Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease

Jeffrey D Hosenpud, Leah E Bennett, Berkley M Keck, Erick B Edwards, Richard J Novick

Summary

Background Although certain forms of end-stage lung disease are debilitating, whether the associated mortality rate exceeds that of transplantation is unclear. We undertook analysis to clarify the survival benefit of lung transplantation for various types of end-stage lung disease.

Methods We analysed data for all patients listed for transplantation in the USA for emphysema, cystic fibrosis, or interstitial pulmonary fibrosis in the years 1992–94. The numbers of patients entered on the waiting list, post-transplantation, died waiting, and currently waiting were: emphysema group 1274, 843, 143, and 165; cystic fibrosis group 664, 318, 193, and 59; interstitial pulmonary fibrosis group 481, 230, 160, and 48. A time-dependent non-proportional hazard analysis was used to assess the risk of mortality after transplantation relative to that for patients on the waiting list.

Findings The clearest survival benefit from lung transplantation occurred in the cystic fibrosis group. The relative risks of transplantation compared with waiting were 0·87, 0·61, and 0·61 at 1 month, 6 months, and 1 year (p=0·008), respectively. For interstitial pulmonary fibrosis, the corresponding relative risks were 2·09, 0·71, and 0·67 (p=0·09). No survival benefit was apparent in the emphysema group. The risks of transplantation relative to waiting were 2·76, 1·12, and 1·10 at 1 month, 6 months, and 1 year, respectively, and the relative risk did not decrease to below 1·0 during 2 years of follow-up.

Interpretation These findings suggest that lung transplantation does not confer a survival benefit in patients with end-stage emphysema by 2 years of follow-up. Other benefits not accounted for in this analysis such as improved quality of life, however, may justify lung transplantation for these patients.

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Joint United Network for Organ Sharing/International Society for Heart and Lung Transplantation Thoracic Registry, Richmond, VA, USA (J D Hosenpud MD, L E Bennett PhD, B M Keck MPH, E B Edwards PhD, R J Novick MD)

Correspondence to: Dr Jeffrey D Hosenpud, Division of Cardiovascular Medicine, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA

Introduction

Although lung transplantation has become an invaluable approach for the treatment of end-stage respiratory disease, rates of successful outcomes are not yet as good as those for other transplanted organs. Based on data from the Joint United Network for Organ Sharing (UNOS)/International Society for Heart and Lung Transplantation (ISHLT) Thoracic Registry, 1-year mortality is more than 25% and 5-year mortality is greater than 50%.[1] In addition, obliterative bronchiolitis affects more than 50% of patients late after transplantation[2] and accounts for 57% of the deaths after 1 year.[1]

The most common indication for lung transplantation is emphysema.[1] Although emphysema is debilitating, mortality from this disorder may not be as high as that from other forms of end-stage lung disease, especially in patients younger than 60 years.[3–6] Moreover, for some patients with emphysema, volume-reduction surgery[7–9] may be an alternative. To clarify the actual survival benefit of lung transplantation for the more common causes of end-stage lung disease, including emphysema, we undertook an analysis of data from the Joint UNOS/ISHLT Thoracic Registry.

Methods

The cohort for this study included all patients listed for transplantation with UNOS (listed for transplantation in the USA) between Jan 1, 1992, and Dec 31, 1994. The cohort included patients with the three most common indications—emphysema, cystic fibrosis, and interstitial pulmonary fibrosis.

