JACC: HEART FAILURE
VOL. 3, NO. 1, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2014.07.011

Delineating Survival Outcomes in Children <10 kg Bridged to Transplant or Recovery With the Berlin Heart EXCOR Ventricular Assist Device

Jennifer Conway, MD,* James St. Louis, MD,† David L.S. Morales, MD,‡ Sabrina Law, MD,§ Christine Tjossem, BS,‖ Tilman Humpl, MD*

ABSTRACT

OBJECTIVES The goal of this study was to delineate outcomes of children weighing <10 kg supported with the Berlin Heart EXCOR Pediatric Ventricular Assist Device (EXCOR Pediatric, Berlin Heart Inc., The Woodlands, Texas) and to identify factors that increased the risk of all-cause mortality in this population.

BACKGROUND Ventricular assist devices have been shown to be an effective bridge to transplant, with improved outcomes compared with use of extracorporeal membrane oxygenation. Smaller patients may be at greatest risk for poor outcomes, but it remains unclear if mortality is uniform across all smaller candidates.

METHODS Patients included in the analysis were part of a multicenter prospective cohort study examining the use of the Berlin Heart EXCOR Pediatric Ventricular Assist Device as a bridge to transplant. All children who received the device between May 9, 2007 and December 31, 2010, and who were enrolled in the sponsor's U.S. regulatory database, were identified and analyzed. Multivariable analysis was performed to determine risk factors associated with mortality.

RESULTS A total of 97 children weighing <10 kg were included (median age 6.2 months; median weight 6.2 kg; median duration of support 26 days). Successful outcomes were achieved in 56.7% of patients. Independent risk factors for mortality in smaller children included pre-existing congenital heart disease (odds ratio: 4.8 [95% confidence interval: 1.5 to 15.0]; $p = 0.007$) and an elevated bilirubin level (odds ratio: 5.3 [95% confidence interval: 2.0 to 14.3]; $p = 0.001$).

CONCLUSIONS Overall results for children weighing <10 kg were inferior to those of their larger counterparts. This outcome was primarily influenced by congenital heart disease and presence of elevated pre-implant bilirubin levels. These factors should be taken into consideration at decision making because reasonable outcomes can be achieved in a select population of children weighing <10 kg. (J Am Coll Cardiol HF 2015;3:70–7) © 2015 by the American College of Cardiology Foundation.

Cardiac transplantation is a well-established approach for end-stage heart failure from cardiomyopathies and some forms of congenital heart disease (CHD) in the pediatric population. However, infants remain at the highest risk for death while on the waitlist (1). Strategies to support infants safely to transplant have included both medical and device therapy. Traditionally, extracorporeal membrane oxygenation (ECMO) has been the predominant support strategy, but its use remains limited due to the ongoing risk of complications and associated mortality (2,3). The mortality burden

From *The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; †University of Minnesota, Amplatz Children's Hospital, Minneapolis, Minnesota; ‡Cincinnati Children's Hospital, Cincinnati, Ohio; §Seattle Children's Hospital, Seattle, Washington; and ‖Berlin Heart Inc., The Woodlands, Texas. Dr. Morales has served on the medical advisory board for Cormatrix; has served as a proctor for TAH for SynCardia; was a member of the clinical events committee for Berlin Heart; and has served as an advisor for Thoratec and HeartWare. For all services, the companies paid for Dr. Morales's travel, but no personal monies were paid. Dr. Tjossem is an employee of Berlin Heart Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 4, 2014; revised manuscript received July 17, 2014, accepted July 28, 2014.

reported with ECMO is not evenly distributed across the age spectrum, with those patients weighing <10 kg, especially in the context of CHD, being at greatest risk (1,2,4). Alternatively, ventricular assist devices (VADs) have been shown to be an effective bridge to transplant with improved outcomes compared with ECMO (2,3,5-10). Similar to experiences seen with support on ECMO, smaller patients (<10 kg) may be at the greatest risk for severe complications and mortality on VAD support (8,11,12); these findings, however, have not been consistent (13,14). Currently, it remains unclear if mortality risk is uniform across all smaller candidates or if there are identifiable risk factors that may guide patient selection to improve overall survival and reduce associated complications in these smaller patients.

The primary aim of the present analysis was to delineate the survival outcomes of children weighing <10 kg supported with the Berlin Heart EXCOR Pediatric Ventricular Assist Device (EXCOR Pediatric, Berlin Heart Inc., The Woodlands, Texas) and to identify factors that increased the risk of all-cause mortality in this population.

METHODS

STUDY POPULATION AND DATA SOURCE. The EXCOR Pediatric is a pneumatically driven, paracorporeal blood pump capable of providing pulsatile flow as a left, right, or biventricular device with different pump sizes, suitable for newborns to adolescents (8,15-17). Patients in the present analysis participated in a multicenter prospective cohort study examining the use of the EXCOR Pediatric as a bridge to transplant. All children who received the EXCOR Pediatric from May 9, 2007, to December 31, 2010, and whose data were included in the sponsor's US regulatory database, were identified and analyzed.

