Published in final edited form as:

Am J Transplant. 2008 July ; 8(7): 1498–1505. doi:10.1111/j.1600-6143.2008.02264.x.

Baseline 6-Min Walk Distance Predicts Survival in Lung Transplant Candidates

T. Martinu^{a,*}, M. A. Babyak^b, C. F. O'Connell^b, R. M. Carney^c, E. P. Trulock^d, R. D. Davis^e, J. A. Blumenthal^b, and S. M. Palmer [on behalf of For the INSPIRE Investigators]^a

^aDivision of Pulmonary & Critical Care Medicine, Duke University Medical Center, Durham, NC

^bDepartment of Psychology, Duke University Medical Center, Durham, NC

^cDepartment of Psychiatry, Washington University, St. Louis, MO

^dDivision of Pulmonary and Critical Care Medicine, Washington University, St. Louis, MO

^eDepartment of Surgery, Duke University Medical Center, Durham, NC

Abstract

In a large, prospectively followed, two-center cohort of patients listed for lung transplantation (n = 376), we used Cox proportional hazards models to determine the importance of baseline 6-min walk distance (6MWD) in predicting patient survival. 6MWD used as a continuous variable was a significant predictor of survival after adjusting for other important covariates when transplant was considered as a time-varying covariate (HR for each 500 ft increase in 6MWD = 0.57, 95% CI: 0.43–0.77, p = 0.0002). 6MWD remained an important predictor of survival in models that considered only survival to transplant (HR for each 500 ft increase in 6MWD = 0.41, 95% CI: 0.27–0.62, p < 0.0001) or survival only after transplant (HR for each 500 ft increase in 6MWD = 0.40, 95% CI: 0.22–0.72, p = 0.002). Unadjusted Kaplan-Meier analysis demonstrates significantly different survival by 6MWD tertiles (<900, 900–1200, or >1200 ft, p-value = 0.0001). In the overall model, 6MWD prediction of survival was relatively homogeneous across disease category (6MWD by disease interaction term, p-value = 0.63). Our results demonstrate a significant relationship between baseline 6MWD and survival among patients listed for lung transplantation that exists across all native disease categories and extends through transplantation. The 6MWD is thus a useful measure of both urgency and utility among patients awaiting lung transplantation.

Keywords

Exercise capacity; exercise testing; lung; lung transplantation; posttransplantation; pretransplant; prognosis; prognostic factors survival; survival analysis

Introduction

Measures of functional status have received increased attention as important prognostic factors in patients with pulmonary diseases. The 6-min walk distance (6MWD) is a simple, well-accepted and standardized measure of functional status and exercise capacity (1) that is commonly performed at most centers as part of recipient evaluation for lung transplantation.

Although 6MWD is highly predictive of survival among patients with pulmonary hypertension (2,3), its role in predicting survival in patients with other advanced lung diseases, which constitute the major indications for lung transplantation, is controversial. The 6MWD has been found to be predictive of mortality in chronic obstructive pulmonary disease (COPD) when considered in conjunction with other components of the BODE index (body-mass index, airflow obstruction, dyspnea and exercise capacity index)(4). Although one study suggests that the 6MWD is an important predictor of 6-month survival in idiopathic pulmonary fibrosis (IPF) (5), prior studies offered conflicting results (6–8) and the value of the 6MWD in patients with cystic fibrosis (CF) is unclear (9,10).

The value of 6MWD in predicting survival after lung transplantation is unknown. Although poor functional status as reflected in a low baseline 6MWD would be expected to increase the risk for posttransplant complications and death, we are unaware of any studies, which have directly considered the impact of baseline 6MWD upon posttransplant outcomes. We hypothesized that increasing 6MWD at the time of transplant evaluation would be associated with improved survival in patients awaiting lung transplantation across all native disease categories and that this benefit would extend into the posttransplant period. In order to test these hypotheses, we used prospectively collected clinical information on 376 patients with diverse native lung diseases awaiting pulmonary transplantation (11). The aim of our current study was to determine the prognostic importance of the 6MWD with regard to survival, adjusting for native disease, transplant status, and other clinical and demographic variables.

