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RESEARCH PAPER

# COVID-19 Related Multi System Inflammatory Syndrome in Children: Scenario from a Tertiary Care Hospital in Bangladesh

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## Abstract

***Background:*** An association of multisystem inflammatory syndrome in children (MIS-C) with SARS-CoV-2 infection is now a well-established serious phenomenon and been increasingly reported from different countries.

***Objectives:*** The present study documents the presentation, management and immediate outcome of MIS-C patients from Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh.

***Study design:*** This was a retrospective study.

***Methods:*** This retrospective study was conducted in the department of pediatrics, BSMMU, Dhaka, Bangladesh. It included all the eligible MIS-C patients diagnosed during the study period (August 2020 to February 2022). Sixty cases fulfilled the diagnostic criteria and they had been included in the study. Data were collected using a pre-designed and pre-tested questionnare from hospital records and also by interviewing the patients/parents over telephone when required.

***Results:*** Mean age of the children was 6.8year with F: M ratio of 1.2:1. All the sixty cases presented with fever associated with gastro-intestinal complications in 68% followed by other symptoms. Fifty two cases (87%) had known contacts. Laboratory evidence ofSARS-CoV-2 infection was present in 55% cases having positive serology or RT-PCR. Twelve patients (20%) had pre-existing co- morbidities. Majority of patients (48%) presented with Kawasaki Disease (KD) like illness. Mean neutrophil count, ESR, CRP, ferritin, LDH and D-dimer were higher and mean platelet and lymphocyte count were lower in this series. Interleukin-6 (IL-6) level was raised in all the seventeen (28%) patients, who were tested. Sixteen patients (27%) had chest X-ray abnormalities and ten of them had HRCT involvement. Fifteen (25%) patients had abnormalities in abdominal ultrasonogram. Coronary artery dilatation and ventricular dysfunction was present in seventeen (28%) and thirteen (22%) of MIS-C cases.

IVIG and intravenous steroid was used in forty one (68%) and thirty nine (65%) children. Aspirin was given to twenty eight (47%) cases. Inotropic support was needed in 17% cases. Antibiotics were prescribed to all the patients. Fifty seven percent and 37% children were discharged without and with complications respectively. Mechanical ventilation was required in 6.6 % children who had pre-existing co-morbidities and all of them expired.

***Conclusion:*** Forty eight percent of MIS-C cases presented with KD like illness. Mortality was 6.6% and all the cases had preexisting comorbidities. MIS-C is a pediatric emergency and is of a great concern especially in children with pre-existing co-morbidities. Early diagnosis and referral to tertiary center for optimum management is essential.

**Keywords:** ACR,CDC, COVID-19, MIS-C, KD like illness, Severe MIS-C.

## Introduction

COVID-19 disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global crisis since the beginning of the year 2020.[1] Pediatric cases account for about 2.1–7.8% of total confirmed COVID-19 cases.[2] Though most children remain asymptomatic or relatively milder infection occurs in children in contrast with severe forms reported in adults, there is a concern of the association between COVID-19 disease and multisystem inflammatory syndrome in children (MIS-C). MIS-C was first diagnosed in April 2020 in The United Kingdom (UK).[3] Subsequently cases were identified in Europe, USA and other countries.[2,4-8]

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These patients had hyper inflammatory shock with features similar to Kawasaki Disease (KD) and toxic shock syndrome (TSS).

The Royal College of Paediatrics and Child Health referred to this acute condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).[5] Later, the illness was labeled as multi system inflammatory syndrome in children (MIS-C) by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) .[4,9] Many of the children tested for SARS-CoV-2 infection were either positive by polymerase chain reaction (PCR) or serology and developed MIS-C days to weeks after initial infection. This was an important reason behind the development of the strong hypothesis of a temporary association with SARS-CoV-2 infection and MIS-C.[5]

As the morbidity and case fatality rate due to MIS-C is very high, documentation of the current situationin different country is a time demanding issue.Scarcity of data related to MIS-C is present in our country. The present study describes the presentation, management and immediate outcomes of MIS-C cases from Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh.

## Materials and Methods

This was a retrospective study, conducted in the department of pediatrics, BSMMU, Dhaka, Bangladesh. It included all the eligible MIS-C patients diagnosed during the study period (August 2020 to February 2022).