A total of 47 pediatric centers from the United States and Canada participated in the study, with 17 being part of the investigational device exemption (IDE) trial. Centers in the United States who were not part of the IDE trial had access to the device through compassionate use regulations. The study design and results for the 48 children in the original IDE trial have been reported previously (10), as have the overall results for the entire cohort (11). All patients whose data were previously captured were included in this study, with a specific focus on those with a weight <10 kg.

All data were collected by using a database adapted from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Etiology of death and adverse events were adjudicated by an independent clinical events committee for the patients in the IDE study but not for the entire cohort. Each center's institutional review board approved the study protocol, and written informed consent was obtained for all patients.

DATA COLLECTION. Pre-implant demographic and clinical characteristics were collected within 48 h of implantation unless otherwise specified. Patients were followed up from the time of EXCOR Pediatric implant until 1 of 3 possible outcomes: transplant, death, or recovery. Patients were censored at the time of transplant or recovery. At the time of this analysis, all patients had achieved 1 of 4 outcomes (definitions were taken from the original IDE trial): "successful" outcomes, 1) transplantation or 2) being weaned from the device with a good neurological outcome within 30 days of explant; "unsuccessful" outcomes, 3) death on the device, or within 30 days of weaning or before hospital discharge after weaning (whichever was longest); or 4) weaning failure, defined as an unacceptable neurological outcome within 30 days of weaning or before hospital discharge, whichever was longer (10). Adverse event definitions after implantation have been previously reported and are also used in this analysis (10,11). In addition, renal dysfunction, estimated according to the glomerular filtration rate (GFR) adjusted for age by using the formula of Schwartz et al. (18), was defined as abnormal if the GFR was ≤59 ml/min/1.73 m^2 for those <2 years of age and ≤89 ml/min/1.73 m^2 for those 2 to 16 years of age. An abnormal pre-implant bilirubin level was defined as ≥1.2 mg/dl.

STATISTICAL ANALYSIS. Data are presented as medians with ranges or frequencies with percentages as appropriate. Statistical significance of differences between groups was assessed by using the chi-square or Fisher exact test for discrete variables and the Kruskal-Wallis test for continuous variables. Odds ratios with 95% confidence intervals were calculated for the logistic regression. Logistic regression models were used with stepwise backward elimination with a p value of 0.025 to retain variables.

Kaplan-Meier methods were used to produce the survival curves, and the log-rank test was used to examine the differences between the survival distributions.

RESULTS

PATIENT DEMOGRAPHIC CHARACTERISTICS. A total of 204 patients were included in this analysis, with 47.5% (97 of 204) of these patients weighing <10 kg.

ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

ECMO = extracorporeal membrane oxygenation

GFR = glomerular filtration rate

IDE = investigational device exemption

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support

VAD = ventricular assist device

Baseline demographic and clinical characteristics are outlined in Table 1. For those children weighing <10 kg, the median weight was 6.2 kg (range: 2.8 to 9.9 kg) and median age was 6.2 months (range: 0.2 to 33.1 months) at the time of implant. CHD, previous cardiac arrest, and infections before transplant were distributed in children weighing <10 kg comparably to those seen in larger patients. However, the smaller patients were not similar in all aspects, with a higher proportion experiencing abnormal GFR before implantation, with a pre-implant creatinine level >1 mg/dl reported more frequently in the larger patients. Although the majority of patients in both cohorts were classified as INTERMACS profile 1 at the time of implantation, patients weighing <10 kg were more likely to have received a blood transfusion (92.8% vs. 78.5%; p = 0.004), been ventilated (85.6% vs. 69.2%; p = 0.005), or required ECMO (48.5% vs. 33.6%; p = 0.03) before VAD insertion.

The majority of patients weighing <10 kg underwent an isolated left ventricular assist device insertion, with rates similar to those found in larger patients (65% vs. 61%; p = 0.54). Seventy-eight percent of patients weighing <10 kg were implanted with a 10-ml pump; the remainder (21.7%) were implanted with either a 25- or 30-ml pump.

When children weighing <10 kg were further analyzed and dichotomized into patients who weighed <5 kg and those weighing 5 to <10 kg, a few differences were observed. A greater proportion of children weighing <5 kg had CHD (39.4% vs. 20.3%; p = 0.04) and were implanted as an INTERMACS profile 1 (66.7% vs. 46.9%; p = 0.06). Online Table 1 outlines the CHD diagnosis and previous surgeries in all patients weighing <10 kg. Children weighing <5 kg were more likely to have an abnormally high pre-implant bilirubin level compared with those weighing 5 to 10 kg (66.7% vs. 29.5%; p < 0.001) and be supported on ECMO before implantation (63.6% vs. 40.6%; p = 0.03). All children with a weight <5 kg received a 10-ml pump; an isolated left ventricular assist device was used in 66.7% of these implants.

