Adult-age donors offer acceptable long-term survival to pediatric heart transplant recipients: An analysis of the United Network of Organ Sharing database

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Objectives: A critical shortage of donor organs has caused many centers to use less restrictive donor criteria, including the use of adult-age donors for pediatric recipients. The purpose of this study is (1) to describe the supply of pediatric (0-18 years) heart donors, (2) to explore the relationship between donor age and long-term survival, and (3) to define threshold age ranges associated with decreased long-term survival.

Methods: The United Network of Organ Sharing provided deidentified patient-level data. Primary analysis focused on 1887 heart transplant recipients aged 9 to 18 years undergoing transplantation from October 1, 1987, to September 25, 2005. Kaplan-Meier analysis and log-rank tests were used in time-to-event analysis. Receiver operating characteristic curves and stratum-specific likelihood ratios were generated to compare survival at various donor age thresholds.

Results: The number of pediatric donors decreased ($P < .001$) over the study period, particularly from 1993 (n = 640) through 2004 (n = 432). Among recipients aged 9 to 18 years, univariate analysis demonstrated a statistically significant ($P < .001$) inverse relationship between donor age and survival. Stratum-specific likelihood ratio analysis generated 3 strata for donor age: the low-risk, intermediate-risk, and high-risk groups consisted of donors aged 13 years or younger (n = 611, 32.41%), 14 to 51 years (n = 1258, 66.7%), and 52 years and older (n = 16, 0.85%), respectively. In the low-risk, intermediate-risk, and high-risk groups median survival was 4069 days (11.1 years), 3495 days (9.57 years), and 1197 days (3.28 years), respectively.

Conclusions: Although donors aged 13 years or less offer pediatric recipients the best chance for achieving long-term survival, donors aged 14 to 51 years offer good outcomes to pediatric recipients. Consideration should be given to expanded use of well-selected adult-age donors for pediatric recipients.

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Pediatric patients listed for transplantation, especially in the adolescent age group, compete with adult patients for pediatric donor hearts; this further encroaches on the already limited supply of available donors in this population. In the setting of a critical scarcity of organs, strategies to maximize the donor pool are crucial.[1-5] One such strategy is the use of adult-age donors in pediatric

Abbreviations and Acronyms
ROC = receiver operating characteristic
SSLR = stratum-specific likelihood ratio
TCAD = transplant coronary artery disease
UNOS = United Network for Organ Sharing

recipients. However, only one published study, a case series of 5 pediatric recipients, has examined this strategy among children.[6]

The purpose of this study is (1) to describe the supply of pediatric (0-18 years) heart donors over time, (2) to explore the relationship between donor age and long-term survival, and (3) to define threshold age ranges associated with decreased long-term survival. This study is based on an analysis of the United Network for Organ Sharing (UNOS) database and provides the first review of a large experience with adult-age donors among pediatric heart transplant recipients.

Methods

Data Collection and Study Population

UNOS provided deidentified patient-level data from the Thoracic Registry (data source #092005-7). This registry includes all heart transplant recipients and donors in the United States since October 1, 1987. Primary analysis focused on 1887 recipients aged 9 to 18 years who underwent transplantation between October 1, 1987, and September 25, 2005. This age range was chosen because, at younger ages, adult heart donors (>18 years) provide fewer than 10% of organs. Data on transplant coronary artery disease (TCAD) were first collected by UNOS in 1995. Separately, all 38,363 heart transplant donors during the same period were examined for trends in donor age.

Data Analysis

The primary outcome measure was survival, and other measures included TCAD-free survival. Continuous variables are reported as means ± standard deviation and compared by using the Student *t* test. The χ^2 test was used to compare categoric variables. All reported *P* values are 2 sided. The risk ratio and 95% confidence interval were reported for each factor. Kaplan-Meier analysis with Cox regression was used for time-to-event analysis. Multivariate regression analysis was also performed (forward, forward stepwise, and backward; enter $P < .10$, remove $P > .15$), where survival was the dependent variable, and the independent variables included donor age, recipient age, donor sex, ischemic time, waiting time, status 1/1A/1B at transplantation, donor heart ejection fraction, ventricular assist device explantation at transplantation, and transplantation year. All data were analyzed with a standard statistical software package, Stata 9 (Stata Corp, College Station, Tex).

