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Contemporary Care and Outcomes of Critically-ill Children With Clinically Diagnosed Myocarditis

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ABSTRACT

Purpose: To describe contemporary management and outcomes in children with myocarditis who are admitted to a cardiac intensive care unit (CICU) and to identify the characteristics associated with mortality.

Methods: All patients in the Pediatric Cardiac Critical Care Consortium (PC[4]) registry between August 2014 and June 2021 who were diagnosed with myocarditis were included. Univariable analyses and multivariable logistic regression evaluated the factors associated with in-hospital mortality.

Results: There were 847 CICU admissions for myocarditis in 51 centers. The median age was 12 years (IQR 2.7−16). In-hospital mortality occurred in 53 patients (6.3%), and 60 (7.1%) had cardiac arrest during admission. Mechanical ventilation was required in 339 patients (40%), and mechanical circulatory support (MCS) in 177 (21%); extracorporeal membrane oxygenation (ECMO)-only in 142 (16.7%), ECMO-to-ventricular assist device (VAD) in 20 (2.4%), extracorporeal cardiac resuscitation in 43 (5%), and VAD-only in 15 (1.8%) patients. MCS was associated with in-hospital mortality; 20.3% receiving MCS died compared to 2.5% without MCS ($P < 0.001$). Mortality rates were similar in ECMO-only, ECMO-to-VAD and VAD-only groups. The median time from CICU admission to ECMO was 2.0 hours (IQR 0−9.4) and to VAD, it was 9.9 days (IQR 6.3−16.8). Time to MCS was not associated with mortality. In multivariable modeling of patients' characteristics, smaller body surface area (BSA) and low eGFR were independently associated with mortality, and after including critical therapies, mechanical ventilation and ECMO were independent predictors of mortality.

Conclusion: This contemporary cohort of children admitted to CICUs with myocarditis commonly received high-resource therapies; however, most patients survived to hospital discharge and rarely received VAD. Smaller patient size, acute kidney injury and receipt of mechanical ventilation or ECMO were independently associated with mortality. (*J Cardiac Fail 2023;00:1−9*)

Key Words: Myocarditis, pediatrics, heart failure, mechanical circulatory support.

Lay Summary

- Despite the high acuity of their illnesses, 94% of children admitted to a cardiac intensive care unit with myocarditis survive to hospital discharge.
- The smallest patients, those presenting with kidney injury and those needing mechanical ventilation and mechanical circulatory support were found to be at the highest risk of dying.
- Intensive care outcomes appear to be improving; future work should focus on standardizing the diagnosis of myocarditis and studying treatment options, especially in the patients at highest risk.

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Myocarditis remains a significant and challenging diagnosis in pediatrics.[1] According to the National Center for Review and Prevention of Child Deaths database, myocarditis accounts for nearly 5% of all cardiac deaths in children.[2]

In sicker adult patients diagnosed with myocarditis and left ventricular ejection fraction < 50%, sustained ventricular arrhythmias and/or low cardiac-output syndrome, the rate of death or heart transplantation at 1 year was 11.3%.[3] It is known that the majority of children hospitalized with myocarditis are admitted to critical care units, but contemporary data regarding the epidemiology and prognosis of critically ill children are lacking.[4] Supportive care remains the mainstay of myocarditis management. Given the lack of evidence-based guidelines for myocarditis, support strategies vary considerably. Available options for both temporary and durable mechanical circulatory support (MCS) in children have increased.[5] To improve outcomes, we must better understand the scope of the problem as well as current pediatric critical-care practices.

We used the Pediatric Cardiac Critical Care Consortium (PC^4) database to describe the contemporary characteristics, cardiac intensive care unit (CICU) management and outcomes of critically ill children diagnosed with myocarditis to identify the characteristics associated with in-hospital mortality.

Methods

Data Source

PC^4 is a quality-improvement collaborative that collects data about all patients with primary cardiac disease admitted to the CICUs of participating hospitals.[6] PC^4 maintains a clinical registry to support research and quality-improvement initiatives. At the time of this analysis, 52 centers were submitting cases to the PC^4 registry.