OUTCOMES. In general, smaller patients were supported for a shorter duration of time before reaching a final outcome. The median duration of support for those children weighing <10 kg was 26 days (range 0 to 232 days) compared with 56 days (range 1 to

TABLE 1 Demographic and Clinical Characteristics Stratified According to Weight

	Category	Overall (N = 204)	Weight Group ≥10 kg (n = 107)	Weight Group <10 kg (n = 97)	Weight Group <5 kg (n = 33)
Age, months		18.6 (0.2-192)	60 (1.9-192)	6.2 (0.2-33.1)	1.3 (0.2-11.3)
Weight, kg		10.0 (2.8-60.0)	16.3 (10.0-60.0)	6.2 (2.8-9.9)	3.7 (2.8-4.8)
Male		107 (52.5%)	57 (52.3%)	50 (51.6%)	18 (54.6%)
INTERMACS profile	1	107 (52.5%)	55 (51.4%)	52 (53.6%)	22 (66.7%)
Primary diagnosis	CHD	55 (27.0%)	29 (27.1%)	26 (26.8%)	13 (39.4%)
Pre-implant cardiac arrest	Yes	49 (24.0%)	25 (23.4%)	24 (24.7%)	6 (18.2%)
Pre-implant infection	Yes	49 (24.0%)	24 (22.4%)	25 (25.8%)	7 (21.2%)
eGFR	Abnormal	54 (26.5%)	20 (18.7%)	34 (35.0%)	15 (45.5%)
Pre-implant creatinine	>1 mg/dl	25 (12.3%)	19 (17.8%)	6 (6.2%)	2 (6.1%)
Pre-implant bilirubin	≥1.2 mg/dl	86 (44.3%)	46 (46.0%)	40 (42.6%)	22 (66.7%)
Comorbidities					
Transfusion history	Yes	174 (85.3%)	84 (78.5%)	90 (92.8%)	31 (93.9%)
Support before EXCOR					
Ventilator	Yes	157 (77.0%)	74 (69.2%)	83 (85.6%)	29 (87.9%)
VAD pre-EXCOR	Yes	7 (3.4%)	5 (4.7%)	2 (2.1%)	0
Inotropes	Yes	187 (91.7%)	98 (91.6%)	89 (91.8%)	28 (84.9%)
ECMO	Yes	83 (40.7%)	36 (33.6%)	47 (48.5%)	21 (63.6%)
ECMO >10 days	Yes	19 (9.3%)	6 (5.6%)	13 (13.4%)	6 (18.2%)
Time on ECMO, days		6.0 (0-38)	5.0 (2-23)	6.0 (0-38)	6.0 (2-38)
Implant characteristics					
Device type	LVAD	128 (62.8%)	65 (60.8%)	63 (65.0%)	22 (66.7%)
Concomitant surgeries	None	107 (52.4%)	66 (61.7%)	41 (42.3%)	12 (36.4%)
Cardiopulmonary bypass time, min		159 (71-599)	159 (71-599)	153 (75-365)	166 (75-365)

Values are median (interquartile range) or n (%).

CHD = congenital heart disease; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EXCOR = Berlin Heart EXCOR Pediatric Ventricular Assist Device; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; VAD = ventricular assist device.

435 days) for those weighing ≥10 kg ($p < 0.001$). For patients weighing <10 kg, 56.7% (55 of 97) achieved a successful outcome: 53 underwent transplantation and 2 were weaned from the device with a good neurological outcome (Table 2). Death occurred in 38% (n = 37) of this cohort, and 5.2% (n = 5) were weaned unsuccessfully. A successful outcome was achieved less often in the lighter-weight cohort compared with those weighing ≥10 kg (56.7% vs. 83.2%; $p < 0.001$). Figure 1 illustrates the Kaplan-Meier survival curve, highlighting the greater freedom from death in the larger patients ($p < 0.001$). As shown, death occurred early after implantation, with the most common cause of death being neurological events, followed by respiratory, bleeding, and multisystem organ failure (Table 3).

When subcategorized according to weight, the outcomes for those weighing <5 kg were significantly worse (Figure 2). Only 27.3% (9 of 33) experienced a successful outcome; 63.6% (21 of 33) died, and 9.1% (3 of 33) were weaned unsuccessfully (Table 2). These findings were significantly different from those in patients weighing between 5 and 10 kg; 71.9% of this cohort achieved a successful outcome ($p < 0.001$), and there was a 25% mortality rate. Of note, the majority of patients weighing <5 kg were supported by ECMO before VAD implantation (64% [21 of 33]), with only 3 of the patients on ECMO transplanted and 15 dying after withdrawal of device support. Of the 15 patients who died who were also supported by ECMO before VAD implantation, 11 had CHD. None of the patients weighing <5 kg and on ECMO pre-implantation with CHD survived (Table 2). This finding differed from patients weighing between 5 and 10 kg with CHD who were supported on ECMO, in whom 66.7% underwent transplantation. The median duration of VAD support was significantly shorter in those weighing <5 kg compared with those weighing between 5 and 10 kg (16 days [0 to 232 days] vs. 33 days [0 to 230 days]; $p = 0.01$).