Receiver operating characteristic (ROC) curves were generated by plotting sensitivity on the ordinate and 1-specificity on the abscissa, with the use of donor age as a continuous variable and death at 5 years as a binary outcome.[7-9] Threshold analysis was performed by using stratum-specific likelihood ratios (SSLRs) and 95% confidence intervals as previously described.[10,11] In this study SSLRs represent the proportion of recipients within a given donor age stratum dead at 5 years divided by the proportion within the same stratum alive at 5 years. Cut points, or threshold values, for donor age were determined by combining adjacent donor age strata in 1-year intervals with other statistically indistinct strata based on the presence of SSLRs with overlapping 95% confidence intervals. Cut points occurred when 2 statistically distinct strata could be formed. This process was repeated until no additional cut points were found.

Results

Recipients and Donors

Analysis included 1887 pediatric heart transplant recipients with 2,892,685 days (7919.7 years) at risk; median survival for all recipients was 3641 days (9.97 years). Over the course of the study period, the number of pediatric donors (≤18 years) decreased ($P < .001$), particularly between 1993 (n = 640) and 2004 (n = 432, Figure 1).

ROC and SSLR

The corresponding area under the curve was 0.56 (95% confidence interval, 0.52-0.59). SSLRs generated 3 strata (Table 1): low risk, intermediate risk, and high risk.

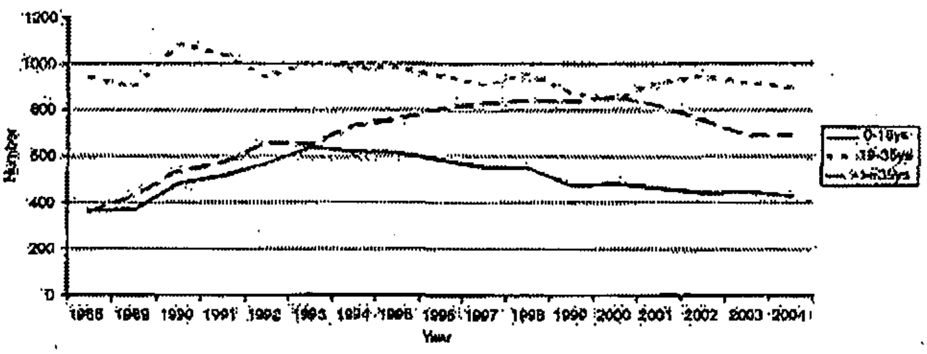

Figure 1. Number of donor hearts for all recipients per year stratified by age category.

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TABLE 1. Recipient-donor characteristics and outcome measures by donor age strata

Risk strata	Low	Intermediate	P value*	High	P value†	Total
Age range (y)	≤13	14-51		≥52		
N	611 (32.4%)	1260 (66.7%)		16 (0.85%)		1887
SSLR	0.80 (0.67-0.98)	1.10 (1.00-1.21)		5.25 (1.23-23.47)		
Recipient-donor characteristics						
Recipient male sex (n)	327 (53.5%)	809 (64.2%)	<.001	10 (62.5%)	.477	1146 (62.4%)
Recipient mean age (y)	12.2 ± 2.44	14.6 ± 2.40	<.001	15.4 ± 2.67	<.001	13.8 ± 2.67
Congenital heart disease (n)	220 (36.0%)	337 (24.3%)	<.001	1 (6.25%)	.014	527 (27.9%)
UNOS status 1 at transplantation (n)	275 (52.1%)	925 (73.4%)	<.001	16 (100%)	.001	1259 (66.7%)
Donor heart ejection fraction (%)	63.3 ± 11.0	62.1 ± 8.17	.11	65.4 ± 7.16	.62	62.4 ± 9.00
Recipient/donor weight ratio	0.99 ± 0.30	0.88 ± 0.26	<.001	.79 ± 0.26	.019	0.91 ± 0.28
Waitlist time (d)	77.7 ± 129.3	87.0 ± 143.1	.19	100.0 ± 186.8	.51	84.5 ± 139.7
Bridge to transplantation (n)	32 (5.24%)	174 (13.8%)	<.001	4 (25.0%)	.001	210 (11.13%)
Ischemic time (h)	3.57 ± 1.19	3.10 ± 1.13	<.001	2.88 ± 1.19	.20	3.25 ± 1.17
Outcomes						
Incidence rate of death (per 100 person-years)	6.43	8.33	.011	16.03	.049	7.68
Median survival (d)	4069	3495		1197		
1-y survival (%)	87.70	87.20		83.10		
5-y survival (%)	73.20	66.20		42.70		
Median TCAD-FS (d)	4114	3302	<.001	799	<.001	

