

# Myocarditis in Children: Impact of Early Presentation on Disease Outcomes at a Single Tertiary Center in Saudi Arabia

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**Purpose:** Myocarditis is the inflammation of the heart muscle and can be caused by a variety of infections, incendiary diseases, and pollutants. It is challenging for an emergency pediatrician to have a sufficiently high degree of suspicion for myocarditis to avoid diagnostic delay given the broad overlap of myocarditis symptoms with other disease processes. The study aimed to evaluate the impact of early presentation and diagnosis on the outcomes of acute myocarditis in children.

**Patients and Methods:** We performed a retrospective analysis of the complete records of 80 pediatric patients diagnosed with acute myocarditis between 2015 and 2019 at a single tertiary center in Saudi Arabia. Patients were two weeks to 14 years of age and were admitted to the pediatric intensive care unit (PICU) for various sequelae of myocarditis. Data from routine clinical and laboratory investigations were collected.

**Results:** The incidence of delayed presentation at the hospital after the onset of symptoms of myocarditis was 42.5%. A total of 22 (27.5%) patients expired during their hospital stay. There was marginally significant association of earlier presentation with in-hospital survival (80.4% vs 61.8%) and delayed presentation with higher proportion of in-hospital mortality (38.2% vs 19.6%,  $p=0.064$ ). The rate of mechanical ventilator was also marginally significant in delayed presentation ( $p=0.068$ ). Shock and multisystem organ failure were the significantly associated manifestations of delayed acute myocarditis presentations. Length of stay in PICU was also significant in delayed presentation group. The impact of presenting symptoms, ECG findings, and use of mechanical ventilator was not significantly associated with delayed presentation.

**Conclusion:** An earlier presentation may have a substantial impact on overall prognosis and length of PICU stay and may lead to comparatively lesser frequency of mechanical ventilation use.

**Keywords:** acute myocarditis, emergency pediatric care, early presentation, prognosis

## Introduction

Myocarditis is the inflammation of the heart muscles that is caused by a variety of infections, incendiary diseases, and pollutants. Pediatric myocarditis presentations range from minor mild upper respiratory tract infections with chest pain to cardiogenic shock. Given the diversity of symptoms that overlap with numerous disease processes, it is challenging to promptly and accurately diagnose myocarditis.<sup>1</sup> Hence, it is important to establish a high index of suspicion for myocarditis to avoid a delay in diagnosis, as most pediatric myocarditis mortalities occur within 72 hours of admission.<sup>2</sup>

Clinical manifestations and echocardiographic abnormalities can arise later in the disease process, creating challenges in making an accurate diagnosis of myocarditis. Thus, patients may have acceptable exercise tolerance early on, with systolic abnormalities occurring only in the late stage of illness.<sup>3</sup> The most common electrocardiogram (ECG) findings in a study of 24 pediatric myocarditis cases were abnormal Q waves (67%), negative T waves (63%), wide QRS waves (58%), and ST segment abnormalities (46%).<sup>4</sup>

Worldwide, the annual incidence of pediatric myocarditis is between 0.26 and 2 cases per 100,000.<sup>5–7</sup> In Korea, the incidence of pediatric myocarditis increased from 1.4 cases per 100,000 children in 2007 to 2.1 cases per 100,000 children in 2016.<sup>8</sup> There is no national record on the exact incidence of myocarditis in Saudi pediatric population, and all the existing data are extrapolated from studies on adults.<sup>9</sup> Only one single-center, retrospective study reported that most of the mortalities due to primary pediatric myocardial disease occurs in the first year of life, while the three-year survival rate was 78%.<sup>10</sup>

The outcomes for patients diagnosed with myocarditis depend on multiple factors including the severity of symptoms, time from symptom onset to hospital presentation, quality of care, expertise of care providers, and the time to initiation of appropriate treatment. This study aimed to evaluate the impact of early presentation and diagnosis on acute myocarditis outcomes in children. To this end, we analyzed a dataset retrospectively collected from hospitalized patients with myocarditis to identify disease manifestations and the effect of early diagnosis and appropriate treatment on pediatric outcomes. This study may provide valuable insight for pediatricians and emergency physicians in the diagnosis and treatment of pediatric myocarditis.

