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The Journal of
Heart and Lung
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The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Lung and Heart-Lung Transplantation Report—2013; Focus Theme: Age

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This section of the 16th official Registry report of the International Society for Heart and Lung Transplantation (ISHLT) summarizes the pediatric lung and heart-lung transplantation activity from January 1986 through June 2012. Since 1986, 1,875 pediatric lung transplants and 667 pediatric heart-lung transplants have been reported. In 2011, the last complete year included in this year's Registry report, 107 pediatric lung transplants were performed, which is comparable to figures in 2007 but lower than in 2010, when 125 procedures were performed.[1] However, it is important to note, that figures included in this Registry report contain only the pediatric lung transplants that were reported to the Registry and, thus, do not necessarily reflect numbers of pediatric lung procedures performed worldwide.

This Registry report includes a summary of data analyses performed by the Registry and is supplemented by further analyses, Figures, and more detailed information available on the ISHLT Web site (www.ishlt.org/registries). The 2013 Registry report on pediatric lung transplantation focuses for the first time on an overall theme together with the Registry reports on adult lung, adult heart, and pediatric heart transplantation. The selected topic for this year's reports is age and age-related aspects of recipients and donors, along with outcome-related analyses wherever sufficient data are available. Data on pediatric heart-lung transplants are not presented in this year's report because those were presented last year,[1] and the number of heart-lung transplant procedures in children and adolescents remains < 10 per year. In summary, this year's Registry report on pediatric lung trans plantation contains data on age and geographic distribution as well as indications for pediatric lung transplantation, donor characteristics, immunosuppressive therapy, outcome, com plications, morbidities, and causes of death.

Statistical methods

Survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test, and adjustments for multiple comparisons were made using Scheffe's method. Survival graphs were truncated when the remaining number of recipients was < 10. Multivariable analyses were done using Cox proportional hazards models. Results of the multivariable analyses were reported as hazard ratios (HR) with a corresponding 95% confidence interval (CI) or p-value. Multiple imputations were used to deal with missing information for continuous data fields, as previously described elsewhere.[2] Additions to the statistical methodology are done on the supplement slides wherever appropriate (www.ishlt.org/registries).

Volume, age distribution, indications, and donor characteristics

The number of pediatric lung transplants reported to the Registry increased during the last decade, from 73 in 2000 to 107 in 2011, which is the last complete year included in the Registry report. The highest numbers of reported

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1053-2498/$ - see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.healun.2013.08.008

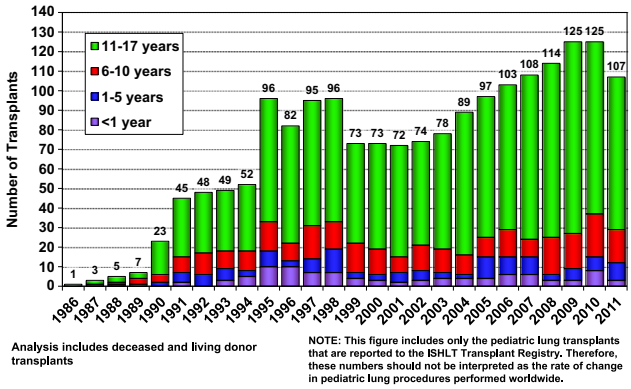

Figure 1 Pediatric lung recipient age distribution by year of transplant. ISHLT, International Society for Heart and Lung Transplantation.

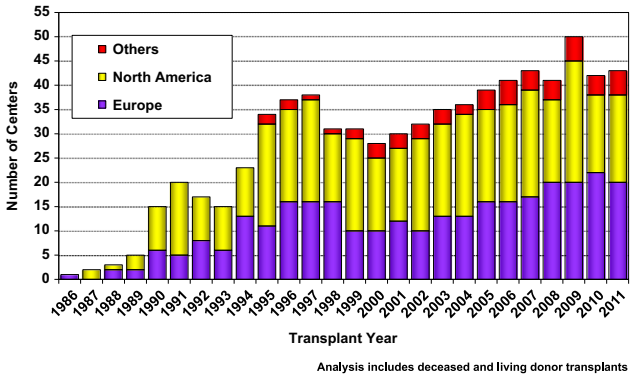

Figure 2 Number of centers reporting pediatric lung transplants by location.

pediatric lung transplants were performed in 2009 and 2010, at 125 in both years (Figure 1). Similar to previous years, most lung transplants were performed in older children (aged 11–17 years). In 2011, 73% of children who received a transplant were 11 years or older compared with 70% in 2010 (Figure 1). In contrast, only 3 infant lung transplants (< 1 year) were reported in 2011.

The number of centers reporting pediatric lung transplants to the Registry was almost equally divided between European and North American centers (20 vs 18 in 2011), whereas only 5 centers were located elsewhere (Figure 2). In 2011, 43 centers worldwide performed lung transplants in children, with 38 centers performing between 1 and 4 transplant procedures per year, a volume distribution that has not changed much over more than 2 decades. Only 2 centers performed 10 to 19 lung transplants per year (Figure 3).

The regional age distribution of pediatric lung transplants (Europe vs North America vs other countries) shows 84% of lung transplant operations in Europe were performed in older children (≥ 11 years) compared with 68% in North America (Figure 4). This pattern of geographic age distribution also remained unchanged during recent years.

