Pediatric Lung Transplantation in Israel: 29 Cases from a Single Center's Experience

Eyal Jacobi MD[1,5], Moshe Heching MD[3,5], Osnat Shtraichman MD[3,5], Dror Rosengarten MD[3,5], Barak Pertzov MD[3,5], Ophir Bar-On MD[1,5], Hagit Levine MD[1,5], Ofer Schiller MD[2,5], Yury Peysakhovich MD[4,5], Dario Prais MD[1,5], Yaron Barac MD[4,5], and Mordechai Reuven Kramer MD[3,5]

[1]1Pulmonary Institute, Schneider Children's Medical Center, Petah Tikva, Israel
[2]Pediatric Cardiac Intensive Care Unit, Schneider Children's Medical Center, Petah Tikva, Israel
[3]Pulmonary Institute, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[4]Department of Cardiovascular and Thoracic Surgery, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[5]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Lung transplantation is an advanced medical therapy reserved for patients with end-stage lung disease. Relative to other solid organ transplants, lung transplantation in children is infrequently performed. The most common etiologies for pediatric lung transplantation worldwide are cystic fibrosis, pulmonary hypertension, and children's interstitial lung disease.

Objectives: To describe our experience in pediatric lung transplants at Israel's largest transplant center.

Methods: We performed a retrospective review of all pediatric lung transplantations conducted in our center since 1997. We recorded demographic characteristics, indication for transplantation, clinical and laboratory parameters, post-transplant complications, and survival rates.

Results: Of 965 lung transplants, 29 (3.0%) were pediatric patients who underwent lung or heart-lung transplants for end-stage lung disease. Age at transplantation ranged from 2 to 18 years, with a median of 14.0 years (IQR 11–15). Primary etiologies for transplantation were cystic fibrosis (44%), pulmonary hypertension (17%), and children's interstitial lung disease (10%). Survival at 1, 5, 10, and 15 years post-transplant were 90%, 65%, 55%, and 20%, respectively, which is consistent with data reported by pediatric lung transplantation registries. The primary cause of mortality post-transplant was chronic lung allograft dysfunction. Four patients (13.8%) underwent re-transplant. There was no association between survival and transplant indication, nor between survival and type of procedure (lung vs. heart-lung transplant).

Conclusions: The short- and long-term outcomes from our program are consistent with published registry data. These outcomes may reflect the benefits of a centralized pediatric lung transplant program, supported by a multidisciplinary team trained in high-capacity international centers.

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KEY WORDS: chronic lung allograft dysfunction (CLAD), cystic fibrosis, pediatric lung transplantation, pulmonary hypertension, transplant outcomes

Pediatric lung transplant is a rare procedure reserved for end-stage lung disease. Lung transplant for pediatric patients was modeled after the success of adult lung transplantation, with the first pediatric lung transplant performed in 1987, 24 years after the first adult lung transplant [1]. Given the limited number of cases annually, pediatric lung transplantations are performed in dedicated high-volume transplant centers [2]. Indications for pediatric lung transplant vary and are age dependent, with most referrals for end-stage cystic fibrosis (CF), pulmonary hypertension (PHT), and children's interstitial lung disease (chILD).

Although pediatric lung transplant volumes lag behind those of adults, the overall post-transplant care, including immunosuppression and management of complications, is similar to that of other solid organ transplants [3]. Due in part to improvements in post-transplant care, both pediatric and adult recipients have experienced a gradual improvement in long-term prognosis post-transplantation. Based on the most recent International Society for Heart and Lung Transplantation (ISHLT) registry, 5-year survival in pediatric lung transplant recipients is approximately 70% [4].

The ideal timing for pediatric patient referral for lung transplant assessment is not well established. In general, it is reasonable to have a patient assessed if the predicted life expectancy is less than 2 years despite maximal medical treatment [5]. Timing of referral for lung transplant assessment must also consider the expected waiting time for donor lungs, especially among pediatric transplant candidates who face a smaller donor pool as well as other challenges, such as limited cumulative experience due to the lower frequency of pediatric compared to adult lung transplantations [6].

Our lung transplant center, located in central Israel, has substantial experience in lung transplant medicine, having performed and followed over 965 lung transplant recipients since the program was established in 1997, including almost all pediatric lung transplants performed in Israel to

date. Given the rarity of pediatric lung transplantation and the complexity of post-transplant care, the integration of pediatric services with experienced adult lung transplant teams may offer important advantages. At our center, such collaboration has been central to the development and continuity of the pediatric program. In this article, we describe the pediatric experience of our lung transplant program.

