

Original Article

Cardiac Findings of Multisystem Inflammatory Syndrome in Children (MIS-C) with Corona Virus Disease 2019 (COVID-19)

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ABSTRACT

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) is an emerging serious consequence or association of COVID 19 disease in children. Along with its acute presentation, MIS-C threatens the patient and clinician alike for its multiple organ or system involvement, specially the heart. We describe cardiac changes of hospitalized MIS-C patients in Asian children, their short-term outcome by early or late presentation and onset of treatment in Evercare Hospital Dhaka, Bangladesh.

Methods: This observational study has been conducted at Evercare Hospital Dhaka on 15 patients with MIS-C. As part of ongoing MIS- C surveillance project, clinically suspected children attending outpatient and emergency room were screened and admitted for further evaluation and management. Cardiac evaluation of those children involved detail echocardiography. Other relevant demographic, clinical data and laboratory data have been collected from hospital surveillance record from 15th May to 30th July 2020.

Results: Among 15 patients, male: female was 1.14, age range 0.3 to 14 years with median age 4 yrs. Out of 15 children, 5 (33.33%) were COVID-19 RT-PCR positive and 10 (66.66%) had strong contact history with COVID 19 patients. All of them had fever at presentation. On clinical evaluation, 5 (33.33%) children had heart failure with hypotension, 5 (33.33%) had myocarditis and 3(19.8%) were in shock.

Troponin I and S. Pro BNP were elevated in 7(46.67%) and 5(33.33%) cases, respectively. Detail cardiac study yielded Coronary Artery Aneurysm (CAA) in 12(79.92%) and 9(59.94%) had irregular coronary vascular wall. There were left ventricular dysfunction in 5(33.3%), mitral regurgitation in 2(13.32%) and trace pericardial effusion in 1 (6.66%) case. Medium aneurysms of Left Main Coronary Artery(LMCA) and Left Anterior Descending Artery (LAD) were found in 2 (13.33%) patients. Small aneurysms were observed in LMCA and LAD and Right Coronary Artery (RCA) in 10 (66.6 %), 7(46.62 %) and 5 (33.3%) children respectively. One patient (6.66%) had dilated LAD. All received traditional treatment. Those with coronary artery changes arriving late and getting treatment at > day 7 of illness (Group A, 9/12, 75%), did not have their coronary artery aneurysm with irregular vascular wall back to normal even at 4-8 weeks of follow up. Group B (3/12, 25%) with coronary artery changes admitted early and treated ≤7 days of illness had good echocardiographic outcome.

Conclusion: Our observational study documented that children who came to hospital after one week of illness with coronary artery aneurysm, irregular coronary vascular wall, myocarditis, heart failure or cardiogenic shock, their response to treatment were delayed or poor based on follow up echocardiography. Further follow up studies and longer surveillance of the MIS-C patients are required to observe the long-term outcome of their coronary artery status and cardiac complications.

Keywords: MIS-C, COVID-19, SARS-CoV-2, Coronary artery aneurysm, Kawasaki disease.

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1. INTRODUCTION:

On April 26, 2020, clinicians in UK recognized increased reports of previously healthy children presenting with severe inflammatory syndrome. A new, serious COVID-19 cardiovascular presentation emerged in late April and early May 2020 in the form of Pediatric Multi-system Inflammatory

Syndrome which includes features like Kawasaki disease. It was first reported in the United Kingdom and then cases began to appear in New York City and elsewhere in the United States. The U.S. Centers for Disease Control and Prevention (CDC) first issued a health advisory statement on the new COVID-19 (SARS-CoV-2) presentation on May 14, 2020. The CDC is calling the new presentation in kids Multi-system Inflammatory Syndrome in Children (MIS-C) (1). WHO briefed on 15 May, 2020 as "Syndrome in children and adolescents temporally related to COVID19" and developed the case definition and case report form for multisystem inflammatory syndrome in children and adolescents (1, 2, and 3). The first case of MIS-C was diagnosed at Evercare Hospital Dhaka in Bangladesh on 15th May, 2020. Our study population was 15 children with MIS-C. These were like Kawasaki disease but clinically and by echocardiography study their clinical deterioration was more rapid. The focus of this study is on short term cardiac outcome of the children with MIS-C having coronary artery aneurysm with irregular coronary vascular wall.

2. METHODS

Participants: Sick children attending Evercare Hospital, Dhaka are triaged in Outpatient and in Emergency department. Children who met the criteria for Multi System Inflammatory Syndrome as per CDC and WHO guideline, were enrolled in the study.

Case definition: Multisystem Inflammatory Syndrome in Children (MIS-C) were diagnosed as per CDC and the WHO protocol. Any child within 0-16 years old having fever ≥ 3 days and two of the 1. rash, 2. Hypotension or shock, feature of myocardial dysfunction, pericarditis, valvulitis/ coronary abnormalities (including echo findings/elevated Troponin/Pro BNP.) (1, 3), evidence of coagulopathy (by PT, PTT, elevated D-Dimers), acute GIT problems (diarrhea, vomiting/abdominal pain), elevated markers of inflammation (CRP, S. Ferritin) and no other microbial causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes and evidence of COVID-19 (RT-PCR positive) with our virologic laboratory evidence, or likely contact with patients with COVID-19 in 6 weeks before hospitalization. In Evercare Hospital Dhaka fifteen children admitted through Paediatric OPD and emergency room met the above criteria and were enlisted for detail study.

Study time: From May 15, 2020 to July 30, 2020.

Data Source: All data were obtained from Paediatrics and Paediatric Cardiology OPD and admitted patients' hospital records by Evercare Hospital Dhaka's electronic, clinical, and laboratory system. The results of RT-PCR COVID-19 were collected from laboratory of Virology department of our hospital.