TABLE 2 Clinical Outcomes Stratified According to Clinical Characteristics for Children Weighing <10 kg

	n	Transplant	Wean Success	Death	Wean Failure
Overall	97	53 (54.6%)	2 (2.1%)	37 (38.1%)	5 (5.2%)
No ECMO	50	34 (68.0%)	1 (2.0%)	15 (30.0%)	0
No ECMO/no CHD	41	30 (73.2%)	1 (2.4%)	10 (24.4%)	0
No ECMO/no CHD/normal bilirubin	32	27 (84.4%)	1 (3.1%)	4 (12.5%)	0
CHD	26	8 (30.8%)	0	18 (69.2%)	0
ECMO	47	19 (40.4%)	1 (2.1%)	22 (46.8%)	5 (5.2%)
ECMO + CHD	17	4 (23.5%)	0	13 (76.5%)	0
ECMO + ↑ biliriubin	29	9 (31.0%)	0	18 (62.1%)	2
ECMO + CHD + ↑ bilirubin	14	2 (14.3%)	0	12 (85.7%)	0
Clinical outcomes stratified by clinical characteristics for children <5 kg					
Overall	33	9 (27.3%)	0	21 (63.6%)	3 (9.1%)
No ECMO	12	6 (50.0%)	0	6 (50.0%)	0
No ECMO/no CHD	10	5 (50.0%)	0	5 (50.0%)	0
No ECMO/no CHD/normal bilirubin	6	4 (66.7%)	0	2 (33.3%)	0
CHD	13	1 (7.7%)	0	12 (92.3%)	0
ECMO	21	3 (14.3%)	0	15 (71.4%)	3 (14.3%)
ECMO + CHD	11	0	0	11 (100%)	0
ECMO +↑ biliriubin	17	2 (11.8%)	0	13 (76.5%)	2 (11.8%)
On ECMO + CHD + ↑bilirubin	10	0	0	10 (100%)	0

Values are n (%)
Abbreviations as in Table 1.

RISK FACTOR ASSESSMENT. Table 4 outlines the univariable predictors of death in children weighing <10 kg. Children who died were more likely to be younger and smaller at the time of device implantation, with an elevated bilirubin level, abnormal GFR findings, and had been supported for a significantly shorter period of time. The majority of these patients were classified as INTERMACS profile 1, with nearly 50% having CHD. Those patients who died were supported for a significantly shorter duration of time compared with the survivors. On multivariable analysis (Table 5), the only independent risk factors for mortality identified were pre-existing CHD (odds ratio: 4.8 [95% confidence interval: 1.5 to 15.0]; $p = 0.007$) and an elevated bilirubin level (odds ratio: 5.3 [95% confidence interval: 2.0 to 14.3]; $p = 0.001$) before implant. Online Figures 1 and 2 illustrate the freedom from death in those patients weighing <10 kg stratified according to the presence of CHD and elevated pre-implant bilirubin levels, respectively.

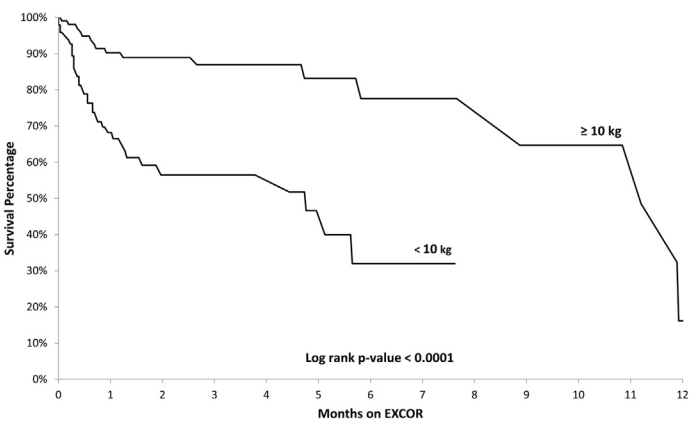

FIGURE 1 Kaplan-Meier Survival Curve, Stratified According to Weight Group

Kaplan-Meier survival curves illustrating a significant difference in survival, with those patients weighing <10 kg experiencing a worse outcome. EXCOR = Berlin Heart EXCOR Pediatric Ventricular Assist Device.

TABLE 3 Etiology of Death (N = 37)

Neurological events	9 (24%)
Respiratory failure	8 (22%)
Bleeding	8 (22%)
Multisystem organ failure	5 (14%)
Infection	2 (5.4%)
Right ventricular failure	1 (2.7%)
Renal failure	1 (2.7%)
Other/unknown	3 (8.1%)

Values are n (%).

Because the patients weighing <5 kg had inferior outcomes compared with those weighing between 5 and 10 kg, an attempt was made to identify risk factors for mortality in this group. Those patients who died were more likely to die early after device implantation, with the median duration of support being 9 days and the maximum duration of support being 2 months. This was significantly shorter compared with the rest of the patients weighing <5 kg (9 [0 to 60] days vs. 28 [7 to 232] days; p = 0.012). In addition to duration of support, the only univariable predictor of death was the presence of CHD with only 1 patient with CHD weighing <5 kg surviving to transplant (Table 2).

