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RESEARCH ARTICLE

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Extracorporeal membrane oxygenation (ECMO) support for children with pulmonary hypertension: A single-institutional experience of outcomes

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Abstract

Pediatric pulmonary arterial hypertension (PAH) can present with a wide spectrum of disease severity. Pulmonary hypertension (PH) crises can lead to acute decompensation requiring extracorporeal membrane oxygenation (ECMO) support, including extracorporeal cardiopulmonary resuscitation (eCPR). We evaluated outcomes for pediatric PH patients requiring ECMO. A single-institution retrospective review of pediatric PAH patients with World Symposium on PH (WSPH) groups 1 and 3 requiring ECMO cannulation from 2010 through 2022 ($n = 20$) was performed. Primary outcome was survival to hospital discharge. Secondary outcomes were survival to decannulation and 1-year survival. Of 20 ECMO patients, 16 (80%) survived to decannulation and 8 (40%) survived to discharge and 1 year follow up. Of three patients who had two ECMO runs; none survived. There were five patients who had eCPR for the first run; one survived to discharge. The univariate logistic regression model showed that venovenous ECMO was associated with better survival to hospital discharge than venoarterial ECMO, (OR: 0.12, 95% CI: 0.01–0.86, $p = 0.046$). PH medications (administered before, during, or after ECMO) were

not associated with survival to discharge. For children with decompensated PAH requiring ECMO, mortality rate is high, and management is challenging. While VA ECMO is the main configuration for decompensated PH, VV ECMO could be considered if there is adequate ventricular function, presence of a systemic to pulmonary shunt, or an intercurrent treatable illness to improve survival to discharge. A multidisciplinary approach with requisite expertise should be utilized on a case-by-case basis until more reliable data is available to predict outcomes.

KEYWORDS
mechanical support, pulmonary arterial hypertension, venoarterial, venovenous

Pediatric pulmonary arterial hypertension (PAH) presents with a wide range of disease severity and frequently has an unpredictable course. Underlying etiologies include idiopathic, cardiac, respiratory, veno-occlusive disease, and autoimmune conditions.[1] Disease management in the pediatric population is challenging and requires individualized treatment strategies. Unfortunately, even in the most stable patients, pulmonary hypertensive crises may occur unforeseeably. This can lead to the need for aggressive interventions including cardiopulmonary resuscitation and extracorporeal membrane oxygenation (ECMO), which have a moderate to high chance of mortality.[2] ECMO has proven utility as a bridge to recovery or a bridge to transplantation in patients with other causes of cardiopulmonary failure; however, its utilization for children with PAH has not been widely described.

The World Symposium on Pulmonary Hypertension (WSPH) hemodynamically defines PH when the mean pulmonary arterial pressure (mPAP) is greater than 20 mmHg and classifies PH into five groups depending on the etiology.[3–5] While many etiologies are more common in the adult population, certain etiologies are more commonly seen in children, including idiopathic pulmonary arterial hypertension (IPAH), congenital heart disease (CHD), and developmental lung diseases.[4] Treatment of pediatric PAH is tailored to the underlying etiology and typically consists of a combination of endothelin receptor antagonists, phosphodiesterase-5 (PDE5) inhibitors, parenteral prostanoids, diuretics, and inhaled vasodilators.[3,4] Pediatric PAH patients can have decompensated right heart failure or superimposed acute illness which can exacerbate PH crises and lead to rapid decompensation or cardiac arrest. This may occur with little warning, which may require urgent ECMO cannulation or extracorporeal cardiopulmonary resuscitation (eCPR). Understanding the pathophysiology, treatment options, and clinical trajectory of PAH may help clinicians identify those at greatest risk of decompensation and those who would most likely to benefit from bridging with ECMO. Optimizing medical treatment may decrease ECMO-associated mortality among pediatric PAH patients.[2]

PH management ranges from outpatient surveillance to ICU admission and multimodal pulmonary vasodilator therapy. When the severity of pediatric PAH reaches levels requiring ECMO support, including medication refractory PAH or PH crises, the risk of mortality is high.[2] The morbidity associated with ECMO is significant and includes neurovascular thromboembolic complications, intracranial hemorrhage, and pulmonary hemorrhage; therefore, optimizing strategies to reduce time on ECMO is critical. Survival in these circumstances is estimated to be around 50%, which seems grim; however, mortality would almost be certain without ECMO support.[2] In this context, improvement in survivability with ECMO is modest, but a relatively promising treatment modality.

This paper describes our early experience and evaluates the outcomes in WSPH groups 1 and 3 PH, which is pre-capillary disease, at a high-volume pediatric ECMO center. We focus on evaluating factors before, during, and after ECMO to identify modifiable and unmodifiable differences between patients who survived to discharge compared to those who did not. Pediatric PH requires multidisciplinary management by experienced specialists, especially when ECMO is required. Factors that distinguish patients who survived to decannulation from those who survived to discharge may provide valuable information to clinicians who treat pediatric PH patients requiring ECMO.

