ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Waitlist outcomes in pediatric lung transplantation: Poor results for children listed in adult transplant programs

Brandi B. Scully, MD, MS,[a] Matthew Goss,[b] Hao Liu, PhD,[c] Michael L. Keuht, MD,[b] Iki Adachi, MD,[a] E. Dean McKenzie, MD,[a] Charles D. Fraser, MD,[a] Ernestina Melicoff, MD,[d] George B. Mallory, MD,[d] Jeffery S. Heinle, MD,[a] and Abbas Rana, MD[b]

From the [a]Department of Surgery, Division of Congenital Heart Surgery, Texas Children's Hospital, Houston, Texas, USA; [b]Department of Surgery, Division of Abdominal Transplantation, Texas Children's Hospital, Houston, Texas, USA; [c]Department of Medicine, Division of Biostatistics, Baylor College of Medicine, Houston, Texas, USA; and the [d]Department of Pediatrics, Division of Pediatric Pulmonology, Texas Children's Hospital, Houston, Texas, USA.

KEYWORDS:
case volume;
lung transplantation;
outcomes;
pediatric lung transplant;
pediatric transplantation;
thoracic surgery;
transplant rate;
waitlist survival

BACKGROUND: Low case volume has been associated with lower survival after pediatric lung transplantation. Our aim was to analyze waitlist outcomes among pediatric lung transplant centers in the USA.

METHODS: We studied a cohort of 1,139 pediatric candidates listed in the Organ Procurement and Transplantation Network for lung transplantation between 2002 and 2014. Of these candidates, 720 (63.2%) received a transplant. Candidates were divided into groups according to the clinical activity of the center of listing: high-volume pediatric (≥4 transplants per year); low-volume pediatric (<4 transplants per year); and adult (transplant volume predominantly in adults). We used multivariate Cox regression analysis to identify independent risk factors for waitlist mortality. We also determined the transplant rate—or likelihood of transplant after listing—over the study period.

RESULTS: Fifty-eight percent of the children and adolescents were listed in adult centers where the resultant transplant rate was low—only 42% received a transplant compared with 93% in pediatric programs. Listing in an adult program was also the most significant risk factor for death on the waiting list (hazard ratio 15.6, 95% confidence interval 5.8 to 42.1).

CONCLUSIONS: Most children (58%) are listed for lung transplantation in adult centers and have a reduced rate of transplantation and a greater chance of waitlist mortality.

J Heart Lung Transplant ■■■■;■:■■■–■■■

After 3 decades of practice, lung transplantation in children remains a formidable challenge.[1,2] Morbidity and mortality before and after transplantation are significant and the required infrastructure and expertise is extensive.[1,3–5] It has recently been reported that low-volume pediatric centers and adult-oriented centers have inferior post-transplant survival outcomes among children.[6] The case volume–outcome relationship has also been more widely applied to the field of adult lung transplantation.[7–9]

The relationship between volume and outcomes has been applied to a variety of surgical procedures of varying

Reprint requests: Abbas Rana, MD, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, One Baylor Plaza, MS: BCM390, Houston, TX Telephone: 713-321-8423. Fax: 713-610-2479.
E-mail address: abbas.rana@bcm.edu

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2017.04.010

degrees of complexity,[10–21] including each type of solid-organ transplant.[22–28] None of these studies, however, have explored differences in waitlist outcomes. In our recent analysis of pediatric liver transplantation, we demonstrated higher waitlist mortality and a lower transplant rate in low-volume centers. The waitlist outcome differences overshadowed the minor differences in post-transplant survival.[29]

Our objective in this analysis was to compare waitlist outcomes for transplant patients at high-volume pediatric centers, low-volume pediatric centers, and adult centers.[6] This parallels a recent study by Khan et al who demonstrated that low-volume pediatric centers (≤4 cases per year) and adult centers (lung transplant volume predominantly in adults) had an increase in post-transplant mortality of 50% and 60%, respectively, in a multivariate analysis.[6] We hypothesized that lower waitlist survival and a decreased transplant rate would occur in low-volume pediatric and adult-oriented centers.

