

# Prognostic factors in children with acute fulminant myocarditis receiving venoarterial extracorporeal membrane oxygenation

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## ABSTRACT

**Background** Pediatric acute fulminant myocarditis (AFM) is a very dangerous disease that may lead to acute heart failure or even sudden death. Previous reports have identified some prognostic factors in adult AFM; however, there is no such research on children with AFM on venoarterial extracorporeal membrane oxygenation (VA-ECMO). This study aimed to find relevant prognostic factors for predicting adverse clinical outcomes.

**Methods** A retrospective analysis was performed in an affiliated university children's hospital with consecutive patients receiving VA-ECMO for AFM from July 2010 to November 2020. These children were classified into a survivor group (n=33) and a non-survivor group (n=8). Patient demographics, clinical events, laboratory findings, and electrocardiographic and echocardiographic parameters were analyzed.

**Results** Peak serum creatinine (SCr) and peak creatine kinase isoenzyme MB during ECMO had joint predictive value for in-hospital mortality (p=0.011, AUC=0.962). Based on multivariable logistic regression analysis, peak SCr level during ECMO support was an independent predictor of in-hospital mortality (OR=1.035, 95% CI 1.006 to 1.064, p=0.017, AUC=0.936, with optimal cut-off value of 78 µmol/L).

**Conclusion** Tissue hypoperfusion and consequent end-organ damage ultimately hampered the outcomes. The need for left atrial decompression indicated a sicker patient on ECMO and introduced additional risk for complications. Earlier and more cautious deployment would likely be associated with decreased risk of complications and mortality.

## KEY MESSAGES

### WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- ⇒ Venoarterial extracorporeal membrane oxygenation for children with acute fulminant myocarditis (AFM) appears to be an effective therapy and is useful for clinical prognosis.
- ⇒ Further studies are needed to discover the molecular mechanisms in order to improve quality of clinical management.

### WHAT ARE THE NEW FINDINGS?

- ⇒ Peak serum creatinine (SCr) level and peak creatine kinase isoenzyme MB (CKMB) level during extracorporeal membrane oxygenation support were predictors of in-hospital mortality in children with AFM.
- ⇒ The need for left atrial (LA) decompression and abnormal serum findings might reflect severity of the states of AFM.

### HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

- ⇒ First, we will pay more attention to SCr level and CKMB level of children with AFM and ensure these serological tests are completed in time.
- ⇒ Second, we will try some new LA decompression modes to obtain more satisfying left ventricular venting, such as atrial septal defect (ASD) shunt, intra-aortic balloon pump (IABP), etc.



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## INTRODUCTION

Acute fulminant myocarditis (AFM) is a very dangerous disease, accounting for 10%–38% of the incidence of acute myocarditis in children.<sup>1</sup> With a rapid progression of circulatory failure, AFM can lead to cardiac shock or malignant arrhythmia within a short time, with a fatality rate of up to 75%.<sup>2</sup> Deaths of patients with AFM are caused by cardiac arrest, irreversible myocardial lesions and secondary irreversible organ damage after cardiac shock, etc. Thus, these patients

often require venoarterial extracorporeal membrane oxygenation (VA-ECMO) to maintain their hemodynamic status. If children are treated in a timely and effective way, the survival rate can be improved significantly with good quality of survival. According to data from the Extracorporeal Life Support Organization in January 2018, patients with AFM supported by ECMO had an average survival rate of 60%–75%.<sup>3</sup> In our center, the survival rate of children with AFM supported by VA-ECMO has been on the rise in recent years; however, our understanding of this group of children remains

limited and their prognostic factors are still unclear. As far as we know, previous reports have identified some predictive risk factors in adult AFM; however, there is no research on prognostic factors for children with AFM on VA-ECMO. The present study aimed to find relevant prognostic factors and thereby improve patients' outcomes.