METHODS

A single-institution retrospective review of all pediatric PH patients ages 1 month to 20 years old, who required ECMO cannulation from 2010 through 2022 was performed. Columbia University Institutional Review Board

approval was obtained for the study. Patients with WSPH groups 1 and 3 PH were included. There were 20 out of 514 (3.9%) total cannulations performed for pediatric PH during the period evaluated. Patients with persistent pulmonary hypertension of the newborn, and WSPH groups 2, 4, and 5 were excluded from the study to focus on WSPH groups 1 and 3 PH (predominantly idiopathic PAH) in the pediatric population. Multiple data elements, including targeted pulmonary hypertension medications (before, during, and after ECMO support), pre-ECMO laboratory values, echocardiographic findings, vasopressor/inotropic requirements, ECMO configuration (venoarterial or venovenous), and need for eCPR were extracted from the patients' medical records and evaluated for association with patient outcomes. The number of medications before initial ECMO run was obtained and labeled as monotherapy, dual-therapy, triple therapy, or quadruple therapy based on if they were on the following PH medications: PDE-5 inhibitor, endothelin receptor antagonist, inhaled vasodilator (such as iloprost or inhaled nitric oxide), and parenteral prostanoids. Laboratory values before initiation of ECMO were obtained and included platelet count, INR, BNP, arterial blood gas with lactate, and creatinine. Echocardiographic findings were reviewed before and after ECMO cannulation, including measures of right ventricular systolic pressure (RVSP), left ventricular ejection fraction (LVEF), and qualitative assessment of left ventricular function. The primary outcome was survival to discharge, and the other outcomes evaluated were survival to decannulation and 1-year survival.

Statistical analysis

R studio version 4.3.1 statistical software was used. Normality was determined using the Shapiro-Wilks normality test on all continuous variables. Non-normally distributed variables were reported as a median with interquartile range (IQR) while the normally distributed variables were reported as a mean with standard deviation. The categorical or binary variables were presented as counts and percentages. Due to the limited number of patients requiring multiple runs, only the index ECMO run was evaluated for analytical purposes. Continuous variables were compared using Wilcoxon rank sum test (Mann–Whitney U test) and categorical variables were compared using Fisher's exact test. The univariate logistic regression statistical model was used to evaluate factors associated with survival to hospital discharge. The reason for multiple statistical models to analyze the same data was because of the limited sample size. An alpha level of less than or equal to 0.05 was considered statistically significant. Missing variables were noted as "unknown" in the tables and excluded from the analysis.

RESULTS

Our retrospective review identified 20 pediatric patients with 23 ECMO runs during the study period. The median age at cannulation was 13.2 years old [2.8–16.1]. The age range was 1 month to 20 years. There were 12 males (60%) and 8 females (40%). The median duration of ECMO support was 12 days [4.75–16.5] (Table 1). There were 8/20 (40%) patients who survived to hospital discharge. All the patients who survived to hospital discharge survived to 1 year follow up (Table 2). None of the three patients requiring two ECMO runs survived to discharge. Of note, only 3 (15%) of patients were WSPH group 3 all of whom survived to decannulation, but only 1 (33%) survived to discharge. ECPR was performed for cardiac arrest in 5/20 (25%) patients for their initial run. Of these five patients, 2 (40%) survived to decannulation and only one of those five

TABLE 1 Patient demographics ($n = 20$).

Age at cannulation	**13.2 years [IQR 2.8–16.1]**
Gender	
Male	60% (12)
Female	12 days [IQR 4.75–16.5]
ECMO duration	40% (8)
ECMO mode	
Venovenous	35% (7)
Venoarterial	65% (13)
ECPR	
Yes	25% (5)
No	75% (15)
WSPH classification	
Group 1	85% (17)
Group 3	15% (3)

Abbreviations: ECMO, Extracorporeal membrane oxygenation; ECPR, Extracorporeal Cardiopulmonary Resuscitation; IQR, Interquartile range; WSPH, World Symposium on Pulmonary Hypertension.

TABLE 2 Outcomes after ECMO.

Survival to decannulation	**80% (16/20)**
Survival to discharge	40% (8/20)
Survival to one-year	40% (8/20)
Lung transplant	
Yes	0
No	100% (20/20)

Abbreviation: ECMO, Extracorporeal membrane oxygenation.

patients (20%) survived to discharge. ECPR was also performed for the second ECMO run in one patient.