Data collection: We used standard triage form of MIS-C patients, standardized OPD case report form, a trained team of Physicians, nurses, technicians who extracted demographic

information, clinical profile, laboratory values, treatment course in hospital, echocardiography and laboratory follow up data and treatment outcome based on day of onset of treatment from May 15, 2020 to July 30, 2020. Data collection forms and patients records included symptoms and signs like fever, heart failure (tachycardia, tachypnea, hypotension), shock, GI symptom (diarrhea, vomiting, abdominal pain), rash, mucocutaneous changes: cracked lip, red tongue, red eye, pneumonia with respiratory distress, chest pain, pedal oedema, lymphadenopathy, joint pain, serositis, neurocognitive disorder (headache/convulsion/syncope), low SPO₂ (94%-95%) or normal SPO₂ (96%). Two authors (paediatrician and Paediatric Cardiologist) independently assessed the MIS-C patients clinically but managed them as a team. They assessed the eligibility of the retrieved references independently.

Echocardiography: Echocardiography were done by Philips Epic 7-C and GE Vivid-6 portable echo machine, performed by Consultant, Paediatric Cardiology, EHD.

Standardized study definition: Coronary artery internal diameter was taken, plotted in z-score (Boston criteria) and classified as AHA guideline of Kawasaki disease (4). We plotted the cases with coronary artery involvement on the recommended z-score classification as - dilation only (z-score 2 to <2.5), small aneurysm (Z score ≥ 2.5 to 5), medium aneurysm (Z score ≥ 5 to <10 and absolute dimension <8mm), and large/giant aneurysm (Z score ≥ 10 or absolute dimension ≥ 8 mm) (4). Irregular coronary vascular wall and perivascular cuffing/brightness was evaluated by qualitative method. Myocarditis was determined by cardiac dysfunction (LVEF <55% by motion mode) on echocardiography and elevated troponin and or elevated Pro BNP level. Cases were categorized as two subgroups: Group A (MIS-C with day of onset of treatment >7 days of illness) and Group B (MIS-C with day of onset of treatment ≤ 7 days). SARS-CoV-2 infection was diagnosed by nasopharyngeal swab Real Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) in our hospital. In our study we could not count antibody test (COVID-19) as it was not allowed by National body. Pneumonia was diagnosed clinically and chest x-ray findings. We did not do CT- chest. We defined the values for tachycardia, tachypnea, hypotension according to CDC guideline.

Laboratory parameters for all investigations were labelled as elevated or depressed in relation to age specific normal ranges of our hospital laboratory parameter.

The MIS-C children were treated after getting admission according CDC protocol of MIS-C and AHA guideline of Kawasaki Disease (4). Intravenous immunoglobulin was given according to CDC protocol.

We recommended IVIG for all patients who met criteria of moderate to severe MIS-C with or without Kawasaki disease

like feature. This includes any of the features as shock/cardiac involvement (depressed left ventricular function on echocardiography, coronary artery (dilation or aneurysm) on echocardiography, elevated pro BNP and or troponin or other severe manifestations requiring ICU care.

Antithrombotic therapy was given to those having medium to giant aneurysm with structural deformity of coronary arteries, patients with left ventricular dysfunction and other coagulation abnormalities.

Statistical analysis: We implemented observational retrospective data analysis that summarized the demographics, clinical presentation, laboratory data, echocardiographic findings, treatment records and outcome of two groups having coronary artery aneurysm (CAA) based on the day of onset of treatment. And data were documented on a Microsoft Excel spread sheet.

Ethics Committee approval was taken from Evercare Hospital Dhaka, Bangladesh.

3. RESULTS

During the study period, total 15 cases were diagnosed as MIS- C in our hospital according to their clinical features and laboratory reports and 2D-Color doppler echocardiography. Out of 15 patients almost same gender prevalence with male 8(53.33%) and female 7 (46.67%), median age 0.3-14 years. Among total (n=15), RT-PCR COVID 19 positive 5(33.33%) and 10(66.67%) had contact with patients with COVID-19 in 6 weeks before hospitalization. All presented with fever 15(100%), gastrointestinal symptoms 14(93.33%) and cardiovascular involvement with coronary artery aneurysm 12 (79.92%), heart failure with hypotension 5(33.33%) and shock 3(19.80%), rash 7,(46.67%), mucocutaneous changes conjunctival congestion (Fig 1) /cracked lips/red tongue 4(26.64%), pneumonia with respiratory distress 5(33.33%), chest pain 4(26.64%), cervical lymphadenopathy 3(19.98%), joint pain 2,(13.33%),serositis (small pleural/pericardial effusion or ascites) 2(13.33%),Pedal oedema 4 (26.64%), neurocognitive disorder (headache, lethargy confusion, convulsion) 2 (13.33%),with SPO2 96% of 10 (66.64%) and low SPO2(94-95%) in 5 (33.33%) (Table 1).

Regarding cardiac biomarker 47.67 % had raised Troponin I and 33.33 % high Pro BNP (Fig 2).

According to echocardiographic evaluation among 15 cases coronary artery aneurysm 12(79.92%), irregular coronary artery wall 9(59.94%), myocardial dysfunction (LVEF<50%) 5 (33.3%), mitral valve regurgitation 2(13.32%), and pericardial effusion in 1 (6.66%). No one had pleural effusion (Table 2).

Our study revealed that Cardiovascular and Gastrointestinal system were predominantly affected with rash and mucocutaneous changes in MIS-C.