PATIENTS AND METHODS

We conducted a retrospective review of all pediatric patients (≤ 18 years old) who underwent lung or heart-lung transplantation at our center from the inception of our transplant program in 1997 through September 2024. Electronic and written medical records were reviewed to collect demographic and clinical data, including sex, age at transplant, underlying diagnosis, prior medical history, relevant pre- and post-transplant clinical parameters (including pulmonary function tests and rejection episodes), and survival status.

The primary outcome evaluated was post-transplant survival. Secondary measures included pulmonary function at one year (FEV1), incidence of acute rejection, CLAD, infections, and need for re-transplantation. Complication data were drawn from structured follow-up documentation and biopsy results.

Missing data were handled by case-wise deletion for variables unavailable at the time of analysis. No imputation was performed. Sensitivity to missingness was descriptively assessed, and its impact on key outcomes was considered minimal.

Continuous variables are presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on distribution. Categorical variables are reported as frequencies and percentages. Group comparisons were conducted using Student's *t*-test or Mann–Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables, as appropriate. Survival analysis was performed using Kaplan–Meier curves with log-rank testing, and Cox regression models were used to assess associations with survival.

Due to sample size limitations and the heterogeneity of the cohort, multivariable models were not applied. Instead, key clinical covariates such as FEV1 and transplant type were included in univariate models and discussed contextually. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

Since inception of our lung transplant program in 1997, we have performed 965 lung transplants at our lung transplant center, of which 29 (3.0%) were performed on pediatric patients, representing on average approximately one pediatric transplant annually. Among the transplants, 17 (58%) were lung transplants and 12 (42%) were combined heart-lung transplants. All patients received double lung transplants, and from 2008 onward, all transplants were lung transplants only. None of our pediatric cohort underwent a lobar or single lobe transplant.

Table 1 presents the demographic characteristics of the transplant recipients, including age and sex, type of transplant procedure, and select baseline laboratory values. The youngest child, who underwent transplantation at 2 years old, had been diagnosed with chILD. Primary indications for lung transplant [Figure 1] were CF (44%), PHT (17%), and chILD (10%). Figure 2 presents Kaplan-Meir survival curves for the pediatric transplant recipients through January 2024. In our cohort, 90% of transplant recipients survived at least 1-year post-transplant. Among pediatric transplant recipients who survived 1-year post-transplant, 5-, 10- and 15-year survival rates were 65%, 55%, and 20%, respectively. The average survival among pediatric transplant recipients was 11.0 years (4.3–17.7), including 12 patients alive at the time of this study.

Table 2 presents the post-transplant complications experienced in our pediatric transplant cohort, with some patients experiencing multiple complications. The most

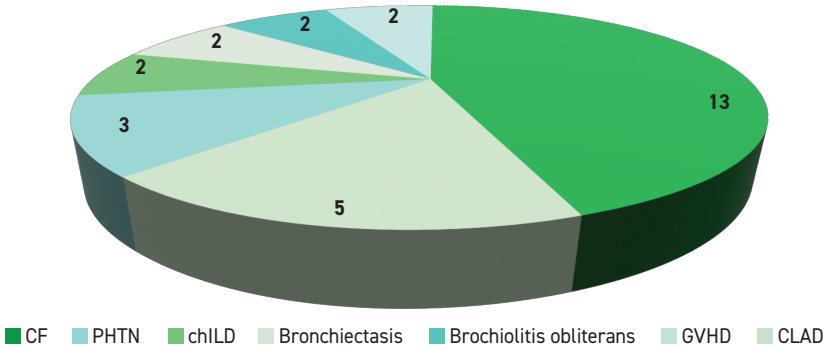
Table 1. Demographics characteristics of pediatric transplant recipients (n=29)

		Median (IQR) or n (%)
Age (years)		14 (11–15)
Male		14 (48)
Double lung transplant		17 (59)
Heart-lung transplant		12 (41)
Laboratory prior to lung transplant	AST (U/L)	27 (18.3–43.5)
	ALT (U/L)	27 (15.0–33.0)
	Hb (g/Dl)	12.3 (10.6–13.3)
	Creatinine (mg/dl)	0.47 (0.36–0.51)
Survival (years)*		11 (4.3–17.7)

AST = aspartate transaminase, ALT = alanine transaminase, Hb = hemoglobin
*Analysis was performed for children who survived 1 year post-lung transplant.

