Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Liou TG, Adler FR, Cox DR, Cahill BC. Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 2007;357:2143-52.

Supplemental Repository

Details of the proportional hazards modeling procedure

To examine baseline wait-list survival, we assigned patients a transplant status of 0, a pre-transplantation observation start day of 0 on the date of listing, and an observation stop day as the number of days from listing to death on the wait list or censoring due to transplantation, withdrawal from the wait list, loss-to-follow up, or December 31, 2002. To examine post-transplant survival, we assigned a transplant status of 1, a post-transplant observation start day equal to the number of days accrued on the wait list, and a post-transplant stop day equal to the post-transplant start day plus the number of days until death or until censoring due to re-transplantation, loss-to-follow up, or December 31, 2002. Thus, patients that had undergone transplantation were counted only once on any day during the study.[1] Because the definition of loss-to-follow up potentially introduced a bias, we re-analyzed using three definitions, censoring 1) on the day after last contact with each patient, 2) on December 31, 2002, and 3) three years after last contact according to CFFPR convention.

We selected additional covariates from the CFFPR that were previously tested modifiers of survival,[2,3] the calendar date of transplantation in order to examine possible improvements in the procedure,[4] infections involved in progressive pulmonary disease,[2,5] and variables similar to those in Aurora *et al*.[6]

We developed models using the last covariate values within the two years prior to listing.[7] All potentially important covariates and interactions with transplantation were considered. Using a backward selection procedure, we eliminated covariates in reverse order of significance beginning with interaction terms followed by primary covariate effects. We judged the impact of removing terms using the likelihood ratio test, which is based on partial likelihood, and stopped model development once the change in likelihood exceeded 2. Because this procedure did not exhaustively test all possible models, we reconsidered potentially important variables using a forward variable selection procedure.

Differences with Aurora et al

Reconciling disparate results between this study and that of Aurora *et al*[6] requires consideration of at least four differences. The two papers differ in analytical methods, post-transplant survival, patients studied, and wait-list management.

First, both papers used proportional hazards models with time dependent covariates. Aurora *et al* reported a single hazard factor of 0.31 (CI 0.13-0.72, p = 0.007) for lung transplantation.[6] Their result implies that transplantation may have been significantly beneficial to all patients meeting entry criteria for their study. However, when characteristics of individual patients were considered in our study, a range of hazard factors were derived (Figure 2) showing that only a few patients had the level of benefit suggested by Aurora *et al*.[6]

Second, children with CF in the US may have had relatively decreased post-transplant survival. US patients had a median survival of 2.84 years (Figure 1), less than their British counterparts at approximately 3.5 years,[6] possibly reducing the likelihood of finding a survival benefit. However, this difference is not clearly statistically significant (Figure 1 and Aurora *et al*) and

may not explain the discrepancy in survival effect with Aurora *et al*.[6]

Third, we studied a different population of patients than Aurora *et al*.[6] We studied more patients (514 vs 124 patients) with more numerous (268 vs. 47) and frequent (52% vs 38%) transplants. Patients were older (mean 14.41 vs. 11.7), had better lung function (FEV1% 34.1 vs 26.0), and potentially had better prognosis (57.2% predicted 5-year survival[2] vs. less than 2 year life expectancy based on a different prognostic model[8]).

Better lung function and potentially better prognosis might have improved wait-list survival in the US and reduced the likelihood of survival benefit. However, we examined hazard factors of transplantation for patients with lower FEV_1% and 5-year predicted survival.[2] These analyses reached the same conclusions even for patients with much poorer lung function and prognosis. The subsets of patients with an $FEV_1 < 30\%$ or with 5-year predicted survival < 50% encompassed about 40% of the patients studied, a group that was still double the size of the group studied by Aurora *et al*.[6]

Finally, physicians from centers in the United States listed patients for transplantation without necessarily following a single set of listing criteria. Patients were transplanted in the order of listing without regard for acuity of illness. Patients in Aurora *et al* were evaluated and listed for transplantation according to a single set of criteria at a single British institution and transplanted according to clinical disease severity.[6] Thus US patients waiting for transplantation might have been more likely to die, increasing the likelihood of finding a survival benefit from transplantation.

