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Extracorporeal Membrane Oxygenation Cannulation Timing in the Pediatric Myocarditis Population: An Exploratory Analysis From the Extracorporeal Life Support Organization Registry

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OBJECTIVES: Children presenting with acute myocarditis may experience rapid clinical deterioration requiring extracorporeal membrane oxygenation (ECMO); however, our understanding of best practices and timing of ECMO initiation are lacking. We explored the relationships between pre-cannulation factors and survival in this high-acuity patient population.

DESIGN: Retrospective review of a large international registry. Primary outcome was survival to hospital discharge, stratified by incident cardiac arrest (CA) prior to ECMO and time to cannulation after intubation.

SETTING AND SUBJECTS: The Extracorporeal Life Support Organization registry was queried for patients less than or equal to 18 years old receiving ECMO support for myocarditis between 2007 and 2018. Exclusion criteria included being nonindex runs, non-venoarterial ECMO or missing data points for main variables studied.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Population characteristics and survival were compared using *t* test, Wilcoxon rank-sum test, or Fisher exact test. Multivariable logistic regression was used for significant factors in the unadjusted logistic regression. Among 506 index ECMO runs in pediatric patients with myocarditis, survival for the cohort was 72%, with no difference between early and late eras (2007–2012 vs 2013–2018; $p = 0.69$). Survivors demonstrated higher pre-ECMO pH levels as well as shorter intubation-to-cannulation (ITC) times (3 hr [interquartile range (IQR)], 1–14 hr vs 6 hr [IQR, 2–20 hr]; $p = 0.021$). CA occurred within 24 hours prior to ECMO cannulation, including extracorporeal cardiopulmonary resuscitation, in 54% of ECMO runs ($n = 273$). Accounting for the interaction between pre-ECMO CA occurrence and ITC time, longer ITC time remained associated with lower survival for patients who did not experience a CA prior to ECMO, with adjusted odds ratio of 0.09 (IQR, 0.02–0.40; $p = 0.002$) for ITC time greater than or equal to 18 hours.

CONCLUSIONS: The results of this multicenter analysis of ECMO utilization and outcomes for pediatric myocarditis suggest that patients approaching ECMO cannulation who have not experienced CA may have better survival outcomes if cannulated onto ECMO early after intubation.

KEY WORDS: acute myocarditis; cardiac arrest; extracorporeal membrane oxygenation; pediatric myocarditis

Acute or fulminant myocarditis can result in rapid and progressive myocardial inflammation, systolic ventricular dysfunction, life-threatening arrhythmias, cardiogenic shock, cardiac arrest (CA), and/or death (1).

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REPORT IN CONTEXT

- Extracorporeal membrane oxygenation (ECMO) is commonly used in the management of acute or fulminant myocarditis and is a formally recognized by the American Heart Association as a life-saving therapy for management of this disease.
- This analysis focuses on identifying potentially modifiable factors associated with mortality in patients with myocarditis who ultimately receive ECMO.

Among children presenting with myocarditis, the use of venoarterial extracorporeal membrane oxygenation (ECMO) as a rescue modality has been shown to confer a significant survival benefit when compared with historical cohorts (2, 3). As the primary form of ECMO to manage myocarditis, venoarterial ECMO utilization has been reported over the last 3 decades with varying survival to hospital discharge rates (61–80%) (4–8). Yet the management of cardiogenic shock associated with myocarditis remains challenging. Several gaps remain in our understanding of risk factors for survival and the ultimate focus on prevention of death from CA. Clinicians aiming to avoid cardiopulmonary resuscitation (CPR) are now advised by American Heart Association consensus guidelines to consider mechanical circulatory support (MCS) in children with myocarditis, although still allowing the clinician to determine the correct timing of deployment of this type of support (8).