Figure 1. Pediatric lung transplantation by disease indication

CF = cystic fibrosis, CLAD = chronic lung allograft dysfunction, chILD = children interstitial lung disease, GVHD = graft versus host disease, PHT = pulmonary hypertension



CF = cystic fibrosis, CLAD = chronic lung allograft dysfunction, chILD = children interstitial lung disease, GVHD = graft versus host disease, PHT = pulmonary hypertension

common complications were CLAD (46%) and acute cellular rejection (44%). Four pediatric transplant recipients (13.8%) underwent re-transplantation following the development of CLAD. Two pediatric heart-lung transplant recipients (7%) exhibited signs of accelerate atherosclerosis and early signs of congestive heart failure. Three recipients (10.3%) required stent emplacement due to bronchial anastomosis narrowing.

Based on Cox regression analysis, no statistically significant association was demonstrated between survival and sex or age at transplant (data not shown). Conversely, a statistically significant association was demonstrated between survival and FEV1 measured one-year post-transplant (hazard ratio 0.93, 95% confidence interval 0.89–0.97, $P = 0.003$). Similarly, Kaplan-Meir analysis demonstrated no survival benefit based on indication for transplant or type of procedure performed.

DISCUSSION

The findings in our pediatric lung transplant recipient cohort are consistent with data from the ISHLT registry [7] and other transplant centers [8]. The majority of our pediatric patients underwent transplantation between ages 12 and 18 years, with no significant gender differences. Like the ISHLT registry data, in our cohort, CF, PHT, and chILD were the three most common indications for pediatric lung transplant.

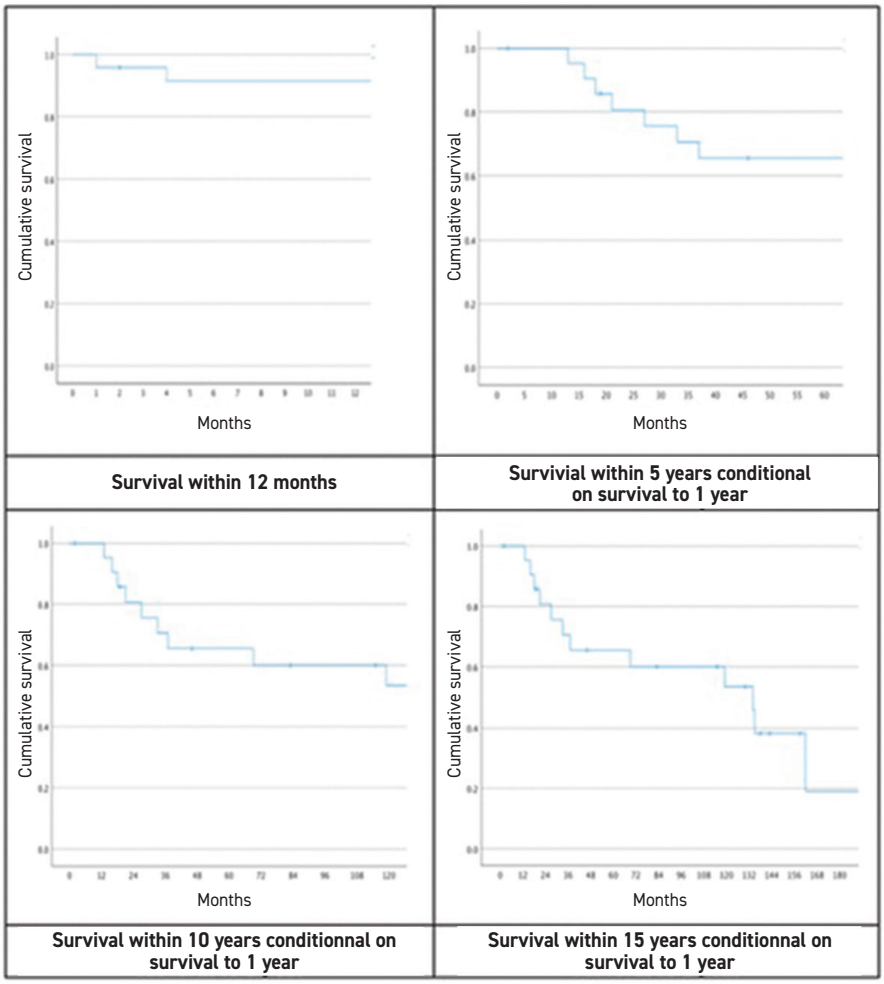
End-stage CF-related pulmonary disease has historically been the most common indication for pediatric referral for lung transplantation. However, the increasing availability of CFTR modulators has substantially improved life expectancy for eligible CF patients, reducing the necessity for early lung transplantation in this young population [9]. As a result, there has been an overall decline in the number of children with CF undergoing lung transplantation in recent years [10]. That said, the number of CF patients in Israel eligible for CFTR modulators is lower than North America, due in part to a higher percentage of patients with ineligible mutations [11]. Consequently, Israel may not have experienced a relative decline in transplants in the pediatric CF population. In fact, four pediatric lung transplants in the recent 2 years were CF patients.

