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Clinical Findings and Predictors of Poor Outcome in Pediatric Viral Myocarditis

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2016

Abstract

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By Nina Hirsch Garza

Background: Myocarditis is an important cause of cardiovascular morbidity and mortality in children. This study sought to characterize the clinical parameters of children diagnosed with viral myocarditis, determine which characteristics were associated with poor outcome, as well as develop a predictive model for poor outcome in this population.

Methods: A retrospective cohort was built from patients admitted with the diagnosis of acute myocarditis, septic myocarditis, or other unspecified myocarditis at Children's Hospital of Atlanta between January 2008 and December 2014. A total of 36 patients were included. Poor outcome was defined as in-hospital death or cardiac transplant. Univariate analysis was performed with assess risk between the groups. Stepwise logistic regression model selection was performed using variables collected at admission and during hospital course.

Results: In hospital mortality was 8.3%, with 17% experiencing poor outcome. Poor outcome was significantly associated in univariate analyses with low baseline ejection fraction (<30), positive viral titers, utilization of dopamine during hospitalization, and mechanical ventilation. Multivariable model selection for prediction of poor outcome identified peak CRP, admission diastolic blood pressure, baseline ESR, and symptomatic emesis as significant.

Discussion: While there appear to be some factors that significantly contribute to the development of poor outcome in children presenting with symptomatic viral myocarditis, multivariate modeling did not yield a robust set using this data. Future multicenter studies should be undertaken with larger sample sizes to more clearly elucidate meaningful predictors.

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Acknowledgements
I would like to thank Dr. Shriprasad Deshpande, MD, for his advice and the opportunity to participate in this project, as well as Dr. Matthew Oster, MD, MPH for his guidance in the preparation of this thesis.

Table of Contents

Background

Myocarditis is an important cause of cardiovascular morbidity and mortality in children. The disease is characterized by myocardial infiltration of inflammatory cells and non-ischemic myocyte necrosis(1). The World Health Organization 1995 Conference defines myocarditis as a type of inflammatory cardiomyopathy, diagnosed by "established histological, immunological, and immunohistochemical criteria"(2). Despite this definition, useful clinical criteria in an emergent setting remains a challenge.

The causes of pediatric myocarditis are diverse, including bacterial, viral, toxic and autoimmune. Infectious etiologies are the most common, particularly viral infections. Because of the predominance of viral infections as the cause of myocarditis, lymphocytic infiltrates are the most commonly documented histological finding(3). While traditionally it was accepted that the most common viral cause was enterovirus or adenovirus, recent advances in testing have found that parvovirus B19 and human herpes virus 6 may play a larger role(4).

In previous studies, the most common physical exam findings in children ultimately diagnosed with myocarditis included tachypnea and abnormal respiratory exam. However, clinical presentation can include many organ systems and can range in severity from mild chest pain to overt hemodynamic failure(5). Other common presenting symptoms include gastrointestinal symptoms (anorexia, abdominal pain, vomiting), chest pain, syncope or fever(6).

Appropriate diagnosis and management have continued to be challenging due to the low sensitivity and specificity of clinical findings or existing diagnostic modalities, and there continues to be no single clinical or imaging finding that definitively confirms the diagnosis. Endomyocardial biopsy is currently considered the gold standard for the diagnosis of myocarditis, and is rated according to the Dallas criteria (7). However, due to the focal nature of the disease and the invasiveness of the procedure, imaging modalities such as echocardiography and cardiac magnetic resonance imaging (cMRI) have become favored. Electrocardiography (EKG) is usually abnormal, and no specific ECG findings have been found to be adequately sensitive or specific. Biomarkers such as troponin, brain natriuretic peptide, and creatinine kinase are also often elevated. However, they have poor sensitivity in the diagnosis of myocarditis because of their overlap in other inflammatory conditions such as pericarditis. Supportive therapy remains the mainstay of therapy, though treatment with immunomodulators and antivirals are currently under study.

Clinical course and outcomes can be variable and are still under study as new diagnostic and treatment modalities are being introduced. Prognosis is closely linked to clinical presentation. While patients with acute myocarditis with preserved left ventricular ejection fraction can expect a full recovery, one study found patients in NYHA functional class III or IV with positive biopsy results can expect a 5-year transplantation free survival rate of only 39% (8).