Methods

Patient population

Six hundred forty-seven potential candidates listed for lung transplantation at Duke University Medical Center and Washington University School of Medicine between September 2000 and August 2004 were initially contacted to be part of the Investigational Study of Psychological Intervention in Recipients of Lung Transplant (INSPIRE). Details of patient selection and study protocol are presented elsewhere (11). In brief, every patient listed for lung transplant during that time period was approached to participate in the study. Patients were listed in accordance with ISHLT guidelines (12). Three hundred eighty-nine (60%) patients agreed to participate and provided written informed consent, as previously approved by the Institutional Review Board at each facility. Incomplete or missing 6MWD data led to the exclusion of 13 patients. There were no differences in age, gender, race, transplant status, transplant list waiting-time, native diseases or disease severity between those who declined to participate or were excluded due to missing 6MWD data and those who consented and included in the analysis. The enrolled patients were randomized to a telephone-based counseling and coping skills intervention, which had no impact on survival.

Pulmonary gas exchange and exercise tolerance

Arterial blood carbon dioxide and oxygen levels as well as pulmonary function tests were obtained at the time of transplant evaluation. Normal reference equations for spirometry values were based on Crapo et al. (13). The 6MWD test employed a standard protocol by measuring the distance that patients were able to walk within a 6-min time limit. Patients were asked to cover as much distance as possible at a self-determined pace and were provided with enough oxygen to maintain a minimum oxygen saturation of 90% as measured by a portable pulse-oximeter. No additional encouragement was provided. The test was performed on stable outpatient basis at the time of transplant evaluation by an experienced physical therapist consistent with ATS standards (1) at a dedicated pulmonary rehabilitation facility at Duke University and Washington University.

Clinical endpoints

The primary medical endpoint for the INSPIRE study was death from any cause, confirmed by medical records or death certificates.

Statistical methods

Descriptive analyses were performed using frequency counts and percentages, and means and standard deviations, or medians and interquartile ranges where appropriate. We evaluated the relation between 6MWD and survival by estimating three separate Cox proportional hazards models. In each model, covariates were selected *a priori* and maintained in the model regardless of statistical significance. The effect of native disease was modeled using four dummy variables: ILD, PPH, CF and ‘other native diseases’ with COPD category serving as the reference group.

MODEL 1: All patients—This model included the following predictors: 6MWD, percent-predicted FEV₁ (%pred-FEV₁), age, native disease (dummy variables for CF, PPH, ILD and ‘Other’ with COPD as the reference) and a binary indicator for transplant modeled as a time-dependent covariate. Time zero was defined as the time of study entry, and all surviving patients were censored at the time of last known contact alive. Survival time was defined as the time from study entry to death or last known contact alive. In this model we also examined the native disease by 6MWD interaction and the native disease by transplant interaction in order to evaluate whether the predictive capacity of 6MWD differed across native diseases or the effect of transplant differed across native disease.

MODEL 2: All patients, censoring at time of transplant—In this model transplanted patients were censored at the time of transplant. Time zero was defined as the time from study entry to pretransplant death or to transplant or last known contact alive. Predictors included 6MWD, %pred-FEV₁, age, native disease (dummy variables for CF, PPH, ILD and ‘Other’ with COPD as the reference); the binary transplant indicator was not included in this model. We again evaluated the 6MWD by native disease interaction.

MODEL 3: Transplanted patients only—Because the increased mortality risk during the immediate postsurgical period might yield a different baseline hazard function compared to nontransplanted patients, we estimated a model that included only transplanted patients. Again the predictors included 6MWD, %pred-FEV₁, age and native disease (dummy variables for CF, PPH, ILD and “Other” with COPD as the reference). Time zero in this model was defined as the time of surgery and cases were censored at the time of last known contact alive. Survival time was defined as the time from transplant surgery to death or last known alive.

In each of the three models, we examined the possibility of a nonlinear relation between 6MWD and survival using restricted cubic splines (14). We also evaluated the proportional hazards assumption in each model by using graphic methods and estimating the interaction between the given covariate and the natural logarithm of survival time. For the native disease category, we used the four degree of freedom test, pooled over the four dummy terms, to determine statistical significance for native disease.

