Clinical Outcome and Risk Factors for Acute Fulminant Myocarditis Supported by Venoarterial Extracorporeal Membrane Oxygenation: an Analysis of Nationwide CSECLS Database in China Mainland

Tong Hao

Southeast University

Yu Jiang

Capital Medical University Affiliated Anzhen Hospital

Changde Wu

Southeast University

Chenglong Li

Capital Medical University Affiliated Anzhen Hospital

Chuang Chen

Southeast University

Jianfeng Xie

Southeast University

Chun Pan

Southeast University

Fengmei Guo

Southeast University

Yingzi Huang

Southeast University

Ling Liu

Southeast University

Haixiu Xie

Capital Medical University Affiliated Anzhen Hospital

Zhongtao Du

Capital Medical University Affiliated Anzhen Hospital

Xiaotong Hou

Capital Medical University Affiliated Anzhen Hospital

Songqiao liu (✉ liusongqiao@ymail.com)

<https://orcid.org/0000-0002-1875-1131>

Yi Yang

Southeast University

Haibo Qiu

Southeast University

Research

Keywords: acute fulminant myocarditis, ECMO, outcome, lactate, cardiac arrest, pH

Posted Date: July 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-739094/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Clinical Outcome and Risk Factors for Acute Fulminant Myocarditis Supported by Venoarterial Extracorporeal Membrane Oxygenation: an Analysis of Nationwide CSECLS Database in China Mainland

Tong Hao^{1#}, Yu Jiang^{2#}, Changde Wu^{1#}, Chenglong Li^{2#}, Chuang Chen¹, Jianfeng Xie¹, Chun Pan¹, Fengmei Guo¹, Yingzi Huang¹, Ling Liu¹, Haixiu Xie², Zhongtao Du², Xiaotong Hou², Songqiao Liu^{1,3*}, Yi Yang^{1*}, Haibo Qiu¹

Affiliations:

¹Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Trauma Center, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu 210009, People's Republic of China

²Center for Cardiac Intensive Care, Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China

³Nanjing Lishui People's Hospital, Zhongda Hospital Lishui Branch, Southeast University, No. 86 Chongwen Road, Lishui District, Nanjing, 211200, Jiangsu, People's Republic of China

Tong Hao, Yu Jiang, Changde Wu and Chenglong Li contributed equally to this manuscript

Corresponding Author Information:

*Dr. Songqiao Liu

Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine, Trauma Center, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, 210009; Nanjing Lishui People's Hospital, Zhongda Hospital Lishui Branch, Southeast University, No. 86 Chongwen Road, Lishui District, Nanjing, Jiangsu, 211200, People's Republic of China

E-Mail: liusongqiao@ymail.com

*Dr. Yi Yang

Jiangsu Provincial Key Laboratory of Critical Care Medicine, Department of Critical Care Medicine,
Trauma Center, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, 210009, People's
Republic of China

E-Mail: yiyiyang2004@163.com

Take-home message

More than 70% of patients with acute fulminant myocarditis supported with VA ECMO survived in China mainland. Cardiac arrest prior to ECMO, lower pH and higher lactate concentration at 24 hours after ECMO initiation were independent risk factors correlated with 90-day mortality.

Abstract

Purpose: To assess the outcomes and risk factors for adult patients with acute fulminant myocarditis supported with venoarterial extracorporeal membrane oxygenation (VA ECMO) in China mainland.

Methods: Data were extracted from Chinese Society of ExtraCorporeal Life Support (CSECLS) Registry database. Data from adult patients who were diagnosed with acute myocarditis and needed VA ECMO in the database were retrospectively analyzed. The primary outcome was 90-day mortality after ECMO initiation in patients with acute fulminant myocarditis supported with VA ECMO. Cox proportional hazard regression model was used to examine the risk factors associated with 90-day mortality.

Results: Among 221 patients enrolled, 186 (84.2%) patients weaned from ECMO and 159 (71.9%) patients survived to 90 days. The median age was 38 years (IQR 29-49) and males (n=115) accounted for 52.0% of the patients. The median ECMO duration was 134 hours (IQR 96-177hrs). The main adverse events during ECMO course was bleeding (16.3%), followed by infection (15.4%). In the multivariate Cox model, cardiac arrest prior to ECMO initiation (adjusted HR 2.529; 95%CI: 1.341-4.767, $p=0.004$), lower pH value (adjusted HR 0.016; 95%CI: 0.010-0.059, $p<0.001$) and higher lactate concentration at 24 hours after ECMO initiation (adjusted HR 1.146; 95%CI: 1.075-1.221, $p<0.001$) was associated with 90-day mortality.

Conclusions: In our study, 71.9% patients with acute fulminant myocarditis supported with VA ECMO survived to 90 days. Cardiac arrest prior to ECMO, lower pH and higher lactate concentration at 24 hours after ECMO initiation were correlated with 90-day mortality closely.

ClinicalTrials.gov registration number: NCT04158479, Registered 8 November 2019, <https://clinicaltrials.gov/ct2/show/NCT04158479?term=hou+xiaotong&draw=2&rank=2>.