Each participating center has trained data managers who have completed a certification exam. The data managers collect and enter data in accordance with the standardized PC^4 Data Definitions Manual. The PC^4 registry shares common terminology and definitions with applicable data points from the International Pediatric and Congenital Cardiac Code, Society of Thoracic Surgeons Congenital Heart Surgery Database, and American College of Cardiology Improving Pediatric and Adult Congenital Treatment (IMPACT) registry, as previously described.[6] Participating centers are audited on a regular schedule, and audit results suggest complete, accurate and timely submission of data across centers, with the most recent published results demonstrating a major discrepancy rate of 0.52%.[7] The University of Michigan Institutional Review Board provides oversight for the PC^4 Data Coordinating Center; this study was reviewed and approved with waiver of informed consent.

Definitions and Patient Selection

Patients admitted to CICUs at participating PC^4 centers between August 2014 and June 2021 were included in this analysis if myocarditis was identified as the primary diagnosis for admission to the CICU. This diagnosis is assigned by the treating clinicians and is recorded at the time of diagnosis during the CICU admission; it is based on information from all diagnostic testing, responses to therapies, evolution of symptoms over time, and consideration of potential alternative diagnoses. Formal, gold-standard diagnosis of myocarditis in pediatrics relies on myocardial biopsy or magnetic resonance imaging, neither of which was required. The confirmatory testing for the diagnosis of myocarditis was not captured. However, the definition of myocarditis is restricted to patients requiring CICU-level care, requiring 1 of the following: (1) continuous infusion of a vasoactive agent; (2) respiratory support (high-flow nasal cannula, noninvasive or invasive ventilation); (3) MCS. Thus, patients with lower risk who were admitted for observation due to elevated cardiac enzymes, electrocardiographic or echocardiographic changes are not included in the analysis.

Patients' characteristics used in the analysis included: demographics (age, sex, race, ethnicity, and insurance type); the source of admission (home/emergency department, non-CICU inpatient bed, or/and outside hospital); the presence of extracardiac abnormalities or chromosomal abnormalities/syndromes; weight and body surface area (BSA) at CICU admission; serum B-type natriuretic peptide (BNP) level or N-terminal-pro hormone BNP (NT-proBNP) level at admission; concomitant congenital heart disease; serum creatinine and estimated glomerular filtration rates according to the modified Schwartz formula[8]; highest lactate at admission; and acute arrhythmia requiring CICU-level treatment, including use of a temporary pacemaker, antiarrhythmic infusion, cardioversion or systemic cooling; as well as the type of arrhythmia.

Outcomes

The primary outcome was death prior to hospital discharge. Secondary outcomes included mechanical ventilation; vasoactive infusion use within 6 hours of CICU admission; and CICU and hospital lengths of stay, as well as complications, including sepsis; pleural effusion requiring a chest tube; MCS, including extracorporeal membrane oxygenator (ECMO) ventricular assist device (VAD) or both. Additional secondary outcomes included cardiac arrest, including the use of ECMO rescue within 20 minutes of CPR (eCPR) and heart transplantation. Notably, due to changes in PC^4 data

collection during the reporting period, heart transplantation and specific vasoactive infusions at the time of, and 6 hours after, admission have been documented only since 2019, so the absolute occurrences and incidences are reported only for that period.

Statistical Analysis

Data are presented as frequency (percentage) for categorical variables and median with interquartile range for continuous variables. To determine patients' clinical characteristics associated with death prior to discharge, univariable comparisons were initially performed in patients who died and in patients who survived; we used the Wilcoxon rank-sum test for continuous variables and the ^{2}or Fisher exact test, as appropriate, for categorical data.

Factors associated with death prior to hospital discharge in univariable analysis ($P < 0.1$) were included in a multivariable logistic regression model to determine associations ($P < 0.05$) with mortality. Multicollinearity was assessed using the variance inflation factor, and variables with variance inflation factor $>$ 10 were excluded from the multivariable model. Adjusted odds ratios and 95% CI for each predictor are reported on the basis of the multivariable model.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) or STATA version 15 (StataCorp, College Station, TX), with statistical significance set at P value < 0.05.

Results

There were 847 patients who were admitted to the CICU across 51 participating centers and who met the inclusion criteria between August 2014 and June 2021. The increasing number of patients in the registry over time was due to the growth of the PC[4] and the increasing number of centers contributing data; there was no change in the yearly case volume per center across the study period. Patients' characteristics are detailed in Table 1.

Survival, Cardiac Arrest and Use of MCS

In this cohort, 53/847 (6.3%) patients died before hospital discharge. Since 2019, 11/426 patients (2.5%) have undergone heart transplantation before hospital discharge.

