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ORIGINAL ARTICLE

Outcomes following venoarterial extracorporeal membrane oxygenation in children with refractory cardiogenic disease

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Abstract

Retrospective analysis was performed at an affiliated university children's hospital with consecutive patients receiving a venoarterial extracorporeal membrane oxygenation (VA-ECMO) for refractory cardiogenic shock from July 2007 to May 2018. Fifty-six patients underwent VA-ECMO for refractory cardiogenic shock with the median age of 39.0 (1.5, 103.5) months were included. Median ECMO duration was 87 h, and the median length of hospital stay was 22 days. Successful ECMO weaning rate was 68%. Thirty-day mortality in this cohort was 39% (22/56), among which the mortality of fulminant myocarditis and postcardiotomy cardiogenic shock (PCS) were 23% (6/26) and 52% (12/23), respectively. Multivariate Cox proportional hazard regression analysis identified prolonged prothrombin time (PT) > 6 s and elevated lactate level 24 h after ECMO initiation were associated with 30-day mortality.

Conclusions: Pediatric VA-ECMO for refractory cardiogenic shock appears to be a satisfactory salvage therapy to various fatal diseases in this retrospective study. Prolonged PT > 6 s and elevated lactate level 24 h were significant predictors of 30-day mortality.

What is Known:
• VA-ECMO is a salvage therapy for refractory cardiogenic shock in pediatrics.

What is New:
• Prothrombin time > 6 s was a significant predictor of 30-day mortality.
• Elevated lactate level 24 h was a significant predictor of 30-day mortality

Keywords Venoarterial extracorporeal membrane oxygenation · Refractory cardiogenic shock · Mortality · Pediatric

Abbreviations

ACT	Activated clotting time
AFM	Acute fulminant myocarditis
ALT	Alanine transaminase
AST	Aspartate transaminase
DIC	Disseminated intravascular coagulation
ECLS	Extracorporeal life support
ECPR	Extracorporeal cardiopulmonary resuscitation
GI	Gastrointestinal
ICU	Intensive care unit
PCS	Postcardiotomy cardiogenic shock
PT	Prothrombin time

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RCS	Refractory cardiogenic shock
VA-ECMO	Venoarterial extracorporeal membrane oxygenation
VIS	Vasoactive-inotropic score
TGA	Transposition of the great arteries

Introduction

Refractory cardiogenic shock (RCS) is associated with significant morbidity and mortality, and current conventional medical therapy appears inadequate in some fatal diseases. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) can provide cardiac support to patients with refractory cardiogenic shock [1, 2]. Despite remarkable advances in the quality of the devices and in the overall intensive care unit (ICU) management, this rescue therapy is still accompanied by a high rate of death and complications such as infection, bleeding, organ failure, or mechanical device complications [3, 4]. ECMO may be lifesaving but requires considerable resources and is expensive. Although there is an increasing use of ECMO support to children with heart disease, survival remains relatively low [5]. Therefore, a clear understanding of ECMO outcomes in this high-risk population, risk factors for mortality, and strategies to improve outcomes are becoming increasingly important. There are limited data on outcomes in the pediatric population, who require VA-ECMO for cardiac support.

This study represents our institution's 11-year experience with pediatric VA-ECMO for RCS, addressing the characteristics of our patient population, the analysis of clinical outcomes including mortality and complications of support, and the identification of risk factors associated with 30-day mortality.

Materials and methods

This retrospective analysis was performed at an affiliated university children's hospital with consecutive patients receiving a VA-ECMO for refractory cardiogenic shock from July 2007 to May 2018. Zhejiang University School of Medicine Children's Hospital Committee on Clinical Investigation approved the review of patient medical records.

Variables and definitions

In this study, RCS is defined as follows: (1) cardiac index < 2.0 L/min/m^2, metabolic acidosis (buffuer excess ≤ 5 mmol/L, lactate level > 3.0 mmol/L), signs of end-organ failure (urinary flow rate < 0.5 mL/kg/h), mean arterial pressure: neonates < 40 mmHg, infants < 50 mmHg, children < 60 mmHg, persisting more than 3 h despite optimized inotropic measures; (2) failure to wean cardiopulmonary bypass despite optimized inotropic measures; and (3) patient undergoing active cardiopulmonary resuscitation upon cannulation. Thirty-day mortality was defined as death from any cause occurring within 30 days after ECMO explantation.

All clinical variables of patients requiring ECMO support were retrospectively collected from our institutional database and extracorporeal life support (ECLS) registry form files. Renal failure was defined as the presence of oliguria (< 0.5 ml/kg/h) or a tripling of creatinine value or with demand for hemodialysis. Liver injury was defined with biochemical evidence of acute liver injury and hepatic-based coagulopathy. Neurological complications were recorded in the presence of clinical symptoms, e.g., seizure, motor dysfunction, or radiological evidence for the neurological deficit or defect, e.g., bleeding, stroke, or severe cerebral edema. Gastrointestinal (GI) complications summarized all complications involving the gastrointestinal tract like GI bleeding, paralytic ileus, mesenteric ischemia, and intestinal perforation. Abdominal interventions combined all procedures for treatment of gastrointestinal complications containing laparotomy. Infection was diagnosed from the evidence of positive blood or sputum culture. Vasoactive-inotropic score (VIS) was calculated as previously described [6]. Lactate peak value prior to ECMO was collected. In emergency cases, if no blood gas analysis was taken before ECMO, the first lactate value 0.5 to 1 h after the ECMO initiation (ECMO 1st) was collected as lactate peak. Lactate values at 6, 12, 24, and 48 h after ECMO implementation were also collected. The trend of lactate over time after ECMO initiation was demonstrated by lactate clearance and was calculated by the following equitation:

$$\text{Lactate clearance (timepoint)} = (\text{lactate on ECMO 1st} - \text{lactate [timepoint]}) / \text{lactate on ECMO 1st.}$$

