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Waiting List Mortality Among Children Listed for Heart Transplantation in the United States

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Background—Children listed for heart transplantation face the highest waiting list mortality in solid-organ transplantation medicine. We examined waiting list mortality since the pediatric heart allocation system was revised in 1999 to determine whether the revised allocation system is prioritizing patients optimally and to identify specific high-risk populations that may benefit from emerging pediatric cardiac assist devices.

Methods and Results—We conducted a multicenter cohort study using the US Scientific Registry of Transplant Recipients. All children <18 years of age who were listed for a heart transplant between 1999 and 2006 were included. Among 3098 children, the median age was 2 years (interquartile range 0.3 to 12 years), and median weight was 12.3 kg (interquartile range 5 to 38 kg); 1294 (42%) were nonwhite; and 1874 (60%) were listed as status 1A (of whom 30% were ventilated and 18% were on extracorporeal membrane oxygenation). Overall, 533 (17%) died, 1943 (63%) received transplants, and 252 (8%) recovered; 370 (12%) remained listed. Multivariate predictors of waiting list mortality include extracorporeal membrane oxygenation support (hazard ratio [HR] 3.1, 95% confidence interval [CI] 2.4 to 3.9), ventilator support (HR 1.9, 95% CI 1.6 to 2.4), listing status 1A (HR 2.2, 95% CI 1.7 to 2.7), congenital heart disease (HR 2.2, 95% CI 1.8 to 2.6), dialysis support (HR 1.9, 95% CI 1.2 to 3.0), and nonwhite race/ethnicity (HR 1.7, 95% CI 1.4 to 2.0).

Conclusions—US waiting list mortality for pediatric heart transplantation remains unacceptably high in the current era. Specific high-risk subgroups can be identified that may benefit from emerging pediatric cardiac assist technologies. The current pediatric heart-allocation system captures medical urgency poorly. Further research is needed to define the optimal organ-allocation system for pediatric heart transplantation. (***Circulation.* 2009;119:717-727.**)

Key Words: pediatrics ■ transplantation, heart ■ heart failure ■ survival ■ heart-assist devices

Of all patients wait-listed for solid-organ transplantation in the United Sates, children listed for heart transplantation face the highest waiting list mortality regardless of age.[1] To address this problem, in 1999, the United Network for Organ Sharing (UNOS) implemented a major change in the way donor hearts were allocated by assigning higher priority to sicker status 1 patients[2] (ie, status 1A patients as determined by circulatory support requirements) who were less likely to survive a prolonged wait period. Over the same timeframe, after the landmark study by West and colleagues in 2001,[3] the practice of listing infants across all blood types has increased steadily, a development that has the potential to shorten wait times for infant candidates considerably.[3,4]

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The collective impact of these changes on present-day waiting list mortality is unknown, in large part because earlier studies were conducted primarily in the 1990s, before changes in organ-allocation practice occurred.[5–12] In addition, earlier studies were limited by smaller sample sizes or single-institution experiences,[9,10,12,13] the findings of which may not be generalizable owing to regional differences in practice or may be underpowered to detect important national trends. A contemporary analysis of the primary risk factors associated with waiting list mortality that included all US patients would be useful for 3 specific reasons: (1) To help policy makers determine whether the current organ-allocation

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The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the Scientific Registry of Transplant Recipients or the US government.

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Table 1. Characteristics of Patients by Cardiac Diagnosis

Variables	CHD (n=1494)	Myocarditis (n=178)	Cardiomyopathy (n=1186)	Other (n=240)	Total (n=3098)	P*
Age, y	1 (0–7)	4 (1–12)	6 (0.8–13)	8 (0.9–14)	2 (0.3–12)	<0.001
Weight, kg	8.2 (3.5–22.3)	16 (9.1–44.9)	18.8 (7.6–49.5)	28.2 (8.2–50.4)	12.3 (5.1–37.6)	<0.001
Body surface area, m^2	0.42 (0.23–0.87)	0.72 (0.44–1.4)	0.78 (0.39–1.5)	1.0 (0.41–1.5)	0.57 (0.3–1.26)	<0.001
Female, %	39	49	49	42	44	<0.001
Nonwhite race, %	37	50	47	38	42	<0.001
UNOS listing status, %						<0.001
1A	63	77	56	59	60	
1B	12	11	15	15	13	
2	25	12	29	26	26	
Blood type, %						0.80
A	37	38	33	34	35	
AB	4	5	4	4	4	
B	11	10	12	11	11	
O	49	47	50	51	49	
Prostaglandin support, %	12	0	<1	2	6	<0.001
Invasive hemodynamic support, %						<0.001
ECMO support	23	28	11	16	18	
Ventilator support	31	31	29	33	30	
Other support (1A)	46	41	60	51	51	
Inotropic support	46	69	54	53	51	<0.001
Dialysis	2	2	1	2	2	0.46
Creatinine, mg/dL	0.6 (0.4 to 0.8)	0.6 (0.4 to 0.9)	0.6 (0.4 to 0.8)	0.7 (0.4 to 1.0)	0.6 (0.4 to 0.8)	<0.001

Values represent median (IQR) or percentage.
*χ^2 Test or Kruskal-Wallis test.

system is serving children with end-stage heart disease optimally, (2) to better define specific high-risk populations that may benefit from emerging mechanical circulatory support technologies, and (3) to determine more precisely where the national organ shortage for pediatric donor hearts is most critical (especially with respect to age and size) as part of a nationwide effort to establish pediatric-specific organ-donation goals.

