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Article

Peak Blood Lactate at 24 h after ECMO Can Predict 30-day Mortality in Infants after Complex Cardiac Surgery

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Abstract

Objective: Peak blood lactate at 24 h after extracorporeal membrane oxygenation (ECMO) can predict 30-day mortality in infants after complex cardiac surgery. **Methods**: Twenty-eight infants with ECMO after complex congenital heart disease surgery were selected from March 2019 to March 2022 in our hospital. The infants were divided into survival group (n = 11) and non-survival group (n = 17) according to 30-day survival after discharge from hospital. The risk factors at 30-day mortality after discharge were analyzed by Cox regression analysis. **Results**: When compared to the non-survival group, there were significant differences in peak blood lactate at 24 h after ECMO, liver dysfunction and multiple organ dysfunction syndrome (MODS) in the survival group ($p < 0.05$). Cox regression analysis showed that peak blood lactate at 24 h after ECMO (HR = 1.074, 95% CI: 1.005–1.149, $p = 0.036$) and MODS (HR = 4.120, 95% CI: 1.373–12.362, $p = 0.012$) were related risk factors affecting the prognosis of infants. The best cutoff value for the peak blood lactate at 24 h after ECMO was 10.2 mmol/L. The area under the curve (AUC) for predicting the 30-day survival rate of the ECMO assisted infants after discharge from hospital was 0.770 (95% CI: 0.592–0.948, $p = 0.018$), with a sensitivity of 94.1% and specificity of 54.5%. **Conclusion**: The peak blood lactate at 24 h after ECMO can predict the 30-day mortality after discharge of infants treated with ECMO after complex cardiac surgery. The best cut-off value for peak blood lactate at 24 h after ECMO was 10.2 mmol/L.

Keywords

congenital heart disease; extracorporeal membrane oxygenation (ECMO); lactate; infant

Introduction

Approximately 10–25% of patients with congenital heart disease have low cardiac output after cardiac surgery, and for these patients who still have continuous dysfunction and end-organ perfusion insufficiency after conventional treatment, extracorporeal membrane oxygenation (ECMO) needs to be considered [1,2]. Due to cardiogenic shock, these patients showed signs of end-organ damage before ECMO implantation, such as increased lactic acid levels or renal dysfunction. Lactic acid is the metabolic product of anaerobic glycolysis, reflecting a lack of oxygen delivery and is considered to be a sign of tissue perfusion affected by macro and microcirculation [3]. Therefore, changes in lactate levels during and before ECMO support may represent an indication of the effectiveness of this support, enabling its potential evaluation.

The study of adults and older children also demonstrated that peak lactic acid before ECMO and its duration can predict patient prognosis [4–6].

However, there are few relevant studies looking at changes in lactate levels before and after ECMO and how this affects infant prognosis with complicated congenital heart surgery. Therefore, we evaluated the relationship between lactate levels tested before ECMO assistance and peak blood lactate during the first 24 h after ECMO, on infant mortality. Here, clinical data on postoperative ECMO in infants of less than 1 year with complex congenital heart disease were reviewed in our hospital in the last 3 years to provide a reference for the use of postoperative ECMO management in infants.

Material and Methods

Study Design

We conducted a retrospective single-center study reviewing the medical records of 31 infants treated with ECMO after complex cardiac surgery between March 2019 to March 2022 in the Children's Heart Center of the Fuwai Central China Cardiovascular Hospital. We excluded one infant who was assisted by ECMO before complex congenital heart surgery and two infants who survived less than 24h after the initiation of ECMO (Fig. 1). There were 16 males (57.14%) and 12 females (42.86%) aged 7 days to 11 months. Exclusion criteria included: (1) ECMO-