## METHODS

### Design and population

A retrospective analysis was performed at an affiliated university children's hospital with consecutive children receiving VA-ECMO for AFM from July 2010 to November 2020. The study's design was single center and retrospective. AFM was diagnosed by seasoned pediatric physicians. Typical symptoms of acute myocarditis are abdominal pain, vomiting, palpitations, or tiredness and fever, with an acute hemodynamic collapse and cardiogenic shock and fatal arrhythmias. High cardiac troponin I (cTNI), increased creatine kinase isoenzyme MB (CKMB), ECG changes (such as widening of the QRS complex or PR prolongation), dilated left ventricle, and markedly reduced LVEF were found in these children. A biopsy was not performed because the operation was invasive. A cardiac MRI or a genetic study was taken after ECMO support only if the patient had a family history of cardiomyopathy or trends in cardiomyopathy after infection. Two groups were compared based on in-hospital mortality: a group of 33 children who survived from fulminant myocarditis and a group of 8 children who died from fulminant myocarditis. All of these patients received VA-ECMO during their treatment process. Data were collected from the pediatric intensive care unit database, patients' electronic medical records, and the extracorporeal life support registry form records. Patient demographics included age, weight, and sex. Cardiopulmonary resuscitation (CPR) included traditional cardiopulmonary resuscitation and extracorporeal cardiopulmonary resuscitation. Left atrial (LA) decompression was finished by a left anterolateral thoracotomy. The vent cannula was placed in the atrium under direct vision. Malignant arrhythmia included high-grade atrioventricular block, ventricular arrhythmia, and escape rhythm. Vasoactive-inotropic score (VIS) was calculated as described previously.<sup>4</sup> Ejection fraction (EF) and left ventricular (LV) volume were measured by B-mode ultrasonography within half an hour before ECMO implantation. Serum lactate, serum creatinine (SCr), alanine transaminase (ALT), brain natriuretic peptide (BNP), creatine kinase isoenzyme MB and cTNI were collected one to three times within 24 hours after ECMO implantation, and the worst results were chosen as the peak values for these laboratory tests. We also tested the duration of ECMO and vasoactive-inotropic scoring at the 24th hour after ECMO implantation as risk factors for death.

## ECMO management

Children diagnosed with AFM presented the following: (1) left ventricular ejection fraction (LVEF) <40%–45%; (2) persistent tissue hypoperfusion, metabolic acidosis, such as pH <7.15, buffer excess (BE) <–5 mmol/L, blood lactic acid >4.0 mmol/L or in progressive aggravation, and urine volume <0.5 mL/kg/hour; (3) persistent hypotension: mean arterial pressure: neonates <40 mm Hg, infants <50 mm Hg, and children <60 mm Hg; (4) two or more positive inotropic/vasoactive drugs were used and there was still hypotension under high-dose maintenance, such as adrenaline >0.4 µg/kg/min, dopamine >10 µg/kg/min, or vasoactive-inotropic score of 20 points or more and/or with progressive increase; (5) in malignant arrhythmia, antiarrhythmic drugs, positive inotropic drug or temporary pacemakers, etc, are still unable to maintain effective circulation; and (6) sudden cardiac arrest, cardiopulmonary resuscitation for 15 min is still unable to maintain spontaneous circulation. If items 1–6 occur, ECMO should be prepared, and if any of items 1–4 lasts for more than 3 hours ECMO should be started in an emergency.

The right internal jugular vein and the common carotid artery were catheterized surgically and heparin 50–100 U/kg anticoagulant was administered before catheterization. Cannulation was performed after injection of heparin (50–100 U/kg) with the target kaolin-activated clotting time (ACT Plus; Medtronic, Minneapolis, Minnesota, USA) value more than 180 s. The VA-ECMO circuit consists of a Rotaflow Centrifugal Pump (MAQUET, Germany) in conjunction with a membrane oxygenator (Hilite 800/2400/7000, Medos Medizintechnik, Stolberg, Germany; Quadrox PLS, MAQUET Cardiovascular, Hirrlingen, Germany; Sorin, Italy) with an integrated heat exchanger. Anticoagulation was initiated as soon as bleeding has been controlled. The target ACT value was 160–200 s. In auxiliary process we let the heart rest adequately to promote its restoration, while ensuring other important viscera effective perfusion to avoid secondary damage. If the LV was significantly dilated, the LA pressure increased, and pulmonary edema occurred, LA drainage tube was placed for LA decompression. Weaning was evaluated cautiously when LVEF was above 40% and vital organ functions were stable. Pump flow was gradually decreased 24 hours before weaning, and the operation was performed under sterile conditions in the intensive care unit (ICU). Some patients underwent carotid artery repair, and all the jugular veins of these patients were ligatured after decannulation.