Quality of Life

To estimate potential QOL changes due to transplantation, we examined the number of hospitalization days and total number of complications during the last complete calendar year prior to transplantation and compared those numbers with the number of hospital days and complications during the first and second complete calendar years post-transplant. Patients were included in the comparisons if they were transplanted and survived through the first or second complete post-transplant calendar years. For example, for a patient who received transplantation March 15, 1999 and died during 2001, we counted hospital days during 1998 and compared them to hospital days during 2000 but not 2001. Because of the way that the CFFPR records these variables, we cannot know which hospital days during 1999 were pre-transplant and which were post-transplant. We used paired *t*-tests[9] to compare pre- and post-transplantation numbers of hospital days and complications.

Hospitalization days per year were substantially reduced in our data during both the first and second calendar years after lung transplantation (Supplemental Figure A, panels A and B). The mean reduction was approximately 30 days. In contrast, the numbers of complications of disease approximately doubled after transplantation (Supplemental Figure A, panels C and D).

Unfortunately, reporting biases may account for some or all of the reduction in hospital days shown in Supplemental Figure A, panels A and B. Pre-transplantation, hospital days were reported by the same CF centers where those days were accrued. Post-transplantation, hospital days were reported by the same CF centers but transplant related hospital days may or may not have been reported to each CF center for inclusion in the CFFPR by the transplant programs even

within the same institution.

Post-transplantation complications shown in Figure A may be underreported for reasons similar to those for post-transplantation hospitalization days. The CFFPR has no specific *bronchiolitis obliterans* variable, and OPTN derived data reported *bronchiolitis obliterans* only if patients re-entered the waiting list due to loss of a transplanted organ due to *bronchiolitis obliterans*. Thus this common post-transplantation complication that significantly reduces post-transplantation QOL[10,11] is likely to be severely underreported.

References

1. Therneau TM, Grambsch PM. Modeling survival data: Extending the Cox model (statistics for biology and health). New York: Springer-Verlag, 2000.

2. Liou TG, Adler FR, Fitzsimmons SC, et al. Predictive five year survivorship model of cystic fibrosis. Am. J. Epidemiol, 2001; 153:345-352.

3. 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.

4. Crowley J, Hu M. Covariance analysis of heart transplant survival data. Journal of the American Statistical Association, 1977; 72:27-36.

5. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2002 annual data report to the center directors. Bethesda, Maryland. Copyright 2003 Cystic Fibrosis Foundation.

6. Aurora P, Whitehead B, Wade A, et al. Lung transplantation and life extension in children with cystic fibrosis. Lancet, 1999; 354:1591-1593.

7. Liou TG, Adler FR, Cahill BC, et al. Survival effect of lung transplantation for patients with cystic fibrosis. JAMA, 2001; 286:2686-2689.

8. Zar JH. Biostatistical analysis. 4th Edition. Upper Saddle River, N.J.: Prentice Hall, 1998.

9. Aurora P, Wade A, Whitmore P, Whitehead B. A model for predicting life expectancy of children with cystic fibrosis. Eur. Resp. J., 2000; 16:1056-1060.

10. Smeritschnig B, Jaksch P, Kocher A, et al. Quality of life after lung transplantation: a cross-sectional study. J. Heart Lung Transplant., 2005; 24:474-480.

11. Kugler C, Fischer S, Gottlieb J, et al. Health-related quality of life in two hundred-eighty lung transplant recipients. J. Heart Lung Transplant., 2005; 24:2262-2268.

12. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am. J. Respir. Crit. Care Med., 1999; 159:179-187.

13. Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. Am. J. Clin. Nutr., 1979; 32:607-629.