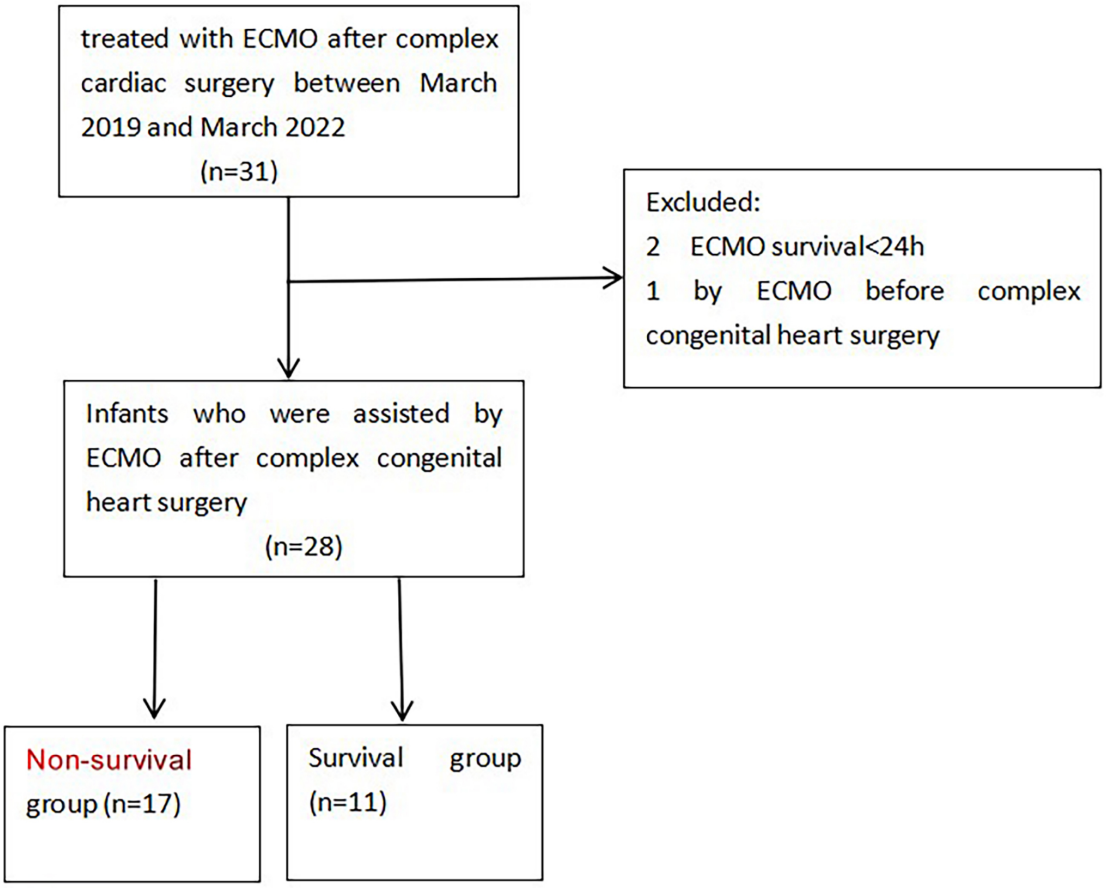

Fig. 1. Outcomes of infants with ECMO who has undergone surgery for congenital heart disease. ECMO, extracorporeal membrane oxygenation.

assisted infants before complex congenital heart surgery, and (2) ECMO auxiliary time ≤24 hours. This study was approved by the Medical Ethics Committee of the Fuwai Central China Cardiovascular Hospital, and informed consent from the infant's parents/guardians was attained.

