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INCIDENCE AND RISK FACTORS FOR MORTALITY IN INFANTS AWAITING HEART TRANSPLANTATION IN THE UNITED STATES

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Abstract

Background—Infants awaiting heart transplantation (HT) face the highest wait-list mortality among all children and adults listed for HT in the United States (US). We sought to determine the risk of death for infants <12 months old while awaiting HT in the current era, and to identify the principle risk factors associated with wait-list mortality.

Methods—We analyzed outcomes for all US infants listed for HT from January 1999 to July 2006 using data reported to the US Scientific Registry of Transplant Recipients.

Results—Of 1133 listed infants, 61% were <3 months of age, 80% were listed status 1A, 64% had a congenital heart disease (CHD) and 31% had cardiomyopathy. Of 724 infants with CHD, 25% were on prostaglandin (PG) and 27% had history of prior surgery. By 6 months after listing, 23% died on the wait-list and 54% were transplanted. Multivariable factors associated with wait-list mortality were weight <3 kg (HR 1.4, 95% CI 1.0–1.9), ECMO support (HR 5.6, CI 4.0–7.9), ventilator support (HR 2.1, CI 1.6–2.8), CHD with PG support (HR 2.8, CI 1.8–4.3), CHD without prior surgery (HR 2.8, CI 1.9–3.9) and nonwhite race/ethnicity (HR 1.8, CI 1.4–2.3).

Conclusions—One in four US infants listed for HT dies before a donor heart can be identified. Wait-list mortality is associated with weight under 3 kilograms, level of invasive support and CHD, but not listing status, which captures medical urgency poorly. Measures to expand infant organ donation, especially among neonates, are urgently needed.

INTRODUCTION

Infants awaiting heart transplantation (HT) face the highest wait-list mortality among all children and adults listed for HT, with studies reporting mortality rates of 25–30%^{1–4}. In

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Disclosures

None

response to internal analysis and reports on pediatric HT wait-list mortality^{3,4}, United Network for Organ Sharing (UNOS) revised the allocation scheme for hearts on January 20, 1999. According to these revisions, children previously listed as status 1 were now listed as either status 1A or 1B based on urgency. The new allocation scheme also began to preferentially direct hearts from blood-type O donors to blood-type O recipients.³

In a recent report, we described risk factors for wait-list mortality among children <18 years of age since the revision of the heart allocation system in 1999.⁵ Infants <1 year of age represent a special subgroup of the pediatric population for two reasons. First, unlike older children, the predominant indication for HT is congenital heart disease (CHD) - often without previous palliation or repair. Second, infants are eligible for a variety of emerging treatment strategies to reduce wait-list mortality that are generally considered experimental, such as transplantation of an ABO-incompatible donor heart⁶, or of a heart from a non-heart-beating donor⁷, and the use of an investigational miniaturized ventricular assist device⁸. As the total number of infant transplants per year have remained relatively constant since the early 1990s^{7,9}, understanding risk factors for wait-list mortality for this population in the current era is critical to develop strategies to reduce wait-list mortality and to improve the donor pool.

Thus, the purpose of this study was to determine the incidence and risk factors for death in infants listed for HT in the US in the current era.

METHODS

Study Population

We identified all infants listed for their first HT between January 20, 1999 and July 12, 2006 through the US Scientific Registry of Transplant Recipients (SRTR). The SRTR is an internally-audited, mandatory, solid-organ transplant registry that collects information on all solid organ transplants in the US. Demographic and clinical information is reported by transplanting centers to the Organ Procurement and Transplantation Network (OPTN) and is supplemented by data from the Social Security Administration and the Center for Medicare and Medicaid Services. We excluded infants listed for heart re-transplantation or multi-visceral transplantation. All infants were followed from the time of listing for HT until death or the day of last observation on August 3, 2007.