The aim of this study was to characterize the presenting history and physical findings of children clinically diagnosed with myocarditis at our institution, and

document their subsequent management. We also investigated the value of biomarkers and imaging in the prediction of clinical outcome in pediatric viral myocarditis.

Methods

Data Source

Patients admitted with a diagnosis of acute myocarditis, septic myocarditis, or other unspecified myocarditis at Children's Hospital of Atlanta between January 2008 and December 2014 were identified between using *International Classification of Diseases, Ninth Revision* (ICD-9) codes (n=88). Electronic medical records of those included above were reviewed, and those patients that had a documented clinically suspected or laboratory confirmed viral myocarditis were included (n=36).

Study Variables

All study data was collected using standardized REDCap data collection forms. Information collected included demographics, baseline laboratory and diagnostic results, histology, imaging and discharge data. Outcome status, interim hospitalization, current medications and one-year follow-up visits were also obtained, where available. For the purpose of univariate and multivariate analyses, outcome variables were dichotomized in to transplant-free outcome (with or without heart failure medications at discharge) and poor outcome (death or transplant during initial hospitalization).

Statistical Analysis

For the purpose of analysis, poor outcome was defined as in-hospital death or transplant. In univariate analysis, chi-square testing was used for nominal data,

with the Cochran-Mantel-Haenszel test used in cases of a zero count in a subset. Fisher's exact test was used in chi-square analysis where the expected cell count was less than five. Statistical significance was defined as a *p*-value less than or equal to 0.05.

Two predictive models were built using stepwise logistic regression analysis with a *p*-value of 0.05 for both entry and exit of the model. The first model was developed for predicting the characteristics of the patients that received cMRI during their hospitalization. A second model was developed to investigate which variables collected at initial presentation predicted poor outcome at discharge. A total of 28 variables were considered as potential predictor variables of poor outcome. The potential selection variables included demographics, baseline physical exam and laboratory values, imaging findings, and treatment modalities received during admission. All 36 cases were included in the model selection process.

Model validation for poor outcome was performed using leave one out cross validation due to small sample size. Receiver operating curves were generated for the developed model as well as the validation data set, and their respective area under the curve were compared for model fitness.

This study was approved by the Institutional Review Board of Emory University/Children's Hospital of Atlanta. All statistical procedures were completed with SAS Version 9.4 (SAS Institute Inc., Cary, NC).

Results

Demographics

Clinical characteristics of patients admitted with a clinical diagnosis of viral myocarditis are listed in Table 1. Gender was equally distributed, with 52.8% male. The median age at admission was 12.5 years, with a range of 11 days to 17 years old. The median length of hospital stay was 9 days, with an interquartile range of 15 days. The cohort was mostly African American (55.6%), followed by Caucasian (22.2%), Hispanic (13.9%), and Asian/Pacific Islander (5.6%). Insurance type was predominantly Medicaid (63.9%). Five patients had previous cardiac diagnoses at admission, which included recent ventricular or atrial septal defect surgical closure, neurocardiogenic syncope, hypertension, supraventricular tachycardia, and a family history of sudden cardiac death.

History and Physical Examination Findings

The most common symptom at presentation was emesis (38.9%), followed by chest pain and respiratory distress (36.1% each). Other common symptoms were dyspnea (19.4%), fatigue (16.7%) and diarrhea (13.9%). Prodromal symptoms were documented in all but three patients. The most common prodromal symptoms were fever, vomiting, and malaise. A significant portion (69.4%) reported nonspecific prodromal “flu-like” or “stomach bug” symptoms.

On physical exam, patients were commonly tachycardic (average heart rate 119.5 bpm) and had tachypnea (average respiratory rate 28.2). Physical exam findings of congestive heart failure were documented in half of the patients, the most common of which was respiratory distress (36.1%), followed by a gallop,

wheezing or crackles (13.9%). Findings of poor perfusion were not as common, with weak pulses or delayed capillary refill documented in 8% of patients.

Biomarkers (including viral serology and myocardial biopsy)

In Table 2, a summary of the collected data on biomarkers is listed. While none of the biomarkers reached significance in association with poor outcome in univariate analyses, there are some notable patterns. Initial and peak brain naturietic peptide had a weak association between rising levels and poor outcomes. Initial troponin levels and peak troponin had a negative association with poor outcome. C-reactive protein at the initial measurement was positively associated with poor outcome, but the peak measurement was strongly negative.

