BRIEF REPORT

Pediatric Acute Myocarditis: Predicting Hemodynamic Compromise at Presentation to Health Care

Ashley E. Wolf, MD,[a] Bradley S. Marino, MD, MPP, MSCE,[b,c] Ahmad Sami Chaouki, MD, PhD,[d] Adin-Cristian Andrei, PhD,[e] Jeffrey G. Gossett, MD[f]

ABSTRACT

BACKGROUND: The clinical spectrum of pediatric acute myocarditis ranges from minimal symptoms with intact hemodynamics to rapid cardiovascular collapse and death. We sought to identify factors on initial presentation associated with subsequent hemodynamic compromise.

METHODS: We performed a retrospective cohort study of patients with acute myocarditis at a freestanding pediatric hospital from 2007 to 2016. We defined 2 cohorts: high-acuity patients with hemodynamic compromise defined as requiring inotropic or vasoactive medications, cardiopulmonary resuscitation, extracorporeal membrane oxygenation, ventricular assist devices, or transplant or who died and low-acuity patients without these interventions. We collected the first recorded set of vital signs, symptoms, laboratory values, and chest radiograph, electrocardiogram, and echocardiography results. Univariate analysis was performed, and 2 multivariable logistic regression models were created to discriminate between cohorts.

RESULTS: A total of 74 patients were included: 33 high acuity and 41 low acuity. There were significant differences in demographics, symptoms, and physical examination, laboratory, electrocardiogram, and echocardiography findings between high- and low-acuity cohorts. Multivariable logistic regression models were highly discriminate in predicting those in the high-acuity cohort. The first model included presence of tachycardia, tachypnea, creatinine, and cardiomegaly on chest radiograph (area under the curve = 0.913). The second model added the presence of pericardial effusion to the above variables (area under the curve = 0.964).

CONCLUSIONS: Models based on factors available at initial presentation with acute myocarditis are predictive of subsequent hemodynamic compromise. If our results can be validated in a multicenter study, these models may help disposition patients with suspected acute myocarditis (with those who meet model criteria being admitted to centers capable of rapidly providing extracorporeal membrane oxygenation, ventricular assist devices, and heart transplant evaluation).

[a]*Division of Critical Care Medicine, Seattle Children's Hospital, Seattle, Washington;* [b]*Department of Pediatrics, Feinberg School of Medicine and* [e]*Department of Preventive Medicine, Northwestern University, Chicago, Illinois;* [c]*Divisions of Critical Care and* [d]*Cardiology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; and* [f]*Division of Cardiology, University of California, San Francisco Benioff Children's Hospital, San Francisco, California*

www.hospitalpediatrics.org
DOI:https://doi.org/10.1542/hpeds.2018-0212

Address correspondence to Ashley E. Wolf, MD, Division of Critical Care, Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, WA 98105. E-mail: ashley.wolf@seattlechildrens.org

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Dr Wolf conceptualized and designed the study, designed the data collection instruments, collected data, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Marino conceptualized and designed the study, designed the data collection instruments, and reviewed and revised the manuscript; Dr Chaouki designed the data collection instruments, collected data, and reviewed and revised the manuscript; Dr Andrei conducted the initial analyses and reviewed and revised the manuscript; Dr Gossett conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Pediatric acute myocarditis is an inflammatory condition of the myocardium commonly secondary to viral infections.[1–5] The clinical course of myocarditis is broad, ranging from an asymptomatic condition to hemodynamic collapse and sudden death.[4–8] Presenting symptoms vary widely and overlap with conditions such as viral illnesses.[1–12] Treatment of myocarditis is matched to clinical need ranging from observation to ICU care, including vasoactive medications, mechanical circulatory support (MCS) with ventricular assist devices (VADs) or extracorporeal membrane oxygenation (ECMO), and heart transplant.[4,11–16] Researchers have found that 35% to 85% of myocarditis patients required pharmacologic hemodynamic support,[4,11,13,14] with a subset requiring invasive cardiorespiratory support or dying.[5,8,12,14,17–19]

Rapid identification in the emergency department (ED) of patients who subsequently have hemodynamic compromise would allow early disposition of patients to an institution with a PICU or cardiac ICU with the ability to escalate care rapidly (ie, MCS). It is unknown which factors after presentation correlate with a more severe course.[6,11,15,18] In this pilot study we sought to find a group of signs and symptoms at presentation in patients with myocarditis differentiating those progressing to hemodynamic compromise.