Cardiac arrest occurred in 60 patients (7.1%), and 43/60 (72%) patients who arrested received eCPR. Of the 60 patients who experienced cardiac arrests in this study, 42 (70.0%) survived to hospital discharge. Of the 43 patients who received eCPR, 31 (72.1%) survived to discharge.

MCS was used in 177 (20.9%) patients; ECMO in only 142 (16.7%); ECMO-to-VAD in 20 (2.4%); and VAD in only 15 (1.8%) patients. The median time from CICU admission to ECMO was 2.0 hours (IQR 0−9.4 hours) and to VAD, it was 9.9 days (IQR 6.3−16.8 days). The median duration of ECMO support was 5.6 days (3.2−8.5 days). Survival to hospital discharge without heart transplantation was 115/142 (81%) in ECMO only; 14/20 (70%) in ECMO-to-VAD; and 12/15 (80%) in patients with VAD only (Table 2). The characteristics of patients who received MCS are detailed in Table 3. Of patients who received a VAD, 49% (17/35) ultimately underwent VAD explant and were discharged alive.

Critical Care Therapies and Morbidity

There were 339 (40.0%) patients who received mechanical ventilation, 49% of whom were already intubated on arrival to the CICU. Among the 172 (51%) patients who underwent endotracheal intubation during their CICU courses, 69 (40%) went on to require ECMO, with a median time from intubation to ECMO of 1.3 hours (IQR 0.8−5.4 hours). The incidence of eCPR associated with or following endotracheal intubation in the CICU was 9%, with a median time to eCPR of 0.1 hour (IQR 0−0.8 hour), suggesting that in most of these events, the cardiac arrest occurred immediately following intubation or that intubation was part of an active arrest resuscitation.

At the time of admission, 40.8% (174/426) of patients were on vasoactive infusion support. Six hours after admission, 57.7% (246/426) were on vasoactive infusion support, including 67.1% on milrinone, 55.8% on epinephrine, 9.1% on norepinephrine, 8.7% on dopamine, 4.3% on vasopressin, and only 2 patients on dobutamine.

There were 195 (23.0%) patients who had significant arrhythmia requiring CICU-level therapy; ventricular tachycardia was present in 99 patients (50.8%), atrial tachycardia in 29 patients (14.9%), and complete heart block in 29 (14.9%) patients. Of the 99 patients, 22 (22%) with ventricular tachycardia died. No patients with complete heart block died. Stroke was diagnosed in 33 (3.9%), sepsis in 47 (5.5%), and pleural effusion requiring a chest tube in 33 (3.9%) patients. Renal-replacement therapy or dialysis was used in 52 (6.1%) patients at some point during their courses.

Diagnostic catheterization was performed in 147 (14.4%) patients, and biopsy was performed in only 33 (3.9%) patients. Central venous catheters were placed in 534 (63.0%) patients for median of 8 days (IQR 4.0−15.0), and arterial catheters we placed in 426 (50.3%) patients for median of 7 days (IQR 4.0−12.0).

Associations With Mortality Before Discharge

The following characteristics were associated with unadjusted mortality rates: younger age, female

Table 1. Characteristics and events of patients admitted to pediatric cardiac intensive care unit with myocarditis and the univariable association with mortality

