

ORIGINAL ARTICLE

Clinical Presentation, Prognostic Factors, and Outcomes of Pediatric patients Diagnosed with Acute Myocarditis: A 10 Year Experience from the Emergency Department of a Tertiary Care Hospital, Pakistan

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ABSTRACT

BACKGROUND

Myocarditis is a rare inflammatory disease of the myocardium with an annual incidence of 1 to 2 per 100,000, with in-hospital mortality identified by one study as high as 24%⁽¹⁾. Patients with myocarditis present with variable signs and symptoms ranging from subclinical disease to arrhythmia, heart failure, and sudden cardiac arrest. This study is aimed to determine the clinical presentations and outcomes of children diagnosed with acute myocarditis in the emergency department of a tertiary care hospital.

METHODS

This single-center cross-sectional study was conducted in the Emergency Department (ED) of the Aga Khan University Hospital, Karachi, Pakistan, from January 2005 to December 2015. All children from six months to sixteen years of either gender admitted with a probable or definitive diagnosis of acute myocarditis from the emergency department were included. All the data were entered and analyzed on SPSS v22. The continuous variables were expressed as mean $\pm$ SD and frequencies, and percentages were computed for categorical data. Univariate and multivariate analysis was

done, and a p-value of less than 0.05 was considered significant.

RESULTS

This single-center cross-sectional study was conducted in the Emergency Department (ED) of the Aga Khan University Hospital, Karachi, Pakistan, from January 2005 to December 2015. All children from six months to sixteen years of either gender admitted with a probable or definitive diagnosis of acute myocarditis from the emergency department were included. All the data were entered and analyzed on SPSS v22. The continuous variables were expressed as mean $\pm$ SD and frequencies, and percentages were computed for categorical data. Univariate and multivariate analysis was done, and a p-value of less than 0.05 was considered significant.

CONCLUSION

Myocarditis in pediatric patients has higher mortality and may present with acute onset of symptoms that may be vague and overlapping. Early identification and prompt management by experienced pediatric emergency physicians may reduce morbidity and mortality.

KEYWORDS

Myocarditis, Pediatric, Clinical Presentation

INTRODUCTION

Myocarditis is an uncommon, acute disease with an infectious or immunologic cellular sequence etiology but can be devastating with life-threatening potential. Histologically myocarditis is characterized by focal or diffuse myocardial inflammation and is one of the most typical causes of acute heart failure. As myocarditis has a wide variety of clinical presentations, an initial diagnosis in ED needs to be made on clinical suspicion.

⁽²⁾ Though unexpected death frequently occurs, while most cases present prodromal symptoms, ^(3,4) long-term comorbidities may be significant.

Patients with myocarditis present with variable signs and symptoms ranging from subclinical disease to arrhythmia, heart failure, and sudden cardiac arrest. ⁽⁵⁾ Diagnosis is challenging because most patients, especially young children, present with nonspecific symptoms like cough, shortness of breath, diarrhea, and vomiting, masquerading the diagnosis as gastrointestinal and respiratory infections. ⁽⁶⁾ Currently, no single clinical presentation confirms the diagnosis of myocarditis with absolute certainty. Instead, an integrated approach

should be used to diagnose the disease and guide treatment, including history, clinical assessment, and noninvasive test results.⁽³⁾ Respiratory symptoms are one of the common presentations; however, characterizing features like unexplained tachycardia, tachypnea, viral prodromal low volume pulses etc., could facilitate earlier diagnosis and help prevent misdiagnosis.

There are limitations in making accurate clinical diagnoses, which leads to a missed diagnosis and bad outcomes in terms of survival and residual cardiac functions. Dallas classification depends on histological characteristics. However, biopsy or cardiac MRI facilities may not be available in resource-limited countries like Pakistan. Hence, clinical diagnosis depends on suggestive clinical history, clinical parameters, ECG changes, ECHO findings, Troponin level, etc. Thus, we use probable diagnostic criteria as determined by a pediatric emergency physician or cardiologist, based on clinical history combined with supporting physical examination and investigation results, either in the absence of an endomyocardial biopsy or in the presence of negative biopsy results for the diagnosis of myocarditis in making the diagnosis of myocarditis.^(6,3)

Pediatric myocarditis mortality ranges from 25% (children) to 75% (infants).⁽⁷⁾ Mortality among patients with confirmed myocarditis is common in children who were initially missed clinically⁽⁸⁻¹⁰⁾ hence a high index of suspicion for a timely diagnosis has to be in mind.