METHODS

Study Design

We conducted a retrospective cohort study of patients diagnosed with acute myocarditis at a freestanding pediatric hospital. Our hospital is the sole pediatric heart transplant center in the state and as a result is a referral center for children in whom advanced heart failure services such as transplant may be required. Institutional review board approval was obtained.

Study Population

Patients 1 day old to 18 years old between January 1, 2007 and January 21, 2016, diagnosed with acute myocarditis by a pediatric cardiologist, cardiac MRI, or endomyocardial biopsy were identified by using the Bio-Information Suite database; *International Classification of Diseases, 9th Revision* codes; and *International Classification of Diseases, 10th Revision* codes. Patients were excluded for a history of cardiac disease (other than defects without intervention) or cardiotoxic chemotherapy.

We defined 2 cohorts: high acuity and low acuity. The high-acuity cohort comprised all patients requiring inotropic or vasoactive medications, cardiopulmonary resuscitation, ECMO, or VADs; progressing to transplant; or dying. The low-acuity cohort comprised all others.

Data Collection

Hospital records, including outside records, were reviewed. Only the first available presenting signs, symptoms, laboratory values, radiographic data, electrocardiogram (ECG) findings, and echocardiographic findings were collected and only if obtained within 24 hours of presentation. Vital signs were dichotomized to abnormal yes or no on the basis of the normal range in *Harriet Lane Handbook, 20th Edition* (American Heart Association normative values).[20] Hypoxemia was Spo_2 $\leq$92%. Symptoms were dichotomized as yes or no on the basis of documentation. Gastrointestinal symptoms were defined as 1 or more of the following: abdominal pain, feeding intolerance, or emesis. Physical examination findings were based on first reported physician documentation. Hepatomegaly was present if hepatomegaly or palpable liver were documented. Perfusion was defined as normal if described as normal, well perfused, or capillary refill $\leq$3 seconds. Pulses were defined as normal if described as normal, strong, or $\geq$2. Our hospital's normative ranges for age were used to define laboratory data. ECGs were reread by a pediatric electrophysiologist (A.S.C.) blinded to cohort.

Statistical Analysis

Continuously distributed variables are reported as medians with first quartiles (Q1s) and third quartiles (Q3s). Variables with discrete distributions are presented as counts and percentages. Comparisons between low- and high-acuity groups were based on Wilcoxon rank sums for continuous variables and χ^2 or Fisher's exact tests for discrete variables. Normalcy was assessed by using the Shapiro–Wilk test and Q-Q plots. Multivariable logistic regression models were created to identify variables associated with low versus high acuity and summarized by using odds ratios, 95% confidence intervals, and *P* values. Only those individuals for whom the outcome and explanatory variables of interest were not missing were included in the respective analysis and model creation. The area under the receiver operating characteristic curve (AUC) was used to summarize the overall model fit. Models were internally validated by using leave-1-out jackknife cross-validation, and the AUC was calculated. Statistical significance was declared at the 5% 2-sided α level, and there were no adjustments for multiplicity. All analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Over the 9-year period, 76 patients were diagnosed with acute myocarditis. Records at presentation were available for 74. Of these, 33 (45%) met high-acuity criteria, and 41 (55%) met low-acuity criteria. All 33 high-acuity patients received inotropic or vasoactive medications, 9 had