As disease progression to cardiogenic shock is unpredictable and often rapid in myocarditis, timing of ECMO cannulation may be an important and modifiable factor that can influence resolution of cardiogenic shock states and survival. In this updated review of the Extracorporeal Life Support Organization (ELSO) registry, we aim to better inform the pediatric cardiac and critical care community by exploring the impact of key pre-ECMO factors, including CA, on survival. Among children who were cannulated onto venoarterial ECMO for myocarditis, we hypothesize that shorter time from the initiation of mechanical ventilation to ECMO cannulation is associated with improved survival to hospital discharge when compared with patients with longer duration to ECMO cannulation after presentation. Additionally, we hypothesize that pediatric myocarditis patients who received ECMO cannulation and experienced any CA occurring prior to ECMO cannulation (including extracorporeal cardiopulmonary resuscitation [ECPR]) will have lower survival to hospital discharge than those who do not experience a CA prior to ECMO cannulation.

METHODS

We conducted a multicenter, retrospective cohort analysis of index ECMO runs submitted to the ELSO registry for pediatric patients including neonates through adolescents (≤ 18 yr) with the diagnosis of myocarditis between January 2007 and December 2018. This study was approved by the ELSO Registry Scientific Oversight Committee. Baylor College of Medicine does not require Institutional Review Board (IRB) approval for external registry studies, as these studies do not fall under IRB guidelines for human subjects research.

The ELSO registry collates data on ECMO runs from more than 400 international centers. Multiple ECMO or venovenous ECMO runs and unknown discharge status at the time of data query were excluded. Runs with intubation-to-cannulation (ITC) time greater than 14 days were excluded as these ECMO runs may represent a uniquely different patient cohort with a lower risk for acute cardiovascular collapse than the target cohort needed to test our hypothesis. Patients with negative admission-to-intubation times were also excluded, as they represent patients who were intubated prior to admission to transfer to the ECMO center. This exclusion eliminated potential bias in the analysis, given our desire to ensure that the primary exposure variable (time from intubation to ECMO cannulation) was reflective of clinical care under the control of the team making the decision to cannulate, not necessarily those of the transferring facility. Similarly, negative ITC times were also excluded (**Supplemental Fig. 1**, http://links.lww.com/CCX/B112). Patients experiencing CA in the 24 hours prior to ECMO cannulation, including those requiring cannulation during active CPR (ECPR), were grouped together due to the significant association of in-hospital CA with poorer survival to hospital discharge rates in critically ill pediatric patients (9).

The primary outcome was survival to hospital discharge. Predictor variables were selected according to

data available from ELSO and previously determined factors affecting mortality for patients with acute myocarditis in the literature (10–14). Continuous variables including time from admission-to-intubation and ITC in hours were transformed into quartiles based on their distribution.

Patient and ECMO run characteristics were summarized using median with 25th and 75th percentiles and frequency with percentage. Pre-ECMO and on-ECMO characteristics are compared by survival with Wilcoxon rank-sum test, Fisher exact test, or chi-square test. Univariate unadjusted logistic regression assesses the association between characteristics and the odds of survival. Significant factors in the unadjusted logistic regression were combined in a multivariable logistic regression model for the odds of survival to hospital discharge. Additionally, the interaction of any CA within 24 hours prior to ECMO (including ECPR) and ITC timing was explored in multivariable logistic regression.

For inclusion in the multivariable analysis, a threshold of missing data was set at 10%. Due to the high missing data for many laboratory variables, a sensitivity analysis imputing the missing values was performed using multiple imputations with iterative chained equations (MICE) with predictive mean matching for continuous values and logistic regression for binary variables (14). The imputed laboratory values include pH, $Paco_2$, Fio_2, Pao_2, bicarbonate, and arterial oxygen saturation. The variables used in the imputations were weight, age, and pre-ECMO factors including use of nitric oxide, neuromuscular blockers, vasodilators/inotropes, CA, intubation-to-ECMO time, and admission-to-ECMO time. Additionally, we sought to use a Kaplan-Meier curve to visualize time to death and/or discharge stratified by distinct ITC quartile among patients not experiencing CA. Time from ECMO to in-hospital death was displayed with survivors censored at the time of hospital discharge. All analyses were performed using Stata v 15 (StataCorp, College Station, TX). A p value of less than 0.05 was considered statistically significant.