## Statistical analysis

SPSS V.20 was used for statistical analysis. Categorical variables were expressed as percentages and were analyzed using  $\chi^2$  test or Fisher's exact test. Continuous data were described as median (IQR) and compared using Mann-Whitney U test. To confirm the results were not influenced by a model overloaded with too many variables for a low occurrence rate of death, a binary logistic

**Table 1** Demographic data and clinical features of patients requiring ECMO for AFM

	Survivors (n=33)	Non-survivors (n=8)	P value
Patient demographics			
Age (mon)*	96 (60–135)	83 (80–108)	0.830
Weight (kg)*	25 (19–36)	25 (20–27)	0.621
Male†	15/33 (45)	2/8 (25)	0.292
Clinical events			
CPR†	11/33 (33.3)	5/8 (62.5)	0.225
Left atrial decompression†	3/33 (9.1)	4/8 (50)	0.018‡
Malignant arrhythmia†	15/33 (45.5)	5/8 (62.5)	0.454
ECMO duration (hr)*	112.5 (83–136)	134.5 (41.2–312.2)	0.063
Complications†	7/32 (21.9)	6/8 (75)	0.007‡

\*Data are presented as mean (IQR).  
†Data are presented as n (percentage).  
‡P < 0.05.  
AFM, acute fulminant myocarditis; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

regression analysis limited the independent variables to those who were found individually to be associated with mortality ( $p \leq 0.07$ ). A forward stepwise logistic regression was used for multiple models. Significance was defined as  $p < 0.05$ .

## RESULTS

### Baseline data

Patient demographics, clinical events, and complications are shown in [table 1](#). There were 17 boys and 24 girls in this study. Their median age was 96 months, ranging from 4 months to 168 months, and their median weight was 25 kg, ranging from 6.5 kg to 60 kg. There were no significant differences in age, weight, or gender between survivors and non-survivors. There were no significant differences in the duration of ECMO, malignant arrhythmia, or need for cardiopulmonary resuscitation between survivors and non-survivors. Demands for LA decompression in the non-survivor group were more frequent (4 of 8 (50%) vs 3 of 33 (9.1%),  $p < 0.05$ ). In addition, non-survivors also tended to have higher incidence of complications (6 of 8 (75%) vs 7 of 32 (21.9%),  $p < 0.05$ ), such as hemorrhage, cerebral infarction, thrombosis, etc.

### Outcomes and complications

In this study the causes of death were irreversible cardiac failure (4 of 8), cerebral death (2 of 8), untreatable coagulopathy (1 of 8), and infection (1 of 8). Due to anticoagulation during ECMO, hemorrhage was the most frequent complication, with an occurrence rate of 17.1%, followed by clots (7.3%), renal failure (7.3%), cerebral infarction (7.3%), infection (4.9%), disseminated intravascular coagulation (DIC) (4.9%), and hemolysis (2.4%). Generally, we supported these patients for 7–10 days. During this period we cautiously evaluated their heart sound, VIS,

and symptoms of pulmonary congestion. Also, electrocardiography and echocardiography were examined every day. If there was no recovery, we defined the patients as ‘irreversible heart failure’. Unfortunately, there were no patients listed for heart transplantation due to heart source shortage and to their low body weight.