The objective of this study was to observe data from ten years of pediatric cases with clinical presentation and outcome of children to facilitate early diagnosis and timely and effective care delivery to prevent mortality and morbidity among children presenting with acute myocarditis to the emergency department of a low-income country.

METHODS

This was a retrospective chart review of all children admitted through the pediatric ED of the study center with the initial diagnosis of myocarditis for ten years from 2005 to 2015. Children from six months to sixteen years of either gender were admitted with a probable or definitive diagnosis of acute myocarditis. Patients with a history of cardiomyopathy, congenital heart disease (cyanotic and cyanotic), and patients with primary arrhythmias or other concurrent acute or chronic illnesses were excluded. The primary outcomes are clinical presentation, while the secondary outcome was morbidity or mortality along with the length of hospital stay and PICU admission.

This was a retrospective chart review by trained and tested volunteers who were either medical students, residents, fellow, or at least with a medical background.

The charts were checked randomly by the investigators to check their accuracy. Charts were extracted from the record room using the International Classification of Disease for Myocarditis, 9th revision (ICD 9).

Patient demographic characteristics, medical history, and physical examination findings at the time of triage, along with vital signs and laboratory variables, were recorded from the charts, the electronic database, and the physicians/cardiologist notes. The results of X-ray, ECG, ECHO, Troponin and other parameters were recorded from their respective databases. Variables were recorded as initial and before discharge and compared for final analysis.

Clinical parameters were divided into six categories: respiratory, GI, cardiac, hypo-perfusion, skin rash, and CNS. ECG was assessed and taken as abnormal if low voltage (<5mm), AV block (I, II, III), Q wave changes, ST depression, Axis deviation, T wave inversion, AV block, and ventricular hypertrophy. Chest X-ray was documented as abnormal in case of measured cardiomegaly or pulmonary edema. ECHO findings such as LVEF of <50%, valvular dysfunction, pericardial effusion, and RV dysfunction (<50%) indicate myocarditis in a previously healthy child.

The principal investigators randomly rechecked the record, and a trained person entered the collected data in the SPSS v 22. Continuous variables were expressed as mean +/- SD, and frequencies and percentages were computed for categorical data. A p-value of less than 0.05 is considered significant. Vitals will be categorized based on the specific age of the child.⁽¹¹⁾

RESULTS

A total of 52 children were enrolled with myocarditis as per the patient record. The mean age was 34.33 months, and the median age of patients was 27.50 months (min. 14.50 & max. 85.00 months) with almost equal gender distribution, with males 25 (48%) and females 27 (52%). Most of the children, 26 (50%), were under two years old and presented with myocarditis symptoms.

Regarding the preceding history and clinical features of myocarditis, we found 29 (56%) children with a history of preceding upper respiratory tract infection, and 36 (69%) had documented fever. The majority, i.e., 35 (67%) had respiratory symptoms presented with respiratory distress, 24 (46%) had CNS symptoms either of irritability or drowsiness, while 20 (38%) had cardiac symptoms mostly with unexplained tachycardia, followed by low volume pulses, and cold peripheries, while 17 (33%) had gastrointestinal symptoms either had anorexia, poor feeding, vomiting or diarrhea. (Table I).

Table II demonstrates the radiological and laboratory parameters of myocarditis. Chest X-ray was done in 48

History of Viral Infection, n= 29 (55.7%)	
URI *	12 (23%)
Flu-like illness	11 (21%)
AGE *	6 (11.5%)
Fever	36 (69%)
Clinical Symptoms	
Respiratory Symptoms (Distress)	35 (67%)
GI Symptoms	17 (32.7%)
CNS Symptoms	24 (46%)
Cardiac Symptoms	20 (38%)
Duration of Symptoms before Presentation	
≤ 3 days	31 (60 %)
> 3 days	21 (40%)
Physical Examination (Isolated)	
Tachycardia	52
Respiratory Distress	35
Cold extremities	29
Oxygen Saturation (<95 at presentation)	28
Low volume pulses	28
Pallor	27
Hepatomegaly	26
Delayed capillary refill	25
Muffled heart sound	17
Congestive Heart Failure	12
Cyanosis	04
Arrhythmias	04

Table I: Common Clinical Presentation and Physical Finding of Myocarditis

cases; 16 (33%) were average, while 14 (29%) showed cardiomegaly. Cardiac enzymes were analyzed in all cases and levels described in Table II. ECG was recorded in 42 (81%), 09 had normal ECG, while low voltage ECG was found in 17 (33%) children; other ECG parameters are described in Table IV. ECHO was performed in 48 (92%), and 40 (77%) had moderate to severe ejection fraction dysfunction, with a predominant left ventricular ejection fraction of <25% found in 27 (52%) children—table III.