Although additional covariates may have been interesting and ultimately relevant, we chose to limit the number of predictors in our primary model to minimize the biases associated with overfitting the model (14). Model assumptions of linearity (using restricted cubic splines) and proportional hazards were evaluated following Harrell (14). In cases where we found that assumptions were not met, the model was modified accordingly. Age, %pred-FEV₁ and 6MWD were modeled in their full continuous form and were centered and scaled such that resulting hazard ratios (HRs) reflected clinically meaningful intervals on the predictor. In other

words, the predictor remains continuous—only the units of the scale are changed. Age was rescaled in 10-year increments, %pred-FEV₁ in 10-percentage point increments, and 6MWD in 500-foot increments. Because the interquartile range of 6MWD was roughly 500 feet (152.4 m), rescaling by 500-foot increments yields a HR that can be interpreted as the hazard of death for a patient in the middle of the upper half of the 6MWD distribution compared to that for a patient in the middle of the lower half of the distribution.

Finally, as suggested by several anonymous reviewers of this article, we conducted a set of supplementary exploratory analyses in which a circumscribed set of additional adjustment covariables were considered in models 1 and 2, including site (Duke vs. Washington U.), body mass index, forced vital capacity (FVC) and time on the transplant wait list. Of primary interest in these latter analyses was whether inclusion of these variables in the multivariable model modified the estimate for 6MWD in a substantively meaningful way. Due to the small number of events in the posttransplant only model (model 3), we did not consider these supplementary covariables in this analysis.

Results

Patient characteristics

The study population consisted of 376 patients with diverse native diseases listed for lung transplantation and prospectively followed from the time of listing onward. Table 1 illustrates baseline characteristics of the patient sample. Eighty patients (21%) died during the course of the study: of these, 47 died on the waiting list and 33 died after transplantation. Overall, 172 patients (46%) underwent transplantation. The median age of the sample was 53 years and a majority of patients were Caucasian (88%) and female (56%). COPD (including Alpha-1 Antitrypsin deficiency) represented the most frequent primary diagnosis in the sample (48%), followed by ILD (22%), CF (14%) and PPH (6%). All other diseases were included in the “other native diseases” category. Median follow-up from time of study entry was 28.4 months and median follow-up from time of transplant for transplanted patients was 18.6 months.

Time-to-event models: Association between 6MWD and survival

MODEL 1: All Patients with transplant as a time-varying covariate—Examination of the nonlinear term for 6MWD suggested little evidence of nonlinearity either before adjustment for covariables ($p = 0.360$) or after adjustment ($p = 0.735$). Before adjusting for covariables, the hazard ratio (HR) for death for each 500-foot increment in 6MWD was 0.57, 95% CI: 0.43–0.77 $p = 0.0002$. Unadjusted Kaplan-Meier analysis demonstrated significantly different survival by 6MWD tertiles (<900, 900–1200, or >1200 ft, p -value = 0.0001), as shown in Figure 1. Table 2 displays the results for Model 1. After adjustment for covariables, the effect size for 6MWD remained statistically significant, HR = 0.49, 95% CI: 0.35–0.66, $p = 0.0001$. Figure 2 displays the relation between 6MWD and the probability of death at 3 years post study entry, adjusted for native disease, %pred-FEV₁, and age. Among the adjustment variables, neither FEV₁ nor age was significantly related to survival. However, there was a trend for native disease to be significantly related to survival (pooled test, $p = 0.056$). Table 2 also shows that after adjustment for transplant, 6MWD, age and %pred-FEV₁, compared to the COPD reference group, the risk of death was higher for patients with CF and ILD. Exploration of additional adjustment variables did not alter the primary findings for 6MWD. Despite the possible loss of power and precision, when site, BMI, FVC, and wait list time were added to the model, the HR for 6MWD changed by only a trivial amount (HR = 0.47, 95% CI: 0.36–0.66). None of the four additional exploratory covariates were significantly associated with survival: site (Duke vs. Washington), HR = 1.1, $p = 0.657$; BMI, HR = 0.98, $p = 0.945$; FVC, HR = 0.86, $p = 0.115$; wait list time, HR = 1.0, $p = 0.828$.