Myocardial biopsy was obtained in ten cases in total, with half yielding pathology revealing inflammatory evidence. In this sample, positive myocardial biopsy was negatively associated with poor outcome. Polymerase chain reaction testing (PCR) for viral etiology was perform in 27 cases, with only five returning a positive result. All five positive cases were detected with nasal secretions. Two of the cases detected enterovirus, two influenza A, and the remaining was influenza B. Positive viral serology was approaching significant association with poor outcome. Positive IgM titers were detected in five cases. Coxsackie A and Epstein-Barr virus were detected in two cases each, and the remaining case was parvovirus B19. Only one case has both a positive viral serology as well as a positive myocardial biopsy, which each detected a different virus (one coxsackie A, the other influenza A). There were no cases of maternal-fetal transmission.

Other Diagnostic Modalities

Table 2 contains summary information on initial chest x-ray, electrocardiogram (EKG) and echocardiography (echo) data. While none reached significance, any abnormal finding on chest x-ray has a positive association with poor outcome. The most common finding in the initial chest x-rays overall was cardiomegaly. Those patients that had a poor outcome had a higher frequency of pulmonary edema as a finding.

The initial EKG was most likely to be read as sinus tachycardia, followed by ST segment elevation (defined as >2mm in two or more leads and not characterized as early depolarization) in both groups. None of the initial EKG findings reached significance in predicting poor outcome.

There is a significant positive association between a baseline ejection fraction of less than 30% and poor outcome, with those patients 1.56 times more likely to experience poor outcome. Interestingly, those patients that did not have a poor outcome most frequently had either a normal ejection fraction (>50%), or very low (<30%), with less cases in the 30-50% subgroups. There was structural heart disease noted in nine cases, six of which were patent foramen ovale. Only one of the structural heart disease cases experienced a poor outcome.

Cardiac Magnetic Resonance Imaging (cMRI)

Fifteen of the patients received cMRI at some point during their hospitalization. Patients that receive cMRI were older (median 15 vs 11, p=0.05), had shorter hospital length of stay (median 4.5 vs 12.5, p=0.03), higher admission ejection fractions on echo (p=0.03) compared to patients that did not undergo cMRI.

The most common finding was early gadolinium enhancement (n=5), with the rest finding late enhancement or both (n=3 for both groups).

cMRI findings did not predict worse outcome alone, but in multivariate model selection lower ejection fraction, higher BNP, ST segment elevation and evidence of early gadolinium enhancement on cMRI were identified as predictors of requiring heart failure medication upon discharge (p=0.008). Cross validation procedures were not possible due to small sample size.

Treatment

Table 3 contains summary information on therapeutics utilized during the admission, as well as univariate statistics. All of the patients that had a poor outcome received at least one kind of inotrope during admission, opposed to 73.3% of the transplant-free patients. The most frequently used inotropes in the poor outcome subset was epinephrine (all six patients), followed by milrinone and dopamine (83.3% for both). The transplant-free category received milrinone more frequently (70%) than the other inotropes. Anti-arrhythmics were used in all the patients in the poor outcome group, as opposed to 63.3% of the transplant-free group.

Mechanical ventilation was used more frequently in the poor outcome group (83.3% vs. 30%). Extracorporeal membrane oxygenation (ECMO) was utilized in 20% of transplant-free patients, vs 33.3% in the poor outcome group. In the two patients that experience poor outcome and received ECMO, one died, while the other was successfully bridged to cardiac transplant.

Immunomodulators were equally prevalent between the poor outcome and transplant-free groups (83.3% in both). Intravenous immunoglobulin (IVIG) therapy was the most common type in both groups. 1 gm/kg dosing was more prevalent in the poor outcome group, while 2 gm/kg dosing was more common in the transplant-free patients. Other dosing methods were used in four patients, all of whom were in the transplant-free group. Steroids were used more frequently in the patients with poor outcome (66.7% vs 43.3%). Anti-viral medications were administered less frequently (10% in transplant free group vs 16.7% in the poor outcome group).

In univariate analysis, the only treatment modalities that were found to be significant for poor outcome were dopamine administration (p=0.03) and mechanical ventilation (p=0.04).