14. Dibley MJ, Goldsby JB, Staehling NW, Trowbridge FL. Development of normalized curves for the international growth reference: historical and technical considerations. Am. J. Clin. Nutr., 1987; 46:736-748.

15. Lai H-C, Kosorok MR, Sondel SA, et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: Evaluation of various criteria used to identify malnutrition. J. Pediatr., 1998; 132:478-485.

Table A. Variables tested for survival and effect on pediatric lung transplantation
age[*]
diabetes status[*†]
Burkholderia cepacia infection[*‡]
Staphylococcus aureus infection[*‡]
gender
FEV1%[§]
functional status[¶]
hospitalization status[**]
Achromobacter xylosoxidans infection[‡]
Aspergillus infection[‡]
Methicillin resistant *S aureus* infection[‡]
Stenotrophomonas maltophilia infection[‡]
Pseudomonas aeruginosa infection[‡]
number of acute exacerbations[‖]
pancreatic sufficiency
pulmonary artery pressure, systolic and diastolic[††]
serum creatinine
six minute walk data
weight-for-age z-score[‡‡]
CF related arthropathy status[§§]
calendar date of transplantation[¶¶]
PaCO2
Use of mechanical ventilation[††]
Use of supplemental oxygen[‖‖]

[*]Variables with a significant effect on survival

[†]Diabetes was inferred by the chronic use of insulin

[‡]Infections were diagnosed by growth of each bacterium listed from sputum or throat swab samples on bacterial cultures.

[§]Raw forced expiratory volume in one second (FEV_1) was used to calculate percent predicted FEV_1 (FEV_1%) using regression equations from the third National Health And Nutrition Evaluation Survey.[12]

¶Functional status was defined for pediatric CF patients as no assistance required, some assistance required, or total assistance required for activities of daily living.

‖Up to five acute exacerbations of CF in the year prior to wait-listing for transplantation were counted.[2]

**Patients were noted to be at home, in the hospital or in the ICU.

††Insufficient data for analysis

‡‡Weight-for-age *z*-score was calculated using approximation methods.[7,13-15]

§§Only 5 children in the study had CF related arthropathy.

¶¶ Borderline significance, see supplemental Table B.

‖‖Use of supplemental oxygen was of uncertain significance, see Results.

Table B. Hazard factors of covariates affecting survival before and after lung transplant including time of referral for transplantation.

Variable	Hazard Factor	Coefficient	Robust Standard Error[†]	*p*-value
All Patients				
B cepacia infection	1.52	0.419	0.200	0.037
Before Transplantation (n=514)				
Age (per year)	0.966	-0.0346	0.029	0.24
Diabetes	2.065	0.725	0.272	0.008
S aureus infection	0.718	-0.332	0.195	0.09
Year Seen[*]	0.947	-0.0542	0.0316	0.08
After Transplantation (n=248)				
Age (per year)	1.148	0.138	0.032	< 0.001
Diabetes	0.746	-0.293	0.335	0.38
S aureus infection	1.475	0.388	0.176	0.028
Year Seen[*]	1.082	0.078	0.041	0.054

[*]Coefficients for Year Seen before and after transplant were not significant, however, addition of the variable increased the log likelihood by more than 2, indicating that this model provides a slightly better fit of the data than that presented in Table 2.

[†]Calculation of the robust standard error for each coefficient uses an approximate jackknife estimate of the variance (coxph function in Splus 7.0).

Table C. Proportional hazards model of survival applied to adults*				
Variable	**Hazard factor**	**Coefficient**	**Robust Standard Error†**	***p*-value**
Lung Transplant	1.49	0.397	0.287	0.17
B cepacia infection	1.45	0.373	0.117	0.001
Age	0.98	-0.015	0.006	0.01
Diabetes	1.40	0.333	0.080	<0.001
Lung Transplant×Age	1.003	0.003	0.010	0.8

*This model illustrates that age is predictive of survival in adults (as we have found before[2]) but has no significant interaction with lung transplantation (Lung Transplant×Age, p = 0.8, n = 2,744). While our main model (Table 2) shows that increasing age in children predicts worsening lung transplant outcomes, this effect disappears when patients attain adulthood. This result demonstrates that for adult patients (older than 18 years), a different model than presented in Table 2 is needed to explore the survival effect of lung transplantation. The model shown here is preliminary in nature and should not be used to assess the efficacy of lung transplantation nor to predict survival among adult patients with CF.