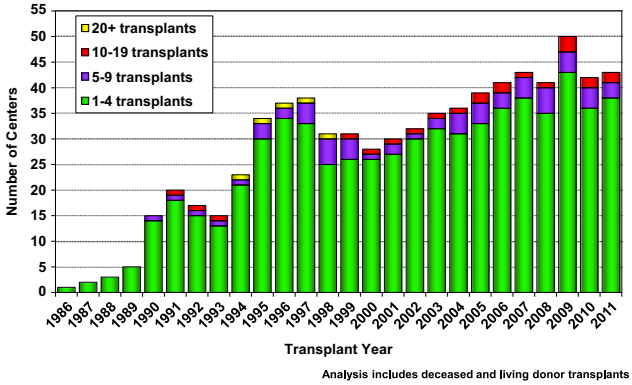

Figure 3 Number of centers reporting pediatric lung transplants by center volume.

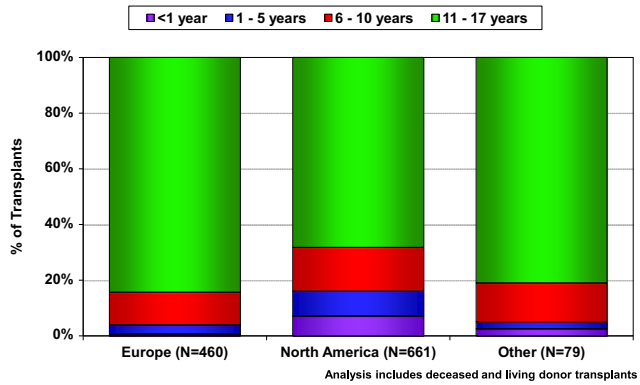

Figure 4 Age distribution by location (pediatric lung transplants: January 2000–June 2012).

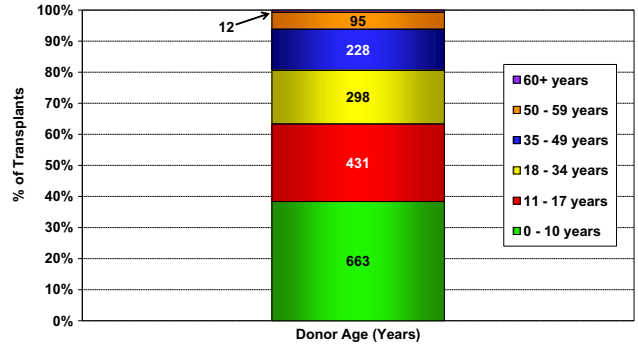

Figure 5 Donor age distribution (pediatric lung transplants: January 1986–June 2012).

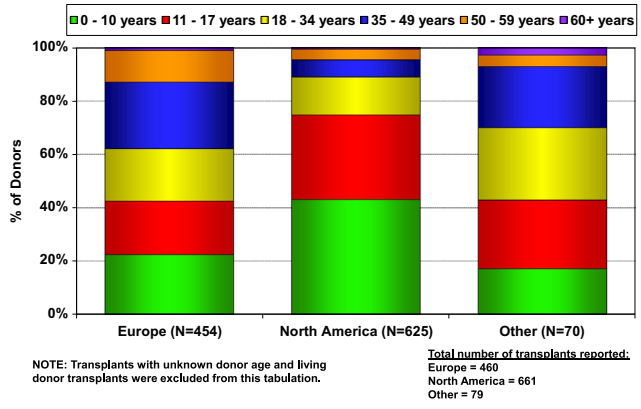

Figure 6 Donor age distribution by location (pediatric lung transplants: January 2000–June 2012).

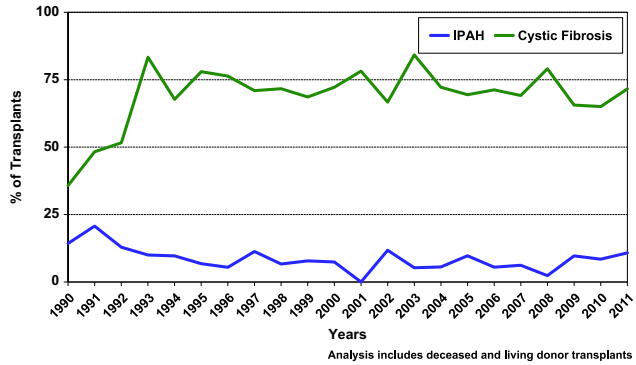

Figure 7 Diagnosis by year of transplant (lung transplant recipients age: 11–17 years). IPAH, idiopathic pulmonary arterial hypertension.

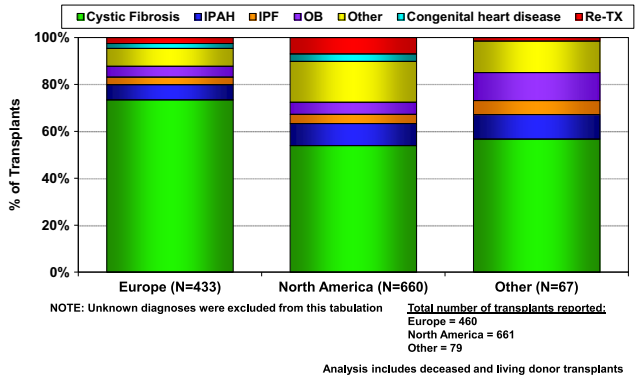

Figure 8 Diagnosis distribution by location (pediatric lung transplants: January 2000–June 2012). IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; OB, obliterative bronchiolitis; Re-TX, retransplant.

The donor age distribution has remained similar compared with previous years, with 63% of pediatric lung transplant donors aged $<$ 18 years (Figure 5). Only 6% of donors were $\geq$ 50 years, and $<$ 1% of donors were aged $\geq$ 60 years (Figure 5). Donor age distribution shows substantial regional variation: in Europe, 43% of donors were aged $<$ 18 years, whereas in North America, 75% of lung grafts came from donors aged $<$ 18 years (Figure 6).