Clinical data and outcome at one year follow up

Table 4 summarizes data regarding discharge outcomes and follow up. At discharge, 22.2% of patients were transplant-free without heart failure medication, 61.1% were transplant-free with heart failure medication, 8.3% had received a transplant, and 8.3% died during the admission. The transplant group had a higher mean ejection fraction at discharge than the transplant-free group (61.9% vs 49.4%). This finding was borderline significant (p=0.07).

The three patients that had a transplant during the course of admission were all discharged on the same medication regimen, a diuretic and aspirin. Transplant-free patients had more varied regimens, with most receiving an angiotensin-converting-enzyme inhibitor (ACE-I) (60%). Other common medications included

beta-blockers (37%), diuretics (43%), aldosterone inhibitors and aspirin (30% each).

Two-thirds of the transplant patients had a readmission event related to their myocarditis diagnosis in the one-year period following discharge, both occurring within 30 days. 20% of the transplant free patients had a readmission event within one year, most frequently more than three months after discharge (13%).

At one-year post-discharge, nine (30%) of the original discharged cohort were lost to follow up, all of which were in the transplant-free group. The three transplant patients were alive and on heart failure medication at one year. In the transplant-free group, two had died of cardiac conditions (6.7%), and one required a transplant after discharge (3.3%). Of the remaining transplant-free cohort, 40% were alive and on medication, and 20% were alive without medication.

Modeling of discharge outcome

Multivariate model selection was performed to determine which of the many data points collected would be the most clinically useful in predicting poor outcome in this population of patients.

In the first analysis, all 28 variables collected at admission were considered in model selection. Using stepwise selection, a four variable predictor model of poor outcome was developed:

Poor Outcome = Peak CRP x Admission Diastolic BP x Admission ESR x Symptomatic Emesis

The resulting model demonstrated an area under the curve of 85% (Figure 1). Interestingly, none of the four variables were found to have significant odds ratio estimates individually. Further, leave one out cross validation studies found a significant difference between the original and training datasets (p=0.03), with the second receiver operating curve demonstrating an area under the curve of 58%, indicating poor external validity.

Discussion

The purpose of this study was to improve our understanding of the presentation and clinical course of viral myocarditis in a pediatric population. Viral myocarditis is relatively rare in prevalence, and studies identifying risk factors and predictor factors are needed to minimize morbidity and mortality.

The cohort in this study was similar in baseline demographic characteristics as other studies (9). Age was nonspecific, ranging from days old up to 18 years, and gender was fairly equally distributed. The most common race was African American, and of those that whose disease course ended up being transplant or in hospital death, most were African American. This is consistent with large scale studies that have found that African American children are at higher risk of cardiovascular death than other races (10).

The presenting history and physical exam findings were variable, which is common in cases of myocarditis (11). The most common presenting prodromal symptoms were viral in nature, which supports the hypothesis that viral myocarditis represents a post-viral immune mediated response (12). Presenting signs and symptoms at admission were equally as nonspecific, varying between

respiratory distress and gastrointestinal illness. This most likely represents the different viral etiologies that have been found to cause myocarditis. The most common physical exam findings were consistent with acute heart failure, including tachycardia, tachypnea, gallop, wheezing or crackles.

The presenting signs and symptoms of heart failure were usually quickly supported by radiographic evidence, whether through chest x-ray, echocardiography or cMRI. The only finding that was significantly correlated to poor outcome was any abnormal finding on initial chest x-ray, which the most common finding was cardiomegaly. This is an important and useful finding as chest x-ray is usually the first imaging ordered due to it being non-invasive, quickly reported and relatively inexpensive. Further, while not significant, those with poor outcome had a higher frequency of pulmonary edema, which in conjunction with evidence of cardiomegaly, could signal for more aggressive treatment to be started sooner.

Very low ejection fraction on echocardiography was also significantly associated with poor outcome, however that was not an exclusive finding, as there were patients in the transplant-free group that had initial ejection fractions of less than 30%. While low ejection fraction may be a warning sign of more severe disease, it may not be a useful predictor for those that will eventually require a heart transplant or die.