Data were collected using a pre-designed and pre-tested questionnaire from hospital records and also by interviewing the patients/parents over telephone when required. The questionnaire included demographic information (age, gender), history (especially family history of COVID 19 disease/ any other contact and history of travel) and clinical features.

Laboratory investigations including complete blood count, C-reactive protein, lactate dehydrogenase (LDH), ferritin, D-dimer, triglycerides, serum glutamate pyruvate transaminase (SGPT) and serum creatinine. Coagulation profile: prothombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT) were also recorded. Other investigations including, cardiac enzymes, chest X-ray, echocardiography, CT scan and abdominal ultrasound was done when indicated. IL-6 level was measured in 17 (28.3%) children.

For identifying SARS-CoV-2, all the cases were tested for RT-PCR using oro/naso-pharyngeal swab (PCR-Fluorescence probing was used for RT-PCR testing). Since serology immune-assay was not available for initial 6 months of study period, only39 (65%) patients were tested by ELISA method, once it became available. Kits used for serological test (IgG):"The ADVIA Centaur® SARS-CoV-2 IgG (COV2G)'.These investigation results were also recorded in the questionnaire.

Patients with evidence of hyperinflammatory state but not fulfilling the WHO preliminary case definition criteria of MIS-C were excluded from the cohort. Parents of all the cases included in this study were informed about the purpose of the study, treatment modalities and outcome of MIS-C over telephone. Informed consent was taken from them prior to data collection and patients or parents not willing to give consent were excluded in the desighn of the study. But all the patients and parents gave verbal consent. Ethical clearance for the study was taken from the institutional review board (IRB) of BSMMU.

Details of treatments and immediate outcomes of MIS-C cases were documented. During discharge, the patients and their care-givers were advised for regular follow-up by the managing paediatricians and the patients are followed up regularly for evaluation of persistence of clinical findings or emergence of any new problems. Relevant investigations are carried out regularly at follow-ups.

After collection, data was checked, verified and compiled manually. Results are presented as frequency and mean ± Standard deviation (SD) in tabulated form.

In this study, we have categorized the MIS-C cases[8,10] as:

i. Febrile inflammatory state/ Persistent fever and elevated inflammatory markers (Mild cases): These patients did not have feature of organ dysfunction, KD or shock.

ii. Moderate MIS-C (presenting with KD like illness), and

iii. Severe MIS-C (presenting with severe multisystem involvement including KDSS).

KD and incomplete KD cases were included in this cohort when there was evidence of COVID-19 (known exposure or positive PCR or serology). Six (10%) KD like cases presented as KD shock syndrome (KDSS) having severe multisystem involvement. These cases were grouped under the category of severe MIS-C.We tried to manage these cases according to ACR (Version I-IV) recommendations by a multi-disciplinary team including pediatric rheumatologists,

cardiologists, general pediatricians and hematologists.[11] Depending on clinical manifestations, other subspecialties including pediatric neurologists, nephrologists and gastroenterologists were also consulted.

## Results

The study describes the experience on 60 cases of MIS-C including demographic, clinical and laboratory features. It also documents their management and immediate outcome. The patients were treated according to ACR guideline (version I-IV). All patients diagnosed as MIS-C according to preliminary case definition (a) given by WHO, were included in this study.[4]

*Epidemiology and Demographics*: Between August 2020 toFebruary 2022, 60 MIS-C cases were admitted in the department of pediatrics, BSMMU. The mean age of the study population was 6.8 year (range 6 month to 15 year) with female: male ratio 1.2:1. History of contact with COVID-19 cases was present in 52 (87%) cases and 47 (>90%) of them were household contacts. Mean duration of hospital stay was 10.5 day (Table I).

*Clinical Characteristics*: Most of the children were previously healthy. Only 12 (25 %) had pre-existing co-morbidities including: X-linked agammaglobulinemia(X-LA) in 2, childhood lupus in 4 and JIA in 6 cases. On admission, all the cases had persistent fever (mean duration 5 days witharangeof 4-17 days). Other sign/ symptoms included gastro intestinal symptoms (n=41, 68.3%), followed by mucocutaneous, cardiovascular, respiratory and other features. Mucocutaneous symptoms included maculo-papular rash, urticarial rash,cheilitis, non-purulent conjunctivitis, edema of extremities and desquamation of skin.

