Extracorporeal Membrane Oxygenation Support After Heart Transplantation in Children—Outcomes of a Single Center Cohort

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Objectives: Extracorporeal membrane oxygenation is used for postcardiotomy low cardiac output but is less established following heart transplantation. We characterized outcomes for children supported with extracorporeal membrane oxygenation after heart transplantation.

Design: Single-center retrospective study.

Setting: Large pediatric cardiac referral center.

Patients: All patients who received heart transplantation and were cannulated to extracorporeal membrane oxygenation between 1995 and 2016.

Interventions: Primary outcome measure was mortality 12 months postextracorporeal membrane oxygenation. Patient characteristics were analyzed for association with outcome according to early graft failure (extracorporeal membrane oxygenation ≤ 7 d after heart transplantation), or late graft failure.

Measurements and Main Results: There were 246 heart transplants during the study period and 50 extracorporeal membrane oxygenation runs in 44 patients. Median time from transplant to extracorporeal membrane oxygenation was 1 day (range, 0–11.7 yr), with early graft failure in 28 patients (median 1, range 0–2 d) and 22 extracorporeal membrane oxygenation runs in 20 late graft failure patients (median, 0.8 yr; range, 8 d to 11.7 yr), including four patients with prior extracorporeal membrane oxygenation for early graft failure. Twenty-six patients (59%) survived to hospital discharge, and survival 12 months postextracorporeal membrane oxygenation was 24 patients (55%), lower in those with late graft failure (40% vs 67%; p 0.02). Independent risk factors for 12-month mortality were congenital heart disease, higher pulmonary vascular resistance indexed to body surface area (> 2.2 Woods U/m^2), and higher creatinine. Higher panel reactive antibody levels were associated with 12-month mortality in the late graft failure group only.

Conclusions: Extracorporeal membrane oxygenation can be effectively used to rescue patients with graft dysfunction after heart transplantation but is associated with high early mortality. Factors associated with mortality within 12 months include presence of congenital heart disease, renal dysfunction, elevated pulmonary vascular resistance indexed to body surface area and in those supported with extracorporeal membrane oxygenation late after heart transplantation, significant human leukocyte antigen sensitization. (*Pediatr Crit Care Med* 2020; 21:332–339)

Key Words: extracorporeal membrane oxygenation; graft dysfunction; mechanical circulatory support; mortality; pediatric cardiac transplantation

Heart transplantation (HT) is established therapy for end-stage heart failure or failed palliation of congenital heart disease (CHD), with survival for children after cardiac transplantation of approximately 85% and 60% at 1 and 10 years, respectively (1). The highest risk of mortality occurs in the first year after transplant, and the most common complication after HT is acute graft failure (1). Etiologies for early acute graft failure (EGF) include pulmonary vascular disease

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pretransplant, surgical complication, hyperacute rejection, or primary graft dysfunction. Factors including longer ischemic time, inadequate myocardial protection at procurement, or failure of the graft to adapt to recipient hemodynamic requirements have also been shown to be associated with EGF which is clinically evident within the first 24–72 hours postoperatively (2–4). Different etiologies lead to late acute graft failure (LGF), beyond 5–7 d post transplantation. These include acute cellular rejection or progressive allograft vasculopathy, which may be associated with multiple organ dysfunction or cardiopulmonary arrest (5–8). Acute cellular rejection can occur within the first 30 days but is the commonest cause of death between 30 days and 3 years after transplant (1). Cardiac allograft vasculopathy is a leading cause of death 3–10 years posttransplant, but can rarely occur as early as the first postoperative month (1). General medical management of graft ventricular dysfunction includes support with inotropic agents, mechanical ventilation, sedation, and paralysis, as well as specific management strategies targeting etiology of dysfunction, such as escalation in immunosuppression for acute rejection, or inhaled nitric oxide for increased pulmonary vascular resistance (PVR) (9–11).

Extracorporeal membrane oxygenation (ECMO) has been successfully used to support children undergoing cardiac surgery presenting with refractory cardiorespiratory failure in the postoperative period (12–14). In post-HT patients with early or late acute graft dysfunction and symptom progression despite maximal medical therapies, mechanical circulatory support (MCS) with ECMO or ventricular assist device (VAD) has been shown to successfully support end-organ function while awaiting recovery of graft function, or as a bridge to retransplantation (5, 7, 15, 16). The objectives of this study were to describe outcomes of children who required ECMO after HT in our institution and to identify independent patient and procedural predictors of mortality in the 12 months following ECMO for EGF and LGF.