Study Design

We analyzed the SRTR data to determine the incidence and risk factors for wait-list mortality in the study population. We hypothesized that the risk of death while awaiting HT in infants is related not only to the level of invasive support at listing but also to their cardiac diagnosis. Time on the wait-list was defined as the duration from initial listing for HT to the time of removal from the wait-list due to HT, death or recovery. Infants who died on the wait-list were considered to have reached the primary endpoint (i.e. had the event). Infants were censored at the time of HT or removal from the list due to recovery; those who remained on the wait-list were censored on August 3, 2007. All clinical and demographic variables were defined at the time of listing for HT unless otherwise specified. Race/

ethnicity data were analyzed as reported by the transplanting center. As a detailed anatomic and surgical diagnosis of infants with CHD was not available, we classified infants with CHD into 3 broad categories (Figure 1): (1) Infants on prostaglandin (PG) infusion, (2) Infants with prior surgery, listed as either “repaired” or with “sternotomy”, and (3) Infants with no prior surgery, listed as those not on PG *and* either “unrepaired” or with no “sternotomy” or if the data fields for repair or sternotomy were left blank by the reporting center.

To analyze hemodynamic support as a risk factor, an infant was defined to be on extra-corporeal membrane oxygenation (ECMO) if supported on ECMO, on ventilator if on a ventilator but not on ECMO and on “other support” if on neither. Glomerular filtration was estimated using the Schwartz Formula ¹⁰.

Statistical Analysis

Summary statistics are presented as median (inter-quartile range [IQR]) or number (percent). Patient characteristics were compared across diagnostic subgroups using the chi-square test and the Kruskal-Wallis test. Univariate relationships between patient characteristics and wait-list mortality were evaluated using the log-rank test. Multivariable analysis was performed using the Cox model. We also performed competing risk analysis so as to model multiple observed outcomes (death, transplant, removal from the wait-list) in the cohort. Analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC) and STATA version 10.0 (StataCorp LP, College Station, TX). The authors had full access to the data and take responsibility for its integrity.

RESULTS

Study Population

We identified 1133 infants who were eligible for the study. The baseline characteristics of these infants are summarized in Table 1. Their median age was 1 month and median weight 4.0 kg. Sixty-four percent of the listed infants had CHD and 31% had cardiomyopathy. At time of listing, 18% of infants were supported by ECMO, 33% by a ventilator and 56% were on inotropes. Eighty percent of the infants were listed on the UNOS waiting list as status 1A, 10% as status 1B and 10% as status 2. Eighty-five percent of all infants who received a HT were status 1A at the time of their transplant.

Infants with CHD were younger than those with cardiomyopathy (Table 1). The use of a ventilator appeared to be similar across the diagnostic groups. There was, however, a significant difference in use of ECMO across diagnostic groups; only 2% of patients with CHD on PG infusion were also supported by ECMO. The proportion of listed infants with CHD on PG decreased during the study period from 43% of all listed infants in 1999 to 9% of listed infants in 2006 (Figure 2).

One in ten infants was listed for a potential ABO-incompatible HT. Compared to those listed for an ABO-compatible HT, infants listed for ABO-incompatible HT (n=100, median age < 1 month, IQR 0–2 months) were younger ($P<0.001$), more likely to be in the “CHD prior surgery” group (34% versus 16% of all listed infants, $P<0.001$ for distribution by diagnosis),

and more likely to be supported by ECMO (37% versus 15%, $P<0.001$ for distribution by hemodynamic support) at time of listing for HT.

Wait-list Mortality and Risk Factors

Figure 3 illustrates the competing outcomes for the study cohort after listing for transplant. Within 6 months of listing, 54% of infants had received a HT, 23% died while waiting, 5% recovered and were removed from the list, and 18% remained on the wait-list 6 months after listing. In univariate analysis (Table 2), higher wait-list mortality was associated with younger and smaller infants, non-white race/ethnicity, status 1A, CHD, blood-type O, ECMO, ventilator, renal dysfunction, and ABO-incompatible listing. Infants on ECMO were at highest risk of wait-list mortality (Figure 4). In infants on neither ECMO nor ventilator, those with CHD on PG had a higher wait-list mortality compared to the other two CHD groups and infants with cardiomyopathy (Figure 5).