Out of 15 patients, 12(79.92%) had coronary artery aneurysm (Fig 3). Out of the 12 patients with coronary artery aneurysm, 9(75%) had structural deformity or irregular coronary vascular wall (Fig 4,5).

Z-score based classification of coronary artery aneurysm (CAA) showed, 10(66.67%) had small aneurysm of Left Main Coronary Artery (LMCA), 7(46.62%) had small aneurysm of Left Anterior Descending Artery (LAD) and 5(33.30%) had small aneurysm of Right Coronary Artery(RCA)(Fig 7). Medium aneurysm of LMCA and LAD were 2 (13.33%) in same and different patients (Fig 6,8) and one had dilated LAD (6.66%) (Fig 8). So, in our study we observed that LMCA and LAD were predominantly involved. One patient (7 years old boy) had medium aneurysm of LMCA and giant aneurysm ($z = +10.89$) of LAD which decrease on further follow up (Table 3). Small RCA CAA 5(33.30%) and RCA was normal in 10 patients (66.6%) (Fig 8).

For comparative assessment, children were divided into two groups by time of presentation to the hospital and onset of treatment. Those who presented late and for whom treatment were started from 8 days onward of illness, they were categorized in Group A. Those who presented early and for whom treatment were started within 7 days, they were categorized in Group B.

Among 12 patients with coronary artery aneurysm, in Group A: 9 (75 %) started treatment on more than 7 days of illness. Their onset of treatment was D8-D23 of their illness. Their serial echocardiography revealed coronary artery aneurysm of most of the patients did not revert in normal caliber even within 4- 8 weeks of follow up echocardiography who had small and medium sized aneurysm with delayed onset of treatment (Table 3). Only one child who had CAA with irregular coronary vascular wall and shock, started treatment on D8 and recovered within two weeks. Our first patient 3 months old child's CAA became normal after 14 weeks of onset of treatment. The baby was diagnosed and treated on D9 of illness (Table 3).

But in Group B: 3 (25 %) children having CAA received the treatment within 7 days of their illness. Follow up echocardiography showed their coronary arteries returned to normal diameter within 3-4 weeks (Table 4, Fig:9).

Coronary artery dilation/aneurysm with irregular coronary vascular wall, perivascular cuffing were also more common in MIS-C. All the children with CAA with irregular vascular wall and raised cardiac and inflammatory biomarkers were treated with intravenous Immunoglobulin (IVIG), intravenous methylprednisolone followed by oral prednisolone and medium dose tab aspirin followed by low dose tab aspirin on follow up. Both the Group A and Group B were treated with same medication. Some of them were treated with additional thromboprophylaxis having severity of the CAA and high cardiac inflammatory markers. Outcome of treatment in acute phase was good without any mortality.

Table 1: Demographic and Clinical Profile of MIS-C (n=15)

Characteristics	Total(n=15)	%
Demographic		
Male	8	53.33
Female	7	46.67
RT-PCR positive	5	33.33
H/o contact with COVID -19	10	66.67
Clinical Symptoms		
Fever	15	100
GI symptom	14	93.33
Rash	7	46.67
Mucocutaneous changes: lip, red tongue, red eye Cracked	4	26.67
Heart failure with hypotension, Myocarditis	5	33.33
Shock	3	19.98
Pneumonia with respiratory distress	5	33.33
Chest pain	4	26.64
Pedal Oedema	4	26.64
Lymphadenopathy	3	19.98
Joint pain	2	13.33
Serositis	2	13.33
Neurocognitive disorder	2	13.33
SPO2 (94%-95%)	5	33.33
SPO2 (96%)	10	66.67

Table 2: Echocardiographic findings of MIS-C (n=15):

Characteristics	Total (n=15)	%
a. Coronary artery changes		
1. Coronary artery aneurysm/ectasia	12	79.92
2. Irregular coronary arterial wall	9	59.94
b. Myocardial dysfunction	5	33.3
c. Mitral regurgitation	2	13.32
d. Serositis		
1. Pericardial effusion	1	6.66
2. Pleural effusion	0	0



Fig 1: MIS-C with congested eye.

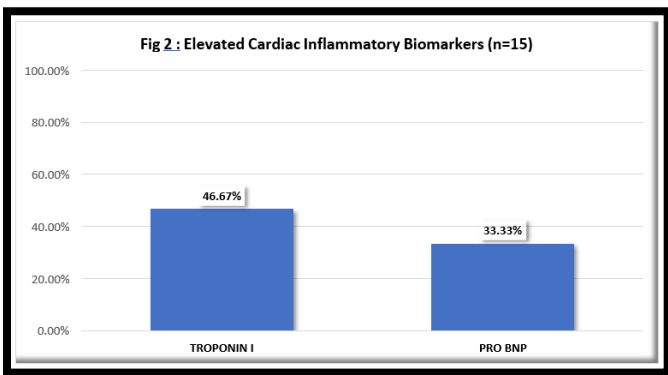


Fig 2: Shows distribution of patients with elevated cardiac inflammatory biomarkers.

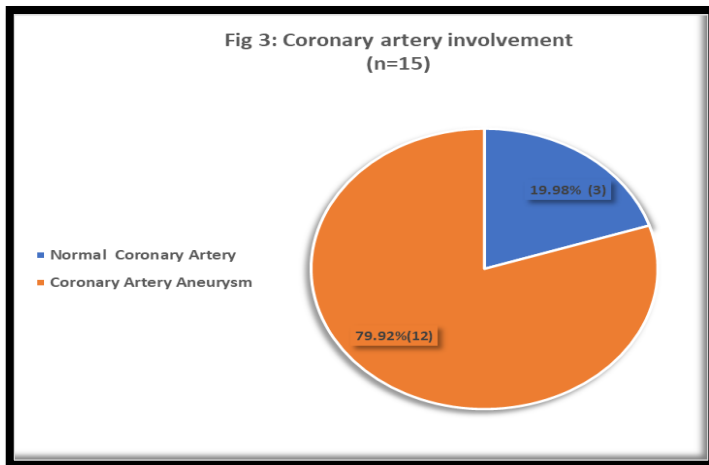


Fig 3: In Pie chart, color code orange reveals the bulk of the patients having coronary artery aneurysm and blue indicates the patients with normal coronaries.