We also explored several interaction terms in this model. We observed no significant interaction between 6MWD and disease category ($p = 0.630$). The analysis demonstrated a significant native disease by transplant interaction ($p = 0.025$), indicating that the survival associated with transplant differed across disease categories. Table 3 displays raw survival rates for transplanted and not-transplanted patients, along with unadjusted HRs associated with transplant from Cox proportional hazards models within each of the four native disease categories. Including the transplant by native disease interaction term in our model with age, ethnicity, gender, %pred-FEV₁, transplant and 6MWD, however, made no material difference in the conclusions drawn from the model regarding 6MWD, with the HR for 6MWD remaining essentially unchanged, HR = 0.45, 95% CI: 0.32–0.62, $p < 0.0001$.

MODEL 2: All Patients, censoring at transplant or last known alive—In this model, transplanted patients were treated as censored, resulting in a sample in which 47 of the 376 patients died while on the wait list. Again, there was no evidence that relation of 6MWD to survival was not linear either unadjusted ($p = 0.801$) or adjusted for covariates ($p = 0.825$). Before adjustment for covariates, 6MWD was significantly associated with mortality, HR = 0.54, 95% CI: 0.37–0.80, $p = 0.002$. Table 4 shows the estimates from the adjusted model. After adjustment for covariates, 6MWD remained significant and became somewhat stronger in magnitude, HR = 0.41, 95% CI = 0.27–0.62, $p < 0.0001$. Neither age nor %pred-FEV₁ was related to mortality (HR for Age = 1.01, 95% CI: 0.71–1.44, $p = 0.945$). Native disease again was a significant predictor (pooled test, $p = 0.007$), with all disease categories having a higher risk of mortality when compared to COPD patients, though only CF and ILD were statistically significant. Exploring more adjustment variables, the inclusion of BMI, site, FVC, and wait list time yielded a slightly stronger estimate for 6MWD: HR = 0.37, 95% CI: 0.24–0.58, $p < 0.0001$. As in Model 1 above, none of the four exploratory covariables were significantly related to mortality: site (Duke vs. Washington), HR = 1.8, $p = 0.117$; BMI, HR = 0.951, $p = 0.121$; FVC, HR = 0.10, $p = 0.393$; wait list time, HR = 1.0, $p = 0.326$. There was no evidence of an interaction between 6MWD and native disease, $p = 0.818$.

MODEL 3: Transplanted patients only—As reported above, there were 33 deaths among the 176 transplanted patients. No evidence of nonlinearity was detected before covariable adjustment ($p = 0.547$) or after adjustment ($p = 0.778$). The unadjusted estimate for 6MWD was 0.59, HR = 0.38–0.90, $p = 0.0154$, demonstrating a significant association between 6MWD and survival after transplantation. After adjustment for covariates, the HR included 1.0 in the 95% CI, HR=0.61, 95% CI=0.37–1.005, $p=0.054$. Neither age, nor FEV₁, nor native disease was significantly related to mortality. Upon examining the assumptions of this model graphically, however, we noted that the proportional hazards assumption was not met, with a tendency for 6MWD to have no effect in the immediate posttransplantation period. We reestimated the model eliminating patients with survival or last known alive times less than one month after surgery. This left a sample of 160 patients with 26 deaths. In this model (See Table 5), 6MWD was again a relatively strong predictor of mortality, HR = 0.40, 95% CI = 0.22–0.72, $p < 0.002$. In addition, we also conducted an analysis using the more sophisticated counting approach in which all patients are included in the model but are designated as not at risk during the immediate transplant period (15). This latter analysis produced essentially the same conclusions as the simpler method of removing the small subset of patients altogether. None of the remaining adjustment variables were significantly related to mortality.

Discussion

These results considerably expand our understanding of the value of the 6MWD as a prognostic variable in patients listed for lung transplantation. The findings in this study demonstrate a significant, and previously unreported, relationship between baseline 6MWD as a continuous variable and patient mortality after adjusting for native disease, FEV₁, age, transplant center,

BMI, FVC or wait list time. Overall, in this two-center patient population with diverse native diseases, there was a greater than 50% reduction in mortality during the 28-month follow-up period for every 500-foot increment in the baseline 6MWD. Furthermore, our results support that this effect extends across all native disease categories and through transplantation. These data suggest that 6MWD is a useful measure of both urgency and utility among patients awaiting lung transplantation.