### Evaluation of perioperative findings

Laboratory examinations and echocardiographic data collected prior to and during ECMO are summarized in [table 2](#). Children with AFM on ECMO in the non-survivor group had higher peak SCr values (61 (44.63–73.5)  $\mu\text{mol/L}$  vs 147.75 (93–207.75)  $\mu\text{mol/L}$ ,  $p < 0.05$ ) than survivors. They also had markedly higher levels of peak ALT values (71 (43.5–631.5) U/L vs 682 (182.25–1361) U/L,  $p < 0.05$ ) during ECMO. Moreover, children with AFM on ECMO in the non-survivor group had higher peak CKMB values (71.94 (43.29–175) ng/mL vs 277.5 (188.25–321.75) ng/mL,  $p < 0.05$ ) than the survivor group. Although statistical analysis showed no significant differences in LVEF between the two groups, we observed a lower EF in the non-survivor group (39% (30%–50.5%) vs 29% (14%–39.8%),  $p = 0.065$ ). There was no statistically significant difference between the two groups in terms of peak lactate before ECMO started and in use of vasoactive drugs in early stage. During ECMO support, there were no significant differences in peak BNP values and peak cTNI values between survivors and non-survivors. Finally, non-survivors tended to have higher VIS at the 24th hour during ECMO.

### Predictors of in-hospital mortality

Comparison of survivors and non-survivor variables is summarized in [table 3](#). In the univariate logistic analysis, LA decompression ( $p = 0.013$ ), peak SCr level

**Table 2** Comparison of in-hospital mortality between the two groups

	Survivors (n=33)	Non-survivors (n=8)	P value
Prior to ECMO			
Peak lactate (mmol/L)	7.2 (3.68–10.40)	6.8 (3.68–13.73)	0.428
VIS	25 (10–40)	30 (12.25–45.5)	0.856
EF (%)	29 (30–50.5)	29 (14–39.8)	0.065
LV (cm)	3.55 (3.25–4.28)	3.80 (3.55–4.15)	0.468
During ECMO			
Peak CRE (μmol/L)	61 (44.63–73.5)	147.75 (93–207.75)	0.000*
Peak ALT (U/L)	71 (43.5–631.5)	682 (182.25–1361)	0.021*
Peak BNP (pg/mL)	6517 (2262–23 096)	5853.50 (3902.75–22 539.25)	0.818
Peak CKMB (ng/mL)	71.94 (43.29–175)	277.50 (188.25–321.75)	0.001*
Peak cTNI (ng/mL)	1.80 (0.52–8.16)	3.91 (0.13–40)	0.742
VIS at the 24th hour	9 (3.5–23)	28.5 (15.2–47.5)	0.003*

Data are presented as mean (IQR).

\*P < 0.05.

ALT, alanine transaminase; BNP, brain natriuretic peptide; CKMB, creatine kinase isoenzyme MB; CRE, creatinine; cTNI, cardiac troponin I; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; LV, left ventricular; VIS, vasoactive-inotropic score.

(p=0.003), and peak CKMB level (p=0.021) were associated with mortality in children with AFM on VA-ECMO. In the multivariable logistic regression model, peak SCr level (p=0.017) remained a significant predictor of mortality (table 3). To confirm the accuracy of the prognosis and to find an optimal cut-off value for the laboratory results, receiver operating characteristic (ROC) curves were constructed based on the multivariable logistic regression reported in table 3. The sensitivity and specificity of using both risk factors (SCr and CKMB) together to jointly predict in-hospital mortality were 100% and 75.8%, respectively (area under the curve (AUC)=0.962, p=0.011; figure 1).

