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A retrospective analysis of clinical characteristics and outcomes of pediatric fulminant myocarditis

Yuhang Zhao[1], Min Da[1*], Xun Yang[1], Yang Xu[1] and Jirong Qi[1*]

Abstract

Background The study aimed to explore clinical indicators that can predict the prognosis of children with acute fulminant myocarditis (AFM) through a retrospective analysis.

Methods A retrospective analysis was conducted on the clinical indices of 79 children diagnosed with AFM and hospitalized from March 2013 to March 2023. Relevant demographic and clinical data, including symptoms at admission, laboratory results, and outcomes were extracted to identify factors associated with in-hospital mortality.

Results A total of 79 children with AFM were analyzed. The survival group ($n=61$) had a longer median hospital stay and higher medical expenses compared to the death group ($n=18$). Significant differences in the levels of left ventricular ejection fraction (LVEF)($P<0.001$), myoglobin (MYO)($P<0.001$), aspartate aminotransferase (AST)($P<0.001$), lactate dehydrogenase (LDH)($P=0.004$), B-type natriuretic peptide (BNP)($P=0.005$), arterial potential hydrogen (PH)($P<0.001$), bicarbonate (HCO_3^-)($P=0.003$), serum lactate (Lac)($P=0.001$), peripheral oxygen saturation (SpO_2) ($P=0.008$), and white blood cell count (WBC)($P=0.007$) were observed between the two groups. Additionally, there were significant differences in the incidences of multi-organ failure ($P=0.003$) and respiratory failure ($P=0.001$) between the two groups.

Conclusions Severe myocardial injury (AST > 194.00 U/L, LDH > 637.50 U/L, MYO > 265.75 μg/L, BNP > 1738.50 ng/L), acidosis (PH < 7.29, HCO_3^- <18.45 mmol/L, Lac > 12.30 mmol/L), hypoxia (SpO_2 < 97.50%), inflammatory response (WBC > 9.69*10^9/L), left ventricular systolic dysfunction (LVEF < 28.25%), multi-organ failure, and respiratory failure are significantly associated with higher mortality rates. These factors can accurately identify AFM children at an increased risk of death.

Keywords Children, Fulminant myocarditis, Extracorporeal membrane oxygenation, Risk factors, Pediatric

*Correspondence:
Min Da
damingirlnanjing@126.com
Jirong Qi
ertongxinlianxin@163.com
[1]Nanjing Medical University Affiliated Nanjing Children's Hospital, Nanjing 210008, China

Background

Acute myocarditis (AM), an inflammatory disease of the myocardium, is often caused by viral infections or autoimmune diseases [1–3], and is clinically manifested by a range of subclinical symptoms that may deteriorate into sudden death, which are more pronounced in children [4]. Currently, the diagnosis of AM is primarily based on clinical presentations, blood tests (elevated biomarkers of myocardial necrosis), electrocardiography, and cardiac magnetic resonance imaging (MRI) showing myocardial dysfunction, edema, and fibrosis [5]. Endomyocardial biopsy is the gold standard for diagnosis [6]. Acute fulminant myocarditis (AFM), a lethal form of AM with a low incidence, can rapidly develop into refractory cardiogenic shock, malignant arrhythmia, or even cardiac arrest [7]. Compared to patients with acute non-fulminant myocarditis, AFM patients have a higher mortality rate and a greater need for heart transplantation. Even long-term after treatment, AFM patients still present a poor left ventricular systolic function [8]. The relationship between clinical manifestations and outcomes in AFM patients remains controversial [9–11]. Clinical criteria for predicting AFM prognosis are conflicting, possibly due to differences in diagnostic tests, methods, and timing [12, 13]. Extracorporeal membrane oxygenation (ECMO) has been proven effective in treating children with AFM, with yielding a better prognosis [14]. Therefore, it is imperative to explore reliable factors to predict the mortality risk among children with AFM [15–17]. Based on a retrospective analysis, this study aimed to identify clinical indicators that can predict the prognosis of children with AFM. The study highlights the importance of vigilant monitoring and timely interventions to improve survival in these high-risk patients.