Majority (n= 29, 48%) of the cases had Kawasaki Disease (KD) like illness, including 23 (79%) incomplete and 06 complete KD. Twentyeight cases (47%) had severe MIS-C including KDSS, who presented with shock, pneumonia, hepatitis and other features (Table I).

**Table I:** Demography and clinical presentation of MIS-C cases (n=60)

| Demographic profile | Mean ± SD | Range |
|---|---|---|
| Age (years) | 6.8± 3.9 | 0.6- 15 |
| Gender (F:M) | 1.2 :1 | |
| Contact | N | % |
| H/O contact with COVID 19 | 52 | 87.0 |
| • Household contact | 47/52 | 90.0 |
| • Outside contact | 05/52 | 10.0 |
| Presentation* | | |
| Fever 60 | 100 | |
| GIT symptoms | 41/60 | 68 |
| Muco-cutaneous Manifestation | 32/60 | 53 |
| CVS (Shock & KDSS) | 20/60 | 33 |
| Respiratory symptoms | 19/60 | 32 |
| CNS 07/60 | 12 | |
| Categories of MIS-C cases | | |
| Febrile Inflammatory (Mild cases 3) | 03/60 | 05 |
| KD like Illness (n=29) | 29/60 | 48 |
| Incomplete KD | 23/29 | 79 |
| Complete KD | 06/29 | 21 |
| Severe MIS-C* (n=28) | 28/60 | 47 |
| KDSS 06/28 | 21 | |
| Shock 14/28 | 50 | |
| Pneumonia | 10/28 | 38 |
| Hepatitis | 05/28 | 18 |
| Heart Failure | 02/28 | 07 |
| Encephalitis/Aseptic Meningitis | 02/28 | 07 |
| Appendicular rupture | 01/28 | 3.5 |

*Some cases of Severe MIS-C had overlapping features

*Laboratory Investigations*: Mean total and neutrophil counts were high but mean lymphocyte and platelet counts were low in this cohort. Mean ESR and CRP were very high. Levels of biochemical markers of inflammation including LDH, ferritin and D-dimer were raised (Table II). Mean serum creatinine level was normal, mean SGPT was high, but mean albumin level was low (Table II). High IL-6 level was present in 17 (28%) patients who were measured.Four patients (6.6%) had mildly raised APTT (mean 41.3 seconds, control: 30 seconds).

RT- PCR was done in all thecases and it was positive in 5 (8.3%).COVID-19 IgG was checked in 39 (65%) cases only after availability of the test in our country after February 2021, and 28 of them (72%) had high titer of antibody. Other cases included in this study had history of contact with COVID-19 cases, meeting the diagnostic criteria of MIS-C.[4]

SARS-CoV-2 infection was confirmed in 55% cases either by positive RT-PCR or by serological evidence (Table II).

*Imaging*: Sixteen cases (27%) had abnormal radiological findings including consolidation in 12, bilateral pneumonitis in 02, pleural effusion in 05 and interstitial lung disease (ILD) in 1 case. All of them underwent HRCT of chest, and 10 (62.5 %) of them had pulmonary involvement in HRCT. Abdominal ultrasound was done in 18 cases where indicated. Positive findings were: presence of hepatomegaly in 12, ascites in 7 and mild splenomegaly in 2 case (Table II). One patient presenting with encephalopathy underwent MRI of brain and found to havesub-acutehemorrhage with mild cerebellar atrophy and suspected acute disseminating encephalomyelitis (ADEM).

Comparison was done between the evidences of COVID-19 infection and categories of MIS-C cases (Table III). History of contact with COVID-19 cases was present in 52 (87%) cases. Among them 44% had severe MIS-C. Among severe MIS-C cases, 7% was RT-PCR positive and 43% was IgG positive.