We observed no significant interaction between the effects of 6MWD and native disease ($p = 0.63$), implying that the predictive effects of the 6MWD extend across all native disease categories. Although the inclusion of multiple native diseases in our patient population adds to the complexity of analysis and limits our ability to draw disease-specific conclusions, the absence of any significant interaction with native disease supports a consistent effect for 6MWD in prediction of survival among all the native disease categories. However, a larger sample of each native disease would be required to confirm the homogeneity of this relation. Collectively our results highlight the possibility of a much broader role for the 6MWD in predicting survival among patients evaluated for lung transplantation regardless of underlying lung disease.

Our results are consistent with several recent studies of 6MWD in predicting survival of patients with IPF or CF awaiting lung transplantation. Similar to our results, Lederer et al. found that lower 6MWD is associated with increased mortality in 454 patients with IPF listed for lung transplantation using UNOS registry data (5). In contrast to our results, however, their study showed that survival outcomes were best dichotomized around a walk distance of 207 m (679 feet). These differences, in part, may be related to the use of UNOS data, in which 16% of patients had a zero-walk distance recorded (vs. none of our patients), thus skewing the nature of the observed relationship between 6MWD and survival. In addition, unless special statistical considerations are undertaken, clinical cutpoints defined in one sample can be surprisingly difficult to replicate in other samples (16–18). Our analysis, however, does not exclude the possibility that a value of 207 m (679 feet) is a useful dichotomization for prediction of survival. Importantly, both our studies differ from previous work such as that of Flaherty et al., which found minimal ability of the 6MWD to predict survival among IPF patients (19). We believe these differences primarily reflect a varying prognostic ability of the 6MWD based on IPF disease severity. The study by Flaherty encompassed a broad range of disease severity, including newly diagnosed IPF patients, while our analysis and that of Lederer included only patients with advanced disease who had undergone transplant evaluation.

Also consistent with our results, a recent study found that the 6MWD was an important prognostic factor in a single center cohort of 146 CF patients awaiting lung transplantation. In this analysis, the 6MWD was significantly lower in patients who died while waiting for transplant as compared to those who survived to transplant or follow-up. In multivariate analysis, each 50-m (164-feet) increase in walk distance was associated with an almost 1.5 greater relative risk of survival. These results are consistent with the relationship we observed between 6MWD and survival in our current study. Although another study failed to observe a relationship between 6MWD and survival in CF patients awaiting transplant, it included a relatively small cohort of patients awaiting heart-lung transplantation in the early 1990s and its results may not be applicable to our current era (10).

Somewhat surprisingly we found that the baseline 6MWD is predictive of survival regardless of transplant status. In model 1, even after adjustment for transplant as a time-dependent covariate, 6MWD remained a highly significant predictor of survival. This effect was confirmed in model 3, when we considered survival among only transplanted patients. In unadjusted analysis, 6MWD was a significant predictor of posttransplant survival. When adjusted for the other variables, the overall effect of 6MWD was reduced (p -value = 0.05) but

in this model 3, the proportional hazard assumption was not met because of differing hazards within the first 30 days as compared to subsequent time periods. Because early postoperative deaths are most likely related to technical factors and donor factors, we reestimated the model 3 using several approaches to account for these differences during the early period. In simplest analysis in which the small subset of patients with early death was excluded, the 6MWD as a continuous variable was highly predictive of survival beyond 30 days in those patients who underwent lung transplantation. Similar results were obtained with more sophisticated modeling approaches. Collectively, all of these results are consistent with the idea that 6MWD is a useful global marker of health status that impacts recovery of patients who survive the initial lung transplant operation. Those patients with higher walk distances might have an enhanced ability to fully participate in postoperative pulmonary rehabilitation leading to reduced atelectasis, improved mucociliary clearance and increased reserve should complications develop. Additional studies focused exclusively on posttransplant recipients would be useful to validate this observation and better define the mechanisms by which pretransplant 6MWD impacts upon posttransplant outcomes.

Our results (in model 1 and model 2) are also consistent with previous reports, which demonstrate increased wait list deaths among patients with CF and IPF relative to COPD (20). In addition, we did test for an interaction between native disease and transplant upon survival (model 1) and found the interaction term significant. Although our relatively small sample size and event rate within each disease subcategory limits any firm conclusions with regards to the survival benefit of transplant by disease, we report the HR and 95% CI by disease in Table 3. This by-category analysis is consistent with prior studies, which suggest that lung transplantation offers greater survival benefit in CF or ILD as compared to COPD, with the greatest benefit observed for CF transplants in our cohort (20–24).