Data Collection

The covariates included pre-operative patient characteristics (gender, age, surgical method, ECMO indication) and the condition of infants during operation (preoperative ejection fraction (EF) value, preoperative hemoglobin, cardiopulmonary bypass time, ascending aorta blocking time, lactic acid at the end of cardiopulmonary bypass, vasoactive drug score). Biochemical indexes and 24 hours after ECMO operation, hemoglobin and lactic acid at ECMO operation; peak value of lactic acid, creatinine and bilirubin 24 h after ECMO; the lowest value of platelet (PLT) during ECMO assistance, the amount of pleural effusion, fluid intake and outflow, and the number of red blood cells and plasma used 24 h after operation. Complications included multiple organ dysfunction syndrome (MODS), liver dysfunction [alanine transaminase (ALT) or aspartate transaminase (AST) >100 IU/L], severe bleeding (cannulation or surgical site bleeding requiring an intervention, central nervous system hemorrhage, gastrointestinal bleeding), infection (culture positive infection), acute renal failure (marked by a serum creatinine >1.5 mg/dL with or without renal replacement therapy (RRT), any RRT utilization), and mechanical complication (oxygenator or pump failure, air in circuits). The infants were followed up by telephone or outpatient services until 30-days after discharge and were divided into two groups according to the optimal cut-off value of the peak blood lactate during the first 24 h after ECMO which was 10.2 mmol/L. The total survival time was from the time the infants received ECMO treatment to the time of last visit or death.

Establishment and Management of ECMO

In our hospital, for those infants who were treated by ECMO, we recorded indication for therapy (defined as failing to wean off cardiopulmonary bypass, low cardiac output Syndrome, post cardiotomy shock, extracorporeal cardiopulmonary resuscitation, or other). The ECMO was established through the ascending aorta and right atrium in twenty-eight infants, and the thoracic closure was delayed. In the early stage, ECMO flow was maintained at 100–150

mL/(kg/min) and vasoactive drugs were gradually reduced according to blood pressure, and the average arterial pressure was maintained at 30–50 mmHg. All infants were routinely treated with antibiotics to prevent infection after operation. Sputum culture and blood culture was carried out every 2–3 days depending on the situation. With heparin anticoagulation, activated clotting time (ACT) was maintained between 160–220 s and activated partial thromboplastin time (APTT) was maintained at 1.5–2 times the normal value. Vasoactive inotropic Score (VIS) = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 100 × adrenaline dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 10,000 × vasopressin dose (units/kg/min). MODS can be diagnosed by two or more organ dysfunction. They were divided into survival group (n = 11) and non-survival group (n = 17) according to their survival condition 30 days after discharge.

Statistical Analysis

SPSS25.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the data. Non-normally distributed data were expressed by the median (interquartile range [IQR]), and comparison between groups was performed by the Mann-Whitney U test. The mean ± standard deviation was used for counting data that obeyed or approximately obeyed a normal distribution, and the *t*-test was used for inter-group comparisons and Fisher's exact probability method was used for counting data. COX regression was used to analyze the relevant influencing factors on the mortality of the venoarterial extracorporeal membrane oxygenation (VA-ECMO) infants at discharge, and receiver operating characteristic (ROC) curves were used to determine the best predictive value for the predictive factors. The Kaplan-Meier (K-M) method was used to estimate the survival rate, and the Log-rank method was used for comparison. Differences were statistically significant with a $p < 0.05$.

Results

Peak Blood Lactate at 24 h after ECMO Is Increased in Non-Survival Infants

Twenty-eight infants were divided into survival group (n = 11) and non-survival group (n = 17) according to the survival 30 days after discharge. Pre-operative patient characteristics and the condition of the infants during operation were similar in the two groups (Table 1 and Table 2). The peak blood lactate at 24 h after ECMO was significantly higher in the non-survival group (18.9 mmol/L; IQR: 13.3–26.6) when compared to the survival group (9.2 mmol/L; IQR: 3.7–17.4; $p = 0.008$) (Table 2).