For example, lactate clearance at 12 h after ECMO initiation is calculated as: (lactate on ECMO 1st − lactate [12 h])/ lactate on ECMO 1st.

Patient management

ECMO implantation was performed either peripheral or central. Peripheral access is used via the right common carotid artery and internal jugular vein or femoral artery and vein with the cut-down method. Intraoperative ECMO was installed via central thoracic cannulation (arterial cannula into the ascending aorta, venous cannula into the right atrium). The VA-ECMO circuit consists of a Rotaflow centrifugal pump (Maquet, Germany) in conjunction with a membrane oxygenator (Hilite 800/2400/7000 LTTM, Medos Medizintechnik AG, Stolberg, Germany; Quadrox PLS® MAQUET Cardiovascular,

Table 1 Demographic data, characteristics, and clinical features of patients requiring ECMO for RCS

Demographics	Overall	Nonsurvivors	Survivors	*p*
Patients (*n*)	56	22	34	
Patient demographics				
Age (month)	39.0 (1.5, 103.5)	5.8 (1.2, 75.0)	77.5 (6.5, 129.0)	0.016
Male	32/56 (57%)	15/22 (68%)	17/34 (50%)	0.179
Weight (kg)	12.3 (4.53, 26.5)	7.9 (3.5, 20.5)	20.5 (5.9, 33.5)	0.016
Etiology of RCS; *n* (%)				0.067
AFM	26/56 (46%)	6	20	
PCS	23/56 (41%)	12	11	
Others	7/56 (11%)	4	3	
Clinical features				
Central cannulation	26/56 (46%)	14/22 (64%)	12/34 (35%)	0.038
Peripheral cannulation	30/56 (54%)	8/22 (36%)	22/34 (65%)	
Left atrial cannula	5/56 (9%)	5/22 (23%)	0/34	0.015
ECPR	14/56 (25%)	7/22 (32%)	7/34 (21%)	0.343

Categorical variables are depicted as *n* (%), continuous variables as median (IQR)

AFM acute fulminant myocarditis, *PCS* postcardiotomy cardiogenic shock, *ECPR* extracorporeal cardiopulmonary resuscitation

*$p < 0.05$

Hirrlingen, Germany; Sorin, Italy) with an integrated heat exchanger. As with all patients, the risk of bleeding must be assessed against the benefits of preventing thrombus. Anticoagulation with IV heparin is initiated as soon as bleeding is controlled. The goal of activated clotting time (ACT) was 160–200 s. Weaning was cautiously initiated when left ventricular ejection fraction was above 40% and respiratory function was stable. Pump flow was gradually decreased 24 h before weaning. ECMO explantation was performed under sterile conditions at ICU. ECMO therapy was terminated in patients with poor prognosis without evidence for cardiocirculatory recovery or in the presence of other severe complications such as intractable bleeding.

Statistical analysis

Statistics were performed using the SPSS statistical software package (Version19; IBM, Armonk, NY, USA). Categorical variables were expressed as percentages and were analyzed using the Pearson ×2 test. All other data are described as medians (IQR) and compared using the Mann-Whitney *U* test. To identify predictors of 30-day mortality, univariate Cox proportional hazard regression analysis was performed utilizing clinical baseline variables. Significance was defined as $p < 0.05$. Those variables found to be significant on univariate analysis were entered into a multivariate Cox proportional hazard regression model.

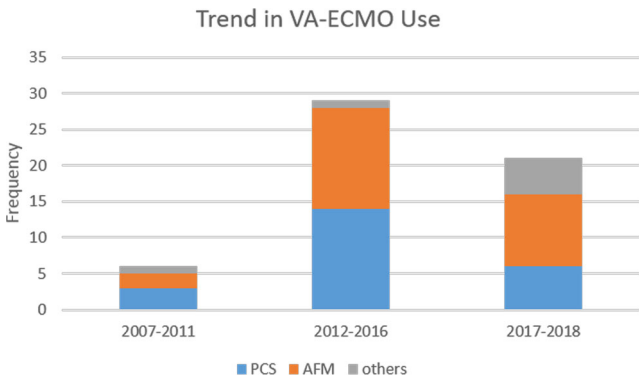

Fig. 1 Overall trends in VA-ECMO use during the study period across etiologies RCS. *AFM* acute fulminant myocarditis, *PCS* postcardiotomy cardiogenic shock, *RCS* refractory cardiogenic shock, *VA-ECMO* venoarterial extracorporeal membrane oxygenation