Methods

Data source

We conducted a retrospective observational study using the inpatient information database of the Children's Hospital Affiliated with Nanjing Medical University. The database included the following information of each child: hospitalization ID number, times of hospitalizations, sex, date of birth, age, age unit, address of household registration, discharge date, discharge department, length of hospital stay, primary diagnosis, primary diagnosis name, physician's primary diagnosis and description, discharge status, etc. Diagnoses were established according to the International Classification of Diseases, 10th Revision (ICD-10). Due to the retrospective nature of the study and the anonymity of the data, the requirement for informed consent was waived.

Patient selection

We included hospitalized children who were discharged between March 2013 and March 2023, and had an ICD-10-based diagnosis of AFM (I40.80 A). We excluded children who were suspected of having AFM at admission, but not confirmed by laboratory and imaging examinations, or ultimately diagnosed with other diseases. To avoid duplication, we manually merged records of AFM for one child hospitalized multiple times. For all children, the diagnosis of AFM was primarily based on clinical features and relevant auxiliary examinations. The diagnostic criteria were as follows: (1) sudden onset, (2) hemodynamic instability caused by cardiogenic shock or arrhythmia, and (3) evidence of myocardial injury indicating impaired cardiac function, such as changes in creatine kinase isoenzyme (CK-MB), electrocardiogram (ECG), and echocardiography.

Drug therapy and ECMO

All enrolled patients received routine glucocorticoid therapy with a high dose of methylprednisolone, 10 mg/ (kg ·d) to 30 mg/ (kg ·d), administered in a continuous infusion for 3 days, followed by a gradual tapering within a short period [18, 19]. For cases suspected of viral AFM, routine antiviral medication was administered. Oseltamivir was used for children with influenza virus infection, acyclovir for those with herpes virus infection, and interferon for children with adenovirus and enterovirus infections. Routine intravenous immunoglobulin was administered at a dose of 200 mg/ (kg ·d)-400 mg/ (kg ·d) for a duration of 3–5 days [20, 21]. ECMO was managed by a dedicated team under expert consensus on the entire ECMO process [22], including indications, timing, establishment, management, weaning, and left ventricular decompression when necessary. Cannulation was performed through a cervical incision (via the right internal jugular vein and carotid artery). In the case of cardiac arrest, extracorporeal cardiopulmonary resuscitation was initiated through a midline sternotomy, draining from the right atrium and infusing into the ascending aorta. A centrifugal pump (MaquetRota flow, Germany), a membrane oxygenator (Medos Hillite, Beijing), and a heparin-coated circuit were used to perform related procedures.

Variables

For statistical analysis, we extracted the following information from the electronic medical system in the hospital: sex, age, total hospitalization costs, chief complaints, symptom onset time, presence of prodromal flu-like symptoms, body mass index (BMI), blood pressure, temperature (T), peripheral oxygen saturation (SpO_2), Vaso-active-inotropic score, white blood cell (WBC), c-reactive protein (CRP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), serum creatinine (Scr), sputum

Table 1 Baseline demographics and hospital admission information

Characteristics	Survival group (*n* = 61)	Death group (*n* = 18)	t /χ^2/Z	*P*-value
Male	23 (37.70%)	5 (27.80%)	0.60	0.439
Age (month)	95.41 ± 38.21	79.00 ± 56.17	1.16	0.257
BMI (kg/m^2)	17.03 ± 3.68	17.21 ± 4.72	-0.15	0.884
Length of hospital stay (day)	19.00 (15.00-35.50)	1.00 (1.00-13.50)	-4.20	< 0.001*
Medical expenses (RMB)	111867.14 (34053.08-273304.51)	15638.33 (8195.63-106284.00)	-2.99	0.003*

n, number of patients; BMI, body mass index; *Statistically significant difference between two groups

Table 2 Symptoms and complications

Characteristics	Survival group (*n* = 61)	Death group (*n* = 18)	χ^2/Fisher	*P*-value
Symptoms				
Vomiting	34 (55.70%)	7 (38.90%)	1.58	0.209
Fever	29 (47.50%)	8 (44.40%)	0.05	0.817
Abdominal pain	23 (37.70%)	4 (22.20%)	1.48	0.224
Chest distress	23 (37.70%)	3 (16.70%)	2.79	0.095
Low mood	12 (19.70%)	5 (27.80%)	0.17	0.683
Complications				
Cardiogenic shock	24 (39.30%)	7 (38.90%)	0.01	0.972
Abnormal electrocardiogram	23 (37.70%)	7 (38.90%)	0.01	0.928
Pneumonia	35 (57.40%)	10 (55.60%)	0.02	0.891
Heart failure	16 (26.20%)	3 (16.70%)	0.27	0.603
Multiple organ failure	8 (13.10%)	9 (50.00%)	9.12	0.003*
Respiratory failure	3 (4.90%)	7 (38.90%)	11.60	0.001*