Keywords: acute fulminant myocarditis; ECMO; outcome; lactate; cardiac arrest; pH

INTRODUCTION

Acute fulminant myocarditis refers to an inflammatory disease of the myocardium characterized by rapid onset of cardiogenetic shock, life-threatening arrhythmias and (or) multiple organ failure[1, 2]. The annual incidence of acute myocarditis was approximately 22 cases per 100,000 population [3] and 30% hospitalized patients with acute myocarditis were considered fulminant [4]. Cardiovascular death is the leading cause of short-term mortality and the risk of cardiovascular mortality is associated with severity of myocarditis [5]. Patients with New York Heart Association (NYHA) functional class III or IV who do not receive optimal treatment for heart failure has poor outcome of 39% transplant-free survival [6]. Mechanical circulatory supports including extracorporeal membrane oxygenation (ECMO) have been used to support patients with rapid onset of circulatory collapse as a bridge to cardiac recovery [7-9].

Venoarterial extracorporeal membrane oxygenation (VA ECMO) is a life-saving treatment option for patients with acute fulminant myocarditis because it can provide stable flow rates and improve organ perfusion[10, 11]. ECMO can be established at the bedside percutaneously and this an obvious advantage for patients in need of urgent hemodynamic stabilization. ECMO provide superior hemodynamic support in comparison to intra-aortic balloon pump (IABP) [12]. Moreover, a recent meta-analysis reported that patients with cardiogenetic shock supported by ECMO had a higher 30-day survival compared to IABP [13]. However, ECMO support demands technically sophisticated care and is related to a high morbidity of adverse events. Complications including infection and bleeding during ECMO support may increase mortality risk[14, 15]. The timing of ECMO initiation remained controversial and might have an influence on the prognosis[16, 17]. Thus, early identification of risk factors associated with the prognosis of acute fulminant myocarditis patients supported by ECMO was very important.

ECMO have been used in patients with acute fulminant myocarditis for many years in China. Some small-scale studies have reported the outcomes and (or) risk factors associated

with death. Of these studies, survival rates ranged from 58.3% to 78.7% [18-20]. Moreover, these studies carried some limitations that impede their widespread applicability, such as study population limited to children patients and (or) lack of generalizability to broader regions. There was no national-level study on outcomes of the adult patients with acute fulminant myocarditis supported by VA ECMO. Therefore, we conducted this retrospective observational national-level study aiming to assess the outcomes and examine the prognostic factors in adult patients with acute fulminant myocarditis supported with VA ECMO in China mainland.

METHODS

Study Design and Population

This was a retrospective multi-center observational study. Data were obtained from the Chinese Society of ExtraCorporeal Life Support (CSECLS) Registry database. CSECLS database maintained the registry of ECMO use in China mainland. Data were submitted on a standardized electronic form. Statistical review and identified datasets extracted were approved by CSECLS database managers. Information available in CSECLS database include patient demographic information, comorbidities, main diagnosis, pre-ECMO details, ECMO indication, ECMO support details including complications, weaning trial details and patient outcomes.

From January 1, 2017 to December 31, 2019, adult patients with acute fulminant myocarditis received VA ECMO therapy were included. Approval from the central Institutional Review Board of Beijing Anzhen Hospital (2019040X), Capital Medical University, Beijing, China and Zhongda Hospital, Southeast University, Nanjing, China were obtained for this study.

Data Collection

Baseline characteristics including demographic information, comorbidities, main diagnose at admission, severity of illness assessed by Sequential Organ Failure Assessment (SOFA)

score [21], survival after veno-arterial-ECMO (SAVE) score [7] and ECMO indication (circulatory failure or extracorporeal cardiopulmonary resuscitation (ECPR)) were collected.

Clinical, echocardiographic and laboratory characteristics related to hemodynamic status prior to ECMO initiation included cardiac arrest, blood pressure, arterial blood gas, ejection fraction (EF), mechanical respiratory and circulatory support excluded ECMO, maximal doses of vasopressors and vasoactive-inotropic score (VIS). VIS was calculated using the maximum doses of vasoactive and inotropic drugs ($\text{VIS} = \text{dopamine dose } [\mu\text{g kg}^{-1} \text{ min}^{-1}] + \text{dobutamine } [\mu\text{g kg}^{-1} \text{ min}^{-1}] + 100 \times \text{epinephrine dose } [\mu\text{g kg}^{-1} \text{ min}^{-1}] + 50 \times \text{levosimendan dose } [\mu\text{g kg}^{-1} \text{ min}^{-1}] + 10 \times \text{milrinone dose } [\mu\text{g kg}^{-1} \text{ min}^{-1}] + 10000 \times \text{vasopressin } [\text{units kg}^{-1} \text{ min}^{-1}] + 100 \times \text{norepinephrine dose } [\mu\text{g kg}^{-1} \text{ min}^{-1}]$) [22].

Moreover, clinical data including blood flow and arterial blood gas at 4 and 24 hours after ECMO initiation, other mechanical circulatory support, ECMO-related adverse events classified as mechanical, bleeding, infectious, neurological and other using Extracorporeal Life Support Organization (ELSO) definitions [23], the reason for ECMO discontinuation, duration of ECMO support and length of hospital and intensive care unit (ICU) stay were collected.

Outcomes

The primary outcome was 90-day mortality after VA ECMO initiation in patients with acute fulminant myocarditis supported with VA ECMO. We also examined the adverse events while on ECMO, the duration of ECMO support, the duration of organ support therapy including mechanical ventilation and IABP, length of hospital and ICU stay.

Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviations for normally distributed data or medians (interquartile range, IQR) for non-normal distributed data. Categorical variables were expressed as percentages and the number of patients. Student's t test

or Kolmogorov-Smirnov test was used for analysis of continuous variables and chi-square or Fisher's exact test for categorical variables between survivors and non-survivors. Cox proportional hazard regression model was used to determine risk factors of 90-day mortality. In this regression model, 90-day mortality was defined as the dependent variable and pre-ECMO and variables during ECMO course at 24 hours after ECMO initiation were investigated as independent risk factors. Severity of illness before ECMO initiation was assessed by SAVE score. Only risk factors with missing values less than 20% and a univariate p value less than or equal to 0.1 were retained in the multivariate Cox model. Unadjusted and adjusted hazard ratio (HR) and 95% confidence interval (CI) were calculated to identify predictors related to 90-day mortality. The discriminative power of the risk factor was evaluated by the area under the receiver operating curve (AUROC). The cut-off value was determined by maximal Youden Index. Patients were assigned into two groups according to the cut-off value. Cumulative survival curves for 90 days follow-up was generated utilizing the Kaplan-Meier method and compared using log rank test among groups. All statistical analysis was using Stata 15.0 (College Station, TX, USA). Statistically significant was set by two-side p value less than 0.05.

RESULTS

Study population

From January 1, 2017 to December 31, 2019, a total of 327 patients supported by VA ECMO treatment for acute fulminant myocarditis were reported to the CSECLS database. 106 patients under the age of 18 years old were excluded. 221 adult patients were included in this study. The median age of ECMO recipients was 38 years (IQR 29-49 yr) and males ($n=115$) accounted for 52.0% patients. The most indication of ECMO was heart failure (89.1%) while 10.9% were cannulated as part of ECPR.

The median duration of ECMO support was 134 hours (IQR 96-177 hr). Of 221 patients, 186 (84.2%) patients successfully weaned from ECMO. 159 (71.9%) patients survived to

hospital discharge and 90 days after ECMO initiation (**Fig. 1**). 35 (67.3%) patients died during ECMO course and 27 (32.7%) patients died after decannulation from ECMO. Of those who had poor prognosis, the main reason of death was multiple organ failure (67.3%) followed by infection (7.7%) and bleeding (7.7%). The delineation of acute fulminant myocarditis patients supported by VA ECMO was shown in **Fig. 2**.

Comparison of pre-ECMO factors between Survivors and Non-survivors

Compared with survivors, non-survivors had lower systolic blood pressure (60 (15, 82) vs 75 (60, 85) mmHg; $p=0.030$), lower diastolic blood pressure (35 (10, 52) vs 45 (37, 56) mmHg $p=0.008$) and lower mean blood pressure (46 (12, 61) vs 54 (45, 65) mmHg; $p=0.044$). Lower pH value (7.23 (7.10, 7.38) vs 7.36 (7.21, 7.41); $p=0.027$) and higher lactate concentration (7.9 (3.8, 14.7) vs 5.4 (3.0, 8.7); $p=0.018$) were more common in the non-survivors. Cardiac arrest prior to ECMO was more obviously commonly observed in non-survivors (41.9% vs 15.1%; $p<0.001$) compared with survivors. There were no significant differences in left ventricular EF, left ventricular end-diastolic diameter, the SOFA and SAVE score before ECMO initiation between survivors and non-survivors (Appendix Table 1 in the Online Supplement).

Comparison of factors during ECMO course between Survivors and Non-survivors

At 24 hours after ECMO initiation, ECMO blood flow was similar between survivors and non-survivors. Compared with non-survivors, survivors had higher pH value (7.44 (7.38, 7.49) vs 7.35 (7.29, 7.43); $p<0.001$), lower lactate concentration (2.0 (1.3, 3.1) vs 5.5 (2.8, 10.4); $p<0.001$), lower dose of norepinephrine (0.6 (0.2, 1.0) vs 1.0 (0.3, 1.5), $p=0.018$) and lower VIS score (16 (6, 48) vs 58 (13, 100); $p=0.008$). There was no significant difference in maximum dose of epinephrine and SOFA score. The occurrence of kidney failure was observed in 153 (96.2%) patients of survivors and 52 (100%) patients of non-survivors. 52 patients and 43 patients of non-survivors received continuous renal replacement therapy (32.7% vs 69.4%; $p<0.001$) (Appendix Table 2 in the Online Supplement).

Adverse events

The main adverse events during ECMO course was bleeding (16.3%) followed by infection (15.4%). The occurrence of cardiac adverse events was more common among non-survivors (19.4% vs 6.2%, $p=0.015$). The prevalence of mechanical (9.7% vs 7.5%, $p=0.592$) and neurologic (11.3% vs 5.6%, $p=0.157$) was similar between two groups. There was no significant difference in IABP duration (5 (2, 12) vs 6 (4, 9), $p=0.073$) and mechanical ventilation duration (7 (3, 11) vs 7 (5, 9), $p=0.090$) (Appendix Table 3 in the Online Supplement).