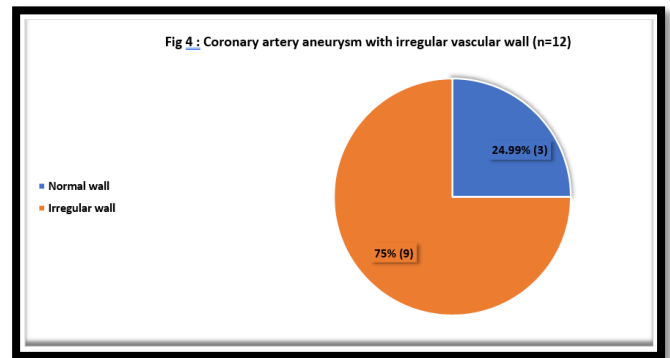


Fig 4: In Pie chart, colour code orange reveals the number of the patients with Coronary artery aneurysm with irregular vascular wall and blue indicates the patients having coronary artery aneurysm with normal vascular wall.



Fig 5: Irregular coronary artery aneurysm of Left Anterior Descending artery.

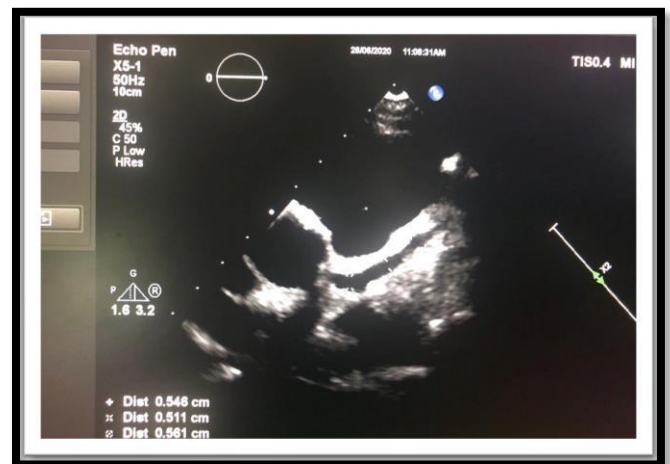


Fig 6: Coronary Artery Aneurysm (CAA) of Left Main Coronary Artery (LMCA) and Left Anterior Descending artery (LAD).

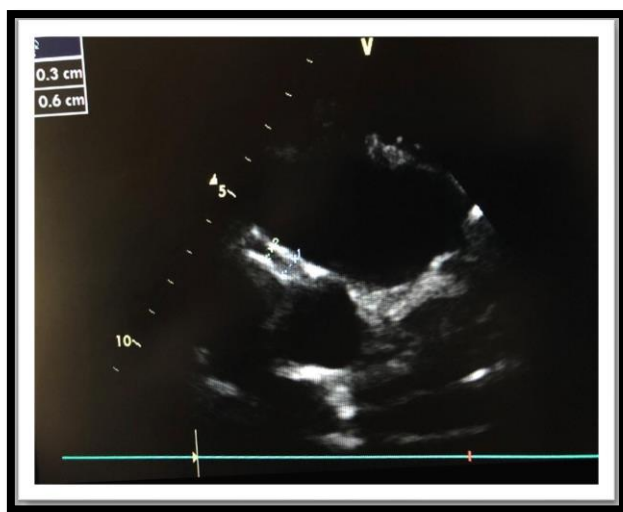


Fig 7: Right Coronary Artery (RCA) aneurysm.

Fig 8: Distribution of patients with coronary artery aneurysm by Z- score (n=15)

