Survival after listing for cardiac transplantation in children

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Abstract

Despite improvement in surgical and medical management of children with congenital and acquired heart disease, cardiac transplantation remains an important therapeutic option for infants and children with end-stage heart disease. Ultimate survival in patients who are listed for transplantation is a function of both mortality while awaiting transplantation and survival after transplantation. Survival of heart transplantation is affected by the severity of illness before transplantation, the unique pathophysiology of certain defects, and the availability of donor hearts. Outcome following listing for transplantation is best studied with the use of recent modifications in statistical methods of competing outcomes analysis. By this analysis a predicted mortality while waiting among all pediatric patients is 20% at 1 year, with 67% undergoing transplantation, 10% still on the list awaiting transplant, and 3% removed from the list. Among infants, most of them with hypoplastic left heart syndrome, 60% will have transplantation by 6 months after listing, with 27% of patients dying while waiting. In infants the major risk factors for death while waiting are the need for inotropic support at listing, smaller size, and recipient blood type. In older children risk factors for death while waiting are Status 1 at listing and a need for mechanical ventilation. Intermediate-term survival after transplant is excellent in all age groups with 86% alive at 6 months, 84% at 1 year, and 73% at 5 years. Survival after transplant in infants is comparable to survival in older children, although the early mortality after transplantation is greater. Infants who have recently undergone sternotomy or received organs from donors who did not die of closed head trauma are more likely to die early after transplant. Among older children risk factors for death after transplantation include the need for a mechanical support device or a younger age in patients greater than 1 year of age. Death following transplantation is primarily related to early graft failure in infants, whereas rejection, infection, and sudden death account for the majority of deaths in older children. Although improved immunosuppressive agents promise to lead to even better survival rates after transplantation, greater access to donors is essential if overall survival is to be improved. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

1.1. Cardiac transplantation for end-stage heart disease in children

With the advent of Cyclosporin and reduced dependence on high-dose corticosteroids cardiac transplantation has become a common approach to the treatment of end-stage heart disease in children. In a number of institutions the successful early experience with transplantation for acquired and congenital heart disease [1–11] has led to a proliferation of centers performing transplantation in both infants and children. The registry of the International Society of Heart and Lung Transplantation (ISHLT) has records of a total of 3857 cardiac transplant procedures in children, ranging from 147 during 1987 to 352 in 1997, and the reports indicate that the frequency of transplantation has reached a plateau since 1990 [12]. In individual institutions survival rates following
transplantation have ranged from 53% to 100% at 1 year after transplant [1–8,10]. However, analysis of survival in a single institutional experience is limited by the relatively small number of patients at any given institution and by institutional bias in patient selection and treatment protocols. Moreover, the great majority of reports from individual institutions emphasize mortality after transplant and ignore important pre-transplant mortality. In 1991 the Pediatric Heart Transplant Study Group (PHTS) was established with the primary purpose of examining the outcomes following listing, including the mortality while waiting for transplantation and after surgery. In this ongoing study, data is collected prospectively from 20 institutions on all listed patients for pre- and post-transplant variables and events following listing. Events that have been analyzed include death while waiting, removal from the list, death after transplant, rejection, and infection. Data collection and analysis began in January 1993 with complete data collection through December 1998. This review summarizes the analysis of outcomes of listing and transplantation in this large multi-center experience.

