Prevalence of myocarditis in critically-ill pediatric patients in Qena University Hospital

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Abstract

Background: Myocarditis is a potentially life-threatening inflammatory disease affecting the myocardium. There are many different etiologies, most of which are infectious. The spectrum of presentations can range between subclinical disease and congestive heart failure, arrhythmias, and sudden death. Endomyocardial biopsy and cardiac magnetic resonance are the cornerstone in diagnosing myocarditis. However, they are not widely used. Therefore, myocarditis can be diagnosed clinically based on clinical presentation, laboratory investigations, and echocardiography.

Objectives: The aim was to evaluate the prevalence of myocarditis in critically-ill patients.

Patients and methods: Creatine kinase-myocardial band (CK-MB) and troponin-I were conducted on 203 critically-ill patients admitted in PICU and NICU as a screening test for myocarditis. If one or both of them were high, echocardiography was done to prove myocarditis. If the patient was diagnosed clinically to have myocarditis, Chest x-ray, ECG, and covid IgG, and IgM were done.

Results: CK-MB and troponin-I were within the normal range in 151 patients. One or both cardiac biomarkers were elevated in 52 patients, therefore, echocardiography was done for all of them and myocarditis was diagnosed clinically in 15 cases. CK-MB sensitivity in predicting myocarditis was 60% and specificity was 73.4%. Troponin-I was more sensitive (86.67%) and more specific (77.01%).

Conclusion: The prevalence of myocarditis was 7.4% in critically-ill pediatric patients. A high index of suspicion is required in diagnosing myocarditis. Troponin-I can be used as a screening test for myocarditis and results can be confirmed with echocardiography.

Keywords: Myocarditis; Critically-ill; Pediatrics.

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Introduction

In the early 19th century, 'myocarditis' was first introduced by the French physician Corvisart. Myocarditis is a potentially life-threatening inflammatory disease affecting the muscular tissues, resulting in ventricular dysfunction **(Caforio et al., 2013; Kim and Cho, 2020).**

Myocarditis may affect the myocardium focally or diffusely and it can be acute, sub-acute, or chronic **(Bracamonte and Čiháková, 2017).** There are many different etiologies, most of which are infectious **(Rroku et al., 2020).** The spectrum of presentations can range between subclinical disease, congestive heart failure, arrhythmias, and sudden death **(Caforio et al., 2013; Bracamonte and Čiháková, 2017).**

Endomyocardial biopsy and cardiac magnetic resonance are the cornerstone in diagnosing myocarditis. However, they are not widely used. Therefore, myocarditis can be diagnosed clinically based on clinical presentation, laboratory investigations, and, echocardiography **(Caforio et al., 2013; Butts et al., 2017).**

Early identification of severe cases and providing the needed critical care for them is crucial. Mortality predictors in acute myocarditis are not yet established. Identifying mortality risk factors is important to provide higher levels of care and circulatory support to higher-risk patients before circulatory collapse occurs. Myocarditis in the pediatric age group had a high mortality rate, mostly in the first three days of hospital admission. Children with very high troponin levels or with a decrease in myocardial contractility in the first 24 hours were at higher risk, and targeting these patients for more intensive care is extremely important **(Chang et al., 2019).**

The current study aimed to evaluate the prevalence of myocarditis in critically-ill patients and to evaluate the efficacy of CK-MB and troponin-I in the diagnosis of myocarditis in critically-ill patients.

Patients and methods

The current study was a cross-sectional study conducted on all critically ill children admitted to the pediatric intensive care unit and neonatal intensive care unit in the pediatric department at Qena University Hospital from March 2022 to March 2023.

After taking an informed consent, CK-MB and troponin-I were done to all patients as a screening test for myocarditis. Troponin-I was done using Tosoh kits and CK-MB was done using Beckman CK-MB reagents. If one or both of them were high, a detailed echocardiographic assessment was done to prove myocarditis. If the patient was suspected to have myocarditis, the patient was subjected to a complete history, examination, and assessment of ROSS classification. In addition, chest x-ray, electrocardiogram, COVID-19 IgG, and IgM were done.

