transplant type, recipient age, donor age, donor smoking status, center volume, and difference in height between donor and recipient (Table 3). For example, the relative survival benefit of transplantation was estimated to be 13.4% greater (95% CI, 5.4–22.0%) for those receiving a bilateral transplant. In addition, an increase in center volume of 30 lung transplants over 2 years is associated with an increase of 19.9% (95% CI, 7.1–34.3%) in the relative survival benefit. Transplantation with lungs from donors under age 55 years and donors without a history of smoking showed similar increases in the relative survival

Figure 1. Relative survival benefit, varying recipient and donor factors. Estimated relative survival benefit at 2 years by changing a single recipient and donor factor from the reference level of the recipient and donor factors (bilateral transplant; restrictive native lung disease; LAS-T = 38.7; recipient age, 58 yr; donor age, <55 yr; donor smoking history, <20 pack-years; height difference [i.e., recipient height – donor height], <0 cm). For example, a 2-year relative survival benefit of 1.5 indicates that a person receiving a transplant with the given recipient and donor characteristics would have the same probability of dying within 2 years posttransplantation as in $2/1.5 = 1.33$ years if never transplanted. A relative survival benefit greater than 1 indicates that for those recipient and donor characteristics transplantation confers a 2-year survival benefit relative to remaining untransplanted on the waiting list. Diff = difference; LAS-T = lung allocation score at transplantation; LTx = lung transplantation.

benefit, 17.9% (95% CI, 4.1–33.5%) and 10.5% (95% CI, 0.73–21.3%), respectively.

Discussion

A comprehensive understanding of the survival benefit of lung transplantation and how that benefit varies by recipient characteristics is imperative to inform recipient selection, to justify the intensive health care resources allocated to this treatment, and to achieve an equitable allocation of donor lungs. The analysis presented here demonstrates that the majority of U.S. lung transplant recipients since the implementation of the LAS were estimated to have a survival benefit at 2 and 3 years (73.8 and 81.9%, respectively). However, the survival benefit varied substantially by LAS at the time of transplantation, with little survival benefit for patients who are transplanted at an LAS below 35. It has been suggested that the LAS system may encourage patients who have clinically deteriorated to undergo

transplantation even though it would be futile (12). However, we found that among patients who remain active on the waiting list, there is no upper limit for the LAS such that transplantation becomes futile. Our results reinforce the notion that lung transplantation should be considered an appropriate treatment option for patients with most advanced lung diseases, and is expected to confer survival benefit in appropriately selected patients.

Our analysis, which directly models those factors that modify the effect of transplantation, helps to contextualize prior conflicting results on survival benefit and addresses the key limitations of these findings. Although we did find that, after adjusting for recipient and donor characteristics, native disease moderates the survival benefit conferred by lung transplantation, differences in LAS-T led to the largest differences. For example, patients with obstructive lung disease not only experience a lesser survival benefit compared with others at constant LAS-T, those patients typically have lower LAS-T

(median, 33.7). Therefore, a slight majority of patients with obstructive lung disease do not experience an expected survival benefit at 2 years. Variability in the average patient acuity in previous study cohorts, typically drawn from only a single or small number of centers, may explain some of the discrepancy between prior studies (4, 5, 8, 13, 14, 18).

Our results are also consistent with two prior studies that showed only the most severely ill patients with obstructive disease experience a survival benefit (9, 39). In fact, our data suggest that LAS may be a useful surrogate for expected survival benefit of lung transplantation, with other characteristics such as native disease providing further refinement to the expected benefit for individual patients.

In contrast to patients with obstructive native lung disease, patients with restrictive native lung disease have a median LAS-T of 44.7; therefore, transplantation confers a survival benefit for the vast majority of those patients, consistent with previous findings (4, 8, 16, 18). Unlike the findings of Liou

Figure 2. Cumulative incidence of death posttransplantation compared with the waiting list. Shown is the estimated cumulative incidence of death after transplantation (solid blue line) and had the candidates never been transplanted (red dashed line) among the 9,091 study participants who were transplanted. LAS = lung allocation score; Tx = transplantation.

and colleagues (10, 11), we found that lung transplantation confers a 2-year expected survival benefit for more than 99% of patients with cystic native diseases (median LAS-T, 40.3). The study by Liou and colleagues included a historically older cohort with worse transplantation outcomes and preceded the implementation of the LAS. The current findings are similar to the conclusions of other research groups, including a more recent analysis by Thabut and colleagues (4, 5, 7–9, 15, 18). Therefore, there should be no reservations about pursuing lung transplantation for appropriately selected patients with cystic fibrosis.