Methods

Study Population and Data Source

All pediatric subjects less than 18 years of age who were listed for first orthotopic heart transplantation in the United States between January 20, 1999, and July 12, 2006, were identified retrospectively through the US Scientific Registry of Transplant Recipients. The Scientific Registry of Transplant Recipients is an internally audited, mandatory, government-sponsored, solid-organ transplant registry that collects information on all solid-organ transplants in the United States. Demographic and clinical information is reported by transplanting centers to the Organ Procurement and Transplantation Network, supplemented by data from the Social Security Administration and the Center for Medicare and Medicaid Services. January 20, 1999, marks the point in time at which status 1 patients were subdivided into status 1A and status 1B patients. July 12, 2006, marks the point in time at which older status 1A children within 500 miles were given priority over status 1B children within the region. Patients listed for heart retransplantation or multivisceral transplants were excluded. All patients were followed up from the time of listing for heart transplantation until death or the day of last observation on August 3, 2007.

Study Definitions and Outcome Measures

The primary study hypothesis was that among children listed for orthotopic heart transplantation, mechanical ventilation is associated with reduced waiting list survival after adjustment for other patient factors. Time on the waiting list was defined as time from initial listing for heart transplantation to the time of waiting list removal due to transplant, death, or recovery. Subjects who died were considered to have reached the primary end point (ie, had an event). Subjects were censored at the time of transplantation or recovery. All other subjects who remained on the waiting list were censored on August 3, 2007. All clinical and demographic variables were defined at the time of listing for heart transplant unless otherwise specified. Race/ethnicity data (categories included black, white, Hispanic, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, multiracial, and other) were analyzed as reported by the transplanting center. Glomerular filtration rate was estimated with the Schwartz formula.[14]

Statistical Analysis

Summary statistics are presented as median (interquartile range [IQR]) or number (percent). Patient characteristics were compared across cardiac diagnostic subgroups with the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Survival time on the waiting list was estimated by the Kaplan-Meier method. Univariate relationships between patient characteristics and waiting list mortality were evaluated with the log-rank test. Multivariable analysis was performed with the Cox proportional hazards model and a stepwise selection technique. Only risk factors that were statistically significant at the 0.05 level were retained in the final multivariable models. These models were then reevaluated with control for UNOS region. Analyses were performed with SAS version 9.1 and Stata version 10.0.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Cohort

Of 3416 pediatric patients listed for heart transplant during the study period, 3098 met the inclusion criteria (308 were excluded owing to heart retransplantation and 10 owing to multivisceral transplantation). The baseline characteristics of the study cohort are summarized in Table 1. Of 3098 children listed for first orthotopic heart transplant, the median age was 2 years (IQR 0.3 to 12 years), and the median weight was 12.3 kg (IQR 5 to 38 kg); 1359 (44%) were female, and 1294 (42%) were nonwhite. The primary cardiac diagnosis that led to heart transplant listing was congenital heart disease (CHD) in 1494 (48%), cardiomyopathy in 1186 (38%), and myocarditis in 178 (6%).

Overall, 1874 children (60%) were listed as status 1A, 418 (13%) as status 1B, and 806 (26%) as status 2. Among children listed as status 1A, 570 (30%) were supported with mechanical ventilation, 346 (18%) were supported by extracorporeal membrane oxygenation (ECMO), and 958 (51%) did not receive either type of support. Overall, children listed because of CHD were younger ($P<0.001$) and smaller ($P<0.001$ for both weight and body surface area) than children listed because of cardiomyopathy or myocarditis. Children with cardiomyopathy were less likely to be supported with ECMO or mechanical ventilation than children with CHD or myocarditis ($P<0.001$).

Survival

Among 3098 children listed for heart transplants, 533 (17%) died, 1943 (63%) received a transplant, 252 (8%) were removed from the waiting list because of recovery, and 370 (12%) remained alive on the waiting list on August 3, 2007. Table 2 summarizes the univariate predictors of waiting list mortality.

Table 3 summarizes the multivariable predictors of waiting list mortality. Among all children listed, independent predictors of waiting list mortality included ECMO support, ventilator support, CHD, listing status 1A, dialysis support, and nonwhite race. A glomerular filtration rate <50 mL · min^{-1} · 1.73 m^{-2} was also found to be an independent predictor of mortality but was collinear with dialysis and thus was not included in the final model. Age, weight, and body surface area were not statistically significant predictors of waiting list mortality after adjustment for other covariates in the model. All of the variables in the final model remained statistically significant after adjustment for region and year of transplantation.

Because a large majority of the 533 deaths occurred among children listed as status 1A, we performed a secondary analysis to determine the risk factors associated with mortality among children listed as status 1A (Table 3). Except for listing year (1999 to 2002 versus 2003 to 2006), which became significant in the 1A subgroup analysis, the multivariate predictors, hazard ratios, and 95% confidence intervals were essentially unchanged compared with the overall analysis.

Table 2. Univariate Predictors of Waiting List Mortality

	Univariate Predictors		
Variable	Survived (n=2565)	Died (n=533)	P*
Age, y	3 (0.3–12)	1 (0.1–8)	
Weight, kg	13.4 (5.5–39.5)	8.8 (3.7–24.8)	
Weight categories			<0.001
<10 kg	42	54	
10–19 kg	17	17	
20–39 kg	16	12	
40–59 kg	14	8	
≥60 kg	11	9	
Female	44	44	0.74
Nonwhite race	40	51	<0.001
UNOS listing status			<0.001
1A	58	74	
1B	15	8	
2	28	18	
Cardiac diagnosis, %			<0.001
CHD	45	64	
Cardiomyopathy	41	23	
Myocarditis	6	5	
Other	8	8	
Blood type			0.10
A	37	27	
O	48	57	
B	11	11	
AB	4	4	
Prostaglandin support	6	9	<0.001
Invasive hemodynamic support			<0.001
ECMO support	16	28	
Ventilator support	29	37	
Other support (1A)	55	36	
Inotropic support	50	57	<0.001
Dialysis	1	4	<0.001
Creatinine, mg/dL	0.6 (0.4–0.8)	0.6 [0.4–0.9]	
GFR <50 mL · min^{-1}1.73 m^{-2}	17	33	<0.001
Year of listing			0.24
1999–2002	52	58	
2003–2006	48	42	

Values represent median (IQR) or percentage. GFR indicates glomerular filtration rate.
*Log-rank test.