1.2. Competing outcomes analysis after listing

After listing for cardiac transplantation any of four potential outcomes may occur including death while waiting, transplantation, removal from the list, or continuing on the waiting list for transplantation. Because each of these outcomes are competing, the use of Kaplan–Meier estimates for any individual outcome may be misleading [13,14], resulting in over-estimates of any given outcome. Competing outcomes analysis allows for the simultaneous time-related analysis of multiple discrete outcomes and is ideal for studying the outcomes of listing for cardiac transplantation. This method uses parametric modeling of these multiple discrete outcomes and a robust time-related analysis of multivariable risk factors, allowing for patient-specific predictions of outcomes after listing. McGiffin et al. [13] described the use of competing outcomes analysis in 264 pediatric patients listed for transplantation. Patients ranged in age from 3 days to 17.9 years with a mean age of 4.7 years. In this initial report from the PHTS, 60% of patients underwent transplantation by 6 months after listing, 23% died while waiting, 14% remained on the list awaiting transplantation, and 4% improved and were removed from the list. In a separate analysis of infants less than 6 months of age who were listed for transplantation [14], nearly one-third died awaiting transplantation. Although 60% did undergo transplantation by 6 months, only 6% remained on the list awaiting transplantation. The majority of infants listed for transplantation (59%, 70 of 118 patients) had hypoplastic left heart syndrome (HLHS) and were prostaglandin-dependent, and the few survivors on the list had undergone interim Norwood surgical palliation. It was clear that the fate of infants listed for transplantation was largely determined within 3 months after listing. The risk factors for death in infants waiting for transplant were the need for inotropic support at listing \((P = 0.02)\), smaller size \((weight) at listing \((P = 0.0007)\), and a recipient with blood type \(O (P = 0.003)\). Similarly, risk factors for a longer time until transplantation were smaller size at listing \((P = 0.001)\), blood type \(O (P = 0.0006)\) for patients with HLHS, and younger age at listing \((P = 0.01)\) for patients without HLHS. Prostaglandin-dependent patients with HLHS were more likely to die waiting and less likely to undergo transplantation than infants without HLHS. The use of blood type \(O\) donors (universal donor) in non-blood type \(O\) recipients resulted in more deaths while waiting among blood type \(O\) patients. In older children death was more likely to occur in Status 1 patients and in those requiring mechanical ventilation [15].

A more recent analysis of the PHTS experience included 1234 patients listed from January 1993 through December 1998. Of these, 893 (72%) were in the most urgent status (Status 1), of which 541 (44%) were less than 6 months of age at listing. Only 342 patients (28%) were Status 2 at listing. Sixty percent were males and 40% were female. Twenty-three percent had HLHS, 37% had other unoperated or operated congenital heart defects, and 40% had myocarditis or cardiomyopathy. In the competing outcomes analysis of all patients (Fig. 1) survival to transplantation was essentially unchanged from the reported initial experience [13]. Likewise, death while waiting occurred in approximately 28% of Status 1 patients during the entire 6-year experience, essentially no different from the initial experience reported by Morrow et al. [14] (Fig. 2). Older Status 1 patients were more likely than infants to survive to transplantation (72%) and fewer died awaiting transplantation (18%); only 6% remained on the waiting list at 1 year after initial listing (Fig. 3). Predictably, the best survival was in Status 2 patients with 78% undergoing transplant, 10% dying, and 10% remaining on the list at 2 years after listing (Fig. 4).

Results of these studies have had a significant impact on organ allocation policy. Effective from 1 January 1999, UNOS policy changed to allow type \(O\) donor hearts to be allocated first to type \(O\) recipients. Similarly, under new urgency status categories (Status 1a, Status 1b, and Status 2) prostaglandin-dependent infants with greater than 50% systemic-to-pulmonary artery pressure ratios (prostaglandin-dependent single ventricle physiology) are prioritized to Status 1a, the most urgent status. The future analysis of the effect
of these changes in policy will be enhanced by the use of competing outcomes analysis and comparison to previous experiences in the PHTS.

2. Early survival in infants and children

As noted above, a number of institutions have reported excellent early and intermediate survival rates in both infants and children [1–11] following orthotopic cardiac transplantation. Shaddy et al. reported the initial PHTS survival experience among 191 children older than 1 year of age who underwent transplantation [16]. Actuarial survival after transplant was 93% at 1 month and 82% at 1 year. Major causes of death were rejection (29%), early graft failure (19%), infection (16%), and sudden death (13%). By multivariable analysis the major risk factor for death was the need for assist devices at the time of transplant ($P = 0.02$). Younger age was a significant risk factor for death in the group of patients who were older than 1 year of age at transplant. Patients in the 1–5-year age range had a 1-year actuarial survival rate of 74%, as compared to 86% for patients over 5 years of age at transplant. This observation of increased mortality in young children has been noted in many different series but it is not always statistically significant. Importantly, overall survival rates among Status 1 and Status 2 patients were not different.