†Calculation of the robust standard error for each coefficient uses an approximate jackknife estimate of the variance (coxph function in Splus 7.0).

Table D. Patients by clinical group and calculated hazard factor for survival with transplantation

Patient Group (*p*-value ranges)	**Significant Harm**	**Indeterminate**	**Significant Benefit**	**Totals**
S aureus infection	121 ($p = 0.046$ to $p < 0.001$)	28 ($p = 0.054$ to $p = 0.96$)	0	149
Diabetes	0	30 ($p = 0.15$ to $p = 0.99$)	2 ($p = 0.04$ and $p = 0.004$)	32
S aureus infection and Diabetes	2 ($p = 0.049$ and $p = 0.035$)	13 ($p = 0.06$ to $p = 0.74$)	0	15
Neither *S aureus* infection nor Diabetes	192 ($p = 0.046$ to $p < 0.001$)	123 ($p = 0.0501$ to $p = 0.998$)	3 ($p = 0.04$ to $p = 0.019$)	318
Totals	315	194	5	514

Table E. Proportional hazards model of survival without interactions				
Variable	**Hazard factor**	**Coefficient**	**Robust Standard Error**[†]	***p*-value**
Lung Transplant	1.89	0.639	0.160	< 0.001
B cepacia infection	1.51	0.410	0.198	0.039
Age	1.05	0.053	0.022	0.016
Diabetes	1.19	0.176	0.208	0.4
S aureus infection	1.06	0.061	0.122	0.62

[*]This model does not consider interactions of the covariates with lung transplantation. Without interactions, the term for transplantation appears uniformly harmful regardless of the values of other covariates. Without considering interactions, diabetes and *S aureus* infection are both insignificant terms. The term for *B cepacia* infection does not interact with transplantation (main text), thus it retains approximately the same value as in the models that include interactions (Table 2). The log likelihood for this model is substantially inferior to the other models presented.

