Eur Respir J 2000; 16: 1061–1064
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

The effect of prelung transplant clinical status on post-transplant survival of children with cystic fibrosis

P. Aurora*, A. Gassas+, S. Ehtisham**, B. Whitehead*, P. Whitmore*, P.G. Rees*, V.T. Tsang*, M.J. Elliott*, M. de Leval*

The effect of prelung transplant clinical status on post-transplant survival of children with cystic fibrosis. P. Aurora, A. Gassas, S. Ehtisham, B. Whitehead, P. Whitmore, P.G. Rees, V.T. Tsang, M.J. Elliott, M. de Leval. ©ERS Journals Ltd 2000.

ABSTRACT: The aim of this study was to determine whether transplanting paediatric cystic fibrosis (CF) patients later in the course of their disease was detrimental to their post-transplant survival. Data was collected from 51 children with CF undergoing lung or heart-lung transplantation May 1988–March 1999. The following risk factors were tested by Cox proportional hazards modelling: age at transplant; sex; donor/recipient sex mismatch; donor/recipient cytomegalovirus (CMV) mismatch; cold and warm graft ischaemic times; and donor age. Pretransplant forced expiratory volume in one second (FEV_1), minimum oxygen saturation obtained during 12 min walk (S_{a,O_2min}), and a survival probability score (SP) calculated from FEV_1, age adjusted resting heart rate, age, sex, blood haemoglobin (Hb), and serum albumin were then added to the model.

None of the risk factors were significantly correlated with death during the study period. No evidence that clinical status prior to transplant has any effect upon the post-transplant survival of children with cystic fibrosis was found.

Eur Respir J 2000; 16: 1061–1064.

*Cardiorespiratory and Critical Care Directorate, Great Ormond Street Hospital for Children, and +Dept of Paediatrics, Chase Farm Hospital, London, UK. **Dept of Paediatrics, City Hospital, Birmingham, UK.

Correspondence: P. Aurora, Portex Anaesthesia, Intensive Care and Respiratory Medicine Unit, Institute of Child Health, 30 Guilford, London, WC1N 1EH, UK. Fax: 44 2073518473

Keywords: Children, cystic fibrosis, paediatrics, prognosis, transplant

Received: February 25 2000
Accepted after revision June 30 2000

Lung or heart-lung transplantation is now an accepted treatment option for patients with severe cystic fibrosis (CF) lung disease, with increasing evidence that the procedure can prolong survival and improve quality of life for appropriately selected patients [1–3]. This has led to an increased demand, with the number of potential recipients vastly exceeding the number of suitable donors.

This frustrating situation adds to the incentive to optimize the timing of acceptance for transplantation, so that the recipient receives the maximal benefit from the procedure, whilst still retaining a good chance of receiving scarce organs. Whilst some countries operate a "first come first served" waiting list, UK transplant centres operate a more flexible waiting system, and are able to prioritize patients who are considered to have the shortest life expectancy. In order to maximize the benefit to potential recipients, it is then necessary to determine whether patients are likely to survive long enough to receive organs, and secondly, whether the risk of transplantation increases for patients with more advanced disease.

The first question has been addressed by previous studies [4, 5]. Current international consensus statements suggest that CF patients should be listed for transplantation when their forced expiratory volume in one second (FEV_1) falls to 30% pred normal or below, as this appears to equate to a life expectancy of $\leq$2 yrs. Sophisticated multivariate modelling techniques are used with increasing frequency, which may prove to be more reliable in predicting life expectancy [6]. Previous studies have attempted to identify risk factors related to reduced survival following lung or heart-lung transplantation [7]. Risk factors studied have included: age of recipient and donor; sex mismatch; cytomegalovirus (CMV) mismatch; donor organ ischaemic time; and rejection and infection episodes post-transplant. However, limited data exist on the impact of pretransplant clinical status on post-transplant survival. The main purpose of this study was to determine whether transplanting paediatric CF patients later in the course of their disease, and consequently in a poorer clinical state, was detrimental to their post-transplant survival. The authors also assessed their own policy of prioritizing patients with the poorest clinical status, to determine whether this affects their waiting-time for organs.