Table 2 highlights the various outcomes in patients weighing <10 kg, and those weighing <5 kg depending on their diagnosis, degree of support, and bilirubin level. In those patients weighing <10 kg, 84.4% (27 of 32) of patients without CHD who were not supported on ECMO and did not have an elevated bilirubin level underwent transplantation. In addition, for the subset of patients weighing <5 kg with the aforementioned characteristics, 66.7% (4 of 6) were successfully transplanted.

POST-IMPLANT COMPLICATIONS. The occurrence of serious adverse events during support, including bleeding, neurological dysfunction, and infection, did not differ between those children weighing <10 kg and those weighing ≥10 kg (Online Table 2).

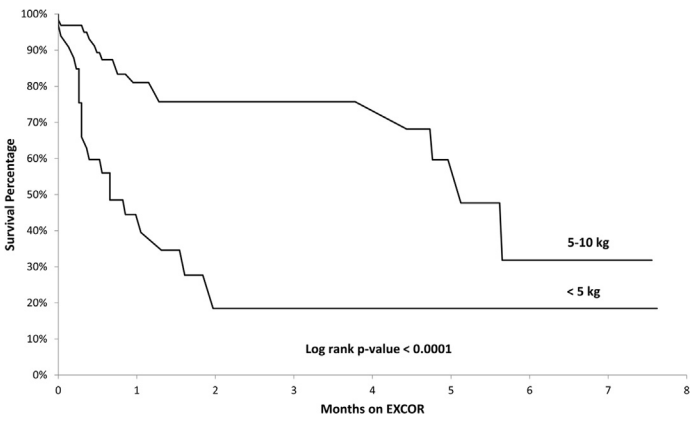

FIGURE 2 Kaplan-Meier Survival Curve, Stratified According to Weight >5 kg to 10 kg and <5 kg

Kaplan-Meier survival curves illustrating a significant difference in survival, with those patients weighing <5 kg experiencing a worse outcome. EXCOR = Berlin Heart EXCOR Pediatric Ventricular Assist Device.

DISCUSSION

The EXCOR Pediatric has allowed children who otherwise would not have survived to transplant to be bridged, with reasonable outcomes (8,10,11). However, as with ECMO, the study findings suggest that this survival advantage may not be equal across the spectrum of pediatric patients, with the smallest patients being the most vulnerable.

The present analysis, representing a cohort of children weighing <10 kg supported with an EXCOR Pediatric, found that patients weighing <10 kg had inferior outcomes compared with patients weighing ≥10 kg, but that reasonable outcomes could be achieved. These findings support a previously published multicenter retrospective review in which younger age was deemed an independent risk factor for death (8). It differed, however, from the study of Karimova et al. (13), which was a single-center report in which children weighing <10 kg had a 91% survival to transplant. This discrepancy in outcomes may be explained by differences in the patient cohorts used within the studies, with the single-center study including patients who were slightly older and including no patients with CHD.

Although children weighing <10 kg are at higher risk of mortality post-implant, this risk is not uniform with CHD, and a pre-implant bilirubin level ≥1.2 mg/dl increased the risk of death. This differs slightly from the overall cohort of 204 patients that was previously reported (in which CHD was not identified as a risk factor for early or late mortality [11]) but supports other previously published reports (19,20). It is well recognized that there are numerous challenges in supporting children with CHD to transplant with mechanical methods (21–25). These challenges are especially difficult in smaller patients due to their complex physiology and hemodynamics, immaturity of the coagulation system, infection risk, and previous surgical correction. These factors may explain the identification of CHD as a risk factor for mortality in this analysis. In the absence of CHD, ~70% of patients weighing <10 kg have undergone transplantation.

In addition to CHD, elevated pre-implant bilirubin levels were also identified as a risk factor for mortality, with ~70% of patients who died having an elevated bilirubin level before the implant. These findings confirm previous reports that also identified elevated bilirubin level as a risk factor for mortality in both adult (26–29) and pediatric (11) studies. Although it is understood that bilirubin often serves as a surrogate for right heart failure, it is unclear if this fully explains the role of elevated bilirubin in younger children. Almost 70% of patients weighing <5 kg had an elevated bilirubin level at the time of implantation, but bilirubin levels are higher after birth and decrease over time post-natally (30–33). In some patients, elevated bilirubin may reflect ongoing hemolysis or serve as a surrogate marker for inadequate decompression of the right ventricle during ECMO. In the <5-kg weight group, 21 (63.6%) patients were supported on ECMO before the implant, and 17 of those patients had an elevated bilirubin level pre-implant. Of note, only 11.8% of these patients survived to transplantation.

Few reports have examined the impact of ECMO as a bridge to implantation in the pediatric population, but several studies have shown increased waitlist mortality in children and decreased survival post-transplant (1,2,34,35). Therefore, it was somewhat surprising that ECMO was only identified as a univariable predictor of mortality in patients weighing <10 kg. Although not specifically analyzed in this study, there was a strong signal that in a subgroup of patients, ECMO does pose an increased risk as illustrated by the fact that no child weighing <5 kg with CHD on ECMO survived post-implant.