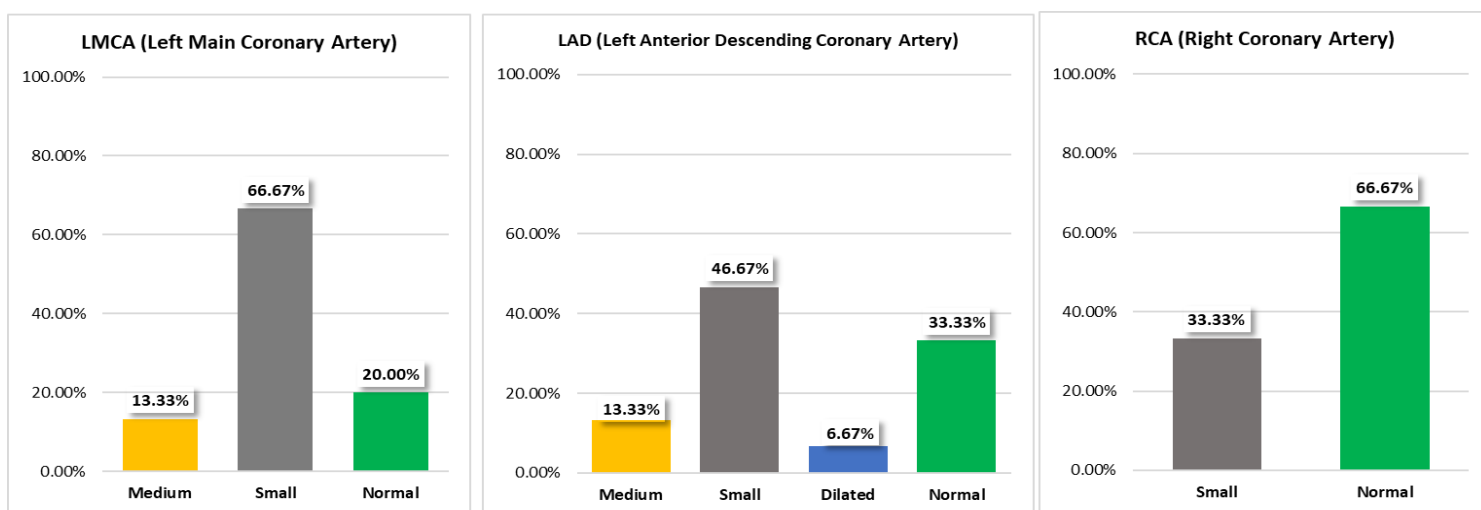


Fig 8: Left panel shows changes in LMCA, mid panel remarks LAD changes and right panel indicates the changes of RCA. Colour coded bars show different types of aneurysm.

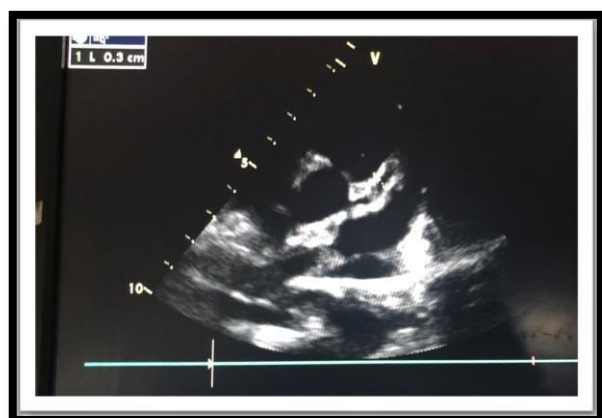


Fig 9: Coronary artery aneurysm after treatment.

Table 3: Group-A: Treatment outcome of CAA according to day of onset of treatment (n=9/12)

S. No	Age/ Sex	Onset of treatment (D/illness)	1st F/U echo after admission Absolute size in mm (Z score)	2nd F/U echo D7 of treatment Absolute size in mm (Zscore)	3rd F/U echo D14 of treatment Absolute size in mm (Z score)	4th F/U echo 3 week - 4 week of treatment, Absolute size in mm (Zscore)	5th F/U echo 6 week-8 week of treatment Absolute size in mm (Z score)
1	4y 9m/F	D8	LMCA: 4 (+3.76) LAD: 3 (+ 2.90) RCA: 2 (-0.44)	LMCA: 4.7 (+5.47) LAD: 3.3 (+3.7) RCA: 1.5 (1.62)	LMCA: 2.8 (+ 0.93) LAD: 2.5 (+ 1.6) RCA: 2 (-0.38)		
2	2y 2m/ M	D9	LMCA:3.8 (+ 4.13) LAD: 2.4 (+ 2.48) RCA: 2 (+ 0.67)		LMCA: 3.6 (+ 3.43) LAD: 2.1 (+ 1.19) RCA: 2.8 (+ 3.11)		LMCA :3.6 (+4.09) LAD: 2 (+ 1.1) RCA:1.8 (-0.03)
3	4y /F	D14	LMCA: 4 (+ 4.92) LAD: 3 (+ 3.85) RCA: 2 (+ 0.33)		LMCA: 3.4 (+ 3.34) LAD: 3(+ 3.85) RCA: 1.8 (+ 0.33)	LMCA :3.6(+3.27) LAD :2.5(+1.97) RCA :2.1(+0.15)	
4	7y /M	D23	LMCA: 6 (+ 6.57) LAD: 5.4 (+ 7.52) RCA: 3.8 (+ 2.48)	LMCA: 5.9(+ 6.57) LAD: 6.8 (+ 10.89) RCA: 2.74 (+ 0.22)		LMCA: 5.9 (+ 6.49) LAD: 4.7 (+ 5.77) RCA: 3 (+ 1.48)	LMCA: 4.6 (+ 3.7) LAD: 3.8 (+ 3.7) RCA: 3.6(+ 2.79)
5	9m /F	D10	LMCA: 3 (+ 3.84) LAD: 2 (+ 2.21) RCA: 2.31(+ 3.16)			LMCA: 2.8 (+ 3.18) LAD: 1.8 (+ 1.52) RCA: 1.37 (+ 0.30)	LMCA: 2.8 (+ 2.9) LAD: 12.2 (+ 2.5) RCA: 1.7 (+ 0.43)
6	3y 9m/ M	D8	LMCA:3.3 (+ 2.73) LAD: 2.2 (+ 1.32) RCA: 2.3 (+ 0.82)	LMCA: 3.5 (+ 3.24) LAD: 3.2(+ 4.09) RCA: 2(+ 0.07)		LMCA: 3.78 (+ 4.01) LAD: (+ 4.09) RCA: 1.6 (- 0.93)	LMCA: 3.4 (+ 3.02) LAD: 2.3 (+ 1.6) RCA: 1.4 (- 1.4)
7	3m /F	D10	LMCA:3.5 (+ 5.03) LAD: 2.5 (+ 5.72) RCA: 1.8 (+ 1.67)		LMCA: 3.9 (+ 6.17) LAD: 2.5 (+ 5.60) RCA: 2.4 (+ 2.9)	LMCA: 2.25(+ 2.35) LAD: 2.2(+ 3.5) RCA: 1.1 (- 0.51)	LMCA: 2.7 (+ 3.4), >after 14 wks > 2(1.17) LAD: 1.8 (+ 1.9) >after 14 wks> 1.6(+1.16) RCA: 1.4 (- 0.20) >after 14 wks1.6(+0.64)
8	3y 6m/ M	D15	LMCA: 3.9 (+ 4.1) LAD: 3.3 (+ 4.22) RCA: 2.5 (+ 1.19)	LMCA: 3.6(+ 3.34) LAD: 3 (+ 3.39) RCA: 2.3 (+ 1.72)		LMCA: 3.6 (+ 3.34) LAD: 3 (+ 3.39) RCA: 2 (+ 0.05)	
9	10m/ M	D12	LMCA:2.3 (+1.71) LAD: 2.7 (+ 4.33) RCA: 2 (+ 1.49)			LMCA: 2 (+ 0.84) LAD: 2.8 (+ 4.49) RCA: 2.1 (+ 1.8)	LMCA: 2 (+ 0.71) LAD: 2.8 (+ 4.49) RCA: 1.7 (+ 0.52)