## Materials and Methods

The complete medical records of 80 consecutive pediatric patients admitted to the PICU of the King Fahd Hospital of the University (KFHU) due to acute myocarditis over a period of 5 years from 2015 to 2019 were retrieved. The patient ages ranged from two weeks to 14 years. The diagnosis of Acute Myocarditis was made based on Sagar et al Diagnostic Classification for Patients With Probable acute myocarditis.<sup>11</sup> The diagnosis of acute Myocarditis is warranted if patient had history of viral illness, signs and symptoms of acute heart failure, left ventricular dysfunction, other abnormal echocardiography (ECG) findings (eg, ST elevation, T inversion, or conduction block), laboratory data (eg, cardiac enzyme and C-reactive protein levels), and an absence of personal or family history of cardiomyopathy.<sup>11</sup> Of note, definite diagnosis of myocarditis requires histological or immunohistological confirmation which was deferred due to its inapplicability. Patients were admitted to the PICU for a core temperature  $>38.5^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , respiratory distress, shock, gastrointestinal (GI) symptoms, chest pain, palpitations, multisystem organ failure, arrhythmias and dehydration. Data from routine clinical and laboratory investigations, including ECG, were available. Tachycardia (mean heart rate  $>2$  standard deviations [SD] above normal for age) or bradycardia (mean heart rate  $<10$ th percentile for age) were also documented.

The in-hospital outcome of pediatric acute myocarditis patients included mortality, length of hospital stay, and length of PICU stay. Early presentation was defined as admission within the first 72 hours of symptom onset, whereas presentation  $>72$  hours after symptom onset was considered a delayed presentation. Patients who were expired within the first 24 h, had cardiac arrest before PICU admission, were admitted to the PICU with known cardiac lesions (either congenital or acquired), had known or suspected metabolic diseases or syndromes, exposure to cardiotoxic agents, or chronic arrhythmia, and had incomplete or missing data were excluded from this study. Cardiac magnetic resonance imaging (MRI) were deferred given the patients' instability and the fact that the results would not change acute management. Also, end myocardial biopsy was not performed due to its unavailability in our institute.

Data analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 22.0. All categorical variables including sex, type of presentation, symptoms, ECG findings and in-hospital outcomes were presented as frequencies and percentages. Chi-square test was used for comparison of proportions of categorical outcome variables between earlier and delayed presentations. Age and length of hospital and PICU stays are presented as mean $\pm$ SD. Unpaired *t*-tests were used to compare length of hospital/PICU stay by presentation time and in-hospital outcomes as appropriate for normally distributed data. Kaplan–Meier survival analysis was performed to determine the probability of survival in relation to the length of hospital or PICU stay.  $P\leq 0.05$  was considered statistically significant.

This study was approved by the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University (IRB-PGS -2021-01-127). Based on the IRB's Policies of Imam Abdulrahman Bin Faisal University, requirement of patients' consents was waived given the retrospective nature of the study. Data confidentiality was ensured following the Declaration of Helsinki principles.

**Table 1** Impact of Early versus Delayed Presentation on Myocarditis Patients' Characteristics and In-Hospital Outcome

Variables	Total (n = 80)	Presentation		P-value
		Early (n= 46)	Delayed (n= 34)	
Sex				
Male	58 (72.5)	34 (73.9)	24 (70.6)	0.742
Female	22 (27.5)	12 (26.1)	10 (29.4)	
Reason for admission				
Respiratory distress	33 (41.3)	23 (50.0)	10 (29.4)	0.064
Shock	12 (15.0)	1 (2.2)	11 (32.4)*	0.001
Gastrointestinal symptoms	9 (11.2)	8 (17.4)	1 (2.9)	0.071
Chest pain	8 (10.0)	3 (6.5)	5 (14.7)	0.228
Palpitations	6 (7.5)	5 (10.9)	1 (2.9)	0.233
Multisystem organ failure	5 (6.2)	0 (0)	5 (14.7)*	0.012
Arrhythmia	3 (3.8)	3 (6.5)	0 (0)	0.258
Other	4 (5.0)	3 (6.5)	1 (2.9)	0.633
Ventilator				
Yes	33 (41.2)	15 (32.6)	18 (52.9)	0.068
No	47 (58.8)	41 (67.4)	16 (47.1)	
ECG findings				
Sinus tachycardia/low voltage QRS	56 (70.0)	34 (73.9)	22 (64.7)	0.592
Arrhythmia	19 (23.8)	10 (21.7)	9 (26.5)	
Sinus bradycardia	5 (6.2)	2 (4.4)	3 (8.8)	
In-hospital outcome				
Expired	22 (27.5)	9 (19.6)	13 (38.2)	0.064
Survived	58 (72.5)	37 (80.4)	21 (61.8)	

Note: \*Denotes statistical significance,  $p < 0.05$ .