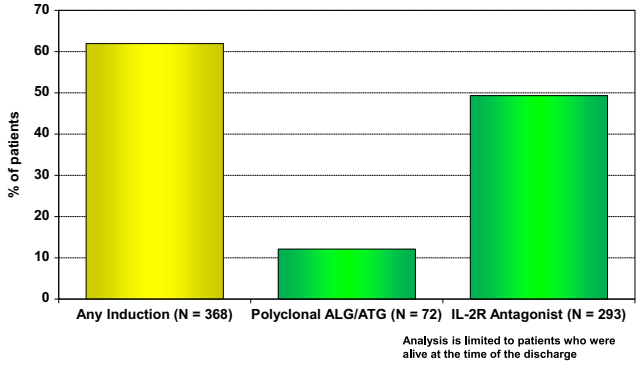

Figure 9 Induction immunosuppression (pediatric lung transplants: January 2001–June 2012). ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; IL, interleukin.

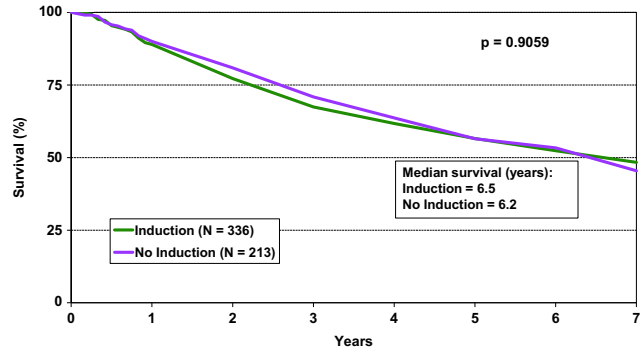

Figure 10 Kaplan-Meier survival stratified by induction use (pediatric lung transplants: January 2001–June 2011).

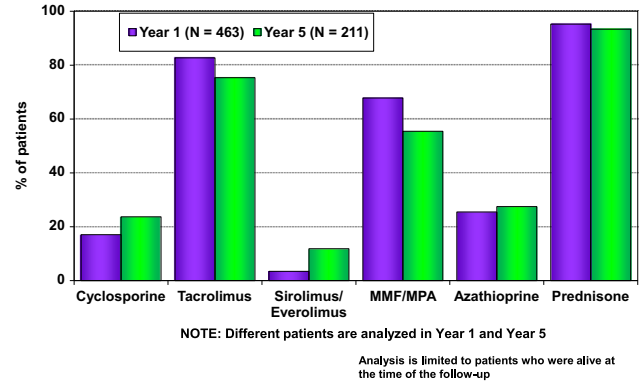

Figure 11 Maintenance immunosuppression at time of follow-up (pediatric lung transplants: January 2001–June 2012). MMF, mycophenolate mofetil; MPA, mycophenolic acid.

In the last 2 decades, most pediatric patients required lung transplant due to end-stage cystic fibrosis (CF) lung disease (Figure 7). The frequency of diagnoses at the time of transplants varies geographically: 54% of children with CF as their diagnosis receive transplants in North America compared with 73% in Europe (Figure 8). The distribution of transplant indications is clearly age-dependent. In older children and adolescents aged 11 to 17 years, about 70% receive transplants for CF, whereas in children aged 6 to 10 years, CF represents 53%. In the age group of 1 to 5 years old, the

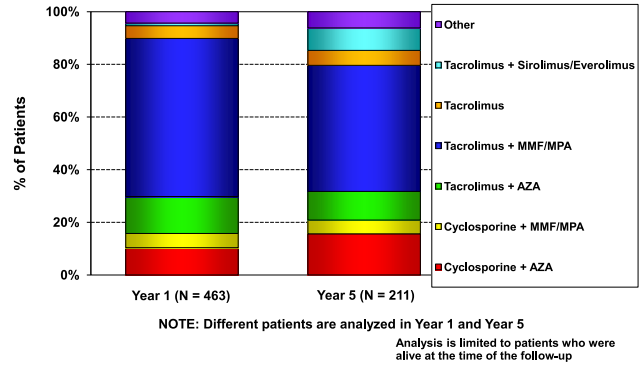

Figure 12 Maintenance immunosuppression drug combinations at time of follow-up (pediatric lung recipients: January 2001–June 2012). AZA, azathioprine; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

Table 1 Indications by Age Group (Pediatric Lung Transplants: January 1990–June 2012)

	Diagnosis age group			
Variable	< 1 year No. (%)	1–5 years No. (%)	6–10 years No. (%)	11–17 years No. (%)
Cystic fibrosis	1 (1.0)	6 (4.8)	140 (53.0)	916 (70.6)
Idiopathic pulmonary arterial hypertension	12 (12.5)	28 (22.4)	23 (8.7)	101 (7.8)
Retransplant				
Obliterative bronchiolitis	…	7 (5.6)	9 (3.4)	39 (3.0)
Not obliterative bronchiolitis	3 (3.1)	4 (3.2)	8 (3.0)	30 (2.3)
Congenital heart disease	16 (16.7)	10 (8.0)	4 (1.5)	11 (0.8)
Idiopathic pulmonary fibrosis	10 (10.4)	21 (16.8)	15 (5.7)	43 (3.3)
Obliterative bronchiolitis (not retransplant)	…	10 (8.0)	18 (6.8)	55 (4.2)
Interstitial pneumonitis	1 (1.0)	2 (1.6)	2 (0.8)	1 (0.1)
Pulmonary vascular disease	8 (8.3)	7 (5.6)	4 (1.5)	1 (0.1)
Eisenmenger's syndrome	1 (1.0)	5 (4.0)	3 (1.1)	9 (0.7)
Pulmonary fibrosis, other	7 (7.3)	11 (8.8)	14 (5.3)	29 (2.2)
Surfactant protein B deficiency	16 (16.7)	3 (2.4)	…	…
Chronic obstructive pulmonary disease/emphysema	4 (4.2)	2 (1.6)	2 (0.8)	10 (0.8)
Bronchopulmonary dysplasia	3 (3.1)	3 (2.4)	6 (2.3)	3 (0.2)
Bronchiectasis	1 (1.0)	…	3 (1.1)	17 (1.3)
Other	13 (13.5)	6 (4.8)	13 (4.9)	32 (2.5)