n, number of patients; *Statistically significant difference between two groups

culture, blood culture, viral serological antibody test, viral antigen test, cardiac troponin I (cTnI), myoglobin (MYO), CK-MB, B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), pericardial effusion description, ECG diagnosis, arterial potential of hydrogen (PH), PaO_2/ FiO_2, bicarbonate (HCO_3^-), lactate (Lac), treatment modalities, renal replacement therapy, complications, and outcome. Microbiological testing was conducted on the first day of admission. Vasoactive-inotropic score was defined as dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 10*milrinone dose (μg/kg/min) + 100*epinephrine dose (μg/kg/min) + 100*norepinephrine dose (μg/kg/min) + 10,000* vasopressin dose (units/kg/min).

Statistical analysis

Qualitative variables were reported as frequencies and percentages and analyzed using Chi-square (χ^2) test. Quantitative variables were reported as mean and standard deviation for parametric data, and median and interquartile range for nonparametric data. Parametric data were analyzed using the t-test, and nonparametric data using the Mann-Whitney U test. We have performed multiple imputations to address all missing data. Utilize Receiver Operating Characteristic (ROC) curves were plotted to determine the optimal cutoff values of quantitative variables that exhibit differences in single-factor analysis. Based on whether they reach this cutoff value, convert quantitative variables into qualitative variables. Utilizing univariate logistic regression analyses to identify independent factors associated with in-hospital mortality. All statistical tests were two-sided, and a *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 26).

Results

Clinical symptoms and laboratory investigations

In this retrospective study, 79 children with AFM (28 males and 51 females; aged 2 months to 13 years, average age 92±43 months) were included. The hospital stay in the survival group (median = 19, IQR = 15-35.5 days) was significantly longer than that in the death group (median = 1, IQR = 1-13.5 days)(P < 0.001). Additionally, medical expenses in the survival group (median = 111867.14, IQR = 34053.08 − 273304.51 RMB) were significantly higher than those in the deceased group (median = 15638.33, IQR = 8195.63 − 106284.00 RMB). Furthermore, there were no statistically significant differences between the two groups in terms of age, gender, or BMI (Table 1).

The top five symptoms were vomiting, fever, abdominal pain, chest tightness, and lethargy. These five symptoms appeared in more than 50% of the cases (Table 2). The number of children with various symptoms showed no significant difference between the survival group and

the deceased group. The most common complication throughout the clinical course was cardiogenic shock (23.45%), followed by arrhythmia (10.34%), pneumonia (6.90%), heart failure (6.55%), multiple organ failure (5.86%), and respiratory failure (3.45%). The incidence of multiple organ failure and respiratory failure significantly differed between the deceased group and the surviving group (Table 2).

ECG abnormalities of cardiac excitation origin were the most common, followed by abnormal cardiac conduction and myocardial ischemic changes. Among the abnormalities of cardiac excitation origin, that of supraventricular origin was the most common. Conduction abnormalities were categorized into atrioventricular block and intraventricular block, both having a similar incidence. Among atrioventricular blocks, third-degree block was predominant, while among intraventricular blocks, right bundle branch block was the most common. In this group, 12 patients were fitted with pacemakers, and 11 of these patients survived, showing no significant arrhythmia on the ECG before discharge. The number of pediatric patients with abnormal electrocardiograms showed no significant difference between the deceased and surviving groups (Table 3).

We conducted an etiological analysis for all patients and found that 60 children (75.9%) tested positive. Among these, viruses were the most common pathogen, followed by mycoplasma pneumoniae, with bacterial infection being the least common. The presence of any pathogenic infection did not have a predictive value for mortality (Table 4). Based on the findings presented in Tables 3 and 4, there are statistically significant differences observed between the deceased and surviving groups across various indicators including LVEF, MYO, AST, LDH, BNP, PH, HCO_3^-, Lac, SpO_2, and WBC indicators.

Table 5 presents the treatment protocols administered to pediatric patients with fulminant myocarditis. Upon comparing these protocols with patient outcomes, no statistically significant differences were observed.