Table 3: Group A: Color code: Blue indicates small coronary artery aneurysm, Amber indicates medium coronary artery aneurysm, and Red specifies giant coronary artery aneurysm and black only dilation / normal coronary artery. Irrespective of age and sex CAA did not become normal even after 8 weeks whose onset of treatment was >7 days of illness.

Table 4: Group-B: Treatment outcome of CAA according to day of onset of treatment (n=3/12)

S.No	Age/ Sex	Onset of treatment (D/Illness)	1st F/U echo after admission Absolute size in mm (Z score)	2nd F/U echo D7 of treatment	3rd F/U echo D14 of treatment Absolute size in mm (Z score)	4th F/U echo 3 week - 4 week of treatment Absolute size in mm (Z score)	5th F/U echo 6 week-8 week of treatment
1	6y /F	D4	LMCA: 4.4 (+ 4.19) LAD: 3.3 (+ 3.25) RCA: 3.2 (+ 3.07) LMCA stenosis: 1.3 (-3.14)		LMCA: 3.2 (+ 0.98) LAD: 2.4(+0.2) RCA: 1.3(- 1.59)	LMCA: 3 (+ 0.88) LAD: 2.2 (+ 0.04) RCA: 1.3(- 1.59)	
2	2y 2m/M	D6	LMCA: 3.4 (+ 3.23) LAD: 2.2 (+ 1.50) RCA: 1.5 (- 0.32)		LMCA: 2.7 (+ 1.51) LAD: 2(+ 1.06) RCA: 1.3 (- 0.56)	LMCA: 2.5 (+ 0.91) LAD: 2 (+ 0.96) RCA: 1.2 (- 1.06)	
3	11y/M	D3	LMCA: 4.1 (+ 2.7) LAD: 2.5 (+ 1.25) RCA: 2(- 0.74)		LMCA: 3 (- 1.7) LAD: 2 (-1.21) RCA: 1.8 (- 0.95)	LMCA: 2.6 (- 0.02) LAD: 1.9 (- 0.29) RCA: 1.8 (- 1.19)	

Table 4: Group B: Blue indicates small coronary artery aneurysm. Their onset of treatment was within 7 days of illness and CAA recovered within 2 weeks of treatment.

4. DISCUSSION

According to Centers for Disease Control and Prevention (CDC) multisystem Inflammatory syndrome in Children is related to COVID-19 and temporally related to previous exposure to SARS-CoV-2 (1,2). On 15th May, WHO developed a preliminary case definition of this hyperinflammatory syndrome which reflects the clinical and laboratory features observed in children to identify suspected or confirmed cases both for the treatment purpose and also for provisional reporting and surveillance (3). Since mid-May to mid- July total 15 patients were successfully managed as MIS-C in Evercare Hospital Dhaka without any mortality. The first case was diagnosed in our hospital, in Bangladesh on 15th May, 2020. The focus of this observational study is on short term cardiac outcome of the children having coronary artery aneurysm. Based on their day of starting of the treatment, the cases were categorized into two subgroups,

Group A (MIS-C with CAA who received treatment on D8-D23 of illness)

Group B (MIS-C with CAA who received treatment on D3-D7 of illness).

Both groups were treated with the same traditional medications. All the children were diagnosed as MIS-C as per the case definition of CDC and WHO (1,3). According to both the definitions patients had fever, elevated inflammatory markers, at least two signs of multisystem involvement, evidence of SARS-CoV-2- infection or exposure, and exclusion of other potential causes. All the study cases had either current SARS-CoV-2 infection by positive

RT-PCR (33.33%) or had highly suspected previous exposure to confirm cases (66.6%). All the children had history of fever for at least more than 3 days. Most of them had cardiac and gastrointestinal system involvement and mucocutaneous changes (Fig: 1) (Table 1). Some of them had respiratory distress with pneumonia and hypoxia. (Table 1).

Raised cardiac inflammatory marker indicated heart failure or myocarditis (Fig: 2). Those children were treated accordingly in ICU.

We performed the echocardiography of all MIS-C patients irrespective of severity of their clinical profile. Echocardiographic evaluation was done to observe coronary artery changes including aneurysm/ectasia and structural abnormalities (irregularities of coronary arterial wall and perivascular cuffing) (Fig 5,6,7) and to assess the status of myocardial dysfunction (EF%), valvular function and to evaluate intracardiac thrombosis, pericardial and pleural effusion (Table 2).