leading diagnosis is idiopathic pulmonary arterial hypertension (IPAH), with 22% of transplants (Table 1). In infants (< 1 year), surfactant B deficiency, congenital heart disease, and IPAH remain the 3 most frequent indications (Table 1).

Immunosuppressive therapy

Induction

Sixty-two percent of recipients received induction therapy, with most receiving an interleukin-2 (IL-2) receptor antagonist, and only a minority receive anti-lymphocyte globulin or anti-thymocyte globulin (Figure 9). As reported in 2012,[1] the number of pediatric lung transplant recipients treated with an IL-2 receptor antagonist induction increased in 2009 and stayed about the same since, but no significant survival benefit was shown in a univariate analysis comparing children who did and did not receive induction therapy (Figure 10).

Maintenance

Most commonly, pediatric lung transplant recipients received a triple maintenance immunosuppressive treatment of tacrolimus, mycophenolate mofetil/mycophenolic acid, and prednisone. Tacrolimus was given to 83% of recipients at 1 year after transplant and cyclosporine to 17% (patient follow-up January 2001–June 2012; Figure 11). Mycophenolate mofetil/mycophenolic acid remained the first choice of cell-cycle inhibitor, used in 68% of children at 1 year after transplantation. By 5 years, 9% of recipients received a combination of tacrolimus plus sirolimus/everolimus (Figure 12). As in the past, > 93% of children were treated with prednisone even 5 years after transplantation (Figure 11).

Outcomes

Survival after pediatric lung transplantation is generally comparable to that reported in adults ($p = 0.3459$) with a median survival of 4.9 years vs 5.4 years, respectively, in recipients undergoing transplantation between January 1990 and June 2011 (Figure 13).

Primary transplants

As shown in previous reports, there was a significantly better survival in children after bilateral/double-lung transplants ($n = 1{,}553$) compared with single-lung transplants ($n = 94$), with a median survival of 5.4 vs 1.9 years, respectively ($p < 0.0001$; Figure 14). No significant difference was seen when overall survival of 987 CF recipients was compared with survival in 689 non-CF recipients, with a median survival of 4.7 years in both groups (Figure 15). Although based on absolute numbers, the patient group that received transplants at age 6 to 10 years appeared to do better in the first several post-transplant years, and none of the differences in survival among the age groups were statistically significant (Figure 16). In recipients surviving past 1 year after transplantation, survival was also similar among the different age groups (Figure 17). Survival improved by era (1988–1999 vs 2000–June 2011), with a median survival improving from 3.3 to 5.8 years, respectively, and median survival conditional to survival at 1 year after transplant improving from 7.2 to 8.7 years, respectively (Figure 18). Donor age for recipients aged 11 to 17 years did not appear to be associated with death after transplant (Figure 19).

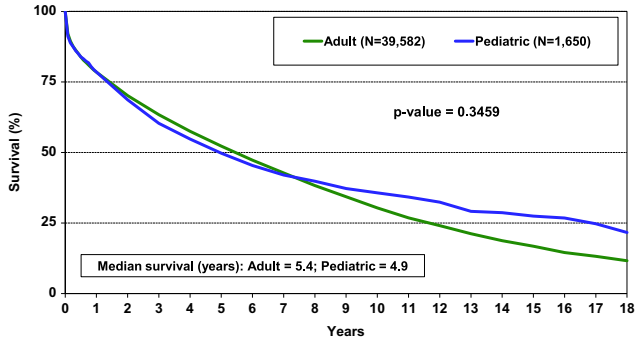

Figure 13 Kaplan-Meier survival by recipient age group (lung transplants: January 1990–June 2011).

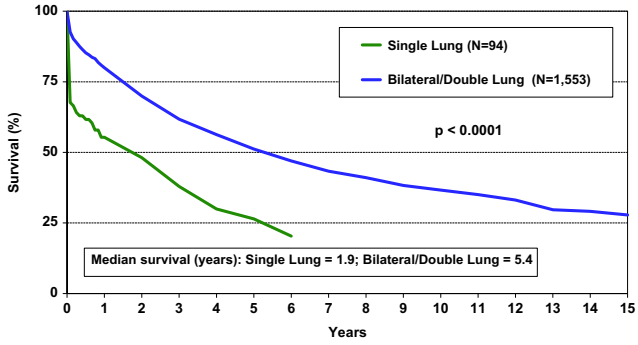

Figure 14 Kaplan-Meier survival by procedure type (pediatric lung transplants: January 1990–June 2011).

