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Survival in pediatric lung transplantation: The effect of center volume and expertise

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BACKGROUND: Institutional operative volume has been shown to impact outcomes of various procedures including lung transplantation (LTx). We sought to determine whether this holds true with pediatric LTx by comparing outcomes of adult centers (with larger overall volume) to those of pediatric centers (with smaller volume but more pediatric-specific experience).

METHODS: A retrospective analysis of the Organ Procurement and Transplant Network data was performed. Centers were categorized as either adult (LTx volume predominantly in adult patients), high-volume pediatric (HVP, $\geq$4 LTxs/year), or low-volume pediatric (LVP, $<$4 LTxs/year). Outcomes were compared in "younger children" ($<$12 years) and "older children and adolescents" (12 to 17 years).

RESULTS: In total, 1,046 pediatric LTxs were performed between 1987 and 2012 at 62 centers (adult 51 [82%], HVP 3 [5%], LVP 8 [13%]). Although adult centers had larger overall LTx volume, their pediatric experiences were severely limited (median 1/year). In younger children, HVP centers were significantly better than LVP centers for patient survival (half-life: 7.3 vs 2.9 years, $p = 0.002$). Similarly, in older children and adolescents, HVP centers were significantly better than adult centers for patient survival (half-life: 4.6 vs 2.5 years, $p = 0.001$). Of note, even LVP centers tended to have longer patient survival than adult centers ($p = 0.064$). Multivariable analysis identified adult centers as an independent risk factor for graft failure (hazard ratio: 1.5, $p < 0.001$) as with LVP (hazard ratio: 1.3, $p = 0.0078$).

CONCLUSIONS: Despite larger overall clinical volume, outcomes among pediatric LTx recipients in adult centers are not superior to those of pediatric centers. Not only center volume but pediatric-specific experience has an impact on outcomes in pediatric LTx.

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Although there have been nearly 2,000 pediatric lung transplantations (LTx) reported worldwide over the past 27 years,[1] pediatric LTx remains a relatively rare operation. Despite its rarity, there are a number of institutions that perform pediatric LTx, which has led to a limited case volume at each center. For instance, according to the 2012 registry report of the International Society for Heart and Lung Transplantation (ISHLT),[2] 42 centers performed LTxs in children (defined as $\leq$17 years of age) worldwide during

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the year 2010, with only 6 centers performing >5 pediatric LTxs annually. More recently, in 2012, 34 pediatric LTxs were carried out in the USA, with only 2 centers having an annual volume of >5.[3]

As demonstrated by Birkmeyer in his landmark studies, center volume, as a surrogate for experience, has a clear impact on surgical outcomes.[4,5] Theoretically, the same principle should be applied to any type of surgery, particularly complex ones such as LTx. In fact, studies have consistently shown higher center volume is associated with better outcomes in adult LTx patients.[6–8] It is not clear, however, if this conclusion holds true in pediatric LTx, because the pediatric-specific experience may also play a major role in post-transplant outcomes in the pediatric population. With these considerations in mind, in this study we tested 2 hypotheses: First, high-volume adult centers (that perform pediatric LTxs) would provide better outcomes than pediatric centers (most of which perform <4 LTxs annually), especially in older children and adolescents. Second, in younger children, pediatric centers would provide comparable outcomes compared with adult centers, because pediatric-specific experience may be more important than surgical volume.

Methods

This was a retrospective analysis of the Organ Procurement and Transplantation Network (OPTN) data from October 1987 to April 2012. The OPTN is a unified transplantation network and is administered by a private, non-profit organization, United Network of Organ Sharing (UNOS), which maintains a database of all transplantations in the USA. Approval for use of the OPTN data from the institutional review board of the Baylor College of Medicine was obtained before the start of this study.

Study population and groups

All pediatric patients (≤17 years) who had undergone isolated LTx were identified for the study period. Multi-organ transplantations such as heart–lung or lung–liver were excluded from the cohort.

The cohort was divided into 2 age groups: younger children (<12 years) and older children and adolescents (12 to 17 years). We set 12 years as a cut-off age for 2 reasons: First, these 2 age groups are distinctly different in terms of dominant indications for LTx. Whereas cystic fibrosis is the predominant etiology (>70%) in older children and adolescents, the incidence of end-stage lung disease related to cystic fibrosis is much less common in younger children.[2] Second, the lung allocation system[9] is different between these 2 age groups; the current lung allocation score applies only to patients >12 years of age.

The 2 age groups were further divided into 3 sub-groups based on the characteristics of the transplant centers as follows:

1. *Adult centers:* Centers that performed LTx predominantly (>50%) in the adult population but who also performed LTx in pediatric patients.
2. *High-volume pediatric (HVP) centers:* Centers that performed a median of ≥4 pediatric LTxs per year.
3. *Low-volume pediatric (LVP) centers:* Centers that performed a median of <4 pediatric LTxs per year.

The cut-off of 4 LTxs per year, used to define HVP and LVP centers, was based on the 2012 ISHLT annual report.[2] It is important to note that both adult centers and LVP centers perform a yearly median of <4 pediatric LTxs. However, adult centers perform a high volume of adult LTxs, and are therefore considered experienced, yet they lack pediatric-specific experience.

Study variables

The variables used in this study were as follows:

Donor factors: Race, gender, age, weight, height and partial pressure of arterial oxygen in the donor at the time of organ recovery.
Recipient factors: Age, weight and height at LTx, gender, race, diagnosis, time on waitlist, serum creatinine level, use of ventilator, extracorporeal membrane oxygenation, steroids and non-LTx lung surgery before LTx, and lung graft and patient survival times.
Transplantation factors: Type of LTx (single vs bilateral), ischemic times and era effect (new: 2001 to 2012; old: 1987 to 2000).

Data analysis

Data are reported as percentages for categorical variables and mean with standard deviation or median with minimum and maximum, as appropriate, for the continuous variables. Categorical variables were compared using chi-square and Fisher's exact tests. Continuous variables were compared using the Mann–Whitney *U*-test and Kruskal–Wallis test. Survival analysis was reported using Kaplan–Meier graphs and life-tables with median survival (half-life) and log-rank *p*-value. Univariate analysis was carried out and $p < 0.2$ was used to select variables for the multivariable model. Cox regression analysis was used to determine the association between different risk factors and graft survival. $p < 0.05$ was considered statistically significant.

Results

Pediatric LTx volume

There were 62 centers that performed 1,046 pediatric LTxs across the USA during the study period. Of these, 3 centers (5%) performed a median of ≥4 pediatric LTxs per year and were classified as HVP centers, whereas 8 centers (13%) performed a median of <4 LTxs per year and were classified as LVP centers. The remaining 51 centers (82%) were classified as adult centers because >50% of their LTx volume consisted of adult patients (≥18 years old). As demonstrated in Figure 1, the vast majority of adult centers have much higher volume experience in LTx, but pediatric-specific experience in these adult centers is quite limited, representing a small fraction of the total. The yearly median for pediatric LTx at adult centers was only 1 (range of 1 to 3). However, Figure 1 shows that 5 adult centers appear to have performed >20 pediatric transplants, whereas the other 46 performed very few. In total, the HVP centers performed 517 pediatric LTxs (49%, out of 1,046), LVP centers performed 193 pediatric LTxs (19%), and the adult centers