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Mini Review on Pediatric Lung Transplantation for Cystic Fibrosis

Theodore G. Liou, MD^{1,2,3,*} and Barbara C. Cahill, MD^{1,4}

¹Department of Internal Medicine, University of Utah, Salt Lake City, Utah.

²Department of Pediatrics, University of Utah, Salt Lake City, Utah.

³Director, Intermountain Adult Cystic Fibrosis Center.

⁴Director, Lung Transplant Program.

Abstract

Pediatric lung transplantation for cystic fibrosis (CF) has uncertain survival effects. Three retrospective studies disagree on survival benefit. The US Lung Allocation Score has changed patient selection for lung transplantation but confounds the analysis of survival outcomes. A prospective trial is needed to resolve clinical equipoise and explore quality-of-life effects.

Keywords

Review; Children; Lung Transplantation; Cystic Fibrosis; Survival Analysis; Cox Proportional Hazards Models

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Lung transplantation remains the most aggressive therapy for end-stage lung disease, and patients with cystic fibrosis (CF) comprise the third largest group undergoing the procedure.

¹ However, CF is the most frequent indication for pediatric lung transplantation.¹

Respiratory failure, including lung transplantation-related deaths, ultimately accounts for 91% of CF deaths.² Consequently, most CF patients consider lung transplantation at some point during life. Median survival following lung transplant is approximately 4.6 years,¹ however such data do not reveal the degree to which transplantation positively or negatively alters survival for recipients. For example, long survival after transplant might be due to an outstanding outcome of transplantation of a severely ill patient, or a poor outcome of inappropriate transplantation of a more healthy patient.

No prospective studies have analyzed lung transplantation outcomes. Existing studies have used two general analysis schemes on existing observational data to evaluate transplantation survival effects: 1) comparison of post-transplant to waiting-list survival or 2) comparison of post-transplant to non-transplanted survival of patients with similar degrees of illness. Both schemes assume that non-transplanted controls are not substantially different from transplanted patients for baseline disease characteristics and are not different in susceptibility to events such as new infections independently of the effects of lung transplantation.

Three peer-reviewed publications have examined lung transplantation for pediatric patients with CF. Aurora *et al*³ analyzed data from 124 children with CF (47 transplanted) in the United Kingdom May, 1988-May, 1998 using a proportional hazards model with transplant as a time-dependent covariate.^{4–6} This method compares survival of post-transplant to waiting-list

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*Correspondence to Theodore G. Liou, MD, 26 North Medical Drive, Salt Lake City, UT 84132 or by e-mail to ted.liou@utah.edu.

patients with two assumptions. First, the hazard of death is dependent upon time from listing and measured explanatory variables but may change at transplantation. Second, because the same patients are in both the control and transplant groups, movement of patients from the wait-list to the post-transplantation group is not determined by the likelihood of death before or after transplant. In Aurora's study,³ the most acutely ill patient was chosen for transplantation when lungs became available. This selection procedure potentially confounded analysis of survival effects because patients at higher risk of death were preferentially transplanted when more than one patient was on the waiting list. After correcting for survival effects of 7 additional covariates previously discovered to predict prognosis,⁷ the analysis found that lung transplantation had a hazard factor of 0.31 (CI 0.13–0.72, $p=0.007$), suggesting a marked improvement in average survival with lung transplantation.³

More recently, in the United States, we analyzed data from the CF Foundation Patient Registry and the Organ Procurement and Transplantation Network for 205 children transplanted 1991–2001 and 1,018 non-transplanted children alive January 1, 1997 and followed through 2001.⁸ We discovered that the 57 pediatric transplant recipients with a baseline predicted 5-year survival less than 50% had no difference in survival compared to 139 non-transplanted control patients with a similar severity of disease ($p=0.88$). Among 127 children with a predicted 5-year survival greater than 50% that were transplanted, we found a substantial decrease in post-transplant survival compared to the control group ($p<0.001$).⁸ The absence of positive results suggests that lung transplantation, even for the most severely ill pediatric patients, may not improve survival. However, unmeasured, but clinically important variables affecting survival might have existed that were excluded from the predicted 5-year survival model used to stratify patients for analysis.⁹ Testing for this potential bias was not directly possible.¹⁰