Biochemical Indicators, Liquid Intake and Outflow during the First 24 h after ECMO Are Similar in Survivors and Non-Survivors

The lactate for ECMO in the non-survivors (14.3 mmol/L; IQR: 6.7–19.3) were similar to the survivors (5.9 mmol/L; IQR: 2.9–15.0; $p = 0.086$). Peak creatinine of the non-survivors (79.0 μmol/L; IQR: 65.5–123.0) was similar to the survivors (116.0 μmol/L; IQR: 54.0–122.0; $p = 0.865$). Peak bilirubin in non-survivors (102.9 μmol/L; IQR: 51.4–174.4) was similar to the survivors (79.1 μmol/L; IQR: 52.8–173.5; $p = 0.744$). The lowest PLT count was similar for survivors and non-survivors ($p = 0.234$). Pleural effusion during the first 24 h after ECMO was similar in survivors (230.0 mL; IQR: 90.0–320.0) and non-survivors (225.0 mL; IQR: 130.5–323.0; $p = 0.689$). Liquid intake and outflow during the first 24 h after ECMO were similar in survivors (–44.0 mL; IQR: –203.0– –9.6) and non-survivors (–37.0 mL; IQR: –172.0–73.0; $p = 0.572$). Blood and plasma transfusion volume between two groups was also the same. There were fourteen cases of peritoneal dialysis in the non-survivors (82.35%) and 9 cases in the survivors (81.82%). Peritoneal dialysis combined with continuous renal replacement therapy (CRRT) was utilized in 3 (17.65%) of the non-survivors but none of the survivors ($p = 0.258$) (Table 2).

Complications in the Two Groups

All twenty-eight infants had different degrees of bleeding at the wound site, where serious bleeding included cerebral hemorrhage, gastrointestinal bleeding, bleeding requiring chest re-exploration; and 6 cases of severe bleeding and coagulation dysfunction (3 cases requiring chest re-exploration; 3 cases of gastrointestinal bleeding, 2 of which were suspected to be complicated with cerebral hemorrhage). MODS was diagnosed in twelve (70.59%) infants in the non-survivors group and 2 (18.18%; $p = 0.018$) infants in the survival group. Liver dysfunction was diagnosed in 8 (47.06%) infants in the non-survivors group and 1 (9.1%; $p = 0.049$) in the survival group. There were 6 cases of severe bleeding where all of the patients died, but there was no statistical significance between the two groups ($p = 0.055$) (Table 3).

Peak Blood Lactate at 24 h after ECMO Predicts 30-day Mortality

ROC analysis indicated that the peak blood lactate value during ECMO in the first 24 h had a significant prognostic accuracy for predicting 30-day mortality. Indeed, according to the Youden index, a lactate value of 10.2 mmol/L predicted 30-day mortality (AUC: 0.770, 95% CI: 0.592–0.948, $p = 0.018$) (Fig. 2). Kaplan–Meier analysis indicated that the risk of 30-day mortality was 75% (21/28) in infants with a peak lactate >10.2 mmol/L and 25% (7/28) in in-

Table 1. Clinical characteristics.

Risk factors	Non-survival group (n = 17)	Survival group (n = 11)	*p*-value	*t*-value
Weight (kg)	4.49 ± 1.79	4.65 ± 1.19	0.298	–0.526
Male (Female)	11 (6)	5 (6)	0.441	
Age classification			1.000	
<1 year	11	7		
Neonate	6	4		
Operation classification			0.266	
CoA	4	3		
F4 or PA	4	1		
TAPVC	5	2		
TGA	2	3		
Right ventricular double outlet	2	0		
Others	0	2		
Indication			0.435	
ECPR [n (%)]	8 (47.06)	3 (27.27)		
Unable to wean off CPB [n (%)]	9 (52.94)	8 (72.73)		
EF of preoperative (%)	62.0 (53.5–68.0)	56.0 (31.0–65.0)	0.131	–1.515

Abbreviations: CoA, coarctation of the aorta; F4, Tetralogy of Fallot; PA, pulmonary atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; ECPR, extracorporeal cardiopulmonary resuscitation; others, Coronary artery-right ventricular fistula and Aortic valvuloplasty; EF, Ejection fraction.

Table 2. Clinical information between the two groups.