SSLR, Stratum-specific likelihood ratio; *UNOS,* United Network of Organ Sharing; *TCAD-FS,* transplant coronary artery disease–free survival. *P values comparing low-risk and intermediate-risk strata. †P values comparing intermediate-risk and high-risk strata.

Outcomes

Among recipients aged 9 to 18 years, univariate analysis demonstrated that increasing donor age was associated with worse survival ($P < .001$). In multivariate analysis only donor age demonstrated a significant relationship with survival. As shown in Figure [illegible], A, survival was significantly better ($P = .0098$) among the low-risk group (median survival, 4069 days) compared with that in the intermediate-risk (3495 days) and high-risk (1197 days) groups. As shown in Figure [illegible], B, TCAD-free survival in the intermediate-risk (median time to event, 3302 days) and high-risk (799 days) groups was significantly worse ($P = .0008$) than in the low-risk group (4114 days).

Discussion

Consistent with previous studies,[12,13] findings here demonstrate that increasing donor age has a strong inverse relationship with recipient survival. However, because the number of transplanted hearts from donors 18 years and younger decreased over time (Figure [illegible]), strategies using adult donors in children are necessary to maintain the number of organs available to pediatric recipients.

Threshold analysis determined that the first cut point occurred at a donor age of 14 years. Thus survival was best among recipients receiving hearts from donors aged 13 years or less. Regression analysis shows that there is an inverse relationship between donor age and survival; however, further threshold analysis demonstrated no statistical difference in survival among recipients of grafts across a broad range of donor ages (14-51 years). Although there was a statistical difference in survival between the low-risk (≤13 years) and intermediate-risk (14-51 years) strata, with the median survival exceeding 10 years in the intermediate-risk stratum, donor hearts in this age range offered an acceptable level of long-term survival.

The use of donor hearts from the high-risk stratum (≥52 years) resulted in worse outcomes. In particular, early TCAD was the norm, and long-term survival was adversely affected. However, it is difficult to draw firm conclusions regarding this group not only because of its small size (n = 16) but also because recipient and donor characteristics were not uniform across groups. Recipients in the intermediate-risk and high-risk strata possessed higher risk profiles by most measures, including UNOS status at transplantation, waiting time, and bridge to transplantation. If less acutely ill children received hearts from these "higher-risk" age strata, survival might improve. Therefore we might in fact be underestimating the acceptable upper limit of donor age. However, in multivariate analysis only increasing donor age was associated with worse survival, and therefore the true significance of these differences in patient characteristics is questionable. Regardless, these observations further support the findings in this study that acceptable long-term survival in pediatric recipients can be achieved with a broad age range of donors.