Materials and methods

Study subjects

The study population comprised 51 CF patients who received lung or heart-lung transplants May 1988–March 1999 at Great Ormond Street Hospital for Children, London. During this period the post-transplant survival figures were similar to those reported by other centres, with 74% survival at 1 yr, and 33% survival at 5 yrs [3].

The majority of patients were referred from other hospitals on the basis of an FEV_1 falling to 30% pred normal or below. During this period, the earlier referral of females and younger patients was encouraged as these patient categories have been shown to have a poorer

prognosis [5]. All patients were from the UK or Eire. Assessment included a review of a variety of clinical and physiological data, and patients were accepted for transplant if they were considered to have a life expectancy of ≤2 yrs, a poor quality of life, and had fully understood and consented to the procedure. The assessment procedure and acceptance criteria used have been detailed elsewhere [8]. The majority of patients were not accepted immediately but were maintained under regular observation for a number of months or even years [9]. After acceptance for transplantation, regular monitoring of clinical and physiological status continued. Suitable organs, when available, were allocated on the basis of greatest need, with patients with the poorest clinical status receiving priority. The allocation decision was made by a senior member of the transplant team at the time the donor organ was offered. None of the patients had ventilator dependent respiratory failure at the time of the transplant.

Study design

Clinical and physiological data were collected prior to transplant to assess the relationship with post-transplant survival. Time from date of transplantation to date of death was the outcome measure for this analysis. Data were also collected at the time of listing for transplant and correlated with the waiting time to transplant. Time from date of listing to date of transplantation was the outcome measure for this analysis.

Methods

Clinical status at the time of transplant (*t*) was estimated from data collected at the child's most recent review. Pretransplant FEV1 (FEV1*t*) was measured by spirometry, and corrected for height, age and sex using Brompton predicted scores [10]. Pretransplant minimum oxygen saturation obtained during a 12-min walk ($S_{a,O_2min}t$) [11] was measured by continuous pulse oximetry. Pretransplant age adjusted resting heart rate (AAHR*t*) was measured by an experienced member of the transplant team in a day ward environment, and expressed as a percentage of expected mean for age. Serum albumin concentration (albumin*t*), blood Haemoglobin concentration (Hb*t*), and age at transplant (age*t*) were also recorded. The following data were collected at the time of listing (*l*) for transplantation: FEV1 (FEV1 *l*), S_{a,O_2min} (S_{a,O_2min} *l*), AAHR (AAHR *l*), age (age *l*), Hb (Hb *l*), albumin (albumin *l*). Evidence of previous exposure to cytomegalovirus (CMV status) was also recorded prior to transplant.

The following data were collected at the time of transplant: donor age, donor sex, donor CMV status, cold graft ischaemic time (GITC), warm graft ischaemic time (GITW). Surgical procedures and postoperative management have been described elsewhere [12, 13].

Data analysis

The mean values and standard deviation (SD) were calculated for FEV1*t*, $S_{a,O_2min}t$, AAHR*t*, albumin*t*, Hb*t*, age*t*, donor age, GITC, and GITW, firstly for the population as a whole, and then in groups according to outcome. Donor and recipient sex, and donor and recipient CMV status were analysed to produce the new variables of sex mismatch (SexMM) and CMV mismatch (CMVMM) respectively. A 2-yr survival probability score (SP) was calculated for each patient according to the formula:

$$SP=0.49^{h} \times 100$$

where $h=e^{x}$ and $x=(8.33-0.0288 \times FEV1+0.014 \times AAHR-0.039 \times S_{a,O_2min}-0.104 \times age-0.054 \times albumin-0.179 \times Hb-0.53$ if female) where SP is the proportion of patients for any given assessment data expected to survive two years from the time of measurement, expressed as a percentage. This formula had been derived from an earlier survival study of children with severe CF lung disease [14].

SP was calculated from data at the time of transplant (SP*t*), yielding for each patient a 2-yr survival probability from time of transplant had the patient not undergone transplantation, and also from data at time of listing (SP L). The latter gives for each patient a 2-yr SP from time of listing had the patient not undergone transplantation.