## DISCUSSION

### Major findings

In this study we retrospectively analyzed the clinical outcomes of pediatric VA-ECMO for AFM with various factors. We found that peak SCr and peak CKMB during ECMO had predictive value for in-hospital mortality. Multivariable logistic regression analysis showed that peak SCr during ECMO was an independent prognosis factor for in-hospital mortality. These results suggested that evidence of end-organ injury (peak SCr and to a smaller extent ALT) and myocardial injury (peak CKMB) predict patients with poor outcomes. The need for LA decompression indicated a sicker patient on ECMO and

**Table 3** Binary logistic models for predictors of in-hospital mortality

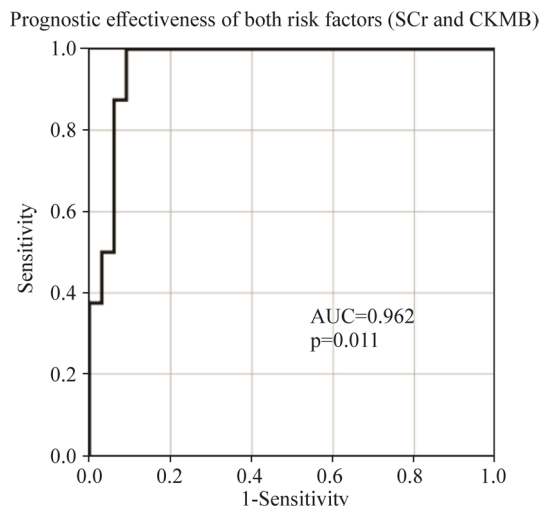
Variables	Univariate analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Clinical features						
LA decompression	0.100	0.016 to 0.620	0.013*	0.93	0.003 to 2.538	0.161
Prior to ECMO						
LVEF	0.938	0.879 to 1.001	0.055			
During ECMO						
Peak SCr (μmol/L)	1.036	1.012 to 1.061	0.003*	1.035	1.006 to 1.064	0.017*
Peak ALT (U/L)	1.001	1.000 to 1.001	0.134			
Peak CKMB (ng/mL)	1.008	1.001 to 1.014	0.021*	1.007	1.000 to 1.015	0.058
VIS at the 24th hour	1.018	0.994 to 1.042	0.140			

OR means increased odds of mortality.

\*P < 0.05.

ALT, alanine transaminase; CKMB, creatine kinase isoenzyme MB; ECMO, extracorporeal membrane oxygenation; LA, left atrial; LVEF, left ventricular ejection fraction; SCr, serum creatinine; VIS, vasoactive-inotropic score.





**Figure 1** ROC curve for both risk factors (SCr and CKMB) together to jointly predict in-hospital mortality (AUC=0.962,  $p=0.011$ ). The sensitivity and specificity of using both risk factors were 100% and 75.8%. AUC, area under the curve; CKMB, creatine kinase isoenzyme MB; ROC, receiver operating characteristic; SCr, serum creatinine.

introduced additional risk for complications. However, peak lactate and LVEF prior to ECMO were not valuable markers.

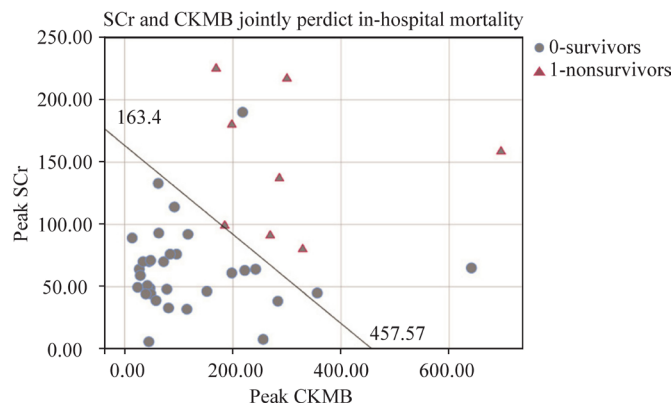
#### Prognosis value of peak CKMB

CKMB exists in the myocardium and indicates the extent of myocardial injury as a sensitive indicator. Previous studies have shown that serum CKMB can be increased for 1–2 weeks in children with AFM.<sup>5</sup> In a clinical study of adult patients with fulminant myocarditis in 2018, Matsumoto *et al.*<sup>6</sup> found that there were significant differences in the level of peak CKMB between the ECMO-weaned group and the unweaned group, and the optimal cut-off value was 183 IU/L with an AUC of 0.89. In the present study, peak CKMB level remained a predictor of mortality, which was highly consistent with adult patients. This means that peak CKMB level could also be used in prognosis diagnosis of in-hospital mortality in children with AFM on VA-ECMO. What is more, a scatterplot of SCr and CKMB was constructed and the line that showed the optimal cut-off values for SCr and CKMB estimated from the multivariable logistic regression was superimposed in figure 2, which helped to jointly predict in-hospital mortality.