The age at cannulation, gender, days on ECMO, and eCPR were not associated with survival to discharge. Of the 20 patients, 12 (60%) were escalated to mechanical ventilation before ECMO activation for their initial run. Of the 12 patients who were on mechanical ventilation before ECMO, 10 (83%) survived to decannulation; however, only 6 (50%) survived to discharge. PH medications before, during and after ECMO run, vasopressors, inotropic agents, and diuretics were not associated with survival to discharge. Of the 20 patients, the number of medications before first ECMO run were obtained with 4 (20%) on monotherapy, of whom all survived to decannulation, but only 2 (50%) survived to discharge; 1 (5%) on dual therapy, who did not survive to decannulation; 11 (55%) on triple therapy, of whom 7 (64%) survived to decannulation and 4 (36%) survived to discharge; and 4 (20%) on quadruple therapy of whom all survived to decannulation, but only 2 (50%) survived to discharge. Of the patients with 2 ECMO runs, one was on dual therapy, one on triple therapy, and one on quadruple therapy before ECMO activation. Thirteen of the 20 patients (65%) were on home medications for PH, which was not associated with survival to discharge. Seven of the 20 (35%) patients were initially diagnosed with PAH during their ECMO hospitalization, which was not associated with survival to discharge. Of 20 patients, 5 (25%) had a confirmed genetic mutation or syndrome. Of the 5 patients who had a genetic syndrome, 3 (60%) survived to decannulation and 2 (40%) survived to discharge.

Thirteen of the 20 patients (65%) were initially cannulated on to VA ECMO, and seven had VV ECMO support as the initial configuration. None of the VV ECMO patients required conversion to VA ECMO. Of the three patients requiring a second ECMO run, one was converted from VA to VV ECMO immediately after a reversed Potts shunt during their first run, one was successfully decannulated after a VV ECMO run and several days later went on unplanned VA ECMO immediately postoperatively after a reversed Potts shunt, and one was a de-escalation from VA to VV ECMO. Initial reasons for ECMO during the first run included ECMO bridge after Potts shunt creation (3/20; 15%), cardiac arrest and eCPR (5/20; 25%), acute right heart failure in the setting of worsening PH (2/20; 10%), pulmonary infection- including viral or bacterial (5/20; 25%), acute respiratory failure associated with recurrent PH crises (4/20; 20%), and pulmonary hemorrhage (1/20; 5%). Five of the 20 patients (25%) had ECMO support postoperatively from a unidirectional, valved, reversed Potts shunt during the initial ECMO run. One patient had a Potts shunt created and immediate ECMO run postoperatively for their second ECMO run. There were 17 out of 20 patients (85%) who had either a congenital or an artificially created systemic shunt, including atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), or atrial septostomy created in the cardiac catheterization lab. There were 3/17 (18%) patients that had a balloon atrial septostomy created during their ECMO run with only one who survived to discharge. The rest of the patients had a congenital or artificially created shunt before ECMO initiation. None of the congenital intracardiac shunts were restrictive based on echocardiogram before cannulation.

As noted above, seven children were initially cannulated onto VV ECMO. In the univariate logistic regression model, VV ECMO was associated with improved survival to discharge when compared to venoarterial (VA) ECMO (p value = 0.046); however, the result was not statistically significant when comparing the ECMO modes using Fisher's exact test (p value = 0.062). The resulted p-value is borderline therefore the difference may be impacted by intrinsic statistical correction for the small sample size. All except for one of the 20 patients (95%) required invasive ventilation during hospitalization, which was not associated with survival to discharge (p value = 0.4). There were 3 out of the 20 patients (15%) who underwent tracheostomy during their hospitalization, which was also not associated with survival to discharge (p value = 0.537). While on ECMO, 4 of 20 (20%) had bleeding complications: 2 were from pulmonary hemorrhage, 1 from a GI bleed that resolved with observation and giving blood transfusions, and 1 from bleeding around the femoral arterial cannula site that resolved with holding heparin and giving blood transfusions.

Reasons for the four of 20 patients not surviving to decannulation after their first ECMO run included: acute PH crises shortly after decannulation, refractory pulmonary hemorrhage leading to withdrawal of care, and an eCPR in which the circuit was unable to flow adequately after a prolonged arrest. Reasons for non-survival to discharge included unpredictable PH crises after decannulation leading to cardiac arrest, prolonged eCPR leading to inability to flow or neurologic injury, one patient had a massive gastrointestinal (GI) bleed a week after decannulation and did not survive because of hemorrhagic shock, refractory respiratory failure, pulmonary hemorrhage, multiorgan failure, and irreversible neurologic injury from thrombotic strokes.