## Results

Of the 80 children with myocarditis included in the study, there were 58 (72.5%) and 22 (27.5%) boys and girls, respectively. The average age of the children was  $6.0 \pm 4.2$  (range: 0–14) years. The primary reasons for hospital admission were respiratory distress ( $n=33$ ; 41.3%), shock ( $n=12$ ; 27.5%), GI symptoms ( $n=9$ ; 11.2%), chest pain ( $n=8$ ; 10%), palpitations ( $n=6$ ; 7.5%), and multisystem organ failure ( $n=5$ ; 6.2%). There were 46 (57.5%) early and 34 (42.5%) delayed presentations. Total 22 (27.5%) mortalities took place during the hospital stay, whereas 58 (72.5%) children survived and were successfully discharged. The mean length of hospital stay was  $12.4 \pm 2.3$  days (range: 7–21). There was substantial impact of earlier presentation on in-hospital survival (80.4% vs 61.8%), although proportion of in-hospital mortality (38.2% vs 19.6%,  $p=0.064$ ) was marginally significant in delayed presentation than earlier presentation group. The rate of mechanical ventilator use was also marginally significant in delayed presentation ( $p=0.068$ ). Shock and multisystem organ failure were the significantly associated manifestations of delayed presentations ( $p<0.05$ ) as shown in (Table 1). Of note, all of the study cohort required inotropic support.

The length of hospital and PICU stays were not significantly associated with presentation time after symptom onset ( $p>0.05$ ). The difference in hospital stay length was also not significantly different between expired and surviving patients ( $p=0.597$ ). However, surviving patients had significantly shorter stays in the PICU compared to expired patients ( $p<0.001$ ), as detailed in (Table 2). The Kaplan–Meier mean survival time in the hospital was 15.9 (95% confidence interval [CI]: 14.4–17.4) days, with the highest probability of mortality ( $\geq 70\%$ ) within the first 14 days of admission (Figure 1). The mean survival time in the PICU was 12.6 (95% CI: 11.2–14.1) days, with the highest probability of mortality within the first 8 days of admission (Figure 2).

**Table 2** Mean Difference in Length of Stay in Relation to Presentation and Outcome

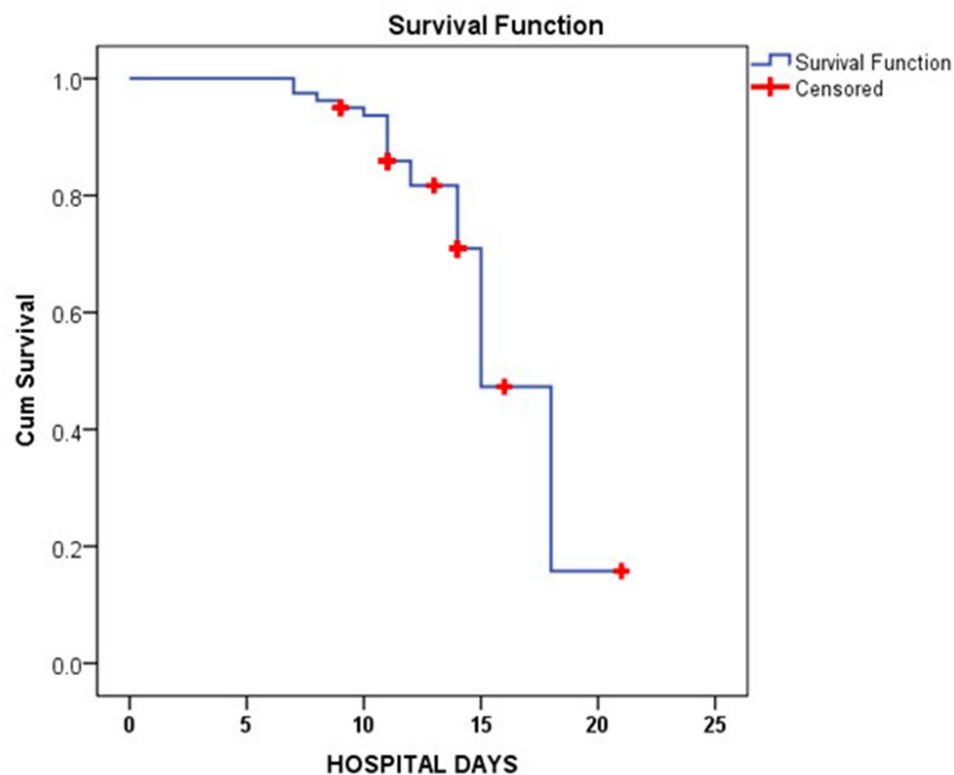
Variables	Length of Stay (Days)			
	Hospital	P-value	Pediatric Intensive Care Unit (PICU)	P-value
Presentation				
Early	12.67±2.13	0.352	7.48±2.93	0.295
Late	12.18±2.62		8.24±3.49	
In-hospital outcome				
Expired	12.14±3.04	0.597	10.32±3.72	<0.001*
Survived	12.59±2.04		6.84±2.35	

