Risk factors for mortality or delisting of patients from the pediatric heart transplant waiting list

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Objective: Current literature assessing factors associated with outcomes of patients waiting for pediatric heart transplants has focused on survival to transplant and mortality. Our aim was to determine risk factors associated with the outcomes of delisting, transplant, or death while waiting.

Methods: In this single-center, retrospective study of patients listed for heart transplants, competing risk analysis was used to model survival from listing to 4 competing outcomes (transplant, death, delisting for clinical deterioration, delisting for clinical improvement or surgical intervention).

Results: There were 308 listing episodes in 280 patients. In competing risk analysis, 11% remained listed at 6 months (transplant 62%, dead 13%, delisted worse 6%, delisted improved 8%). Extracorporeal membrane oxygenation and ventricular assist devices were associated both with higher probability of transplant (hazard ratio [HR], 2.8; $P < .001$) and delisting for clinical deterioration (HR, 2.7; $P = .06$). Younger age at listing and complex congenital heart disease were shared risk factors for mortality (HR, 1.07; $P = .05$; HR, 2.9; $P = .003$) and delisting because of clinical deterioration (HR, 1.17; $P = .01$; HR, 2.8; $P = .02$). Younger age at listing and fetal listing were associated with delisting for clinical improvement or surgical intervention (HR, 1.13; $P = .01$; HR, 2.9; $P = .02$).

Conclusions: Overall survival to transplant depends on risk factors including age at listing, cardiac diagnosis, and mechanical circulatory support. Knowledge of risk factors for death and delisting for clinical deterioration or improvement can assist patient selection and timing of transplant listing. (J Thorac Cardiovasc Surg 2014;147:462-8)

Pediatric patients waiting for heart transplants have the highest waiting list mortality relative to all other solid organ transplant groups.[1-4] Many factors affect how long a patient is expected to wait for a transplant such as weight, blood group, age, underlying diagnosis, and HLA sensitization.[2,5,6] Organ allocation algorithms aim to stratify patients by risk factors for death to optimize organ allocation and reduce waiting list mortality. Recent studies, however, highlight that the current systems may be imperfect and point out that there is a need for ongoing review of the existing algorithms with a clear view to achieving optimal patient outcomes during the wait for transplant.[7,8] Currently, the Canadian organ allocation system (COAS) for pediatric heart transplantation stratifies patients according to level of medical urgency, with further definitions for each level of "critical illness" comparable to the one in use by the United Network for Organ Sharing (UNOS; Table 1). Thus a patient that who is receiving mechanical ventilation and mechanical circulatory support (MCS) will have a higher waiting list status than that of a patient receiving high-dose inotropes alone, regardless of time spent on the waiting list.

Almond and colleagues[8] reported waiting list mortality in the United States according to data from the Scientific Registry of Transplant Recipients (SRTR). Overall waiting list mortality was 17%, but more importantly there was considerable heterogeneity within the highest medical urgency category, status 1A, which comprised 60% of the listings. Status 1A patients had a waiting list mortality that ranged from 5% to 39%, depending on their level of hemodynamic support. This study concluded that, despite improvements in the organ allocation system since 1999, pediatric waiting list mortality continues to remain unacceptably high, and the current organ allocation system in the United States remains suboptimal for characterizing medical urgency.[8]

Previous studies assessing factors associated with waiting list outcomes have mainly focused on survival to transplant and mortality.[2,4,6,9-13] Of equal importance, however, are factors associated with removal from the waiting list, or "delisting," whether for clinical

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Abbreviations and Acronyms

ABO-I = ABO incompatible
CAV = cardiac allograft vasculopathy
CHD = congenital heart disease
COAS = Canadian organ allocation system
ECMO = extracorporeal membrane oxygenation
HLHS = hypoplastic left heart syndrome
MCS = mechanical circulatory support
SRTR = Scientific Registry of Transplant Recipients
UNOS = United Network for Organ Sharing

deterioration or for clinical improvement, surgical intervention, or both. These expansions on the conventional risk factor analyses for delisting may help with decision making related to heart transplant eligibility and timing of listing, and they may contribute to optimal risk stratification within organ allocation algorithms.

