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Cardiac biomarkers comparison between acute myocarditis/ myopericarditis and multisystem inflammatory syndrome in children

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ABSTRACT

Objectives: Acute myocarditis/myopericarditis is a heterogeneous disorder of unknown origin, the viral etiology leading the first row. There could be also myocardial involvement in multisystem inflammatory syndrome in children (MIS-C). In this study, we aimed to investigate cardiac biomarkers of acute myocarditis/myopericarditis and MIS-C and to compare these parameters between the two diseases.

Methods: Patients who are diagnosed with MIS-C, isolated viral myocarditis/myopericarditis at a university hospital from October 2021 to March 2023 are included in this study.

Results: There were 38 MIS-C patients and 53 patients with myocarditis/myopericarditis. The mean age was 141.2 ± 38.2 months (4 to 18 years old) in MISC, and 145.8 ± 52.1 months (7 to 18 years old) in myocarditis/myopericarditis. Median troponin I level was 145 ng/L in MIS-C patients and it was 901 ng/L in myocarditis/myopericarditis patients. Creatinine kinase-myocardial band (CK-MB) median was 2.25 ng/mL (0.6-6.3) versus 6.7 ng/mL in MIS-C and myocarditis/myopericarditis, respectively. Pro Brain natriuretic peptide (Pro-BNP) median level was 2714.5 pg/mL (< 300) in MIS-C, and it was 294 in patients with myocarditis/myopericarditis. Troponin I, CK-MB was significantly higher in myocarditis/myopericarditis, while Pro-BNP was significantly higher in MIS-C patients ($p < 0.05$). The separating power of CK-MB, troponin I, and Pro-BNP level was significantly higher in the differential diagnosis of these two group patients ($p < 0.001$). MIS-C patients with high pro-BNP levels had more prolonged hospitalization and left ventricular function impairment according to myocarditis/myopericarditis.

Conclusions: Cardiac biomarkers (CK-MB, troponin I, and Pro-BNP) could be good markers to estimate the course of the diseases.

Keywords: Cardiac biomarkers, myocarditis/myopericarditis, troponin, pro-BNP, multisystem inflammatory syndrome

Isolated myocarditis/myopericarditis is an inflammatory disease of the myocardium and pericardium with many various reasons, most of which are viral infections. In some other systemic diseases, hypoxia could also affect the myocardial tissue and start the inflammatory process. The clinical spectrum could be mild to lethal and varies individually [1, 2].

A novel coronavirus came about in late 2019 [3].

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It was called COVID-19, meaning coronavirus 2019, by The World Health Organization (WHO). The virus was officially designated as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). Although the acute illness was usually mild in children, there could be a systemic inflammatory response with a severe shock-like illness in children with features of incomplete Kawasaki disease (KD) or toxic shock syndrome in rare cases after the acute phase [4]. This manifestation is called multisystem inflammatory syndrome in children (MIS-C). Whilst the 2020 Centers for Disease Control and Prevention (CDC) MIS-C case definition did not entitle Kawasaki disease (KD) as a different diagnosis, the Council of State and Territorial Epidemiologists (CTSE)/CDC MIS-C case definition does specify KD as an alternative diagnosis that should activate telling the CDC KD passive surveillance organization [5, 6]. It will be more cumbersome to characterize patients with incident KD who have seroconverted from past SARS Co-V2 infections from patients with MIS-C who supply KD criteria. Thus, it is crucial to accentuate treatment if KD high-risk criteria exist.

Myocardial involvement may be present in MIS-C and Kawasaki-like patients thought to be an inflammatory vasculitis response [3]. However, distinguishing myocardial involvement in this and other similar systemic diseases from isolated viral myocarditis/myopericarditis seems important in the treatment plan and subsequent follow-up [7]. Because the cases are intertwined, it may be useful to use cardiac-specific markers outside the clinic [8]. While anti-inflammatory agents, including intravenous immunoglobulin (IVIG), are frequently used in the treatment plan in patients with MIS-C and Kawasaki-like syndrome with the new definition, supportive treatment is usually given in mild myocarditis/myopericarditis [3, 9].

Cardiac biomarkers such as creatinine kinase-myocardial band (CK-MB), troponin I, and pro Brain natriuretic peptide (pro-BNP) can be used in both diagnosis, follow-up, and treatment to show myocardial involvement and to determine the severity and prognosis of the clinic [10, 11]. Cut-off values for these markers may not be as clear in children as in adults [12]. Studies on the exact importance of these markers continue [13].

In this study, we aimed to investigate the clinical, laboratory, and imaging characteristics of acute myocarditis/myopericarditis and MIS-C (Kawasaki-like disease), and to compare the differences between them. It is also aimed to check out the usefulness of these characteristics and cardiac biomarkers on the course of diseases.