While chest x-ray proved to be a useful diagnostic modality, EKG was not significantly associated with poor outcome, which is consistent with previous studies (13). While EKG may not be useful in prognosticating death or the requirement of transplantation, it may be more useful in predicting which patient is

more likely to experience arrhythmia during hospitalization or after discharge. Future studies in larger cohorts should investigate the value of EKG findings in acute viral myocarditis and their implication in development of arrhythmogenic disease post hospital discharge.

Cardiac MRI was a less frequently employed modality, probably due to necessitating patient cooperation, requiring contrast administration, and transport to the MRI scanner itself which is difficult in patients requiring more aggressive interventions like vasopressors or ECMO. This was substantiated by the population that received cMRI in this cohort, as they were older, had shorter lengths of stay, and high admission ejection fractions, thus representing a more stable patient that could be transported and tolerate the procedure. These characteristics could also represent that cMRI is used more frequently in patients whose etiology of acute heart failure is unclear, warranting more imaging to try to come to a conclusive diagnosis. The more frequent finding of early gadolinium enhancement was at odds with the existing literature, which has found in several studies that late enhancement is more associated with active myocarditis and higher all-cause mortality (14). Further, model selection procedures in this study found that early enhancement with baseline EKG findings of ST segment elevation were the most sensitive predictors of patients requiring heart failure medication at discharge. The contradictor nature of these results can be most likely attributed to small sample size, as only 15 patients received cMRI, and were already biased towards those that were more stable. However, positive findings on cMRI did not significant change the likelihood that the patient would receive IVIG. While cMRI may be useful in

predicting morbidity and mortality, its cost effectiveness may be in question if the results from the imaging may not change a clinicians likelihood to use more expensive therapies. Due to the cost of MRI procedures, further study should be done to determine if the findings on cMRI could be detected by other non-invasive or less expensive means.

Myocardial biopsy, which is still considered gold standard for the diagnosis of viral myocarditis, had about a 50% positive yield for histological evidence of inflammation in those that underwent the procedure in this cohort. While this represents a higher rate of positivity than some other studies, here we found that it was negatively correlated with poor outcome. It is possible that those patients that clinicians thought would be good candidates for the procedure also were those that they considered as good candidates for more aggressive treatment, resulting in a higher likelihood of good outcome simply due to their medical stability versus severity of disease. However, the small number of patients that ultimately underwent biopsy limits forming a robust hypothesis in this case. Also, the Dallas criteria have been found to have a high degree of inter-observer variability, contributing to the questionable nature of this finding.

PCR was performed on blood or nasal secretions in most cases, with very low yield. Interestingly, all five of the positive cases came from nasal secretions. This is contrary to what other studies have found, where blood sample testing is generally more sensitive (15)(16). The resulting viruses were also atypical for the type usually detected in these cases, which is generally parvovirus B19 or HHV-6. It is possible that these results represent contamination with other virus in the

nasopharynx due to the fact that the samples were nasal secretions. The lower rate of positivity could also be attributable to evidence that PCR testing tends to have higher sensitivity in younger populations (<13 months of age), and only four cases in this cohort were. None of the cases that had PCR had myocardial biopsies taken.

Viral serology also had low yield in this cohort, with only five positive IgM results out of 21 patients that underwent testing. Despite this low number of cases, positive serology was associated with poor outcome. Contrasting the nasal secretion PCR results, however, the titers resulted in a completely different set of detected virus. Further, only one case had both positive PCR results and positive IgM titers, which detected two different viruses. Only one of the cases with positive titers underwent myocardial biopsy, which was also positive for evidence of inflammation. Because of the small sample size, it is difficult to draw conclusions as to the utility of these tests. In this cohort, the significance of positive IgM titers association versus the lack of association with PCR testing could represent the presence of significant immune response to the infection resulting in worse outcome. There would be great utility in investigating which of these represents a more sensitive and specific test to more clearly guide medical decision making.

In the analysis of treatment modalities in poor outcome, only dopamine administration and mechanical ventilation resulted as significantly associated. The odds ratios were very high (13.75 and 11.67 respectively), indicating a very strong effect. This result is clinically realistic, as those that had an initial presenting picture of fulminant heart failure are more likely to require aggressive inotropic support and are more likely to experience respiratory failure secondary to the cardiac

failure. The finding that all of the patients that had poor outcome require vasopressor support in the form of epinephrine also supports these findings. None of the immunomodulators, including IVIG of any dose were associated with outcome. While there seemed to be a pattern of higher IVIG dosages used in those that experienced transplant free discharge, the lack of significant association may be due to the variable usage between providers as the clinical utility of these treatments is still controversial and under investigation (17).