Our finding that that 6MWD is a useful measure of both urgency and utility among patients awaiting lung transplantation has certain implications for lung allocation decisions. For example, the use of a dichotomized 6MWD score at 150 feet (or 45.72 m) as is employed by the current US lung allocation system (LAS) appears relatively insensitive to the broad range of predictive ability captured in the use of the 6MWD as a continuous variable (model 2) (25). Furthermore, our results suggest that 6MWD also provides a useful measure of transplant utility, such that higher walk distances identify patients at greater risk for survival after the initial transplant operation (model 1 and model 3). Although our results are not directly applicable to the population of patients currently undergoing transplant under the LAS, our results should prompt a careful reexamination of the use of 6MWD as a predictor across the entire range of values in estimation of both pre- and posttransplant survival in future revisions of the LAS.

Our analysis has several limitations. First, results of our interaction testing should be interpreted in light of the relatively smaller patient numbers and event rates in the native disease subgroups. A second limitation of our study occurs as a result of the sample composition based on patients listed for lung transplantation. Our results are not generalizable to all populations of patients with end-stage lung diseases. In addition, because of the changing demographic characteristics of the population undergoing lung transplantation in the United States, validation of our results in a recently transplanted cohort of patients listed under the new allocation schema would be useful. Thirdly, multivariable adjustment is interpreted here as evidence for the independence of 6MWD as a predictor of survival rather than as evidence of a causal role. Indeed, it is conceivable that other markers of functional capacity, such as NYHA class as employed in the current LAS, that overlap with 6MWD also may predict survival in a manner similar to 6MWD. Even if a variable correlating with 6MWD also predicted survival and “eliminated” 6MWD from a multivariable analysis, it would not change the univariate association; thus, 6MWD remains a relatively inexpensive and objective measure that predicts of survival. Finally, the

decision to exclude patients with early postsurgical death or censoring for the analysis of transplanted patients only (model 3) was based on the data at hand rather than an explicit *a priori* hypothesis. Although we believe this was a substantively reasonable approach, replication is warranted. Additional studies are needed to explore mechanism by which 6MWD predicts survival among patients awaiting lung transplantation and to confirm the relation among transplanted patients.

In summary, we demonstrate that a significant relationship exists between baseline 6MWD and survival in lung transplant candidates. We found that this relationship is similar across all native lung disease categories. Our results are quite consistent with previous studies, which implicated a role for the 6MWD in the prognostication of survival among patients awaiting lung transplantation with CF or IPF. Novel contributions of our study include the observations that the relationship between 6MWD and survival (1) extends across a broad range of baseline 6MWD values, (2) extends across diverse native disease and (3) extends through transplantation. Our results, thus, suggest a role for baseline 6MWD in assessing the urgency and utility in lung transplant candidates.

Our results also suggest several opportunities for future research. First, further studies are needed to determine if inclusion of a broader range of 6MWD values and consideration of the 6MWD on posttransplant survival would be useful to better model net transplant benefit in current US LAS organ allocation. Second, serial measurements of the 6MWD would be useful to determine if a single baseline measurement or subsequent measurements (or change in measurements over time) offer the greatest predictive ability in this population. Finally, our study also raises the possibility that rehabilitative measures that lead to improvements in walk distance can favorably impact upon pre- or postlung transplant survival, an idea that should be tested through further randomized prospective studies.

Acknowledgment

This work was presented in part at the annual American Thoracic Society (ATS) meeting, 2007, as an oral presentation. It was funded by HL 65503-01 from the National Institutes of Health.