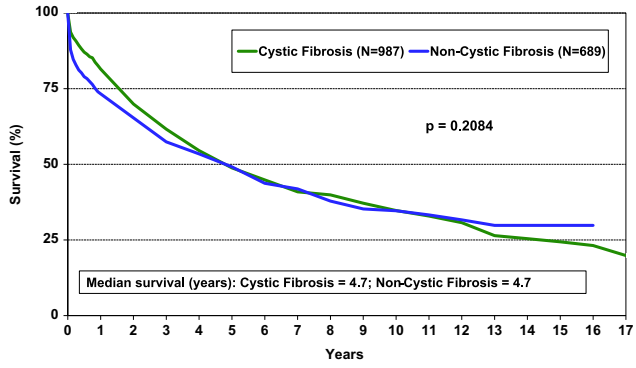

Figure 15 Kaplan-Meier survival by diagnosis (pediatric lung transplants: January 1990–June 2011).

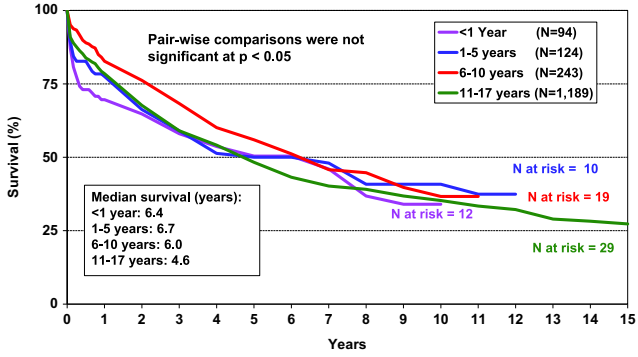

Figure 16 Kaplan-Meier survival by recipient age group (pediatric lung transplants: January 1990–June 2011).

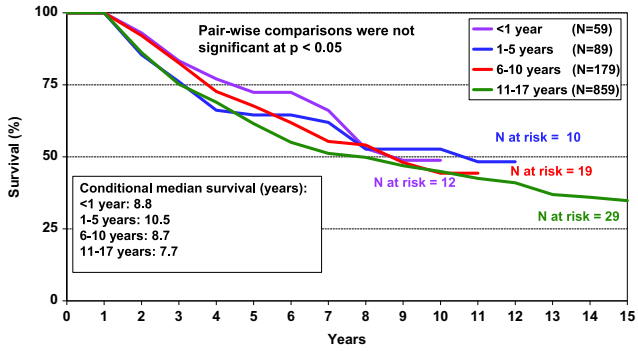

Figure 17 Conditional Kaplan-Meier survival by recipient age group (pediatric lung transplants: January 1990–June 2011).

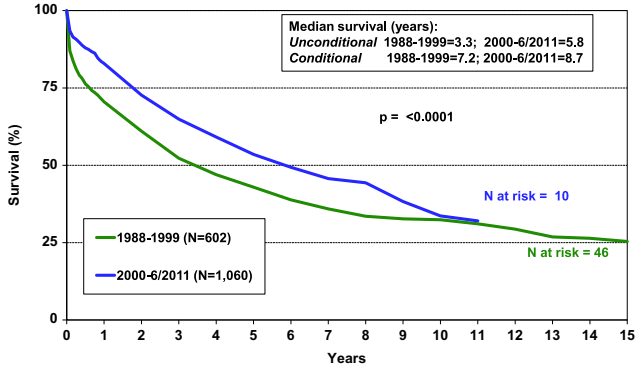

Figure 18 Kaplan-Meier survival by era (pediatric lung transplants: January 1988–June 2011).

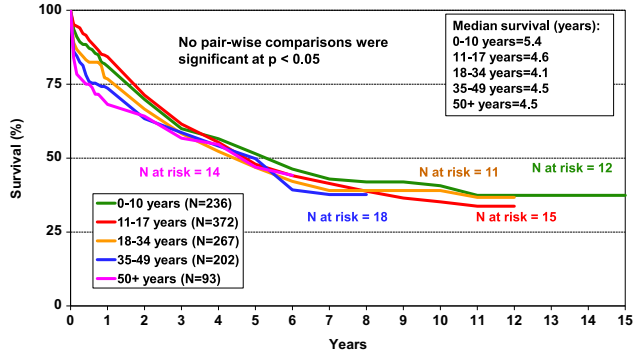

Figure 19 Kaplan-Meier survival by donor age for recipients aged 11–17 years (pediatric lung transplants: January 1990–June 2011).

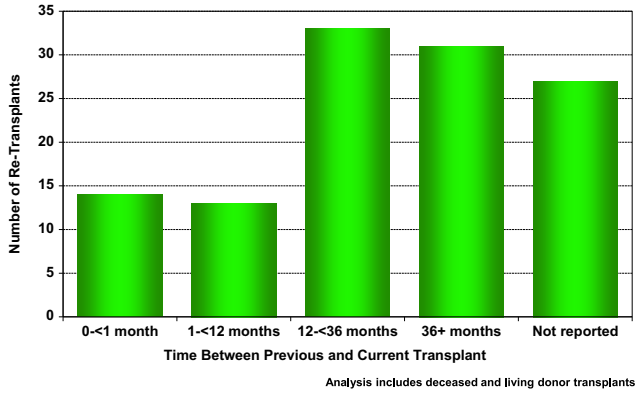

Figure 20 Number of pediatric lung retransplants (retransplants: January 1994–June 2012).

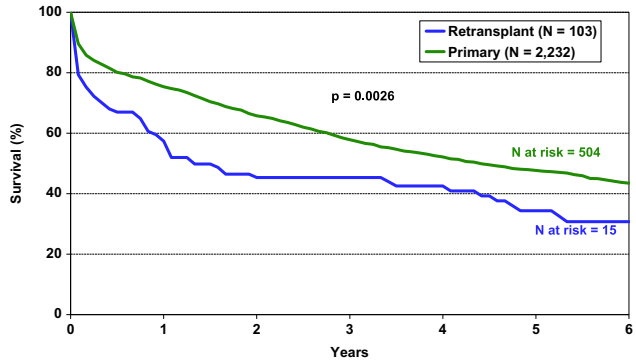

Figure 21 Kaplan-Meier survival by transplant type (pediatric lung transplants. January 1994–June 2011).