Evaluation of structural changes of coronary artery were the main focus of our study (Fig 3). Our children with MIS-C had CAA/ectasia with irregular vascular wall (Fig 4) with associated myocardial dysfunction, valvular regurgitation, and pericardial effusion (Table 2) which are common findings of MIS-C (2).

In our observation, coronary artery aneurysm was noticed in all three major coronary arteries (LMCA, LAD and RCA). Among them LMCA and LAD were commonly affected (Fig 6,8). Z-score

based classification of coronary artery aneurysm (CAA) plotted in Table 3, 4 showed their outcome by follow up echocardiogram based on the day of onset of treatment. One patient (7 years old boy) had giant aneurysm ($z = +10.89$) on follow up which decreased on further follow up. Most of the patients had normal RCA (Fig 8).

Coronary artery diameter were taken, plotted in Z-score (Boston criteria) and classified the aneurysm as AHA guideline of Kawasaki disease (4).

We used intravenous immunoglobulin for the patient with CAA, myocardial dysfunction, shock and who had criteria of moderate to severe MIS-C even with or without typical and atypical KD features (1). We used IVIG (2 gm/kg over 12-24 hours in single infusion) and medium dose tab aspirin (50 mg/kg/day in 4 divided doses) 48-72 hours of defervescence of fever. We treated the baby with intravenous methylprednisolone (1 mg/kg/dose once daily) to control cytokine storm of MIS-C followed by oral prednisolone.

Thromboprophylaxis was also used for them having typical or atypical KD like feature, CAA with irregular vascular wall, severe myocardial dysfunction or moderate to severe MIS-C (1).

For treatment purpose we followed CDC and WHO protocol and AHA -KD guideline (4). At our center first echocardiography was done with D1-D3 of admission. Timing of follow up echocardiography were performed according to the protocol of Paediatric Cardiology. First follow up echocardiogram was performed after completion of intravenous immunoglobulin, and medium dose tab aspirin till 48-72 hours of defervescence of fever to check the status of coronary artery or to take decision to shift the baby from ICU. 2nd follow up echocardiography was done just before discharge. Further follow up study were done every 2 weeks for next 4 to 8 weeks of illness. After 8 weeks follow up echocardiography, further follow ups were planned monthly to avoid any new or fatal changes of CAA, stenosis, or myocardial dysfunction. For the patients whose coronary arteries became normal in follow up echocardiogram after acute phase should be followed up at least monthly to assess any further coronary arterial changes.

For comparative observational study, children were categorized into two groups according to their time of presentation to the hospital and onset of treatment. Group A had delayed onset of treatment (>7 days) because of their delayed reporting to hospital. Group B was treated early because of their early admission.

In our cohort, those in Group A (9 out of 12 cases) had CAA with profound irregular vascular wall which did not revert to normal caliber or normal architecture within 4-8 weeks of illness despite their proper management. They were admitted lately, and their treatment started within D8- D23 of illness.

Because of disease process their cardiac complications were more. Their recovery was delayed because of the severity of multi organ dysfunction as well. Even on 3rd to 5th follow up (4th week of illness to 8th week of illness) their CAA were observed with irregular coronary artery wall (Table 3). Some of them had same z-score of coronary artery aneurysm or had minimal improvement on further follow up echocardiography. Three months old girl (Case 7) having medium CAA of LMCA and LAD came lately and was treated with traditional medications by D10 of illness. After 14 weeks of treatment her coronary artery reverted to normal z score (Table 3). On the other hand, 4 years 9 months old girl (Case 1) who got IVIG on D8 had prominent coronary artery aneurysm with irregular vascular wall. But on follow up, normal measurement of coronary artery with prominent irregular vascular wall was seen on 2nd week of treatment (Table 3). However, the patient had myocardial dysfunction, cardiogenic shock and required inotropic support in ICU with appropriate treatment.

Both girls are on follow up. On the contrary, the 7 years old boy (Case 4) who came very lately and received treatment at D23, had medium aneurysm LMCA and LAD (Fig 6) and on D7 follow up his LAD aneurysm became giant ($Z + 10.89$) (Table 3). He had medium CAA on 4th and 8th week of illness with distorted vascular wall (Table 3). He is on low dose aspirin and additional thromboprophylaxis.

Out of 12 cases 3 patients in Group B had coronary artery aneurysm with irregular vascular wall who came within 7 days and received treatment accordingly. Their CAA and coronary artery structure returned to normal diameter with smooth regular inner coronary arterial wall by 2 week-follow up. (Table 4, Fig 9).

Regarding the studies of MIS-C patients in UK Levin said "The cardiac findings were striking, with 8 out of 19 patients who had echocardiograms having evidence of impaired left ventricular function. Coronary artery dilation or aneurysms were present in 5 of the 19 patients. One patient had a giant left coronary artery aneurysm" (5).

Mary Beth F Son, Kevin Friedman et al noted that for patients who had evidence of coronary artery involvement or systolic dysfunction/myocarditis in acute phase, cardiac magnetic resonance imaging can be considered after two to six months of acute illness to assess ventricular function and evaluate edema, diffuse fibrosis and scar by myocardial delayed enhancement (6).

As MIS-C is new era in medical science, we are not having any follow up- protocol for this patient. Hence, we are following the research studies of Kawasaki disease and CDC guideline of MIS-C in this purpose.

Michael Portman, MD, of Seattle Children's Hospital and a member of the American College of Cardiology committee group is looking to track Kawasaki disease patients to see if they were exposed to COVID-19, to look for genetic susceptibility, and to see what happens to their immunity to the corona virus (5).