The risk of death in patients with lower body weight was not found to be equal across the weight spectrum, with >60% of patients weighing <5 kg dying post-implant. Although weight was not an identified risk factor for mortality when analyzed as a continuous variable, when dichotomized into those weighing <5 kg versus those weighing 5 to 10 kg, weight <5 kg was an independent risk factor for early mortality (results not shown), and pre-implant bilirubin level was found to be no longer significant. Furthermore, examination of those weighing <5 kg suggests that these patients were a higher risk group, with a number of patients having CHD (42.4%) and a majority being supported on ECMO (63.6%) at implantation. It is clear from this analysis that the presence of CHD in children weighing <5 kg portends a poor prognosis, especially in those supported with ECMO. These findings do raise the question as to whether there is any survival advantage in this group of children.

TABLE 4 Univariable Predictors of Mortality in Subjects Weighing <10 kg

	Category	Survivor (N = 60)	Nonsurvivor (N = 37)	p Value
Age, months		6.9 (0.4–26.8)	2.9 (0.2–33.1)	0.003
Weight, kg		7.0 (3.0–9.9)	4.4 (2.8–9.7)	<0.001
BSA, m^2		0.37 (0.20–0.46)	0.27 (0.19–0.53)	<0.001
Cardiopulmonary bypass time, min		148.0 (75–315)	178.0 (96–355)	0.053
Days on support		36.0 (1–232)	15.0 (0–172)	0.002
Weight group	< 5 kg 5–10 kg	12 (20.0%) 48 (80.0%)	21 (56.8%) 16 (43.2%)	<0.001
Male		32 (53.3%)	18 (48.7%)	0.65
INTERMACS profile	1	27 (45.0%)	25 (67.6%)	0.03
Primary diagnosis	CHD	8 (13.3%)	18 (48.7%)	<0.001
eGFR	Abnormal	15 (25.0%)	19 (51.3%)	0.01
Pre-implant creatinine	>1 mg/dl	3 (5.0%)	3 (8.1%)	0.67
Pre-implant bilirubin	≥1.2 mg/dl	14 (24.6%)	26 (70.3%)	<0.001
Pre-implant cardiac arrest	Yes	16 (26.7%)	8 (21.6%)	0.58
Pre-implant implant	Yes	19 (31.6%)	6 (16.2%)	0.09
Ventilator	Yes	51 (85.0%)	32 (86.5%)	0.84
VAD	Yes	2 (3.3%)	0	0.52F
Inotropes	Yes	57 (95.0%)	32 (86.5%)	0.25F
ECMO	Yes	25 (41.7%)	22 (59.5%)	0.09
ECMO >10 days	Yes	8 (13.3%)	5 (13.5%)	1.00F
Device type	BVAD	18 (30.0%)	16 (43.2%)	0.18
Pump size 10 ml	Yes	43 (71.7%)	33 (89.2%)	0.04

Values are median (interquartile range) or n (%).
BSA = body surface area; BVAD = biventricular assist device; eGFR = estimated glomerular filtration rate; F = Fisher exact test; other abbreviations as in Table 1.

Although overall survival was decreased for those patients weighing <10 kg, there was a similar pattern of adverse events after implantation compared with the larger patient cohort. Neurological complications were seen in one-third of the patients and accounted for the most deaths in this patient cohort. Both the incidence and pattern of neurological complications, with ischemic strokes being more common, were similar to those patients >10 kg. The lack of difference in neurological outcomes in these smaller patients has been previously shown in a single-center report (13) but does differ from 2 other reports in which children weighing <10 kg were at higher risk (19,36). This variability in reporting may stem from differences in duration of support, as both this patient

TABLE 5 Multivariable Predictors of Death in Subjects Weighing <10 kg

	Odds Ratio	95% Confidence Interval	p Value
CHD	4.8	1.54–15.04	0.007
Pre-implant bilirubin level ≥1.2 mg/dl	5.3	1.95–14.26	0.001

Abbreviation as in Table 1.

cohort and the cohort reported by Polito et al. (36) were supported for a significantly shorter duration, whereas others have shown that neurological complications increase with duration of support. Further analysis is required to examine time-dependent outcomes post-implantation, both in the overall cohort of patients and the smaller-weight patients, to determine ongoing risk of morbidity.

STUDY LIMITATIONS. The present study had several limitations inherent in a retrospective analysis, including the analysis of data that was not prespecified in the clinical trial protocol. However, we believe that the medical community is in need of information for this smaller group of patients and suggest care be taken in the interpretation of these results. In addition, the multivariable analysis focused on pre-implant factors, and therefore the effects on post-implant management and complications on survival were not analyzed. Lastly, adjudication of the causes of death and complications only occurred for the 109 patients in the IDE cohort, and it is therefore possible that some patients may have been incorrectly classified.