Figure 1 shows the estimated survival for all children listed for heart transplant according to UNOS listing status (Figure 1A) and for all children listed as status 1A according to the level of invasive hemodynamic support (Figure 1B). No appreciable difference was found in overall waiting list mortality for patients listed as status 2 versus status 1B (11.7% versus 10.5%). By contrast, among patients listed as

Table 3. Multivariate Predictors of Waiting List Mortality*

	Adjusted HRs			
	All Patients		Status 1A Only	
Variable	HR (95% CI)	P	HR (95% CI)	P
ECMO	3.1 (2.4–3.9)	<0.001	3.0 (2.3–3.8)	<0.001
Ventilator support	1.9 (1.6–2.4)	<0.001	1.9 (1.5–2.4)	<0.001
Cardiac diagnosis of CHD	2.2 (1.8–2.6)	<0.001	2.1 (1.7–2.6)	<0.001
Dialysis	1.9 (1.2–3.0)	0.006	2.0 (1.3–3.2)	0.004
UNOS listing status 1A	2.2 (1.7–2.7)	<0.001	...	
Nonwhite race, %	1.7 (1.4–2.0)	<0.001	1.7 (1.4–2.0)	<0.001
Year of listing 1999–2002			1.2 (1.0–1.5)	0.040

*Cox proportional hazards model.

status 1A, a substantial difference was found in risk of waiting list mortality based on the level of invasive hemodynamic support (ie, required ECMO, mechanical ventilation, or neither).

Status 1A Risk Stratification

Table 4 summarizes the observed waiting list mortality of status 1A patients with risk stratification by subgroup. Among children listed as UNOS status 1A, a 7-fold difference was found in the 90-day risk of death on the waiting list on the basis of patient characteristics, with a range from 5% to 39%. The 14- and 30-day waiting list mortality variation for patients listed as status 1A was even more striking. For example, a child weighing <10 kg who was supported on ECMO for CHD (n=155) had a 12-fold higher risk of death by 14 days without transplantation (20.7% versus 1.5%) and an 8-fold higher risk of death by 30 days without transplantation (32% versus 4%) than a child weighing >10 kg with cardiomyopathy who was supported with inotropes alone (n=263). Figure 2 shows the competing outcomes for waitlisted children based on UNOS status at the time of listing and competing outcomes for children listed as status 1A according to their level of invasive hemodynamic support.

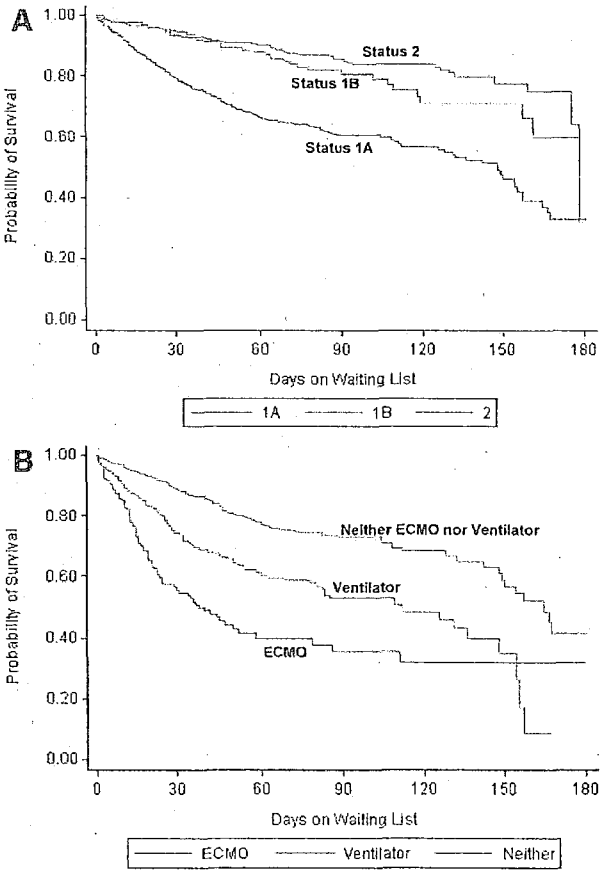

Figure 1. Kaplan-Meier survival for all children listed for heart transplant according to listing status (A) and for those children listed as status 1A according to invasive hemodynamic support (B).

Among those listed as status 1A, the following subgroups of children were found to be at 30% or greater risk of waiting list mortality based on observed mortality (Table 4): (1) Children weighing <10 kg who were listed because of CHD and who required mechanical ventilation (mortality 32%, n=231), and (2) children weighing <10 kg who were listed because of CHD and who required ECMO (mortality 36.1%, n=155). Children with a predicted risk of waiting list mortality of ≥20% included most children listed as status 1A for CHD and most children who required either mechanical ventilation (waiting list mortality 25%, n=570) or ECMO (waiting list mortality 31.5%, n=346).

Figure 3 summarizes the weight distribution of children who died while on the waiting list in the current era. Overall, 10% of patients weighed <3 kg, 34% weighed <5 kg, 54% weighed <10 kg, 64% weighed <15 kg, and 71% weighed <20 kg.