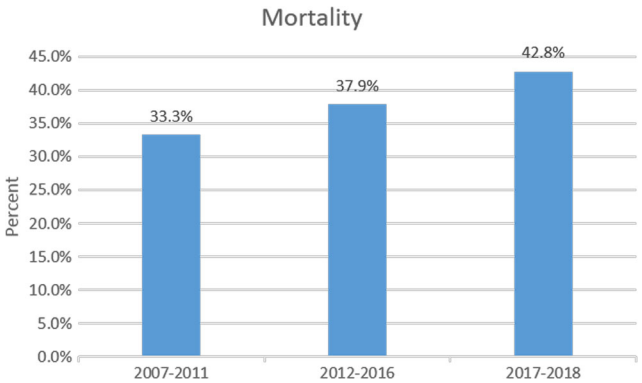

Fig. 2 Mortality in VA-ECMO use with RCS during the three stages in the study period. *RCS* refractory cardiogenic shock, *VA-ECMO* venoarterial extracorporeal membrane oxygenation

Table 2 Cardiac anatomic diagnosis in postcardiotomy cardiogenic shock patients

Diagnosis	Number = 23	
	n	(%)
d-Transposition of the great arteries	9	(39.1)
Tetralogy of Fallot	3	(13.0)
Total anomalous pulmonary venous connection	2	(8.7)
Pulmonary atresia	2	(8.7)
Single ventricle with hypoplastic aortic arch	1	(4.3)
Endocardial cushion defect	1	(4.3)
Interruption of the aortic arch	1	(4.3)
Coarctation of the aorta	1	(4.3)
Double outlet of the right ventricle (Taussing-Bing)	1	(4.3)
Mitral stenosis	1	(4.3)
Ventricular septal defect	1	(4.3)

Results

Baseline characteristics

From July 2007 to May 2018, 56 patients underwent VA-ECMO for refractory cardiogenic shock. Patient demographics, etiology, and clinical features have been summarized in Table 1. Since 2007, the major protocol of VA-ECMO management and the equipment (a centrifugal pump, RotaFlow, Maquet) have not changed for 11 years, but the experience of ECMO specialists and the details of the ECMO program have been advanced. Overall use of VA-ECMO for RCS increased in our hospital during the study period and can be divided into 3 stages: (1) the early period from 2007 to 2011 with 1–2 RCS cases per year; (2) steady developing period from 2012 to 2016 with nearly 5 RCS cases per year; and (3) rapid developing period from 2017 till May 2018 with almost 15 RCS cases per year. The distribution of different etiologies for VA-ECMO with RCS was similar in three stages (Fig. 1). The mortality of these 3 stages was 33.3, 37.9, and 42.8%, respectively (Fig. 2). In our cohort, 11% of patients were neonates, 32% of patients were ranged between 28 days to 1 year, and 57% of patients were greater than 1 year. The median age of our patients was 39.0 (1.5, 103.5) months. Among these patients, the most common cardiac indication was fulminant myocarditis, comprising 46% of cases (26/56); followed by postcardiotomy cardiogenic shock (PCS) accounting for 41% (23/56); 11% (6/56) patients presented with cardiac arrest with other various causes including malignant arrhythmia, toxic enteritis, airway obstruction, carbonic oxide intoxication, and cardiomyopathy; and the left one was diagnosed with transposition of the great arteries who underwent RCS due to severe hypoxia before surgery. Cannulation was mostly performed at ICU bedside (64%,$n = 36$), and the left was performed in the operation room. Forty-six percent of patients were cannulated centrally (46%, $n = 26$). Peripheral access is used via the right common carotid artery and internal jugular vein (52%, $n = 29$) except one case was performed via the femoral artery and vein (2%, $n = 1$). Five patients underwent left atrial decompression, and extracorporeal cardiopulmonary resuscitation (ECPR) rate among our cohort was 25% (14/56). Vasoactive-inotropic score was 46 (23,100) prior to ECMO cannulation. Patients required at least one vasoactive medication prior to ECMO cannulation. Patients most commonly received epinephrine and dopamine followed by dobutamine and milrinone, norepinephrine, and vasopressin. Before ECMO initiation, median lactate peak level was 10.3 (5.8, 14.3) mmol/L, median arterial pH was 7.298 (7.170, 7.375), median alanine transaminase (ALT) was 31.0 (16.0, 113.0) U/L, and median creatinine was 60.0 (44.2, 80.0) μmol/L.

During the study period, 7963 children had cardiac surgery requiring cardiopulmonary bypass, among which 23 patients

Table 3 Initial surgical procedure performed in postcardiotomy cardiogenic shock patients

Procedure	Number = 23	
	n	(%)
Arterial switch procedure ± ventricular septal defect closure	8	(34.8)
Arterial switch procedure + aortic arch reconstruction + ventricular septal defect closure	2	(8.7)
Tetralogy of Fallot	3	(13.0)
Repair, total anomalous pulmonary venous connection	2	(8.7)
Complex palliation	2	(8.7)
Norwood stage I + Sano	1	(4.3)
Repair, endocardial cushion defect	1	(4.3)
Aortic arch reconstruction + ventricular septal defect closure	2	(8.7)
Mitral valve replacement	1	(4.3)
Ventricular septal defect closure	1	(4.3)

(0.29%) were treated with VA-ECMO. The rate of ECMO application was lower than other institutions mainly for two reasons: (1) overall incidence of PCS remains low in our institution and (2) the attitude of the treatment team was passive when cardiac failure exists following cardiopulmonary bypass at the early period. Anatomic lesions and initial surgical procedures in PCS patients are presented in Tables 2 and 3. VA-ECMO was prominently applied after cardiac surgeries for repair of congenital heart lesions (91.3%) and d-transposition of the great arteries (TGA) was accounted for 39.1%. Demographic data and clinical features of patients requiring ECMO with PCS have been summarized in Table 4. The incidence of renal failure prior to ECMO implantation was significantly higher in nonsurvival patients.