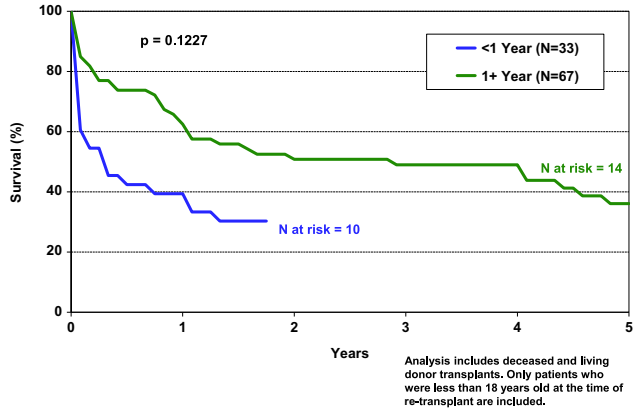

Figure 22 Survival by time between primary transplant and retransplant (pediatric lung transplants: January 1988–June 2011).

Retransplants

A total of 118 lung retransplants performed between January 1994 and June 2012 were reported to the Registry, 23% of which were undertaken < 12 months after the primary transplant procedure (time between previous and current transplant was not reported in 23%; Figure 20). Overall, survival was significantly inferior when primary transplant was compared with retransplant (58% vs 45% at 3 years, respectively; $p = 0.026$; Figure 21). However, a trend was noted ($p = 0.1227$) for better outcome for lung retransplants in a small group of 100 children if procedures were performed ≥ 1 year after the primary transplant (1-year survival was 62% vs 39%, respectively; Figure 22). Survival after retransplant for the different indications of non-obliterative bronchiolitis vs obliterative bronchiolitis was similar (Figure 23).

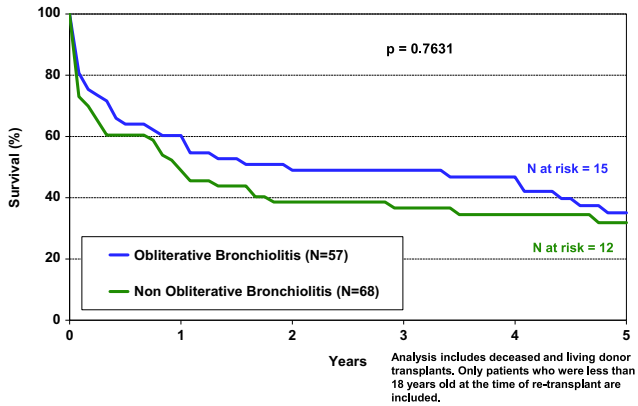

Figure 23 Survival by diagnosis (pediatric lung retransplants: January 1988–June 2011).

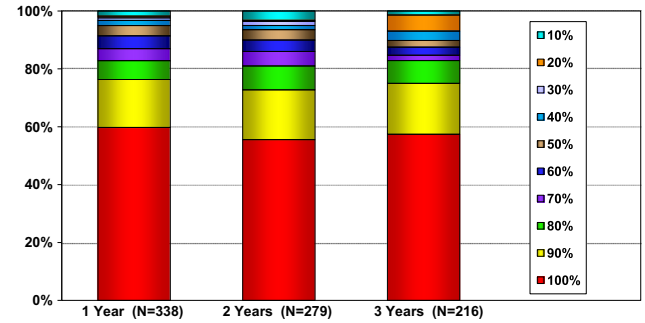

Figure 24 Functional status of surviving recipients (follow-ups: March 2005–June 2012).

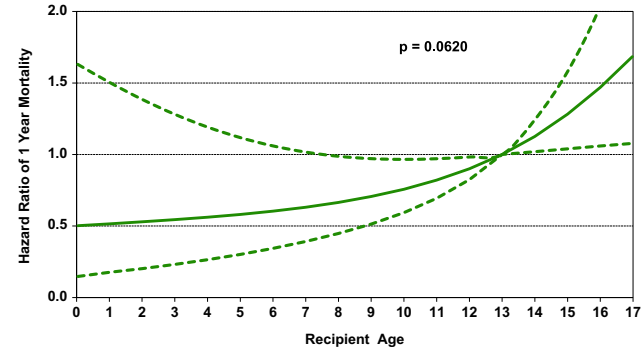

Figure 25 Recipient age and hazard ratio of mortality/graft failure 1 year after transplant (pediatric lung transplants: April 1994–June 2011). Dashed lines indicate the 95% confidence interval.

Functional status

Physician-reported overall functional status of pediatric lung transplant recipients was good. More than 80% of surviving

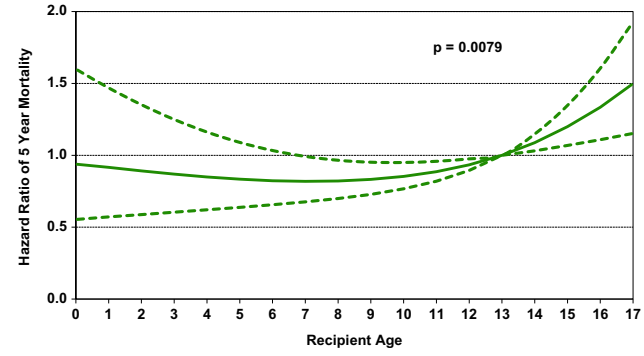

Figure 26 Recipient age and hazard ratio of mortality/graft failure 5 years after transplant (pediatric lung transplants: April 1994–June 2007). Dashed lines indicate the 95% confidence interval.