Characteristic	Total (n = 847)	Alive at Discharge (n = 794)	In-hospital Mortality (n = 53)	*P* value
Age (yrs)	12.0 (2.7–16.0)	12.6 (3.4–16.1)	1.6 (0.2–8.2)	<0.001
Gender (male)	535 (63.2%)	511 (64.4%)	24 (45.3%)	0.005
Race				
White	318 (37.5%)	301 (37.9%)	17 (32.1%)	0.77
Black	221 (26.1%)	205 (25.8%)	16 (30.2%)	
Hispanic	171 (20.2%)	161 (20.3%)	10 (18.9%)	
Other	137 (16.2%)	127 (16.0%)	10 (18.9%)	
Public insurance	401 (47.3%)	377 (47.5%)	24 (45.3%)	0.92
Weight (kg)	45.5 (13.3–71.4)	47.5 (15.4–73.0)	11.5 (4.9–25.0)	<0.001
Body surface area (m^2)	1.4 (0.5–1.8)	1.4 (0.6–1.8)	0.5 (0.2–0.9)	<0.001
Congenital heart disease	45 (5.3%)	37 (4.7%)	8 (15.1%)	0.001
Highest lactate within 2 hours of admission (mmol/L)	2.2 (1.3–4.9)	2.1 (1.3–4.5)	4.9 (2.0–13.4)	0.002
eGFR (mL/min/1.73m^2)	83.1 (59.2–104.8)	84.9 (62.9–104.9)	48.9 (26.1–88.8)	<0.001
Maximum BNP (pg/mL)	1325.0 (344.0–3735.0)	1250.0 (310.0–3531.0)	3522.5 (1524.0–7964)	0.004
Mechanical ventilation	339 (40.0%)	288 (36.3%)	51 (96.2%)	<0.001
Mechanical circulatory support	177 (20.9%)	141 (17.8%)	36 (67.9%)	<0.001
ECMO	162 (19.1%)	129 (16.2%)	33 (62.3%)	<0.001
VAD	35 (4.1%)	26 (3.3%)	9 (17.0%)	<0.001
Duration of days of ECMO	5.6 (3.2–8.6)	5.5 (3.4–8.0)	6.4 (1.7–11.3)	0.65
Cardiac arrest	60 (7.1%)	42 (5.3%)	18 (34.0%)	<0.001
eCPR	43 (5.1%)	31 (3.9%)	12 (22.6%)	<0.001
Dialysis	52 (6.1%)	34 (4.3%)	18 (34.0%)	<0.001
Chest tube placed for pleural effusion	33 (3.9%)	28 (3.5%)	5 (9.4%)	0.031
Stroke	33 (3.9%)	22 (2.8%)	11 (20.8%)	<0.001
Sepsis	47 (5.5%)	30 (3.8%)	17 (32.1%)	<0.001
Arrhythmia requiring ICU-level therapy	195 (23.0%)	167 (21.0%)	28 (52.8%)	<0.001
Atrial tachycardia	29 (14.9%)	28 (16.8%)	1 (3.6%)	0.028 (for patients with any arrhythmia)
Ventricular tachycardia	99 (50.8%)	77 (46.1%)	22 (78.6%)	
Junctional tachycardia	4 (2.1%)	4 (2.4%)	0 (0.0%)	
Complete heart block	29 (14.9%)	29 (17.4%)	0 (0.0%)	
Other/multiple types	34 (17.4%)	29 (17.3%)	4 (17.8%)	

Data are presented as median (interquartile range) for continuous measures, and n (%) for categorical measures.

BNP, b-type natriuretic peptide; ECMO, extracorporeal membrane oxygenation; eCPR, extracorporeal cardiopulmonary resuscitation; eGFR, estimated glomerular filtration rate creatinine-based Schwartz equation (0.413 x height in cm/creatinine); VAD, ventricular assist device.

sex, lower weight, smaller BSA, higher lactate levels, lower eGFRs, and higher peak BNP at admission (Table 1). The use of mechanical ventilation and dialysis was associated with mortality in univariable analysis, as were complications of cardiac arrest, arrhythmia, stroke, pleural effusion, and sepsis. MCS (ECMO and VAD) was also associated with in-hospital mortality on univariable analysis; 20.3%

Table 2. Characteristics of patients admitted to pediatric cardiac intensive care units with myocarditis and univariable association with use of mechanical circulatory support

Characteristic	Total (n =847)	No MCS (n = 670)	MCS (n = 177)	*P* value
Age (yrs)	12.0 (2.7–16.0)	13.3 (4.6–16.3)	4.7 (1.1–13.0)	<0.001
Gender (male)	535 (63.2%)	453 (67.6%)	82 (46.3%)	<0.001
Weight (kg)	45.5 (13.3–71.4)	52.0 (17.7–76.0)	20.0 (9.0–54.3)	<0.001
Body surface area (m^2)	1.4 (0.5–1.8)	1.5 (0.7–1.9)	0.8 (0.4–1.5)	<0.001
Highest lactate within 2 hours of CICU admission (mmol/L)	2.2 (1.3–4.9)	1.8 (1.1–3.5)	4.9 (2.3–9.6)	<0.001
eGFR (mL/min/1.73m^2)	83.1 (59.2–104.8)	88.8 (70.8–106.8)	57.8 (36.0–84.0)	<0.001
Maximum BNP (pg/mL)	1325.0 (344.0–3735.0)	1117.0 (205.0–3245.0)	3007.0 (994.0–5000.0)	<0.001
Arrhythmia requiring ICU-level therapy	195 (23.0%)	100 (14.9%)	95 (53.7%)	<0.001

Data are presented as median (interquartile range) for continuous measures and n (%) for categorical measures.