**Table II:** Laboratory findings of MIS-C patients (n=60)

| Variables | Mean ±SD /% | Range | Normal range |
|---|---|---|---|
| Total WBC Count (Thousand/cmm) | 13.18± 8.37 | 2.4 – 37 | 4-11 |
| Neutrophil (%) | 78.9±13.5 | 19-92 | 40-70 |
| Lymphocyte (%) | 12.20±8.2 | 5 –46 | 20-40 |
| Platelet Count (lac/cmm) | 1.2 ±3.7 | 0.13 – 4.5 | 1.5-4 |
| Erythrocyte Sedimentation Rate (mm in 1$^{st}$hr) | 70.7 ±31.4 | 10- 125 | 10-20 |
| C-Reactive Protein(mg/dl) | 89.9± 87.7 | 8– 415 | < 6 |
| SGPT (U/L) | 94± 38 | 7 – 949 | < 40 |
| S. Creatinine(mg/dl) | 0.40±0.25 | 0.17 – 0.89 | 0.7-1.4 |
| S. Albumin ( gm/L) | 26±7.3 | 17 – 45 | 3.5-4.5 |
| S. LDH (U/L) | 896± 614 | 102 – 4420 | < 286 |
| S. Ferritin (ng/ml) | 5120.3±1772.6 | 95 – 42483 | 7-140 |
| D dimer (ng/ml) | 6.4±3.0 | 0.7 – 13.2 | <0.5 |
| Prolonged APTT (seconds) n=44 | 4/60 (6.6%) | | |
| Interleukin 6 (pg/ml) n=17(28.3%) | 34.9± 32.7 | 8 – 116 | < 7.5 |
| Positive RT PCR for COVID 19 | 5/60 (8.0%) | | |
| COVID 19 Ig G Antibody Index (n=39/60, 65%) | 28/39 (72%) | | |
| Imaging Abnormality | | | |
| Chest X ray abnormality (n=16) | 16/60 (27%) | | |
| HRCT abnormality (n=10 ) | 10/16 (63%) | | |
| USG of Whole Abdomen (n=18) | 15/18 (83%) | | |

**Table III:** Comparison of evidences of COVID -19 infection with categories of MIS-C cases (n=60)

| Evidence | Mild (n= 03) | KD like Illness (n=29 ) n (%) | Severe MISC (n=28) n (%) |
|---|---|---|---|
| Positive RT PCR for COVID-19 (n=05) | 0 | 3/29 (10) | 2/28 (7) |
| Positive COVID 19 IgG (n=28) | 3/3 | 13/29 (44.8) | 12/28 (43) |
| Total (Laboratory evidence of COVID 19) | 3/3 | 16/29 (55%) | 14/28 (50) |
| *H/O COVID -19 contact (n=52) | 3/3 | 26/29 (90) | 23/28 (82) |

*Twenty five cases of MIS-C (42%) had more than one evidence of COVID-19 infection (History of contact plus laboratory evidence)

*Echocardiography :* All the MIS-C cases were evaluated by echocardiography. Coronary arteries dilatation (Z score >2) was present in 17(28%) patients. Among them, most commonly affected artery was left main coronary artery(n= 13, 76.5%), followed by left anterior descending in 7 (41%) and right coronary artery in 2 (12%) cases.Ventricular dysfunction and pericardial effusion was present in 13 (22%) and 03 (05%) patients respectively (Table IV).

*Treatment*: All the cases were managed with general care, supportive measures and antibiotics. Thirty nine (65%) patients received intravenous steroids (20 to 30 mg/kg/day methylprednisolone) for 3 to 5 days followed by low to moderate dose of oral corticosteroid (1 to 1.5 mg/kg/day) in divided doses for 2to 3 weeks, depending upon the clinical condition and inflammatory markers.IVIG (2 gm/kg single dose or in 2 divided doses) was given to 41 (68%) cases including all the KD like illness and KDSS cases. Aspirin was prescribed in 28 (47%) cases including 24 KD and 04 KDSS (severe MIS-C) cases at a dose of 3 to 5 mg/kg/day in divided doses (Table V).

*Outcomes*: After clinical improvement, 57% cases were discharged without any complication and 37% with residual complications. Residual complications included coronary artery dilatation,ventricular dysfunction, raised ALT, features of ILD and ADEM. Mechanical ventilation was required in 04 (6.6%) children who eventually expired (Table V).