Correlation of clinical variables with mortality

We have performed ROC curve analysis for quantifiable variables showing discrepancies in single-factor analysis, and used them to establish an optimal cutoff point. The cutoff point aids in converting the quantifiable variables into qualitative ones based on whether they meet the threshold. All ROC curve plots have been included

Table 3 Examination results

Characteristics	Survival group ($n=61$)	Death group ($n=18$)	t/χ^2/Z/Fisher	*P*-value
Electrocardiographic				
Sinus tachycardia	25 (41.00%)	4 (22.20%)	2.10	0.147
Ventricular tachycardia	4 (6.60%)	2 (11.10%)	0.02	0.893
Ventricular premature beat	6 (9.80%)	1 (5.60%)	0.01	0.929
Degree I atrioventricular block	5 (8.20%)	0 (0.00)	0.50	0.481
Degree II type 1 atrioventricular block	1 (1.60%)	0 (0.00)	0.30	0.587
Degree II type 2 atrioventricular block	1 (1.60%)	0 (0.00)	0.30	0.587
Degree III atrioventricular block	14 (23.00%)	2 (11.10%)	0.59	0.445
QT interval prolongation	1 (1.60%)	0 (0.00)	0.30	0.587
Complete right bundle branch block	10 (16.40%)	3 (16.70%)	0.01	0.978
Incomplete right bundle branch block	1 (1.60%)	0 (0.00)	0.30	0.587
Complete left bundle branch block	2 (3.30%)	0 (0.00)	0.60	0.439
Left anterior branch block	7 (11.50%)	2 (11.10%)	0.01	0.966
Atrial tachycardia	2 (3.30%)	1 (5.60%)	0.20	0.659
Atrial flutter	0 (0.00)	1 (5.60%)	3.39	0.066
Junctional escape	6 (9.80%)	0 (0.00)	0.77	0.380
Ventricular escape	1 (1.60%)	0 (0.00)	0.30	0.587
ST changes	2 (3.30%)	0 (0.00)	0.60	0.439
ST-T changes	7 (11.50%)	0 (0.00)	1.07	0.301
T wave changes	2 (3.30%)	0 (0.00)	0.60	0.439
Myocardial infarction	6 (9.80%)	1 (5.60%)	0.01	0.929
Supraventricular tachycardia	3 (4.90%)	0 (0.00)	0.91	0.341
Low voltage in leads	3 (4.90%)	0 (0.00)	0.91	0.341
Echocardiography				
Left ventricular ejection fraction (%)	47.76 ± 12.63	37.41 ± 13.50	3.01	0.004*
Left ventricular fractional shortening (%)	25.53 ± 7.20	22.91 ± 5.72	1.42	0.161
Pericardial effusion (mm)	0.00 (0.00-5.60)	1.61 (0.00-3.21)	-0.19	0.853

n, number of patients; *Statistically significant difference between two groups

Table 4 Laboratory test results and others

Characteristics	Survival group (*n* = 61)	Death group (*n* = 18)	t/χ^2/Z/Fisher	*P*-value
Myocardial enzyme				
Cardiac troponin I (μg/L)	7.30 (3.18–22.40)	9.45 (0.45–23.02)	-0.77	0.444
Myoglobin (μg/L)	88.00 (34.40-225.25)	447.10 (153.43-2657.70)	-3.76	< 0.001*
CK-MB (μg/L)	44.00 (24.20–85.00)	94.00 (19.05–215.30)	-1.34	0.180
BNP (ng/L)	1338.00 (544.50-2371.50)	2575.50 (1508.75-4375.25)	-2.11	0.035*
Aspartate aminotransferase (U/L)	129.00 (58.00-292.50)	299.00 (214.50-682.66)	-2.89	0.004*
Lactate dehydrogenase (U/L)	594.00 (427.50-981.87)	859.50 (666.00-1059.15)	-2.32	0.021*
Arterial blood gas analysis				
PaO_2/ FiO_2 (mmHg)	440.40 (74.55-659.55)	116.90 (69.95-389.08)	-0.51	0.612
PH	7.39 ± 0.08	7.17 ± 0.28	3.25	0.005*
HCO_3^- (mmol/L)	19.53 (19.53–20.25)	19.53 (15.93–19.53)	-2.69	0.007*
Serum lactate (mmol/L)	3.30 (1.60–5.23)	5.23 (3.15–16.90)	-2.84	0.005*
Others				
Symptom onset time (day)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	-0.78	0.438
Systolic blood pressure (mmHg)	101.88 ± 15.12	98.25 ± 23.84	0.58	0.570
Diastolic blood pressure (mmHg)	64.00 (57.00–70.00)	63.50 (42.50–73.50)	-0.70	0.485
Temperature (℃)	36.90 (36.90–37.30)	37.00 (36.35–37.80)	-0.04	0.966
Peripheral oxygen saturation (%)	100.00 (97.00-100.00)	97.00 (84.50–100.00)	-2.75	0.006*
White blood cell (*10^9/L)	8.80 (5.86–11.07)	10.95 (9.21–16.81)	-2.74	0.006*
C-reactive protein (mg/L)	8.00 (6.40–9.19)	8.00 (8.00-10.30)	-0.86	0.392
Serum creatinine (μmol/L)	47.00 (35.00–71.00)	85.95 (34.40-121.75)	-1.74	0.082
Prodromal flu-like symptoms	41 (67.20%)	14 (77.80%)	0.73	0.392
Positive pathogen examination	50.00 (82.00%)	10.00 (55.60%)	1.17	0.279