BNP, b-type natriuretic peptide; eGFR, estimated glomerular filtration rate creatinine-based Schwartz equation (0.413 x height in cm/creatinine).

Table 3. Characteristics of patients admitted to a pediatric cardiac intensive care unit with myocarditis who received mechanical circulatory support, stratified by type

Characteristic	Total MCS patients (n = 177)	ECMO only (n = 142)	ECMO and VAD (n = 20)	VAD only (n = 15)	*P* value
Age (y)	4.7 (1.1–13.0)	4.9 (1.0–13.0)	1.5 (1.0–7.2)	14.0 (3.2–15.8)	0.047
Gender (male)	82 (46.3%)	66 (46.5%)	8 (40.0%)	8 (53.3%)	0.73
Weight (kg)	20.0 (9.0–54.3)	19.9 (9.5–53.0)	9.8 (8.6–25.3)	61.0 (12.9–78.0)	0.052
Body surface area (m^2)	0.8 (0.4–1.5)	0.7 (0.4–1.5)	0.4 (0.4–1.1)	1.7 (0.5–1.9)	0.086
Highest lactate within 2 hours of admission (mmol/L)	4.9 (2.3–9.6)	5.2 (2.3–10.1)	3.3 (1.8–8.7)	3.8 (3.6–6.7)	0.67
eGFR (mL/min/1.73m^2)	57.8 (36.0–84.0)	54.3 (34.4–80.0)	62.5 (36.1–77.1)	80.5 (49.6–92.9)	0.18
Maximum BNP (pg/mL)	3007.0 (994.0–5000.0)	3044.0 (1016.0–5000.0)	5000.0 (4245.0–6630.0)	1191.5 (723.0–2721.0)	0.2
Hospital mortality	36 (20.3%)	27 (19.0%)	6 (30.0%)	3 (20.0%)	0.52
Heart transplant during hospitalization	10 (5.6%)	0 (0.0%)	6* (30.0%)	4 (26.7%)	<0.001
Explanted and discharged	n/a	n/a	9 (45.0%)	8 (53.3%)	0.63

Data are presented as median (interquartile range) for continuous measures and n (%) for categorical measures.

BNP, b-type natriuretic peptide; ECMO, extracorporeal membrane oxygenation; eCPR, extracorporeal cardiopulmonary resuscitation; eGFR, estimated glomerular filtration rate creatinine-based Schwartz equation (0.413 x height in cm/creatinine); MCS, mechanical circulatory support; VAD, ventricular assist device.

*One patient died after heart transplantation.

receiving MCS died, compared to 2.5% without MCS ($P < 0.001$). Among the patients receiving MCS, the mortality rate was not different for those supported with ECMO only, ECMO-to-VAD or VAD only (Table 3). Among the patients with MCS, neither time to ECMO nor time to VAD from ECMO was associated with mortality. The median time to VAD was 9.9 days (IQR 5.5–17.6) in patients alive at discharge and 10.1 days (IQR 7.1–15.9) in patients who died before discharge. The overall duration of ECMO support was not associated with mortality; 14/20 patients (70%) supported for ≥ 14 days survived to discharge (Fig. 1).

In multivariable modeling including only patients' characteristics at admission, BSA ≤ 0.3 m^2 (OR 7.4, CI 1.2–44.8), BSA 0.3–1.5 m^2 (OR 2.9, CI 1.1–7.8), and eGFR < 30 mL/min/1.73m^2 (OR 6.2, CI 2.0–19.4) remained significantly associated with in-hospital

