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Demystifying the three different types of COVID-19 associated multisystem inflammatory syndrome in children: Experience from a tertiary care hospital

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Abstract

Background: Following the coronavirus disease-2019 (COVID-19) pandemic, a new entity emerged termed as multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 (MISC) by the World Health Organization (WHO). Infection with COVID-19 triggers the formation of antibodies to viral surface epitopes. It is believed that low titer non-neutralizing antibodies may accentuate virus-triggered immune responses. The study aimed to describe the various clinical presenting features, deranged laboratory parameters, echocardiographic findings, and immediate outcome and to categorize into 3 types of MISC and find any difference among the 3 types.

Methodology: Children 29-days old to 12-years old who clinically satisfied the published WHO's case definition for MISC were included in the study. All children were subjected to serological testing for total immunoglobulin to viral spike glycoprotein, relevant blood investigations, and echocardiography.

Results: Out of 50 cases, we had 24(48%) cases of MISC without shock, 12(24%) cases of Kawasaki disease-like phenotype, and 14(28%) cases of MISC with shock. Fever (96%) and respiratory complaints (64%) predominate followed by gastrointestinal (45%) and red eye (32%). The inflammatory markers were notably elevated- the median CRP was 39.6mg/L, median ESR was 70mm 1sthr, median procalcitonin was 8.2 ng/ml. There is a significant drop in inflammatory markers post-treatment (p=0.019, p=0.000, p=0.016 respectively for CRP, ESR and procalcitonin). Abnormal echocardiographic findings were seen in 46% of cases in terms of decreased ejection fraction and coronary artery aneurysms (CAA). There were 7 deaths (14%), and 42(84%) patients were successfully discharged.

Conclusion: Following the COVID-19 pandemic, MISC has emerged with its characteristic clinical pattern which needs early identification and prompt treatment to prevent mortality and morbidity.

Keywords: MISC; non-COVID; Eastern India; Kawasaki disease; PIMS-TS; IVIG; immunity

Introduction

Following the pandemic of COVID-19 (Corona virus disease- 2019), a new hyperinflammatory entity emerged, termed paediatric inflammatory multisystem syndrome- temporally associated with SARS-CoV-2 infection (PIMS-TS). It is also called multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 (MIS-C) by the World Health Organization (WHO) and CDC [1]. MIS-C is defined by WHO as – 1. Children and adolescents 0-19 years of age with fever >= 3 days and two of the following 1. Rash or bilateral non-purulent conjunctivitis or

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mucocutaneous inflammation signs, 2. Hypotension or shock, 3. Features of myocardial dysfunction or coronary abnormalities (including ECHO findings or elevated troponin/NT- proBNP), 4. Evidence of coagulopathy, 5. Acute gastrointestinal problems and Elevated markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or procalcitonin and no other obvious cause of sepsis and inflammation and evidence of COVID-19 (RT-PCR, antigen test or serology positive) [2].

In countries with high rates of SARS-Cov-2 transmission, this form of affection in children was noticed as children started presenting with an unusual syndrome of Multisystem inflammation. Many fulfilled complete and/or partial criteria for Kawasaki disease(KD) [2, 3]. First noticed in USA, later followed by Europe, Italy, France, and then India [1-4]. The exact data on the number of cases of MIS-C is not known so far, however, it is observed after the peak of SARS-CoV-2 infection. The knowledge of MIS-C is important as it mimics diseases like Kawasaki disease (KD), staphylococcal, and streptococcal toxic shock syndrome. Prompt identification and appropriate management is the key to prevent mortality [5].

The core concept is immune-mediated multisystem inflammation. Infection with COVID-19 triggers the formation of antibodies to viral surface epitopes. It is believed that low titer non-neutralizing antibodies may accentuate virus-triggered immune responses instead, thereby increasing the risk of severe illness in affected individuals [6]. The weak antibody-coated virus gets internalized by Fc receptors, followed by the endosomal release of the virion and subsequent Toll-like receptor and cytosolic RNA sensor-triggered IFN-α responses [6, 7]. These antibody-dependent enhancement (ADE) responses have been implicated in COVID-19 induced immune injury. In addition, MIS-C patients may also show signs of vasculitis, endothelial damage, and thrombosis, hence antiplatelet and anticoagulation management in MIS-C represent important additional considerations [8]. The tropism of SARS-CoV-2 to myocytes and endothelial cells with the facilitated entry by binding to the angiotensin-converting enzyme 2 may contribute to high incidence of cardiac manifestations [9]. Although evidence base for this pathway is demonstrated for coronaviruses, the exact role in MISC is only speculative [7, 8].

The purpose of this report is to throw light on the clinical features, laboratory findings, 2D-echocardiographic findings, treatment received, and short-term outcomes of children diagnosed with MISC.

What is already known: The clinical presenting features and complications of MISC have been published in multiple studies.

What does this study add: Studies till now have not categorized the disease spectrum of MIS-C into its 3 types. Our study has divided the study population into three types and the correlation with various parameters, which is unique to this study. Also, we have thrown light upon some atypical findings in our study. This study also highlights the significant change in inflammatory markers post-immunomodulatory treatment.

Material and methods

This is a single-center based prospective observational study, conducted in the Pediatric ward and Pediatric Intensive Care Unit (PICU) of a tertiary care, non-COVID hospital of Eastern India during the month of August 2020 to February 2022. The study has been approved by the institutional ethical committee.