Table 3 summarizes the risk factors in a multivariable Cox model. Predictors of death on the wait-list were listing weight <3 kg, ECMO support, ventilator support, CHD on PG support, CHD with no prior surgery and nonwhite race/ethnicity. Of note, listing status, age, and blood-type were not found to be associated with wait-list mortality after adjusting for other factors. Being listed for an ABO-incompatible heart was associated with wait-list mortality even after adjusting for the risk factors in Table 3 (hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.1, 2.6, $P=0.01$). However, we chose not to include this variable in the final multivariable model because being listed for an ABO-incompatible heart is, by itself, not a demographic or clinical risk factor.

DISCUSSION

In this study, we found that between 1999 and 2006, one in four infants less than 12 months old listed for HT in the US died before a donor heart could be identified. Three-quarters of deaths occurred within the first 45 days after listing, underscoring the importance of timely transplant for higher-risk infants^{3, 11}. Infants at higher risk for wait-list mortality included those on ECMO or ventilator support, those with CHD, small infants with weight <3 kg, and infants of non-white race/ethnicity. The most important patient factor associated with higher risk of mortality was the level of hemodynamic support, with ECMO support predicting the worst wait-list survival. For infants who were on neither ECMO nor ventilator support, those with ductal-dependent CHD had the highest mortality. Of note, age, listing status and blood type were not significant as predictors of death while awaiting HT.

Our findings are consistent with prior studies that found that CHD, mechanical support and small body size were independent risk factors for death while awaiting HT in infants³. However, we observed several important differences. First, unlike the era prior to the 1999 organ allocation revision, infants with blood-type O are no longer at higher risk for wait-list mortality suggesting that the current allocation scheme for allocating organs is neutral to patient blood type. Second, the proportion of infants listed for HT due to CHD has decreased from 86% in the 1990s to 64% in the current era^{3, 5}. This trend over the past two decades likely reflects a broader shift in clinical practice across the US where infants born with HLHS are more likely to undergo surgical palliation rather than primary HT^{4, 12}. This

decrease in high-risk cases among infants listed for HT may explain, in part, the gradual decline in wait-list mortality for infants in the current era (23% versus 31% in the 1990s). Lastly, while prior studies have found patient size to be an independent risk factor for wait-list mortality, to our knowledge, this is the first study to report infants <3 kilograms to be at especially high risk.

Our finding that infants on PG for ductal-dependent CHD were at higher risk of death is similar to earlier reports which showed higher wait-list mortality in infants with HLHS^{3, 4, 13}. Unlike infants with cardiomyopathy and other forms of CHD, infants on PG for ductal-dependent CHD face a relatively constant hazard of death that does not flatten beyond 90 days after listing^{3, 4}. This unique hazard curve is likely related to progressive pulmonary over-circulation with physiologic fall in pulmonary vascular resistance. In infants with unrestricted pulmonary blood flow, this may result in progressive heart failure, respiratory failure, decreased systemic perfusion and end-organ dysfunction. These infants do not need mechanical support when first listed (only 2% of these infants were on ECMO in our cohort) and are poor candidates for mechanical support if severe heart failure develops¹⁴. In contrast, the diagnostic group that was most likely to be on ECMO in our cohort was CHD with prior surgery (32% on ECMO). However, after adjusting for hemodynamic support, this diagnostic group had lower wait-list mortality compared to infants with PG-dependent CHD.

The findings of this study have important implications. First, our analysis suggests that it is possible to risk-stratify infant HT candidates for wait-list mortality however risk factors for infants differ slightly from those identified for older children (Tables 3 and 4). For example, a one week old infant with a diagnosis of CHD on PG had a 30-day mortality risk of 11% in our cohort. In contrast, a one week old on ECMO following a stage I palliation had a 30-day mortality risk of 31%. Risk stratification of infants awaiting HT can help inform candidate selection for new or unproven treatment strategies intended to reduce wait-list mortality, such as the use of an investigational cardiac assist device, or deliberately listing a candidate as eligible to receive an ABO-incompatible or a DCD heart.