Discussion

In this study, we found that over a 6-year period, 533 US children with severe heart failure died while on the heart transplant waiting list before a suitable donor heart could be identified. Expressed as a rate, children awaiting heart transplantation experience the single highest waiting list mortality compared with all other age groups and all other solid organs in transplant medicine.[1] Although the average status 1A pediatric patient is at higher risk of waiting list mortality statistically, status 1A patients as a group represent a large and heterogeneous population whose risk of waiting list

Table 4. Risk Stratification of Status 1A Candidates Based on Observed Waiting List Mortality for Patient Subgroups

	7 Days	14 Days*	30 Days	60 Days	90 Days	6 Months	Overall
All status 1A candidates (n=1874)	4.9	8.5	13.7	18.0	18.9	20.3	21.1
ECMO (n=346)	10.1	17.9	25.7	29.8	30.4	30.6	31.5
Cardiomyopathy	5.7	11.4	15.7	21.4	21.4	21.4	24.3
Weight ≥10 kg (n=34)	0	8.8	14.7	23.5	23.5	23.5	26.5
Weight <10 kg (n=36)	11.1	13.9	16.7	19.4	19.4	19.4	22.2
Myocarditis	7.7	12.8	20.5	23.1	23.1	25.6	25.6
Weight ≥10 kg (n=26)	3.9	7.7	15.4	15.4	15.4	19.2	19.2
Weight <10 kg (n=13)	15.4	23.1	30.8	38.5	38.5	38.5	38.5
CHD	11.2	19.6	28.5	32.7	33.6	33.6	33.6
Weight ≥10 kg (n=56)	5.4	14.3	17.9	21.4	25.0	25.0	25.0
Weight <10 kg (n=155)	13.6	20.7	31.6	36.1	36.1	36.1	36.1
Mechanical ventilation (n=570)	6.0	10.4	17.0	22.1	23.5	25.1	25.4
Cardiomyopathy	4.6	8.3	16.0	17.0	18.0	19.6	19.6
Weight ≥10 kg (n=69)	10.1	17.4	27.5	29.0	29.0	29.0	29.0
<10 kg (n=122)	1.6	3.3	9.0	9.8	11.5	13.9	13.9
Myocarditis	2.4	7.1	7.1	9.5	9.5	9.5	11.5
Weight ≥10 kg (n=20)	5.0	15.0	15.0	15.0	15.0	15.0	20.0
<10 kg (n=22)	0	0	0	4.6	4.6	4.6	4.6
CHD	7.3	12.5	19.8	27.4	29.2	30.9	31.3
Weight ≥10 kg (n=55)	9.1	14.6	16.4	25.5	27.3	27.3	27.3
Weight <10 kg (n=231)	6.9	12.1	20.4	27.7	29.4	31.6	32.0
No ventilation or ECMO (n=958)	2.3	4.1	7.4	11.3	12.1	13.8	14.7
Cardiomyopathy	1.3	2.3	4.3	6.3	6.8	7.1	7.6
Weight ≥10 kg (n=263)	0.8	1.5	3.8	4.9	5.7	5.7	6.1
Weight <10 kg (n=127)	2.4	3.9	5.5	9.5	9.5	10.2	11.0
Myocarditis	1.8	3.6	7.1	10.7	10.7	12.5	14.3
Weight ≥10 kg (n=45)	2.2	4.4	6.7	11.1	11.1	13.3	15.6
Weight <10 kg (n=10)	0	0	10.0	10.0	10.0	10.0	10.0
CHD	3.5	5.8	10.8	16.6	18.0	21.0	22.1
Weight <10 kg, *no* PGE (n=159)	1.9	4.4	8.2	12.6	14.5	16.4	17.0
Weight ≥10 kg (n=161)	4.4	6.8	13.0	18.6	19.9	24.2	24.8
Weight <10 kg, PGE (n=107)	3.7	5.6	11.2	19.6	20.6	23.4	26.2

Values represent percentage of eligible patients who were removed from the waiting list due to death during the specified time frame. PGE indicates prostaglandin E infusion.

*14 Days is the standardized time interval for status 1A justification by UNOS.

mortality varies by as much as 10-fold or more based on patient-specific factors. The single most important patient factor predictive of waiting list mortality is the level of invasive hemodynamic support, as defined by ECMO versus mechanical ventilation versus inotropic support alone. Other patient factors associated with waiting list mortality include cardiac diagnosis, dialysis, and nonwhite race/ethnicity.

These findings are consistent with earlier reports from the 1990s that found that ECMO, former listing as status 1 (predecessor of the 1A/1B classification system), and CHD were associated with waiting list mortality in children[5–7,9,10,13]; however, no studies have analyzed waiting list outcomes since the pediatric heart-allocation system was revised in 1999. Consequently, the present report has 2 advantages over earlier reports in that (1) it analyzes outcomes since 1999, which permits a focused look at waiting list mortality under the present allocation system and practice conditions, and (2) it captures all children officially listed for a heart transplant in the United States, which provides the necessary statistical power to identify several important national trends for the first time. Specifically, this is the first published report (1) to identify nonwhite race and mechanical ventilation as powerful independent risk factors for waiting list mortality across the pediatric age spectrum, (2) to describe the striking variability in waiting list mortality observed among children listed as status 1A, and (3) to exclude blood type as an independent factor associated with waiting list mortality in the current era.