There was no association between post-cannulation LV function and survival to hospital discharge. One limitation of the study is that six out of 20 patients did not have post-cannulation qualitivate LV function evaluated, which can account for why no difference was detected in addition to the small sample size. No difference was detected in survival to discharge with RVSP, LVEF, before and post-ECMO cannulation, and before cannulation LV qualitative function. Tables 3 and 4 show

TABLE 3 Evaluation of risk factors associated survival to discharge with fisher's exact test.

	Hospital mortality ($n = 12$)	Survival to discharge ($n = 8$)	Standard mean difference	p-value
Gender			0.343	0.648
- Male	33% (4)	50% (4)		
- Female	67% (8)	50% (4)		
Age at cannulation (years)	13.8 [IQR 2.8–16.8]	10.4 [IQR 3.9–14.3]	0.129	0.699
Days on ECMO	14 [6–22]	7 [5–13]	0.365	0.44
ECMO mode			1.06	0.062
- VV	83% (10)	38% (3)		
- VA	17% (2)	62% (5)		
ECPR			0.512	0.603
- Yes	33% (4)	13% (1)		
- No	67% (8)	87% (7)		
WSPH classification			0.118	>0.999
- Group 1	83% (10)	87% (7)		
- Group 3	17% (2)	13% (1)		
Diagnosed this hospitalization			0.087	>0.999
- Yes	33% (4)	37% (3)		
- No	67% (8)	63% (5)		
On home PH medication			0.087	>0.999
- Yes	67% (8)	63% (5)		
- No	33% (4)	37% (3)		
Before ECMO PDE-5 inhibitor			0.206	>0.999
- Yes	83% (10)	75% (6)		
- No	17% (2)	25% (2)		
During ECMO PDE-5 inhibitor			0.087	>0.999
- Yes	67% (8)	63% (5)		
- No	33% (4)	37% (3)		
After ECMO PDE5- inhibitor			1.16	0.6084
- Yes	33.3% (4)	75% (6)		
- No	33.3% (4)	25% (2)		
- Deceased at decannulation	33.3% (4)	0		
Before ECMO endothelin receptor antagonist			0.535	0.373
- Yes	50% (6)	75% (6)		
- No	50% (6)	25% (2)		
During ECMO endothelin receptor antagonist			0.695	0.325
- Yes	42% (5)	13% (1)		
- No	58% (7)	87% (7)		
After ECMO endothelin receptor antagonist			1.15	0.6084
- Yes	17% (2)	50% (4)		
- No	50% (6)	50% (4)		

(Continues)

TABLE 3 (Continued)

	Hospital mortality ($n = 12$)	Survival to discharge ($n = 8$)	Standard mean difference	p-value
- Deceased at decannulation	33% (4)	0		
Before ECMO inhaled vasodilator			0.459	0.537
- Yes	92% (11)	75% (6)		
- No	8% (1)	25% (2)		
During ECMO inhaled vasodilator			0	
- Yes	100% (12)	100% (8)		
- No	0	0		
After ECMO inhaled vasodilator			1	1
- Yes	58.3% (7)	87% (7)		
- No	8.3% (1)	13% (1)		
- Deceased at decannulation	33.3% (4)	0		
Before ECMO parenteral prostanoid			0	>0.999
- Yes	50% (6)	50% (4)		
- No	50% (6)	50% (4)		
During ECMO parenteral prostanoid			0.184	>0.999
- Yes	67% (8)	75% (6)		
- No	33% (4)	25% (2)		
After ECMO parenteral prostanoid			1.06	1
- Yes	50% (6)	87% (7)		
- No	17% (2)	13% (1)		
- Deceased at decannulation	33% (4)	0		
Before ECMO diuretic			0.087	>0.999
- Yes	67% (8)	63% (5)		
- No	33% (4)	37% (3)		
During ECMO diuretic			0.816	0.242
- Yes	75% (9)	100% (8)		
- No	25% (3)	0		
After ECMO diuretic			1	1
- Yes	58.3% (7)	87% (7)		
- No	8.3% (1)	13% (1)		
- Deceased at decannulation	33.3% (4)	0		
Before ECMO inotropy			0.206	>0.999
- Yes	83% (10)	75% (6)		
- No	17% (2)	25% (2)		
During ECMO inotropy			0.816	0.147
- Yes	100% (12)	75% (6)		
- No	0	25% (2)		
After ECMO inotropy				
- Yes	58.3% (7)	75% (6)	1.06	1

TABLE 3 (Continued)