Second, our findings suggest that the current UNOS listing status captures medical urgency poorly – and arguably more poorly for infants than for older children⁵. The final Cox model suggests that other covariates are superior to listing status in predicting risk of death and therefore medical urgency. The limited ability for listing status to discriminate patient risk can be explained, in part, by the fact that the vast majority of infants are grouped in the same listing tier (1A) (i.e. 80% of infants at the time of listing and 85% at the time of transplant). As a result, waiting time has functionally replaced medical urgency as the primary determinant for organ allocation for all children, especially infants, which is not consistent with contemporary organ allocation standards as outlined in the Final Rule on Organ Allocation which strongly discourages the use of waiting time as a primary criterion for organ allocation¹⁵. We recognize that the risk factors for wait-list mortality strongly overlap with those for mortality *after* HT in infants⁹. However, our results suggest that a formal review of the current organ allocation system should again be considered. The goal of any potential change in allocation scheme should be to minimize overall mortality (wait-list *and* post-transplant mortality) in infants listed for HT. The results of our study will be of

potential help in developing and testing simulation models of alternative allocation strategies.

Lastly, our findings suggest that measures to increase the supply of infant and neonatal donor hearts are urgently needed. For example, West *et al.* demonstrated a marked reduction in wait-list mortality for Canadian infants after initiation of routine ABO-incompatible HT¹⁶. This strategy effectively expands the supply of suitable donor hearts for a given candidate by eliminating the blood group restriction. At present, ABO-incompatible listing appears under-utilized in the US based on the relatively small percentage of infants listed for potential ABO-incompatible HT (9%). Two other under-utilized strategies to expand the infant donor pool include, (1) greater acceptance within the transplant community for using DCD hearts, while controversial, could increase organ supply by as much as 70% or more^{7, 17, 18}, and (2) greater acceptance within the neonatology community for routine organ donation after declaration of brain death.

We were surprised to find that being listed for a potential ABO-incompatible HT in our cohort was associated with an *increased* risk of death in both univariate and multivariable analyses. Since the effect of ABO-incompatible listing is simply to reduce the waiting time for an infant to receive a heart (either ABO-compatible or incompatible), and hearts are allocated for ABO-incompatible recipients only after an ABO-compatible recipient cannot be found, this counter-intuitive finding may be best attributable to selection bias and residual confounding (infants listed for a potential ABO-incompatible HT were much sicker) in the multivariable analysis. Further research is needed to better understand the relationship between ABO-incompatible listing and wait-list mortality among infants.

This study has limitations inherent in a retrospective database analysis. First, we treated patient characteristics including listing status and hemodynamic support as baseline variables. Changes in listing status or patient removal from the wait-list due to clinical deterioration were not accounted for. This may have underestimated the true strength of association between risk factors and outcome. Retrospective studies are also inherently susceptible to selection bias if a non-random sample from a large population is selected. However, because the SRTR consists of data on *all* infants listed in the US, selection bias is not likely to play a major role in the findings of this analysis. Finally, detailed anatomic and surgical diagnostic data for listed infants were not available in the database. This limited our ability to draw diagnosis-specific inferences in infants with CHD.

In conclusion, wait-list mortality in infants awaiting HT in the current era remains high at 23%. The current allocation system captures medical urgency poorly, largely because the overwhelming majority of infants are listed as status 1A. Clinical characteristics, listing diagnosis and level of invasive support at the time of listing can be used to risk-stratify infants listed for HT and identify those at high risk for wait-list mortality. Measures to expand donor pool, especially among neonates and young infants, are urgently needed.

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Figure 1. Distribution of study infants listed for heart transplant by diagnosis. PG – Prostaglandin infusion.

Figure 2.

Percentage of infants with congenital heart disease (CHD) on prostaglandin (PG) infusion at the time of listing for heart transplant (n = 724). The percent of patients on PG infusion decreased from 43% of all infants in 1999 to 9% in 2006.

Figure 3.
Competing outcomes for all infants in the study cohort (n=1133).

Figure 4. Kaplan-Meier survival curves for wait-list mortality in infants according to their level of invasive hemodynamic support at the time of listing for heart transplant. Patients were censored at transplant. ECMO – Extra-corporeal membranous oxygenation.

Figure 5. Kaplan-Meier survival curves for wait-list mortality in infants, on neither extra-corporeal membranous oxygenation (ECMO) nor inotropic support, according to their listing diagnosis (n = 527). Patients were censored at transplant.
CHD – Congenital heart disease; CMP – Cardiomyopathy; PG – Prostaglandin infusion.