	Cystic fibrosis	Interstitial pulmonary fibrosis	Emphysema
Total cohort	664	481	1274
Outcome at time of analysis			
Died on waiting list	193	160	143
Underwent transplantation	318	230	843
Removed from waiting list and censored for other reasons	94	43	123
Still on waiting list	59	48	165
Died after transplantation	68	55	142
Mean (SD) days on waiting list			
Non-transplant patients	398 (18)	361 (23)	560 (16)
Transplant patients	304 (17)	250 (14)	260 (17)
Mean (SD) post-transplant follow-up days	354 (19)	327 (21)	391 (12)
Mean (SD) total follow-up (days)			
All patients	512 (15)	454 (17)	616 (10)
Transplant patients only	658 (21)	577 (24)	651 (12)
Mean (range) age in years*	25·8 (1·0–49·3)	49·6 (16·1–71·4)	53·5 (17·8–68·4)
Sex			
M	357 (54%)	293 (61%)	567 (45%)
F	307 (46%)	188 (39%)	757 (55%)
White patients	616 (93%)	382 (79%)	1187 (93%)

*At time of analysis.

Table 1: **Characteristics of patients, outcomes, and time spent in each clinical stage**

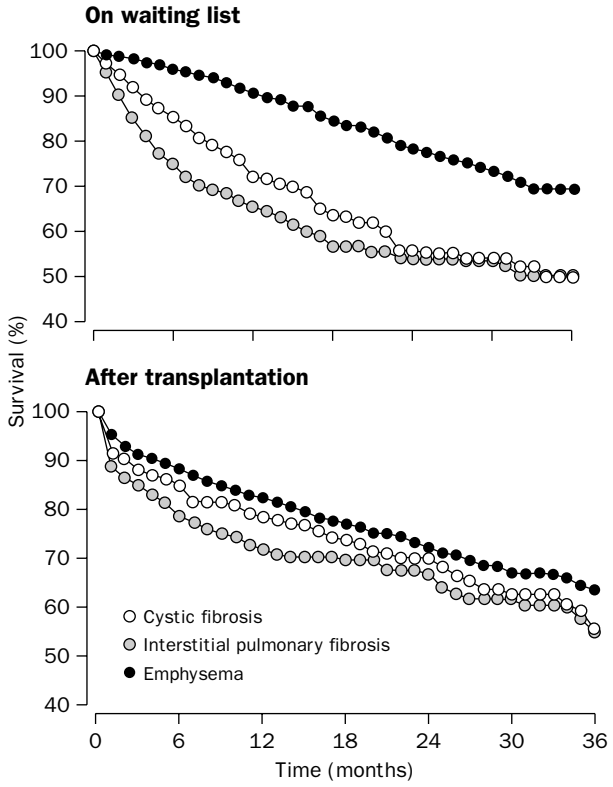

Figure 1: **Survival curves by diagnosis for patients waiting for transplantation (censored at time of transplantation) and after transplantation**

The UNOS lung allocation scheme does not take into account disease severity; organs are allocated solely on the basis of waiting time, blood type, and body size. We included only patients undergoing primary transplantation. Because patients supported by ventilators at the time of transplantation have a high risk of death, these patients were excluded from analysis. In addition, because of small numbers of patients, we excluded children (younger than 16 years) with emphysema (three) or interstitial pulmonary fibrosis (12) and all patients with cystic fibrosis who were older than 50 years (seven).

First, univariate survival curves were generated for survival on the waiting list (patients censored at transplantation) and survival after transplantation for the three diagnoses. We compared survival for the diagnoses at each stage by the log-rank statistic (corrected for multiple comparisons). Direct comparison between stages (waiting *vs* post-transplantaton) was not done because the stages are interdependent and because patients moved from the waiting list to transplantation. For the comparison between pretransplantation and post-transplantation survival, we used a time-dependent non-proportional hazards analysis[10] to assess the risk of mortality after transplantation relative to that on the waiting list:

$$r_{TX}(t)=r_{WL}(t)*\exp(\alpha+\delta e^{-\gamma(t-u)})$$

where r(t)is the risk for a post-transplantation patient (TX) or a patient still waiting (WL), and u is the days between listing and transplantation. In this analysis, we assumed a constant death rate on the waiting list, on the basis of our own data as well as those previously published for renal-transplant patients.[11] This type of model allows for a high initial risk followed by an exponential decay to a constant, which is appropriate for the post-transplantation period. It also incorporates both the time on the waiting list and the survival time after transplantation.