Our finding that the level of invasive hemodynamic support (ie, ECMO support versus mechanical ventilation

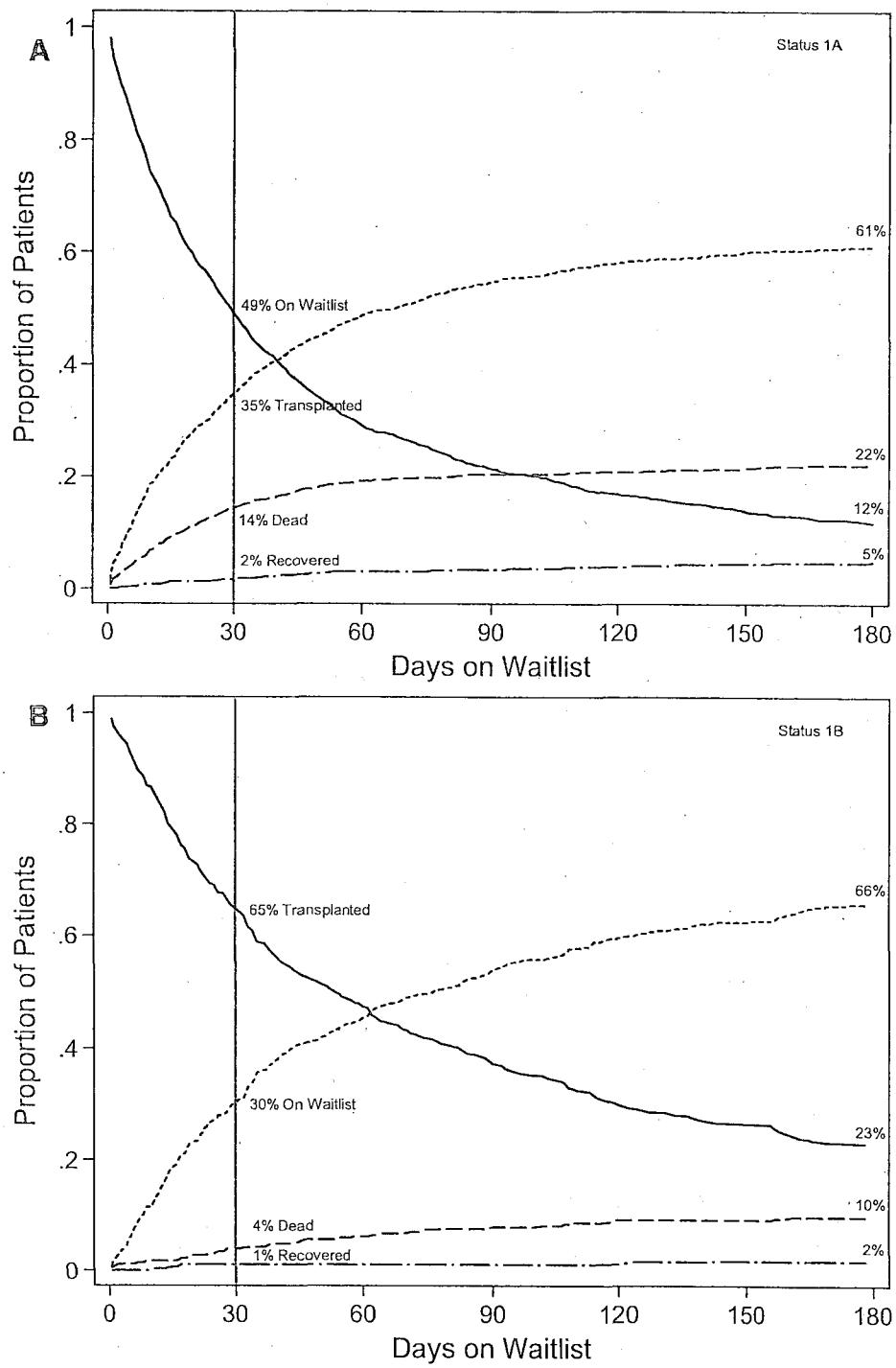

Figure 2. Competing outcomes for wait-listed children according to UNOS status at the time of listing (A, B, and C), and for children listed as status 1A according to their level of invasive hemodynamic support: ECMO (D), mechanical ventilation (E), and neither ECMO nor mechanical ventilation (F).

versus inotropic support alone) is associated with waiting list survival is reasonably intuitive; however, we were surprised at the magnitude of effect, specifically, that the level of invasive hemodynamic support appears to be a much stronger predictor of waiting list mortality and therefore a more accurate reflection of medical urgency than UNOS listing status itself, the current system used to categorize children according to medical urgency.[2,15] We believe the relatively poor correlation between UNOS listing status and medical urgency in pediatrics stems largely from the heterogeneity of the status 1A patient cohort resulting in greater waiting list mortality variability within UNOS listing groups than between listing groups. This heterogeneity is likely driven by 2 factors: (1) Greater numbers of high-risk children are listed as status 1A because of more widespread use of technologies like