The ROSS heart failure classification was developed to provide a global assessment of heart failure severity **(Ross, 2012).**

The socioeconomic class was evaluated using Fahmy El-sherbini's scoring of socio-economic class. The main indicators of social class are the level of education, occupation of the parents, family size and crowding index. **(El-Sherbini and Fahmy, 1983)**.

The most important symptoms we searched for were presence of viral prodrome, respiratory or gastrointestinal symptoms. The most important signs we searched for were presence of tachycardia, murmur, signs of shock or heart failure. The patient is then diagnosed clinically by a pediatric cardiologist as having probable myocarditis based on history, examination, and investigations.

Ethical approval code: SVU-MED-PED025-1-22-3-360.

Statistical analysis

The data were tested for normality using the Kolmogorov-Smirnov test. Categorical variables were described by number and percent (N, %), whereas continuous variables were described by mean and standard deviation Mean±SD or Median (IQ range). The chi-square test and Fisher exact test were used to compare categorical variables. Differences between the two groups were detected using the Independent samples T-test for parametric data and the Mann-Whitney test for non-parametric data. Differences between more than two groups were detected using the One-Way ANOVA test for parametric data and the Kruskal-Wallis test was used for nonparametric data.

For correlation, we used Pearson correlation coefficients. The ROC curve was used to assess the best cutoff value of (CKMB and Troponin) sensitivity, specificity, PPV, NPV, and accuracy. All analyses were performed with the IBM SPSS 26.0 software.

Results

The present study was carried out on 203 patients with an age ranging from 0.08 years to 13 years with a median age of 0.25 years and an Interquartile Range (IQ range) between 0.02 and 2 years. They were 121(59.6%) male and 82(40.4%) female. Most patients 164(80.8%) were living in rural areas in comparison to 39(19.2%) patients who were living in urban areas. The socioeconomic class was evaluated using Fahmy El-sherbini's scoring of socio-economic class **(El-Sherbini and Fahmy, 1983)**. Most patients 170(83.7%) were of low socio-economic level, 27(13.3%) were intermediate and 6(3%) were of high socioeconomic level, **(Table 1).**

Table 1. Demographic data of the studied cases.

Variables	Total (n=203)
Age (years)	
Range	0.08 - 13
Median (IQ range)	0.25(0.02-2)
Sex	
Male	121(59.6%)
Female	82(40.4%)
Residence	
Urban	39(19.2%)
Rural	164(80.8%)
Socioeconomic	
Low	170(83.7%)
Medium	27(13.3%)
High	6(3%)