Inotropic support was administered in 47 (90%) children; Dopamine was given in 33 (63%) cases, while Epinephrine was used in 14 (27%) children. Ventilator support was required in 33 (63%) cases; most children need less than 04 days of ventilatory support. Cardiopulmonary resuscitation during the whole length of stay was observed in 14 (27%) children. The mean length of the hospital stay was 8 ± 4.7 days. Nineteen children were admitted

to the general ward; however, 33 (63%) needed PICU or HDU monitoring, and we found 13 (25%) mortality. Table VII. Steroids were given in 29 (56%) cases, while IVIG was used in 21 (40%) children; among 14 (27%), both steroids and IVIG were used.

The seasonal variation observed in this study is explained in Figure I; we observed the maximum cases from March to July. We found 30 (58%) children with the highest number, followed by myocarditis on April 10 (19%).

DISCUSSION

Myocarditis is a rare but life-threatening disease with varying degrees of clinical presentation. Hence early identification and prompt management are of utmost importance to reduce mortality related to myocarditis. Diagnosis of myocarditis depends on a high index of clinical suspicion and few supportive investigations. Myocardial biopsy and cardiac MRI or viral serology

Radiological Finding (48 Cases)			
	Male	Female	Total
Normal (16)	7	9	48
Cardiomegaly (14)	8	6	
Pulmonary Edema (13)	6	7	
Pleural Effusion (01)	1	0	
Cardiomegaly and Pulmonary Edema (02)	1	1	
Peri-hilar Consolidation (01)	1	0	
Collapse (01)	1	0	
Laboratory Results (Cardiac Enzymes)			
Troponin I (< 0.3)			
Normal (10)	5	5	52
Raised (42)	20	22	
CK MB			
Normal (13)	8	5	52
Raised (39)	17	22	
Pro BNP			
Normal (20)	12	8	52
Raised (32)	13	19	

Table II: Laboratory and Radiological Findings

ECHO Findings (done in 48 cases)			
LVEF	Male	Female	Total
<25% Severe) (27)	12	15	48
25-40% (Moderate) (13)	7	6	
40-50% (Mild) (06)	3	3	
>50% (Normal) (02)	1	1	
RV Dysfunction			
<25% Severe) (09)	6	3	
25-40% (Moderate) (07)	5	2	
40-50% (Mild) (12)	5	7	
>50% (Normal) (20)	7	13	

Table III: ECHO Finding among Myocarditis

are the few invasive and expensive gold standards of diagnosis but are not available in most LIC settings. ⁽²⁾

Severe or fulminant myocarditis presents early and usually has a short duration of prodromal symptoms, which may generally be < 3 days, which was observed in this study. ⁽¹²⁻¹⁴⁾ Common prodromal symptoms are a

history of viral illness, increasing fatigue, fever, and respiratory distress. ⁽¹⁴⁾ Hence, it is difficult for emergency physicians to identify a precise, straightforward, and early diagnosis of myocarditis, which may lead to misdiagnosis or delays leading to increased morbidity and mortality.

	Male (n = 25)	Female (n = 27)	Total (n = 52)
ECG p-value 0.010			
Not Done/Missed (10)	1	9	52
Normal (09)	7	2	
Abnormal (33)	17	16	
Low Voltage ECG (<5 mm) p-value 0.015			
Not Done/Missed (10)	1	9	52
Low Voltage (17)	9	8	
Normal Voltage (25)	15	10	
A V Block (Lead I, II, III) p-value 0.019			
Not Done/Missed (10)	1	9	52
Present (07)	5	2	
Absent (35)	19	16	
ST Depression p-value 0.027			
Not Done/Missed (10)	1	9	52
Present (09)	5	4	
Absent (33)	19	14	
Axis Deviation p-value 0.027			
Not Done/Missed (10)	1	9	52
Present (05)	3	2	
Absent (37)	21	16	
T Wave inversion p-value 0.024			
Not Done/Missed (10)	1	9	52
Present (06)	4	2	
Absent (36)	20	16	
VT or SVT p-value 0.019			
Not Done/Missed (10)	1	9	52
Present (03)	1	2	
Absent (39)	23	16	
Ventricular Hypertrophy p-value 0.062			
Not Done/Missed (10)	1	9	52
RVH (3)	2	1	
LVH (5)	3	2	
Not Present (34)	19	15	