Canter et al. [17] examined early survival after heart transplantation in the PHTS experience among infants less than 1-year-old at transplant. The majority of infants (66%) had HLHS. Survival rates were lower than in older children, with 70% of infants alive at 1 year compared to 82% in children older than 1 year.
The peak risk for death was within the first month after transplant with 16% of patients dying during this interval. Risk factors for death included a history of previous sternotomy and a donor cause of death other than closed head trauma. A previous history of sternotomy in this age group implied a very recent attempt at surgical repair and, therefore, represented a particularly high-risk group of patients for any intervention. Most deaths after transplantation occurred as a result of early graft failure or pulmonary hypertension. When combined, these two causes of death accounted for 75% of deaths in the infant age group.

3. Intermediate survival in the PHTS

Recently, the entire 6-year experience of the PHTS with cardiac transplantation was analyzed. In this experience 847 patients underwent transplantation from 1 January 1993 through 31 December 1998. There were 511 males (60%) and 336 females (40%) who underwent an initial transplantation procedure. Of the 847 patients, 44% were less than 1 year of age, 33% were between 1 and 12 years, and 23% were greater than 12 years of age at transplant. A greater percentage of patients were Status 1 (72%) than in adult series [18], in large part due to the large number of infants in this study. Overall actuarial survival in all age groups was 84% at 1 year and 73% at 5 years (Fig. 5). Univariate analysis indicated that the age at transplant was not a significant risk factor for death ($P = 0.29$). Interestingly, the 1-year survival rate was 82% among infants less than 1 year of age at transplant, compared to 70% in the initial PHTS experience [17] (Fig. 6). Also, the 1-year survival rate among children 1–5 years of age was 80%, compared to 74% in the initial report by Shaddy et al. [16]. Among children older than 5 years of age, survival was 86–88%, essentially no different from the initial experience reported by the PHTS. The urgency status at transplant did not affect 5-year survival (Fig. 7), nor did interoperative myocardial ischemia time. However, infants with HLHS were more likely to have early death than patients with cardiomyopathy or myocarditis. In infants with HLHS, however, survival was 80% at 6 months, compared to patients with cardiomyopathy or myocarditis with a survival rate of approximately 90% at 6 months (Fig. 8). Nonetheless, 5-year survival was no different between diagnostic groups, indicating a more significant constant phase of mortality and a late attrition of patients transplanted for diastolic and other forms of cardiomyopathy. This experience compared very favorably with both individual institutional experiences [1–11] and the ISHLT registry experience [12]. In the ISHLT experience, which began in 1987, the 1-year actuarial survival for all age groups was 75% and survival at 5 years was 64%. The 1-year actuarial survival among infants less than 1 year of age was approximately 68%, with a 5-year survival of 60%, far less than the experience in PHTS institutions. The 5-year survival rate in children was also lower than that observed in the PHTS experience with approximately 65% of children in the ISHLT registry analysis surviving to 5 years post-transplant. Although all institutions currently in the PHTS are also represented in the ISHLT registry, there are important differences in data between the registry and the PHTS. Not only does the PHTS represent a different and later era of transplantation, it also has a more complete data set. More recent studies have emphasized improving survival at individual institutions [19,20] with 5-year actuarial survival rates of 95–100%. A current analysis is underway in the PHTS to establish whether there is, in fact, an improved survival in the current era.

Five-year survival rates in pediatric patients in the PHTS study are also virtually identical to survival rates among adults [21]. Analysis of recent data from
the Cardiac Transplant Research Database demonstrated a 1-year actuarial survival of 85% among adults with a 5-year survival of 71%, slightly lower than the pediatric experience.

4. Causes of death after transplantation

An understanding of the causes of death after transplantation is essential to improving survival. In virtually all series the most common primary cause of death is transplantation rejection. Rejection death is most likely in the first month after transplant, and thereafter it assumes a constant phase of risk which continues throughout follow-up. Death from rejection is more likely to occur after late rejection episodes and those associated with severe hemodynamic compromise. It is not surprising that the risk factors for rejection — late rejection, recurrent rejection, and rejection with hemodynamic compromise — are virtually the same, and they identify a group of patients at higher risk.