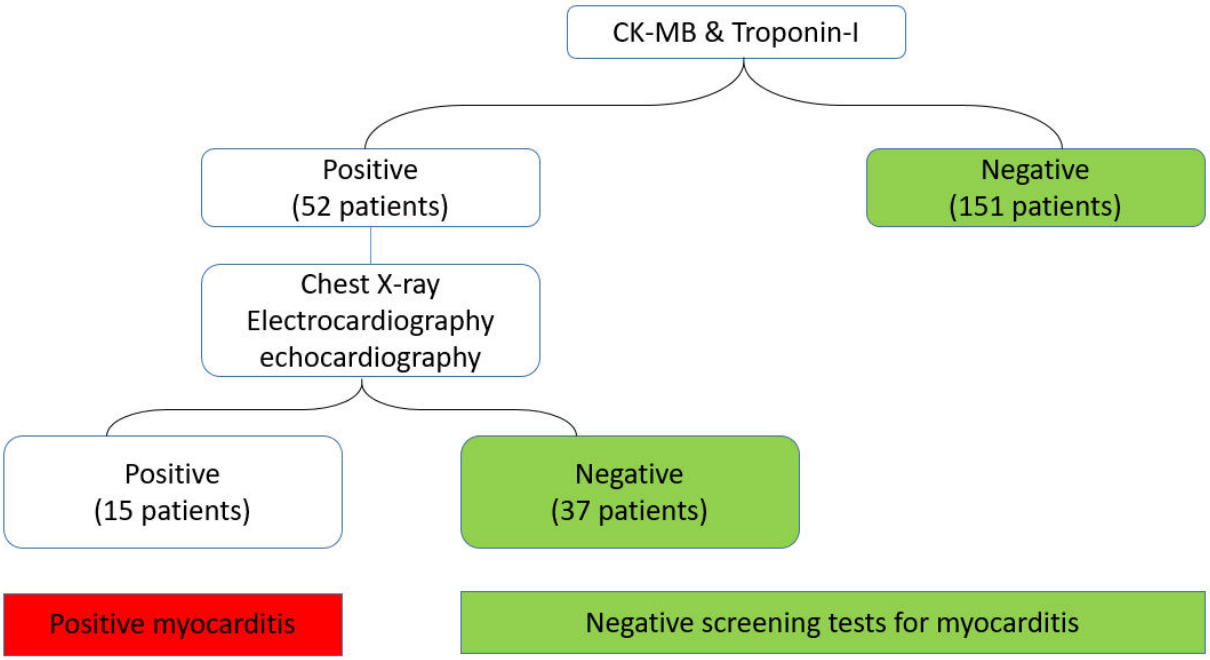


Fig.1 shows that CK-MB and troponin-I were within the normal range in 151 patients. On the other hand, one or both cardiac biomarkers were elevated in 52 (25.6%) patients. Echocardiography was done for all of them where myocarditis was excluded in 37(18.2%) cases and it was confirmed in 15(7.4%) cases. The group of patients without myocarditis was composed of 101 patients (53.7%) from PICU and 87 patients (46.3%) from NICU. The group of patients with probable myocarditis was composed of 13 patients (86.7%) from PICU and 2 patients (13.3%) from NICU.

Table 2. Demographic data of patients with probable myocarditis in comparison to patients without myocarditis

Variables	Probable myocarditis group (n=15)	Group of patients Without myocarditis (n=188)	P value
Age (years)			
Range	0.08 - 10	0.08 - 13	
Median (IQ range)	2.4(0.33-9)	0.17(0.02-1.5)	0.009**
Sex			
Male	13(86.7%)	108(57.4%)	0.026*
Female	2(13.3%)	80(42.6%)	
Residence			
Urban	3(20%)	36(19.1%)	0.936
Rural	12(80%)	152(80.9%)	
Socioeconomic			
Low	15(100%)	155(82.4%)	
Medium	0(0%)	27(14.4%)	0.208
High	0(0%)	6(3.2%)	

There was a statistically significant difference between the ages of patients with probable myocarditis and patients without myocarditis. Myocarditis was statistically significantly higher among males. The male-to-female ratio of the group of patients without myocarditis was 1.35:1 in comparison to the group of patients with probable myocarditis which was 6.5:1. **(Table 2).**

Table 3. Cardiac enzymes of patients with probable myocarditis in comparison to patients without myocarditis

Variables	Probable myocarditis group (n=15)	Group of patients Without myocarditis (n=188)	P value
CK-MB (U/L)			
Range	7.5 – 415	0.98 – 517	
Median (IQ range)	35.16(14.5-64)	18.94(12-31.98)	0.139
Troponin-I (ng/ml)			
Range	0.01 – 2251.3	0.0 – 1329.5	
Median (IQ range)	2.9(0.15-52)	0.03(0.01-0.07)	<0.001**

Our study revealed that CK-MB ranged from 0.98 U/L to 517 U/L with a median of 18.94 U/L in patients negative for myocarditis in comparison to a range from 7.5 U/L to 415 U/L with a median of 35.16 U/L in patients with probable myocarditis. There was a significant difference between Troponin-I levels between the two groups with a range from 0.01 ng/mL to 2251.3 ng/mL in patients with probable myocarditis with a median of 2.9 ng/mL in comparison to a range between 0 and 1329.5 ng/mL with a median of 0.03 ng/mL in patients without myocarditis, **(Table 3).**

Table 4: Clinical evaluation of cases with probable myocarditis

History and Examination	Probable myocarditis group (n=15)	
	No.	%
Viral prodrome		
Yes	8	53.3
No	7	46.7
Consanguinity		
Positive	8	53.3
Negative	7	46.7
Family history		
No	15	100.0
Vaccination		
up to age	15	100.0
Vital signs		
Heart rate		
Range	67 - 200	
Mean±SD	130.8±34.12	
Median (IQ range)	122(118-150)	
Respiratory rate		
Range	22 – 93	