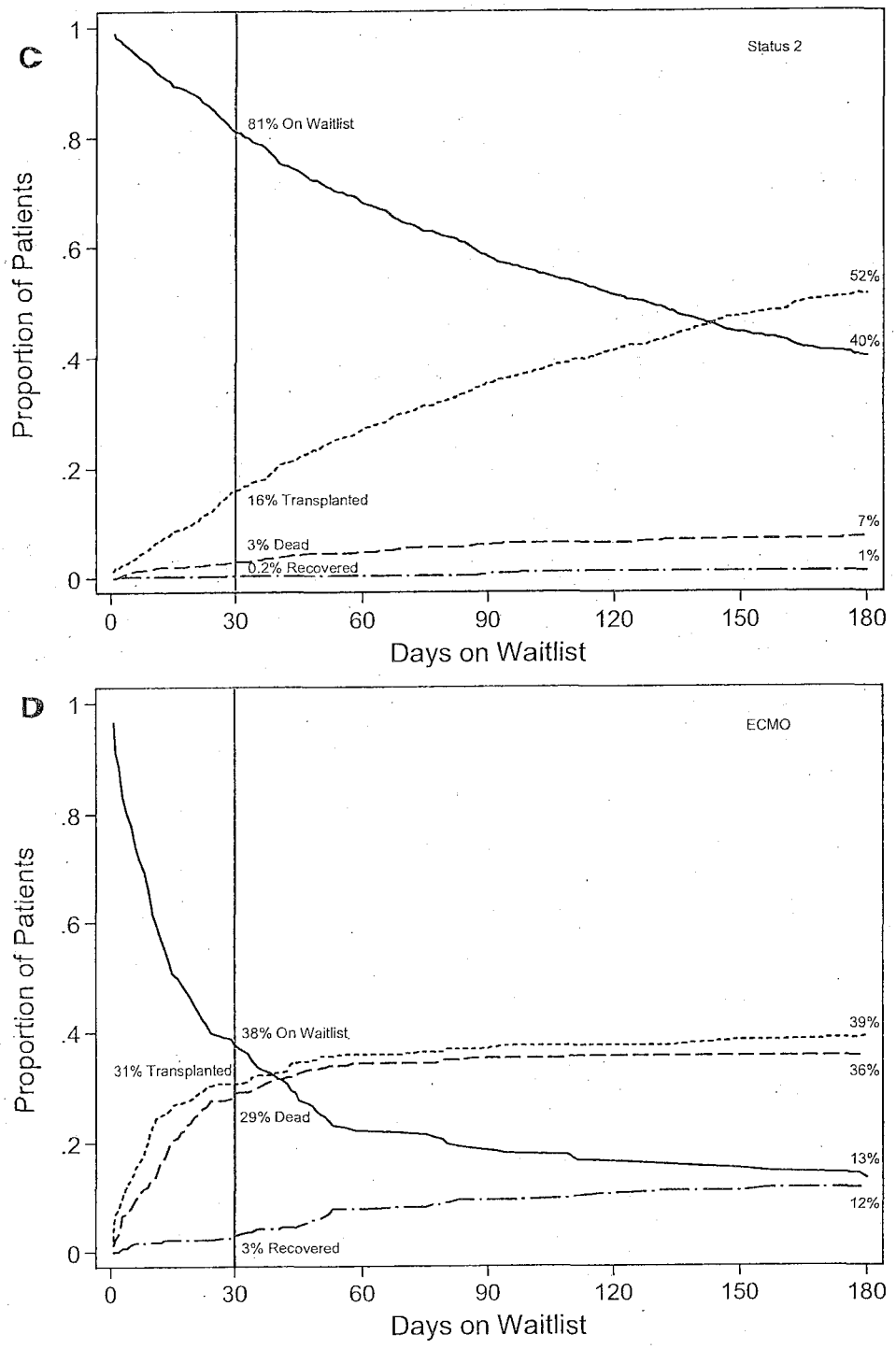

Figure 2 (Continued).

ECMO[16] in pediatrics, combined with fewer absolute contraindications to transplant,[17] and (2) greater numbers of low-risk patients are listed as status 1A because of less stringent status 1A criteria for children. (*NB*: Adult status 1A criteria generally necessitate pulmonary artery catheter placement, whereas pediatric status 1A criteria can be met with as little as minor dosing adjustments in intravenous medications.) It is likely that the less stringent status 1A criteria in pediatrics are largely responsible for the disproportionately large number of children who qualify for the highest tier of medical urgency (>60% of children at the time of listing and nearly three quarters [72%] by the time of transplantation).

The findings of the present study have several implications. First, our findings raise questions about whether the current allocation system is structured optimally to reduce pediatric transplant mortality. Because the current system captures medical urgency poorly, children facing markedly