Previous research has demonstrated that patients transplanted at high-volume centers have better posttransplantation survival (34, 35). We have demonstrated that patients listed at high-volume centers

have significantly greater relative survival benefit conferred by transplantation than those listed at small-volume centers. The effect of an increase of 30 transplants in the 2-year center volume is similar to the increase in benefit seen from transplants using a younger donor or donor without smoking history.

Because the 2-year relative survival benefit estimate depends on all recipient and donor characteristics considered in this analysis, no simple criterion perfectly classifies whether or not a transplant is predicted to confer a 2-year survival benefit for a particular patient. However, specific combinations of characteristics can identify substantial populations that would not be expected to benefit. On the basis of our model, no patients transplanted with obstructive lung disease, and with an LAS-T less than 35 and at a center with an annual

volume less than 25 transplants, could expect a 2-year survival benefit.

Unfortunately, more than 8% of donor lungs were transplanted in this group. Scrutiny of potential transplant candidates with these characteristics could help prevent exposing such patients to the risks of transplantation without expected benefit, and increase the availability of donor organs for patients with expected survival benefit. In addition, further research on improving outcomes in low-volume centers is warranted.

We are the first to use an SNAFTM estimated by G-estimation to assess the survival benefit of lung transplantation. These models have been used to evaluate the causal effect of a time-varying treatment in the presence of time-varying confounding for a variety of applications (20–31). As noted by Kotloff and Thabut (1), most researchers have estimated the survival

Table 4. Percentage of patients with expected survival benefit conferred by transplantation, by strata of recipient/donor characteristics

Recipient/Donor Characteristic	1 Year*	2 Years*	3 Years*
Overall	64.4	73.8	81.9
Native disease grouping			
Obstructive	22.1	39.2	56.3
Pulmonary vascular	52.9	64.6	73.0
Cystic fibrosis	95.3	98.9	99.7
Restrictive	90.0	94.8	97.7
LAS at transplantation			
0.0–32.4	0.3	6.8	26.8
32.5–34.9	13.9	36.7	55.2
35.0–39.9	68.1	84.9	94.2
40.0–44.9	98.5	99.9	100.0
45.0–49.9	99.9	100.0	100.0
50.0–100.0	100.0	100.0	100.0
Two-year center volume			
0–24	49.2	56.5	63.8
25–49	53.2	60.7	67.9
50–74	62.2	71.1	79.3
75–99	70.4	82.1	90.7
≥100	75.2	85.9	94.2
Donor age			
<55 yr	65.3	74.7	82.8
≥55 yr	56.0	65.2	73.1
Donor cigarette history			
<20 pack-years	65.5	74.8	82.6
≥20 pack-years	56.9	67.0	76.5
Type of transplant			
Bilateral transplant	68.8	78.7	86.7
Single transplant	56.1	64.6	72.9

Definition of abbreviation: LAS = lung allocation score.

*The proportion of the 9,091 transplanted study participants for whom transplantation was estimated to result in an expected survival benefit at 1, 2, and 3 years by strata of recipient and donor characteristics.

benefit of lung transplantation either by fitting a Cox model with a time-varying covariate for transplantation or by fitting separate models for the posttransplantation and waitlist survival, where follow-up is censored at the time of transplantation. These methods, unlike our approach, assume that the likelihood and timing of transplantation are independent of prognosis (i.e., the risk of death on the waiting list), an untenable assumption due to the use of the LAS to prioritize organ allocation. Because patients with worse waitlist prognosis have a higher likelihood of receiving a donor lung, such an assumption will generally underestimate the waitlist mortality and, consequently, underestimate the survival benefit of transplantation (as described in detail in the online supplement).