Table 2 Risk Factors for 1-Year Mortality and Graft Failure (Pediatric Lung Transplants: April 1994–June 2011)

Variable	No.	HR (95% CI)	*p*-value
On ventilator	141	3.13 (2.03–4.81)	< 0.0001
Year of transplant: May 1994–2001 vs 2002–June 2011	330	1.82 (1.30–2.53)	0.0004
Donor CMV+/recipient CMV–	261	1.49 (1.09–2.06)	0.0135
Chronic steroid use	309	1.41 (1.02–1.96)	0.0391
Borderline			
Recipient age			0.0620
Pediatric transplant center volume			0.0716
Bilirubin			0.0924

CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio.

Table 3 Risk Factors for 5-Year Mortality and Graft Failure (Pediatric Lung Transplants: April 1994–June 2007)

Variable	No.	HR (95% CI)	*p*-value
On ventilator	97	1.92 (1.29–2.87)	0.0014
Year of transplant: April 1994–2001 vs 2002–June 2007	330	1.37 (1.08–1.73)	0.0095
Chronic steroid use	234	1.32 (1.06–1.66)	0.0151
Recipient age			0.0079
Pediatric transplant center volume			0.0022
Height difference			0.0075

CI, confidence interval; HR, hazard ratio.

recipients followed up between March 2005 and June 2012 had a functional status of ≥ 80% on the Lansky score, as documented at 1 and at 3 years after transplantation (Figure 24).

Complications and morbidities

Significant risk factors for the combined outcome of death or graft failure within 1 and 5 years in pediatric patients were pre-transplant ventilator use, older transplant era, and chronic steroid use (Tables 2, 3). Further, a trend for an increased risk of 1-year mortality or graft failure in recipients who received transplants during adolescent age (Figure 25) became significant at 5 years (Figure 26). The most common morbidity in survivors at 1 year after transplant was hypertension in > 40% of patients, followed by diabetes mellitus in 23% (Table 4). Within 5 years post-transplant, hypertension had developed in almost 70% of survivors followed up between April 1994 and June 2012 (Table 5). Further, chronic kidney disease and diabetes mellitus were also frequent morbidities in survivors within 5 years post-transplant. The incidence of renal dysfunction within 5 years after transplantation was 32% in survivors followed up between April 1994 and June 2012, and 3% of survivors required dialysis or a renal transplant (Table 5). Details regarding malignancies after lung transplantation in children were discussed in last year's report.[1]

Table 4 Cumulative Morbidity Rates in Pediatric Lung Transplant Survivors Within 1Year Post-transplant (Follow-ups: April 1994–June 2012)

Outcome	Within 1 year (%)	Total with known response (No.)
Hypertension	41.7	701
Renal dysfunction	9.5	723
Abnormal creatinine < 2.5 mg/dl	6.6	
Creatinine > 2.5 mg/dl	1.9	
Chronic dialysis	0.7	
Renal transplant	0.3	
Hyperlipidemia	5.1	720
Diabetes	23.3	724
Bronchiolitis obliterans syndrome	12.8	674

Table 5 Cumulative Morbidity Rates in Pediatric Lung Transplant Survivors Within 5 Years Post-transplant (Follow-ups: April 1994–June 2012)

Outcome	Within 5 years (%)	Total with known response (No.)
Hypertension	69.1	194
Renal dysfunction	31.7	205
Abnormal creatinine < 2.5 mg/dl	23.9	…
Creatinine > 2.5 mg/dl	4.9	…
Chronic dialysis	1.5	…
Renal transplant	1.5	…
Hyperlipidemia	17.2	198
Diabetes	36.2	207
Bronchiolitis obliterans syndrome	34.6	159

Bronchiolitis obliterans syndrome

Bronchiolitis obliterans syndrome (BOS), the most common form of chronic lung allograft dysfunction (CLAD), was one

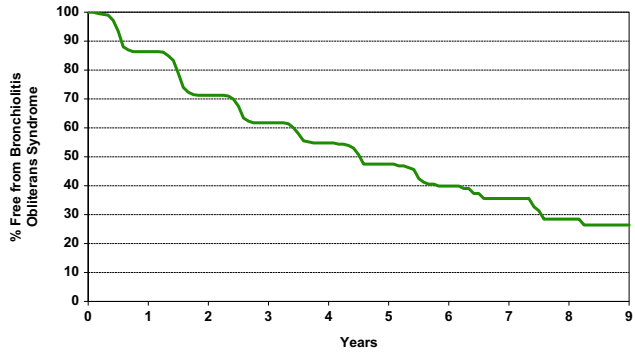

Figure 27 Freedom from bronchiolitis obliterans syndrome in pediatric lung transplant recipients (follow-ups: April 1994–June 2012).

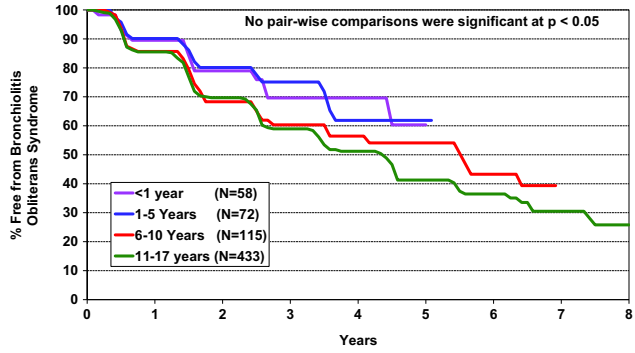

Figure 28 Freedom from bronchiolitis obliterans syndrome by age group (follow-ups: April 1994–June 2012).