Outcomes and complications

Outcomes and complications are depicted in Table 5. Median ECMO duration was 87 h, ranging from 8 to 344 h, and the median length of hospital stay was 22 days, ranging from 1 to 96 days. Successful ECMO weaning rate was 68%. Thirty-day mortality in this cohort was 39% (22/56), among which the mortality of acute fulminant myocarditis (AFM) and PCS were 23% (6/26) and 52% (12/23), respectively. The causes of death were irreversible cardiac failure (8/22), multiple organ failure (6/22), untreatable bleeding (3/22,), cerebral death (3/22), antibiotic-associated enteritis leading to severe malnutrition (1/22), and cardiac tamponade (1/22). Two of those patients who survived within 30 days died in-hospital because of insufficient cardiac function. One patient died after transferring to a rehabilitation hospital due to rupture of the reconstructed airway. After 3 months to 1-year follow-up, overall mortality was 45% (Fig. 3).

The most common complication was surgical site bleeding with an occurrence rate of 23%, followed by renal failure (18%), pneumorrhagia (18%), cannular site bleeding (18%), neurological complications (16%), hepatic failure (13%), disseminated intravascular coagulation (DIC) (13%), gastrointestinal hemorrhage (13%), hemolysis (7%), and infection (7%). Gastrointestinal hemorrhage and surgical site bleeding occurred at a higher rate of 27 and 46% in nonsurvivors, respectively, compared to 3 and 9% in survivors. Renal failure and DIC were also found to be significantly different between those patients who survived and those who did not.

Table 4 Demographic data, characteristics, and clinical features of patients requiring ECMO with postcardiotomy cardiogenic shock

Demographics	Overall	Nonsurvivors	Survivors	*p*
Patients (*n*)	23	12	11	
Patient demographics				
Age (month)	1.3 (1.0, 6.4)	1.6 (0.6, 6.1)	1.3 (1.0, 7.1)	0.877
Male	16/23 (69.6%)	10/12 (83.3%)	6/11 (54.5%)	0.193
Weight (kg)	4.5 (3.0, 8.0)	4.0 (3.1, 7.8)	4.5 (3.0, 8.2)	0.666
ECMO duration	72.0 (22.0, 98.0)	71.0 (19.8, 153.8)	72.0 (44.0, 88.0)	0.829
Emergency surgery	2/23 (8.7%)	2/12 (16.7%)	0/11 (0%)	0.478
CPB time (minute)	273 (170, 360)	290 (189, 366)	286 (222, 352)	0.843
Clamp time (minute)	116 (83, 145)	106 (95, 149)	120 (68, 138)	0.644
Prior to ECMO				
Renal failure	5/23 (21.7%)	5/12 (41.7%)	0/11 (0%)	0.037*
Peak lactate (mmol/L)	9.4 (5.6, 14.8)	12.6 (6.5, 15.7)	8.8 (5.5, 10.7)	0.147
MAP	44 (33, 53)	41 (34, 51)	47 (33, 60)	0.262
VIS	40 (20, 56)	35 (20, 46)	41 (20, 79)	0.476
Timing of ECMO				
Failure to wean CPB	18/23 (78.3%)	10/12 (83.3%)	8/11 (72.3%)	0.640
RCS after surgery	5/23 (21.7%)	2/12 (16.7%)	3/11 (27.3%)	0.640
Indications for ECMO				
Ventricular failure	9/23 (39.1%)	3/12 (25%)	6/11 (54.5%)	0.214
Ventricular failure due to coronary malformation	2/23 (8.7%)	2/12 (16.7%)	0/11 (0%)	0.478
Ventricular failure without spontaneous returned heartbeat	2/23 (8.7%)	2/12 (16.7%)	0/11 (0%)	0.478
Multiple indications	10/23 (43.5%)	5/12 (41.7%)	5/11 (45.5%)	1.0

Categorical variables are depicted as *n* (%), continuous variables as median (IQR)

CPB cardiopulmonary bypass, *MAP* mean arterial pressure, *VIS* vasoactive-inotropic score, *RCS* refractory cardiogenic shock