The variables: donor age; CMVMM; SexMM; GITC; GITW; age*t*; and sex were modelled against survival post-transplant using the Cox proportional hazards technique [15]. This model was then tested against two further models which included measures of clinical status. The second model included donor age, CMVMM, SexMM, GITC, GITW, age, sex, FEV1*t*, and $S_{a,O_2min}t$. The third model included donor age, CMVMM, SexMM, GITC, GITW and SP*t*. Recipient age and sex were not included in model 3 as these variables are included in SP. The significance of the 3 models was compared *via* their -2 log likelihoods (-2LL). A p-value of ≤0.05 was considered significant. If the test variables did not contribute significantly to the model fit, an estimate of their importance was obtained by repeatedly multiplying the dataset and rerunning the same models.

The relationship between SP L and time from listing to transplant (wait) was examined by Pearson correlation. A p-value of ≤0.05 was considered significant, equating to a Pearson correlation coefficient (*r*) of ≥0.34.

Results

Of the 51 patients receiving transplants, 45 received heart-lung transplants, 5 bilateral lung transplants, and one a single lung transplant (the patient having had a previous pneumonectomy). The mean values for each of the following parameters were: age at transplant, 13.1 yrs, FEV1*t* 25.8% pred; AAHR*t* 128.1%; $S_{a,O_2min}t$ 83.9%; GITC, 177.5 min; GITW, 48.2 min; donor age, 11.9 yrs; 2-yr SP*t* 39%. The population was then split into three groups and the data reanalysed. Group A comprised patients dying within three months of transplant, group B comprised patients surviving at least three months post-transplant but dying before study end, and group C comprised patients still alive at study end. There were no significant differences in assessment data between the three groups. Full patient characteristics are listed in table 1. Mean duration from date of most recent assessment

Table 1. – Characteristics of transplanted patients

Variable	All patients	Group A	Group B	Group C
Subjects n	51	7	24	20
Age*t* yrs	13.1±3.6	12.1±3.9	13.1±3.0	13.5±4.3
FEV1*t* %	25.9±11.5*	26.8±10.4	28.1±13.7	22.9±8.3
S_{a,O_2}min*t* %	83.9±7.6	83.3±9.2	84.7±7.3	83.2±7.6
SP*t* %	39.3±22.3^{+}	33.5±24.6	40.3±21.5	40.1±23.2
GITC min	177.5±65.9	160.4±31.0	159.8±52.8	204.8±81.1
GITW min	48.2±22.6	41.6±10.9	45.2±18.4	54.2±29.0
Donor age yrs	11.9±7.1$^{\#}$	9.7±5.9	11.0±4.6	13.7±9.4
SexMM Yes	13 (25.5)	2 (29)	7 (29)	4 (20)
CMVMM Yes	12 (23.5)	1 (14)	6 (25)	5 (25)

Data are presented as mean±SD or as n (%). Median: *: 23; $^{+}$: 42.4; $^{\#}$: 10. Group A: patients dying within 3 months of transplant; Group B: patients surviving at least 3 months post-transplant but dying before study end; Group C: patients still alive at study end; Age*t*: recipient age at transplant; FEV1*t*: forced expiratory volume in one second prior to transplant; AAHR*t*: age adjusted resting heart rate prior to transplant; S_{a,O_2}min*t*: minimum oxygen saturation measured during a 12 min walk prior to transplant; SP*t*: 2-yr survival probability (without transplant) calculated prior to transplant; GITC: cold graft ischaemic time; GITW: warm graft ischaemic time; SexMM: donor/recipient sex mismatch; CMVMM: donor/recipient cytomegalovirus status mismatch.

(at which time FEV1*t*, S_{a,O_2}min*t*, and SP*t* were measured) and date of transplant was 0.39 yrs.

Seven patients died within three months of transplantation. Two died of primary graft failure on day 1, two died as a result of adenovirus infection (on day 35 and day 69), one died on day 39 following an episode of severe acute rejection, and two died of recurrent acute rejection leading to bronchiolitis obliterans or bronchiolitis obliterans organizing pneumonia (BOOP), both on day 56 post-transplant. Preoperative clinical data for these patients is detailed separately in table 1.