METHODS

Patients diagnosed with MIS-C, isolated viral myocarditis/myopericarditis, at a university hospital from October 2021 to March 2023 were included in this study. The local ethics committee (Mersin University Clinic Research Ethics Committee, Decision no.: 608, Date 08.09.2021) approved the protocol. The Helsinki Declaration was taken into consideration. The data was collected retrospectively.

MIS-C is diagnosed according to the CDC and the World Health Organization (WHO) criteria (5, 14). Myocarditis/myopericarditis diagnosis is made according to the algorithm of the American Heart Association and European Society of Cardiology [1, 2]. It includes history, clinical, laboratory, electrocardiography (ECG), and echocardiography findings with the addition of cardiac magnetic resonance imaging (CMRI) confirming the diagnosis [15, 16]. All patients had chest pain and elevation of cardiac biomarkers (troponin I and CK-MB). There was a viral prodrome within 1-4 weeks in all patients with myocarditis/myopericarditis. Electrocardiography showed ST segment changes/ T wave inversion.

Complete blood count, acute phase reactants [C-reactive protein (CRP)], creatinine kinase (CK), cardiac biomarkers (troponin I and CK-MB), Pro-BNP were also evaluated in MIS-C and myocarditis/myopericarditis.

Inclusion criteria for patients were to be diagnosed and followed up in this single-center clinic, and that they could have no other cardiologic diseases including structural heart diseases and arrhythmia syndromes. The exclusion criteria for patients were that they have other systemic diseases. Therefore, children with chronic illnesses and those taking daily medications were excluded from the study.

Standard 12-lead ECG was performed for the patients at a paper speed of 25 mm/second under similar conditions. A Nihon Kohden ECG 1250 Cardio fax S

(2009, Tokyo, Japan) device was used at standard velocity and amplitude. Transthoracic echocardiography, performed via Vivid E9 Pro Ultrasound System (GE Medical Systems, Canada) by using 3 and 6 MHz transducers as 2D, M-mode and colored Doppler, conventional continuous-wave (CW) and pulse wave (PW) Doppler visualizing methods. Two experienced pediatric cardiologists performed all studies.

Statistical Analysis

Categorical data were summarized through numbers and percentages. Normal distribution control of continuous data was done with Shapiro-Wilk's test. The continuous data were summarized as mean (± standard deviation) or median and quartiles according to normality assumption. Group comparisons were made with an independent t-test or Mann-Whitney U test. In addition, diagnostic performances of Troponin I and CK-MB parameters were evaluated using Receiver Operating Curve analysis. The sensitivity and specificity values for the obtained cut-off values were summarized. The statistical significance value was taken as $p < 0.05$. Statistical analyses were performed with the STATISTICA 13.0 package program. Power analysis is done to determine the number of patients and control participants.

RESULTS

There were 38 patients with MIS-C and 53 patients with myocarditis/myopericarditis. The mean age was 141.2 ± 38.2 months (4 to 18 years old) in MISC, and 145.8 ± 52.1 months (7 to 18 years old) in peri/myocarditis. Whilst 11 of the MIS-C patients suffered from hypotension requiring follow-up in the intensive care unit, the clinical progress was better in myocarditis/myopericarditis, and hypotensive value was observed in only one patient.

Imaging and Other Examination Results

Left ventricular systolic function slightly decreased (EF: 45-53%), in 11 patients with MIS-C; while it was in 5 patients with myocarditis/myopericarditis. The median ventricular ejection fraction was significantly lower in the MISC group (62.1% vs 69.6%; $p = 0.023$) and the median and z score of left ventricular end-diastolic dimension (LVEDD) was normal in all patients. All patients had recovery of cardiac function at discharge.

Considering the duration of hospitalization, the median hospitalization day was 16 days (5- 67 days) in patients with MIS-C, the median stay was 5 days (2-21 days) in patients with isolated viral myocarditis/myopericarditis. It was significantly longer in patients with MIS-C ($p = 0.034$).

Systolic and diastolic blood pressures were lower in MIS-C patients than in the others. The baseline characteristics of all participants are summarized in Table 1.

Laboratory Biomarkers

Complete blood count and biochemistry markers are all evaluated in both groups. Acute phase reactants

Table 1. Demographic features and physical examination results of the groups

	MIS-C	Isolated PERI/ myocarditis	*p* value
Age (months)	141.2 ± 38.2	145.8 ± 52.1	**0.192**
Gender, n (%)			
Male	23 (60.5)	29 (54.7)	**0.092**
Female	15 (39.4)	24 (45.2)	
Systolic blood pressure (mmHg)	102.45 ± 21.52	117.85 ± 11.24	**0.045**
Diastolic blood pressure (mmHg)	68.23 ± 15.33	76.21 ± 12.68	**0.038**
Height (cm)	138.13 ± 26.54	144.53 ± 38.21	**0.321**
Weight (kg)	37.21 ± 16.35	45.76 ± 23.72	**0.233**

Data are shown as mean ± standard deviation or n (%). MIS-C = Multi-system inflammatory disease in children.