Risk factors of 90-day mortality

Variables associated with 90-day mortality by univariable analysis were cardiac arrest prior to ECMO, lower diastolic blood pressure, SAVE score, lower pH value before ECMO initiation, higher lactate concentration before ECMO initiation, higher VIS before ECMO initiation, higher pH value at 24 hours after ECMO initiation and lower lactate concentration. Multivariable Cox logistic regression analysis identified cardiac arrest prior to ECMO (adjusted HR 2.529; 95%CI 1.341-4.767, $p=0.004$), higher lactate concentration (adjusted HR 1.146; 95%CI 1.075-1.221, $p<0.001$) and lower pH value (adjusted HR 0.016; 95%CI 0.010-0.059, $p<0.001$) at 24 hours after ECMO initiation was independent risk factors of 90-day mortality (Appendix Table 4 in the Online Supplement). The Kaplan-Meier survival curves until 90 days for patients with cardiac arrest prior to ECMO or not was shown in **Fig. S1** (Log rank test $p<0.001$).

The AUROC of serum lactate concentration at 24 hours after ECMO initiation for predicting 90-day mortality was 0.792 (95% CI 0.712-0.871, $p<0.001$) (Appendix Fig. S2A in the Online Supplement). The cut-off value was 3.0mmol/L with a sensitivity 74.4% and a specificity of 74.8%. Patients were divided into two categories depending on cut-off value of 3.0mmol/L and Kaplan-Meier survival curve was performed. Patients whose serum lactate level were less than 3.0mmol/L at 24 hours after ECMO support initiation may have better

outcome (Log rank test $p<0.001$) (Appendix Fig. S2B in the Online Supplement). The AUROC of pH value at 24 hours after ECMO initiation for predicting 90-day mortality was 0.729 (95% CI 0.640-0.818, $p<0.001$). The cut-off value of 7.35 had a sensitivity 88.0% and a specificity of 55.1% (Appendix Fig. S3A in the Online Supplement). The risk of death increased significantly when pH value at 24 hours after ECMO initiation less than lower normal range of 7.35 (Log rank test $p=0.029$) (Appendix Fig. S3B in the Online Supplement).

DISCUSSION

In our study, the 90-day survival rate of patients with acute fulminant myocarditis supported by ECMO was 71.9% between January 2017 to December 2019. We found that cardiac arrest prior to ECMO initiation was a risk factor of 90-day mortality. As the predictors for poor prognosis of critical ill patients, lactate concentration and pH value at 24 hours after ECMO initiation was also risk factors associated to 90-day mortality. To our knowledge, this is the largest retrospective multi-center observational study on the outcome of patients with acute fulminant myocarditis supported by ECMO.

ECMO is the cornerstone therapy in the management of acute heart failure[1, 24]. The survival rates of acute fulminant myocarditis patients supported by ECMO ranged from 61.2% to 71.9% [7, 17, 25]. In our study, the survival rate was 71.9% which was consistent or even better compared with previous studies. The study by Diddle JW et al [17] showed that the survival rate was 61.2% lower than that of our study and patients had higher incidence of cardiac arrest prior to ECMO(55/147, 37.4%) compared to our study (50/221, 22.6%). Another retrospective study by Lorusso R et al[7] reported that survival rate was 71.9% the incidence of cardiac arrest before ECMO initiation (12/57) was 21.0%. Survival rates and the incidence of cardiac arrest before ECMO initiation were roughly identical. These results suggest that cardiac arrest prior to ECMO was a potential predictor of poor outcome which was in line with our findings.

Early ECMO initiation improved outcome before cardiac arrest in patients with cardiogenic shock. Cardiac arrest and post-cardiac arrest myocardial dysfunction results in circulatory collapse and tissue hypoperfusion. Survival rate after cardiac arrest is quite low ranging from 13% - 22% [26-28]. Persistently poor prognosis triggered the interest in ECMO proposed for patients suffering cardiac arrest refractory to the conventional cardiopulmonary resuscitation or post-cardiac arrest myocardial dysfunction [29]. Percutaneous cannulation techniques have resulted in immediate start of ECMO under emergent circumstance. Mechanical cardio-pulmonary assist device including ECMO could be provided as a bridge to recovery or transplant for patients with hemodynamic instability according to European Society of Cardiology statements published in 2015 [30]. The use of ECMO for cardiac arrest considerably increased in recent years [30]. Recently, several studies reported that ECMO support could improve prognosis of patients suffering from cardiac arrest [13, 31]. Our study demonstrated that cardiac arrest prior to ECMO support was associated with a 2.5-fold increase risk of 90-day death after ECMO initiation.

Furthermore, our study verified the lactate concentration at 24 hours after ECMO initiation was associated with 90-day mortality. Inadequate tissue perfusion and oxygen imbalance (oxygen delivery and consumption) were the key issues under cardiogenetic shock [32]. Aerobic glycolysis was impaired and anaerobic glycolysis became the main pathway to provide energy under the circumstance. Lactate was the metabolic product of anaerobic glycolysis secondary to tissue hypoperfusion and hypoxia[33]. So elevated lactate concentration can be viewed as a warning sign of tissue perfusion and shock. It has been demonstrated that hyperlactatemia was good correlation related with increased mortality [34-38]. Persistent hyperlactatemia was strongly associated with poor clinical outcome [34, 39, 40]. 24-hour lactate kinetics also was proved as an indicator of higher mortality of critically ill patients [40-42]. Elevated lactate level was the result of increased production and (or) reduced consumption. Stabilization of hemodynamics and adequate tissue perfusion after VA ECMO could ameliorate hypoxia. Some studies had reported the correlation between higher lactate level obtained at different timepoints and the poor prognosis of patients supported by ECMO

[42-44]. Our study demonstrated that the cut-off value of 3.0mmol/L at 24 hours after ECMO initiation contributed to risk stratification.