Of the three proportional hazards models, none were significant predictors of post-transplant death within the study period, and none provided a significantly better fit for the dataset than the others. None of the individual variables within any of the models made a significant contribution to the fit. From model 2, FEV1*t* had a partial hazard ratio of 1.015, indicating an increased risk of post-transplant death of 15% for every 10% fall in pretransplant FEV1. This increased hazard was nonsignificant, and only attained significance ($p<0.05$) when extrapolated to a population of 300 patients studied over the same period. Also from model 2, S_{a,O_2}min*t* had a partial hazard ratio of 1.007, indicating an increased risk of post-transplant death of 7% for every 10% fall in pretransplant S_{a,O_2}min. This increased hazard was nonsignificant, and remained nonsignificant when extrapolated to a population of 800 patients studied over the same period. From model 3, SP*t* had a partial hazard ratio of 0.9996, indicating a reduced risk of post-transplant death of 0.4% for every 10% fall in pretransplant SP. This reduced risk was also nonsignificant when extrapolated to 800 patients. These results indicate that clinical status prior to transplant (whether measured by FEV1, S_{a,O_2}min, or SP) has no effect upon post-transplant survival. Mean wait from date of listing to date of transplant was 0.81 yrs (standard deviation (SD) 0.83 yrs, median 0.60 yrs). The Pearson correlation coefficient for 2-yr SP L *versus* wait was -0.027, which was nonsignificant (2-tailed p-value=0.9). This suggests that the authors policy of prioritizing patients with the poorest clinical status is not successful in reducing waiting time for these patients.

Discussion

Survival following lung or heart-lung transplantation is inferior to that reported for most other solid organ transplant procedures, with the International Society for Heart and Lung Transplantation Registry reporting survival of 70–80% at 1 yr and 30–40% at 5 yrs [16]. The authors centre has previously reported 1 yr survival of 74% and 5 yr survival of 33% for children with CF undergoing lung or heart lung transplantation 1988–1998 [3]. The majority of early deaths are due to primary graft failure or overwhelming infection, whilst the majority of late deaths are related to bronchiolitis obliterans syndrome (BOS) [16]. Furthermore, there is an increasing awareness of the discrepancy between the number of organs available and the number of potential recipients, with a consequently high attrition rate amongst patients awaiting transplants.

The authors centre only accepts CF patients for transplant when they have a predicted life expectancy of $\leq$2 yrs, a poor quality of life, and have fully understood and consented to the procedure [9]. The estimation of prognosis is based upon review of a wide variety of clinical and physiological data, with an FEV1 of $\leq$30% predicted being the most important criterion. A recent review of the waiting list survival data confirms that the great majority of the CF patients listed for transplant either receive organs or die on the waiting list within 2 yrs of listing [3].

Patients with ventilator dependent respiratory failure are not transplanted. This policy reflects the authors belief that such patients are unlikely to receive organs, and that the possibility of transplant, however remote, will merely compromise appropriate terminal care.

The referral of all patients who wish to consider the option of transplant and who fit the referral criteria is encouraged, bearing in mind that there is a belief amongst some referring centres that patients with more advanced lung disease who are not ventilator dependent may also have poorer post-transplant outcome. The authors are not aware of any patients who have been denied referral for this reason, but have noted the increased anxiety that "late" referral can engender.

This hypothesis was tested by modelling the post-transplant survival data with three subsets of variables, the first designed to correct for any operative confounding factors, the latter two to detect any effect of pretransplant clinical status on post-transplant survival.

No operative factors that had a significant effect upon survival were detected. The lack of effect of graft ischaemic time, recipient sex, and recipient age upon development of primary graft failure has been reported by other groups, although it has been suggested that there is a time threshold for graft ischaemic time beyond which acute lung injury is more likely to occur [17, 18]. Subsequent development of BOS has been related to early acute rejection, and no operative factors have been identified as risk factors for the development of this condition [19, 20].

The addition of clinical status to the model, either *via* separate variables, or *via* a survival probability score, had no impact upon the significance of the model. This observation held when the dataset was multiplied and the same models constructed, indicating that clinical status, as measured in the present study, has minimal impact upon post-transplant survival.

The relationship between waiting time for organs and clinical status at time of listing was also studied but no significant correlation was detected. This suggests that the policy of prioritizing patients with the poorest clinical status has no significant effect upon the allocation of organs.