Our approach also avoids the difficulty in interpretation of time-varying covariates in Cox models in the context of transplantation. For example, if LAS were included as a

time-varying factor in a Cox model, this would estimate the effect of transplantation compared with a group that was not transplanted and for whom LAS remained constant, an unrealistic comparator group. Other methods to overcome the challenges of dependent censoring within the context of organ transplantation, including using inverse probability of censoring-weighted (IPCW) pseudo-observations and multiple imputation, have been discussed (40, 41). These methods may allow for other models of the survival benefit to be fit, although IPCW methods tend to work well over shorter follow-up (e.g., 1 yr), when the weights are more reasonable in magnitude.

Limitations

Although this work brings a novel approach to determine the survival benefit of lung transplantation, there are limitations to our analysis. First, despite using a different statistical analysis that provides a novel and

robust approach to estimate net transplantation benefit, there remain inherent limitations to the data set, and the potential for bias due to failure to adjust for important confounders always exists. Our conclusions are relevant only to those patients listed for lung transplantation in the United States and not necessarily the global population of patients with advanced lung disease. External validation of our findings, ideally using additional prospective UNOS data or cohorts of patients from different parts of the world, is needed. Furthermore, the purpose of this article was to estimate the survival benefit of lung transplantation among those currently listed for transplantation and is likely not applicable for those never listed or once a patient is delisted.

Second, our analysis focuses on the survival benefit of transplantation; it does not address other important outcomes such as quality of life (QOL), improvements in which have been demonstrated in previous analyses of lung transplantation (42–48). Other end points including composite end points of survival, QOL, and cost could change our interpretation of the relative benefit of transplantation. Importantly, the QOL benefit conferred by transplantation might justify transplantation for certain recipients in the absence of a clear survival benefit, particularly those with chronic obstructive pulmonary disease.

Third, our model is based on data self-reported by transplant centers, which may be subject to misclassification and measurement error. However, the goal of the analysis is to assess how certain recipient and donor characteristics, as measured by and reported to transplant centers, moderate the effect of transplantation, and therefore statistical methods for measurement error were not used. Finally, updates have been made to the LAS since the data set for this analysis was generated (e.g., addition of some hemodynamic and laboratory values); although these changes would be likely to introduce only subtle if any differences in our results, it will be important to confirm our findings using the most recent iteration of the LAS.

Conclusions

We have applied novel statistical methods to a modern national registry to define the survival benefit of lung transplantation, given recipient and donor characteristics. Our analysis has demonstrated that the

majority of patients undergoing lung transplantation in the United States can expect a long-term survival benefit, but the likelihood of benefit for individual patients varies widely by patient and donor characteristics. LAS-T and native disease grouping have the greatest impact on transplant survival benefit. In particular, transplantation in patients with increasingly high LAS-T provides

increasing survival benefit, whereas transplantation of patients with low LAS-T scores, particularly in those with obstructive lung disease at low-volume centers, does not confer a survival benefit. Consideration of these factors may help prioritize future donor lung allocation. ■