In infants the most common primary cause of death early after transplantation continues to be graft failure, even in the current era [12,17,22]. The primary risk factors for death from early graft failure are, as expected from the mortality data presented above, donor death other than that due to closed head trauma ($P = 0.03$) and longer interoperative myocardial ischemia time ($P = 0.06$). After graft failure and rejection, infection accounts for a majority of the remaining deaths. Death from myocardial infarction remains decidedly uncommon within 5 years of transplantation, although a disturbing increase in sudden deaths has been observed. However, the future mortality from rejection may be reduced with improved rejection surveillance and treatment of these high-risk patients, and with new, more effective, immunosuppressive regimens on the horizon. Likewise, since graft atherosclerosis is at least in part a rejection phenomenon, improved treatment of rejection could lead to a reduced incidence and severity of graft coronary disease.

5. Late survival after cardiac transplantation

Little data is available regarding long-term survival in pediatric heart transplant recipients. Long-term survival is particularly important in children who have undergone heart transplantation because of a reasonable expectation for greater longevity. The continuing occurrence of late rejection [23], rejection deaths [22–24], late appearing coronary disease, deaths from coronary disease, and retransplantation [22,23,25] raises concern about the ultimate fate of children who have undergone cardiac transplantation. The ISHLT registry report gives a 12-year actuarial survival of 45% for all ages. As noted above, survival rates in the registry experience are less than in the PHTS, possibly due to different eras of transplantation or to institutional variables. Likewise, in some institutions, patients who had heart transplantation early in the pediatric experience appear to have lower survival rates than in current patients. Webber reported a 10-year survival of approximately 45% in a cohort of 37 patients transplanted between 1982 and 1989 [19]. However, in this same cohort 5-year survival was approximately 50%, less than what has been achieved at other institutions in more recent cohorts. In the same report Webber notes a much-improved contemporary 4-year survival of greater than 90%. Sigfusson et al. [26] analyzed survival rates of patients among three institutions with long-term experiences. Actuar-
ial survival rates of patients who had survived at least 5 years was 80% at 10 years post transplant, but 67% at 15 years, emphasizing an ongoing mortality primarily due to rejection and coronary disease. Again, only patients who had survived at least 5 years were included in the analysis and, therefore, these data do not reflect overall 10- and 15-year survival rates, which would be higher.

Thus, predicting late survival is significantly affected by early survival after transplant from different eras in the practice of pediatric heart transplantation. Nonetheless, the PHTS experience, though only in its seventh year, confirms the presence of an ongoing constant phase of mortality (Fig. 5), which could result in a 10-year survival rate in the range of 50%. It is unclear whether this constant phase of mortality applies equally to all age groups and to all types of cardiovascular disease. For instance, although early mortality is greater in infants, it appears that the constant phase of mortality and graft loss may be less for those patients transplanted before 6 months of age, and especially for those undergoing transplant during the first month of life. If, indeed, there is a greater early survival in the current era, this survival will ultimately translate into improved long-term outcomes.

6. Conclusions

In pediatric patients awaiting heart transplantation a deficiency of available donors results in significant mortality, although most patients eventually undergo successful transplantation. This mortality is virtually equal to the 1–5-year rates after transplant. Despite deaths while waiting, for some infants and children with end stage heart disease transplantation is effective and can provide good intermediate survival. Survival rates in infants and children are equal to, if not better than, those in adults. Death after transplantation is primarily the result of early graft failure in infants and rejection in older children. Even in infants rejection remains a major cause of death. Moreover, recent studies at individual institutions suggest that early and intermediate survival rates may be improving. Long-term survival rates in children have not been established in the current era and there is concern regarding the ongoing constant phase of mortality seen in both children and adults. The recent development of new immunosuppressive agents may significantly affect long-term survival by reducing the incidence and severity of acute and chronic rejection. However, increased organ donation or strategies to increase the size of the pool of organ donors, such as xenotransplantation, are needed to significantly reduce overall mortality.

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