	Hospital mortality ($n = 12$)	Survival to discharge ($n = 8$)	Standard mean difference	p-value
- No	8.3% (1)	25% (2)		
- Deceased at decannulation	33.3% (4)	0		
Before ECMO vasopressor			0.816	0.167
- Yes	75% (9)	37% (3)		
- No	25% (3)	63% (5)		
During ECMO vasopressor			0.272	0.642
- Yes	75% (9)	63% (5)		
- No	25% (3)	37% (3)		
After ECMO vasopressor				
- Yes	50% (6)	37% (3)	1.34	0.3147
- No	17% (2)	63% (5)		
- Deceased at decannulation	33% (4)	0		
Before ECMO labs:				
Platelet count	118 [97–168]	109 [70–148]	0.321	0.537
INR	1.20 [1.20–1.47]	1.35 [1.10–1.58]	−0.082	0.876
BNP	2342 [1380–4624] (unknown = 1)	1787 [580–2646] (unknown = 2)	0.7	0.58
Arterial pH	7.25 (SD 0.23)	7.22 (SD 0.18)	0.177	0.711
Arterial lactate	1.8 [1.0–5.6]	3.3 [0.8–4.4]	0.207	0.908
PaCO2 (mmHg)	48 [41–69]	61 [47–85]	−0.534	0.375
PaO2 (mmHg)	49 [34–56]	53 [45–72]	−0.228	0.316
Serum creatinine	0.60 [0.41–0.91]	0.54 [0.45–0.60]	0.622	0.354
Reversed pott's shunt			1.03	0.109
- Yes	8% (1)	50% (4)		
- No	92% (11)	50% (4)		
Presence of intracardiac shunt[a]			0.118	>0.999
- Yes	83% (10)	87% (7)		
- No	17% (2)	13% (1)		
Required recannulation			0.816	0.242
- Yes	25% (3)	0		
- No	75% (9)	100% (8)		
Invasive ventilation during hospitalization			0.535	0.4
- Yes	100% (12)	87% (7)		
- No	0	13% (1)		
Tracheostomy during hospitalization			0.459	0.537
- Yes	8% (1)	25% (2)		
- No	92% (11)	75% (6)		
Before cannulation echocardiogram				
RVSP (mmHg)	119 (SD 9)	88 (SD 34)	1.33	0.056

(Continues)

TABLE 3 (Continued)

	Hospital mortality ($n = 12$)	Survival to discharge ($n = 8$)	Standard mean difference	p-value
	(unknown = 7)	(unknown = 2)		
LVEF (%)	69.3 (SD 7.3)	60.5 (SD 4.4)	1.63	0.117
Qualitative LV function			0.667	0.485
- Normal/hyperdynamic	82% (9)	100% (8)		
- Reduced	18% (2)	0		
	(unknown = 1)			
First after cannulation echocardiogram				
RVSP (mmHg)	73 (SD 18)	61 (SD 36)	0.453	0.662
	(unknown = 7)	(unknown = 2)		
LVEF (%)	60.7 (SD 5)	59.8 (SD 5.6)	0.213	>0.999
	(unknown = 9)	(unknown = 4)		
Post-cannulation qualitative LVEF				
- Normal	100% (6)	100% (8)	0	
	(unknown = 6)			

Abbreviations: ASD, atrial septal defect; ECMO, Extracorporeal membrane oxygenation; ECPR, Extracorporeal Cardiopulmonary Resuscitation; INR, International normalization ratio; IQR, Interquartile range; LVEF, Left ventricular ejection fraction; PaCO2, pressure of arterial carbon dioxide; PaO2, pressure of arterial oxygen; PDE-5, phosphodiesterase-5; PFO, patent foramen ovale; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; SD, standard deviation; VSD, ventricular septal defect; WSPH, World Symposium on Pulmonary Hypertension.

[a]Intracardiac shunt defined as (ASD, VSD, PFO, or atrial septostomy).

the factors evaluated for each patient and the statistical model.

DISCUSSION

The mortality from patients with refractory PH is extremely high, however, ECMO continues to be utilized as a last-resort intervention given the almost certain mortality that would occur in those who do not undergo cannulation. This single-institution study aimed to describe our experience with pediatric PH patients requiring ECMO and evaluating our outcomes. Our institution does not have specific selection criteria for ECMO in this patient population; rather, each patient is evaluated on a case-by-case basis and the trigger for ECMO is usually the failure of maximal medical therapy and the presence of a viable exit strategy. Before ECMO cannulation, several of the patients were on PH medical therapy, including a PDE-5 inhibitor, endothelin receptor antagonist, inhaled vasodilator (such as iloprost or inhaled nitric oxide), parenteral prostanoids, diuretic, inotropic agent, and a vasopressor. In our study, a conclusion cannot be drawn whether mono, dual, triple, or quadruple therapy before ECMO influences outcomes because of the limited sample size.