Risk factors	Non-survival group (n = 17)	Survival group (n = 11)	*p*-value	*t*/*Z*-value
CPB				
CPB time (min)	207.0 (173.5–291.0)	185.0 (143.0–222.0)	0.158	–1.411
Crossclam time (min)	97.0 (76.0–122.5)	94.0 (67.0–136.0)	0.672	–0.423
Lactate of weaing from CPB (μmol/L)	4.40 (2.28–7.12)	3.16 (1.31–4.30)	0.165	–1.388
VIS	14.0 (8.0–20.0)	14.0 (9.0–19.0)	0.85	–0.189
Hemoglobin of preoperative (g/dL)	10.50 (8.50–12.80)	11.10 (9.30–12.10)	0.707	–0.376
ECMO				
Duration of ECMO (hours)	144.0 (93.5–182.0)	146.0 (106.0–259.0)	0.323	
Hemoglobin of ECMO initiation (g/dL)	8.70 (6.15–10.8)	9.7 (8.3–11.4)	0.151	–1.435
Lactate of ECMO initiation (μmol/L)	14.3 (6.7–19.3)	5.9 (2.9–15.0)	0.086	–1.717
The peak blood lactate at 24 h after ECMO (μmol/L)	18.9 (13.3–26.6)	9.2 (3.7–17.4)	0.018	–2.376
Peak creatinine (μmol/L)	79.0 (65.5–123.0)	116.0 (54.0–122.0)	0.865	0.171
Peak bilirubin (μmol/L)	102.9 (51.4–174.4)	79.1 (52.8–173.5)	0.744	0.330
Lowest PLT count ($\times 10^9$/L)	31.65 ± 5.81	25.55 ± 15.44	0.234	16.126
Pleural effusion of ECMO 24 h (mL)	225.0 (130.5–323.0)	230.0 (90.0–320.0)	0.689	–0.4
Fluid intake and outflow of ECMO 24 h (mL)	–37.0 (–172.0–73.0)	–44.0 (–203.0– –9.6)	0.572	–0.565
Blood transfusion of ECMO 24 h (mL)	160.0 (108.0–265.0)	240.0 (110.0–320.0)	0.620	–0.495
Plasma transfusion of ECMO 24 h (mL)	100.0 (75.0–210.0)	100.0 (50.0–250.0)	0.552	–0.595
Peritoneal dialysis n (%)	14 (82.35)	9 (81.82)	1.000	
Peritoneal dialysis and CRRT n (%)	3 (17.65)	0 (0.00)	0.258	

Abbreviations: CPB, cardiopulmonary bypass; VIS, vasoactive inotropic score; ECMO, extracorporeal membrane oxygenation; PLT, platelet; CRRT, Continuous renal replacement therapy.

fants with lactate ≤10.2 mmol/L ($p = 0.012$, Log Rank test, Fig. 3). For multivariate hazard ratio (HR), the peak blood lactate at 24 h after ECMO independently predicted 30-day mortality (HR = 1.074, 95% CI: 1.005–1.149, $p = 0.036$, Table 4). As expected, MODS during ECMO was also independently associated with 30-day mortality (Table 4).

Discussion

Timely ECMO assistance is an effective postoperative treatment for children with complex congenital heart disease who cannot be separated from cardiopulmonary bypass, have severe heart failure or cardiac arrest [7]. It can

Table 3. Complications [n (%)].

Complication	Non-survival group (n = 17)	Survival group (n = 11)	*p*-value
MODS (50.00%)	12 (70.59)	2 (18.18)	0.018
Liver dysfunction (32.14%)	8 (47.06)	1 (9.1)	0.049
Infectious (32.14%)	6 (35.29)	3 (27.27)	1.000
Acute renal faiure (25.00%)	5 (29.41)	2 (18.18)	0.668
Severe bleeding (21.43%)	6 (35.29)	0 (0.00)	0.055
Bleeding requiring chest re-exploration	3 (17.65)	0 (0.00)	
Gastrointestinal bleeding	3 (17.65)	0 (0.00)	
Mechanical complication (10.71%)	1 (5.88)	2 (18.18)	0.543

Abbreviations: Data presented as median (interquartile range) or n (%). MODS, multiple organ dysfunction syndrome.