**Table IV:** Echocardiographic findings of MIS-C cases (n=60)

| Type of MIS-C | Echo. Findings | n (%) |
|---|---|---|
| Mild (n=3) | Normal | 0 |
| KD Like Illness (n=29) | Normal | 17 (39) |
| | Major vessel dilatation | 9/29 (31) |
| | LCA | 5/9 (56) |
| | LAD | 3/09 (33) |
| | RCA and LCA | 1/9 (11) |
| | Ventricular Dysfunction* | 6/29 (21) |
| Severe MISC (n=28) | Normal | 18/28 (64) |
| | Major vessel dilatation | 8/28(28.5) |
| | LCA | 3/8 (38) |
| | LCA and LAD | 4/8 (50) |
| | RCA and LCA | 1/8 (12.5) |
| | Ventricular Dysfunction* | 7/28 (25) |
| | Pericardial effusion* | 3/28 (11) |
| | Cardiomegaly * | 4/28 (14) |

*Co-existed with other abnormalities

**Table V:** Management and outcomes of MIS-C cases (n=60)

| Treatment options | N | % | |
|---|---|---|---|
| General and supportive care | 60 | 100 | |
| Antibiotics | 60 | 100 | |
| • 1st line Antibiotics (Ceftriaxone ) | 60 | 100 | |
| • 2nd line Antibiotics (Meropenem, Vancomycin) | 22 | 37 | |
| IV Steroids | 39 | 65 | |
| Aspirin | 28 | 47 | |
| IVIG | 41 | 68 | |
| Inotropes | 10 | 17 | |
| Digoxin | | 03 | 5.0 |
| Outcomes | | | |
| Recovery without complication | 34 | 57 | |
| Recovery with complication | 22 | 37 | |
| Death | 04 | 6.6 | |

## Discussion

Multisystem inflammatory syndrome in children (MIS-C), a severe manifestation of COVID-19 disease, has been reported worldwide. According to CDC (January 03, 2022), in the USA the total MIS-C cases were 6,431 and total MIS-C deaths were fifty five .[6]

In this cohort, 60 MIS-C cases from BSMMU are documented. This is a single centered study carried out in BSMMU. As BSMMU is the apex medical institute in Bangladesh, most of the critical cases are referred to this institute from all over the country. Moreover, pediatric rheumatology service is only available in this institute, so difficult rheumatological cases are also referred to this center. Therefore, this study could be a near reflection of the MIS-C related information from Bangladesh.

Though higher numbers of male children were found to have MIS-C and critical illness in different multicenter studies[12-14], the present series documents more female children having MIS-C than males (1.2:1). A male bias in mortality has emerged in the COVID-19 pandemic. Biological sex differences may manifest themselves in the susceptibility to infection, pathogenesis, immune responses, and balance of inflammation and tissue repair in the resolution of infection.[15] These are also described for KD, where males are more vulnerable. The previous study done on COVID-19 disease from our institute also found male predominance.[16] The reasons behind the higher number of females in this series have not been found. Could it be due to smaller number of study samples or due to referral bias? Further multi-centered studies with larger sample size are needed to answer these questions.

About 87% of patients had contact with known COVID-19 cases and more than 90% of them had household contact. No children had history of travel. These findings are consistent with the previous report on COVID-19 children from our institute where history of known contact was present in more than 84% of children.[16]

MIS-C is reported to present with persistent fever and a constellation of symptoms including hypotension, multi-organ (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) involvement, and elevated inflammatory markers.[6-8] The present series documents similar findings including persistent fever, gastrointestinal involvement followed by mucocutaneous, cardio vascular, respiratory, and other symptoms. These children may present with overlapping features of toxic shock syndrome (TSS), KD and KDSS, and it is at times challenging for the clinicians to differentiate patients with MIS-C from KD and TSS.[8] We also faced similar challenges, as many of our moderate and severe MIS-C cases had overlapping features.

KD-like illness (Moderate MIS-C) was the most common type found in our series followed by severe

MIS-C which also included KDSS (Table I). In this cohort only 3 (5%) febrile inflammatory state (mild) cases were found. May be most of these cases were managed in the OPD as COVID-19 cases and not identified as MIS-C and thereby not referred to us. Echocardiographic findings similar to those of KD were common in this cohort. A total of 25 cases (42%) in this cohort had coronary abnormalities (28%) and other cardiac complications including ventricular dysfunction (22%), pericardial effusion and cardiomegaly. Multiple cardiac problems were also present in the same patients (Table IV). These findings are compatible with cardiac involvements described in other reports.[17-18] Although the mechanism of myocardial involvement is not fully understood, it may be related to micro-vascular damage, stress cardiomyopathy and systemic inflammatory response syndrome.[12] The duration of illness prior to coming to our center, irrespective of cardiac involvement or severity of illness, was similar for all patients. Mean duration of illness was 7±2 days.