The 1- and 5-year survival in our cohort was similar to ISHLT registry data for pediatric lung transplant recipients (median 9.1 years, 1-year survival 90%, and 5-year survival 70%), reflecting a trend toward improved life expectancy in pediatric lung transplant recipients [12]. Consistent with ISHLT registry data, in our cohort, there was no statistically significant relationship between indication for transplantation and survival [6,13].

CLAD was the most common chronic complication in our cohort (44%) and the primary cause of morbidity after lung transplant. An unexplained decline in FEV1 is a nonspecific, yet commonly used, clinical indicator of chronic lung rejection [15,16]. Maintaining FEV1 was found to be an indicator for long term survival ($P < 0.05$). Despite developments in lung transplant care, CLAD complications remain high and is the leading cause of mortality among pediatric lung transplant recipients surviving over one year [6].

While 41% of our cohort received a combined heart-lung transplant, since 2008 all our pediatric transplants have been lung transplants only. Improvements in surgical techniques have led to a steady decline in combined heart-lung transplants globally and are now reserved for

Figure 2. Kaplan-Meier survival rates showing survival curves for pediatric lung transplant recipients
Survival is shown at 1, 5, 10, and 15 years post-transplant, conditional on survival beyond the first year



end-stage cardiopulmonary failure, such as patients with Eisenmenger syndrome due to uncorrected congenital heart disease [17]. In our cohort, we did not identify a statistically significant correlation between survival and type of transplant. In contrast, analysis of ISHLT registry data suggests that the overall survival rate for pediatric heart-lung transplant recipients tends to be lower than that for double lung transplants, although this difference is not statistically significant [4]. Two heart-lung transplant recipients developed signs of accelerated atherosclerosis and congestive heart failure during long-term follow-up. Cardiovascular diseases post-solid organ transplants are a known long-term complication, often described more in the elderly [18]. Reasons may stem in part from side effects of immunosuppression therapy as well as prior diabetes and hypertension. Heart transplantation, as evidenced by a national database analysis, is itself identified as a risk factor for developing Acute Coronary Syndromes [19].

Our pediatric transplant program functions in close collaboration with the adult transplant service, which may contribute significantly to the favorable long-term outcomes observed. The medical and surgical teams caring for pediatric recipients have gained extensive experience through formal training in high-volume adult transplant centers. This close collaboration ensures continuity of care, facilitates clinical decision-making, and supports the management of complex cases. Given that pediatric lung transplantations are far less frequent than adult procedures, such collaboration offers a structural advantage that may be important for achieving outcomes compara-

Table 2. Complications following lung transplantation

	Number	% from cohort
CLAD/ BO	13	44
Acute cellular rejection	12	41
Infection	10	34
Retransplant	4	13
PTLD	2	6
ACS/CHD	2	6

ACS = acute coronary syndrome, BO = bronchiolitis obliterans, CHD = congestive heart disease, CLAD = chronic lung allograft dysfunction, PTLD = post-transplant lymphoproliferative lung disease

ble to those of larger international programs [14].

Weaknesses in our study may derive from being a single-center retrospective chart review and a small sample size. This might have influenced the significance of some of our results. Long term trajectories, for example – the rate of infections, might have been underestimated.