MATERIALS AND METHODS

This protocol was approved as a retrospective single-center study by the local Institutional Review Board. Patients who were supported with ECMO post-HT from January 1, 1995, to January 1, 2016, were identified from cross-referencing local HT and ECMO databases. Patient demographics and pretransplant workup including indication for HT, human leukocyte antigen (HLA) panel reactive antibody (PRA) status, PVR indexed to body surface area (PVRi) were collated, together with HT procedural, donor and immunosuppression details. Characteristics of ECMO support including indication, ECMO cannulation, end-organ complications during support, and patient survival were collected from the medical record. The primary endpoint was survival to 12 months post-ECMO, with survival to most recent follow-up also reported.

Cardiac Transplantation Management

Institutional standard practice for immunosuppression and graft surveillance have been previously reported (17). Between 1998 and 2005, the majority of patients received immunosuppressive induction regimen with IV methylprednisolone and azathioprine followed with triple drug maintenance therapy with prednisone, azathioprine, and cyclosporine. From 2005, the standard immunosuppression regimen was changed to a steroid avoidance protocol, with induction including thymoglobulin and IV methylprednisolone for 5 days, followed by a two-drug tacrolimus and mycophenolate mofetil based, corticosteroid-free regimen (17). Graft rejection on cardiac muscle biopsy was graded using the International Society for Heart and Lung Transplantation grading scheme. PRAs were compiled from clinical results. Patients with suspected or biopsy-proven rejection were treated with high dose methylprednisolone (30 mg/kg/dose given once a day for 3 d) with additional adjuvant therapy of other agents including IV immunoglobulin infusion (1 g/kg/dose) and plasmapheresis, as indicated by individual patient circumstances according to our institution's protocol for management of acute posttransplant rejection. EGF was defined as cannulation to ECMO less than or equal to 7 days post-HT, with all others classified as LGF. Survivors of EGF who had multiple post-HT ECMO run(s) were censored at the time of subsequent run and included in the LGF analysis (**Fig. 1**).

ECMO Management

ECMO was the primary MCS option for hemodynamically unstable patients in our center. ECMO indication was determined by the patient's clinical team based on post-HT stability, need for and escalation of inotropic agents or cardiac arrest, in the absence of contraindication including severe neurologic injury or irreversible underlying etiology of cardiopulmonary deterioration. All patients received venoarterial ECMO, either by a transthoracic approach or via peripheral arteries and veins. Arterial and venous cannulation sites, cannulation technique, and size were at the discretion of the cannulating surgeon. ECMO circuits were primed with crystalloid solution for children greater than 20 kg or for emergent cannulation, otherwise primed with whole blood. ECMO flow was managed at 80 to 150 mL/kg/min and surrogate markers of end-organ oxygen delivery were trended as evidence of adequacy of support. Circuit hematocrit was maintained at 35% throughout the ECMO run. Crystalloid removal using an ultrafiltration system incorporated in the ECMO circuit was employed according to patient clinical condition. Anticoagulation for ECMO was provided with heparin infusion and titrated using activated clotting time, or anti-Xa activity and activated partial thromboplastin time according to local protocol. Coagulation products (fresh frozen plasma, cryoprecipitate, and platelets) were transfused according to institutional ECMO guidelines. ECMO patients received daily consultation with a pediatric neurologist, and evaluations for neurologic injury included a combination of serial head ultrasounds, electroencephalography, and portable head computerized tomography scans. Decisions regarding the care of the patient, investigating the cause of cardiopulmonary failure and weaning from ECMO are patient-specific.