Regarding MIS-C, Dr. R. Mathew, Jones' colleague and a Paediatric infectious disease specialist at Stanford's Lucile Packard Children's Hospital, said "the general thought is, this is a post-infectious trigger causing the immune system to hyper-react." Infections of any kind can cause inflammation in the body. So, it's possible that SARS-CoV-2, the virus that causes COVID-19, is kickstarting inflammatory responses in small numbers of children, she said⁽⁵⁾.

As MIS-C is related to COVID-19 and it is hypothesized that the disease is immune mediated similar to KD. Therefore, structural variation of coronary arterial wall could change over according the day of illness. Our echocardiographic study also showed clearly that the structural changes of CAA with irregular vascular wall depends upon the day of illness if it remains untreated like KD.

To describe the natural history Brian W. McCrindle, Anne H. Rowley et. al in circulation reported that coronary artery abnormalities were determined by serial angiographic follow up which could pick up the future outcome of CAA⁽⁴⁾.

Kato et al reported outcomes in 598 KD patients over 1973- 1983 and followed up to 10-21 years. They reported one quarter of the study population had CAA and 49 % of their coronary artery reduced to normal dimension 6-18 months later. But 55% had increasing dimension of CA with ongoing follow up. All aneurysm that reduced in size to a normal luminal dimension were originally small to moderate in size. Among them 28 patients developed stenosis. More than half of those patients developed MI who had giant aneurysm⁽⁷⁾.

Late development or increases in size of aneurysms have been reported in case reports (8,9,10). Tsuda et al in an angiographic reported that out of 562 patients 15 patients had new dilated or expanding lesions in coronary artery. The new aneurysm developed at the site of previous aneurysm had reduced in size and these were all associated with localized stenosis⁽¹¹⁾.

Therefore, long term changes in coronary artery should be followed up initially by serial echocardiography to detect any new CAA/ectasia, thrombosis to take the proper measure in time to avoid MI or bypass surgery. Although giant aneurysms are more prone to develop MI (4). Permanent disorganized coronary vascular wall leads to poor long-term outcome⁽¹¹⁾.

In KD, pathological changes of coronary artery occur in variable stages from acute, subacute or chronic vasculitis. The pathological process of necrotizing arteritis during acute illness stage 1, which results in destruction and weakening of the arterial wall leading to aneurysms and thrombus formation stage 2. Coronary artery aneurysm causes destruction of intima, elastic intima, media and variably, adventitia.

This stage may lead to subacute and chronic vasculitis and luminal myofibroblastic proliferation. This process may lead to marked intimal thickening stage 3 and stenosis, scarring calcification and recanalization of major coronary arteries stage 4.^(4,12) During our follow up, we observed the barely change of coronary artery aneurysmal diameter and irregular inner wall of coronary arteries in some patients who were admitted and received treatment after 8-9 days of illness (Group: A, Table: 3) And the patients who came early, though treated with same traditional medicine, their outcome was favorable (Group: B, Table: 4). In severe form of MIS-C cytokine storm also were controlled with timely and appropriate medications and their coronary aneurysm reduced in dimension on 2nd or 3rd follow up visit.

Elizabeth M. Dufort, et al reported 99 cases of MIS-C in New York with coronary aneurysm in 9 % cases, and myocarditis 52% cases. They also observed that 59 had evidence of cardiac abnormalities according to s. Troponin, pro BNP levels, echocardiogram, and electrocardiogram reports⁽²⁾.

Tristan et al described in their one-month retrospective study among 15 children, 14 children (93%) had coronary artery abnormalities with normalization in 6, left ventricular dysfunction in 12 (80%), resolution in all but 2 cases⁽¹³⁾. Their observational retrospective study showed that most of the children had coronary artery involvement with cardiac involvement, and that degree of involvement was significantly higher than in other recent studies⁽¹³⁾. In their study, 7 children had aneurysmal dilation, involving LMCA in 2 patients, LAD in 4 patients and RCA in 1 patient. Other 6 had prominent coronary artery.

Among 23 patients in Mumbai reported by Shreepal Jain et al, 26 % had coronary artery dilation; and this coronary involvement was independent of status of shock or age variation⁽¹⁴⁾.

Feldstein LR, Rose EB et al reported on 8th July, 2020, out of 186 patients of 26 states US, 80 % had cardiovascular involvement and half of them had cardiogenic shock requiring inotropic support. In their series, coronary involvement were less (8%)⁽¹⁵⁾.

In our study coronary artery involvements were more than cardiogenic shock or myocardial dysfunction. It was also obvious that CAA returned to normal within very short time in those who received the treatment within two weeks of illness. We have plan for surveillance follow up of every patient with MIS-C irrespective of their coronary artery status. In future CT or MRI might be required for them whose coronary artery did not return to normal caliber or in those who develop new aneurysm or stenosis in previously normal coronary artery. Although MIS-C has similarities with Kawasaki disease, the cardiovascular involvement was different in severity and duration of deterioration. Even for the children with medium to giant CAA/ectasia with irregular vascular wall/perivascular cuffing, we suggested additional thromboprophylaxis along with low dose tab aspirin. Some of them were suggested to refrain from competitive or vigorous activities as well.

5. CONCLUSION

Multisystem Inflammatory Syndrome in Children (MIS-C) is an emerging illness which can be fatal due to cardiac and other systemic complications if the children could not be diagnosed and treated timely. Our observational study documented that the children who came in hospital after one week of illness and with more cardiac involvement, e.g. coronary artery aneurysm, myocarditis, heart failure or cardiogenic shock, their response to treatment were delayed or poor on follow up echocardiography. Further follow up surveillance of the MIS-C patients are required to observe the long-term outcome of their coronary artery changes.

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