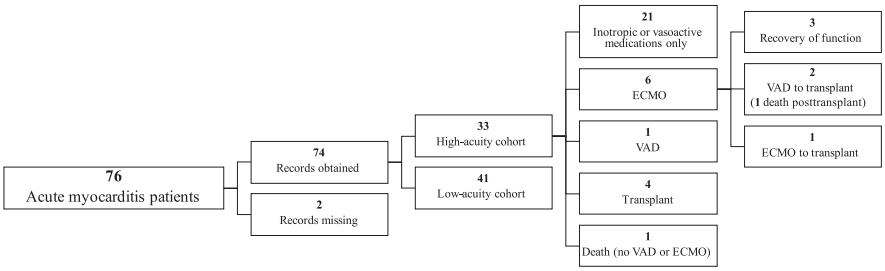


FIGURE 1 Breakdown of patient cohorts.

cardiopulmonary resuscitation, 6 were placed on ECMO, 3 required VADs, 7 progressed to transplant, and 2 died (Fig 1). Of the 6 who required ECMO, 3 were cannulated within 24 hours of presentation. Overall, 21 of 33 (63%) high-acuity patients were supported with inotropic or vasoactive medications alone, and 12 of 33 (37%) required additional intensive therapies or died.

High-acuity patients were younger, smaller, and more likely to be girls. High-acuity patients were more likely to be tachycardic, tachypneic, hypotensive, and hypoxemic at presentation. High-acuity patients endorsed more abdominal pain, feeding intolerance, gastrointestinal symptoms, and shortness of breath. High-acuity patients were more likely to manifest wheezing, gallop, hepatomegaly, and abnormal perfusion and pulses. On initial laboratory tests, high-acuity patients were more likely to have abnormal hemoglobin, albumin, alanine aminotransferase, blood pH, bicarbonate, and creatinine levels as well as B-natriuretic peptide (BNP). Troponin level was not different between cohorts. High-acuity patients were more likely to have cardiomegaly and pulmonary edema on initial chest radiograph (CXR) and bundle branch block on ECG. Echocardiograms of high-acuity patients were more likely to reveal pericardial effusion, mitral or aortic regurgitation, lower ejection, and shortening fractions (Table 1).

We constructed 2 multivariable logistic regression models to discriminate between cohorts. We included variables easily obtained in the ED on a first pass workup, which would result quickly. We chose variables widely available to make the models applicable in a variety of medical settings. Model 1 included tachycardia, tachypnea, abnormal creatinine, and cardiomegaly on CXR and had an AUC of 0.913 for predicting inclusion in the high-acuity cohort (Fig 2). Model 2 added pericardial effusion; this model could be used at facilities with ultrasound, such as EDs, performing a focused assessment with sonography for trauma examination but