Table 4. Multivariate analysis of the peak lactate for ECMO in the first 24 h, liver dysfunction, severe bleeding and MODS.

Risk factors	HR (95% CI)	*p*-value	χ^2-value	$\bar{x} \pm s$	β-value
Peak lactate of ECMO 24 h	1.074 (1.005–1.149)	0.036	4.417	0.034	0.072
Liver dysfunction	0.584 (0.178–1.921)	0.376	0.784	0.607	–0.538
Severe bleeding	1.341 (0.387–4.643)	0.644	0.214	0.634	0.293
MODS	4.120 (1.373–12.362)	0.012	6.378	0.561	1.416

Abbreviations: HR, Hazard ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.

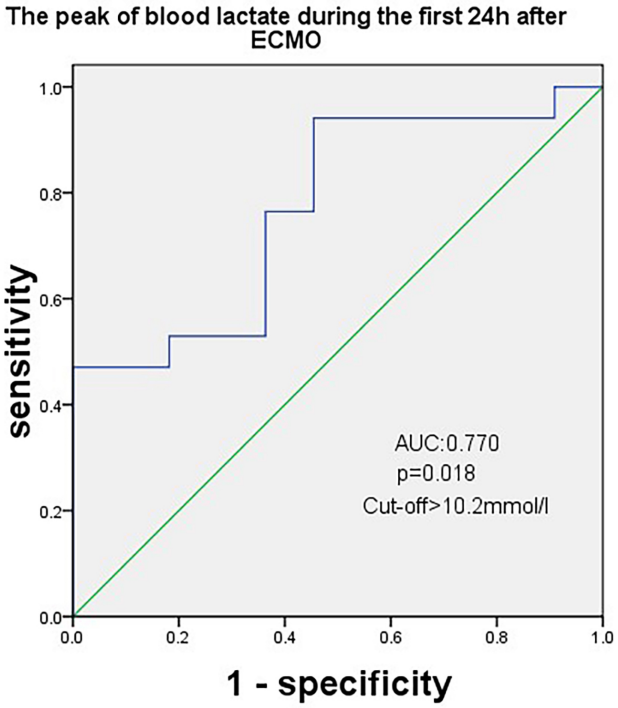

Fig. 2. Receiver operating characteristic (ROC) analysis for the peak blood lactate during the first 24 h after ECMO. The figure shows the best prediction value for the peak blood lactate during the first 24 h after ECMO (cut-off point: 10.2 mmol/L) according to the Youden index. AUC, Area Under Curve.

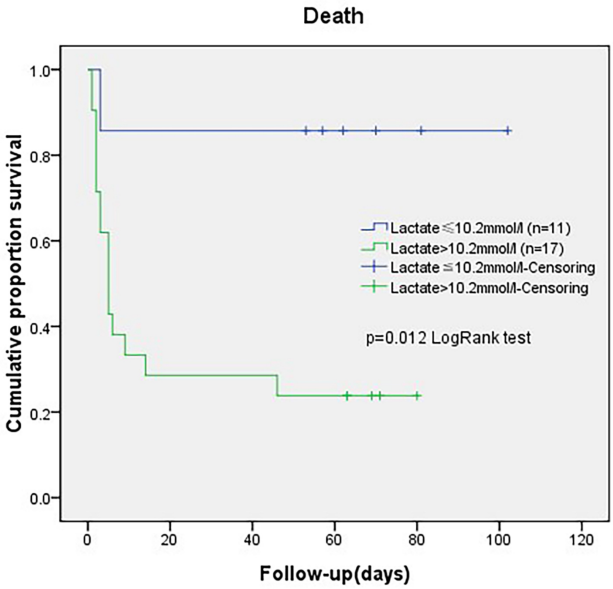

Fig. 3. Kaplan-Meier time-to-events plot for death at 30 days after discharge, according to the peak blood lactate during the first 24 h after discharge from hospital (cut-off value lactate peak $\leq$ or $>$10.2 mmol/L).

improve children with shock, win time for recovery of cardiac function, and improve their prognosis [8]. Our research showed that the weaning rate of ECMO-assisted infants after surgery for complex congenital heart disease was 53.57%, and the survival rate was 39.29%, which is equivalent to the reported average survival rate (40%) reported in the literature [9,10]. In our univariate and multivariate analyses, we found that the hospital survival rate for ECMO-supported infants with complex congenital heart surgery was related to the 24 h peak lactate and MODS after ECMO.