RESULTS

The total cohort analyzed included 506 index veno-arterial ECMO runs after exclusions (Supplemental Fig. 1, http://links.lww.com/CCX/B112). Overall survival to hospital discharge was 72%. The population demographics and pre-cannulation parameters are presented in **Table 1**. There were no significant differences between the survivors and nonsurvivors for age, gender, or weight. Neonatal patients are included in this cohort and comprised 12.9% of the population (age ≤ 28 d). The cohort was also divided into two eras with no significant difference in survival between the time periods 2007–2012 and 2013–2018 (p = 0.69). **Supplemental Figure 2** (http://links.lww.com/CCX/B113) displays survival-to-discharge rates per year of the study with individual bars representing survival rates for patients who had any CA prior to cannulation versus those who did not. The laboratory data obtained prior to ECMO cannulation and reported to ELSO was noted to have up to 23% of missing data. These results are presented in Table 1, given the clinical relevance they present. Pre-cannulation pH was significantly lower in nonsurvivors compared with survivors. No other significant differences were noted between survivors and nonsurvivors for additional pre-cannulation laboratory values including $Paco_2$ and bicarbonate levels. The factors related to ECMO cannulation and subsequent complications are also described in Table 1. The median of days on ECMO support was the same for survivors and nonsurvivors (6.2 d [4.3–8.8 d] vs 6.6 d [3.8–11.7 d]; p = 0.44). No differences were observed in survival between patients cannulated via central or peripheral ECMO cannulation techniques (p = 0.11). Similarly, need for left heart decompression via balloon atrial septostomy or a left atrium vent was not different between survivors and nonsurvivors (25.5% vs 24.1%; p = 0.82). While the time from admission-to-intubation was not significantly different between survivors and nonsurvivors for the overall cohort, ITC time was shorter in survivors at a median of 3 hours (interquartile range [IQR], 1–14 hr), compared with nonsurvivors at a median of 6 hours (IQR, 2–20 hr; p = 0.021).

Table 2 describes the same variables of demographics, pre-ECMO, and ECMO factors comparing the intubation-to-ECMO quartiles. Quartile 1 includes patients cannulated less than or equal to 1 hour after intubation, quartile 2 are patients cannulated 2–4 hours after intubation, quartile 3 are those cannulated 5–17 hours, and quartile 4 includes those cannulated greater than or equal to 18 hours after intubation. Patient age

TABLE 1.
Demographics and Extracorporeal Membrane Oxygenation Parameters by Survival

Variables ($n = 506$ Runs)	Survivors (365), Median (IQR), *n* (%)	Nonsurvivors (141), Median (IQR), *n* (%)	*p*
Demographics			
Age (yr)	4.5 (0.8–11.1)	4 (0.5–11.9)	0.72
Male[a]	168 (46.5)	63 (45.0)	0.77
Weight[b] (kg)	18 (9.1–40.0)	17.9 (7.5–44.8)	0.97
Era			0.69
2007–2012	143 (39.2)	58 (41.1)	
2013–2018	222 (60.8)	83 (58.9)	
Pre-ECMO variables			
pH[d]	7.3 (7.1–7.3)	7.2 (7.0–7.3)	< 0.001
Pao_2 (torr)[e]	76 (46–130)	59 (35–110)	0.03
$Paco_2$ (torr)[f]	42 (34.4–52)	46.2 (36–69)	0.08
Bicarbonate (mmol/L)[g]	19 (15.4–23)	18 (13.4–22)	0.22
Intubation-to-cannulation time (hr)	3 (1–14)	6 (2–20)	0.02
Intubation-to-cannulation time (hr)			0.09
≤ 1	115 (31.5)	30 (21.3)	
2–4	89 (24.4)	35 (24.8)	
5–17	80 (21.9)	34 (24.1)	
≥ 18	81 (22.2)	42 (29.8)	
Admission-to-cannulation time (hr)			0.68
≤ 5	102 (28.0)	33 (23.4)	
6–16	87 (23.8)	34 (24.1)	
17–40	90 (24.7)	35 (24.8)	
≥ 41	86 (23.6)	39 (27.7)	
Admission-to-intubation time (hr)	4 (0–17)	4 (1–16)	1
Viral diagnosis[j]	131 (35.9)	60 (42.6)	0.18
Pre-ECMO cardiac arrest[k]	187 (51.2)	86 (61.0)	0.059
ECMO variables			
ECMO duration (d)[h]	6.2 (4.3–8.8)	6.6 (3.8–11.7)	0.44
Central cannulation[i]	45 (12.9)	25 (18.7)	0.11
Balloon atrial septostomy or LA vent	93 (25.5)	34 (24.1)	0.82