Mean±SD	63.8±18.41	
Median (IQ range)	65(55-75)	
Temperature		
Range	36.5 - 40	
Mean±SD	38.01±1.16	
Median (IQ range)	37.8(37-39.1)	
Cardiac examination		
Murmurs		
Yes	8	53.3
No	7	46.7
Rhythm		
irregular	5	33.3
regular	10	66.7
Capillary refill >3s	2	13.3
Pulses not felt	2	13.3
Abdominal examination		
Organomegaly		
hepatomegaly	3	20.0
Chest examination		
Respiratory distress grade at rest		
No	2	13.3
II	6	40.0
III	6	40.0
IV	1	6.7
Air entry		
Decreased	4	26.7
Adventitious sounds		
Crepitations	5	33.3
Wheezes	1	6.7
No	9	60.0

Regarding patients with probable myocarditis, 8 patients (53.3%) were preceded with the viral prodrome, and 4 patients (26.7%) were having GI symptoms. Regarding vital signs upon admission, the heart rate ranged from 67 b/m to 200 b/m with a mean of 130.8 ±34.12 standard deviation and a median of 122 b/m, and an IQ range of 118-150. The respiratory rate ranged from 22 to 93 b/m with a mean of 63.8 ± 18.41 standard deviation and a median of 65 b/m and an IQ range of 55-75. The temperature ranged from 36.5 to 40 with a mean of 38.01 ±1.16 standard deviation and a median of 37.8 and an IQ range of 37 - 39.1. There were only two patients (13.3%) with delayed capillary refill time and weak pulses. By cardiac examination, there was a heart murmur in 8 patients (53.3%) of cases. By chest examination, 6 patients (40.0%) were having respiratory distress grade II, 6 patients (40.0%) were having respiratory distress grade III, one patient (6.7%) with respiratory distress grade IV and one patient presented to us without respiratory distress. In the abdominal examination, there was a palpable liver in 3 (20.0%) cases, **(Table 4).**

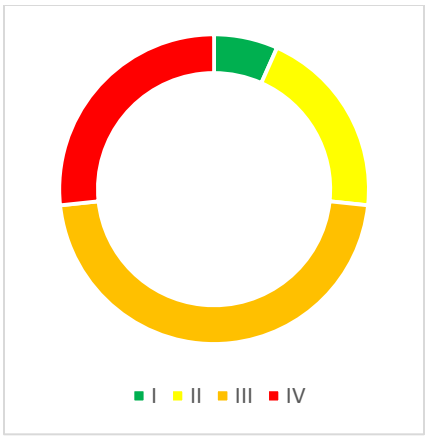


Fig.2. ROSS classification of patients with probable myocarditis

Regarding ROSS classification of heart failure, 7 patients (46.7%) were class III, 4 patients (26.7%) were class IV, 2 patients (20.0%) were class II and only one patient (6.7%) was class one, **(Fig. 2).**

Table 5. Echocardiographic findings of patients with probable myocarditis.

Echo	**Probable myocarditis group (n=15)**	
	No.	%
Fraction shortening		
Range	6 - 22	
Median (IQ range)	15	
Chamber dilatation	10	66.7
Valvular regurge	6	40
Pulmonary hypertension	3	20.0

Regarding echocardiography findings, the Fraction shortening ranged from 6 to 22 with a median of 15. There was chamber dilatation in 10 cases (66.7%) and there was valvular regurge in 6 cases (40%). There was associated pulmonary hypertension in 3 cases (20%), **(Table. 5).**

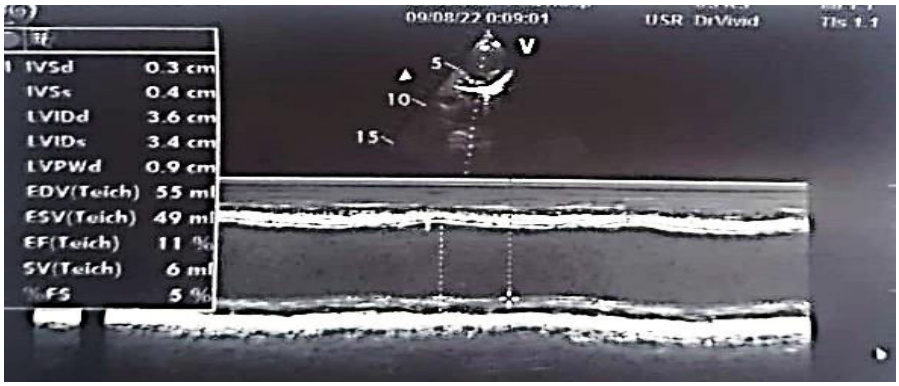


Fig.3. Echocardiography of a 4-month-old female patient with myocarditis revealing a marked decrease in fraction shortening.