Note: \*Denotes statistical significance,  $p < 0.05$ .

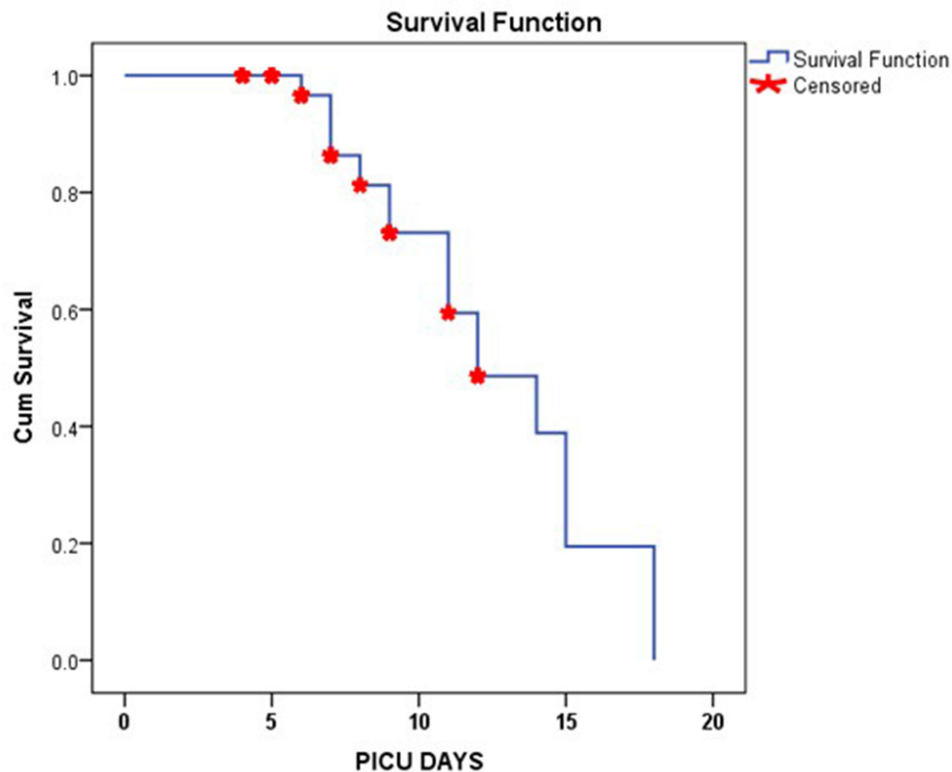
## Discussion

Early presentation after symptom onset for both myocarditis and other conditions facilitates prompt diagnosis and treatment, which may affect clinical outcomes. Our study demonstrates that early presentation after onset of acute myocarditis symptoms was associated with increased in-hospital survival and a decreased proportion of in-hospital mortality in pediatric patients. Our results were consistent with a previous study by Chang et al<sup>2</sup> who found that of 94 patients diagnosed with myocarditis over a 12-year period, 16 (17%) patients died; 12 (75%) of these patients died in the first 72 hours after admission.