Hemodynamic measurements, cardiac shunts, and cardiopulmonary anatomy can be evaluated using echocardiography or cardiac catheterization. Although cardiac catheterization is the gold standard for PH, echocardiography remains an efficient and less invasive tool, which is beneficial in unstable patients.[6–8] Our study evaluated echocardiogram findings to determine if they were associated with survival to discharge. Echocardiogram is important for assessing the degree of PH, including the assessment of right ventricular function. PH has such wide disease severity; however, normal RV function portrays a lower risk patient than having decreased RV function.[9] We found no significant association with survival to discharge from RVSP, LVEF, before and post-ECMO cannulation, and LV qualitative function in this study. Echocardiograms are important especially considering the underlying etiology of PH because this changes treatment algorithms and the ability to predict prognosis. For example, PH associated with congenital heart disease (CHD) may have a better prognosis than other etiologies after correction.[7] Additionally, associated pulmonary arterial hypertension (APAH) may have a mildly improved prognosis compared to idiopathic pulmonary arterial hypertension (IAPH).[10] Even with these assessment modalities, there is no consensus from echocardiogram findings on which

TABLE 4 Evaluation of risk factors associated survival to discharge with univariate logistic regression.

	Sample size	OR	95% CI	*p*-value
Gender	20	2	(0.32–13.4)	0.46
-Male				
-Female				
Age at cannulation (days)	20	1	(1.0–1.0)	0.78
Days on ECMO	20	1.04	(0.95– 0.15)	0.44
ECMO mode (VV/VA)	20	0.12	(0.01–0.86)	0.046
ECPR (Y/N)	20	3.5	(0.39– 7.6)	0.31
WSPH classification (Group 1 + 3)	20	1.4	(0.11–33.7)	0.8
Diagnosed this hospitalization (Y/N)	20	0.83	(0.13–5.77)	0.85
On home PH medication (Y/N)	20	1.2	(0.17–7.97)	0.85
Before ECMO PDE-5 inhibitor (Y/N)	20	1.67	(0.16–17.2)	0.65
During ECMO PDE-5 inhibitor (Y/N)	20	1.2	(0.17–7.97)	0.85
After ECMO PDE5- inhibitor (Y/N)	16	0.33	(0.03–2.6)	0.31
Before ECMO endothelin receptor antagonist (Y/N)	20	0.33	(0.04–2.17)	0.27
During ECMO endothelin receptor antagonist(Y/N)	20	5	(0.59–110)	0.19
After ECMO endothelin receptor antagonist(Y/N)	16	0.33	(0.03–2.6)	0.31
Before ECMO inhaled vasodilator (Y/N)	20	3.67	(0.29–89.2)	0.33
During ECMO inhaled vasodilator (Y/N)	20	-	-	-
After ECMO inhaled vasodilator (Y/N)	16	1	(0.03–28.8)	>0.99
Before ECMO parenteral prostanoid (Y/N)	20	1	(0.16–6.19)	>0.99
During ECMO parenteral prostanoid (Y/N)	20	0.67	(0.07–4.72	0.69
After ECMO parenteral prostanoid (Y/N)	16	2.33	(0.18–58)	0.53
Before ECMO diuretic (Y/N)	20	1.2	(0.17–7.97)	0.85
During ECMO diuretic (Y/N)	20	0	-	>0.99
After ECMO diuretic (Y/N)	16	1	(0.03–28.8)	>0.99
Before ECMO inotropy (Y/N)	20	1.67	(0.16–17.2)	0.65
During ECMO inotropy (Y/N)	20	-	-	>0.99
After ECMO inotropy (Y/N)	16	0.43	(0.02–5.61)	0.53
Before ECMO vasopressor (Y/N)	20	5	(0.77–40.6)	0.1
During ECMO vasopressor (Y/N)	20	1.8	(0.25–13.4)	0.55
After ECMO vasopressor (Y/N)	16	5	(0.65–53.7)	0.14
Before ECMO labs:				
-Platelet count	20	1	(0.99–1.02)	0.52
-INR	20	0.79	(0.06–11.8)	0.86
-BNP	17	1	(1.0–1.0)	0.28
-Arterial pH	20	2.35	(0.02–258)	0.71

(Continues)

TABLE 4 (Continued)

	Sample size	OR	95% CI	*p*-value
-Arterial lactate	20	1.05	(0.85–1.36)	0.67
-PaCO2 (mmHg)	20	1		0.74
-PaO2 (mmHg)	20	1	(0.97–1.02)	0.63
-Serum creatinine	20	7.86	(0.66–1069)	0.29
Reversed pott's shunt (Y/N)	20	0.09	(0–0.84)	0.057
Presence of intracardiac shunt[a] (Y/N)	20	0.71	(0.02–8.97)	0.8
Required recannulation (Y/N)	20	-	-	>0.99
Invasive ventilation during hospitalization (Y/N)	20	0		>0.99
Tracheostomy during hzaszospitalization (Y/N)	20	0.27	(0.01–3.43)	0.33
Before cannulation echocardiogram findings				
-RVSP (mmHg)	15	1.06	(1.01–1.14)	0.062
-LVEF	10	1.38	(1.01–2.64)	0.16
-Qualitative LV function	19	0		>0.99
- Normal/hyperdynamic				
- Reduced				
First after cannulation echocardiogram findings				
-RVSP (mmHg)	11	1.02	(0.97–1.07)	0.49
-LVEF	7	1.05	(0.74–1.56)	0.78
Post-cannulation qualitative LVEF	20	0		>0.99