Although outcomes of children being bridged to transplant are encouraging, this study does highlight several facts. Most important, we showed that the overall results for children weighing <10 kg are inferior to those of their larger counterparts, with an impact of CHD and elevated pre-implant bilirubin. Although the numbers are small, there are differences in survival between different patients groups (those weighing <10 kg and those weighing <5 kg), illustrating that regardless of size, survival seems to be improved in the presence of normal bilirubin, structurally normal hearts, and without use of ECMO. Therefore, caution is advised using the EXCOR Pediatrics as a salvage strategy for patients with CHD (especially those on ECMO and weighing <5 kg) and with end-organ dysfunction. Although there is growing interest in the use of other types of mechanical support (e.g., continuous flow pumps) for smaller children, few data exist addressing outcomes and complication profiles.

CONCLUSIONS

The factors discussed here should be taken into account when making decisions regarding candidacy and timing of VAD implantation. Favorable outcomes can be achieved in those smaller children without CHD, mild end-organ dysfunction, and without ECMO support. Conversely, the role of patient selection and optimizing patients before implantation is likely paramount for the overall outcomes in these smaller children. Lastly, alternative management strategies, including palliative care, should be discussed with families, especially when implantation is proposed as a salvage strategy in those smaller children with CHD and end-organ dysfunction due to the poor outcomes. Further efforts are required to improve outcomes in these smaller patients through the generation of newer devices and alternative management strategies for heart failure.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Tilman Humpl, Department of Critical Care Medicine and Pediatrics, Division of Cardiology, 555 University Avenue, Toronto, Ontario M5G1X8, Canada. E-mail: tilman.humpl@sickkids.ca.

REFERENCES

1. Almond CS, Thiagarajan RR, Piercey GE, Gauvreau K, Blume ED, Bastardi HJ, et al. Waiting list mortality among children listed for heart transplantation in the United States. Circulation 2009;119:717–27.

2. Almond CS, Singh TP, Gauvreau K, Piercey GE, Fynn-Thompson F, Rycus PT, et al. Extracorporeal membrane oxygenation for bridge to heart transplantation among children in the United States: analysis of data from the Organ Procurement and Transplant Network and Extracorporeal Life Support Organization Registry. Circulation 2011;123:2975–84.

3. Imamura M, Dossey AM, Prodhan P, Schmitz M, Frazier E, Dyamenahalli U, et al. Bridge to cardiac transplant in children: Berlin Heart versus extracorporeal membrane oxygenation. Ann Thorac Surg 2009;87:1894–901, discussion 901.

4. Gandhi MJ, DeGoey SR, Bundy K, Kremers WK, Knauer R, Pereira N, et al. Effect of pretransplant human leukocyte antigen antibodies detected by solid-phase assay on heart transplant outcomes. Transplant Proc 2011;43:3840–6.

5. Blume ED, Naftel DC, Bastardi HJ, Duncan BW, Kirklin JK, Webber SA. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multi-institutional study. Circulation 2006;113:2313–9.

6. Humpl T, Furness S, Gruenwald C, Hyslop C, Van Arsdell G. The Berlin Heart EXCOR Pediatric—The SickKids Experience 2004-2008. Artif Organs 2010;34:1082–6.

7. Stein ML, Robbins R, Sabati AA, Reinhartz O, Chin C, Liu E, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)-defined morbidity and mortality associated with pediatric ventricular assist device support at a single US center: the Stanford experience. Circ Heart Fail 2010;3:682–8.

8. Morales DL, Almond CS, Jaquiss RD, Rosenthal DN, Naftel DC, Massicotte MP, et al. Bridging children of all sizes to cardiac transplantation: the initial multicenter North American experience with the Berlin Heart EXCOR ventricular assist device. J Heart Lung Transplant 2011;30:1–8.

9. Hetzer R, Potapov EV, Alexi-Meskishvili V, Weng Y, Miera O, Berger F, et al. Single-center experience with treatment of cardiogenic shock in children by pediatric ventricular assist devices. J Thorac Cardiovasc Surg 2011;141:616–23, 623.e1.

10. Fraser CD Jr., Jaquiss RD. The Berlin Heart EXCOR Pediatric ventricular assist device: history, North American experience, and future directions. Ann N Y Acad Sci 2013;1291:96–105.

11. Almond CS, Morales DL, Blackstone EH, Turrentine MW, Imamura M, Massicotte MP, et al. Berlin Heart EXCOR pediatric ventricular assist

device for bridge to heart transplantation in US children. Circulation 2013;127:1702–11.

12. Brancaccio G, Amodeo A, Ricci Z, Morelli S, Gagliardi MG, Iacobelli R, et al. Mechanical assist device as a bridge to heart transplantation in children less than 10 kilograms. Ann Thorac Surg 2010;90:58–62.

13. Karimova A, Van Doorn C, Brown K, Giardini A, Kostolny M, Mathias M, et al. Mechanical bridging to orthotopic heart transplantation in children weighing less than 10 kg: feasibility and limitations. Eur J Cardiothorac Surg 2011;39:304–9.