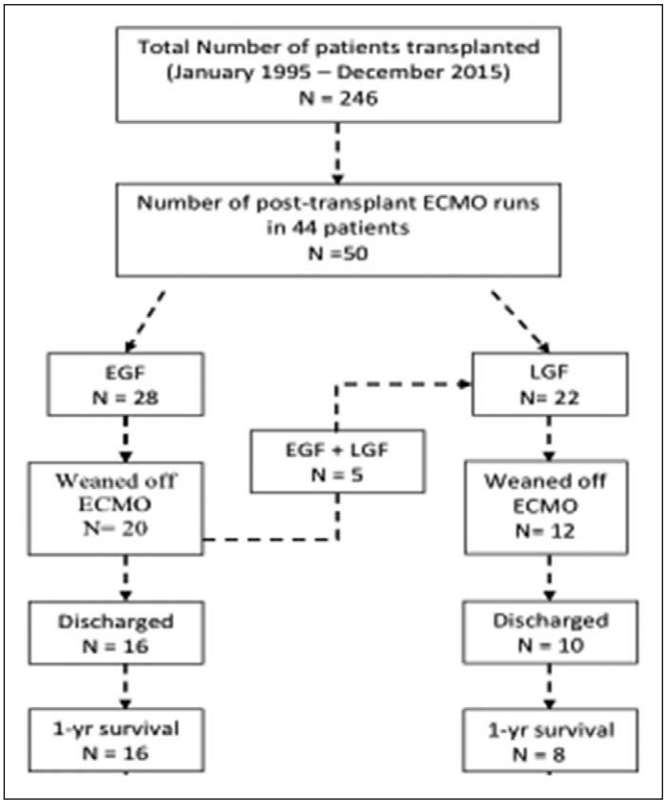

Figure 1. Outcomes for patients supported with extracorporeal membrane oxygenation (ECMO) after cardiac transplantation. Note—ECMO runs are the unit of analysis. There were 50 ECMO runs in 44 patients. EGF = early graft failure (< 7 d postcardiac transplant), LGF = late graft failure (≥ 7 d postcardiac transplant).

Statistical Methods

Age-specific mean imputation of creatinine, alanine aminotransferase, and aspartate aminotransferase was employed for six ECMO runs. Differences in characteristics between the EGF and LGF groups were assessed with Fisher exact test for categorical variables and Student *t* test or Wilcoxon rank-sum test for continuous variables, without correction for the multiple ECMO runs that occurred in five patients. Time-to-event analysis was used to estimate mortality after post-HT graft failure managed with ECMO. The unit of analysis was the ECMO run. For patients with more than one ECMO run, follow-up time was censored at the time of subsequent ECMO initiation. Survival distributions were estimated using the Kaplan-Meier method. Analysis of potential prognostic factors for the endpoint of 12-month mortality was undertaken using Cox proportional hazards modeling for repeated measures (proportional rates and means model). The Wald test *p* value from the Cox model was used to assess significance for predictors and for differences between unadjusted survival curves. Continuous measures were examined as predictors in continuous form as well as in categorical form determined by the data tertiles. For PVRi and PRA, prespecified dichotomous cutoffs were also used (e.g., PVRi ≥ 3, PRA ≥ 20%). For selected variables, two tertiles were also combined to form a dichotomous predictor to address sparse data (zero count) issues and/or no significant difference between two tertiles. A differential effect of a predictor on survival for the early versus late groups was evaluated using a test of the predictor versus ECMO timing group interaction. A multivariable model was constructed with stepwise selection, using all predictors with a univariate *p* value of less than or equal to 0.20 considered as candidate predictors. Associations are presented as hazard ratios (HRs) and 95% CIs. Analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

There were 246 HT in the study period, including 11 retransplantations. Of these, 44 patients (17%) received a total of 50 ECMO runs post-HT, 28 runs for EGF and 22 for LGF. No post-HT patients were managed primarily with VAD. Study sample demographics are shown in **Table 1** and study cohort in Figure 1. For 17 (34%) of the ECMO runs, patients had received HT for cardiomyopathy while CHD was underlying diagnosis for 33 (66%) of the ECMO runs. ECMO duration was not different between the ECMO timing groups (EGF median 97 hr, interquartile range [IQR], 84–134; LGF median 106 hr, IQR 80–138). CNS injury was diagnosed during 16 ECMO runs (32%), including focal regions of cerebral infarctions (5), intracranial hemorrhage (1), clinical seizures (2), subclinical seizures on electroencephalogram (2), subdural hemorrhages (1), six patients with cerebral edema and loss of gray-white matter differentiation consistent with hypoxic-ischemic injury. Four patients received ECMO in both the early and late groups, including two LGF ECMO runs for one patient. Data for each ECMO run was included into their respective timing categories for analysis, with patient outcome censored at the time of subsequent ECMO run/s. Survival to hospital discharge for patients without further ECMO was 16 patients (57%) in the EGF group and 10 patients (45%) for those supported for LGF.