#### Prognosis value of peak SCr and peak ALT

End-organ perfusion reflects the severity of oxygen deficit and gives an accurate depiction of circulatory shock conditions. Although we gave ECMO support to these patients, the ECMO flow could not fully replace their pulsing flow; thus, an irreversible cardiac failure might lead to end organ damages.

Among all the organs, the kidney is the one sensitive to ischemia and reperfusion. In a renal ischemia-reperfusion model of mice, it was found that ischemia



**Figure 2** Scatterplot of SCr and CKMB was constructed and the line that showed the optimal cut-off values for SCr and CKMB was estimated to help jointly predict in-hospital mortality. CKMB, creatine kinase isoenzyme MB; SCr, serum creatinine.

time of more than 5 hours would cause poor prognosis even in a low temperature environment.<sup>7</sup> Several studies have shown that changes in SCr are associated with death in adult patients with AFM.<sup>8,9</sup> Children with AFM had hypotension and hypoperfusion of systemic circulation before ECMO support, which would lead to an acute renal ischemia-reperfusion injury. The initiation of virus-mediated immune response after prodromic viral infection also leads to acute renal injury.<sup>10</sup> Therefore, change in SCr reflects both the severity of hypoperfusion and the fierceness of immune response, which are both confounders leading to poor outcomes. Based on kidney disease improving global outcomes-acute kidney injury (KDIGO-AKI) rating, even the slightest renal functional changes during pediatric mechanical circulatory support (MCS) should not be ignored.<sup>11</sup>

As a tried-and-true predictor, although peak SCr was proven to be an independent predictor of mortality in this study, it is not a timely indicator because it usually increases 24–72 hours after renal injury.<sup>12</sup> During ECMO support, tissue hypoperfusion and consequent end-organ damage ultimately hampered the outcomes of ECMO patients, so early detection of hypoperfusion is crucial in improving perfusion. Recently, liver-fatty acid binding protein, neutrophil gelatinase-associated lipocalin, cystatin-C, kidney injury molecule-1, and interleukin 18 have been shown to be early indicators of AKI<sup>13</sup> and may become more valuable markers and may improve patients' outcomes in the future.

#### LA decompression

VA-ECMO can replace the heart pump function and can effectively restore systemic perfusion in children with AFM, but VA-ECMO increases pulmonary circulation blood flow and LV afterload.<sup>14</sup> LA decompression can quickly reduce LV load, lowering cardiac work and oxygen consumption.<sup>15</sup> Many clinical centers have moved to prophylactic LA decompression because it is hypothesized as the best way to rest the heart. Late LA

decompression deployment is likely to lead to worse outcomes. In the present study, univariate analysis showed that there was a significant difference in LV decompression between survivors and non-survivors, which seemed counterintuitive. There were some reasons behind this phenomenon.