pH at 24 hours after ECMO initiation was also associated with 90-day mortality. Metabolic acidosis was common in patients with shock resulting from increasing levels of lactate and acute kidney failure[45]. Furthermore, metabolic acidosis worsened artery vasodilatation [46] and cardiac output [47]. Previous studies have demonstrated the high level of acidosis was association with poor prognosis in critical ill patients [48, 49]. Duration of insufficient tissue perfusion was significantly related to poor prognosis [50, 51]. We observed that pH value at 24 hours after ECMO initiation was risk factor of 90-day mortality. The pH at 24 hours after ECMO initiation cut-off value of 7.35 contributed to risk stratification. Clinicians should be prudent with patients whose lactate concentration at 24 hours after ECMO initiation higher than 3.0mmol/L or pH value at 24 hours after ECMO initiation less than 7.35.

There are some limitations of this study which should be considered when interpreting the results. Firstly, the inhering limitations of retrospective studies limits the power of conclusions about the casual relationship between risk factors and mortality. Secondly, there exists possible selective bias because data reported to CSECLS database were voluntary. Thirdly, the limitation of reflecting the pooled data of numerous centers with patients receiving different therapy must be highlighted. Our results might not be appropriate for every single center. Finally, some important detailed data which may be related to patient prognosis, such as intravenous immunoglobulin[52], no-flow or low-flow duration[53], time to ECMO cannulation [17], malignant arrhythmia of ventricular tachycardia (VT) or ventricular fibrillation (VF) [54] data were not available. The present study demonstrated that cardiac arrest prior to ECMO initiation was in relation with worse outcomes. Further research about the more exact timing of ECMO initiation is needed.

Conclusions

VA ECMO provided a bridge to cardiac recovery in most patients with acute fulminant myocarditis. Our study indicates that cardiac arrest prior to ECMO initiation, lactate concentration and pH value at 24 hours after ECMO initiation were independent risk factors of 90-day mortality.

Abbreviations

NYHA, New York Heart Association; ECMO, extracorporeal membrane oxygenation; VA ECMO, venoarterial extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; CSECLS, Chinese Society of ExtraCorporeal Life Support; SOFA, sequential organ failure assessment; SAVE, survival after veno-arterial-ECMO; ECPR, extracorporeal cardiopulmonary resuscitation; EF, ejection fraction; VIS, vasoactive-intropic score; ELSO, Extracorporeal Life Support Organization; ICU, intensive care medicine; IQR, interquartile range; HR, hazard ratio; CI, confidence interval; AUROC, the area under the receiver operating curve.

Ethics approval and consent to participate

All the data in this study were anonymized and provided with permission from the CSECLS database. The Ethics Committee of Zhongda Hospital, Southeast University approved the study. Patient informed consent was waived due to the retrospective study design.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request, but not publicly available.

Conflict of interest

The authors declared that they have no competing interests.

Funding

This work was supported, in part, by the National Science and Technology Major Project for Control and Prevention of Major Infectious Diseases of China (2017ZX10103004), National Key Research and Development Program of China (No. 2016YFC1301001), National Natural Science Foundation of China (81971885, 81971888, 81930058), Jiangsu Provincial Special Program of Medical Science

(BE2018743, BE2019749) and the Scientific Research Project of Jiangsu Health Committee (H2018048). The funders had no role in the study design, data collection, data analysis, interpretation of data and in writing the manuscript.

Acknowledgements

The authors are grateful to all intensive care unit doctors, residents, nurses and personnel, whose sacrifice, efforts, devotion to patients and passion have made possible this timely report.

Authors' Contributions

TH, CW, SL, YY and HQ developed concept and study design. TH, YJ, CW, CL, YJ and SL contributed to data extraction, and database management. TH and SL contributed to data review, statistical analysis and manuscript preparation. TH, YJ, CW and CL contributed to data analysis and results presentation. TH, YJ, CW, CL, and SL were responsible for results interpretation. The initial manuscript was drafted by TH, SL. TH, YJ, CW, CL, CC, JX, CP, FG, YH, LL, HX, ZD, XH, SL, YY and HQ participated in critical revisions of the manuscript and had final responsibility for the decision to submit for publication.

Figure Legends

Fig. 1 The delineation of acute fulminant myocarditis patients supported by VA ECMO. VA ECMO venoarterial extracorporeal membrane oxygenation, ECMO extracorporeal membrane oxygenation.

Fig. 2 Kaplan-Meier curves of cumulative probabilities of 90-days survival for all patients with myocarditis supported by Venoarterial Extracorporeal Membrane Oxygenation.