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, LA = left atrium.
Final cohort sizes:
[a]$n = 501$; [b]$n = 504$; [c]$n = 476$; [d]$n = 443$; [e]$n = 435$; [f]$n = 440$; [g]$n = 426$; [h]$n = 502$; [i]$n = 484$.
[j]Any virus identified on cultures or coded by *International Classification of Diseases*, 9th Revision or 10th Revision.
[k]Pre-ECMO cardiac arrest: Any cardiac arrest within 24 hr prior to ECMO cannulation and/or extracorporeal cardiopulmonary resuscitation.

and weight were significantly lower in the longer ITC quartiles. In addition, ITC times were significantly longer in early era runs compared with the most recent era ($p < 0.01$).

CA at any time in the 24 hours prior to ECMO cannulation, including those placed onto ECMO during active CPR (ECPR), was observed in over half of ECMO runs 273 (54%). Among these patients, 152

TABLE 2.
Demographics and Extracorporeal Membrane Oxygenation Parameters, by Intubation to Extracorporeal Membrane Oxygenation Quartiles

Variables (*n* = 506 Runs)	Q1 ≤ 1 hr, Median (IQR), *n* (%)	Q2 2–4 hr, Median (IQR), *n* (%)	Q3 5–17 hr, Median (IQR), *n* (%)	Q4 ≥ 18 hr, Median (IQR), *n* (%)	*p*
Demographics					
Age (yr)	6.9 (1.4–12.3)	6.2 (1.2–12.0)	2 (0.5–8.7)	1.3 (0.1–10.3)	< 0.001
Male[a]	60 (42.3)	58 (47.2)	46 (40.7)	67 (54.5)	0.129
Weight (kg)[b]	23.5 (10.9–45.0)	22.9 (10.1–50.0)	12.6 (7.9–31.0)	11 (3.6–37.5)	< 0.001
Era					
2007–2012	43 (29.7)	47 (37.9)	56 (49.1)	55 (44.7)	0.008
2013–2018	102 (70.3)	77 (62.1)	58 (50.9)	68 (55.3)	
Pre-ECMO variables					
pH[d]	7.2 (7.0–7.4)	7.2 (7.0–7.3)	7.3 (7.1–7.3)	7.3 (7.2–7.4)	0.276
Pao_2 (torr)[e]	74.5 (36.0–127.5)	60 (34.1–110.5)	80.1 (48.0–143.5)	77 (52.0–122.0)	0.167
$Paco_2$ (torr)[f]	41 (31.0–56.0)	45 (33.0–63.0)	41.2 (35.0–51.0)	44 (37.7–55.0)	0.163
Bicarbonate (mmol/L)[g]	17.1 (11.9–22.1)	18.6 (13.5–22.6)	18 (16.0–21.0)	21 (17.0–24.2)	0.003
Viral diagnosis[j]	60 (41.4)	42 (33.9)	35 (30.7)	54 (43.9)	0.112
Pre-ECMO cardiac arrest[k]	100 (69)	72 (58.1)	53 (46.5)	48 (39.0)	< 0.001
ECMO variables					
ECMO duration (d)[h]	6.5 (4.7–9.0)	5.4 (3.5–8.6)	6.9 (4.3–10.5)	6.7 (4.6–9.9)	0.057
Central cannulation[i]	16 (11.9)	15 (12.5)	15 (13.8)	24 (20.0)	0.273
Balloon atrial septostomy or LA vent	34 (23.4)	35 (28.2)	25 (21.9)	33 (26.8)	0.648

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, LA = left atrium.