Severe MIS-C cases in the present study had varied presentation including shock, heart failure, pneumonia, hepatitis, encephalitis, appendicular rupture, severe multisystem involvement etc. (Table I). There are reported cases of MIS-C misdiagnosed as appendicitis and concomitant cases of MIS-C associated with acute appendicitis.[19-20] One case of appendicular rupture is also reported from the US.[21]

There were presence of neutrophilic leukocytosis, lymphopenia, thrombocytopenia and raised ESR (range of ESR was 10 to 125 mm in 1st hour, only 3 cases had normal ESR) and CRP in the present cohort, which have been described as distinct hematological features of MIS-C.[22] As part of the criteria for defining MIS-C, majority of children in the present cohort had increased inflammatory markers including CRP, ESR and ferritin (ferritin is normal in 5 cases), which is similar to other reports from the UK, US and Europe.[3,18,23,24] A systematic narrative review of the literature on MIS-C incorporating major medical databases between December 2019 and August 2020 reported that the most frequently observed symptoms of MIS-C included fever (82%), shock (67%), gastrointestinal problems (87%), skin disorders (71%) and cardiac disorders (75%)[25]. Our study documents similar findings, excepting lower frequency of shock and cardiac disorders. The review also documented that more than 90% of MIS-C cases had increased CRP and marked elevation of ferritin (2-10 times its normal value). In the review, severe coagulopathy including very high D-dimer and raised PT and PTT was seen in 70-80% of the cases. Our cohort also found marked elevation of ferritin and high D-dimer. High serum ferritin level may act as an immunomodulator that may induce both pro-inflammatory cytokines and immunosuppression.[26]

All cases in the present series, where IL-6 were measured, had higher levels. IL-6 along with other cytokines including IL-8 and TNF-á can lead to hyperpermeability of vessel wall and multi-organ failure.[27] Due to logistic constraints we could not measure IL-8 and TNF-á. IL-6 was measured in only 28.3% of cases. All of them had raised levels. In a recent study, Italian physicians evaluated the prognostic value of IL-6 for severe COVID-19 and mortality and reported the IL-6 levels at hospital admission as the best prognosticator for negative outcome.[28]

It is to be mentioned here that we measured expensive IL-6 level to those patients who could afford it, as serology was not available initially in our country. SARS-COV-2 infection was detected by RT-PCR in 05(8 %) and serological test in 28 (47%) cases.

Sixty percent of 5 RT-PCR positive cases in the present cohortpresented to us with KD like illnessand 40% had severe illness. None of these cases had any previous comorbidity. Patients tested positive for SARS-CoV-2 by RT-PCR reflect an acute phase of the infection, although the virus or its fragments may be detected for longer periods in some patients and could be responsible for these results.[29] However, it is not clear how long it might take for the first symptoms of MIS-C to appear after the acute phase of SARS-COV-2 infection, and whether it may occur during the acute phase or not. But most of the reports document that MIS-C manifests 3 to 4 weeks after SARS-CoV-2 infection.[3,17,30]

Children with severe MIS-C are reported to have higher levels of antibody response to SARS-CoV-2.[31-32] However we found 72% (28/39) of MIS-C cases having positive serology. Among them, 43% had severe and 46 % had KD like illness. All the 3 febrile inflammatory state cases had positive serology (Table III). In our series, only total COVID-19 IgG antibodies were measured. As evidence of COVID-19 infection defined by WHO[4], history of contact with COVID-19 infection was present in 52 (87%) cases. Among them, 44%

had severe MIS-C. It is to be noted, that 25 (42%) of our MIS-C cases had both the history of contact and laboratoryevidence of COVID-19 infection.