The one possible bias in this study concerns the time at which the pretransplant assessments were performed. The authors centre operates a policy of reassessing all listed patients at six-monthly intervals and more frequently if necessary. For the purpose of this study data from the child′s most recent assessment was considered as pre-transplant data, although there was a mean wait of 0.39 yrs from this assessment until the subsequent transplant. These data were used for two reasons: firstly, collecting assessment data immediately prior to transplant is not possible, and incorporating more recent data from the child′s referring centre would have introduced an unacceptable observer bias; secondly, a decision to prioritize a patient on the waiting list nearly always follows an assessment at a transplant centre, rather than an assessment by the referring centre. Therefore, it is suggested that the methodology chosen in the present study provides results which are of practical value.

This study showed no evidence that clinical status prior to transplant has any effect upon post-transplant survival of children with CF. Whilst early referral is advisable, allowing more time for preparation and greater flexibility regarding listing, patients with poor clinical status who are not ventilator dependent should still be referred for transplant assessment if they wish to consider this option.

References

1. Geertsma A, TenVergert 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.
2. 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.
3. Aurora P, Whitehead B, Wade A, *et al*. Lung transplantation and life extension in children with cystic fibrosis. *Lancet* 1999; 354: 1591–1593.
4. Maurer JR, Frost EF, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. *Transplantation* 1998; 66: 951–956.
5. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992; 326: 1187–1191.
6. Hayllar KM, Williams SGJ, Wise AE, *et al*. A prognostic model for the prediction of survival in cystic fibrosis. *Thorax* 1997; 52: 313–317.
7. Sharples LD, Scott JP, Dennis C, *et al*. Risk factors for survival following combined heart-lung transplantation. *Transplantation* 1994; 57: 218–223.
8. Whitehead B, Helms P, Goodwin MG, *et al*. Heart-lung transplantation for cystic fibrosis: 1. Assessment. *Arch Dis Child* 1991; 66: 1018–1021.
9. Aurora P, Whitmore P, Whitehead BF. Assessment for lung transplantation in cystic fibrosis. *J R Soc Med* 1999; 92 (Suppl. 37): 31–34.
10. Rosenthal M, Bain SH, Cramer D, *et al*. Lung function in white children aged 4 to 19 yrs: I - Spirometry. *Thorax* 1993; 48: 794–802.
11. Henke KG, Orenstein DM. Oxygen saturation during exercise in cystic fibrosis. *Am Rev Respir Dis* 1984; 129: 708–711.
12. Mankad PS, de Leval MR. Heart-Lung Transplantation. *In*: Franco KL, ed. Pediatric Cardiopulmonary Transplantation. Armonk, New York Futura, 1997; pp. 167–184.
13. Whitehead BF, Rees PG, Sorenson K, *et al*. Results of heart lung transplantation in children with cystic fibrosis. *Eur J Cardiothoracic Surg* 1995; 9: 1–6.
14. Aurora P, Wade A, Whitmore P, Whitehead B. A model for predicting life expectancy of children with cystic fibrosis. *Eur Respir J* 2000; 16: 1056–1060.
15. Cox DR, Oakes D. Analysis of survival data, London, Chapman and Hall, 1984.
16. Hosenpud JD, Bennet LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Report - 1999. *J Heart Lung Transplant* 1999; 18 (7): 611–626.
17. Christie JD, Bavaria JE, Palevsky HI, *et al*. Primary graft failure following lung transplantation. *Chest* 1998; 114: 51–60.
18. Glanville AR, Marchman D, Keogh A, *et al*. Outcome in paired recipients of single lung transplants from the same donor. *J Heart Lung Transplant* 1997; 14: 878–882.
19. Sharples LD, Tamm M, McNeil K, Higenbottam TW, Stewart S, Wallwork J. Development of bronchiolitis obliterans syndrome in recipients of heart-lung transplantation - early risk factors. *Transplantation* 1996; 61: 560–566.
20. Kroshus TJ, Kshettry VR, Savik K, John R, Hertz MI, Bolman RM. Risk factors for the development of bronchiolitis obliterans syndrome after lung transplantation. *J Thoracic Cardiovasc Surg* 1997; 114: 195–202.