



## ORIGINAL CLINICAL SCIENCE

# Influence of graft ischemic time and geographic distance between donor and recipient on survival in children after lung transplantation

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**KEYWORDS:**

donor;  
geographic distance;  
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recipient;  
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**BACKGROUND:** The optimal ischemic time in pediatric lung transplantation (LTx) is unclear, as recent studies have challenged the relevance of 6 hours as an upper limit to acceptable ischemic time.

**METHODS:** Pediatric LTx recipients transplanted between 1987 and 2013 were identified in the United Network for Organ Sharing (UNOS) registry to compare survival according to ischemic time, which was categorized as <4 hours, 4 to 6 hours and >6 hours.

**RESULTS:** Nine hundred thirty patients, all <18 years of age and receiving a first-time LTx from a cadaveric donor, were included in our investigation. Compared with <4 hours of ischemic time, univariate analysis showed a significant reduction in mortality hazard with 4 to 6 hours (hazard ratio [HR] = 0.640; 95% confidence interval [CI] 0.502 to 0.816;  $p < 0.001$ ) but not >6 hours (HR = 0.985; 95% CI 0.755 to 1.284;  $p = 0.909$ ). A multivariate Cox model confirmed the lowest mortality hazard to be 4 to 6 hours, as compared with <4 hours (HR = 0.533; 95% CI 0.376 to 0.755;  $p < 0.001$ ). A prolonged ischemic time of >6 hours was associated with increased mortality hazard relative to the 4 to 6 hours (HR = 1.613; 95% CI 1.193 to 2.181;  $p = 0.002$ ). Supplementary analyses examining geographic distance between donor and recipient identified no association between geographic distance and recipient mortality hazard.

**CONCLUSIONS:** An ischemic time of 4 to 6 hours was associated with optimal long-term survival in first-time pediatric LTx recipients, whereas a very short ischemic time of <4 hours and a prolonged ischemic time >6 hours were both associated with higher mortality hazard in this population.

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Lung transplantation (LTx) is a surgical treatment option for children with certain end-stage parenchymal lung diseases and pulmonary vascular disorders,<sup>1,2</sup> yet a restricted donor organ pool limits the number of candidates who undergo transplantation.<sup>3,4</sup> Organ procurement for LTx

involves geographic restrictions, as clinicians attempt to avoid long distances between a potential donor and recipient to reduce graft ischemic times. Recent studies in adults and children receiving LTx have argued that prolonged ischemia of lung allografts in excess of 6 hours does not limit recipient survival as was previously believed.<sup>5,6</sup> Those studies, focusing on a dichotomous threshold for prolonged ischemic time, left unstated whether there were any differences observed in patient survival across ischemic times within the range previously considered acceptable (i.e., <6 hours).

The research on prolonged ischemic times in adult LTx recipients has increasingly questioned the clinical implications of this factor and the validity of 6 hours as an upper limit to acceptable ischemic time. A 2001 study indicated that, in adults, a cold graft ischemic time of  $\geq 6$  hours did not increase the risks of short- or long-term mortality, or other adverse outcomes, such as reperfusion injury, acute rejection, cytomegalovirus infection, bacterial or fungal pneumonia or bronchiolitis obliterans syndrome (BOS).<sup>7</sup> Prolonged geographic distances between donors and recipients, as well as allograft ischemic times up to 9 to 12 hours, have been reported as leading to acceptable survival outcomes in adults in both single-center and national registry studies.<sup>6,8,9</sup> Those findings conflict with data showing an association between prolonged graft ischemic times and worse outcomes of LTx, such as older data from the USA<sup>10</sup> or data from a multicenter study in France.<sup>11</sup>

The lack of influence of prolonged ischemia in pediatric LTx was argued by Zafar et al based on an analysis of the United States national registry of LTx recipients,<sup>5</sup> but there are several important characteristics of the pediatric LTx cohort that highlight the need for a better understanding of long-term outcomes of ischemic time in this population. First, allocation of donor lungs to children <12 years of age was not revised to incorporate the lung allocation score (LAS) when the latter was introduced in May 2005. Second, the availability of appropriately sized allografts is limited in children by the fact that many pediatric donor lungs are received by adult recipients. Third, pediatric transplant programs may have different criteria for donor organs than adult centers. These conditions imply potential differences between the adult and pediatric settings in the trade-offs of waiting for an appropriate allograft to become locally available to minimize ischemic time, as opposed to pursuing an earlier transplant of a donor organ recovered from a greater distance. Therefore, we sought to assess the influence of ischemic time on outcomes after LTx in children using available national data extending the pediatric LTx cohort examined in earlier work.<sup>5</sup> Based on the recent adult literature, we hypothesized that graft ischemic times do not influence survival in children after LTx, both beyond and within the 6-hour range.

## Methods

The institutional review board at Nationwide Children's Hospital approved this study with a waiver of individual consent

(IRB14-00716). We retrospectively evaluated data from LTx recipients <18 years of age who were registered in the United Network for Organ Sharing (UNOS) thoracic database between October 1987 and September 2013.<sup>12</sup> Following earlier studies, this cohort was divided into 3 categories of ischemic time: <4 hours; 4 to 6 hours; and >6 hours.<sup>7</sup> As ischemic times are substantially determined by geographic distance between recipients and donors, supplemental analyses examined the implications of the latter factor, defined as a continuous variable or categorical distance with a threshold of 360 miles, chosen based on previous research.<sup>10</sup> All analyses were performed using Stata/MP, version 13.1 (StataCorp LP, College Station, TX). For all analyses,  $p \leq 0.05$  was considered statistically significant.

Descriptive statistics for continuous variables were presented as means, standard deviations and medians, and were compared across ischemic time categories using analysis of variance (ANOVA). Descriptive statistics for categorical variables were presented as counts and proportions, and compared using chi-square tests. Survival duration was analyzed from the date of the transplant until the date of death or censoring. Cox proportional hazards models were used to adjust for potential confounders, which included: donor and recipient gender; donor and recipient race; diagnosis; donor and recipient age; transplant year; recipient body mass index (BMI) at the time of transplant; recipient time on the waiting list; recipient forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) at the time of the transplant; recipient reliance on steroids and mechanical ventilation at the time of the transplant; and the ratio of donor to recipient predicted total lung capacity.<sup>13</sup>

## Results

### Study population

Figure 1 presents inclusion and exclusion criteria for our study, leading to an analytic sample of 930 patients under the age of 18 years receiving a first-time lung transplant, among whom 874 had data on ischemic time. Exclusion criteria consisted of identical waiting list entry and exit dates for survival analysis, missing ischemic time data for Kaplan–Meier analysis and missing covariate data for multivariate survival analysis. Table 1 compares the characteristics of patients classified according to ischemic times of <4 hours, 4 to 6 hours and >6 hours. Patients with cystic fibrosis (CF) undergoing LTx were more likely to have a longer ischemic time, and there was a trend for transplants involving ischemic time >6 hours being performed more recently (median year = 2005) than transplants involving ischemic time <4 hours (median year = 2001). Recipient race varied by ischemic time category, with the highest proportion of white recipients found in the 4- to 6-hour group, and the <4-hour and >6-hour groups having higher proportions of recipients who were neither white nor black.

### Survival analysis

Up to 924 patients were included in univariate survival analysis for each covariate, depending on the completeness of the data (Table 2), and 869 patients were included in the Kaplan–Meier function analysis stratified by ischemic time

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