While none of the presenting symptoms or testing were predictive in a univariate context other than positive viral titers and low ejection fraction, multivariable logistic regression for model selection yielded a collection of these characteristics with fairly good predictive value overall initially. The resulting model is also fairly simple to use, given that the four factors remaining are available in nearly every patient presenting with acute heart failure in an emergent setting. Despite the models promising initial diagnostics, leave one out cross validation resulted a poor area under the curve, demonstrating the models poor performance in external validity. Whether this represents that the model is a poor fit, or just difficult to validate with the limited data at hand, is hard to tell. The fact that the four variables in the model were not significant in univariate analysis suggests that the model may well be a poor candidate in a larger clinical context.

At discharge, there was an overall survival rate of 92%. The heart failure treatment regimens varied greatly among cases, though most frequently employing an ACE inhibitor and/or diuretic, which are accepted components of symptomatic heart failure treatment. Interestingly, aldosterone inhibitors and beta blockers, two

of the classes of heart failure medications that have been found to prolong patient survival along with ACE inhibitors, were used in only 30-37% of cases. The variable use of regimens is most likely due to the continued controversy in which pharmacologic therapy is most effective while minimizing side effects (18). Research in this area is seriously lacking, as seen by the absence of any evidence recommendations greater than a level B in recent guidelines, with the main issue being a lack of large randomized clinical trials (19).

Of the three children that died during admission, two died in the first 48 hours of presentation. This represents a limitation in our understanding of effective therapeutics in this group, as most did not survive long enough to receive treatment, or assess their response to any treatment they did receive. The patients that survived to cardiac transplantation during the initial admission had the best survival rate at one year of the remaining groups, in which all three were alive and on medication. This seemingly paradoxical finding has been substantiated in many previous studies, which have found that patients presenting with fulminant myocarditis are the ones that are most likely to experience long term survival (20). There was a lost to follow up rate of 30% in the transplant-free survival group, which is expected as this pediatric center accepts transfers from a large geographical area, and it is likely that a subsection will seek follow up treatment closer to their residence. 40% of the children that were discharged without transplantation were still being treated for chronic heart failure at one year, illustrating the long term impact of this condition. Further, three of the patients that had been discharged on heart failure medication went on to have poor outcome by

the one year follow up mark, with one requiring heart transplantation and two ultimately dying from sudden cardiac death or acute fulminant heart failure. Only 18% were alive and not receiving heart failure treatment. A pattern in survival seen in this study have been well documented in others, where those who survive fulminant heart failure or had minimal left ventricular dysfunction at initial presentation are the patients that have the greatest chance of survival, while those outside of these classification follow a variable and often progressive path to dilated cardiomyopathy and ultimately heart transplant or death.

Strengths of this study include the extensive collection of a variety of data points on each case, representing a clear natural history of this fairly rare condition all the way to the one year follow up (where available). The comprehensive nature of the data collection allowed for comparisons between many different aspects of the presentation, treatment and management of the disease.

However, while the sample size in this study was comparable in that of some others, it was ultimately not big enough to power all of the analyses as planned. The lack of cases could explain some of the seemingly contradictory findings in this study, such as the finding of significant association of early gadolinium enhancement in cMRI and poor outcome discussed previously. The smaller sample size could be partially explained by the selection of cases from ICD coding, which could have missed subclinical cases that were miscoded or used a more generic coding (such as chest pain) that was not picked up by our search. This is turn could have biasing our results to the cases that were severe enough to warrant recording myocarditis as an assessment. The lack of definitive criteria for the diagnosis of viral myocarditis

could help this issue in forth coming studies. A related problem that is common to many studies that build cohorts of patients with conditions with high mortality is a left truncation of the severity of cases, where there is likely a number of patients that died before a diagnosis could be made.

Another limitation, for the variables recording management decision in particular, is that all the cases recorded in the cohort were from one institution. Some of the findings pertaining to the management and treatment decisions could be influenced simply by institutional culture, and in future studies it would be useful to compare patterns across different institutions and patient demographic compositions. Because of the rarity and complexity of viral myocarditis in the pediatric population, a multi-institutional longitudinal cohort would help to resolve many of these issues.