*$p < 0.05$

Table 5 Outcomes and complications of patients requiring ECMO for RCS

Variables	All	Nonsurvivor	Survivor	*p*
ECMO duration	87.0 (48.8, 131.5)	71.0 (21.8, 171.8)	88.0 (70.5, 122.5)	0.502
Length of ventilation	6.5 (4.0, 11.8)	4.5 (2.8, 13.3)	7.0 (5.0, 10.0)	0.173
Length of ICU stay	12.0 (7.0, 18.0)	5.0 (2.0, 13.0)	14.0 (11.0, 23.0)	0.000*
Length of hospitalization	22.0 (12.0, 31.0)	10.0 (4.0, 19.5)	28.0 (22.0, 39.0)	0.000*
Renal failure	10/56 (18%)	8/22 (36%)	2/34 (6%)	0.011*
Hepatic failure	7/56 (13%)	4/22 (18%)	3/34 (9%)	0.535
Neurological complication	9/56 (16%)	6/22 (27%)	3/34 (9%)	0.143
Pneumorrhagia	10/56 (18%)	6/22 (27%)	4/34 (12%)	0.262
GI hemorrhage	7/56 (13%)	6/22 (27%)	1/34 (3%)	0.023*
Infection	4/56 (7%)	2/22 (9%)	2/34 (6%)	1.0
DIC	7/56 (13%)	7/22 (32%)	0/34 (0%)	0.002*
Surgical site bleeding	13/56 (23%)	10/22 (46%)	3/34 (9%)	0.002*
Cannular site bleeding	10/56 (18%)	6/22 (27%)	4/34 (12%)	0.262
Hemolysis	4/56 (7%)	2/22 (9%)	2/34 (6%)	1.0

Categorical variables are depicted as *n* (%), continuous variables as median (IQR)

ICU intensive care unit, *DIC* disseminated intravascular coagulation

*$p < 0.05$

Predictors of 30-day mortality

Comparison of the survivors and nonsurvivors variables prior to and during ECMO support was summarized in Table 6. The longitudinal data of lactate over time was shown in Fig. 4. The trend of lactate clearance between survivors and nonsurvivors are depicted in Table 7 and Fig. 5. Univariate and multivariate Cox proportional hazard regression models are summarized in Table 8. Through univariate proportional hazard regression analysis, age, weight, lactate prior to ECMO initiation, prolonged prothrombin time (PT) > 6 s, and elevated lactate level 24 h after ECMO initiation were found to be significantly associated with 30-day mortality. On multivariate Cox analysis, prolonged PT > 6 s and elevated lactate level 24 h after ECMO initiation were significant predictors of 30-day mortality (Figs. 6 and 7).

Discussion

This study retrospectively analyzed the contemporary outcomes of pediatric VA-ECMO for RCS with various etiologies. The primary findings of interest were (1) a 30-day mortality of 39% and overall mortality of 45%. (2) Multivariate Cox

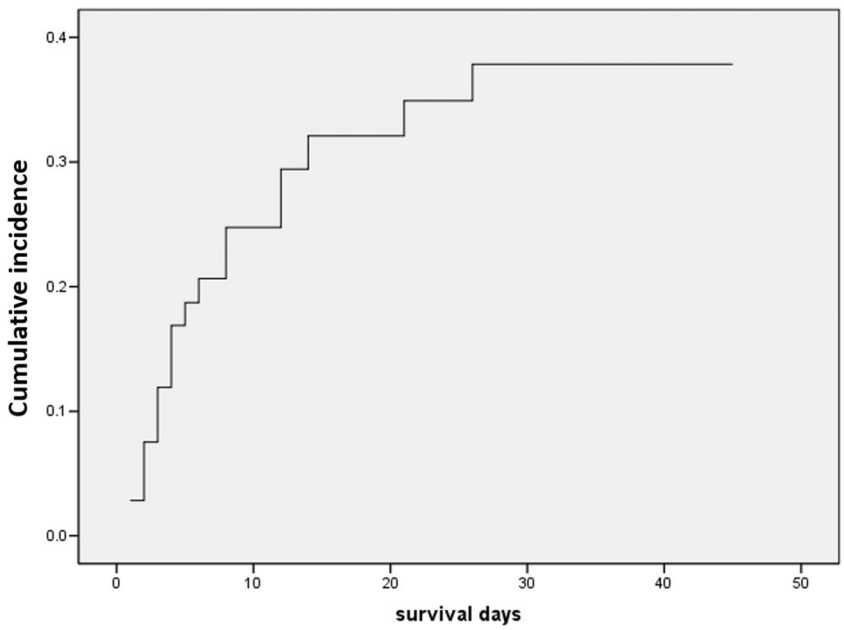

Fig. 3 Overall cumulative incidence of mortality following VA-ECMO support

Table 6 Comparison of the survivors and nonsurvivors variables during ECMO support