The most recent analysis of lung transplantation in children with CF returned to using proportional hazards modeling with transplantation as a time-dependent covariate^{4–6} to analyze outcomes for 514 children listed for transplantation (248 transplanted) in the United States from 1992–2002.¹¹ The study examined transplantation and 24 additional variables pertinent to predicting survival in CF including infection status for 7 organisms and 17 other physiologic variables including PaCO₂ and functional status. Variables were included only if they were available to clinicians when the decision to list patients for transplantation was made. Thus the study analyzed outcomes of decisions to pursue transplant. This study¹¹ does not suffer from the potential biases of the earlier Liou *et al* study⁸ but is subject to the biases that may have been present in Aurora *et al*.³ The study reported hazards of death following transplantation after risk stratification according to age, diabetes status and *Staphylococcus aureus* infection status in order to facilitate application to individual patients.^{12,13} Older age and *S aureus* infection indicated an increased hazard of death following lung transplantation. Diabetes increased the hazard of death while waiting for transplantation, but tended to reduce the hazard of death following transplantation. After accounting for interactions of age, *S aureus* infection status and diabetes, transplantation significantly increased the hazard of death in 283 of 514 patients and significantly reduced the hazard in 5 patients. Transplantation did not significantly affect the hazard of death for the remaining 226 patients studied.

Transplantation selection criteria in the United States changed in 2005 for patients 12 years and older and may have altered the survival effect for older children. The Lung Allocation Score (LAS) attempts to rank patients by the potential gain in survival following lung transplantation.¹⁴ Unfortunately, the effect on survival outcomes is not evaluable with current data because the LAS directly links the risk of death before and after transplantation with the decision to perform transplantation.

The favorable aggregated hazard of transplantation from Aurora *et al*³ and the near absence of positive, risk-stratified results of our studies^{8,11} illustrate a state of clinical equipoise¹⁵ for pediatric lung transplantation. No systematic quality-of-life data specific to pediatric lung transplantation for CF are available that would help resolve the state of equipoise. What data exist are of uncertain quality and are only indirect measures of quality-of-life.¹¹ Additional retrospective analyses using data collected in the United States after introduction of the LAS cannot resolve the uncertainty about transplantation because of confounding. A prospective randomized study is our best hope for providing the much needed data to define the true survival and quality-of-life effects of lung transplantation for children with CF.

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References

1. U.S. Department of health and Human Services. Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1995–2004. Rockville, MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation;
2. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2002 annual data report to the center directors. Bethesda, Maryland: Copyright 2003 Cystic Fibrosis Foundation;
3. Aurora P, Whitehead B, Wade A, et al. Lung transplantation and life extension in children with cystic fibrosis. *Lancet* 1999;354:1591–1593. [PubMed: 10560673]
4. Cox DR. Regression models and life-tables. *J. R. Statist. Soc. B* 1972;34:187–220.
5. Cox, DR.; Oakes, D. Analysis of survival data. Vol. 1st Edition. London: Chapman and Hall; 1984.
6. Crowley J, Hu M. Covariance analysis of heart transplant survival data. *Journal of the American Statistical Association* 1977;72:27–36.
7. 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.
8. 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. [PubMed: 15695493]
9. Sweet SC, Faro A. International Pediatric Lung Transplant Collaborative. Not so fast--don't deprive children with cystic fibrosis of the option for lung transplantation. *Am. J. Respir. Crit. Care Med* 2006;173:246a–247. [PubMed: 16391305]
10. Liou TG, Adler FR, Huang D. Not so fast--don't deprive children with cystic fibrosis of the option for lung transplantation. Authors' reply. *Am. J. Respir. Crit. Care Med* 2006;173:247–248.
11. Liou TG, Adler FR, Cox DR, Cahill BC. Lung transplantation and survival in children with cystic fibrosis. *New Engl. J. Med* 2007;357:2143–2152. [PubMed: 18032764]
12. Kent DM, Hayward RA. Limitation of applying summary results of clinical trials to individual patients. *JAMA* 2007;299:1209–1212. [PubMed: 17848656]
13. Cox DR, Wermuth N. Causality: a statistical view. *Int. Statist. Rev* 2004;72:285–305.
14. Egan TM, Murray S, Bustami RT, et al. Development of the new Lung Allocation System in the United States. *Am. J. Transplant* 2006;6:1212–1227. [PubMed: 16613597]
15. Freedman B. Equipoise and the ethics of clinical research. *New Engl. J. Med* 1987;317:141–145. [PubMed: 3600702]