Final cohort sizes:

[a]*n* = 501; [b]*n* = 504; [c]*n* = 476; [d]*n* = 443; [e]*n* = 435; [f]*n* = 440; [g]*n* = 426; [h]*n* = 502; [i]*n* = 484.

[j]Any virus identified on cultures or coded by *International Classification of Diseases*, 9th Revision or 10th Revision.

[k]Pre-ECMO cardiac arrest: Any cardiac arrest within 24 hr prior to ECMO cannulation and/or extracorporeal cardiopulmonary resuscitation.

(55.7%) received ECPR. The remaining 121 runs were myocarditis patients who experienced a CA with return of spontaneous circulation who went on to undergo ECMO cannulation within 24 hours of the CA. Among these patients experiencing CA in the 24 hours prior to ECMO cannulation, 68% survived to discharge, while 76% of patients who did not experience a CA survived to discharge ($p = 0.059$). The majority of patients who experienced any CA in the 24 hours prior to cannulation were cannulated less than 1 hour after intubation (100 [69%]; $p < 0.001$; Table 2). Differences in demographic and pre-ECMO factors between patients experience pre-ECMO CA and those who did not can be found in **Supplemental Table 1** (http://links.lww.com/CCX/B111). The influence of CA prior to ECMO was further explored in **Table 3**, which describes patient demographics and pre-ECMO factors based on pre-ECMO CA occurrence. Hemodynamic parameters and laboratories such as pH and Pao_2 are significantly lower in those with CA.

TABLE 3.
Multivariable Logistic Regression Modela for Survival With Intubation-to-Cannulation Quartiles

Variable (n = 443 Runs)	OR (95% CI)	p
pH (0.1 increase)	1.18 (1.05–1.31)	0.005
Pre-ECMO cardiac arrest: No		< 0.001
Intubation-to-cannulation quartiles		
Quartile 1	Reference	
Quartile 2	0.47 (0.09–2.56)	0.38
Quartile 3	0.14 (0.03–0.63)	0.011
Quartile 4	0.09 (0.02–0.40)	0.002
Pre-ECMO cardiac arrest: Yes		0.89
Intubation-to-cannulation quartiles		
Quartile 1	Reference	
Quartile 2	0.76 (0.37–1.55)	0.45
Quartile 3	0.94 (0.42–2.12)	0.89
Quartile 4	0.85 (0.37–1.97)	0.71
Interaction term: Pre-ECMO cardiac arrest and intubation-to-cannulation quartiles		0.01

ECMO = extracorporeal membrane oxygenation, OR = odds ratio.
[a]Model includes: pH, pre-ECMO cardiac arrest, intubation-to-cannulation quartiles, pre-ECMO cardiac arrest, and intubation-to-cannulation quartile interaction.

The unadjusted logistic regression for survival shown in **Supplemental Table** 2 (http://links.lww.com/CCX/B111) and revealed significant effects from pre-ECMO factors. Increasing pH (categorized by incremental changes of 0.1) was associated with higher odds of survival (odds ratio [OR], 1.21; 95% CI, 1.09–1.34; $p < 0.001$). Higher $Paco_2$ values were associated with lower odds of survival (OR, 0.99; 95% CI, 0.98–1.00; $p = 0.003$). Of note, both time from ITC and pre-ECMO CA were found to be significantly associated with survival to discharge (OR, 0.99; 95% CI, 0.99–1.00; $p = 0.031$) and OR (0.67; 95% CI, 0.45–1.00; $p = 0.049$, respectively).

The multivariable regression model is shown in Table 3. We evaluated the impact of CA on each ITC quartile and found a significant interaction. When evaluating the population of patients who did not experience a CA prior to ECMO, the odds of survival are lower as ITC duration increases, specifically quartiles 3 and 4 compared with quartile 1 (Adjusted odds ratio, 0.14; 95% CI, 0.03–0.63; $p = 0.011$ and Adjusted odds ratio, 0.09; 95% CI, 0.02–0.40; $p = 0.002$, respectively). This trend is assessed by a Kaplan-Meier curve in **Figure 1**, showing a similar survival for the first two quartiles, while the third and fourth have a significant decline prior to the 50 days after ECMO, and quartile 4 continues to decrease with no one surviving after 150 days. However, among patients experiencing CA prior to ECMO cannulation, no significant association between ITC and odds of survival was observed as displayed in **Figure 2**. Last, our additional analyses utilizing MICE for imputed values reveal no significant difference in our findings without imputation and are available in **Supplemental Tables 3** and **4** (http://links.lww.com/CCX/B111).