Separate hazards models were fitted for each diagnosis. Analyses were adjusted for race, sex, and age through stratification. The age stratifications depended on diagnosis (emphysema <55 *vs* ⩾55 years; interstitial pulmonary fibrosis <50 *vs* ⩾50 years; cystic fibrosis 0–18, 19–30, and >30 years).

From this model, curves were generated for the relative risk of death (the risk of death from transplantation divided by the risk of death while waiting) over a 1-year period. Two calculations were done—first, the time when risk of mortality for remaining on the waiting list was equal to the risk for mortality after transplantation. In other words, for a given patient what was the "cross-over" time in days, when the risk of dying on the waiting list exceeded the risk of dying after undergoing transplantation? Second, and derived from the first, was the time when overall survival for remaining on the waiting list was equal to the overall survival after transplantation. These analyses were undertaken for each diagnosis. Significance was defined as $p<0{\cdot}05$.

Results

Characteristics of the patients and their outcomes at the time of analysis are given in table 1. As expected, the group with cystic fibrosis was younger on average. Table 1 also gives the mean duration of follow-up in each of the clinical stages for each diagnosis. For the entire cohort, mean follow-up exceeds 18 months, with adequate follow-up for the data to be analysed over a 2-year period.

Survival while awaiting transplantation was significantly greater for patients with emphysema than for those with cystic fibrosis or interstitial pulmonary fibrosis ($p<0{\cdot}0001$ for each comparison; figure 1). There was also a slight but statistically significant difference in survival while awaiting transplantation between patients with cystic fibrosis and those with interstitial pulmonary fibrosis ($p<0{\cdot}03$). By contrast, after transplantation, the only difference that approached significance was a small difference between the emphysema and interstitial pulmonary fibrosis groups ($p=0{\cdot}06$).

The mortality rate within the first 30 days after transplantation was 8% for patients with cystic fibrosis, 12% for those with interstitial pulmonary fibrosis, and 5% for those with emphysema. Causes of death after

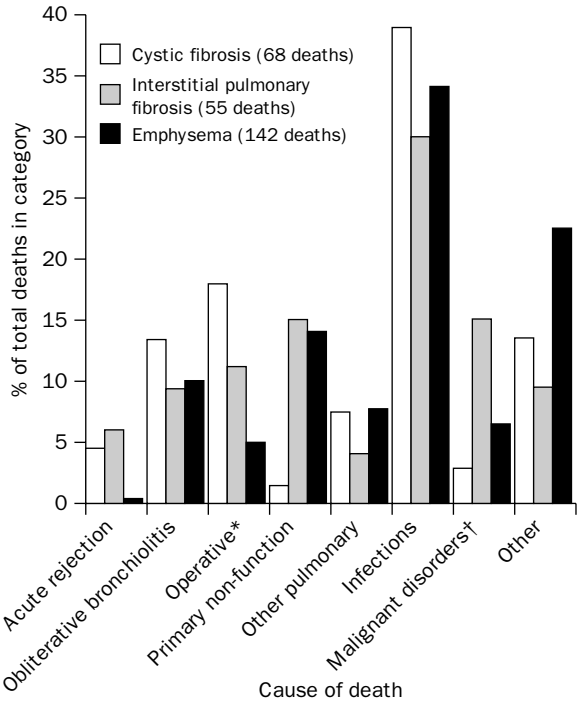

Figure 2: **Causes of death after transplantation**
*Operative and technical difficulties, including dehiscence and haemorrhage. †Including post-transplantation lymphoproliferative disorder.