The overall survival rate in our study was 72.5% which is less than the 78% survival rate reported by Azhar et al<sup>10</sup> and the remarkably higher survival rate of 86% (95% CI: 65–96) reported Abe et al.<sup>4</sup> Klugman et al reported a 92% survival rate for acute myocarditis, and mortality was confined to those who presented with severe illness and



**Figure 1** Survival analysis of acute myocarditis in hospital. The mean survival time in hospital was 15.9 (95% confidence interval: 14.4–17.4) days, highest probability of mortalities (70% or above) within first 14 days.



**Figure 2** Survival analysis of acute myocarditis in pediatric intensive care unit. The mean survival time in PICU was 12.6 (95% confidence interval: 11.2–14.1) days, highest probability of mortalities (70% or above) within first 8 days.

required prompt extracorporeal membrane oxygenation (ECMO) and other complex therapies.<sup>12</sup> The reason for the comparatively lower survival rate in our study may be due to the delayed health-seeking behavior of parents in case of persistent symptoms in their children. Further targeted education community level is needed to address such culturally false behavior. In addition, the unavailability of ECMO in our institute during the study period may contributed to such survival rate.

Since pediatric patients with acute myocarditis present with inconsistent symptoms and disease severities, they often require the use of more interventions and expire more often than children with other diagnoses. In our study, respiratory distress, shock, and GI symptoms were the major clinical manifestations of acute myocarditis in our cohort, while shock and multisystem organ failure were the significantly associated manifestations of delayed presentations ( $p < 0.05$ ). Toma et al<sup>13</sup> also reported respiratory (80%) and GI (20%) symptoms were common in acute myocarditis. However, unlike our study, previous investigations have found that fever is the most common non-specific symptom (59.6%), whereas heart failure (30.3%) and cardiogenic shock (4.5%) were the most common specific symptoms at the time of acute myocarditis symptom onset.<sup>14</sup> Shu-Ling et al<sup>15</sup> reported a 10-year case series and described symptoms consistent with those found in our study. However, they reported that GI symptoms were very common (59.0%) in their patients and respiratory symptoms were less common (23.1%), whereas cardiac symptoms were only found in 10.3% of their study population. Furthermore, decreased appetite and high core temperature were a shared finding across age groups but were found to be more common in older children than infants. Cardiopulmonary collapse was most prevalent among infants. Hsiao et al<sup>16</sup> reported three significant predictors of poor outcome in acute myocarditis: 41% of patients had GI symptoms (odds ratio (OR)=12.5,  $p=0.027$ ), 30% had hepatomegaly (OR=8.5,  $p=0.044$ ), and 15% had hypotension (OR=1.53,  $p=0.025$ ).

Previous studies of myocarditis have reported that the condition is more common in young males,<sup>7,17,18</sup> which is consistent with our results (>70% male patients). The average hospitalization duration in our study was  $12.4 \pm 2.3$  days, which was consistent with the previously reported  $11.42 \pm 21.67$  days,<sup>8</sup> but considerably less than the  $18.52 \pm 13.47$  days

reported by Hsiao et al.<sup>16</sup> The length of hospital stay may vary according to the severity of disease, length of time on a mechanical ventilator, and other ICU therapies.<sup>19</sup>

Our study included a medium sample population of pediatric patients with acute myocarditis in a shorter timespan than previous work. Thus, designing prospective studies to identify acute myocarditis with complex clinical manifestations at presentation will be valuable to improve patient outcomes across the spectrum of disease severity. Also, our study has a major obstacle related to unavailability of biopsy to support the diagnosis of definite acute myocarditis. Finally, since most of our statistical measures were not statistically significant ( $p > 0.05$ ), we could not perform logistic regression analysis to evaluate the predictors of poor in-hospital outcomes in relation to delayed presentation after symptom onset.

This study concluded that shock and multisystem organ failure were the significantly associated manifestations of delayed presentations. Length of stay in PICU was also significant in delayed presentation group. Although the impact of presenting symptoms, ECG findings, and use of mechanical ventilator was not significantly associated with delayed presentation, nevertheless, an earlier presentation, may have had a substantial impact on overall patient's prognosis, length of PICU stay and may lead to comparatively lesser frequency of mechanical ventilation use.

## Disclosure

The author reports no conflicts of interest in this work.

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