DISCUSSION

Acute myocarditis in the pediatric population remains a challenging disease entity for pediatric critical care and cardiology specialists due to the unpredictable and variable clinical presentation as well as potential for rapid clinical deterioration leading to CA. It is estimated that 6–20% of children with myocarditis will go on to receive venoarterial ECMO support (1, 12, 13). Although the use of venoarterial ECMO support is associated with significant morbidity and mortality, children with acute myocarditis have higher survival-to-discharge rates

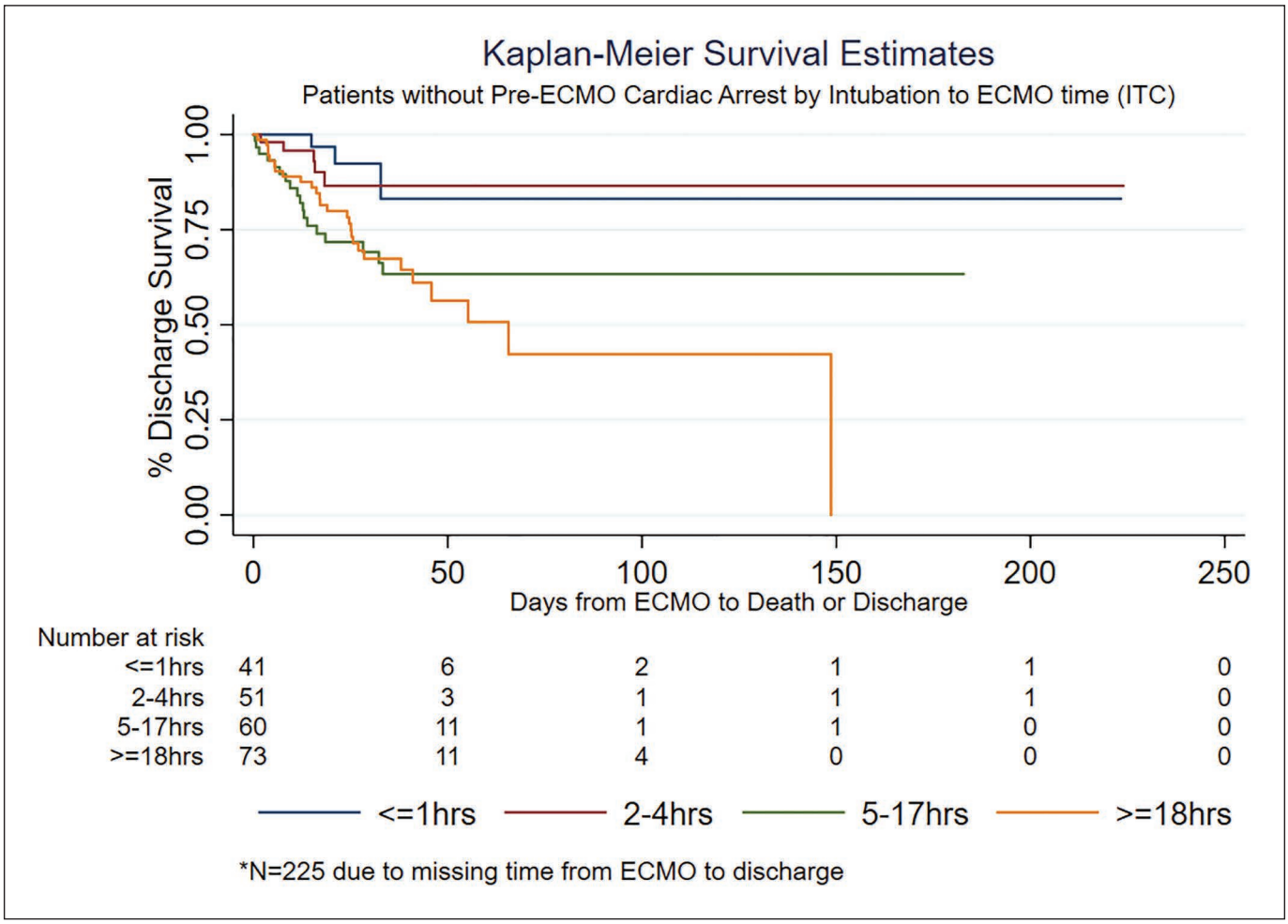

Figure 1. Kaplan-Meier curve demonstrating time from extracorporeal membrane oxygenation (ECMO) to death or discharge among patients without pre-ECMO cardiac arrest (CA) by intubation-to-cannulation (ITC) time quartiles.

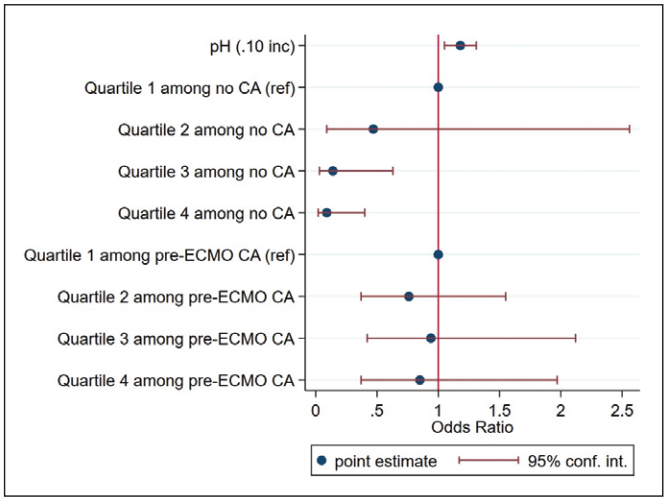

Figure 2. Adjusted odds of survival using first quartile of intubation-to-cannulation time as reference (ref). CA = cardiac arrest, ECMO = extracorporeal membrane oxygenation, inc = increase.

AT THE BEDSIDE

- In children with acute or fulminant myocarditis who have not suffered cardiac arrest, earlier cannulation onto ECMO after intubation is associated with improved survival-to-discharge rates.
- Advanced planning and consideration for venoarterial ECMO support may be warranted for pediatric myocarditis patients who require undergo intubation and mechanical ventilation.

than other populations that receive ECMO support, with historical survival rates ranging as high as 80% (15–17). In this contemporary analysis of the ELSO registry, we found survival rates for pediatric patients requiring ECMO for myocarditis remain high, and we found higher pH and higher Pao_2 prior to ECMO cannulation to be associated with improved survival.