Table 6.CXR of patients with probable myocarditis.

CXR	Probable myocarditis group (n=15)	
	No.	%
Pulmonary opacities	8	53.3
Increased Broncho vascular markings	15	100.0
Cardiophrenic angle		
Acute	12	80.0
Obtuse	3	20.0
Increased Cardiothoracic ratio	12	80.0

Regarding chest x-ray of patients with probable myocarditis, there was cardiomegaly in 12 patients (80% of cases). There were associated pulmonary opacities in 8 cases (53.3%). The cardiophrenic angle was acute in 12 patients (80%) and obtuse in 3 patients (20%), **(Table 6).**

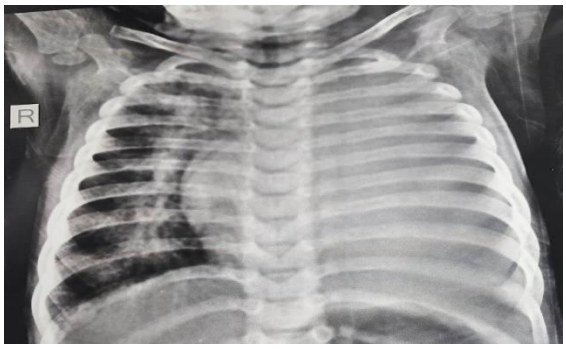


Fig.4. Chest x-ray with an increase in cardiothoracic ratio.

Regarding ECG findings, there was an abnormal rhythm in 11 (73.3%) of cases, and T wave abnormalities in 10 (66.7%) cases. There was a right axis deviation in 6 (40%) of cases, **(Table 7).**

Table 7: ECG of patients with probable myocarditis

ECG	Probable myocarditis group (n=15)	
	No.	%
Rhythm		
Normal	4	26.7
Abnormal	11	73.3
Chambers enlargement		
Yes	3	20.0
No	12	80.0
Axis		
normal	9	60.0
right	6	40.0
T wave abnormalities		
Yes	10	66.7
No	5	33.3

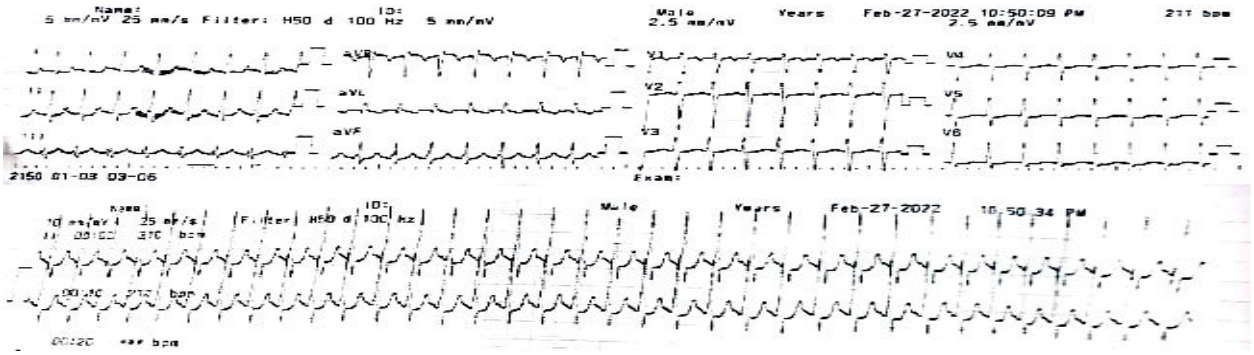


Fig.5. Electrocardiogram in a 9y old male patient with myocarditis. The ECG is demonstrating supraventricular tachycardia with a heart rate of 211 beats/minute.