Methods

Study population

We performed a retrospective analysis of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) de-identified patient-level data of all candidates listed for lung transplant between March 1, 2002 and December 31, 2014. We analyzed the lung registry data for all transplant candidates <18 years of age. Donor and recipient characteristics were reported at the time of transplant, and follow-up information was collected at 6 months and then yearly after transplantation for the period of study. Patients undergoing combined or multivisceral transplantations and candidates placed on the waitlist for combined or multivisceral transplants were excluded from the study. A total of 1,139 patients were followed from the date of listing, and 720 candidates received a transplant during the study period. All patients were followed to either death on the waitlist ($n = 221$), date of transplant ($n = 720$) or the date of last known follow-up ($n = 198$).

Statistical analysis

We analyzed the data using STATA version 12.1 (StataCorp, College Station, TX) statistical software. Continuous variables are reported as mean ± standard deviation and compared using the Student's *t*-test. Contingency table analysis was used to compare categorical variables. Results were considered significant at a $p < 0.05$, and all reported *p*-values were 2-sided.

In this analysis, candidates were followed from the time of listing to date of death on the transplant waitlist as established by the Social Security Death Master File and the UNOS death date. We used Kaplan–Meier analysis with log-rank test and Cox regression for time-to-event analysis. The primary outcome measure was death on the waitlist. Time to death was assessed as the time from the date of listing to the date of death while on the waitlist. The waitlisted candidates who received a transplant were censored on the date of transplantation. We also performed a competing risk regression analysis based on the method by Fine and Gray, where transplantation was the competing outcome.[30] The primary outcome was death on the waitlist. Candidates listed in programs that did not perform any transplants in the study period were dropped from the analysis. Eleven candidates from 7 adult programs were dropped for this reason.

Waitlist survival was the dependent variable and the risk factors were independent variables in the regression analysis. Risk factors that were significant in univariate analysis ($p < 0.05$) were included in the multivariate analysis. Multivariate Cox regression was performed combining 100 bootstraps.

Risk factors

The pediatric lung transplant volume for each center was the average number of cases performed yearly from 2002 to 2014. We followed the categorization system established by Khan and colleagues[6]: high-volume pediatric centers were defined as ≥4 cases per year; low-volume pediatric centers as <4 cases per year; and adult centers as those where transplant volume consisted of primarily adults. Two pediatric centers had ≥4 cases per year, 9 pediatric centers had <4 cases per year, and 45 centers were adult centers.

To account for geographic inequities in the supply and demand of lung allografts for transplantation, we included the UNOS region of listing as a covariate.

Stratified analysis for children and adolescents

Because adult centers had a skewed population toward adolescents, we conducted separate Kaplan–Meier analyses for children (<12 years old) and adolescents (12 to 18 years old).

Table 1 Risk Factors Considered in Univariate Analysis Cox Regression

Candidate risk factors the time of listing	Entry completion	Univariate analysis (hazard ratio [confidence interval])
African-American	100	1.47 (0.88 to 2.45)
Age	100	0.98 (0.96 to 1.00)
Age <1 year	100	2.42 (1.56 to 3.75)[a]
Blood type A	100	0.84 (0.63 to 1.11)
Blood type B	100	0.82 (0.52 to 1.29)
Blood type O	100	1.30 (0.98 to 1.70)
Blood type AB	100	0.88 (0.43 to 1.78)
BMI	99.7	1.02 (0.98 to 1.04)
Creatinine clearance	99.0	1.00 (0.99 to 1.01)
Diagnosis cystic fibrosis	100	0.88 (0.67 to 1.16)
Diagnosis primary pulmonary hypertension	100	0.65 (0.42 to 1.01)
Dialysis or creatinine clearance ≤40	98.4	1.62 (0.40 to 6.53)
ECMO	100	2.91 (1.28 to 6.62)[a]
Inotropes	100	3.50 (1.90 to 6.43)[a]
Life support	99.9	2.22 (1.58 to 3.12)[a]
Previous transplantation	100	2.50 (1.57 to 3.97)[a]
Ventilator	100	2.63 (1.81 to 3.82)[a]
Weight (kg)	99.9	0.98 (0.98 to 1.00)
Weight <5 kg	99.9	3.24 (1.79 to 5.84)[a]
Center risk factors		
High-volume pediatric center: ≥4 cases/year	100	0.09 (0.03 to 0.23)[a]
Low-volume pediatric center: <4 cases/year	100	0.56 (0.42 to 0.76)[a]
Adult center	100	6.56 (3.87 to 11.11)[a]

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; UNOS, United Network for Organ Sharing.
[a]Statistically significant ($p < 0.05$).