Table IV: ECG Findings among Myocarditis cases

Drugs in ED	Male	Female	Total
Dopamine p-value 0.358			
Given (33)	17	16	52
Not Given (19)	8	11	
Dobutamine p-value 0.054			
Given (09)	7	2	52
Not Given (43)	18	25	
Epinephrine p-value 0.315			
Given (14)	8	6	52
Not Given (38)	17	21	
Milrinone p-value 0.290			
Given (26)	11	15	52
Not Given (26)	14	12	
Steroids p-value 0.420			
Given (29)	13	16	52
Not Given (23)	12	11	

Table V: Inotropic and Ventilatory Support and Outcome.

Age younger than two years are more vulnerable to the deadly disease, as we found most of them in this age group, similar to Ohki et al. study.⁽¹⁾ The overall mortality was 13 (25%), as was identified by a Japanese hospital-based analysis, and most 8 (62%) were under two years of age,⁽¹⁾ while 09 (70%) were below five years of age.

The most common presentation of pediatric myocarditis is respiratory distress or shortness of breath, which has been well documented in the literature. We found this the most common clinical symptom with clear lungs in most cases. However, the initial clinical assessment in ED may be pneumonia, asthma, bronchiolitis, and sepsis, but with clinical worsening and progressive shock state, subsequently suspicious of myocarditis was made⁽¹⁵⁾; hence cardiac etiology may be considered as a differential diagnosis in most cases of shortness of breath with clear lung. Freedman et al. and Durrani et al.^(2,3) also reported 68% - 69% of patients with respiratory distress, while Shu-Ling et al.⁽¹⁶⁾ identified 69% of cases in pain. Almost all children in distress had a history of poor feeding or feeding difficulties.

TACHYCARDIA, BP, TACHYPNEA

Tachycardia was another joint clinical presentation of myocarditis observed in this study. We found tachycardia

in 100% of cases. Similarly (90%) was followed by Haider N et al.⁽¹⁵⁾, and Shu-Ling et al.⁽¹⁶⁾ also documented tachycardia in 61.5% of cases. In comparison, Freedman et al.⁽³⁾ had tachycardia in 73% of children above ten years of age, while Durrani et al.⁽¹⁾ observed only 33% of children with tachycardia. We observed hypoperfusion in 56% of children. Similarly, 66.7% of hypoperfusion was identified by Shu-Ling et al.⁽¹⁶⁾ Freedman observed only 22% of cases with hypo-perfusion.⁽³⁾ Hepatomegaly was identified in 50% of patients while Shu-Ling et al.⁽¹⁶⁾ observed 41% of cases, and few other studies had in the range between 36-50%^(6,9), gallop rhythm muffled heart sound was found among 17 (33%) cases.⁽¹⁶⁾

Younger children commonly present with respiratory symptoms, while older children and adolescents with myocarditis or cardiac failure may have primary abdominal symptoms, as documented by in Taiwan study⁽¹⁷⁾; Haider et al.⁽¹⁵⁾ identified 23% of cases with abdominal discomfort.

Cardiac enzymes for myocarditis were also analyzed, but we found high troponin levels in only 09 cases. Cardiac troponins are highly sensitive markers for myocardial inflammation. A cutoff value of 0.05ng/ml has a sensitivity of 71%, and specificity of 86%⁽¹⁸⁾, Lauer et al.⁽¹⁹⁾ reported that 35% of cases with myocarditis

Duration of CPR (in minutes) n = 14 p-value 0.696				
Duration (Minutes)		Male	Female	
< 15 minutes		4	3	
>15 minutes		3	4	
Total Number of CPRs p-value 0.552				
Number of CPRs		Male	Female	
No CPR at all (38)		18	20	52
≤02 (04)		5	2	
≥03 (06)		2	5	
Ventilatory Support p-value 0.483				
		Male	Female	
Given (33)		16	17	52
Not Given (19)		09	10	
	≤ 2 Cycle	≥ 3 Cycle		Total
Number of CPR	7	7		14
Death	5	4		09**
	≤ 15 minutes	≥ 15 minutes		Total*
Duration of CPR	7	7		14
Death	5	4		09**