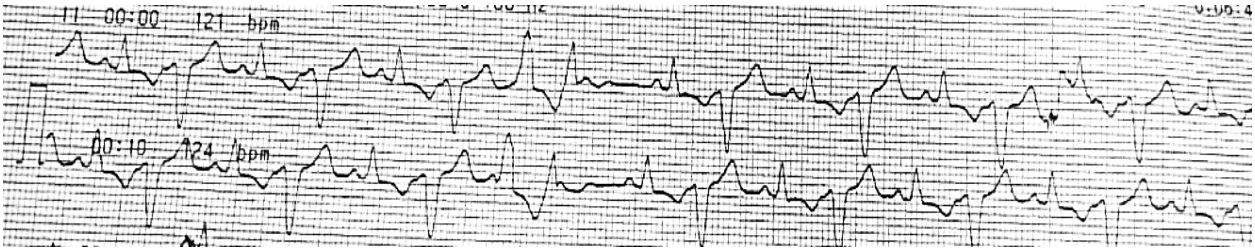


Fig.6. Electrocardiogram in a 9-year-old male patient with myocarditis. The ECG is demonstrating ventricular bigeminy.

In the current study, Polymerase chain reaction (PCR) was done on 12 cases with a positive result in only 2 cases (13.3%). However, the IgM was negative in all cases. The IgG was positive in 12 cases (80.0%), **(Table 8).**

Table 8: COVID 19 screen among cases with probable myocarditis

COVID-19	**Probable myocarditis group (n=15)**	
	No.	%
Ig G		
Positive	12	80.0
Negative	3	20.0
Ig M		
Negative	15	100.0
PCR		
Positive	2	13.3
Negative	10	66.7
Not done	3	20.0

Table 9. Correlation between ROSS classification and vital signs

Vital signs	ROSS classification				P value
	I (n=1)	II (n=3)	III (n=7)	IV (n=4)	
Heart rate	140	134	135.71	117.5	0.905
Respiratory rate	22	47.33	72.14	72	**0.003****
temperature	37	37.87	38.13	38.18	0.832
Systolic blood pressure	85	93.33	88.57	78.75	0.080
Diastolic blood pressure	60	56.67	56.43	48.75	0.412

In the current study, there is a statistically significant correlation between respiratory rate and ROSS classification. The median respiratory rate of patients with ROSS grade I was 22. The median respiratory rate of patients with ROSS grade II was 47.33. The median respiratory rate of patients with ROSS grade III was 72.14. The median respiratory rate of patients with ROSS grade IV was 72, **(Table 9).**

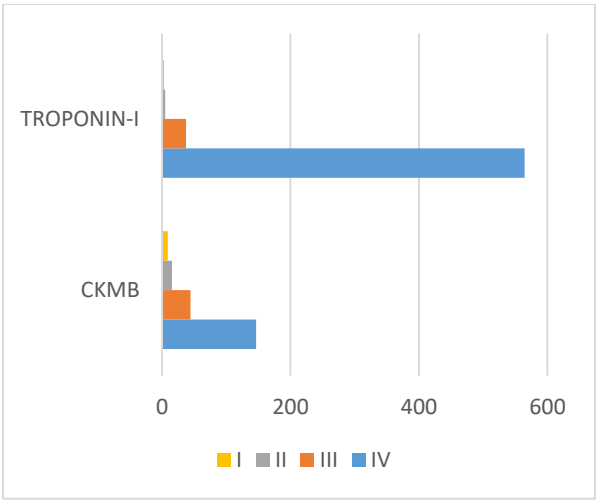
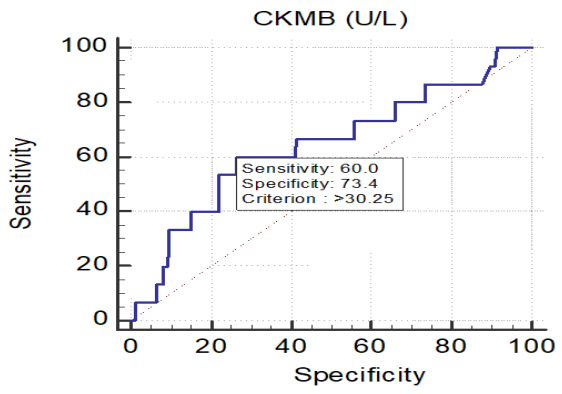


Fig.7. The relation between cardiac enzymes and ROSS classification.