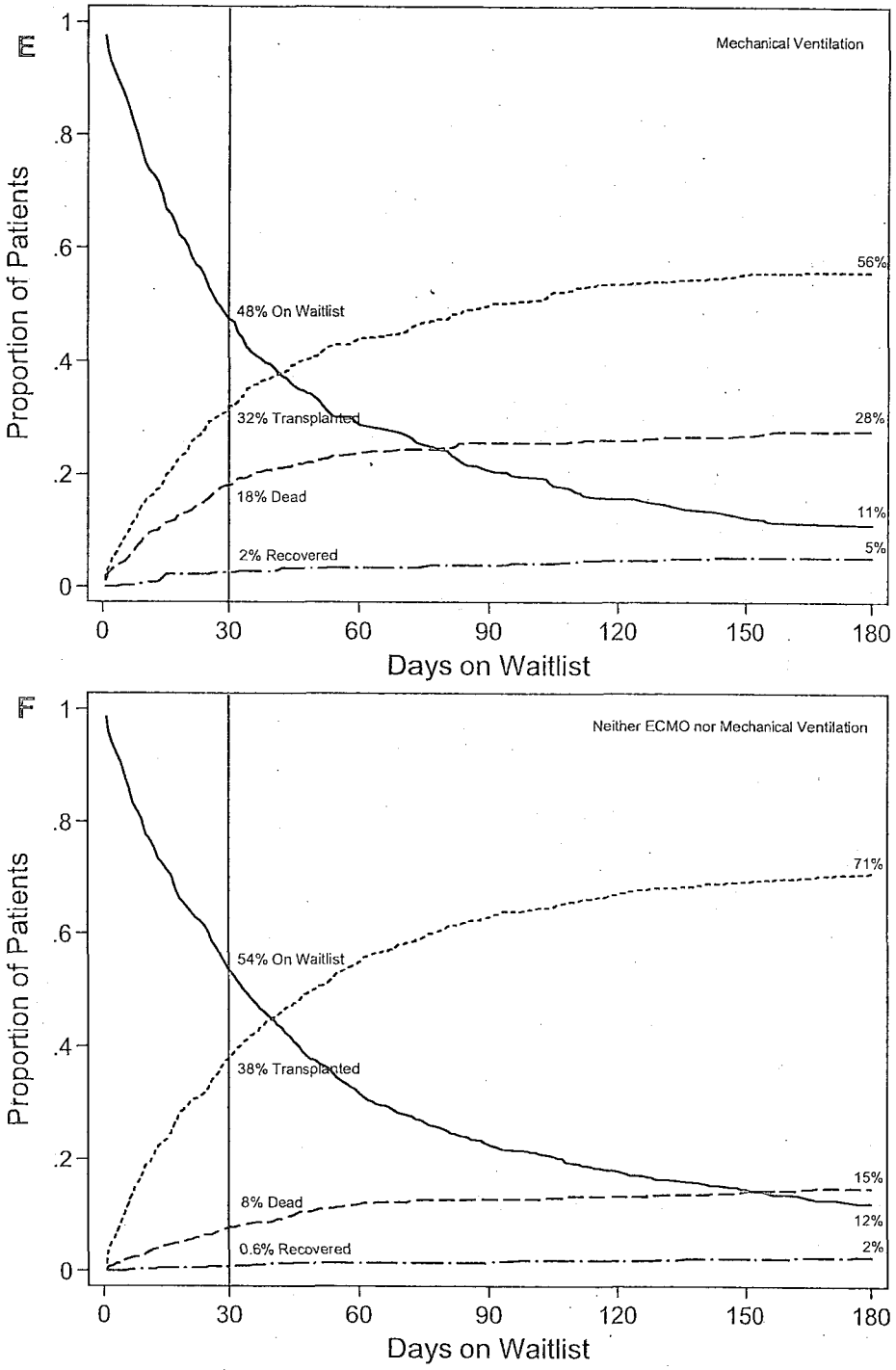

Figure 2 (Continued).

different short-term mortality risks are forced to compete directly for the same scarce donor organs. For example, under the current system, a child actively listed for heart transplant who is on ECMO support with days to live must compete directly with a child being supported by inotropes alone, who, according to our data, has a relatively low imminent risk of death. Consequently, an available heart is offered first to the child who has accumulated more status 1A wait time, rather than to the child who is likely to die without transplant. Ultimately, because the majority of pediatric patients and virtually all at-risk pediatric patients are listed as status 1A, "first come, first served" has functionally supplanted medical urgency as the primary determinant of pediatric donor heart allocation for the majority of children awaiting heart transplantation.

The discrepancy between medical urgency and waiting list seniority, a major problem in solid-organ transplantation historically, raises the possibility that some pediatric deaths

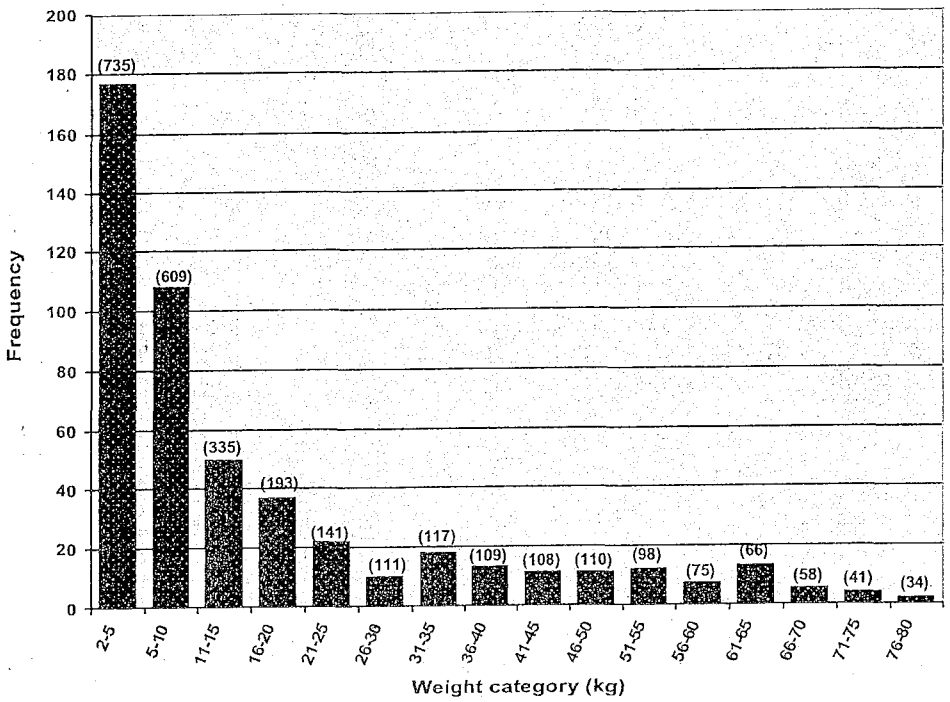

Figure 3. Number of children who died while on the waiting list according to weight at listing (n=533). The numbers above each bar denote the total number of children who were listed for heart transplant within each weight category.

could be prevented by moving away from an allocation system that relies heavily on waiting time toward an allocation system that better reflects medical urgency while also incorporating potential transplant benefit. Such a shift would be consistent with the Final Rule on Organ Allocation published by the US Department of Health and Human Services,[15] which discourages the use of waiting time as a criterion for organ allocation and encourages organ sharing based on medical urgency (while avoiding futile transplantations) with the use of objective medical criteria that cannot be manipulated by patients or physicians. Accordingly, the US allocation systems for liver and lung allografts[18–23] have undergone major revisions recently to bring them into compliance with contemporary standards. We believe a similar reappraisal is warranted for pediatric hearts, not only because of the excessively high waiting list mortality[1] but also because of better data on the factors that drive pretransplantation and posttransplantation attrition.[24,25] Because some factors such as ECMO may be associated with both pretransplantation[5–7,9,10] and posttransplantation[24,25] mortality, revising the current system will require complex simulation analyses to balance competing risks, as has been done successfully with the lung-allocation score recently.[26]