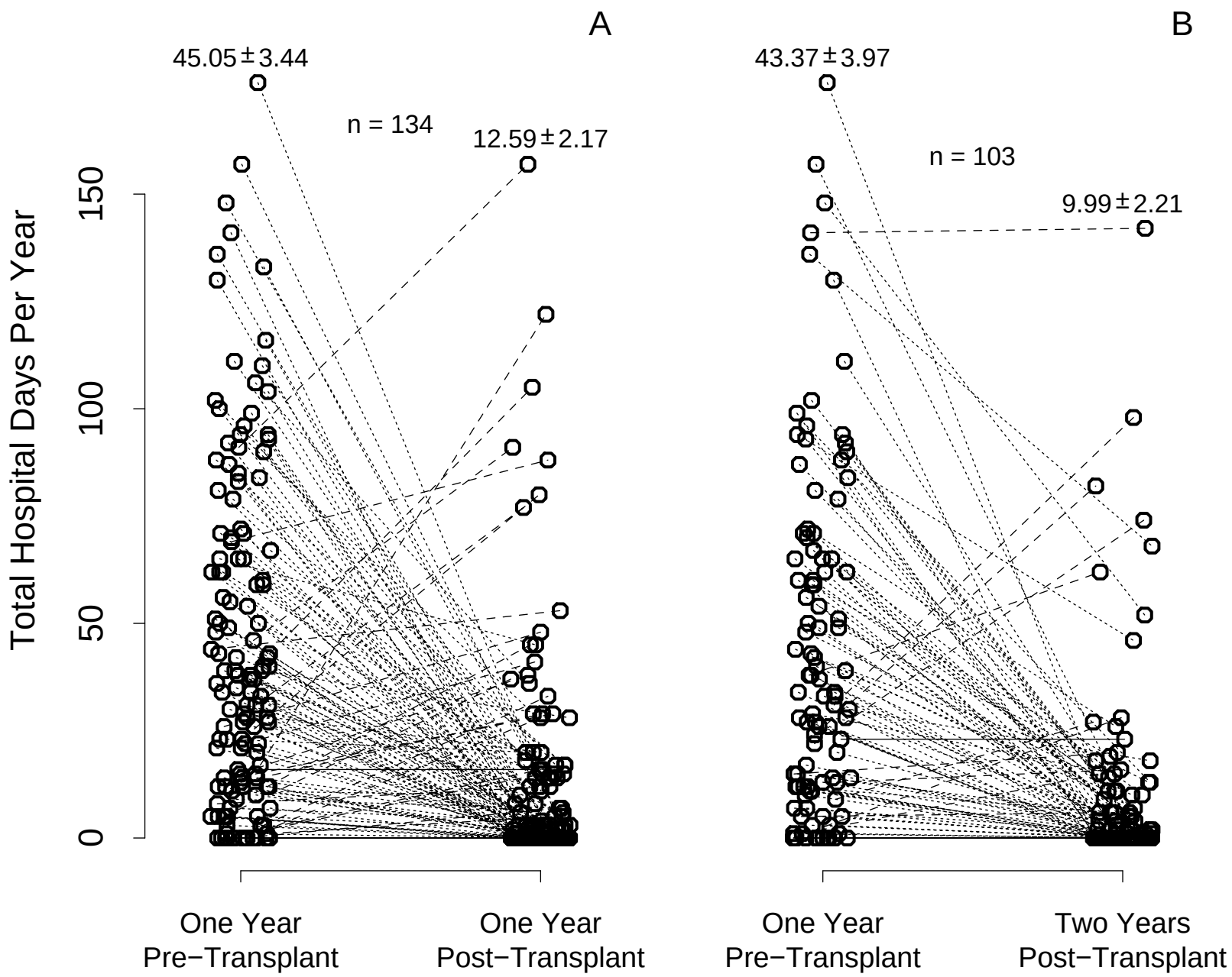
[†]Calculation of the robust standard error for each coefficient uses an approximate jackknife estimate of the variance (coxph function in Splus 7.0)

Supplemental Figure A

Panels A and B show recorded hospitalization days for patients before and after lung transplantation for patients who survived to the end of one or two complete calendar years following the year of transplantation. Panel A shows the comparison made between the last complete pre-transplantation calendar year and the first complete post-transplantation calendar year. Panel B shows the comparison made between the last complete pre-transplantation calendar year and the second complete post-transplantation calendar year. Both panels show substantial drops in hospital days of as much as 150 days per year for individual patients but increases of more than 60 days for some patients. Panels C and D show recorded raw numbers of complications of CF before and after lung transplantation. Complications considered for this analysis were retinopathy, hearing loss, sinusitis, allergic bronchopulmonary aspergillosis, hemoptysis, pneumothorax, peptic ulcers, GI bleeds, pancreatitis, hepatic cirrhosis and other liver disease, gallbladder disease, small and large intestinal obstructions, rectal prolapse, glucose intolerance, diabetes, albuminuria, renal failure, hypertension, vasculopathy, CF related arthropathy, fractures, osteopenia, osteoporosis, cancer, depression, and other. Panel C shows the comparison made between the last complete pretransplantation calendar year the first complete post-transplantation calendar year. Panel D shows the comparison made between the last complete pre-transplantation year and the second complete post-transplantation calendar year.

While paired t-tests[8] showed that the changes in hospitalization days and complications were highly significant in all four panels, reporting biases explain part or even all the changes post-transplantation.

Supplemental Figure A



Supplemental Figure A, Continued