ECMO was becoming increasingly used in pediatric AFM in our medical center, but mortality rate was not decreasing year by year during the most recent years. Lack of cardiac recovery or multiorgan failure represented the most frequent causes of poor outcome. The effect of retrograde flow in the aorta towards LV during VA-ECMO was an inevitable problem. These reasons both increased the LV load, and LV overloads increased wall stress and myocardial oxygen consumption, jeopardizing ventricular recovery particularly in the presence of ischemia-induced myocardial impairment.<sup>14</sup> Not only that, the implantation of VA-ECMO introduced additional risks for complications because these procedures were invasive, thus increasing bleeding risk and complication rate. Consequently, the risk/benefit should be assessed carefully. In the present study seven children in our center underwent left cardiac decompression, of whom two had cerebral hemorrhage, one had stroke, one had cerebral hemorrhage combined with stroke, one had LV thrombosis, and one had limb thrombosis; only three children survived. In the statistical analysis LA decompression was proved to be significantly related to complications (Pearson's correlation=0.527), so maybe we have done several late LA decompression during VA-ECMO support or some of the venting was insufficient. According to the classification of unloading techniques,<sup>16</sup> the most common locations of unloading were the LA (31%), followed by the aorta/IABP (27%) and transaortic (27%). The LV itself (11%) and the pulmonary artery (4%) were also used for unloading. Among these methods, LA decompression is an indirect venting way. However, is it more helpful to unload the LV using a direct approach, such as the LV itself? If so, what about the potentially increased risk? In this area, we still lack knowledge to answer these questions.

Because there were only eight mortalities in the present study, removal of complications from mortality analysis was very difficult. It is not completely clear whether the children died as a result of AFM or as a complication of ECMO or LA decompression. It is clear that LA decompression during VA-ECMO may either provide an actual LV functional rest or may reduce its counterflow; however, at present there is still no consensus on the timing of LA decompression and on an exhaustive protocol for catheterization. More forthcoming clinical experience and communication among centers are needed to solve the problems encountered in this study.

#### Electrocardiographic and echocardiographic changes

In previous studies of AFM, malignant arrhythmia, expanding LV diameter, and low LVEF were considered to be important factors affecting the prognosis.<sup>17-19</sup> In the

present study, we observed that the non-survivor group had obviously larger LV diameter and lower LVEF, and the frequency of malignant arrhythmia was also higher than that of the survivor group; however, there was no significant difference in either the U test or the univariate regression analysis, which remains a question worthy of consideration.

Most of these studies were based on all acute myocarditis cases from an entire medical center. In these studies patients without ECMO, or without other MCS support, had a reduced risk of ECMO-related complications, but medical therapy could not reduce their left cardiac load in time, so rapid reverse reconstruction of ventricle had not occurred and sometimes their coronary perfusion was not guaranteed. Therefore, this may exacerbate LV dysfunction, allowing arrhythmia to appear. As a result, the recovery of LV might be slow, and some children may even have irreversible low LVEF and expanding LV diameter. In the present study, according to the above indications, these children were all supported with VA-ECMO and LA decompression was deployed for the extremely sick hearts, which ensured all children's LV unloaded so that their LVEF might not deteriorate further. The recovery of cardiac rhythm and LVEF is a key factor affecting the prognosis of children with AFM. As a result of active treatment, there were only eight cases in the non-survivor group, and the median differences between the two groups were small, which may affect the conclusion of the data analysis. For the reasons described above, more cases in the study may help to obtain more accurate conclusions.

In conclusion, owing to the unstable hemodynamics of AFM, nearly all patients with AFM will require vasoactive drug support or temporary MCS to bridge them to a stable stage at which their own circulation or a more durable solution can provide support of their end-organ function.<sup>20</sup> Correspondingly, pediatric VA-ECMO for children with AFM appears to be an effective therapy in this retrospective study. Peak SCr level during ECMO support was an independent predictor of in-hospital mortality. Peak CKMB level also predicted poor outcome in children with AFM on VA-ECMO. The need for LA decompression and the abnormal serum findings might reflect severity of the states of AFM and are useful for clinical prognosis. Further studies are needed to discover their molecular mechanisms in order to improve quality of clinical management.

There are still some limitations regarding this study. First, this is a retrospective study from a single center, which limits the universality of the findings. Second, given the nature of the therapy, most tests for AFM were performed on an emergent or semi-emergent basis without endomyocardial biopsy and MRI. Last, the present study consisted of a small number of children. Owing to the small number of cases, the sensitivity of some factors even reached 100%, which is undoubtedly biased. Because AFM has a lower incidence than other common diseases, a multicenter clinical study across the country may be better in the future.

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