There was a linear relation between the ROSS class and CKMB and troponin values. There were 4 patients with ROSS grade IV. The median of CKMB values was 146.61 and the median of troponin-I was 564.57. There were 7 patients with ROSS grade III. The median of CKMB values was 44.66 and the median of troponin-I was 37.44. There were 3 patients with ROSS grade II. The median of CKMB values was 15.77 and the median of troponin-I was 4.96. There was 1 patient with ROSS grade I. The median of CKMB values was 9 and the median of troponin-I was 2.9, **(Fig.7).**

Table 10: ROC curve analysis of Troponin & CKMB in predicting patients with Probable myocarditis.

Variables	AUC	Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy
Troponin (ng/ml) n= 203	0.840	>0.08	86.67	77.01	23.2	98.6	81.8
CKMB (U/L) n=203	0.643	>30.25	60	73.4	15.3	95.8	66.7



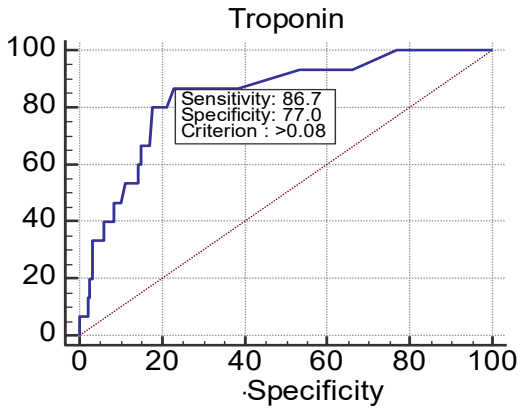


Fig. 8 (a) **Fig. 8 (b)**

Fig.8 (a, b): Cardiac enzymes sensitivity and specificity.

CK-MB sensitivity in predicting myocarditis was 60% and specificity was 73.4 with a cut-off value of >30.25, positive predictive value of 15.3, negative predictive value of 95.8, accuracy of 66.7, and air under the curve 0.643. Troponin-I was more sensitive and specific with a sensitivity of 86.67% and specificity of 77.01 with a cut-off value of >0.08, positive predictive value of 23.2, negative predictive value of 98.6, accuracy of 81.8, and air under the curve 0.840, **(Table.10 and Fig.8 (a, b)).**

Discussion

Myocarditis is a rare disease in children. Because of its rarity, few large-scale studies have reported acute myocarditis in children **(Saji et al., 2012; Arola et al., 2017; Kim and Cho, 2020)**.

In this study, the prevalence of myocarditis in critically-ill pediatric patients was 7.38%. In **Butts et al. (2017),** myocarditis represents about 0.05% of tertiary care hospital pediatric admissions.

The current study showed that there was a bimodal age distribution with two peaks in infancy and adolescents in patients with probable myocarditis. This is in concordance with **Butts et al. (2017)**, a retrospective study performed at seven tertiary pediatric hospitals, 24% of patients were < 2 years and 46% were between 13 and 18 years with a median age of 13.1 years. **Kim and Cho (2020)**, a study on Korean children using data between 2007 and 2016 from the Health Insurance Review and Assessment database revealed also that there was a bimodal age distribution.

In the current study, there is a male predominance as there were 13 males (86.7%) and only 2 females (13.3%) with a male-to-female ratio of 6.5:1. This is in concordance with **Ghelani et al. (2012)**, a study on 514 cases of acute myocarditis using the Pediatric Health Information System database where males were 64% of cases. In **Kim and Cho (2020)**, there was also a significant male preponderance (482 boys vs. only 152 girls). In **Rady and Zekri (2015)**, there were more females (62%) than males (37.5%).