Table VI: CPR with Ventilatory Support and Outcome

*Mean of 3.88 minutes and P value of 0.000

**04 children died in which CPR was not opted.

had high troponin by using a cutoff level of 0.1ng/ml with a sensitivity of 53% and specificity of 94%, and a positive predictive value of 93%, and a negative predictive value of 56%. Our data revealed troponin of >0.3ng/ml among 42 (80.7%) cases with a sensitivity of 85.7% (95% CI: 71%-94.5%) and specificity of 70% (95% CI: 34.7%-93.3%), and a positive predictive value of 92.3%, and a negative predictive value of 53.8% with accuracy of 82% (95% CI: 69.6%-91.7%). The cut-off value of 0.3ng/ml might be the reason for such high sensitivity and specificity.

CKMB and Pro-BNP were raised in 39 (75%) and 32 (62%) cases, respectively, though CKMB generally has a low sensitivity of 64 % (95% CI: 47%-78%) and specificity of 46% (95% CI: 19.2%-74.8%) and accuracy of 45%.

One-third had normal radiology, 66% with some radiological changes, either cardiomegaly (most abundant findings), also observed by Shu-Ling et al. ⁽¹⁶⁾ (60%), abnormal

chest radiology/cardiomegaly; few others had similar results which range from 19-42%. ⁽¹⁶⁾

ECG was followed in 63% of cases and demonstrated either a combination of low voltage, AV block, ST depression, or T-wave abnormalities. In comparison, the most common findings were ST or T-waves abnormalities 15 (45%) followed by AV block 7 (21%) cases as contrary to 30% and 28.6% respectively by Shu-Ling et al. ⁽¹⁶⁾. Freedman et al. ⁽³⁾ reported that the combination of an abnormal ECG and chest radiograph in suspected cases of myocarditis might have a good sensitivity for diagnosing acute myocarditis, as we observe the sensitivity of 80% (95%CI: 44%-97%) and specificity of 11% (95% CI: 0.28%-48%).

Among the inotropic support, we found dopamine in most cases, followed by epinephrine with a cumulative number of 47(90%). In this study, cardiopulmonary resuscitation was carried out in 14 patients (either due

Primary Outcome		p-value 0.725		
Outcome		Male	Female	
Died	(13)	5	8	52
Survived	(37)	19	18	
Not Known *	(02)	1	1	
*These were patients who were referred out, got admitted elsewhere the study center				
Secondary Outcome				
<u>Duration of Hospital Stay (days)</u>				
Duration (days)		Male	Female	
1-2 days	(04)	2	2	
3-4 days	(11)	5	6	
5-6 days	(10)	3	7	
7-8 days	(07)	4	3	
9-10 days	(06)	4	2	
11-14 days	(12)	5	7	
≥ 15 days	(02)	2	0	
<u>Duration of PICU/HDU Stay (days)</u>				
Duration (days)		Male	Female	
1-2 days	(10)	4	6	52
3-4 days	(08)	3	5	
5-6 days	(07)	4	3	
7-8 days	(03)	2	1	
9-10 days	(01)	0	1	
11-14 days	(03)	2	1	
>15 days	(01)	0	1	
Didn't need	(19) PICU/HDU	(10)	(09)	

Table VII: Primary and Secondary Outcomes

to arrhythmias or sudden collapse), 05 had the CPR for more than 15 minutes, and all didn't survive. Ventilatory support was provided to 33 (63%) cases.

Myocarditis, especially those with a short duration of symptoms, has higher mortality; among 14 (27%) cases who need CPR at some time during their stay, we found a pretty massive mortality of 25% (13 children); it may be multifactorial and, might link with delays in seeking medical support, missed or delayed diagnosis, hindrance in the appropriate care like intubation, inotropic supports, PICU care, cardiology expert consultation, non-availability

of IVIG, ECMO or transplant facilities etc. A study from a well-developed society, the US, reports mortality of 7.2% where all advanced facilities are available, and patients are usually identified early, transported, and managed promptly as compared to third world countries.⁽²⁰⁾

LIMITATION

There are quite a few limitations of this study; firstly, in a single-center study with quite a small data size, only those patients who were initially suspected on clinical and laboratory parameters as myocarditis in a