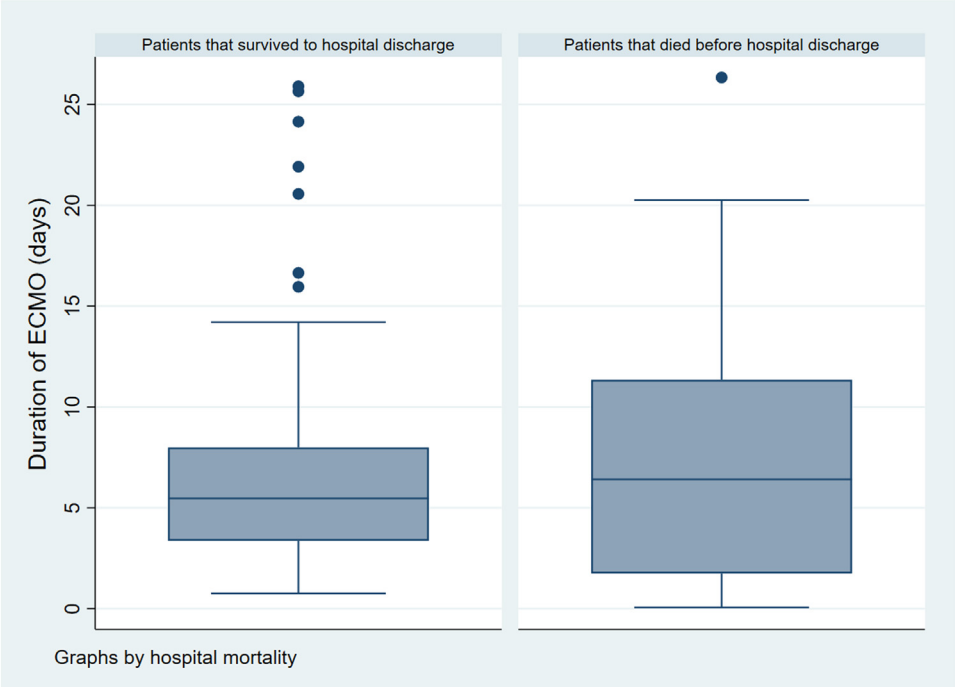

Fig. 1. Box plot showing the number of days on extracorporeal membrane oxygenation (ECMO) for patients with myocarditis who did and did not survive to hospital discharge.

Table 4. Multivariable associations with mortality in patients admitted to pediatric cardiac intensive care units with myocarditis (including patient characteristics at admission and critical care therapies received)

	Odds Ratio for Mortality	*P* value	95% Confidence Interval	
Age group (child: 1−17 years, ref)				
Neonate: 0−29 days	0.4	0.3	0.07	2.37
Infant: 30−364 days	1.3	0.6	0.45	3.66
Adult:18+ years	1	1	0.10	9.95
BSA (>1.5 m^2 ref)				
≤0.3 m^2	7.9	0.04	1.12	55.32
0.3−1.5 m^2	2.4	0.1	0.78	7.57
Male	0.9	0.7	0.45	1.77
Weight group (normal ref)				
Underweight (weight-for-age z-score <-2)	1.8	0.4	0.46	6.69
Overweight (weight-for-age z-score >2)	0.7	0.6	0.17	2.57
Congenital heart disease	4.1	0.01	1.37	12.16
eGFR (>90 mL/min/1.73m^2 ref)				
<30	3.6	0.04	1.08	12.27
30−60	0.7	0.5	0.22	2.11
60−90	0.6	0.4	0.18	2.08
Maximum BNP (<25 percentile among study patients ref)				
25−75 percentile	2.9	0.4	0.28	29.88
≥75 percentile	2.5	0.4	0.24	26.84
ECMO	2.9	0.004	1.40	6.14
Mechanical ventilation	22.3	0.000	4.74	104.41

BNP, brain natriuretic peptide; BSA, body surface area; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate creatinine-based Schwartz equation (0.413 x height in cm/creatinine).

mortality. The C-statistic for this model was 0.80, indicating strong discrimination among those who survived to hospital discharge and those who did not. When critical-care therapies were added to the multivariable model, BSA ≤ 0.3 m^2 (OR 7.9, CI 1.1−55.2) and eGFR < 30 mL/min/1.73m^2 (OR 3.6, CI 1.1−12.3) remained significantly associated with in-hospital mortality. Diagnosis of congenital heart disease (OR OR 4.1, CI 1.4−12.2), receipt of mechanical ventilation (OR 22.3, CI 4.7−104.4) or ECMO (OR 2.9, CI 1.4−6.1) were also demonstrated to be independent predictors of in-hospital mortality (Table 4). The C-statistic for the model, including critical therapies, was 0.91, indicating very strong discrimination between individuals with in-hospital mortality and survivors.