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References

- Kotloff RM, Thabut G. Lung transplantation. *Am J Respir Crit Care Med* 2011;184:159–171.
- Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, Levvey BJ, Lund LH, Meiser B, Rossano JW, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-Second Official Adult Lung and Heart–Lung Transplantation Report—2015; focus theme: early graft failure. *J Heart Lung Transplant* 2015;34:1264–1277.
- Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Lund LH, Rahmel AO, et al.; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart–Lung Transplant Report—2013; focus theme: age. *J Heart Lung Transplant* 2013;32:965–978.
- Charman SC, Sharples LD, McNeil KD, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis. *J Heart Lung Transplant* 2002;21:226–232.
- De Meester J, Smits JM, Persijn GG, Haverich A. Listing for lung transplantation: life expectancy and transplant effect, stratified by type of end-stage lung disease, the Eurotransplant experience. *J Heart Lung Transplant* 2001;20:518–524.
- Geertsma A, Ten Vergert EM, Bonsel GJ, de Boer WJ, van der Bij W. Does lung transplantation prolong life? A comparison of survival with and without transplantation. *J Heart Lung Transplant* 1998;17:511–516.
- Hofer M, Benden C, Inci I, Schmid C, Irani S, Speich R, Weder W, Boehler A. True survival benefit of lung transplantation for cystic fibrosis patients: the Zurich experience. *J Heart Lung Transplant* 2009;28:334–339.
- Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet* 1998;351:24–27.
- Lahzami S, Bridevaux PO, Soccal PM, Wellinger J, Robert JH, Ris HB, Aubert JD. Survival impact of lung transplantation for COPD. *Eur Respir J* 2010;36:74–80.
- Liou TG, Adler FR, Cahill BC, FitzSimmons SC, Huang D, Hibbs JR, Marshall BC. Survival effect of lung transplantation among patients with cystic fibrosis. *JAMA* 2001;286:2683–2689.
- Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. *Am J Respir Crit Care Med* 2005;171:1053–1059.
- Russo MJ, Worku B, Iribarne A, Hong KN, Yang JA, Vigneswaran W, Sonett JR. Does lung allocation score maximize survival benefit from lung transplantation? *J Thorac Cardiovasc Surg* 2011;141:1270–1277.
- Stavem K, Bjørtuft Ø, Borgan Ø, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. *J Heart Lung Transplant* 2006;25:75–84.
- Tanash HA, Riise GC, Hansson L, Nilsson PM, Piitulainen E. Survival benefit of lung transplantation in individuals with severe α_1 -antitrypsin deficiency (PiZZ) and emphysema. *J Heart Lung Transplant* 2011;30:1342–1347.
- Thabut G, Christie JD, Mal H, Fournier M, Brugière O, Leseche G, Castier Y, Rizopoulos D. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. *Am J Respir Crit Care Med* 2013;187:1335–1340.
- Thabut G, Mal H, Castier Y, Groussard O, Brugière O, Marrash-Chahla R, Lesèche G, Fournier M. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. *J Thorac Cardiovasc Surg* 2003;126:469–475.
- Thabut G, Ravaud P, Christie JD, Castier Y, Fournier M, Mal H, Lesèche G, Porcher R. Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;177:1156–1163.
- Titman A, Rogers CA, Bonser RS, Banner NR, Sharples LD. Disease-specific survival benefit of lung transplantation in adults: a national cohort study. *Am J Transplant* 2009;9:1640–1649.
- Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, Coke MA, Garrity ER, Sweet SC, Heiney DA, et al. Development of the new lung allocation system in the United States. *Am J Transplant* 2006;6:1212–1227.
- Hernán MA, Cole SR, Margolick J, Cohen M, Robins JM. Structural accelerated failure time models for survival analysis in studies with time-varying treatments. *Pharmacoepidemiol Drug Saf* 2005;14:477–491.
- Lok J, Gill R, van der Vaart A, Robins JM. Estimating the causal effect of a time-varying treatment on time-to-event using structural nested time failure models. *Stat Neerl* 2004;58:271–295.
- Robins JM. Structural nested time failure models. In: Armitage P, Colton T, editors. *Encyclopedia of Biostatistics*. New York: John Wiley & Sons; 2005.
- Robins JM, Blevins D, Ritter G, Wulfsohn M. G-estimation of the effect of prophylaxis therapy for *Pneumocystis carinii* pneumonia on the survival of AIDS patients. *Epidemiology* 1992;3:319–336.
- Chevrier J, Picciotto S, Eisen EA. A comparison of standard methods with G-estimation of accelerated failure-time models to address the healthy-worker survivor effect: application in a cohort of autoworkers exposed to metalworking fluids. *Epidemiology* 2012;23:212–219.
- Joffe MM, Hoover DR, Jacobson LP, Kingsley L, Chmiel JS, Visscher BR. Effect of treatment with zidovudine on subsequent incidence of Kaposi's sarcoma. *Clin Infect Dis* 1997;25:1125–1133.
- Joffe MM, Hoover DR, Jacobson LP, Kingsley L, Chmiel JS, Visscher BR, Robins JM. Estimating the effect of zidovudine on Kaposi's sarcoma from observational data using a rank preserving structural failure-time model. *Stat Med* 1998;17:1073–1102.
- Joffe MM, Yang WP, Feldman H. G-estimation and artificial censoring: problems, challenges, and applications. *Biometrics* 2012;68:275–286.
- Keiding N, Filiberti M, Esbjerg S, Robins JM, Jacobsen N. The graft versus leukemia effect after bone marrow transplantation: a case study using structural nested failure time models. *Biometrics* 1999;55:23–28.
- Mark SD, Robins JM. Estimating the causal effect of smoking cessation in the presence of confounding factors using a rank preserving structural failure time model. *Stat Med* 1993;12:1605–1628.
- Robins JM. Causal models for estimating the effects of weight gain on mortality. *Int J Obes* 2008;32:S15–S41.
- Wittman JC, D'Agostino RB, Stijnen T, Kannel WB, Cobb JC, de Ridder MA, Hofman A, Robins JM. G-estimation of causal effects:

- isolated systolic hypertension and cardiovascular death in the Framingham Heart Study. *Am J Epidemiol* 1998;148:390–401.
- 32 Mason DP, Batizy LH, Wu J, Nowicki ER, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH. Matching donor to recipient in lung transplantation: how much does size matter? *J Thorac Cardiovasc Surg* 2009;137:1234–1240.e1.
 - 33 Reyes KG, Mason DP, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackstone EH. Guidelines for donor lung selection: time for revision? *Ann Thorac Surg* 2010;89:1756–1764, discussion 1764–1765.
 - 34 Thabut G, Christie JD, Kremers WK, Fournier M, Halpern SD. Survival differences following lung transplantation among US transplant centers. *JAMA* 2010;304:53–60.
 - 35 Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. *JAMA* 2015;313:936–948.
 - 36 Vock DM, Tsiatis AA, Davidian M, Laber EB, Tsuang WM, Finlen Copeland CA, Palmer SM. Assessing the causal effect of organ transplantation on the distribution of residual lifetime. *Biometrics* 2013;69:820–829.
 - 37 Schaubel DE, Wolfe RA, Port FK. A sequential stratification method for estimating the effect of a time-dependent experimental treatment in observational studies. *Biometrics* 2006;62:910–917.
 - 38 Schaubel DE, Wolfe RA, Sima CS, Merion RM. Estimating the effect of a time-dependent treatment by levels of an internal time-dependent covariate: application to the contrast between liver wait-list and posttransplant mortality. *J Am Stat Assoc* 2009;104:49–59.
 - 39 Thabut G, Christie JD, Ravaud P, Castier Y, Brugière O, Fournier M, Mal H, Lesèche G, Porcher R. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. *Lancet* 2008;371:744–751.
 - 40 Xiang F, Murray S. Restricted mean models for transplant benefit and urgency. *Stat Med* 2012;31:561–576.
 - 41 Xiang F, Murray S, Liu X. Analysis of transplant urgency and benefit via multiple imputation. *Stat Med* 2014;33:4655–4670.
 - 42 Finlen Copeland CA, Vock DM, Pieper K, Mark DB, Palmer SM. Impact of lung transplantation on recipient quality of life: a serial, prospective, multicenter analysis through the first posttransplant year. *Chest* 2013;143:744–750.
 - 43 Gerbase MW, Soccal PM, Spiliopoulos A, Nicod LP, Rochat T. Long-term health-related quality of life and walking capacity of lung recipients with and without bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2008;27:898–904.
 - 44 Gerbase MW, Spiliopoulos A, Rochat T, Archinard M, Nicod LP. Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. *Chest* 2005;128:1371–1378.
 - 45 Kugler C, Fischer S, Gottlieb J, Welte T, Simon A, Haverich A, Strueber M. Health-related quality of life in two hundred-eighty lung transplant recipients. *J Heart Lung Transplant* 2005;24:2262–2268.
 - 46 Singer LG, Chowdhury NA, Faughnan ME, Granton J, Keshavjee S, Marras TK, Tullis DE, Waddell TK, Tomlinson G. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. *Am J Respir Crit Care Med* 2015;192:965–973.
 - 47 Smeritschnig B, Jaksch P, Kocher A, Seebacher G, Aigner C, Mazhar S, Klepetko W. Quality of life after lung transplantation: a cross-sectional study. *J Heart Lung Transplant* 2005;24:474–480.
 - 48 Vasiliadis HM, Collet JP, Poirier C. Health-related quality-of-life determinants in lung transplantation. *J Heart Lung Transplant* 2006;25:226–233.