Six of 28 patients (21%) with EGF had endomyocardial biopsies on ECMO, none with evidence of cellular or humoral rejection. Two of these patients were later diagnosed with acute cellular rejection. Of the 22 ECMO runs for LGF, endomyocardial biopsies were performed in 16 (73%) during ECMO. Four were diagnostic of acute cellular rejection (grade ≥ 2), four with features consistent with mild cellular rejection (grade < 2), four biopsies had no features of rejection, and four with indirect immunofluorescence staining positive for C4d together with features consistent with humoral rejection on microscopy. There was no difference in ECMO duration according to biopsy diagnosis of cellular or humoral rejection.

Factors Associated With 12-Month Mortality

Figures 1 and 2 show outcomes of the study sample. Of 28 patients supported on ECMO for EGF, four patients had a further five ECMO run/s in the LGF group. Those EGF patients who did not receive further ECMO had 12-month post-ECMO survival of 67% (16/24). Only eight of 20 patients supported for LGF (40%) survived to 12 months post-ECMO. Univariate factors associated with 12-month mortality are shown in **Table 2**. ECMO cannulation in the operating room (OR) for

TABLE 1. Characteristics of the Study Sample, Overall and by Timing of Graft Failure

Characteristic	Overall	Early Graft Failure	Late Graft Failure	*p*[a]
Number of ECMO runs	50	28	22	
Gender, male, *n* (%)	27 (54)	16 (57)	11 (50)	0.776
Age at transplant, yr, median (IQR)	2.9 (1.6–10.3)	4.3 (1.6–10.3)	2.6 (1.6–11.0)	0.75
Age at ECMO, yr, median (IQR)	5.2 (1.8–11.8)	4.3 (1.6–10.3)	5.8 (2.1–13.9)	0.245
Diagnosis, *n* (%)				
Congenital heart disease	33 (66)	18 (64)	15 (68)	1.000
Cardiomyopathy	17 (34)	10 (36)	7 (32)	
ECMO prior to heart transplant, *n* (%)	14 (28)	8 (29)	6 (27)	1.000
Cardiopulmonary resuscitation prior to ECMO, *n* (%)	21 (42)	6 (21)	15 (68)	**0.001**
CNS injury, *n* (%)	16 (32)	10 (36)	6 (27)	0.559
Posttransplant endomyocardial biopsy grade ≥ 2, *n* (%)	6 (14)	2 (8)	4 (20)	0.387
Location of ECMO cannulation, *n* (%)				**< 0.001**
Catheterization laboratory	5 (10)	0 (0)	5 (23)	
Cardiac ICU	34 (68)	17 (61)	17 (77)	
Operating room	11 (22)	11 (39)	0 (0)	
ECMO indication, *n* (%)				**0.028**
Left ventricular failure	7 (14)	3 (11)	4 (18)	
Biventricular failure	21 (42)	12 (43)	9 (41)	
Right ventricular failure	15 (30)	12 (43)	3 (14)	
Respiratory failure	7 (14)	1 (4)	6 (27)	
Pre-ECMO creatinine, mg/dL, median (IQR)	0.53 (0.3–1.1)	0.45 (0.3–0.8)	0.65 (0.4–1.9)	0.072
Peak creatinine, mg/dL, median (IQR)	1.40 (0.8–2.0)	1.05 (0.6–1.7)	2.00 (1.2–2.9)	**0.007**
Pre-ECMO BUN, mg/dL, median (IQR)	21.0 (16–40)	19.5 (15–26)	25.5 (21–52)	**0.017**
Peak BUN, mg/dL, median (IQR)	72.0 (51–88)	72 (44–92)	72 (63–81)	0.504
Peak aspartate aminotransferase, U/L, median (IQR)	234 (142–324)	238 (150–303)	205 (121–397)	0.565
Peak alanine aminotransferase, U/L, median (IQR)	62 (47–123)	64 (47–112)	69 (47–123)	0.895
Panel reactive antibodies at transplant wait-listing, %, median (IQR)	0.85 (0–32)	1.28 (0–34)	0 (0–29)	0.266
Panel reactive antibodies at transplant wait-listing, > 20%, *n* (%)	15 (30)	8 (29)	7 (32)	1.000
PVRi Woods U/m^2, median (IQR)	2.90 (2.1–3.9)	2.9 (1.9–4.8)	2.9 (2.3–3.1)	0.875
PVRi > 3 Woods U/m^2, *n* (%)	21 (42)	13 (46)	8 (36)	0.569
Ischemic time, min, median (IQR)	220 (168–258)	220 (182–257)	222 (160–260)	0.859
Weight at transplant, kg, median (IQR)	11.5 (8.1–34.9)	11.3 (7.6–29.9)	11.8 (8.7–42)	0.714
Donor weight, kg, median (IQR)	16.0 (12.1–44.3)	16.0 (10.5–40.8)	15.5 (13.1–54.5)	0.850
Donor:recipient weight ratio, median (IQR)	1.3 (1.1–1.6)	1.3 (1.0–1.7)	1.3 (1.2–1.5)	0.892