As the pathogenesis of MIS-C is not well established, different therapeutic approaches have been used, but till now no specific therapy is available. Treatment modalities of MIS-C include intravenous immunoglobulin, aspirin, steroids, biological agents, antibiotics and other supportive measures.[10,11] In the present cohort, we tried to follow the ACR (version I to IV) guidelines, but it was not always possible to adhere the guidelines because of logistic constraints. In most of the cases in this series, IVIG, corticosteroid and aspirin were used to treat the children. Although there is no evidence of the benefit of corticosteroid for pediatric patients with severe COVID-19 and/or MIS-C, the use of corticosteroid has been described in many studies as an attempt to reduce the hyper-inflammatory response.[10,11] Though no information on associated bacterial infection was available, the use of antibiotics in 100% cases in this series may be justified by the recommendation of empirical antibiotic therapy in hospitalized patients with MIS-C, as symptoms overlap with severe bacterial sepsis.[11] Moreover infection control measures in our pediatric ward, including high dependency unit, was not very satisfactory. After sending investigations, ceftriaxone I/V was started as the first line antibiotic to all MIS-C cases.[10] When the condition deteriorated in 22 (37%) cases, ceftriaxone was replaced with second line antibiotics (Meropenom + Vancomycin).

Outcomes of the MIS-C children in this cohort were guarded and not comparable with other reports. Four of the children (6.6%) whom we lost had pre-existing co-morbidities including X-LA in 02 and childhood lupus in 02 cases. Both the X-LA patients were diagnosed very late at the age of 14 and 15 years. Case 1 was a fourteen-year-old boy who had very irregular treatment with IVIG along with other supportive measures for the last 3 years. Case 2 was a fifteen-year-old boy, a newly diagnosed case of X-LA, who had problems since early childhood and had not received any treatment before this admission. The lupus patients had organ involvement (renal and hematological in one and neurological in the other). Both the lupus cases were having regular treatment and had been stable prior to development of MIS-C. All the four children came to us with severe MIS-C with less than one week duration, and their management was also started immediately. All of them were RT-PCR negative. Serology was positive (in high titre) in one case (a lupus patient). Serology was not done to the other three because of non-availability. But they had positive family history of COVID-19 disease.

All the 4 children presented with severe MIS-C with shock.They received intensive care management and needed ventilation. But unfortunately they did not survive. The majority of the children went home without having any complications. Children who went home with complications had major coronary artery dilatation, other cardiac abnormalities and features of ADEM (in one patient). They are kept on appropriate management and are on regular follow up.

## Conclusion

From this cohort, it may be concluded that, most of the MIS-C (48%) cases presented with KD like illness. Mortality was 6.6% and all of them presented with severe MIS-C and had pre-existing comorbidies. So, A strong index of suspicion should be kept for early diagnosis and management of MIS-C cases. Children with pre-existing co-morbidities are much more vulnerable and so their families should take extra care.

A pragmatic low cost approach in the management of MIS-C focusing on low-income countries like us is also very much needed, as many of our patients cannot afford IVIG.

*Conflict of Interest:* None

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*Ethical approval:* Ethical clearance was taken from IRB (Institutional Review Board) of BSMMU, Shahbag, Dhaka, Bangladesh.

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## References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020; 55:105924. DOI:10.1016/j.ijantimicag.2020.105924

2. Centers for Disease Control and prevention (CDC). Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). 2020. Available from: https://www.cdc.gov/mis-c/hcp/R

3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395:1607-08. DOI: 10.1016/S0140-6736(20)31094-1.

4. World Health Organisation. Multi system inflammatory syndrome in children and adolescents with COVID-19: Scientific brief, 15; 2020. Available from: https://apps.who.int/iris/handle/10665/332095

5. Royal College of Paediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Londres (Royaume-Uni) 2020. Available from: https://www.rcpch.ac.uk/resources/

6. Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States 2020. Available from: https://www.cdc.gov/mis-c/cases/index.html

7. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: a systematic review. E Clinical Medicine 2020; 24:100433. DOI: 10.1016/j.eclinm.2020.100433.

8. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020; 324:259-69. DOI: 10.1001/jama.2020.10369.

9. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children 2020. Available from: https://www.cdc.gov/mis-c/index.html

10. Son MBF, Friedman K. Multisystem Inflammatory syndrome in children. Available from: https://www.uptodate.com/contents/

11. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol 2020; 72; 1791-1805. DOI: 10.1002/art.41454

12. Lima-Setta F, de Magalhães-Barbosa MC, Rodrigues-Santos G, das NevesFigueiredo EA, de Lorena Jacques M, de SeixasZeitel R, et al. Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: a multicenter, prospective cohort study. Jornal de pediatria. 2021; 97:354-61. DOI: 10.1016/j.jped.2020.10.008.