The description of the population in our report has remained similar to that reported by Rajagopal et al (8) with no significant difference in weight, age or era between survivors and nonsurvivors. Our study differs in that we did not find male gender to be significantly associated with survival (12). We continue to find the pre-cannulation pH to be associated with mortality in this patient population.

There has been much focus in the past to predict survival of patients on both venoarterial and venovenous ECMO with both pre- and post-cannulation clinical variables contributing to mortality modeling. Many have found that complications while on support are strongly associated with a higher likelihood of hospital mortality (14). While this helps shine a light on the most significant complications that occur after cannulation, some of these may be very difficult to modify (e.g., hemorrhagic and CNS complications) and do not provide guidance in the early and acute clinical management of patients presenting with evolving myocardial inflammation and cardiogenic shock. Accordingly, we sought to identify earlier, pre-ECMO and potentially modifiable variables that can affect survival.

The management of patients in cardiogenic shock with suspected or confirmed myocarditis can vary along a spectrum of urgency including the use of mechanical ventilation, vasoactive infusions, elective cannulation onto ECMO, or rapid cannulation onto ECMO in the setting of CA (ECPR). Patients experiencing CA prior to ECMO cannulation either within 24 hours prior to ECMO or as ECPR should be considered a subpopulation of patients who have altered risk factors for survival, given the known morbidity associated with CA. In acknowledging the important interaction between CA occurrence and survival, our study reports a novel finding related to timing of ECMO cannulation.