BUN = blood urea nitrogen, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, PVRi = pulmonary vascular resistance indexed to body surface area.

[a]*p* assumes independence of ECMO runs.

Late graft failure is defined as ECMO initiation ≥ 7 d postcardiac transplant.

Extracorporeal membrane oxygenation run is unit of analysis.

Boldface values indicate statistically significant results.

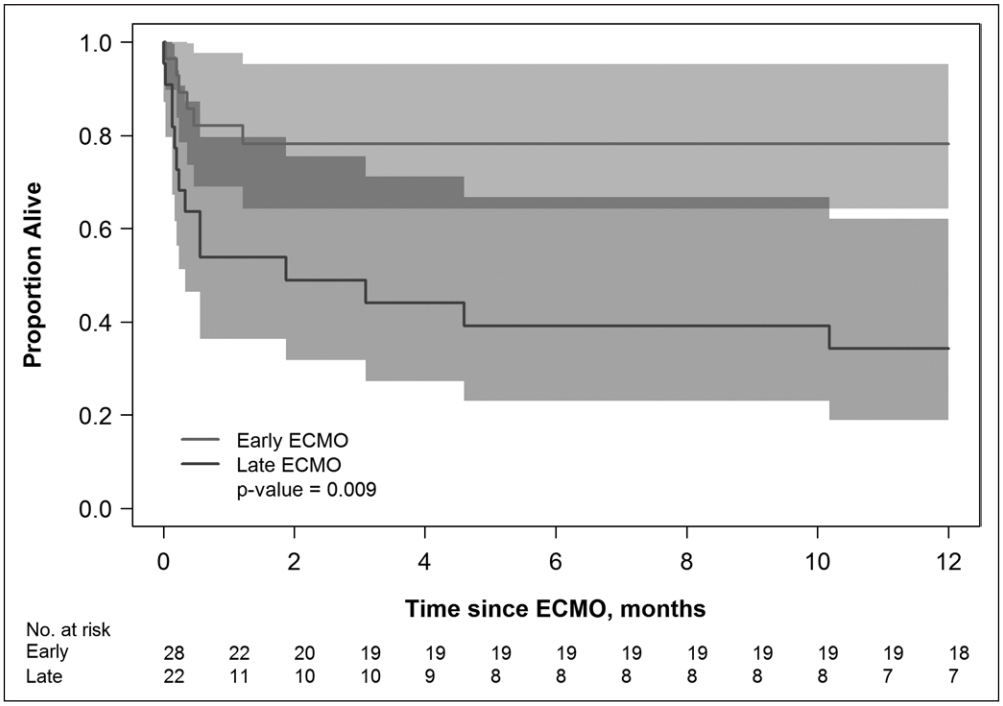

Figure 2. Kaplan-Meier estimated survival for early graft failure (early) versus late graft failure (late) extracorporeal membrane oxygenation (ECMO) groups with pointwise 95% confidence bands (univariate Cox $p = 0.009$). Late graft failure ECMO is defined as ECMO initiation greater than or equal to 7 d postcardiac transplant.

failure to wean from cardiopulmonary bypass was associated with lower survival in the EGF group (OR vs cardiac ICU: HR = 8.84; 95% CI, 1.02–76.92; $p < 0.05$). Other factors, including peak blood urea nitrogen (interaction $p = 0.021$), and PRA levels at listing for transplantation (interaction $p = 0.018$) were associated with 12-month mortality in LGF but not EGF group (Table 2).