Variables	All	Nonsurvivor	Survivor	*p*
Prior to ECMO				
Peak lactate (mmol/L)	10.3 (5.8, 14.3)	13.5 (8.4, 18.3)	9.1 (5.1, 12.9)	0.006*
CRE (μmol/L)	60.0 (44.2, 80.0)	60.2 (45.9, 88.4)	60.0 (43.3, 79.3)	0.595
ALT (U/L)	31.0 (16.0, 113.0)	32.0 (14.5, 117.5)	30.5 (18.5, 156.5)	0.479
PT (s)	13.5 (12.3, 16.2)	13.8 (12.0, 15.4)	13.4 (12.5, 18.8)	0.688
VIS	46.0 (22.5, 100.0)	46 (30, 100)	56 (20, 100)	0.715
EF (%)	0.40 (0.27, 0.53)	0.40 (0.23, 0.50)	0.40 (0.29, 0.54)	0.531
During ECMO				
CRE (μmol/L)	65.5 (48.5, 104.8)	70.0 (52.3, 142.4)	60.1 (41.9, 90.3)	0.113
PT (s)	18.2 (14.8, 24.5)	22.2 (15.7, 42.0)	17.1 (14.6, 21.4)	0.025*
BNP (pg/mL)	23,728 (7458, 35,000)			
12 h lactate (mmol/L)	2.3 (1.4, 4.3)	5.3 (2.2, 11.2)	1.8 (1.3, 2.8)	0.003*
24 h lactate (mmol/L)	1.7 (1.2, 2.2)	2.5 (1.4, 7.5)	1.5 (1.2, 1.8)	0.005*
VIS	20 (12, 39)	30 (16, 42)	17 (10, 30)	0.026*
4 h ECMO flow (mL/kg/min)	85 (63, 106)	95 (67, 106)	84 (54, 109)	0.363
24 h ECMO flow (mL/kg/min)	89 (63, 112)	95 (72, 109)	82 (57, 116)	0.288

Continuous variables are depicted as median (IQR)

CRE creatinine, *ALT* alanine aminotransferase, *PT* prothrombin time, *VIS* vasoactive-inotropic score, *EF* eject fraction, *BNP* brain natriuretic peptide

*$p < 0.05$

proportional hazard regression analysis identified prolonged PT > 6 s and elevated lactate level 24 h after ECMO initiation were significant predictors of 30-day mortality.

According to the most recent ELSO report published in 2017, neonatal and pediatric cardiac ECLS survival to hospital discharge was 45 and 57%, respectively [1]. Among pediatric cardiac ECLS patients, those with myocarditis had the highest survival rate (76%), while those requiring ECLS for congenital heart disease had a survival rate of 54%. Our findings suggest that survival rate in the pediatric population requiring VA-ECMO for cardiac indications over the past 11 years was 61%. Similar to the ELSO report, ECMO run for AFM had the highest survival rate (77%), followed by PCS (48%). The lower survival rate in PCS patient compared to AFM patients might have to do with the passive attitude of the treatment team when cardiac failure exists following cardiopulmonary bypass, which resulted in the worse timing of ECMO initiation compared to other etiologies and had contributed to the significantly higher incidence of renal failure in PCS patients. Moreover, the underlying lesions (such as TGA with coronary malformation and ventricular failure without spontaneous returned heartbeat) might be related to death. Despite the discrepancy in survival between myocarditis and PCS patients, our data do not suggest an association between etiologies requiring VA-ECMO and mortality. In adults, some reports suggest that different etiologies for VA-ECMO support could account for different mortality. However, indications attributed to VA-ECMO with RCS between adults and pediatrics are not identical [7, 8].

When a multivariate Cox proportional hazard regression model was generated to assess the association between variables and 30-day mortality, prolonged PT > 6 s and elevated lactate level 24 h after ECMO cannulation were two variables significantly associated with outcome. To date, the timing of VA-ECMO and signs of end-organ failure that can predict outcome are still ongoing debates. Previous studies show that renal failure [9, 10], hepatic failure [11], peak lactate level prior to ECMO, and elevated lactate level after ECMO initiation [9, 12, 13] are factors that associated with worse survival. Generally, most pediatric patients do not have underlying diseases before ECMO. All of these variables imply that patients who are already showing signs of end-organ failure as a consequence of hypoxia shock and hypoperfusion have poorer outcomes. Hence, the evaluations of vital organs before and after VA-ECMO are critical for

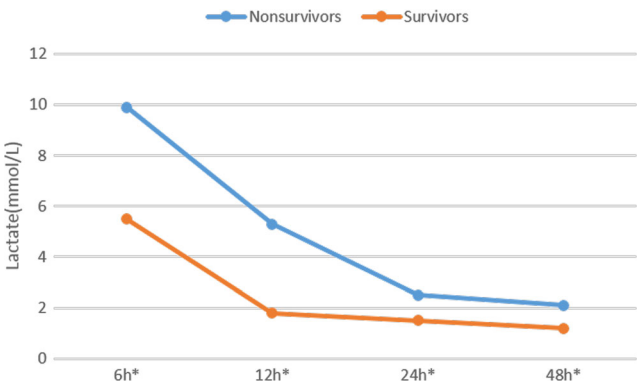

Fig. 4 The longitudinal data of lactate over time. *$p < 0.05$

Table 7 Comparison of the survivors and nonsurvivors in lactate clearance after ECMO implantation of RCS patients

Lactate clearance (h)	Overall (56)	Nonsurvivors (22)	Survivors (34)	*p*
6	0.16 (0.05, 0.28)	0.17 (− 0.01, 0.26)	0.16 (0.07, 0.34)	0.492
12	0.68 (0.39, 0.77)	0.53 (0.14, 0.80)	0.71 (0.48, 0.77)	0.282
24	0.76 (0.52, 0.84)	0.66 (0.44, 0.84)	0.78 (0.56, 0.87)	0.337
48	0.75 (0.54, 0.85)	0.58 (0.45, 0.75)	0.80 (0.63, 0.88)	0.020*

Continuous variables are depicted as median (IQR)