n, number of patients; CK-MB, creatine kinase isoenzyme; BNP, B-type natriuretic peptide; PH, arterial potential hydrogen; HCO_3^-, bicarbonate; *Statistically significant difference between two groups

Table 5 Treatment and outcomes in all patients

Characteristics	Survival group (*n* = 61)	Death group (*n* = 18)	t/χ^2/Z	*P*-value
Vasoactive-inotropic score	23.34 ± 9.09	30.06 ± 17.64	-1.56	0.136
ECMO	22 (36.07%)	5 (27.78%)	0.42	0.515
Renal replacement therapy	10 (16.39%)	4 (22.22%)	0.05	0.569
Pacemaker	11 (18.03%)	1 (5.56%)	0.85	0.356
Antiviral medication	27 (44.26%)	7 (38.89%)	0.16	0.686

n, number of patients; ECMO, extracorporeal membrane oxygenation

in the supplementary files. The findings indicated that an AST level of 194.00 U/L, LDH level of 637.50 U/L, MYO level of 265.75 μg/L, BNP level of 1738.50 ng/L, PH level of 7.29, HCO_3^- level of 18.45 mmol/L, Lac level of 12.30 mmol/L, SpO_2 level of 97.50%, WBC level of 9.69*10^9/L, and LVEF level of 28.25% could serve as thresholds for predicting mortality. Furthermore, we employed single-factor logistic regression analyses to identify independent factors associated with inpatient mortality rates. A higher in-hospital mortality rate was significantly associated with the following factors (Table 6): more severe myocardial injury (AST > 194.00 U/L [OR 11.94; 95% CI 3.01–46.36; $P < 0.001$]; LDH > 637.50 U/L [OR 7.20; 95% CI 1.88–27.51; $P = 0.004$]; MYO > 265.75 μg/L [OR 8.17; 95% CI 2.55–26.20; $P < 0.001$]; BNP > 1738.50 ng/L [OR 5.78; 95% CI 1.70–19.70; $P = 0.005$]); more severe acidosis (PH < 7.29 [OR 17.81; 95% CI 4.50-70.49; $P < 0.001$]; HCO_3^- <18.45 mmol/L [OR 7.13; 95% CI 1.91–26.61; $P = 0.003$]; Lac > 12.30 mmol/L [OR 18.77; 95% CI 3.44-102.58; $P < 0.001$]); worse left ventricular systolic function (LVEF < 28.25% [OR 11.40; 95% CI 2.88–45.11; $P < 0.001$). Additionally, admission SpO_2 < 97.50% (OR 4.42; 95% CI 1.46–13.36; $P = 0.008$) and WBC > 9.69*10^9/L (OR 5.40; 95% CI 1.59–18.35; $P = 0.007$) were also significantly associated with an increased in-hospital mortality rate.