Reference

1. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on M, Pericardial D, (2013) Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 34: 2636-2648, 2648a-2648d. <https://doi.org/10.1093/eurheartj/eh210>
2. Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, Shah RV, Sims DB, Thiene G, Vardeny O, American Heart Association Heart F, Transplantation Committee of the Council on Clinical C, (2020) Recognition and Initial Management of Fulminant Myocarditis: A Scientific Statement From the American Heart Association. *Circulation* 141: e69-e92. <https://doi.org/10.1161/CIR.0000000000000745>
3. Global Burden of Disease Study C, (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 386: 743-800. [https://doi.org/10.1016/S0140-6736\(15\)60692-4](https://doi.org/10.1016/S0140-6736(15)60692-4)
4. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, Petrella D, Garascia A, Pedrotti P, Roghi A, Bonacina E, Moreo A, Bottiroli M, Gagliardone MP, Mondino M, Ghio S, Totaro R, Turazza FM, Russo CF, Oliva F, Camici PG, Frigerio M, (2017) Survival and Left Ventricular Function Changes in Fulminant Versus Nonfulminant Acute Myocarditis. *Circulation* 136: 529-545. <https://doi.org/10.1161/CIRCULATIONAHA.117.026386>

-
5. Chang JJ, Lin MS, Chen TH, Chen DY, Chen SW, Hsu JT, Wang PC, Lin YS, (2017) Heart Failure and Mortality of Adult Survivors from Acute Myocarditis Requiring Intensive Care Treatment - A Nationwide Cohort Study. *Int J Med Sci* 14: 1241-1250. <https://doi.org/10.7150/ijms.20618>
 6. Kindermann I, Kindermann M, Kandolf R, Klingel K, Bultmann B, Muller T, Lindinger A, Bohm M, (2008) Predictors of outcome in patients with suspected myocarditis. *Circulation* 118: 639-648. <https://doi.org/10.1161/CIRCULATIONAHA.108.769489>
 7. Lorusso R, Centofanti P, Gelsomino S, Barili F, Di Mauro M, Orlando P, Botta L, Milazzo F, Actis Dato G, Casabona R, Casali G, Musumeci F, De Bonis M, Zangrillo A, Alfieri O, Pellegrini C, Mazzola S, Coletti G, Vizzardi E, Bianco R, Gerosa G, Massetti M, Caldaroni F, Pilato E, Pacini D, Di Bartolomeo R, Marinelli G, Sponga S, Livi U, Mauro R, Mariscalco G, Beghi C, Miceli A, Glauber M, Pappalardo F, Russo CF, Investigators G, (2016) Venoarterial Extracorporeal Membrane Oxygenation for Acute Fulminant Myocarditis in Adult Patients: A 5-Year Multi-Institutional Experience. *Ann Thorac Surg* 101: 919-926. <https://doi.org/10.1016/j.athoracsur.2015.08.014>
 8. Chen YS, Yu HY, Huang SC, Chiu KM, Lin TY, Lai LP, Lin FY, Wang SS, Chu SH, Ko WJ, (2005) Experience and result of extracorporeal membrane oxygenation in treating fulminant myocarditis with shock: what mechanical support should be considered first? *J Heart Lung Transplant* 24: 81-87. <https://doi.org/10.1016/j.healun.2003.09.038>
 9. Miller PE, Solomon MA, McAreavey D, (2017) Advanced Percutaneous Mechanical Circulatory Support Devices for Cardiogenic Shock. *Critical care medicine* 45: 1922-1929. <https://doi.org/10.1097/CCM.0000000000002676>
 10. Pineton de Chambrun M, Brechot N, Combes A, (2020) The place of extracorporeal life support in cardiogenic shock. *Curr Opin Crit Care* 26: 424-431. <https://doi.org/10.1097/MCC.0000000000000747>
 11. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD, (2018) Venoarterial Extracorporeal Membrane Oxygenation for Cardiogenic Shock and Cardiac

Arrest. *Circ Heart Fail* 11: e004905.

<https://doi.org/10.1161/CIRCHEARTFAILURE.118.004905>

12. Wong ASK, Sin SWC, (2020) Short-term mechanical circulatory support (intra-aortic balloon pump, Impella, extracorporeal membrane oxygenation, TandemHeart): a review. *Ann Transl Med* 8: 829.
<https://doi.org/10.21037/atm-20-2171>
13. Ouweneel DM, Schotborgh JV, Limpens J, Sjaauw KD, Engstrom AE, Lagrand WK, Cherpanath TGV, Driessen AHG, de Mol B, Henriques JPS, (2016) Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med* 42: 1922-1934.
<https://doi.org/10.1007/s00134-016-4536-8>
14. Grasselli G, Scaravilli V, Di Bella S, Biffi S, Bombino M, Patroniti N, Bisi L, Peri AM, Pesenti A, Gori A, Alagna L, (2017) Nosocomial Infections During Extracorporeal Membrane Oxygenation: Incidence, Etiology, and Impact on Patients' Outcome. *Critical care medicine* 45: 1726-1733.
<https://doi.org/10.1097/CCM.0000000000002652>
15. Dalton HJ, Garcia-Filion P, Holubkov R, Moler FW, Shanley T, Heidemann S, Meert K, Berg RA, Berger J, Carcillo J, Newth C, Harrison R, Doctor A, Rycus P, Dean JM, Jenkins T, Nicholson C, Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network, (2015) Association of bleeding and thrombosis with outcome in extracorporeal life support. *Pediatr Crit Care Med* 16: 167-174.
<https://doi.org/10.1097/PCC.0000000000000317>
16. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, Hodgson C, Scheinkestel C, Cooper DJ, Thiagarajan RR, Brodie D, Pellegrino V, Pilcher D, (2015) Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J* 36: 2246-2256. <https://doi.org/10.1093/eurheartj/ehv194>
17. Diddle JW, Almodovar MC, Rajagopal SK, Rycus PT, Thiagarajan RR, (2015) Extracorporeal membrane oxygenation for the support of adults with