Abbreviations: ASD, atrial septal defect; CI, confidence interval; ECMO, Extracorporeal membrane oxygenation; ECPR, Extracorporeal Cardiopulmonary Resuscitation; INR, International normalization ratio; IQR, Interquartile range; LVEF, Left ventricular ejection fraction; OR, odds ratio; PaCO2, pressure of arterial carbon dioxide; PaO2, pressure of arterial oxygen; PDE-5, phosphodiesterase-5; PFO, patent foramen ovale; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; VSD, ventricular septal defect; WSPH, World Symposium on Pulmonary Hypertension.

[a]Intracardiac shunt defined as (ASD, VSD, PFO, or atrial septostomy).

patients have better or worse outcomes when bridged with ECMO and further studies are warranted.

In this data set, inotropic medications and vasopressors were not associated with survival to discharge; however, a multicenter retrospective analysis on pediatric PH patients requiring ECMO showed that vasopressor medications were associated with increased mortality.[2] This same study showed that eCPR, not surprisingly, had increased mortality for pediatric PH patients, which is consistent in our study.[2] Another study in pediatric PH, ICU patients showed a higher mortality associated with vasoactive infusions even without ECMO.[11] Even though 80% of our cohort survived to decannulation, only half survived to discharge emphasizing the high mortality of pediatric PH when ECMO is required regardless of prior therapy. All patients who survived to discharge survived to 1-year follow-up, which indicates that survival to hospital discharge may be a better indicator of longer-term outcomes than survival to decannulation. Reasons for nonsurvival in our cohort are not unique to pulmonary hypertension patients; however, they emphasize how medically fragile these patients are.

ECMO configuration is an important topic to discuss early in the management of pediatric PH. The results of this study show a statistically significant association between VV ECMO and survival to discharge. A similar adult study showed that initial VV ECMO configuration was associated with a poor outcome and a higher in-hospital mortality compared to VA ECMO in patients who were bridging to transplant.[12] One main difference between this paper and our study is that our population only included WSPH groups 1 and 3, compared to the

other paper which included all adult PH WSPH groups, including group 2. This is counter-intuitive and may be impacted by selection bias with those who had preserved RV function, presence of a congenital systemic to pulmonary shunt including the reversed Potts shunt, or a treatable cause of decompensation such as pneumonia being placed on VV ECMO.

Each VV ECMO case was investigated to assess the key differences between ECMO runs. There was a total of seven patients initially configured to VV ECMO. Of the 13 patients who were initially configured to VA ECMO for their first run, two were converted to VV ECMO after a Potts shunt creation, one of whom survived to discharge. There were three VV ECMO configurations performed initially after reversed Potts shunt operations, who all survived to discharge; two of which were planned postoperatively and one placed on ECMO due to hypoxia shortly after the operation. The remaining three Potts shunt creations were performed during their VA ECMO run. There was one patient with two ECMO runs who was initially configured to VA ECMO and then was converted to VV ECMO after receiving a Potts shunt during their first run; however, this patient suffered cardiac arrest due to a PH crisis 1 day after decannulation. ECPR was attempted; however, the flows were inadequate, so the patient did not survive to discharge. The patient who survived with VA ECMO after an ECPR received a Potts shunt during their ECMO run and was converted VV ECMO after surgery. The final Potts shunt during VA ECMO was performed on a patient initially configured to VV ECMO, who was successfully decannulated. Ten days later the patient had an acute PH crisis during Potts shunt creation that required VA ECMO intraoperatively. This patient suffered from an ischemic stroke and multiorgan failure during the second week of ECMO so palliative decannulation was performed. There were two patients configured to VV ECMO due to hypoxia associated with PH crises; one who survived to discharge and another who survived to decannulation only. Both of these patients with PH crises had intracardiac shunts. There were two patients initially configured to VV ECMO because of infection: one patient, with an ASD, had human metapneumovirus causing acute respiratory distress syndrome (ARDS), who survived to decannulation after a 41-day run, but did not survive to discharge. The other patient was configured to VV ECMO for 7 days due to bacterial pneumonia and this patient survived to discharge. Interestingly, this patient did not have an intracardiac shunt and had qualitative normal RV function before cannulation. The patient who was de-escalated from VA to VV ECMO for their second run was bridging to transplant, had an atrial septostomy, and survived for 57 days on the VV configuration until the patient had worsening end organ function, increased pressor requirement and family withdrew care. The qualitative RV function before cannulation onto VV ECMO varied from decreased to normal; however, it was deemed adequate to support them with a VV configuration. This emphasizes that pediatric PH requires specialized and experienced care because there may be key differences between adult and pediatric PH management and instances where VV ECMO may be appropriate.