References

1. ATS statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117. [PubMed: 12091180]
2. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;161(2 Pt 1):487–492. [PubMed: 10673190]
3. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. *N Engl J Med* 1996;334:296–302. [PubMed: 8532025]
4. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012. [PubMed: 14999112]
5. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;174:659–664. [PubMed: 16778159]
6. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis. Are they helpful for predicting outcome? *Chest* 1997;111:51–57. [PubMed: 8995992]
7. Miki K, Maekura R, Hiraga T, et al. Impairments and prognostic factors for survival in patients with idiopathic pulmonary fibrosis. *Respir Med* 2003;97:482–490. [PubMed: 12735664]

8. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: Predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1063–1072. [PubMed: 9563720]
9. Vizza CD, Yusen RD, Lynch JP, Fedele F, Alexander Patterson G, Trulock EP. Outcome of patients with cystic fibrosis awaiting lung transplantation. *Am J Respir Crit Care Med* 2000;162(3 Pt 1):819–825. [PubMed: 10988089]
10. Sharples L, Hathaway T, Dennis C, Caine N, Higenbottam T, Wall-work J. Prognosis of patients with cystic fibrosis awaiting heart and lung transplantation. *J Heart Lung Transplant* 1993;12:669–674. [PubMed: 8369328]
11. Blumenthal JA, Babyak MA, Keefe FJ, et al. Telephone-based coping skills training for patients awaiting lung transplantation. *J Consult Clin Psychol* 2006;74:535–544. [PubMed: 16822110]
12. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society. *J Heart Lung Transplant* 1998;17:703–709. [PubMed: 9703236]
13. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–664. [PubMed: 7271065]
14. Harrell, FE. *Regression Modeling Strategies: With Applications To Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer; 2001. p. 74-75.
15. Therneau, TM.; Grambsch, PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer; 2000. p. 74-75.
16. Hollander N, Sauerbrei W, Schumacher M. Confidence intervals for the effect of a prognostic factor after selection of an ‘optimal’ cutpoint. *Stat Med* 2004;23:1701–1713. [PubMed: 15160403]
17. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using “optimal” cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst* 1994;86:829–835. [PubMed: 8182763]
18. Schulgen G, Lausen B, Olsen JH, Schumacher M. Outcome-oriented cutpoints in analysis of quantitative exposures. *Am J Epidemiol* 1994;140:172–184. [PubMed: 8023805]
19. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: Prognostic value of changes in physiology and six-minute-walk test. *Am J Respir Crit Care Med* 2006;174:803–809. [PubMed: 16825656]
20. 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. [PubMed: 9433425]
21. 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. [PubMed: 11834351]
22. 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. [PubMed: 11343978]
23. Thabut G, Mal H, Castier Y, et al. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. *J Thorac Cardiovasc Surg* 2003;126:469–475. [PubMed: 12928646]
24. 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. [PubMed: 9628571]
25. UNOS website. Available at http://www.unos.org/SharedContent-Documents/Calculation_Guide.pdf.

Figure 1. Unadjusted Kaplan-Meier survival estimates by tertile of 6 MWD

Log rank test for difference among tertile groups, $p = 0.0001$. Values at bottom of figure represent number at risk for each tertile group

Figure 2. Relation of 6MWD and predicted probability of survival 3 years after study entry adjusted for age, native disease, and FEV₁

Dashed lines represent 95% confidence limits. Tick marks on top axis represent case density for the 6MWD.

Table 1

Baseline patient demographic characteristics (n = 376)

Variable	
Age, years, median (interquartile range)	53 (43, 59)
Female, n (%)	212 (56)
Caucasian, n (%)	331 (88)
Native disease, N (%)	
COPD	153 (41)
Alpha-1 Antitrypsin deficiency	25 (7)
CF	51 (14)
¹ ILD	84 (22)
Sarcoidosis	16 (4)
PPH	24 (6)
Eisenmenger's syndrome	7 (2)
² Miscellaneous diseases	16 (4)
Transplanted during study, N (%)	172 (46)
Arterial pO ₂ , mmHg, median (interquartile range)	65 (57, 73)
Arterial pCO ₂ , mmHg, median (interquartile range)	41 (37, 46)
FEV ₁ , L, median (interquartile range)	0.82 (0.59, 1.41)
6-min walk test, ft/m, median(interquartile range)	1092/335 (794/242, 1326/407)
Time on transplant waiting list, days, median (interquartile range)	29 (13, 61)
Using O ₂ therapy, N (%)	225 (60)

COPD = chronic obstructive pulmonary disease; CF = cystic fibrosis; ILD = interstitial lung diseases; PPH = primary pulmonary hypertension; pO₂ = partial pressure of oxygen; pCO₂ = partial pressure of carbon dioxide; FEV₁ = forced expiratory volume in 1 second.