-
- acute myocarditis. Crit Care Med 43: 1016-1025.
<https://doi.org/10.1097/CCM.0000000000000920>
18. Liao X, Li B, Cheng Z, (2018) Extracorporeal membrane oxygenation in adult patients with acute fulminant myocarditis : Clinical outcomes and risk factor analysis. Herz 43: 728-732. <https://doi.org/10.1007/s00059-017-4617-7>
 19. Wu HP, Lin MJ, Yang WC, Wu KH, Chen CY, (2017) Predictors of Extracorporeal Membrane Oxygenation Support for Children with Acute Myocarditis. Biomed Res Int 2017: 2510695.
<https://doi.org/10.1155/2017/2510695>
 20. Yang ZH, Ning BT, Zhang CM, Lin R, Ye S, Liu T, (2016) Clinical application of extracorporeal membrane oxygenation in children with refractory cardiopulmonary failure. World J Pediatr 12: 364-367.
<https://doi.org/10.1007/s12519-016-0030-1>
 21. Lambden S, Laterre PF, Levy MM, Francois B, (2019) The SOFA score- development, utility and challenges of accurate assessment in clinical trials. Crit Care 23: 374. <https://doi.org/10.1186/s13054-019-2663-7>
 22. Koponen T, Karttunen J, Musialowicz T, Pietilainen L, Uusaro A, Lahtinen P, (2019) Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery. Br J Anaesth 122: 428-436.
<https://doi.org/10.1016/j.bja.2018.12.019>
 23. Thiagarajan RR, Brogan TV, Scheurer MA, Laussen PC, Rycus PT, Bratton SL, (2009) Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in adults. Ann Thorac Surg 87: 778-785.
<https://doi.org/10.1016/j.athoracsur.2008.12.079>
 24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD, (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic

-
- heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37: 2129-2200. <https://doi.org/10.1093/eurheartj/ehw128>
25. Rajagopal SK, Almond CS, Laussen PC, Rycus PT, Wypij D, Thiagarajan RR, (2010) Extracorporeal membrane oxygenation for the support of infants, children, and young adults with acute myocarditis: a review of the Extracorporeal Life Support Organization registry. Crit Care Med 38: 382-387. <https://doi.org/10.1097/CCM.0b013e3181bc8293>
26. Schluep M, Gravesteyn BY, Stolker RJ, Endeman H, Hoeks SE, (2018) One-year survival after in-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation 132: 90-100. <https://doi.org/10.1016/j.resuscitation.2018.09.001>
27. Nolan JP, Soar J, Smith GB, Gwinnutt C, Parrott F, Power S, Harrison DA, Nixon E, Rowan K, National Cardiac Arrest A, (2014) Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. Resuscitation 85: 987-992. <https://doi.org/10.1016/j.resuscitation.2014.04.002>
28. Sinha SS, Sukul D, Lazarus JJ, Polavarapu V, Chan PS, Neumar RW, Nallamothu BK, (2016) Identifying Important Gaps in Randomized Controlled Trials of Adult Cardiac Arrest Treatments: A Systematic Review of the Published Literature. Circ Cardiovasc Qual Outcomes 9: 749-756. <https://doi.org/10.1161/CIRCOUTCOMES.116.002916>
29. Panchal AR, Berg KM, Hirsch KG, Kudenchuk PJ, Del Rios M, Cabanas JG, Link MS, Kurz MC, Chan PS, Morley PT, Hazinski MF, Donnino MW, (2019) 2019 American Heart Association Focused Update on Advanced Cardiovascular Life Support: Use of Advanced Airways, Vasopressors, and Extracorporeal Cardiopulmonary Resuscitation During Cardiac Arrest: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 140: e881-e894. <https://doi.org/10.1161/CIR.0000000000000732>

-
30. Richardson AS, Schmidt M, Bailey M, Pellegrino VA, Rycus PT, Pilcher DV, (2017) ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. *Resuscitation* 112: 34-40.
 31. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, Chen WJ, Huang SC, Chi NH, Wang CH, Chen LC, Tsai PR, Wang SS, Hwang JJ, Lin FY, (2008) Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 372: 554-561.
 32. Vincent JL, De Backer D, (2014) Circulatory shock. *N Engl J Med* 370: 583. <https://doi.org/10.1056/NEJMc1314999>
 33. Kraut JA, Madias NE, (2014) Lactic acidosis. *N Engl J Med* 371: 2309-2319. <https://doi.org/10.1056/NEJMr1309483>
 34. Lee WC, Fang CY, Chen HC, Chen CJ, Yang CH, Hang CL, Yip HK, Fang HY, Wu CJ, (2016) Associations with 30-day survival following extracorporeal membrane oxygenation in patients with acute ST segment elevation myocardial infarction and profound cardiogenic shock. *Heart Lung* 45: 532-537. <https://doi.org/10.1016/j.hrtlng.2016.08.006>
 35. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, Kluge S, (2016) Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. *Intensive Care Med* 42: 202-210. <https://doi.org/10.1007/s00134-015-4127-0>
 36. Juneja D, Singh O, Dang R, (2011) Admission hyperlactatemia: causes, incidence, and impact on outcome of patients admitted in a general medical intensive care unit. *J Crit Care* 26: 316-320. <https://doi.org/10.1016/j.jcrc.2010.11.009>
 37. Khosravani H, Shahpori R, Stelfox HT, Kirkpatrick AW, Laupland KB, (2009) Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care* 13: R90. <https://doi.org/10.1186/cc7918>