Table 2. The comparison of cardiac biomarkers between MIS-C and isolated myocarditis/myopericarditis

Groups	MIS-C (n = 38)			Myocarditis/ Myopericarditis (n = 53)			*p* - value
	Median	1st Quarter (Q1)	3rd Quarter (Q3)	Median	1st Quarter (Q1)	3rd Quarter (Q3)	
Troponin I*	145.00	114.98	207.50	901.00	234.00	2802.00	**< 0.001**
CK[ɜ]	125.00	118.00	189.00	226.00	101.25	456.00	**0.035**
CK-MB[Ψ]	2.25	0.88	3.30	6.70	2.75	19.20	**< 0.001**
Pro-BNP[Φ]	2714.50	136.00	19219.50	294.00	92.25	3744.25	0.225

MIS-C = Multi-system inflammatory disease in children.

*Troponin I normal range: 12-20 ng/L

[ɜ]Creatinin kinase (CK) normal range: < 170 U/L

[Ψ]Creatinin kinase-myocardial band (CK-MB) normal range: 0.6-6.3 ng/mL

[Φ]pro Brain natriuretic peptide (ProBNP) normal range: < 300 pg/mL.

were higher in all patients with MIS-C. CRP normal range was below 5mg/L, and it was significantly higher in MIS-C patients than in isolated myocarditis/myopericarditis [median 121.6 mg/L (36.5-221) versus 12.6 mg/L (4.2- 90), respectively].

Troponin I level was high in all of the patients (Normal range is 12-20 ng/L). The median troponin I level was 145 ng/L (95-1220) in MIS-C patients, and it was 901 ng/L (196- >20.000) in myocarditis/myopericarditis. Normal values for CK-MB were between 0.6 to 6.3 ng/mL. CK-MB median was 2.25 ng/mL versus 6.7 ng/mL in MIS-C and myocarditis/myopericarditis, respectively. Pro-BNP level should be below 300 pg/mL, and it was 2714.5 pg/mL in MIS-C, and 294 pg/mL in patients with myocarditis/myopericarditis. Troponin I, CK-MB was significantly higher in myocarditis/myopericarditis, while Pro-BNP was significantly higher in MIS-C patients ($p < 0.05$) (Table 2).

The discriminating power of troponin I and CK-MB parameters on patients with MIS-C and myocarditis/myopericarditis was evaluated. The success of the parameters in classification was found to be statistically significant ($p < 0.001$). The area under the curve was Receiver Operating Curve (ROC) = 0.908 [0.82 – 0.96] and ROC = 0.800 [0.68 – 0.88], respectively. According to this model, individuals with a Troponin l parameter value below 100 were classified as MIS-C, while individuals with a CK-MB parameter value below 4.30 were classified as MIS-C (Table 3).

DISCUSSION

This study highlights the important differences between isolated myocarditis/myopericarditis and MIS−C myocarditis. Compared with isolated viral myocarditis/myopericarditis, those with MIS−C had

Table 3. The differential diagnosis power of cardiac biomarkers in isolated myocarditis/myopericarditis and MIS-C

Parameter	ROC [CI]	*p* value	Cut off	Sensitivity	95%CI	Specificity	95% CI
Troponin l	0.908 [0.82-0.96]	**< 0.001**	≤ 100	76.67	57.7-90.1	93.02	80.9-98.5
CK-MB	0.800[0.68-0.88]	**< 0.001**	≤ 4.3	90.00	73.5-97.9	64.29	48.0-78.4

CK-MB = Creatinin kinase-myocardial band, MIS-C = Multiystem innflammatory disease in children, ROC = Receiver Operating Curve

more significant elevation in pro-BNP value, and worse inflammation at presentation, but had lower troponin values with a much longer hospitalization stay. Cut-off values were calculated by this study for each entity with myocardial involvement.

It seems challenging to diagnose isolated myocarditis/myopericarditis in the pediatric population, especially in the era of other systemic diseases such as MIS-C. The clinical course and treatment could vary between these diseases and optimal clinical care and prognosis would be predictable due to laboratory markers. This study showed that laboratory markers could be utilized to make a differential diagnosis between the MIS-C and isolated myocarditis/myopericarditis. Although other clinical findings and history could help clinicians distinguish them, in some controversial situations, it is better to use a reliable marker to be sure of the diagnosis and treatment. Also, this comparison could give us the point that elevation of cardiac enzymes like troponin I doesn't correlate with the worse clinical condition all the time in the means of myocardial involvement. To our knowledge, this is the first study to analyze the cardiac biomarkers between these two groups.