Second, the present findings suggest that specific high-risk subgroups of patients can be identified who may be suitable candidates for emerging pediatric mechanical support devices. By the same token, our findings suggest that low-risk subgroups can also be identified for whom investigational devices should generally not be used at the present time. Because of this heterogeneity, clinicians and investigators will need to use caution in selecting patients for evolving mechanical circulatory support devices[26,27] and in developing selection criteria for clinical trials to obtain regulatory approval.[28,29] For example, patients with an estimated waiting list mortality of less than 10% (eg, stable children with cardiomyopathy who are on inotropes) are unlikely to benefit from device therapy if the device itself carries a risk that could be higher. The use of such devices in such patients could not only expose children to unnecessary risks but could also undermine the interpretability of data in support of a regulatory claim of efficacy or probable benefit, the legal threshold for Food and Drug Administration approval in the United States.

Third, although age and size were not independently associated with waiting list mortality, the present findings indicate that the vast majority of children dying while on the waiting list weigh <10 to 15 kg (Figure 3). The skewed weight distribution draws needed attention to precisely where the national organ shortage for pediatric donor hearts is most critical: among infants and toddlers. Creating greater public awareness is a key first step for organ-donation advocates who are looking for high-impact strategies to reduce pediatric waiting list mortality.[30] Although it would be beneficial to improve organ donation among children of all ages and sizes, the present findings suggest that the greatest benefit would come from a successful campaign to increase organ donation among infants and toddlers. The disproportionate number of deaths among infants and toddlers further underscores the need to develop reliable miniaturized mechanical circulatory support devices for infants and smaller children,[26,27] similar to the approved ventricular assist devices that are widely available for larger children and adults.[31–34]

We were surprised to find that nonwhite race/ethnicity was associated with waiting list mortality, particularly among

children listed as status 1A, a group that is uniformly hospitalized and usually under the watchful eye of intensivists. Contributing factors may include differences in timing of presentation, access to care, delivery of medical treatment, disease progression, regional heterogeneity, misclassification of race/ethnicity by centers, or some combination thereof. Adult studies of waiting list mortality have reported mixed findings on the relationship between race/ethnicity and waiting list mortality.[13,35] Further research is needed to explore the effect of race/ethnicity on waiting list mortality in transplant candidates across all ages.

The findings of the present study should be interpreted within the context of the study design. First, the analysis did not account for changes in listing status while patients were on the waiting list; however, changes in status would be expected to result in misclassification of risk factor assignment, which would lead to an underestimate of the true effects of a given risk factor, which in this analysis were all highly significant. Second, the primary analysis did not account for patients who were removed from the waiting list because of clinical deterioration rather than death; however, secondary analyses using the combined outcome of death or delisting due to clinical deterioration yielded similar results. Lastly, all retrospective studies are inherently susceptible to selection bias that could skew findings if a nonrandom population of patients were selected for analysis; however, because the Scientific Registry of Transplant Recipients captures all patients officially listed for transplant in the United States, it is unlikely that patient selection bias would play a major role in the findings of this retrospective analysis.

In summary, despite improvements in pediatric heart allocation over the past decade, pediatric heart transplant waiting list mortality remains unacceptably high in the current era and is an outlier in transplant medicine. The current pediatric heart-allocation system captures medical urgency poorly, which raises the possibility that the current allocation system may not be prioritizing scarce donor hearts optimally. Although status 1A patients are at higher risk of waiting list mortality statistically, status 1A patients as a group represent a large and heterogeneous population. Independent risk factors for waiting list mortality can be used to risk-stratify children, which can help facilitate patient selection of emerging pediatric cardiac assist devices and guide pediatric donor allocation in a manner that is consistent with contemporary organ-allocation standards. Lastly, most children who die while on the waiting list are those who weigh <10 kg, which underscores the tremendous need for reliable pediatric mechanical support devices for the smallest children. Targeted efforts to expand infant donation through expanded neonatal intensive care unit donation or more widespread acceptance of donation after cardiac death[36] are urgently needed.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Despite improvements in pediatric heart allocation over the past decade, children listed for heart transplantation face the highest waiting list mortality in solid-organ transplant medicine. Data on waiting list outcomes since the pediatric heart-allocation system was revised in 1999 are limited. This study examines waiting list outcomes from all 3098 children <18 years of age listed in the United States for primary heart transplant during the period from 1999 to 2006. Overall, 533 children (17%) died, whereas 63% received transplants and 8% recovered. Although status 1A patients were at higher risk of waiting list mortality than status 1B or status 2 patients, waiting list mortality varied by a greater degree within status 1A and was best predicted by the level of invasive hemodynamic support (defined as extracorporeal membrane oxygenation versus ventilator versus neither). The study thus demonstrates that the current pediatric heart-allocation system captures medical urgency among those waiting for a heart poorly. Because patients on a higher level of invasive support at listing may also be at higher risk of posttransplantation death, further research is needed to determine what changes in the current pediatric allocation system will reduce overall (pretransplantation and posttransplantation) mortality in children listed for a heart transplant. Lastly, the study demonstrates that the vast majority of children who die on the waiting list weigh <10 to 15 kg, which underscores the need to develop and refine new technologies to support the smallest children with advanced heart failure and to expand opportunities for infant organ donation.