-
38. Bou Chebl R, El Khuri C, Shami A, Rajha E, Faris N, Bachir R, Abou Dagher G, (2017) Serum lactate is an independent predictor of hospital mortality in critically ill patients in the emergency department: a retrospective study. *Scand J Trauma Resusc Emerg Med* 25: 69. <https://doi.org/10.1186/s13049-017-0415-8>
 39. Houwink AP, Rijkenberg S, Bosman RJ, van der Voort PH, (2016) The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: a retrospective cohort analysis. *Crit Care* 20: 56. <https://doi.org/10.1186/s13054-016-1243-3>
 40. Vincent JL, Quintairos ESA, Couto L, Jr., Taccone FS, (2016) The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care* 20: 257. <https://doi.org/10.1186/s13054-016-1403-5>
 41. Masyuk M, Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig JM, Zimmermann G, Lauten A, Schulze PC, Hoppe UC, Kelm M, Bakker J, Jung C, (2019) Prognostic relevance of serum lactate kinetics in critically ill patients. *Intensive Care Med* 45: 55-61. <https://doi.org/10.1007/s00134-018-5475-3>
 42. Slottosch I, Liakopoulos O, Kuhn E, Scherner M, Deppe AC, Sabashnikov A, Mader N, Choi YH, Wippermann J, Wahlers T, (2017) Lactate and lactate clearance as valuable tool to evaluate ECMO therapy in cardiogenic shock. *J Crit Care* 42: 35-41. <https://doi.org/10.1016/j.jcrc.2017.06.022>
 43. Yang L, Ye L, Fan Y, He W, Zong Q, Zhao W, Lin R, (2019) Outcomes following venoarterial extracorporeal membrane oxygenation in children with refractory cardiogenic disease. *Eur J Pediatr* 178: 783-793. <https://doi.org/10.1007/s00431-019-03352-5>
 44. Biesenbach P, Ghanpur R, Martensson J, Crisman M, Lindstrom S, Hilton A, Matalanis G, Bellomo R, (2017) Peripheral venoarterial extracorporeal membrane oxygenation for severe hyperlactataemia after cardiac surgery: a pilot study. *Crit Care Resusc* 19: 274-279.

-
45. Seifter JL, (2014) Integration of acid-base and electrolyte disorders. *N Engl J Med* 371: 1821-1831. <https://doi.org/10.1056/NEJMra1215672>
 46. Kellum JA, Song M, Venkataraman R, (2004) Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest* 125: 243-248. <https://doi.org/10.1378/chest.125.1.243>
 47. Kellum JA, Song M, Li J, (2004) Science review: extracellular acidosis and the immune response: clinical and physiologic implications. *Crit Care* 8: 331-336. <https://doi.org/10.1186/cc2900>
 48. Jung B, Rimmele T, Le Goff C, Chanques G, Corne P, Jonquet O, Muller L, Lefrant JY, Guervilly C, Papazian L, Allaouchiche B, Jaber S, AzuRea G, (2011) Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. *Crit Care* 15: R238. <https://doi.org/10.1186/cc10487>
 49. Gunnerson KJ, Saul M, He S, Kellum JA, (2006) Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Crit Care* 10: R22. <https://doi.org/10.1186/cc3987>
 50. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW, (2013) Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? *Circulation* 128: 2488-2494. <https://doi.org/10.1161/CIRCULATIONAHA.113.002408>
 51. Nagao K, Nonogi H, Yonemoto N, Gaieski DF, Ito N, Takayama M, Shirai S, Furuya S, Tani S, Kimura T, Saku K, Japanese Circulation Society With Resuscitation Science Study G, (2016) Duration of Prehospital Resuscitation Efforts After Out-of-Hospital Cardiac Arrest. *Circulation* 133: 1386-1396. <https://doi.org/10.1161/CIRCULATIONAHA.115.018788>
 52. Cooper LT, Jr., Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, Menon S, Mullen GM, Jaski B, Bailey KR, Cunningham MW, Dec GW, Giant Cell Myocarditis Treatment Trial I, (2008) Usefulness of immunosuppression

for giant cell myocarditis. Am J Cardiol 102: 1535-1539.

<https://doi.org/10.1016/j.amjcard.2008.07.041>

53. Wengenmayer T, Rombach S, Ramshorn F, Biever P, Bode C, Duerschmied D, Staudacher DL, (2017) Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). Crit Care 21: 157.
<https://doi.org/10.1186/s13054-017-1744-8>
54. Chou HW, Wang CH, Lin LY, Chi NH, Chou NK, Yu HY, Chen YS, (2020) Prognostic factors for heart recovery in adult patients with acute fulminant myocarditis and cardiogenic shock supported with extracorporeal membrane oxygenation. J Crit Care 57: 214-219.
<https://doi.org/10.1016/j.jcrc.2020.03.007>

Figures

Figure 1

The delineation of acute fulminant myocarditis patients supported by VA ECMO. VA ECMO venoarterial extracorporeal membrane oxygenation, ECMO extracorporeal membrane oxygenation.

Figure 2

Kaplan-Meier curves of cumulative probabilities of 90-days survival for all patients with myocarditis supported by Venoarterial Extracorporeal Membrane Oxygenation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [2.Table1.pdf](#)
- [3.Table2.pdf](#)
- [4.Table3.pdf](#)
- [5.Table4.pdf](#)
- [6.SupplementAppendix.pdf](#)