Pediatric viral myocarditis continues to be a challenging condition to identify and treat. Future directions should emphasize meaningful diagnostic criteria, as well as high value testing. The continued uptake of cMRI in the diagnosis of myocarditis could represent a better gold standard, versus the current standard of endomyocardial biopsy. Identifying biomarkers that have significant prognostic abilities can assist health care providers to quickly identify and triage cases, hopefully leading to faster and more effective treatment. As the diagnostic and therapeutic techniques improve with time and study, it will be useful to follow the survivors in longer longitudinal cohorts to determine their risk for other cardiac disorders such as arrhythmias and other cardiomyopathies.

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Table 1: Characteristics of Patients Diagnosed with Viral Myocarditis, 2008-2014

Characteristic	**Overall**	Transplant-Free	Poor Outcome
	n=36	*n= 30*	*n= 6*
Male Gender (n,%)	19 (52.8)	18 (94.7)	1 (5.3)
Age at Admission in Years (Median, IQR)	12.5 (10.5)	15.5 (2.5)	11.5 (14.0)
Length of Stay (Median, IQR)	9.0 (15.0)	8.0 (11.0)	31.0 (50.0)
Race (n,%)			
Caucasian	8 (22.2)	8 (100)	0 (0)
African American	20 (55.6)	15 (5.0)	5 (25.0)
Hispanic/Latino	5 (13.9)	4 (80.0)	1 (20.0)
Asian/Pacific Islander	2 (5.6)	2 (100)	0 (0)
Other	1 (2.8)	1 (100)	0 (0)
Insurance Type (n,%)			
Medicaid	23 (63.9)	18 (78.3)	5 (21.7)
Private	10 (27.8)	10 (100)	0 (0)
Other Government	1 (2.8)	1 (100)	0 (0)
Other/Unknown	2 (5.6)	1 (50.0)	1 (50.0)
Previous Cardiac Medical History	5 (13.9)	4 (80.0)	1 (20.0)

Table 2: Univariate Analysis of Clinical Parameters and Poor Outcome

Clinical Parameter	Transplant-Free	Death or Transplant				
	n=30	*n=6*	**RR**	**95% CI**		***p* value**
				Lower	*Upper*	
Baseline Ejection Fraction (n, %) ♦						
>50	10 (33.3)	0 (0)	ref			
40-50	4 (13.3)	1 (16.7)	1.17	0.86	1.58	0.23
30-40	7 (23.3)	0 (0)	n/a			
<30	9 (30.0)	5 (83.3)	**1.56**	**1.05**	**2.30**	**0.04**
Initial BNP (n, %) ✝						
<1000	17 (56.7)	2 (33.3)	ref			
>1000	13 (43.3)	4 (66.7)	1.17	0.86	1.59	0.21
Peak BNP (n, %) ✝						
<1000	15 (50.0)	2 (33.3)	ref			
>1000	15 (50.0)	4 (66.7)	1.12	0.84	1.49	0.27
Initial Troponin (n, %) ✝						
<1	13 (43.3)	5 (83.3)	ref			
>1	17 (56.7)	1 (16.7)	0.76	0.56	1.04	0.08
Peak Troponin (n, %) ✝						
<1	13 (43.3)	5 (83.3)	ref			
>1	17 (56.7)	1 (16.7)	0.76	0.56	1.04	0.08
Initial CRP (n, %) ✝						
<10	26 (86.7)	4 (66.7)	ref			
>10	4 (13.3)	2 (33.3)	1.30	0.73	2.33	0.26
Peak CRP (n, %) ✝						
<10	2 (6.7)	1 (16.7)	ref			
>10	28 (93.3)	5 (83.3)	0.40	0.04	3.74	0.43
Initial chest x-ray (n, %) ♦						
Normal	8 (26.7)	0 (0)	ref			
Cardiomegaly	12 (40.0)	4 (66.7)	1.33	1.00	1.77	0.13
Pulmonary edema	9 (30.0)	4 (66.7)	1.44	1.01	2.08	0.09
Pleural effusion	7 (23.3)	2 (33.3)	1.29	0.91	1.82	0.17
Abnormal Initial EKG (n, %) ♦						
Normal Sinus	9 (30.0)	1 (16.7)	ref			
ST Segment Depression*	4 (13.3)	0 (0)	0.91	0.75	1.10	0.55
ST Segment Elevation*	10 (33.3)	2 (33.3)	1.50	0.29	7.88	0.41
Low QRS voltage	3 (10.0)	1 (16.7)	1.54	0.37	6.35	0.48
Sinus Tachycardia	11 (36.7)	3 (50.0)	1.90	0.33	11.02	0.60
Endocardial Biopsy (n, %) ✝	4 (13.3)	1 (16.7)				
Negative	3 (10.0)	2 (33.3)	ref			
Postive	4 (13.3)	1 (16.7)	0.75	0.32	1.74	0.51
Viral PCR, any source (n, %) ✝						
Negative	18 (60.0)	4 (66.7)	ref			
Postive	4 (13.3)	1 (16.7)	1.02	0.63	1.65	0.93
Viral Titers (n, %) ✝						
Negative	15 (50.0)	2 (33.3)	ref			
Positive	2 (6.7)	3 (50.0)	**2.21**	**0.74**	**6.54**	**0.05**