CONCLUSIONS

This study presents the first long-term report of pediatric lung transplantation outcomes from Israel's main center performing these procedures. Pediatric lung transplantation is relatively rare worldwide, and our experience over more than two decades demonstrates that, despite the low frequency of such cases, outcomes, including 1-, 5-, and 10-year survival, are comparable to international registry data. These findings suggest that successful long-term outcomes can be achieved in a centralized national program supported by a multidisciplinary team with formal training and experience gained in high-capacity international transplant centers.

Correspondence

Dr. E. Jacobi
Pulmonary Institute, Schneider Children's Medical Center, Petah Tikva 49202, Israel
Phone: (972-3) 925-3654
Fax: (972-3) 925-3308
Email: eyaljac11@clalit.org.il

References

1. Panchabhai TS, Chaddha U, McCurry KR, Bremner RM, Mehta AC. Historical perspectives of lung transplantation: connecting the dots. *J Thorac Dis* 2018; 10 (7): 4516-31.
2. Vanholder R, Domínguez-Gil B, Busic M, et al. Organ donation and transplantation: a multi-stakeholder call to action. *Nat Rev Nephrol* 2021; 17 (8): 554-68.
3. Solomon M, Grasemann H, Keshavjee S. Pediatric lung transplantation. *Pediatr Clin North Am* 2010; 57 (2): 375-91.
4. Hayes D Jr, Cherikh WS, Harhay MO, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-fifth pediatric lung transplantation report - 2022; focus on pulmonary vascular diseases. *J Heart Lung Transplant* 2022; 41 (10): 1348-56.
5. Brugha R, Wu D, Spencer H, Marson L. Disparities in lung transplantation in children. *Pediatr Pulmonol* 2024; 59 (12): 3798-805.
6. Werner R, Benden C. Pediatric lung transplantation as standard of care. *Clin Transplant* 2021; 35 (1): e14126.
7. Hayes D Jr, Harhay MO, Cherikh WS, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-fourth pediatric lung transplantation report - 2021; Focus on recipient characteristics. *J Heart Lung Transplant* 2021; 40 (10): 1023-34.
8. Schiavon M, Camagni S, Venuta F, et al. A multicentric evaluation of pediatric lung transplantation in Italy. *J Thorac Cardiovasc Surg* 2023; 165 (4): 1519-27.e4.
9. Avdimiretz N, Benden C. The changing landscape of pediatric lung transplantation. *Clin Transplant* 2022; 36 (4): e14634.
10. Solomon M, Mallory GB. Lung transplant referrals for individuals with cystic fibrosis: A pediatric perspective on the cystic fibrosis foundation consensus guidelines. *Pediatr Pulmonol* 2021; 56 (2): 465-71.
11. Kerem B, Chiba-Falek O, Kerem E. Cystic fibrosis in Jews: frequency and mutation distribution. *Genet Test* 1997; 1 (1): 35-9.
12. Otani S, Yamamoto H, Tanaka S, et al. Paediatric lung transplantation: the impact of age on the survival. *Surg Today* 2022; 52 (11): 1540-50.
13. Hayes D Jr, Cherikh WS, Chambers DC, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric lung and heart-lung transplantation report-2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant* 2019; 38 (10): 1015-27.
14. Khan MS, Zhang W, Taylor RA, et al. Survival in pediatric lung transplantation: The effect of center volume and expertise. *J Heart Lung Transplant* 2015 Aug; 34 (8): 1073-81.
15. Glanville AR, Verleden GM, Todd JL, et al. Chronic lung allograft dysfunction: Definition and update of restrictive allograft syndrome-A consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019; 38 (5): 483-92.
16. Bedair B, Hachem RR. Management of chronic rejection after lung transplantation. *J Thorac Dis* 2021; 13 (11): 6645-53.
17. Carvajal HG, Costello JP, Miller JR, Eghtesady P, Nath DS. Pediatric heart-lung transplantation: Technique and special considerations. *J Heart Lung Transplant* 2022; 41 (3): 271-8.
18. Serrano OK, Bangdiwala AS, Vock DM, et al. Incidence and magnitude of post-transplant cardiovascular disease after pediatric kidney transplantation: risk factor analysis of 1058 pediatric kidney transplants at the university of Minnesota. *Pediatr Transplant* 2018; 22 (7): e13283.
19. Shah Z, Rali A, Vuddanda V, et al. Acute coronary syndromes in heart transplant recipients (from a National Database Analysis). *Am J Cardiol* 2018; 122 (11): 1824-9.