Factors associated with in-hospital mortality in infants undergoing heart transplantation in the United States

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Objective: Infants undergoing heart transplantation have the highest early posttransplant mortality of any age group. We sought to determine the pretransplantation factors associated with in-hospital mortality in transplanted infants in the current era.

Methods: All infants under 12 months of age who underwent primary heart transplantation during a recent 10-year period (1999–2009) in the United States were identified using the Organ Procurement and Transplant Network database. Multivariable logistic regression was used to identify independent pretransplantation factors associated with in-hospital mortality.

Results: Of 730 infants in the study (median age 3.8 months), 462 (63%) had congenital heart disease, 282 (39%) were supported by a ventilator, 94 (13%) with extracorporeal membrane oxygenation, and 22 (3%) with a ventricular assist device at the time of transplantation. Overall, 82 (11.2%) infants died before their initial hospital discharge. In adjusted analysis, in-hospital mortality was associated with repaired congenital heart disease (odds ratio [OR], 3.6; 95% confidence interval [CI], 1.8, 7.2), unrepaired congenital heart disease not on prostaglandin E (OR, 2.8; CI, 1.3, 6.1), extracorporeal membrane oxygenator support (OR, 6.1; CI, 2.8, 13.4), ventilator support (OR, 4.4; CI, 2.3, 8.3), creatinine clearance less than 40 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} (OR, 3.1; CI, 1.7, 5.3), and dialysis (OR, 6.2; CI, 2.1, 18.3) at transplantation.

Conclusions: One in 9 infants undergoing heart transplantation dies before hospital discharge. Pretranplantation factors associated with early mortality include congenital heart disease, extracorporeal membrane oxygenator support, mechanical ventilation, and renal failure. Risk stratification for early posttransplant mortality among infants listed for heart transplantation may improve decision-making for transplant eligibility, organ allocation, and posttransplant interventions to reduce mortality. (J Thorac Cardiovasc Surg 2011;141:531-6)

⌒ᐟ Supplemental material is available online.

Infants undergoing heart transplantation (HT) face the highest early mortality of all children undergoing HT.[1,2] However, those who survive the early period have the best long-term survival.[2,3] Because infants account for approximately one fourth of pediatric heart transplants performed in the United States, reduction in early posttransplant mortality in this group not only will improve long-term survival in infants undergoing HT but also will benefit overall pediatric HT survival.

Although age has been evaluated as a risk factor for early posttransplant mortality within the broad context of pediatric HT, few studies have focused on the infant population alone. Infants undergoing HT are unique by virtue of the prevalence of congenital heart disease (CHD) compared with older children, their internal heterogeneity with respect to prostaglandin-dependent circulation, and their exposure to cardiac surgery.[3,4] In addition, infants' size constraints result in a relative scarcity of donor organs and long waiting times before HT, which may increase the risk of end-organ dysfunction from prolonged exposure to insufficient organ perfusion and complications from medications used to support cardiac function.[5] Moreover, most previous studies have analyzed mortality at arbitrary intervals after HT, which may have been useful to assess center performance[1,3,4,6] but may not be optimal for designing strategies to improve early posttransplant outcomes. In-hospital mortality as an end point is important, not only because hospital discharge after HT is a clinical milestone, but

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also because an improved understanding of factors driving early mortality in this high-risk group may influence decisions about criteria and timing for listing and for emerging mechanical support devices.

The purpose of this study, therefore, was to identify the pretransplant factors associated with in-hospital mortality among infants undergoing HT in the current era.

METHODS
Study Population

All patients less than 12 months of age who underwent their first orthotopic HT in the United States (US) between January 20, 1999, and January 20, 2009, were identified in the Organ Procurement and Transplantation Network (OPTN) database. The OPTN is an internally audited, mandatory, solid-organ transplant registry that includes data on all solid-organ transplants in the US as submitted by the members of the network. The US Department of Health and Human Services provides oversight of the activities of the OPTN contractor, the United Network for Organ Sharing. We excluded infants who underwent multivisceral transplantation. All children were followed up from the time of HT until death or hospital discharge.