There have been some previous studies comparing myocarditis and MIS-C in terms of clinical findings and prognosis [7, 17]. Cardiac involvement is not always present in MIS-C, it may occur secondary to systemic involvement [3]. In some cases, these two clinical conditions could be confused with each other. The course and severity of these two diseases and the use of cardiac biomarkers in the diagnosis and differential diagnosis were evaluated in this study.

The importance of cardiac biomarkers in the diagnosis of isolated myocarditis/myopericarditis is known. Elevated troponin I and pro-BNP are found to be associated with presentation in shock and LV dysfunction in some studies [18]. Although some studies have shown that the disease progresses more severely in cases with COVID-19-related myocarditis with high cardiac biomarkers [19], it has been reported that the very high troponin value in isolated viral myocarditis/myopericarditis doesn't mean severe myocardial damage [20]. Although troponin is more effective in demonstrating cardiac damage than CK-MB, it still has a low specificity. In this study, while elevated cardiac enzymes were higher in patients with isolated myocarditis/myopericarditis, troponin I was lower in patients with systemic involvement, such as MIS-C. However, clinical deterioration and worsening of cardiac functions were not evident in this disease group with myocarditis/myopericarditis. We attributed this to the predominance of pericardial involvement rather than myocardial damage in the isolated myocarditis/myopericarditis group. Pericardial involvement could also lead to higher troponin I levels [21].

Another cardiac biomarker is Pro-BNP. Elevated pro-BNP was also found to be associated with bad prognosis in diseases with myocardial involvement [22]. Higher pro-BNP values in MIS-C are another important parameter that may benefit clinicians in terms of both differential diagnosis and clinical course. The increase in pro-BNP value was found to be more pronounced in MIS-C patients than troponin in another study, and pro-BNP elevation was correlated with worse left ventricular function and a higher risk of cardiogenic shock [22, 23]. In fact, MIS-C patients also had higher troponin levels, but troponin was lower according to the myocarditis/myopericarditis patients in this study. MIS-C could be defined as a kind of vasculitis and systemic effects due to cytokines may affect cardiac functions [24]. Especially, pro-BNP may be more effective in demonstrating cardiac involvement in this kind of patient with multisystemic involvement.

In MIS-C patients, high pro-BNP levels were associated with prolonged length of stay in this study. The decrease in EF values was more pronounced in some MIS-C patients. ROC analyses were also performed, and limit values specific to cardiac involvement seen in MIS-C were found with cardiac biomarkers. Cut-off values that distinguish MIS-C and myocarditis and that may be useful in the diagnosis were determined. ROC analyses have been evaluated in other systemic diseases in the literature and the results supported the clinical use of these cut-off values [25].

Acute phase reactants were also higher in the MIS-C group, which is also consistent with widespread systemic inflammation and intensive care unit needs. In another study, acute phase reactants increased significantly in MIS-C and adversely affected the prognosis [17].

The management of acute myocarditis/myopericarditis is mainly conducive [2]. The use of IVIG and

steroids which have antiviral, anti-inflammatory, and immunomodulatory effects, remains controversial; IVIG has been shown to provide meaningful benefit in some pediatric patients, though not definitively [2]. On the contrary, in MIS-C, there is some evidence supporting that combination therapy with IVIG and steroids is related to good prognosis with reduced intensive care unit hospitalization [18]. Management of MIS-C and myocarditis/myopericarditis could differ among institutional protocols. When we evaluate the effects of cardiac biomarkers on treatment, as the higher troponin I didn't correlate with bad clinical course in this study, it seems higher pro-BNP correlates more with longer hospital stay and EF decrease. Thus, compatible with the literature, it seems that IVIG and steroid therapy are not essential in patients with myocarditis/myopericarditis associated with higher troponin I and lower pro-BNP.

Limitations

This is a single-center study and these diseases are so scarce, especially MIS-C. Finally, further large sample works should be accompanied to analyze the clinical usage of cardiac biomarkers in different clinical situations that comprise myocardial involvement and differential diagnosis.

CONCLUSION

In conclusion, both MIS-C and isolated viral myocarditis/myopericarditis could cause pro-BNP elevation, in which MIS-C is most prominent. Cardiac enzymes could rise in both diseases but most significantly in myocarditis/myopericarditis. These values will be useful in determining the diagnosis and risk of intensive care unit need for cardiac, and other systemic effects. Randomized controlled studies with a larger number of patients should be done in this manner.

Authors' Contribution

Study Conception: DD, DK; Study Design: DD, DK; Supervision: DD, DK; Funding: N/A; Materials: DD, DK; Data Collection and Processing: DD, DK; Statistical Analysis and Data Interpretation: DD, DK; Literature Review: DD, DK; Manuscript Preparation: DD and Critical Review: DD, DK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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