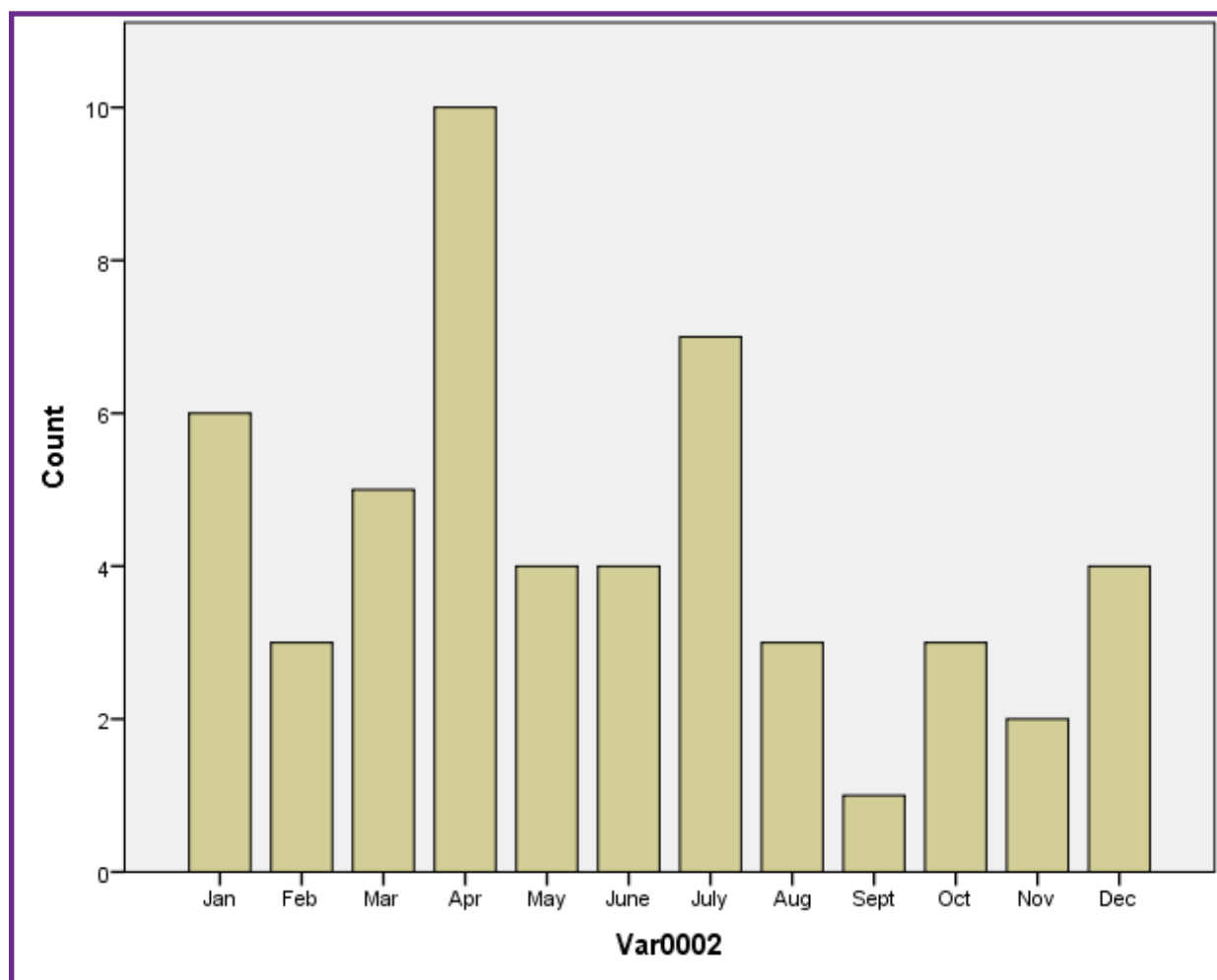


Figure I: Seasonal Variation of Myocarditis

pediatric emergency were included. The definitive diagnosis via myocardium biopsy, cardiac MRI, or viral culture was not considered.

CONCLUSION

Myocarditis among children has higher mortality and may present with short onset symptoms. Moreover, the signs and symptoms may be vague and overlapping; hence unexplained tachycardia, clear chest, distant heart sound coupled with a dusky look, cold peripheries, or poor pulses followed by viral symptoms should raise the suspicious of myocarditis. Early identification and prompt management by experienced pediatric emergency physicians may reduce morbidity and mortality.

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