The purpose of this study was to assess our institution's waiting list mortality within the current COAS and the associated risk factors for delisting because of clinical deterioration or delisting because of clinical improvement or surgical intervention.

MATERIALS AND METHODS

This was a retrospective study of all patients listed for heart transplants for congenital or acquired heart disease at The Hospital for Sick Children, Toronto, Ontario, Canada, between 1990 and 2008. Research ethics board approval was obtained,. Detailed medical history was reviewed, including cardiac diagnosis, medical condition leading to the transplant, blood group, requirement for MCS, fetal listing, and waiting list outcomes. Status at the time of listing was according to the COAS. Table 1 outlines the comparison between the COAS and that of UNOS.

Data are described as means with SD, medians with minimum and maximum values, and frequencies as appropriate. A competing risks analysis was performed to characterize outcomes after pediatric patients were listed for heart transplants. The competing risk analysis estimates, at each time point after listing, the likelihood of each competing event occurring against all others, according to a parametric survival model for each event. To create the competing risks, parametric survival models were created for each of the following competing outcomes: (1) heart transplant, (2) death on the transplant list, (3) delisting because of clinical deterioration or loss of transplant candidacy, and (4) delisting because of clinical improvement or other surgical intervention. Factors associated with each of these outcomes were sought from demographic and clinical characteristics in univariate models and excluded patient status at listing, which was considered a surrogate marker of likelihood of outcomes. Factors with associations at the level of $P < .10$ were included in multivariable models with backward selection to obtain a final model. All statistical analyses were performed with SAS Statistical Software version 9.2 (SAS Institute Inc, Cary NC).

RESULTS

Patient Population

There were 308 listing episodes for heart transplants among 280 pediatric patients, 45% of whom were male, with a median age at listing of 1.6 years (ranging from fetal listing to 17.9 years). A total of 121 patients (39%) were eligible and listed for ABO-incompatible (ABO-I) heart transplants. There was a slight predominance of patients with congenital heart disease (CHD) listed for their first heart transplant (58%), and approximately a third of those had undergone a previous surgical procedure (37%). There was the expected predominance of patients belonging to blood group O (49%). Detailed characteristics of the study population can be found in Table 2.

Overall Outcomes After Listing for Transplant

For the entire cohort, 70% patient listings (n = 216) eventually resulted in transplants, 13% of patients (n = 40) died while on the waiting list, 7% (n = 21) were delisted because of clinical worsening, 9% (n = 29) were delisted because of clinical improvement or other surgical intervention, and 1% (n = 2) had yet to reach an outcome at the 2-year mark (Figure 1). Median time from listing to reaching an outcome was 29 days (1-930 days). Despite a low overall waiting list mortality of 13%, the range according to the underlying diagnosis or level of support was quite variable. Factors associated with the highest percentage waiting list mortality while waiting in our cohort were being relisted for primary graft failure (30%), Canadian transplant status 4 (23%), extracorporeal membrane oxygenation (ECMO) support (21%), age younger than 1 month (18%), and complex CHD other than hypoplastic left heart syndrome (HLHS; 16%).

Patients who were listed status 4, the highest status according to the COAS, had the shortest time to an outcome (death, transplant, or delisting) relative to status 1 patients (median 10 days vs 64 days; $P < .001$) but the lowest transplant rate (52% vs 83%, $P < .001$). Status 4 at the time of listing was also associated with younger age at listing ($P = .04$), listing eligible for an ABO-I transplant ($P = .01$), use of ventricular assist device (VAD) or ECMO ($P < .001$), diagnoses other than restrictive cardiomyopathy ($P = .004$) or cardiac allograft vasculopathy (CAV) ($P = .04$), and primary graft failure ($P < .001$).

Risk Factor Analysis

Multivariate analysis indicated that patients with blood group A possessed an expected competitive edge, with a significantly higher likelihood of surviving to transplant (hazard ratio [HR] 2.1 vs all other blood groups; $P < .001$), whereas those with blood group O were significantly less likely to survive to transplant (HR, 0.5; $P < .001$). Differences between blood groups were negated in young patients listed for ABO-I transplant, resulting in a higher likelihood of successfully surviving to transplant (HR, 1.4; $P = .03$). Younger age at listing (<1 month) was associated with increased likelihood of death on the