*$p < 0.05$

physicians. In our cohort, we find PT instead of alanine transaminase (ALT) is a valuable marker for worse outcome. Markers of liver injury at initiation of VA-ECMO and during ECMO were independently predictors of mortality [14]. PT is one of the important indexes to evaluate the degree of liver failure [15] because liver injury is likely to contribute to acquired hemostatic abnormalities. Furthermore, PT test is available for 24 h in our institute and produces a fast result. Thus, all these conditions make PT as a convenient and available choice for evaluation of liver injury in our hospital. In our routine evaluation of an ECMO candidate, we usually apply PT to assess the liver injury. However, regarding this study, in ECPR cases, we failed to collect data of PT before ECMO initiation. Moreover, in PCS cases, patients directly switched to ECMO might not have altered PT before cardiopulmonary bypass. Thus, we included the first PT after ECMO cannulation into the analysis. PT prolonged more than 6 s indicates moderate to severe liver injury. There were quite a few studies between liver injury and VA-ECMO in children. In an ECPR pediatric study, Prodhan et al. reported that serum ALT after ECMO initiation was significantly associated with risk of death prior to hospital discharge [16]. In another pediatric study, Park et al. found that, during mechanical circulatory support, aspartate transaminase (AST) and bilirubin were significantly higher in nonsurvivors than survivors, but ALT was not [17]. In the adult cohort, Blandino et al. reported that the elevation of AST and ALT was not significantly related to mortality. In this study, initial AST and ALT values were higher in acute liver failure patients than in others, but total bilirubin and international normalized ratio (INR) were similar. Mortality rate was not significantly higher in patients with elevated liver enzymes or acute liver failure when compared to others [18]. In Luke's study, all the markers of liver injury most frequently occur postcannulation, and the total serum bilirubin appears to be a biomarker of considerable clinical significance. When the liver injury occurs, AST/ALT are the fastest peaking markers, with a median peak of 1 day postcannulation. Serum bilirubin and serum alkaline phosphatase are more delayed markers of injury, rising and peaking far more slowly. In the multivariate Poisson regression model, peak serum bilirubin, admission and peak serum AST, and peak serum ALT were not significant predictors for mortality [19]. However, besides liver injury, PT can also elevate in DIC, severe hypofibrinemia, and hyperfibrinolysis, suggesting disorders in the coagulation system, which are all cofounders leading to poor outcome.

Lactate reflects the severity of cardiogenic shock and serves as the best-available routine point-of-care testing in critical-care patients. Lactate represents the low blood flow state which can cause multiple organ injuries. The normal plasma lactate level in our hospital is 0.5 to 1.6 mmol/L, which represents a balance between lactate production and removal. Failure of serum lactate clearance within 24 h after ECMO initiation is associated with late mortality [13]. In our study, we also conclude that elevated lactate 24 h after ECMO cannulation is an independent factor for 30-day mortality. This result may suggest that we should try to normalize the blood lactate in 24 h after ECMO cannulation, for the better survival.

The dynamic lactate has been reported as with the higher significance compared to the presented values

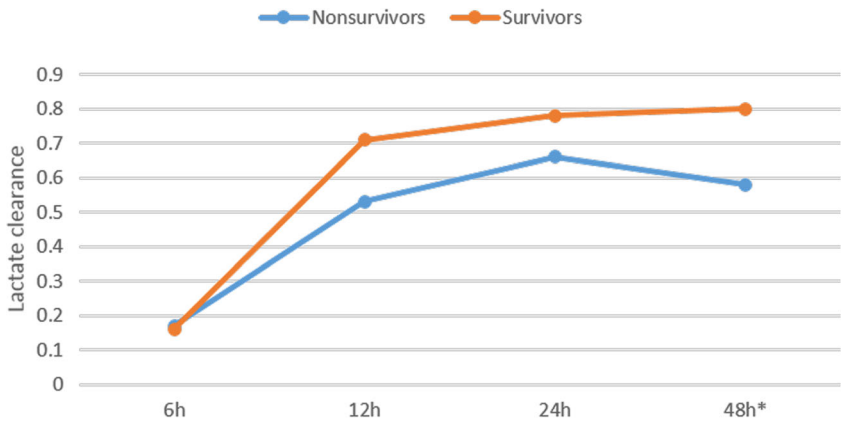

Fig. 5 The trend of lactate clearance between survivors and nonsurvivors. *$p < 0.05$

Table 8 Predictors of 30-day mortality

Variables	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	*p*
Etiology		0.079		
AFM	Reference			
PCS	2.864 (1.072, 7.652)			
Others	3.179 (0.895, 11.297)			
Age < 1 year	2.470 (1.052, 5.795)	0.038*	1.408 (0.303, 6.637)	0.663
Weight < 15 kg	2.564 (1.042, 6.311)	0.040*	2.241 (0.448, 11.217)	0.326
Gender	1.768 (0.720, 4.342)	0.214		
ECPR	1.550 (0.631, 3.804)	0.339		
Prior to ECMO				
Lactate > 7 mmol/L	1.925 (0.709, 5.227)	0.199		
Lactate > 10 mmol/L	2.661 (1.082, 6.545)	0.033*	2.138 (0.831, 5.502)	0.115
During ECMO therapy				
Elevated creatinine	1.939 (0.837, 4.489)	0.122		
Elevated ALT	2.278 (0.955, 5.439)	0.064		
Elevated PT	3.855 (0.518, 28.696)	0.188		
PT prolonged > 6 s	4.010 (1.563, 10.287)	0.004*	3.013 (1.126, 8.061)	0.028*
Elevated lactate 12 h	2.884 (0.975, 8.536)	0.056		
Elevated lactate 24 h	4.559 (1.538, 13.513)	0.006*	3.157 (1.040, 9.579)	0.042*