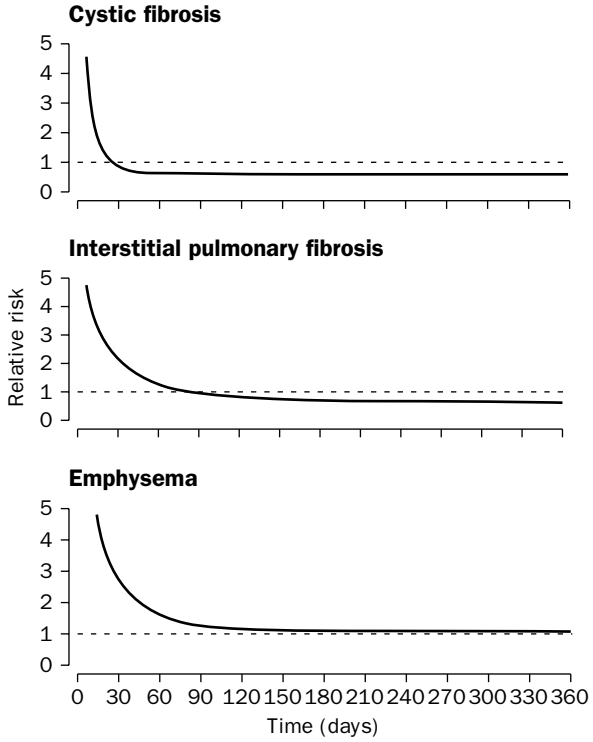

Figure 3: **Relative (transplantation/continued waiting) risk of death according to diagnosis**
Relative risk of 1·0 (broken line) indicates transplantation risk=waiting risk of mortality.

transplantation in each group are given in figure 2. Of the deaths from infections, bacteria accounted for 40, cytomegalovirus for four, other viruses for seven, fungi for 18, and mixed or unspecified infections for 21. In the group of "other" causes of death, there were 21 cardiovascular deaths, seven from multiorgan failure, and six from cerebrovascular causes, as well as deaths from gastrointestinal haemorrhage, pancreatitis, renal failure, liver failure, non-compliance, and motor-vehicle accidents.

The ratio of the risk of death after transplantation to the risk of death while remaining on the waiting list is shown in figure 3. For cystic fibrosis, the benefits of transplantation were apparent within 1 month, with the relative risk falling below 1·0 at 26 days (table 2). For interstitial pulmonary fibrosis, the benefits were seen later, with the cross-over point at 83 days. By contrast, for emphysema, the relative risk did not fall below 1·0 during at least 2 years of follow-up (shown to 360 days). Survival after transplantation equalled survival on the waiting list at about 6 months for cystic fibrosis and within 1 year for interstitial pulmonary fibrosis. For patients with emphysema, transplantation did not improve survival in comparison with remaining on the waiting list for at least the 2-year analysis period.

Diagnosis	Time when risk of death on waiting list= risk after transplantation	Time when survival on waiting list= survival after transplantation	Relative risk transplantation *vs* continued waiting			p*
			1 mo	6 mo	1 yr	
Cystic fibrosis	26 days	182 days	0·87	0·61	0·61	<0·008
Interstitial pulmonary fibrosis	83 days	350 days	2·09	0·71	0·67	<0·09
Emphysema	· ·†	· ·†	2·76	1·12	1·10	· ·

+p value (*t* testing) for difference in relative risk at 1 year from relative risk of 1·0.
†Risk of mortality after transplantation never declined below risk of remaining on waiting list.

Table 2: **Risk of death after transplantation relative to continued waiting**

Discussion

The data reported here support a survival benefit of lung transplantation for patients with cystic fibrosis and interstitial pulmonary fibrosis. Although there was a high mortality risk immediately after transplantation, by 1 year later survival was better than that for patients on the waiting list for both diagnoses. By contrast, for patients with emphysema, the mortality rate while they were on the waiting list was low, so post-transplantation survival did not exceed waiting-list survival during the 2-year follow-up. Estimation of whether this relation would change with longer follow-up is difficult, because of increasing post-transplantation mortality due to obliterative bronchiolitis.