At the same time, the 24 h peak lactate after ECMO support was greater than 10.2 mmol/L, which could predict the 30-day mortality rate of infants with complex congenital heart surgery after discharge.

The pediatric patients in this study were all infants with low cardiac output after operation for complex congenital heart disease. They were directly converted from cardiopulmonary bypass to ECMO in the operating room or underwent extracorporeal cardiopulmonary resuscitation for ventricular tachycardia or ventricular fibrillation in the intensive care unit. There were different levels of increased lactic acid before ECMO, which was mainly related to the disturbance of tissue hypoxia microcirculation perfusion caused by shock. Kim and his colleagues [11] also pointed out that lactate before ECMO could predict the prognosis of shock patients receiving ECMO treatment, and also found that the best cut-off value was 9.8 mmol/L. Some studies have also shown that the mortality rate of children with lactate level >20 mmol/L before ECMO can be as high as 100% [12]. The level of lactic acid is related to prognosis in these children. The continuous high lactic acid levels after ECMO represents severe tissue ischemia and hypoxia [13]. Our results show that the peak blood lactate at 24 h after ECMO can predict prognosis in infants, but the lactate level before ECMO has no such effect. There are also related studies that agree with ours and found that the peak lactate after ECMO can predict the 30-day mortality of children with cardiogenic shock supported by ECMO, and pointed out that the critical value was 14.2 mmol/L [14]. This may be due to the peak blood lactate at 24 h after ECMO, which not only reflects the metabolic level of the infants before boarding, but also indirectly reflects the lactate clearance rate after ECMO. Furthermore, this can better reflect the prognosis of the infants when compared to the lactate levels at the beginning of ECMO. Rissel and other researchers [5] further confirmed our conjecture, pointing out that the increase in lactate levels and the impairment of lactate clearance rate during ECMO are related to poor prognosis in patients undergoing cardiac surgery.

Lactate contains hydrogen ions that affect potential of hydrogen (pH), and this acid transfer and accumulation may also aggravate organ dysfunction on the basis of shock [15]. MODS, which is combined with two or more complications, is an independent risk factor affecting the prognosis of infants. The incidence of MODS in this study was 50%, higher than the 28–43% reported in other studies [16,17]. This requires us to prevent complications in ECMO assistance, especially avoiding the simultaneous occurrence of two different complications and thus improve prognosis in children [18,19].

Conclusion

We found that the peak blood lactate at 24 h after ECMO and MODS are independent risk factors affecting the prognosis of ECMO-assisted infants with complex congenital heart disease. The peak blood lactate at 24 h after ECMO is greater than 10.2 mmol/L, which can predict the mortality of ECMO-assisted infants with complex congenital heart disease.

Limitations

It was a retrospective single center study using observationsal analysis. The sample size of this study was small, which does not meet the requirements of events per variable. However, considering the relatively small number of infants who have received ECMO after surgery for complex congenital heart disease, the results are valuable. However, the reliability of this result needs further confirmation.

Availability of Data and Materials

All data included in this study are available upon request by contact with the corresponding author.

Author Contributions

FM, JL and ZC designed and performed the research study. WL, HD and BL implemented ECMO surgery and postoperative management. XQ and LY have contributed to the acquisition, analysis, and interpretation of data in their works. FM analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of the Fuwai Central China Cardiovascular Hospital (2019-Q009-01), and informed consent from the infant's parents/guardians was attained. There are ethical review opinions and seals from the hospital.

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Conflict of Interest

The authors declare no conflict of interest.

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