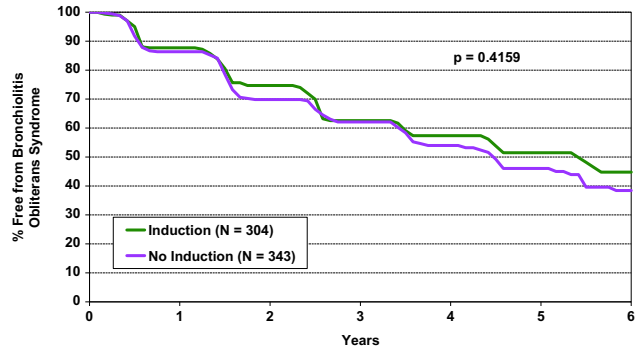

Figure 29 Freedom from bronchiolitis obliterans syndrome by induction use (follow-ups: April 1994–June 2012).

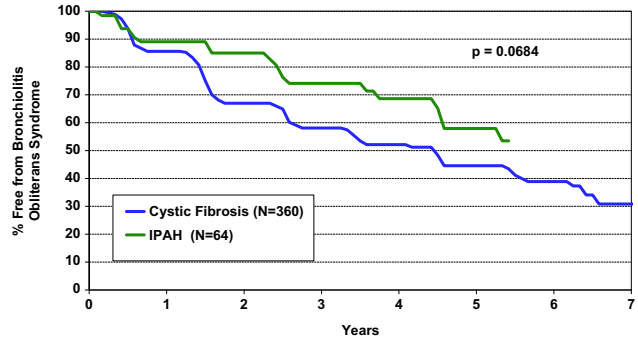

Figure 30 Freedom from bronchiolitis obliterans syndrome in pediatric lung recipients by diagnosis (follow-ups: April 1994–June 2012). IPAH, idiopathic pulmonary arterial hypertension.

of the most frequent overall causes of morbidity. BOS was prevalent in > 50% of surviving transplant recipients by 5 years post-transplant (Figure 27). Numerically, freedom from BOS was more common in younger recipients aged ≤ 5 years than in older children aged ≥ 11 years, but this difference did not achieve statistical significance (Figure 28). No difference in freedom from BOS was found if recipients were stratified according to induction vs no induction use (Figure 29). There was also a trend for lower freedom from BOS in recipients who received transplants for CF, the most common diagnosis in older children, compared with recipients who received transplants for IPAH, at 45% vs 58% at 5 years, respectively ($p = 0.0684$; Figure 30).

Cause of death

As in previous reports, graft failure was the most common cause of death within the first 30 days post-transplant, occurring in almost 30% of recipients (Table 6). In the first year after transplantation, non-cytomegalovirus infection was the cause of death in 24% of pediatric lung transplant recipients. Beyond 1 year after transplantation, BOS was by

Table 6 Cause of Death in Pediatric Lung Recipients (Deaths: January 1992–June 2012)

Cause of death	0–30 days ($n = 123$) No. (%)	31 days–1 year ($n = 171$) No. (%)	>1–3 years ($n = 225$) No. (%)	>3–5 years ($n = 104$) No. (%)	>5 years ($n = 97$) No. (%)
Bronchiolitis	…	17 (9.9)	85 (37.8)	40 (38.5)	46 (47.4)
Acute rejection	3 (2.4)	4 (2.3)	2 (0.9)	2 (1.9)	
Lymphoma	…	8 (4.7)	7 (3.1)	4 (3.8)	5 (5.2)
Malignancy, non-lymphoma	…	2 (1.2)	1 (0.4)	…	3 (3.1)
CMV	…	6 (3.5)	…	…	…
Infection, non-CMV	16 (13.0)	56 (32.7)	35 (15.6)	19 (18.3)	9 (9.3)
Graft failure	36 (29.3)	33 (19.3)	55 (24.4)	22 (21.2)	19 (19.6)
Cardiovascular	19 (15.4)	7 (4.1)	3 (1.3)	1 (1.0)	1 (1.0)
Technical	14 (11.4)	5 (2.9)	6 (2.7)	3 (2.9)	1 (1.0)
Multiple organ failure	13 (10.6)	21 (12.3)	11 (4.9)	4 (3.8)	5 (5.2)
Other	22 (17.9)	12 (7.0)	20 (8.9)	9 (8.7)	8 (8.2)

CMV, cytomegalovirus.

far the leading cause of death recorded in recipients between January 1992 and June 2012, and this figure increased from 38% deaths at 1 to 5 years after transplantation to 47% of deaths beyond 5 years after transplantation (Table 6).

Conclusions

More than 2,000 pediatric lung and heart-lung transplants have been reported to the ISHLT Registry to date, the largest data collection of its kind in the field of pediatric lung transplantation; hence, it is an important data source to illustrate the increasing pediatric lung transplant activity worldwide and its overall outcomes and complications. The 2013 ISHLT Registry report on pediatric lung transplantation documents an improved overall survival after lung transplantation in children and adolescents and results that compare well with adult lung transplantation. However, BOS, the most common form of CLAD, remains the Achilles heel, preventing better long-term outcomes, and is the overall leading cause of why long-term survival after pediatric lung transplantation is lower compared with pediatric heart transplantation or other solid-organ transplantation in children.

Disclosure statement

All relevant disclosures for the Registry Director, Executive Committee Members, and authors are on file with the ISHLT and can be made available for review by contacting the Executive Director of the ISHLT.

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