COVID-19

In the study's cohort, 227/847 (26.8%) patients diagnosed with myocarditis were admitted after March 2020, the approximate beginning of the pandemic in the United States, through June 2021, the end of this study. The PC^4 registry collected COVID-specific data, and only 75/847 (8.9%) of the overall study cohort had COVID listed as a diagnosis or complication. Multisystem inflammatory syndrome in children was a separate diagnosis in the registry. There was no statistically significant difference in mortality rates after March 2020 compared with the rates before that date.

Discussion

In this study, we detailed the characteristics, management and outcomes of children admitted to a CICU with a clinical diagnosis of myocarditis in a large, multicenter, contemporary patient cohort. Myocarditis often requires intensive supportive care, such as vasoactive support, mechanical ventilation and MCS. The diagnosis carries important risk of renal failure, cardiac arrest and death. The smallest patients and patients with severe acute kidney injury are at the highest risk of in-hospital mortality. Despite the gravity of this condition, contemporary critical care has resulted in high survival rates and discharge.

This analysis provides a contemporary and accurate update that includes the largest cohort of patients with myocarditis managed in a CICU; they were identified by using the rigorously audited PC^4 database.[9] Myocarditis and, particularly, acute fulminant myocarditis, is generally survivable with appropriate and timely support. Earlier studies were based on administrative databases or smaller retrospective cohorts,[4,10,11] and they preceded the recent changes in the field of pediatric MCS, now that more temporary and durable VAD options are available. In an earlier study of all patients with acute decompensated heart failure admitted to PC^4 CICUs, the overall heart-failure cohort was younger and smaller, more likely to have congenital heart disease, more likely to die, and more likely to need to undergo heart transplantation in comparison to this present study's patients with myocarditis.[12] Only 8%

of the overall heart failure cohort had myocarditis, and myocarditis was previously found to be protective against mortality in multivariable modeling (odds ratio 0.22, 95% CI 0.1−0.8). In this present study of patients admitted to a cardiac critical care unit with myocarditis, in-hospital mortality and transplant rates were low, at 6.3% and 2.5%, respectively. These outcomes are better than the 11%−13% transplant rate that has been reported previously, even though the older studies included both critically ill patients and patients not requiring CICU admission.[4,11,13] This is also noteworthy because recent data show that myocarditis remains a significant risk factor in early post-transplant graft loss.[14]

Our higher transplant-free survival rate also is likely to reflect improvements in pediatric cardiac critical care and potentially increased knowledge of the importance of early diagnosis and transfer of patients to a CICU able to provide high-level support. ECMO remains the most commonly used MCS strategy in critically ill children with myocarditis; 19.1% of the cohort received ECMO, consistent with the rates previously reported.[4] The in-hospital mortality rate for patients supported by ECMO was, overall, 20.3% (27.9% vs 17.6%, respectively, for patients who did or did not receive eCPR). This survival rate is higher than that published in reports from the Extracorporeal Life Support Organization registry.[15,16] We found that nearly one-quarter of the patients who died had ventricular tachycardia. Earlier mechanical support in patients with significant ventricular tachyarrhythmia may be an area for possible improvement. Of note, eCPR survival to hospital discharge is remarkably higher in patients with myocarditis who are admitted to PC[4] centers compared with the 43% survival rate reported by the Extracorporeal Life Support Organization for all pediatric recipients of eCPR.[17] These improving ECMO and eCPR outcomes correlate with other improved metrics seen in PC[4] centers and may be a benefit of the collaboration and quality-improvement efforts in the critical care community.[18]

Contrary to expectations, given the significant increase in VAD use this past decade,[5] our study shows that the proportion of pediatric patients supported by VADs for myocarditis has remained relatively stable at 4%−5%.[4,11] Acknowledging the small number of patients with VADs and the risk of type II error, there was no difference in mortality rates in patients supported with VADs and also no difference with respect to the timing of VAD placement. Of note, a significantly higher percentage of these patients with myocarditis underwent VAD explant for recovery, compared with the percentage reported in pediatric VADs overall.[19] These findings support careful assessment for recovery and possible explant in patients with myocarditis who are supported by VADs, and such findings warrant further investigation.