Table 1

Baseline Characteristics of Patients by Cardiac Diagnosis.

	All Infants (n=1133)		Congenital Heart Disease			CMP (n=349)	Other (n=60)	p value [‡]
	On PG (n=177)		Prior Surgery (n=195)	No prior Surgery (n=352)				
Age, mo [†]	1 [0 to 5]		2 [0 to 5]	0 [0 to 2]	4 [2 to 7]	2 [0 to 5]	<0.001	
Age categories							<0.001	
<1	495 (44%)	169 (95%)	67 (34%)	197 (56%)	39 (11%)	23 (38%)		
1–2	203 (18%)	7 (4%)	44 (23%)	72 (20%)	70 (20%)	10 (17%)		
3–5	205 (18%)	1 (1%)	36 (18%)	41 (12%)	113 (32%)	14 (23%)		
6–12	230 (20%)	0 (0%)	48 (25%)	42 (12%)	127 (36%)	13 (22%)		
Weight, kg [†]	4.0 [3.2 to 5.6]	3.2 [2.8 to 3.5]	4.1 [3.3 to 5.8]	3.6 [3.0 to 4.5]	5.0 [4.5 to 6.9]	4.5 [3.5 to 5.3]	<0.001	
Weight categories	n=1111	n=176	n=194	n=339	n=344	n=58	<0.001	
<3	179 (16%)	64 (36%)	23 (12%)	69 (20%)	18 (5%)	5 (9%)		
3–5	710 (64%)	112 (64%)	131 (68%)	238 (70%)	185 (54%)	44 (76%)		
6	222 (20%)	0 (0%)	40 (21%)	32 (9%)	141 (41%)	9 (16%)		
Female (%)	516 (46%)	70 (40%)	73 (37%)	147 (42%)	203 (58%)	23 (38%)	<0.001	
Non-white (%)	438 (39%)	60 (34%)	74 (38%)	136 (39%)	148 (42%)	20 (33%)	0.34	
Listing Status							0.01	
1A	910 (80%)	159 (90%)	155 (79%)	286 (81%)	263 (75%)	47 (78%)		
1B	114 (10%)	13 (7%)	17 (9%)	37 (11%)	40 (11%)	7 (12%)		
2	109 (10%)	5 (3%)	23 (12%)	29 (8%)	46 (13%)	6 (10%)		
Blood-type	n=1131	n=177	n=195	n=350	n=349	n=60	0.39	
A	391 (35%)	68 (38%)	73 (37%)	118 (34%)	115 (33%)	17 (28%)		
AB	43 (4%)	3 (2%)	6 (3%)	14 (4%)	20 (6%)	0 (0%)		
B	133 (12%)	21 (12%)	23 (12%)	40 (11%)	43 (12%)	6 (10%)		
O	564 (50%)	85 (48%)	93 (48%)	178 (51%)	171 (49%)	37 (62%)		
HD Support							<0.001	
ECMO	199 (18%)	3 (2%)	63 (32%)	86 (24%)	38 (11%)	9 (15%)		
Ventilator	377 (33%)	54 (31%)	53 (27%)	122 (35%)	127 (36%)	21 (35%)		
Other support	557 (49%)	120 (68%)	79 (41%)	144 (41%)	184 (53%)	30 (50%)		
Inotropic support	630 (56%)	49 (28%)	112 (57%)	201 (57%)	232 (66%)	36 (60%)	<0.001	

	All Infants (n=1133)	Congenital Heart Disease				p value [‡]
		On PG (n=177)	Prior Surgery (n=195)	No prior Surgery (n=352)	CMP (n=349)	Other (n=60)
Dialysis	24 (2%)	1 (1%)	10 (5%)	9 (3%)	4 (1%)	0 (0%)
Creatinine, mg/dL [†]	n=887	n=131	n=189	n=250	n=277	n=40
	0.5 [0.3 to 0.7]	0.6 [0.5 to 0.8]	0.5 [0.3 to 0.6]	0.6 [0.4 to 0.9]	0.4 [0.3 to 0.5]	0.4 [0.30 to 0.7]
						<0.001

Abbreviations: BSA, body surface area; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; HD, hemodynamic support; PG, prostaglandin-E infusion; UNOS, United Network for Organ Sharing.