Discussion

In our center, we found that AFM was more prevalent in females than in males among children, which is inconsistent with the results of two previous studies [23, 24], but aligns with the results reported by Shanghai Children's Medical Center [25]. Pediatric AFM can be non-specific, commonly presenting with symptoms such as vomiting, fever, abdominal pain, and chest tightness. Some children also present with syncope, poor appetite, coughing, dizziness, shortness of breath, headache, edema,

Table 6 Results of univariate logistic regression analysis

Variables		OR	95%CI	*P*-value
Indicators of myocardial injury				
	AST > 194.00 U/L	11.94	3.01–46.36	< 0.001
	LDH > 637.50 U/L	7.20	1.88–27.51	0.004
	MYO > 265.75 μg/L	8.17	2.55–26.20	< 0.001
	BNP > 1738.50 ng/L	5.78	1.70–19.70	0.005
Arterial blood gas analysis				
	PH < 7.29	17.81	4.50-70.49	< 0.001
	HCO_3^- <18.45 mmol/L	7.13	1.91–26.61	0.003
	Lac > 12.30 mmol/L	18.77	3.44-102.58	0.001
Complication				
	Multiple organ failure	6.63	2.02–21.69	0.003
	Respiratory failure	12.30	2.75–55.04	0.001
Others				
	SpO_2 < 97.50%	4.42	1.46–13.36	0.008
	WBC > 9.69*10^9/L	5.40	1.59–18.35	0.007
	LVEF < 28.25%	11.40	2.88–45.11	< 0.001

OR, odds ratio; CI, confidence interval; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; MYO, myoglobin; BNP, B-type natriuretic peptide; PH, arterial potential hydrogen; HCO_3^-, bicarbonate; Lac, lactate; SpO_2, peripheral oxygen saturation; WBC, white blood cell; LVEF, left ventricular ejection fraction

pallor, discomfort in the precordial area, coma, drowsiness, sudden respiratory and cardiac arrest, diarrhea, and other symptoms. Additionally, AFM may simultaneously involve multiple systems, such as the digestive, nervous, and respiratory systems [24]. Therefore, AFM may not be timely identified promptly in a significant portion of children, thus delaying the implementation of interventions. In our group, the most common symptoms were vomiting, fever, abdominal pain, chest tightness and poor consciousness. These can easily lead to wrong or missed diagnosis of AFM, necessitating vigilance on outpatient children with such symptoms.

The pathogenesis of AFM may involve direct viral damage or an excessive immune response to viruses [26]. Common viral pathogens include Parvovirus, Coxsackie virus, and Cytomegalovirus [27, 28]. Our center has found that viruses are the culprit of AFM, predominantly Epstein-Barr virus (EB), herpes simplex virus (HSV), cytomegalovirus (CMV), and rubella virus (RV). Previous studies have indicated that 90% of patients present prodromal symptoms of viral infection [29], and our center has found that 70% of children exhibit flu-like symptoms. Importantly, current detection methods are limited by a low sensitivity and a high false-negative rate, as indicated by a detection rate of just 38% for viral myocarditis [30]. In our study, the detection rate for viruses was 43.3%.

Literature shows that AFM predisposes children to cardiac conduction block [31]. While our study found that the most common ECG feature was sinus tachycardia. Sinus tachycardia is a primary compensatory mechanism, and the most prevalent arrhythmia is atrioventricular conduction block. For cases with third-degree atrioventricular block or a combination of atrioventricular and intraventricular blocks with a very low ventricular rate, our center invariably opts for the placement of pacemakers. If circulation remains unstable after pacemaker placement, ECMO treatment is initiated. A retrospective study of 18 children diagnosed with AFM has shown encouraging outcomes achieved by ECMO in patients with arrhythmia, with none requiring a permanent pacemaker or heart transplant [32]. Similarly, no children in our study required a permanent pacemaker or a heart transplant, and the survival rate was 87% for children with arrhythmia treated with ECMO.

Currently, no consensus has reached regarding the indications of ECMO in patients with AFM. To identify patients who may benefit from ECMO support, scholars have evaluated clinical features before ECMO and identified those associated with survival. Lower PH, blood pressure, cardiac arrest and necessity of cardiopulmonary resuscitation before ECMO are associated with a high risk of death, suggesting that clinicians should initiate ECMO earlier to reduce organ damage and improve the survival [33]. Previous studies have found that ECMO is efficient in treating AFM patients, with a cure rate ranging from 64.3 to 83.3% [14, 34], which is consistent with that observed in our center over the past decade.