HR hazard ratio, *CI* confidence interval, *AFM* acute fulminant myocarditis, *PCS* postcardiotomy cardiogenic shock, *ECPR* extracorporeal cardiopulmonary resuscitation, *ALT* alanine aminotransferase, *PT* prothrombin time

*$p < 0.05$

being static lactate [20]. Buijs et al. from the Netherlands reported dynamic arterial lactate indices predict mortality in pediatric ECMO patients with primary respiratory disease [21]. In our previous study, there was no significant connection between lactate clearance (12 h, 24 h, 48 h) and mortality in 43 ECMO patients with RCS [22]. However, there was a trend that the nonsurvival group had lower lactate clearance. In this cohort, we found lactate clearance 48 h after ECMO implantation had a statistical significance between survivors and

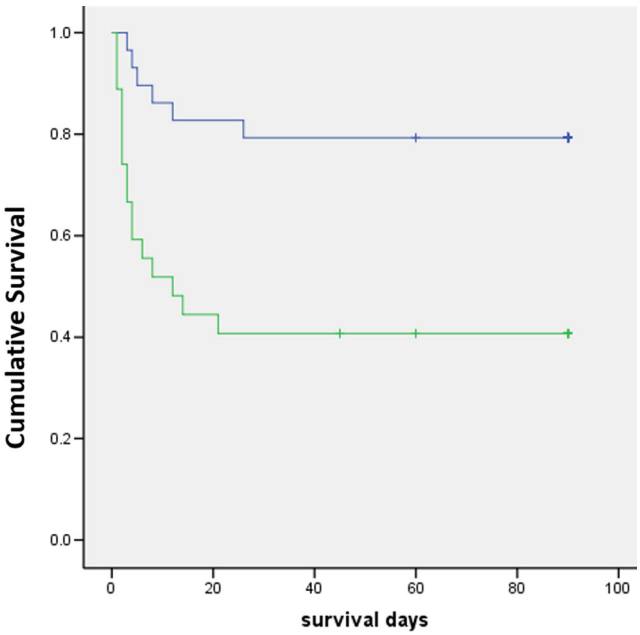

Fig. 6 Kaplan Meier survival estimates by PT prolonged > 6 s

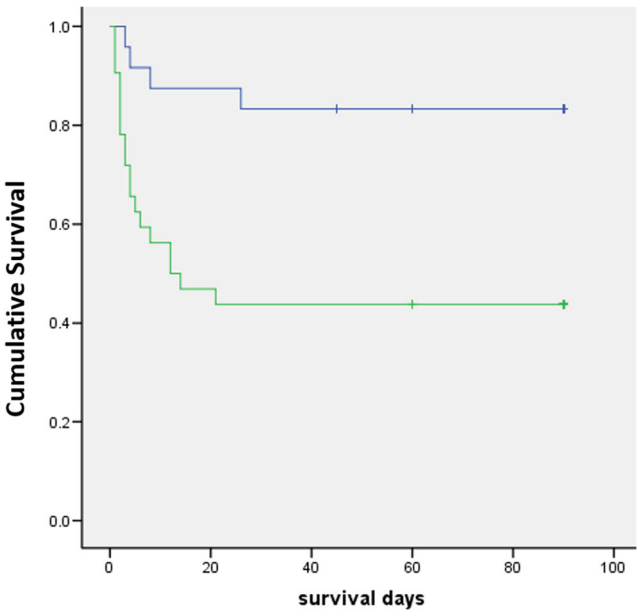

Fig. 7 Kaplan Meier survival estimates by elevated lactate after 24 h ECMO initiation

nonsurvivors. However, not all the patients had ECMO support up to 48 h, and more cases supported less than 48 h in the nonsurvivors. Therefore, further study with a larger sample size should be undertaken.

Limitations

First, although few pediatric patients undergo ECMO support, and even fewer require VA-ECMO compared with VV-ECMO for cardiac indications in children, our cohort with 56 patients was relatively small. Second, this is a retrospective cohort study from a single center, which limits the generalization of the findings. Third, since it is a retrospective study, variables prior to ECMO were missing in urgent situations; we cannot analyze these variables.

Conclusions

Pediatric VA-ECMO for refractory cardiogenic shock appears to be satisfactory as a salvage therapy in various fatal diseases, with a 30-day mortality of 39% in this retrospective study. Prolonged PT >6 s and elevated lactate level 24 h after ECMO initiation were independent predictors of 30-day mortality. This study adds to the existing body of literature working toward improvements in pediatric patient selection for VA-ECMO. Further studies are needed to establish the optimal timing of device implantation and patient management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Zhejiang University School of Medicine Children's Hospital Committee on Clinical Investigation approved the review of patient medical records. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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