TABLE 1 Univariate Analysis Results

Variable	*n*	High Acuity, %	Low Acuity, %	*P*
Demographics				
Wt, kg, median (Q1, Q3)	74	9.6 (3.5, 25.0)	59.2 (54.0, 70.8)	<.001
Age, y, median (Q1, Q3)	74	1.3 (0.0, 7.2)	15.6 (14.0, 16.8)	<.001
Girls	74	61	12	<.001
Symptoms				
Length of symptoms, d, median (Q1, Q3)	74	4.0 (1.0, 7.0)	3.0 (2.0, 5.0)	.64
Chest pain	49	54	94	<.001
Palpitations	37	17	29	.53
Shortness of breath	66	74	36	.002
Diaphoresis	29	38	33	.83
Fever	69	65	58	.58
Rash	52	10	10	.99
Abdominal pain	49	94	30	<.001
Emesis	64	64	42	.07
Feeding intolerance	27	90	14	<.001
Gastrointestinal symptoms	70	94	51	<.001
Syncope	43	7	3	.59
Vital signs				
Tachycardic	71	77	17	<.001
Bradycardic	71	3	7	.47
Tachypneic	71	73	29	<.001
Hypotensive	71	6	7	<.001
Hypoxemic	64	23	3	.01
Physical examination				
Wheezing	71	13	0	.016
Systolic murmur	71	20	10	.22
Diastolic murmur	71	0	0	—
Gallop	71	40	0	<.001
Hepatomegaly	70	86	5	<.001
Abnormal perfusion	71	50	0	<.001
Abnormal pulses	71	37	0	<.001
Laboratory findings				
WBC, abnormal	69	17	10	.43
Hemoglobin, abnormal	69	43	13	.004
CRP, abnormal	63	38	74	.004
ESR, abnormal	52	33	26	.6
AST, abnormal	56	62	57	.71
ALT, abnormal	56	65	37	.032
Albumin, abnormal	53	33	7	.014
pH, abnormal	28	76	0	<.001
Bicarbonate, abnormal	71	80	24	<.001
Creatinine, abnormal	70	41	7	<.001
BNP, abnormal	56	100	41	<.001
BNP, median (Q1, Q3)	52	2842.5 (1247.0, 4535.2)	82.9 (43.8, 185.0)	<.001
Troponin, median (Q1, Q3)	61	4.3 (0.6, 11.8)	8.9 (2.0, 19.7)	.26
CXR findings				
Cardiomegaly	66	64	8	<.001

TABLE 1 Continued

Variable	*n*	High Acuity, %	Low Acuity, %	*P*
Pulmonary edema	66	50	5	<.001
ECG findings				
First-degree block	66	4	0	.2
Second-degree or higher block	66	4	0	.2
Ventricular tachycardia	66	8	0	.07
ST segment changes	66	40	56	.2
Bundle branch block	66	12	0	.023
Decreased voltages	66	24	7	.06
Abnormal axis	66	20	10	.24
Echocardiography findings				
Pericardial effusion	65	58	7	<.001
EF, median % (Q1%, Q3%)	59	35 (21, 50)	60 (52, 64)	<.001
SF, *z* score, median (Q1, Q3)	60	−8.3 (−10.8, −6.2)	−1.2 (−2.3, 0.0)	<.001
LVEDD, *z* score, median (Q1, Q3)	63	1.0 (−0.8, 2.6)	0.2 (−0.5, 0.0)	.29
LVESD, *z* score, median (Q1, Q3)	62	3.3 (1.0, 5.2)	0.6 (−0.2, 1.4)	<.001
MR, moderate or severe	64	36	0	<.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; EF, ejection fraction; ESR, erythrocyte sedimentation rate; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; MR, mitral regurgitation; SF, left ventricular fractional shortening; WBC, white blood cell count; —, not applicable.

without echocardiography. This model had an AUC of 0.964 for predicting inclusion in the high-acuity cohort (Fig 2 B).