Study Definitions and Outcome Measures

The primary outcome measure was in-hospital mortality, defined as infants who received heart transplants and died before their initial hospital discharge. All clinical and demographic variables were defined at the time of HT. Pretransplant mechanical cardiorespiratory support was categorized as extracorporeal membrane oxygenation (ECMO) support, ventilator support (without ECMO), or no support (neither ECMO nor ventilator support). Creatinine clearance was calculated using the formula presented by Schwartz and associates.[7] We also assessed the primary cause of death in infants who died.

Statistical Analysis

Summary statistics are presented as median (interquartile range [IQR]) or number (percent). Patient characteristics were compared among diagnostic subgroups using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Characteristics of patients who died versus those who survived were compared by the Wilcoxon rank sum test or χ^2 test, as appropriate. Hospital mortality rates are displayed with 95% exact binomial confidence intervals. A multivariable logistic regression model was used to identify independent factors associated with in-hospital mortality. Only risk factors that were statistically significant at the .05 level were retained in the final model. Analyses were performed using statistical software SAS version 9.1 (SAS Institute Inc, Cary, NC) and STATA version 10.0 (StataCorp LP, College Station, Tex). All authors had full access to the data and take responsibility for its integrity.

RESULTS
Study Cohort

A total of 730 infants underwent orthotopic HT in the US during the study period. The baseline characteristics of these infants are summarized in Table 1 and Figure E1. The primary cardiac diagnosis was CHD in 462 (63%), cardiomyopathy in 224 (30%), and other in 44 (6%) patients. The median age of the cohort was 3.8 months (IQR, 1.7–6.6 months) and the median weight was 4.7 kg (IQR, 3.6–6.0 kg). The median donor weight was 7.0 kg (IQR, 5.0–10.0 kg), and the donor/recipient weight ratio was 1.5 (IQR, 1.1–1.9). Overall, infants receiving heart transplants due to CHD were younger ($P < .001$) and smaller ($P < .001$ for weight and body surface area) than infants listed for cardiomyopathy. Ninety-four (13%) infants were supported by ECMO at the time of transplant, 213 (29%) were supported with mechanical ventilation without ECMO, 22 (3%) were supported with a ventricular assist device (VAD), 120 (16%) were receiving prostaglandin E (PGE), and 20 (3%) were supported with dialysis. Of the 113 patients with repaired CHD who were supported with PGE, 20 carried the diagnosis of hypoplastic left heart syndrome. Infants with CHD were more likely to have a creatinine clearance less than 40 mL · min^{-1} · 1.73 m^{-2} ($P = .10$), and infants with cardiomyopathy were more likely to be using a VAD at the time of transplant ($P < .001$).

In-Hospital Mortality

Eighty-two (11.2%) of 730 infants died before their hospital discharge. Table 2 summarizes univariate variables of early hospital mortality before discharge. Infants who died were younger and smaller than survivors. Other factors associated with in-hospital mortality included ECMO or ventilator support at HT, prior sternotomy, creatinine clearance less than 40 mL · min^{-1} · 1.73 m^{-2}, dialysis at the time of HT, and a bloodstream infection within 2 weeks preceding HT. VAD and PGE use were not associated with higher in-hospital mortality and only 1 patient supported with a VAD died; however, the total number of patients using a VAD (n = 22) was small.

Figure 1 summarizes unadjusted in-hospital mortality for infants receiving heart transplants according to diagnosis (Figure 1, A), level of invasive support (Figure 1, B), and renal function (Figure 1, C). Infants with repaired CHD were far more likely to die before hospital discharge than were the infants with cardiomyopathy (21% vs 5%; $P < .001$). A substantial increase in mortality was seen on the basis of the level of invasive support, with patients supported by ECMO having the highest mortality. Finally, infants with renal failure, estimated by creatinine clearance less than 40 mL · min^{-1} · 1.73 m^{-2}, had a significantly worse outcome than did those with creatinine clearance of 40 mL · min^{-1} · 1.73 m^{-2} or more.