The timing of MCS initiation in this disease process has also been a longstanding subject of debate; this analysis sheds light on the subject. Deciding on the timing and form of support can be vexing. A provider must balance the risk that the myocarditis disease process may plateau and then reverse without necessitating the risks incurred by MCS against the risk of waiting too long and facing a cardiac arrest or multiorgan failure. The overall survival rate of those on MCS, in particular on ECMO, found in this cohort is strikingly high in comparison to other disease processes requiring ECMO. In terms of decision making for MCS, this analysis appears to support the idea of moving to ECMO proactively since mechanical ventilation, not MCS, is the strongest independent risk factor associated with mortality. This justifies recommendations to referring institutions that patients with myocarditis requiring endotracheal intubation should be urgently transferred to a center that supports ECMO.[20] Further, in terms of time spent on ECMO, there was no difference between survivors and nonsurvivors in duration of support, indicating that eventual recovery to the point of not requiring MCS should be the expectation.

The analysis also highlighted specific areas for improvement. Small BSA, specifically infant patients, was independently associated with mortality. We must find better ways to medically and mechanically support the smallest patients who have myocarditis. There was a small number of patients with congenital heart disease who were diagnosed with myocarditis. These patients were at increased risk of mortality, which is not surprising, given their associated anatomical abnormalities and comorbidities. Challenges concerning timely diagnosis, supporting immature extracardiac organs and, potentially, different disease and immunological processes in infants may also be contributing to increased mortality rates.

Not unexpectedly, significant end-organ dysfunction at CICU admission was also an independent risk factor. Promoting and facilitating timely referral of these patients to pediatric CICUs for the specialized support they require may further improve outcomes. It will be important to see whether newer percutaneous circulatory support devices, which are gaining traction in pediatrics, can further mitigate risks in the pediatric patient with myocarditis.[21]

Limitations

There are limitations to this study. As stated previously, the PC[4] diagnosis of myocarditis is assigned during each patient's CICU course after thorough

review, and it represents the center's final, best explanation. Despite the retrospective diagnosis made by a clinician at the conclusion of the hospitalization, there may be other etiologies of heart failure with reduced ejection fraction and cardiomyopathy that are misclassified as myocarditis in our study, and they could impact the findings. We also considered the effect that COVID may have had on our findings. Only 75/847 (8.9%) of our study's patients had mention of COVID in their records (65 of these as an "other complication"); mortality rates were similar during the COVID period. Thus, COVID did not appear to change the overall findings and their generalizability. The PC[4] diagnosis is limited strictly to patients requiring CICU-level care; thus, the actual morbidity and mortality rates for all patients with myocarditis will be lower than those we report. Only 33 patients (3.9%) underwent biopsy in our data, and PC[4] does not collect cardiac magnetic resonance data. Thus, we believe this PC[4] diagnosis reflects accurately how myocarditis is currently, and imperfectly, diagnosed, because there is no universally accepted, widely implemented definition. We acknowledge the potential impact of unmeasured confounders not captured by this data set. The incidence of transplant has been captured and reported in patients only since 2019. Nevertheless, with the inclusion of 426 patients, we believe these data reflect accurately how many critically ill children with myocarditis undergo transplant in the most recent era.

A universal diagnosis of myocarditis remains a challenge. The Pediatric Cardiomyopathy Registry data showed that outcomes in the clinically diagnosed vs biopsy-confirmed myocarditis groups did not differ and, therefore, these groups were combined in their analysis.[13] Nevertheless, to further study and improve outcomes in those with myocarditis, we strongly support the recent statement that calls for the field to collaborate on establishing and implementing a standardized definition.[1]

In summary, this contemporary cohort of children with diagnoses of myocarditis managed in a CICU received high-resource therapies, such as mechanical ventilation and ECMO. Most patients survived to hospital discharge and rarely received VAD or heart transplantation. Creating a uniform and implementable way to diagnose myocarditis and improving temporary circulatory support, especially in the smallest patients, should be priorities for future collaborative work.

3 Brief Bullet Points About How Their Work Applies to Patients and a Brief Lay Summary

We sought to study the latest characteristics, management and outcomes in children admitted to cardiac intensive care units with the diagnosis of myocarditis. We used data from the Pediatric Cardiac Critical Care Consortium (PC[4]), a groundbreaking quality-improvement collaborative. Myocarditis often requires intensive supportive care, such as intravenous medications, mechanical ventilation and mechanical circulatory support. Nevertheless, the vast majority of these critically ill children survive to hospital discharge and do not require heart transplantation. In these PC[4] centers, outcomes appear to be improving compared with historical data. Future improvement efforts should target a more standardized approach to diagnosis and treatment.

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Disclosures

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