We considered several methods of analysis to compare these data. The simplest method would have been direct comparison of post-transplantation survival with waiting-list survival, with censoring at transplantation. Time 0 would be the date on which patients joined the list. The drawback of this approach is that patients must survive long enough to receive a transplant before they can transfer to the transplant group, so there is bias towards transplantation. Alternatively, a direct comparison between waiting-list survival (with censoring at transplantation) and transplantation survival, with time 0 being the listing date or the transplantation date, respectively, biases towards the waiting list, because of the substantial early post-transplantation mortality. A time-dependent proportional hazards model would account for the switch between waiting and transplantation. This method, however, assumes a constant hazard after transplantation, which does not reflect clinical reality. We therefore decided to use the time-dependent non-proportional hazard model,[10] which allows for switching from waiting to transplantation and a non-constant risk.

The following assumptions and limitations to our data should be emphasised. First, because the data are derived from many centres, an important assumption is that when a patient is listed, he or she is deemed sick enough to need a transplant operation, and that if a donor lung became available, it would be accepted for a particular patient. This is clearly the intent of the US Organ Procurement Transplant Network (administered by UNOS); however, the participating centres are highly unlikely to have a uniform listing policy for all patients. For instance, some patients may be listed at an earlier stage in the development of severe lung dysfunction, given the long waiting time for lung-transplant candidates.[12,13] If this practice were widespread, it would clearly bias our analysis towards waiting-list survival.

A second assumption in our analysis is that we have taken account of all of the major risk factors for transplant-related mortality in our model. The Registry collects data on most factors that are known to increase the risk of the transplant procedure. We have accounted for (by modelling) or eliminated (by exclusion) those shown to be major independent predictors for post-transplantation survival. We cannot, however, exclude the possibility that other factors have an effect on outcome

but have not been taken into account. Furthermore, little is known about risks of mortality on the waiting list, and the contributing factors, therefore, cannot be accounted for.

Third, we have assumed a constant death rate on the waiting list on the basis of our own data as well as those published for candidates for renal transplantation.[11] No peer-reviewed data on waiting-list mortality in candidates for lung transplantation are available.

Finally, we must emphasise that this analysis assessed only duration of survival, not quality of life. Several studies have shown substantial improvement in quality-of-life indices in patients undergoing lung transplantation, including those with a preoperative diagnosis of emphysema.[14–16] Decisions on whether to offer lung transplantation to patients with emphysema are therefore complex and must take into account not only the duration of expected survival, but also quality-of-life issues.

The availability of volume-reduction surgery[7–9] has already altered the management and referral patterns of emphysema patients with significant lung dysfunction.[7–9,14] Some of these patients undergo volume-reduction surgery while still officially on the lung-transplantation list, whereas others will be listed for transplantation only several years after volume-reduction surgery, when the clinical benefit of this procedure has waned.[17] Such treatment of patients on the waiting list would tend to increase waiting-list mortality, since volume-reduction surgery carries a mortality rate of 10–15%;[18] listing after volume-reduction surgery would tend to increase post-transplantation mortality, since the recipients would be older and present more technical challenges at the time of transplantation. We expect that the impact of volume-reduction surgery on the management of patients with severe emphysema will become clearer during the next 5 years, that survival rates after lung transplantation will continue to increase, and that improved treatments to mitigate the development of obliterative bronchiolitis will evolve. In the interim, the results of this study suggest that lung transplantation for patients with emphysema is difficult to justify on the grounds of survival considerations alone.

Contributors

Jeffrey Hosenpud conceived the idea and wrote the paper. Leah Bennett and Erick Edwards developed the statistical analysis methods and did all of the data analyses. Berkley Keck manages the Registry and supervised all the data input, and Richard Novick added lung-transplant expertise, suggested several of the analyses, and provided substantial changes to the paper.

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