♦ Mantel-Hanzel Chi-Square Analysis for zero cells ✝ Fishers Exact Test for expected cell counts less than five

* Defined as >2 mm in two or more leads and not early depolarization

Table 3: Univariate Analysis of Treatment Modalities utilized during Admission by Discharge Outcome

Treatment	Transplant-Free	Death or Transplant				
	n=30	*n=6*	**OR**	**95% CI**		***p* value**
				Upper	*Lower*	
Inotropes						
Milrinone	21(70.0)	5 (83.3)	2.14	0.22	21.05	0.51
Dopamine	8 (26.7)	5 (83.3)	**13.75**	**1.39**	**136.38**	**0.03**
Dobutamine	3 (10.0)	2 (33.3)	4.50	0.57	35.83	0.16
Digoxin	1 (3.3)	1 (16.7)	5.80	0.31	108.61	0.24
Epinephrine	15 (50.0)	6 (100)	n/a			
Mechanical Ventilation	9 (30.0)	5 (83.3)	**11.67**	**1.19**	**114.59**	**0.04**
ECMO	6 (20.0)	2 (33.3)	2.00	0.29	13.62	0.48
Antiarrythmics	19 (63.3)	6 (100)	n/a*			
Immunomodulators	25 (83.3)	5 (83.3)				
IVIG	23 (76.7)	5 (83.3)	1.52	0.15	15.30	0.72
Steroids	13 (43.3)	4 (66.7)	2.62	0.41	16.54	0.31
Anti-viral medication	3 (10.0)	1 (16.7)	1.80	0.15	20.99	0.64
IVIG Dosing						
Any Dose	23 (76.7)	5 (83.3)	1.522	0.151	15.296	0.7214
1 gm/kg	5 (16.7)	3(50.0)	n/a*			
2 gm/kg	14 (46.7)	2 (33.3)	n/a*			
Other	4 (13.3)	0 (0)	n/a*			

* Model unable to converge

Table 4: Discharge Outcomes and One Year Follow-Up

	No Transplant	Transplant
	n=30	*n=3*
Heart Failure Medication at discharge		
ACE-I	18 (60.0)	0
Digoxin	1 (3.3)	0
Beta Blocker	11 (36.7)	0
Aldosterone Inhibitor	9 (30.0)	0
Diuretic	13 (43.3)	3 (100)
Inotrope	1 (3.3)	0
Anti-arrhythmic	2 (6.7)	0
Aspirin	9 (30.0)	3 (100)
EF at discharge (Mean, SD)	49.4% (17.7)	61.9% (7.3)
Readmission within one year	6 (20.0)	2 (66.7)
None	24 (80.0)	1 (33.3)
0-30 Days	2 (6.7)	2 (66.7)
31-90 Days	3 (10.0)	0
91-365 Days	4 (13.3)	0
Outcome at one year		
Alive (not on medication)	6 (20.0)	0
Alive (on medication)	12 (40.0)	3 (100)
Death	2 (6.7)	0
Tranplant	1 (3.3)	0
Lost to follow up	9 (30.0)	0

Figure 1: (a) ROC Curve for Developed Predictive Model and (b) ROC Curve Comparison in Leave One Out Cross Validation