^{*} Values represent number (percentage) of reported values unless otherwise indicated.

[†] Median [inter-quartile range].

[‡] Chi-squared test or Kruskal-Wallis test.

Table 2

Univariate Predictors of Wait-List Mortality.

Variable	Hazard Ratio	95% Confidence Interval	p Value
Age (vs 6–12 mo)			
< 1 mo	2.1	(1.5, 3.0)	<0.001
1–2 mo	1.7	(1.1, 2.6)	0.01
3–5 mo	1.0	(0.6, 1.5)	0.88
Weight (vs 6 kg)			
< 3 kg	2.4	(1.5, 3.6)	<0.001
3–5 kg	1.5	(1.1, 2.2)	0.02
Gender female	1.1	(0.8, 1.3)	0.69
Race non-white	1.5	(1.2, 1.9)	0.001
Listing Status (vs 2)			
1A	2.0	(1.3, 3.2)	0.004
1B	0.8	(0.4, 1.5)	0.42
Diagnosis (vs CMP)			
CHD/Prior Surgery	1.6	(1.0, 2.5)	0.05
CHD/PG	2.3	(1.5, 3.4)	<0.001
CHD/No Prior Surgery	3.1	(2.2, 4.4)	<0.001
Other	1.7	(0.9, 3.2)	0.09
Blood type (vs A)			
O	1.4	(1.0, 1.8)	0.03
B	1.3	(0.8, 2.0)	0.29
AB	1.2	(0.5, 2.6)	0.67
Prostaglandin support	1.2	(0.9, 1.6)	0.29
HD Support (vs other)			
ECMO	5.1	(3.7, 7.0)	<0.001
Ventilator	2.0	(1.5, 2.7)	<0.001
Inotropic support (vs not)	1.2	(0.9, 1.5)	0.24
Dialysis	1.9	(1.0, 3.8)	0.05
GFR (vs 50 ml/min/1.73 m ³)			
< 50 ml/min/1.73 m ³	1.8	(1.4, 2.4)	<0.001
Missing	1.5	(1.1, 2.1)	0.02
Year of listing (vs 2003–2006)			
1999–2002	1.0	(0.7, 1.2)	0.69
ABO incompatible listing	1.9	(1.3, 2.8)	0.001

Table 3

Multivariable Predictors of Wait-List Mortality.

Variable	<u>Adjusted Hazard Ratios (HR)</u>	
	HR (95% CI)	p Value
ECMO	5.6 (4.0–7.9)	<0.001
Ventilator	2.1 (1.6–2.8)	<0.001
CHD/PG	2.8 (1.8–4.3)	<0.001
CHD/No Prior Surgery	2.8 (1.9–3.9)	<0.001
Weight <3kg	1.4 (1.0–1.9)	0.04
Non-white race	1.8 (1.4–2.3)	<0.001

Table 4

Observed Wait-List Mortality for Infants According to Patient Characteristics.

	7-day	14-day	30-day	60-day	90-day	6-month	Overall
Cardiomyopathy (N=349)	3%	4%	8%	11%	11%	13%	13%
ECMO (n=38)	13%	18%	26%	29%	29%	29%	32%
Ventilator (n=127)	2%	2%	9%	11%	13%	14%	14%
Other support (n=184)	2%	3%	4%	7%	7%	8%	9%
Congenital Heart Disease (N=724)	6%	10%	16%	22%	23%	25%	26%
PG support (N=177)	5%	7%	14%	20%	21%	24%	26%
ECMO (n=3)	0%	0%	67%	67%	67%	67%	67%
Ventilator (n=54)	9%	13%	19%	20%	24%	28%	28%
Other support (n=120)	3%	5%	11%	18%	19%	22%	24%
No PG support (N=547)	6%	11%	17%	22%	24%	25%	26%
ECMO (n=149)	14%	22%	31%	36%	36%	36%	36%
Ventilator (n=175)	5%	11%	19%	28%	30%	31%	32%
Other support (n=223)	2%	4%	6%	9%	12%	14%	16%