AFM complications are complex, often resulting in death due to cardiogenic shock, ventricular arrhythmia, or multiple organ failure [35]. Similarly, the present study found that multiple organ failure was predictive of death. Additionally, respiratory failure is an important predictor of in-hospital mortality in children with AFM. Managing the complications involving the cardiovascular and respiratory systems in children with AFM is challenging. Yuji Tominaga et al. have proposed a biventricular assist device that has proven effective in AFM patients with severe complications of cardiogenic shock and

respiratory failure [36]. Left ventricular systolic dysfunction is an important characteristic of AFM, emphasizing the importance of inotropic drug use and circulatory support [37]. Therefore, providing immediate interventions for complications of AFM is crucial to improve the survival rate of children.

Here, we compared clinical data between survivors and non-survivors, finding that prognostic factors for in-hospital survival in children with AFM included heart damage, arterial PH, HCO_3^-, Lac, SpO_2, WBC, and LVEF. Consistent with prior research [38], non-survivors exhibited significantly lower LVEF. Research indicates that the peaking time of troponin levels is a key predictive factor for myocardial recovery, along with cardiac enzyme, arrhythmia, and thickness of the left ventricular posterior wall (LVPWT) at admission [16]. Here, we found that indicators of heart damage, such as AST, LDH, MYO, and BNP, were significant determinants of survival. Ohki et al. have reported that younger age (less than 5 years old) is a high-risk factor for death [39]. Another meta-analysis has found that the efficacy of ECMO decreases with age in adults [40]. Here, we found that any age above or below cut-off point was not significantly associated with a high mortality. Additionally, previous studies have identified acidosis indicators, including serum bicarbonate level and lactate level, as predictors of in-hospital survival in ECMO patients [15, 41]. Their predictive values were confirmed in this study, which revealed that PH and peak lactate values, indicating the occurrence of poor tissue perfusion, were important predictors of in-hospital mortality in children with AFM. In AFM, renal dysfunction can induce metabolic acidosis and electrolyte disturbances (hyperkalemia and hypocalcemia), which may be related to ventricular tachycardia or fibrillation.

Limitations

This study has some limitations. First, being retrospective, it was not possible to autonomously select the required clinical data, and some data were missing, which may have affected the results. The study was based on the data from a single center, and the results may not be generalizable. Second, due to various constraints, we did not obtain post-discharge follow-up data, making it impossible to determine the long-term prognosis of in-hospital survivors. Third, although ECMO has been used for AFM for a long time, there is still no consensus on when to use ECMO.

Conclusion

Severe myocardial injury, acidosis, hypoxia, inflammatory response, left ventricular systolic dysfunction, multi-organ failure, and respiratory failure are significantly associated with higher mortality rates. These factors can accurately identify AFM children at an increased risk of death.

Abbreviations

ECMO	Extracorporeal membrane oxygenation
AFM	Acute fulminant myocarditis
AST	Aspartate aminotransferase
LDH	Lactate dehydrogenase
MYO	Myoglobin
BNP	Brain natriuretic peptide
PH	Potential hydrogen
HCO_3^-	Bicarbonate
Lac	Lactate
SpO_2	Peripheral oxygen saturation
WBC	White blood cell
LVEF	Left ventricular ejection fraction
AM	Acute myocarditis
MRI	Magnetic resonance imaging
T	Temperature
CRP	C-reactive protein
Scr	Serum creatinine
cTnI	Cardiac troponin I
CK-MB	Creatine kinase isoenzyme
LVFS	Left ventricular fractional shortening
ECG	Electrocardiogram
ROC	Receiver operating characteristic
BMI	Body mass index
OR	Odds ratio
CI	Confidence interval
EB	Epstein-Barr virus
HSV	Herpes simplex virus
CMV	Cytomegalovirus
RV	Rubella virus
LVPWT	Thickness of the left ventricular posterior wall

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: YZ, MD; data collection: YZ; analysis and interpretation of results: XY, YX, JQ; draft manuscript preparation: YZ, MD. All authors reviewed the results and approved the final version of the manuscript.

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Data availability

The data used in this manuscript are available upon reasonable request by contacting the corresponding author via email.

Declarations

Ethics approval and consent to participate

This study had been approved by the hospital Ethics Committee of Children's Hospital of Nanjing Medical University to exempt patients' informed consent. (Ethical approval number: 202404029-1)

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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