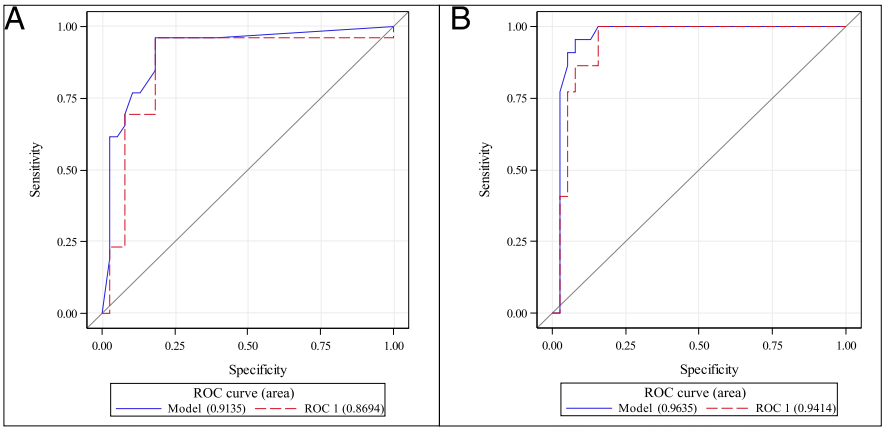
DISCUSSION

Many clinicians identify children with acute myocarditis who are admitted to facilities without MCS capability, deteriorated rapidly, and were transferred to a tertiary-care hospital in extremis. Similar to previous studies, we demonstrate that myocarditis has significant variability in presenting signs and symptoms.[9] Our data reinforce that complaints such as gastrointestinal upset with persistent tachycardia should be seen as red flags and trigger additional evaluation such as BNP measurement, CXR, etc. To add to the literature, we sought to develop a simple tool to identify which patients were at highest risk of deterioration. In this pilot study, we were able to develop models that are highly predictive of hemodynamic compromise. To our knowledge, this is the first study predicting these outcomes at presentation.

The variables more likely present in the high-acuity cohort (ie, tachycardia, tachypnea, hypotension, hepatomegaly, etc.) suggest that patients progressing to hemodynamic compromise have signs of cardiac dysfunction at presentation. Although multiple variables were different between cohorts, there was considerable overlap. As a result, no single variable discriminated between cohorts, and only our multivariable models were highly predictive of severe outcome.

Despite 37% of the high-acuity cohort progressing to MCS, transplant, or death, our sample size precluded creating a model predicting these end points. We suggest that when myocarditis is suspected, signs of early cardiac dysfunction should be sought and our models applied. Until we are better able to make predictions within this high-acuity group, those fitting our models should be triaged to institutions with MCS, heart failure treatment, and transplant, acknowledging that many will not require this care. Conversely, low-acuity patients may be considered for disposition to facilities without MCS or transplant capability with a high probability of good outcome.

Our single-center retrospective study has limitations, such as sample size, incomplete data, and clinical diagnosis. As the sole pediatric transplant center for the state, our population is biased toward sicker patients more likely to require advanced heart failure therapies, and we were unable to determine the denominator of patients with mild myocarditis not referred. We did not capture medications (ie, antipyretics) impacting symptoms and relied on clinical reporting and documentation. The models are not intended to diagnose myocarditis or to differentiate myocarditis from viral



OR Estimates (Model 1, Figure 2A)

Variable	OR	OR 95% CI		*P*-Value
Tachycardia	8.07	1.65	39.54	0.010
Tachypnea	1.27	0.23	6.87	0.78
Abnormal creatinine	5.71	0.68	47.92	0.109
Cardiomegaly	7.67	1.30	45.25	0.025

OR Estimates (Model 2, Figure 2B)

Variable	OR	OR 95% CI		*P*-Value
Tachycardia	3.93	0.57	26.96	0.16
Tachypnea	6.41	0.47	87.72	0.16
Abnormal creatinine	1.48	0.13	17.24	0.75
Cardiomegaly	9.90	1.18	82.88	0.035
Pericardial effusion	44.35	3.25	605.83	0.005

FIGURE 2 Odds Ratio estimates and ROC curves for comparisons. A, Model 1. B, Model 2. CI, confidence interval; OR, odds ratio; ROC, receiver operating characteristic.

illnesses. They should only be applied to triage decisions in patients for whom there is a high suspicion for myocarditis. Our findings should be validated with prospective studies.

CONCLUSIONS

Symptoms, signs, laboratory values, and radiographic, ECG, and echocardiographic findings at initial presentation with acute myocarditis are associated with hemodynamic compromise. We developed 2 models from easily obtained initial factors that predict the need for vasoactive medications, MCS, heart transplant, or death. Although our pilot study requires larger-scale validation, we suggest that these variables and models may be able to triage patients with acute myocarditis. Patients meeting our high-acuity cohort criteria should be considered for initial admission to centers capable of providing MCS and heart transplant, whereas patients not meeting these criteria may be considered for disposition to centers without these capabilities.

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Hospital Pediatrics 2019;9;455
DOI: 10.1542/hpeds.2018-0212 originally published online May 30, 2019;

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