In settings where cardiac magnetic resonance (CMR) and endomyocardial biopsy (EMB) are not available or if they are associated with very high risks, pediatric cardiologists have a difficult task of diagnosing myocarditis clinically **(Caforio et al., 2013; Rady and Zekri, 2015; Butts et al., 2017).** Probable myocarditis is a clinically diagnosed myocarditis by a pediatric cardiologist based on the history, examination, and investigations in the absence of endomyocardial biopsy **(Chang et al., 2019).**

Echocardiography is the most commonly used tool to assess heart structure and function **(Canter and Simpson, 2014).** Echocardiography also helps in monitoring changes in cardiac chamber size, wall thickness, and ventricular function **(Caforio et al., 2013; Chang et al., 2019).**

In the current study, all patients had a decrease in fraction shortening. In **Rady and Zekri (2015)**, an observational study of 16 cases with myocarditis, there was a decrease in fraction shortening in 75% of patients with myocarditis.

In the current study, there was an abnormal ECG in 11 patients (73.3%), T wave abnormalities in 10 (66.7%) cases, and right axis deviation in 6 cases (40%). This is in concordance with **Caforio et al. (2013)** which stated that ECG changes in myocarditis are neither specific nor sensitive, however, it is usually abnormal.

The current study showed cardiomegaly in 12 patients (80%) with chest X-rays. In **Rady and Zekri (2015)**, there was a significant association between the myocarditis group and cardiomegaly in a chest X-ray.

Cardiac biomarkers elevation reflects an ongoing myocardial injury and troponin I was well established as a diagnostic marker for myocarditis **(Eisenberg et al., 2012; Chang et al., 2019).** In the current study, CKMB was elevated in 9 patients (60%). Troponin was elevated in 11 patients (73.3%). Troponin-I had a specificity of 77.01%, a sensitivity of 86.67%, an accuracy of 81.8%, positive predictive value of 23.2%, negative predictive value of 98.6% and a cut-off value of 0.08 ng/ml.

In **Rady and Zekri (2015),** there was a significant association between the myocarditis group and high cardiac enzymes. Troponin-I had a specificity of 100%, sensitivity of 62.5%, accuracy of 90.5%, positive predictive value of 100% and negative predictive value of 88.7%.

Bohn et al. (2021) stated that Troponin-I had a sensitivity of 71% and specificity of 86% with a cut-off value of < 0.052 ng/ml. **Eisenberg et al., (2012)** revealed that Troponin-I has a sensitivity of 100% and specificity of 85% with a cut-off value of <0.01 ng/ml.

In the current study, there was a linear relation between ROSS classification and cardiac biomarkers values. This is in concordance with **Kantor (2013)** who reported that troponin I levels correlate with the severity of cardiac affection and that it is likely to be more elevated in myocarditis-induced heart failure.

This is also in concordance with **Clerico (2022)** who stated that the degree of elevation of Troponin-I was correlated with the severity of cardiac affection.

The data regarding the relationship between COVID-19 and pediatric myocarditis is limited **(Ho et al., 2020; Kohli et al., 2022)**. In the current study, COVID-19 PCR was done to 12 cases with a positive result in only 2 cases.

This is in concordance with **Kohli et al. (2022)** who revealed that cardiac affection is rare in pediatric patients with COVID-19. **Buitrago et al. (2022)** stated that the incidence of COVID-19 induced myocarditis is < 2%. However, some case reports reported acute myocarditis in pediatric patients with COVID-19. **Kesici et al. (2020)** reported a 2-year-old boy who was admitted in PICU with respiratory distress, weak pulse, and hepatomegaly. Chest x-ray revealed bilateral interstitial infiltration, pleural effusion and cardiomegaly. The endomyocardial biopsy revealed acute myocarditis and COVID-19 PCR was positive. **Gnecchi et al. (2020)** also reported a 16-year-old boy who presented with intense pain in his chest. Cardiac magnetic resonance showed a picture suggesting acute myocarditis and the nasopharyngeal swab test was positive for

COVID-19. The mechanism of COVID-19 myocarditis is suggested to be due to the cytokine storm caused by the body's immune response. **(Siripanthong et al., 2020, Castiello et al., 2022).**

Conclusion

The prevalence of myocarditis was 7.4% in critically-ill pediatric patients. A high index of suspicion is required in diagnosing myocarditis. Troponin-I can be used as a screening test for myocarditis and results can be confirmed with echocardiography.

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