Multivariable analysis showed CHD diagnosis prior to HT (HR, 11.6; 95% CI, 2.52–53.3; $p = 0.002$), higher pre-ECMO creatinine (HR, 10.5; 95% CI, 1.88–58.7; $p = 0.007$), PVRi greater than 2.2 Woods U/m^2 (HR, 16.5; 95% CI, 4.95–55.0; $p < 0.001$) were independent risk factors for mortality at 12 months post-ECMO (**Table 3**). Higher PRA at listing was also independently associated with mortality at 12 months (interaction $p < 0.001$), but only for the LGF group (HR, 1.62; 95% CI, 1.31–2.01; $p < 0.001$).

Causes of Death and Long-term Outcomes

Table 4 shows the outcomes of patients at most recent follow-up and collated timing and causes of death. Early post-ECMO death was most commonly associated with redirection of care from ECMO. These were patients with ongoing graft ventricular dysfunction and progressive multiple organ failure. One patient was transitioned to left VAD for isolated left ventricular dysfunction but died soon after discharge to another institution for ongoing care. Although graft failure was associated with early deaths in the EGF cohort, those who survived to hospital discharge did not have ongoing ventricular dysfunction. Graft failure remained a late cause of death in the LGF cohort.

DISCUSSION

Cardiopulmonary failure managed with ECMO support in children after HT differs in outcome according to etiology and timing of graft failure. In our study, EGF was associated with right or biventricular systolic dysfunction with 12-month survival of 67% for those who did not receive additional ECMO. LGF patients had more diverse indications for ECMO, higher proportion of cellular and/or humoral rejection, higher PRA levels and were more likely to suffer cardiopulmonary arrest prior to ECMO. Survival to 12 months post-ECMO in the LGF population was 40%. CHD, elevated PVRi, and higher creatinine were associated with mortality within 12 months of ECMO support in both EGF and LFG patients.

Graft failure after HT in children is associated with significant morbidity and mortality (1). ECMO is an established form of cardiorespiratory support for children postcardiotomy when standard therapies have failed (13, 18, 19). Against this background, we have used ECMO to rescue children with hemodynamically significant graft dysfunction. Over the 21-year study period, we deployed ECMO for EGF in 17% of all HT performed, a proportion consistent with other reports (8, 16, 20). The EGF group were generally considered high-risk for transplantation, due to a predominance of pretransplant CHD diagnoses, significant HLA sensitization, and/or abnormal PVR in a major portion of the cohort. In the same time period, 22 ECMO runs were used to support patients with LGF associated with a combination of rejection, progressive allograft vasculopathy, and pulmonary failure. This group often had evidence of pre-ECMO renal dysfunction; almost 70% underwent cardiopulmonary resuscitation prior to ECMO. Risk factors including background history of elevated PRA at listing and PVRi were observed in the LGF cohort also. Our study supports previous reports that ECMO can be used to successfully bridge these vulnerable populations to end-organ recovery, although with higher early mortality than non-ECMO requiring transplant recipients (5, 7, 8, 16, 18, 21–25).

After bridging to recovery and weaning from ECMO support, this population remains at ongoing risk. Multiple ECMO runs were not uncommon in our cohort, and four of 28 (14%) of those supported for EGF were cannulated for multiple runs of ECMO. Other investigators have shown 5-year post-EGF ECMO survival as low as 40%, accompanied by increased early rejection episodes (16, 20, 24). ECMO for cardiopulmonary