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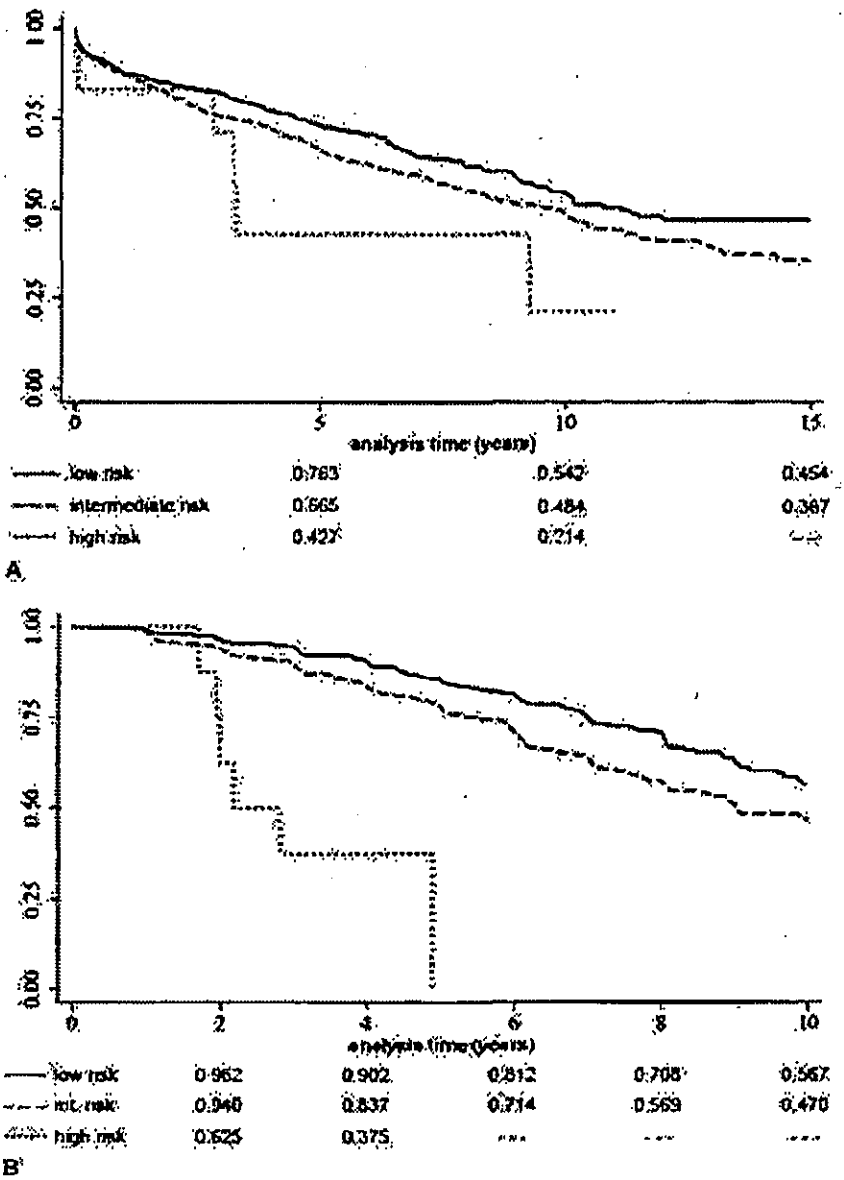

Figure 2. A, Kaplan-Meier analysis for survival among the low-risk, intermediate-risk, and high-risk groups. B, Kaplan-Meier analysis for transplant coronary artery disease–free survival among the low-risk, intermediate-risk, and high-risk groups.

As with all large datasets collected across multiple institutions, data entry across institutions might vary. However, fields were generally well populated, with a 95% to 99% data entry rate. In addition, although the UNOS reporting system provided definitions for conditions such as TCAD in data guidelines, specific definitions might vary by center. Finally, in this threshold analysis (SSLR and ROCs) the effect of only a single factor (donor age) can be assessed on the outcome of interest (death). Because multiple factors varied across the resultant strata, it is possible that this analysis was confounded by these differences. However, in multivariate analysis only donor age and no other donor or recipient characteristic was associated with survival. Therefore differences in other patient characteristics across strata should, in fact, not be expected to affect these findings.

Conclusions

Among pediatric heart transplant recipients, increasing donor age is inversely associated with survival. Donors aged 13 years or less offer pediatric recipients the best long-term survival. However, donors aged 14 to 51 years offer good outcomes to pediatric recipients. With a decreasing number of pediatric heart donors and the acceptable long-term survival provided to pediatric recipients by a broad age range of adult donors, consideration must be given to expanded use of well-selected adult-aged donors in the pediatric population.

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