Treatment of pediatric PH is driven mainly by data in the adult literature.[13,14] Pulmonary hypertension medications target prostacyclin pathways, endothelin receptors, and nitric oxide pathways to cause pulmonary vasodilation, thereby reducing pulmonary arterial pressures.[15] Targeted medications included endothelin receptor antagonists, prostacyclin agonists, PDE-5 inhibitors, and calcium channel blockers. The consensus is that as disease severity worsens, combination therapy shows improvements over monotherapy.[13,15–18] Another factor to consider is the treatment of patients with intravenous medications, such as prostanoids, which can become systemically delivered from congenital or created intracardiac shunts leading to hypotension.[12] Similarly, VV ECMO can shunt blood systemically when there are intracardiac shunts present. This further emphasizes the complexity and individualized treatment that each pediatric PAH patient required, especially in the setting of ECMO. We evaluated inpatient PH medications before, during, and after ECMO runs for 20 patients. There was no significant difference in survival to discharge for PH patients treated with endothelin receptor antagonists, prostacyclin agonists, inhaled vasodilators, and PDE-5 inhibitors. Although there was no statistically significant difference in this study, further evaluation is warranted to optimize medical management on ECMO.

Inpatient PH medications are not the only important factor for pediatric PH patients. We evaluated patients on home medications and if they were diagnosed during hospitalization. Though no statistical association was found between patients who survived to discharge and if they were on home PH medication, it is still worth evaluating medications in the outpatient setting that may prevent decompensation requiring hospitalization and ECMO. Diagnosis of PAH during hospitalization showed no significant difference for those who survived to discharge and those who did not, which signifies how unpredictable decompensation can be despite whether they are well controlled on home medications or newly diagnosed. PH in the pediatric population is complex and is best treated by specialists with extensive clinical experience. Collaboration among pediatric PH centers may

help improve treatment, especially in the inpatient setting and on ECMO.[17,18]

This study has a few important limitations. The primary limitation is our sample size; this single-center study looks at 12 years of data for an already rare disease process with a limited subset requiring ECMO cannulation. While our institution has no specific selection criteria for decompensated PH, these patients typically fail maximal medical therapy before escalating to ECMO. Additionally, the escalation to ECMO is usually as a bridge to recovery because we do not have a pediatric lung transplant program, which may affect the total number of cannulations for pediatric PH during this period. The benefit of looking at a single center is that all the data entered is reliable, and all the information obtained can be confirmed in the electronic medical record. The fact that there are few patients makes it difficult to power a strong statistical conclusion. It cannot be denied that this study is consistent with the literature regarding pediatric PH requiring ECMO, which has a significant mortality rate.[2] Another limitation of this study is those inherent to a retrospective review of the electronic medical record. An important point to note is the persistent pulmonary hypertension of the newborn, and WSPH groups 2, 4, and 5 were excluded from the study to focus on WSPH group 1 (idiopathic pulmonary arterial hypertension) and WSPH group 3 in the pediatric population. This confines the generalizability of our results to children with WSPH groups 1 and 3. Additional investigation using echocardiogram and cardiac catheterization findings could be helpful in further understanding the etiologies of decompensation of pediatric PH patients in future studies.

Pediatric PAH refractory to medical treatment is unpredictable and often requires extreme measures including ECMO as a bridge to recovery or a bridge to transplant. Without ECMO, mortality with this disease during decompensation is almost a certainty. Our cohort of patients were considered for ECMO once medical management was exhausted. Unmodifiable risk factors can help guide physicians to prognosticate and counsel patients' and their families. Modifiable risk factors will help optimize treatment to improve outcomes. This single-center study evaluated factors associated with survival to discharge to guide multidisciplinary teams treating pediatric PH on ECMO. While VA ECMO is the main configuration for decompensated PH, VV ECMO initiation in children could be considered when there is adequate ventricular function, presence of a systemic to pulmonary shunt or an intercurrent treatable illness such as pneumonia to improve survival to discharge. Further studies evaluating modifiable risk factors, including PH medications, should be performed with larger populations to enhance medical treatment with ECMO.

AUTHOR CONTRIBUTIONS

All of the authors listed in the manuscript have contributed sufficiently to be listed.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICAL APPROVAL STATEMENT

Columbia University Institutional Review Board approval was obtained for the study. IRB Approval number AAAR0525.

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