In patients with myocarditis who were ultimately cannulated onto ECMO but did not suffer a preceding CA or undergo ECPR, shorter time between intubation and cannulation onto ECMO is significantly associated with survival. The relationship between intubation and cannulation onto ECMO is delicate. Our findings suggest that shorter ITC time could be associated with better outcomes in those patients not experiencing CA prior to their cannulation. It is important to note that there may be confounding factors in those patients that suffer CA potentially related to their intubation and that the patients who tolerated intubation without arrest may have better chance of survival. Nonetheless, we must consider that all these patients went onto ECMO at some point in their course, allowing us to consider them within a similar clinical acuity. Similarly, some patients may have been intubated with the plan to cannulate onto ECMO and undergoing cannulation shortly thereafter, as opposed to being in respiratory failure at the time of intubation with subsequent decision to cannulate onto MCS. Translating these findings into clinical practice, once a clinical team decides a patient's condition has deteriorated to the point of needing intubation/mechanical ventilation, subsequent discussions regarding candidacy for ECMO are warranted. Those unfortunate patients experiencing CA in the setting of myocarditis are uniquely different in their disease process and evident by their accelerated ITC times demonstrated in our study. Although this analysis does not provide insight into candidacy for ECMO, prior studies have informed critical care practice regarding key clinical risk factors associated with mortality and need for ECMO in the pediatric myocarditis population. Prior work by Ghelani et al (1) evaluating the Pediatric Health Information System administrative database for pediatric admissions for myocarditis revealed that a nearly half of myocarditis patients admitted to the critical care setting undergo mechanical ventilation, and half of those ultimately received ECMO support (21.8% overall). In an effort to improve our understanding of risk stratification and need for MCS in myocarditis patients, several additional studies have sought associations between laboratory, electrocardiographic, and patient level factors and outcomes after ECMO (7, 10, 12, 18). These reports describe higher creatine kinase MB isoenzyme levels, higher peak brain natriuretic peptide levels, higher peak inotropic score, lower ejection fraction, and development of arrhythmias as pre-ECMO factors of patients with

myocarditis that were associated with receiving MCS (7, 9, 11, 13, 19). These laboratory findings are helpful retrospectively, but it is difficult to know if the patient has reached peak levels when at the bedside. Should providers combine the findings of our study with this accrued knowledge of clinical factors predicting need for MCS, then patients identified as high risk for MCS upon presentation should have expedited cannulation onto ECMO after intubation in order to avoid potential CA and improve survival outcomes.

This is a retrospective multicenter database study, and as such, it comes with unavoidable limitations. Due to the nature of utilizing clinical registry data, we were unable to clarify the reason for initiating ECMO at each ELSO institution. Similarly, the complexity of the decision to cannulate must be taken with great caution, and more information is needed to make any recommendations of change in practice. To keep from assumptions and interpretations, many patients were excluded due to missing data points or negative values. This reduced our cohort and affects the power of the study. Similarly, we cannot confirm timing of laboratory results to perform any interpretation for the appropriate time to consider ECMO cannulation once the patient has been intubated. These in-depth studies are needed to most accurately predict which patients will need ECMO and find markers of the right time to deploy ECMO cannulation in this population. Last, selection bias was inherent in this analysis as we were only evaluating survival and time to ECMO cannulation among patients who ultimately received ECMO.

The results of this multicenter registry analysis of pediatric myocarditis patients receiving ECMO suggest that pre-cannulation factors, including avoidance of CA and earlier cannulation after intubation, may play a role in improving survival outcomes. Avoiding CA is paramount in the care of myocarditis patients given the association with poorer survival. Yet even for patients who are able to avoid CA, timing of ECMO cannulation after intubation is potentially modifiable and warrants further investigation to better describe pre-ECMO clinical and patient level factors that may inform of best practice for ECMO cannulation in this high-risk population.

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