14. Stiller B, Weng Y, Hubler M, Lemmer J, Nagdyman N, Redlin M, et al. Pneumatic pulsatile ventricular assist devices in children under 1 year of age. Eur J Cardiothorac Surg 2005;28:234–9.

15. Hetzer R, Alexi-Meskishvili V, Weng Y, Hübler M, Potapov E, Drews T, et al. Mechanical cardiac support in the young with the Berlin Heart EXCOR pulsatile ventricular assist device: 15 years' experience. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2006:99–108.

16. Almond CS, Buchholz H, Massicotte P, Ichord R, Rosenthal DN, Uzark K, et al. Berlin Heart EXCOR Pediatric ventricular assist device investigational device exemption study: study design and rationale. Am Heart J 2011;162:425–35.e6.

17. Stiller B, Lemmer J, Schubert S, Ewert P, Schulze-Neick I, Hubler M, et al. Management of pediatric patients after implantation of the Berlin Heart EXCOR ventricular assist device. ASAIO J 2006;52:497–500.

18. Schwartz GJ, Haycock GB, Edelmann CM Jr., Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259–63.

19. Fan Y, Weng YG, Xiao YB, Huebler M, Franz N, Potapov E, et al. Outcomes of ventricular assist device support in young patients with small body surface area. Eur J Cardiothorac Surg 2011;39:699–704.

20. Fan Y, Weng YG, Huebler M, Cowger J, Morales D, Franz N, et al. Predictors of in-hospital mortality in children after long-term ventricular assist device insertion. J Am Coll Cardiol 2011;58:1183–90.

21. Mackling T, Shah T, Dimas V, Guleserian K, Sharma M, Forbess J, et al. Management of single-ventricle patients with Berlin Heart EXCOR Ventricular Assist Device: single-center experience. Artif Organs 2012;36:555–9.

22. Irving CA, Cassidy JV, Kirk RC, Griselli M, Hasan A, Crossland DS. Successful bridge to transplant with the Berlin Heart after cavopulmonary shunt. J Heart Lung Transplant 2009;28:399–401.

23. Chu MW, Sharma K, Tchervenkov CI, Jutras LF, Lavoie J, Shemie SD, et al. Berlin Heart ventricular assist device in a child with hypoplastic left heart syndrome. Ann Thorac Surg 2007;83:1179–81.

24. Calvaruso DF, Ocello S, Salviato N, Guardi D, Petruccelli DF, Rubino A, et al. Implantation of a Berlin Heart as single ventricle by-pass on Fontan circulation in univentricular heart failure. ASAIO J 2007;53:e1–2.

25. Vanderpluym C, Urschel S, Buchholz H. Advanced therapies for congenital heart disease: ventricular assist devices and heart transplantation. Can J Cardiol 2013;29:796–802.

26. Imamura T, Kinugawa K, Shiga T, Endo M, Kato N, Inaba T, et al. Novel risk scoring system with preoperative objective parameters gives a good prediction of 1-year mortality in patients with a left ventricular assist device. Circ J 2012;76:1895–903.

27. Holman WL, Kormos RL, Naftel DC, Miller MA, Pagani FD, Blume E, et al. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. J Heart Lung Transplant 2009;28:44–50.

28. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163–72.

29. Reinhartz O, Farrar DJ, Hershon JH, Avery GJ Jr., Haeusslein EA, Hill JD. Importance of preoperative liver function as a predictor of survival in patients supported with Thoratec ventricular assist devices as a bridge to transplantation. J Thorac Cardiovasc Surg 1998;116:633–40.

30. Lauer BJ, Spector ND. Hyperbilirubinemia in the newborn. Pediatr Rev 2011;32:341–9.

31. Burke BL, Robbins JM, Bird TM, Hobbs CA, Nesmith C, Tilford JM. Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988-2005. Pediatrics 2009;123:524–32.

32. Maisels MJ. Neonatal jaundice. Pediatr Rev 2006;27:443–54.

33. Maisels MJ. What's in a name? Physiologic and pathologic jaundice: the conundrum of defining normal bilirubin levels in the newborn. Pediatrics 2006;118:805–7.

34. Jeewa A, Manlhiot C, McCrindle BW, Van Arsdell G, Humpl T, Dipchand AI. Outcomes with ventricular assist device versus extracorporeal membrane oxygenation as a bridge to pediatric heart transplantation. Artif Organs 2010;34:1087–91.

35. Mah D, Singh TP, Thiagarajan RR, Gauvreau K, Piercey GE, Blume ED, et al. Incidence and risk factors for mortality in infants awaiting heart transplantation in the USA. J Heart Lung Transplant 2009;28:1292–8.

36. Polito A, Netto R, Soldati M, Brancaccio G, Grutter G, Amodeo A, et al. Neurological complications during pulsatile ventricular assistance with the Berlin Heart EXCOR in children: incidence and risk factors. Artif Organs 2013;37:851–6.

KEY WORDS pediatrics, ventricular assist device, weight

APPENDIX For supplemental tables and figures, please see the online version of this article.