TABLE 2. Univariate Cox Regression Model Association for Mortality at 12 Months

Characteristic	*n*	No. of Deaths	Hazard Ratio (95% CI)	*p*	Interaction *p*
Gender male	50	20	1.03 (0.42–2.55)	0.948	0.542
Age at transplant, yr	50	20	0.98 (0.90–1.08)	0.701	0.839
Age at ECMO, yr	50	20	1.02 (0.94–1.10)	0.653	0.815
Late graft failure ECMO (≥ 7 d posttransplant)	50	20	3.89 (1.4–10.8)	**0.009**	NE
Congenital heart disease diagnosis	50	20	3.71 (1.11–12.4)	**0.033**	0.829
ECMO prior to heart transplant	50	20	1.28 (0.49–3.34)	0.610	0.168
Cardiopulmonary resuscitation prior to ECMO	50	20	2.59 (0.98–6.85)	0.056	0.274
CNS injury	50	20	0.63 (0.20–1.99)	0.431	0.367
Posttransplant endomyocardial biopsy grade ≥ 2 vs < 2	44	15	1.15 (0.29–4.51)	0.841	NE
Location of ECMO cannulation	50	20		0.828	NE
Catheterization laboratory vs CICU			0.63 (0.07–5.99)		
Catheterization laboratory vs operating room			0.50 (0.05–5.44)		
CICU vs operating room			0.80 (0.28–2.27)		
Indication for ECMO	50	20		0.068	NE
Biventricular vs left ventricular failure			0.56 (0.17–1.80)		
Biventricular vs respiratory failure			0.26 (0.07–0.95)		
Biventricular vs right ventricular failure			1.76 (0.47–6.52)		
Left ventricular vs respiratory failure			0.47 (0.12–1.90)		
Left ventricular vs right ventricular failure			3.15 (0.76–13.0)		
Respiratory vs right ventricular failure			6.67 (1.47–30.3))		
Pre-ECMO creatinine, per 0.1 mg/dL increase	50	20	1.10 (1.05–1.16)	**< 0.001**	0.984
Peak creatinine, per 0.1 mg/dL increase	50	20	1.03 (1.01–1.05)	**0.001**	0.825
Pre-ECMO BUN mg/dL	50	20	1.04 (1.02–1.06)	**0.001**	0.435
Peak BUN, mg/dL	50	20		0.189	**0.021**
Early graft failure ECMO	28	6	0.93 (0.82–1.06)[a]	0.283	
Late graft failure ECMO	22	14	1.14 (1.02–1.27)[a]	0.026	
Peak alanine aminotransferase, per 100 U/L increase	50	20	0.96 (0.88–1.05)	0.363	0.307
Panel reactive antibodies at transplant wait-listing, %	50	20		0.739	**0.018**
Early graft failure ECMO	28	6	0.98 (0.95–1.01)	0.249	
Late graft failure ECMO	22	14	1.02 (1.01–1.04)	0.007	
PVRi, Woods U/m^2	50	20	1.41 (0.55–3.60)	0.477	0.222
PVRi > 2.2 Woods U/ m^2	50	20	3.06 (0.96–9.71)	0.058	NE
Ischemic time, per 5 min increase	50	20	1.00 (1.00–1.01)	0.462	0.315
Weight at transplant, kg	50	20	1.00 (0.97–1.02)	0.834	0.937
Donor:recipient weight ratio	50	20	1.78 (0.41–7.63)	0.441	0.645

BUN = blood urea nitrogen, CICU = cardiac ICU, ECMO = extracorporeal membrane oxygenation, *n* = number of ECMO runs, NE = not estimable due to small subgroup frequencies, PVRi = pulmonary vascular resistance indexed to body surface area.

[a]Per 10 mg/dL increase.

An interaction $p < 0.05$ indicates that the association of the risk factor with mortality is not the same for the early and late ECMO groups.

Boldface values indicate statistically significant results.

TABLE 3. Multivariable Model for 12-Month Mortality, With Interaction for Early Versus Late Deaths ($n = 50$ Extracorporeal Membrane Oxygenation runs, 20 Deaths; Generalized $R^2 = 0.56$)

Predictor	Hazard Ratio (95% CI)	p
ECMO timing—late vs early graft failure		0.366
Congenital heart disease diagnosis	11.6 (2.52–53.3)	0.002
Pre-ECMO creatinine ≥ 0.4 vs < 0.4 mg/dL	10.5 (1.88–58.7)	0.007
Pulmonary vascular resistance indexed to body surface area > 2.2 Woods U/m^2	16.5 (4.95–55.0)	< 0.001
Panel reactive antibodies at transplant wait-listing, %		0.169
Panel reactive antibodies at transplant wait-listing according to ECMO timing		< 0.001
Early graft failure ECMO	0.83 (0.64–1.08)	
Late graft failure ECMO	1.62 (1.31–2.01)	

ECMO = extracorporeal membrane oxygenation.