13. Kurz H, Gombala T. Multisystem Inflammatory Syndrome in Children (MIS-C)-A Case Series in December 2020 in Vienna, Austria. Frontiers in Pediatrics 2021; 9:564. DOI: 10.3389/fped.2021.656768.

14. Patnaik S, Jain MK, Ahmed S, Dash AK, Sahoo B, Mishra R, et al. Short-term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Rheumatology international 2021; 14:1-6. DOI: 10.1007/s00296-021-04932-1

15. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020;11:1-6.

16. Haque M, Laila K, Al-Mamun MH, Supti SH, Rahman SA. Profile and Outcome of Children with COVID-19 Attending Bangabandhu Sheikh Mujib Medical University. Am. J. Pediatr. 2021; 7:72-8. DOI: 10.11648/j.ajp.20210702.17

17. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020; 383:334-46. DOI: 10.1056/NEJMoa2021680

18. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, CiuffredaM, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020; 395:1771-78.

DOI: 10.1016/S0140-6736(20)31103-X

19. Jackson RJ, Chavarria HD, Hacking SM. A case of multisystem inflammatory syndrome in children mimicking acute appendicitis in a COVID-19 pandemic area. Cureus. (2020) 12:e10722. DOI: 10.7759/cureus.10722.

20. Lishman J, Kohler C, de Vos C, van der Zalm MM, Itana J, Rederm A, et al. Acute appendicitis in multisystem inflammatory syndrome in children with COVID-19. Pediatr Infect Dis J. 2020; 39:472–3. DOI: 10.1097/ inf.000000000000290.

21. Anderson JE, Campbell JA, Durowoju L, Greenberg SL, Rice-Townsend SE, Gow KW, et al. COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) presenting as appendicitis with shock. J PediatrSurg Case Rep. 2021;71:101913. DOI: 10.1016/j.epsc.2021.101913

22. Feng X, Li S, Sun Q, Zhu J, Chen B, Xiong M, et al. Immune-inflammatory parameters in COVID-19 cases: a systematic review and meta-analysis. Front med. (2020) 7:301. DOI:10.3389/fmed.2020.00301

23. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoul-vant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. BMJ. 2020, 369:m2094.8. DOI: 10.1136/bmj.m2094

24. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, AbramsJ, et al. COVID-19-associated multisystem inflammatory syndrome in children-United States. Morb Mortal Wkly Rep. 2020; 69:1074-80. DOI: 10.15585/mmwr.mm6932e2

25. Fernández-Sarmiento J, De Souza D, Jabornisky R, Gonzalez GA, López MD, Palacio G. Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): a narrative review and the viewpoint of the Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee. BMJ paediatrics open. 2021;5: 1-9. DOI: 10.1136/bmjpo-2020-000894

26. Carcillo JA, Kernan KK, Horvat CM, Simon DW, Aneja RK. Why and how is Hyperferritinemic sepsis different from sepsis without Hyperferritinemia? PediatrCrit Care Med. 2020; 21:509-12.
DOI: 10.1097/PCC.0000000000002285

27. Waltuch T, Gill P, Zinns LE, Whitney R, Tokarski J, Tsung JW, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. Am J EmergMed ,2020;38:2246-e3.
DOI: 10.1016/j.ajem.2020.05.058

28. Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AM, Ciambotti B, et al. Interleukin-6 as prognosticator in patients with COVID-19. J Infect. 2020;81:452-82.
DOI: 10.1016/j.jinf.2020.06.008

29. John G, Sahajpal NS, Mondal AK, Ananth S, Williams C, Chaubey A, et al. Next-Generation Sequencing (NGS) in COVID-19: A Tool for SARS-CoV-2 Diagnosis, Monitoring New Strains and Phylodynamic Modeling in Molecular Epidemiology. Curr. Issues Mol. 2021;43:845-67.
DOI: 10.3390/ cimb43020061

30. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. E Clinical Medicine. 2020;100527.
DOI: .org/10.1016/j.eclinm.2020.100527

31. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). Pediatrics. 2020;146:e2020018242.
DOI: 10.1542/peds.2020-018242

32. Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature. 2020; 584:120-24.
DOI: 10.1038/s41586-020-2381-y6656