¹The interstitial lung disease category includes mostly patients with idiopathic pulmonary fibrosis but also 1 patient with hyper-sensitivity pneumonitis, 1 patient with desquamative interstitial pneumonitis, 1 patient with nonspecific interstitial pneumonitis, and 1 patient with scleroderma-related pulmonary fibrosis.

²Miscellaneous diseases include: bronchiectasis (n = 6), lymphangiomyomatosis (LAM) (n = 6), langerhans histiocytosis (N = 2), neurofibromatosis (n = 1), and pulmonary thromboembolic disease (n = 1).

Table 2

Time to event analysis. Model 1: All patients with transplant modeled as intervening event

Predictor of death	Hazard ratio	95% Confidence limits	p-Value
Six-Min Walk Distance (500 ft increase)	0.47	0.34, 0.64	<0.0001
Age (10 year increase)	1.04	0.78, 1.38	0.800
Percent-predicted FEV ₁ (10 percentage point increase)	1.01	0.85, 1.20	0.926
Transplanted vs. not transplanted	1.01	0.58, 1.77	0.957
CF vs. COPD	3.32	1.22, 9.02	0.019
ILD vs. COPD	2.42	1.09, 5.40	0.031
PPH vs. COPD	2.22	0.55, 9.00	0.265
Other native disease vs. COPD	1.33	0.50, 3.52	0.570

Pooled (4df) test of native disease effect, $p = 0.056$.

CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung diseases; PPH = primary pulmonary hypertension.

Table 3

Survival and transplant within native disease categories

Native disease category	Number deceased/ Total number (Percent deceased)		Unadjusted hazard ratio associated with transplant from time to event analysis	95% Confidence limits
	Transplanted	Not transplanted		
COPD (n = 178)	16/84 (19)	15/94 (16)	1.93	0. 90, 4.12
ILD (n = 84)	7/36 (19)	15/48 (31)	0.91	0.32, 2.65
CF (n = 51)	5/36 (14)	8/15 (53)	0.15	0.28, 0.79
PPH (n = 24)	4/20 (20)	4/20 (20)	*	*
'Other native diseases' (n = 39)	3/12 (25)	5/27 (19)	0.82	0.09, 7.58

Note: COPD includes Alpha-1 Antitrypsin deficiency.

* Not estimable by Cox model due to sparse data.

COPD = chronic obstructive pulmonary disease; ILD = interstitial lung diseases; CF = cystic fibrosis; PPH = primary pulmonary hypertension.

Table 4

Time to event analysis. Model 2: All patients censored at time of transplant

Predictor of death	Hazard ratio	95% Confidence limits	p-Value
Six-Min Walk Distance (500 ft increase)	0.41	0.27, 0.62	<0.0001
Age (10 year increase)	1.01	0.71, 1.44	0.945
Percent predicted FEV ₁ (10 percentage point increase)	0.99	0.81, 1.29	0.994
CF vs. COPD	6.49	1.89, 22.35	0.003
ILD vs. COPD	3.79	1.40, 10.3	0.009
PPH vs. COPD	2.67	0.47, 15.13	0.266
Other native disease vs. COPD	1.78	0.51, 6.24	0.362

Pooled test (4 df) of native disease effect: $p = 0.007$.

CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung diseases; PPH = primary pulmonary hypertension.

Table 5

Time to event analysis. Model 3: Transplanted patients only

Predictor of death	Hazard ratio	95% Confidence limits	p-Value
Six-Min Walk Distance (500 ft increase)	0.39	0.22, 0.71	0.002
Age (10 year increase)	0.83	0.46, 1.47	0.515
Percent predicted FEV ₁ (10 percentage point increase)	1.40	0.92, 2.11	0.114
CF vs. COPD	0.42	0.06, 3.19	0.400
ILD vs. COPD	0.43	0.07, 2.50	0.347
PPH vs. COPD	0.09	0.24, 7.06	0.538
Other native disease vs. COPD	0.41	0.05, 1.32	0.078

Pooled test (4 df) of native disease effect: $p = 0.352$.

CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung diseases; PPH = primary pulmonary hypertension.