TABLE 4. Outcomes of the Cohort at Latest Follow-up

Outcome	Early Acute Graft Failure, $n = 24$	Late Acute Graft Failure, $n = 20$
Alive at latest follow-up, *n* (%)	11 (46)	4 (20)
Median follow-up duration, mo, median (IQR)	28 (0–90)	1.5 (0–51)
Median survivor follow-up duration, mo, median (IQR)	69 (30–134)	Range 85–165 mo
Early death, *n* (%)		
Redirection of care from extracorporeal membrane oxygenation	6 (25)	7 (35)
Survived decannulation	2 (8)	3 (15)
Early death, cause, *n* (%)		
Graft failure	5 (21)	7 (35)
Right ventricular failure	3 (12)	1 (5)
Sudden cardiac death	0	2 (10)
Late death, *n* (%)	5	6
Time post discharge, range, yr	1–13	0.4–70
Late death, cause, *n* (%)		
Graft failure	0	3 (15)
Sudden cardiac death	2 (8)	2 (10)
Infectious etiology	2 (8)	0
Other	1 (4)	1 (5)
Acute rejection, *n* (%)	2 (8)	15 (75)

IQR = interquartile range.

Note—only those with a single extracorporeal membrane oxygenation (ECMO) run for early acute graft failure are included in this cohort for outcomes. Any patient with an ECMO run for late acute graft failure is included in that cohort. Early death is defined as any death before ECMO admission hospital discharge; late death is any death after hospital discharge.

failure secondary to rejection, including progressive allograft vasculopathy, has been associated with survival to hospital discharge of 40–75% (5, 7, 8, 23). Evidence of additional end-organ dysfunction, persistent elevation of PVR, and elevated PRA levels seen in our cohort of post-HT ECMO patients have also been associated with increased long-term mortality risk in HT patients (9, 24–26). Exploratory analyses of association between ongoing risk of mortality after recovery from EGF are beyond the scope of our analysis but bear future consideration.

Post-HT ECMO support has been associated with death from cerebrovascular accidents and intracranial hemorrhage (25). ECMO complications were uncommon in this cohort, however, almost one-third of our population had a neurologic injury. Alternative cardiopulmonary support strategies, including VAD in the post-HT population have been described (6, 15, 23, 27). For patients exhibiting exclusively hemodynamic pathophysiology, strategies to avoid the use of an oxygenator with durable VAD support may be favored. In a series of LGF patients managed with MCS, investigators reported successful VAD management in seven patients, with overall 3-year survival of 38% (6). Of 22 children supported for LGF with MCS in another study, only three were supported with VAD (23). Adult patients supported with VAD for primary graft dysfunction were found to have longer cardiopulmonary bypass times for cannulation, longer duration of support, higher frequency of major bleeding requiring reoperation, and higher frequency of renal failure (27). We report comparatively favorable survival in our ECMO-supported cohort and with ECMO duration less than 6 days in the majority of runs, our institutional MCS strategy will remain ECMO rather than primary VAD for these patients.

Our study is limited by being from a single center, retrospective in nature and describing a relatively small cohort of patients. The 21-year study period spans eras of transplant candidate selection, evolving medical therapies for pulmonary hypertension, immunosuppression strategies, and ECMO management protocols. These features may decrease the strength of specific conclusions that can be inferred.

CONCLUSIONS

Cardiopulmonary failure after HT differs in etiology and outcome according to timing of graft failure. ECMO can be effectively used to rescue patients with graft dysfunction after HT but is associated with high early mortality. CHD as indication for transplantation, elevated PVRi, and creatinine were independently associated with 12-month mortality, and elevated PRA levels were also associated with 12-month mortality in those patients with graft failure more than 7 days post-HT. Future work exploring the association with post-HT ECMO and specific factors contributing to ongoing risk of mortality will be essential in realizing the benefits of this support modality for HT recipients.

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