During the study period, 65 children presented to us with clinical features suggestive of MIS-C, fulfilling the case definition criteria of MIS-C. All the suspected 65 children were subjected to RT-PCR for SARS-CoV-2 and serological testing for total immunoglobulin to viral spike glycoprotein using ELISA test. 5 children were RT-PCR positive, hence sent to COVID dedicated hospital and 8 children were negative for both RT-PCR and antibody testing and 2 children found to be with alternate diagnosis, hence excluded from our study. Remaining 50 Children from 29 days old to 12 years who clinically satisfied the published WHO's case definition for MIS-C and positive for antibody testing were included in the study. All the consecutive patients who satisfied the WHO criteria during the study period were included in the study and no exact sampling technique was used.

We analysed demographic details, presenting clinical characteristics, underlying comorbidities, lab markers, ECHO findings, PICU admission rate, treatments received, and immediate outcomes. We categorized MISC into 3 types based on Latent class analysis (LCA) done by CDC and also by the Ministry of health and family welfare, govt of India guidelines [3] – 1. MISC with Undifferentiated fever and not immediately life-threatening, 2. Kawasaki disease like with or without shock, 3. MISC with shock or life-threatening disease.

Children were subjected to relevant blood investigation at the discretion of treating physician. Blood and urine cultures were done to rule out alternative etiology. All patients were subjected to 2D-echocardiography by

Pediatric cardiologist on vivid s70GE by using 6S/12S probe and analysed using Echopac software. Parameters studied are i) global LV systolic function as assessed by linear and 2D methods and is represented by ejection fraction ratio, ii) Coronary artery measurements - from the inner edge to inner edge & appropriate z-scores calculated (Kobyachi score). Echocardiography was performed on day-1 of admission and repeated after clinical response. Patients had 12-lead ECG done on day 3 of admission to maintain uniformity and was analyzed by a single author (SB).

Our patients were treated according to the guidelines provided by the American College of Rheumatology [4]. Patients with KD phenotype were treated with IVIG 2gm/kg over 24 hours and methylprednisolone 1-2mg/Kg. Patients with shock or life-threatening disease were given methylprednisolone 10mg/kg/day for 3-5days plus IVIG 2gm/kg over 12 to 18 hours, and patients without shock or life-threatening disease were given either methylprednisolone 1-2mg/kg/day (first-line) or IVIG as per the availability. Refractory cases were given methylprednisolone 10-30mg/kg/day for 3-5days. Inflammatory markers were done initially on admission (pre-treatment) and again 24 hours after completion of treatment(post-treatment).

Statistical analysis

All the data collected was compiled in Microsoft excel. Continuous data are presented as median with interquartile range (IQR) and Categorical data as numbers and percentages. Statistical analysis was done by using SPSS-21 software. Chi-squared or Fisher's exact tests were used to compare proportions of categorical variables; numeric variables with medians and interquartile ranges were compared using the Mann Whitney's U test; Student paired t-test was done to compare the pre and post-treatment results of inflammatory markers; a one-way ANOVA test with post-hoc Tuckey test was administered to compare the means between the three groups, and a p value <0.05 was taken as statistically significant.

Results

In our study, there were 50 children, median age of the study population being 5yrs (IQR- 2 months to 11 years). 56% were males (n=28) and 44% were females (n=22). Out of 50 cases, we had 24(48%) cases of MISC without shock, 12 (24%) cases of Kawasaki phenotype, and 14 (28%) cases of MISC with shock (Figure 1). There were 7 deaths (14%), and 42 (84%) patients were successfully discharged, whereas one patient left against medical advice. 12 cases (24%) belonged to 1st COVID wave and 38 cases (76%) belonged to second wave.

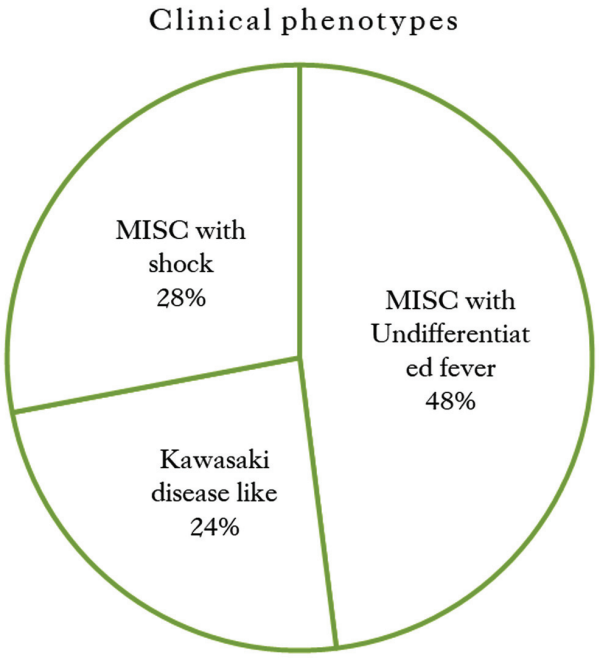

Figure 1: Pie chart showing the distribution of cases in this study.

Fever was the most predominant presenting feature, present in 96% of patients (n=48); median duration was 4.5 days (IQR- 3 to 7 days). 32 patients(64%) had cough, 23(46%) had respiratory distress, 21(42%) had diarrhea and other GI symptoms, 23(45%) presented with rash, 13(26%) had red-eye, 16(32%) had puffiness of limbs, 12 children (24%) had cracked lips, 9(18%) had convulsion during hospital stay. 19 out of 50 children had pre-existing comorbidities (Figure 2).

On physical examination, we found 35 patients (70%) had hepatomegaly, 12(24%) had splenomegaly, 20(40%) had lymphadenopathy. It has been observed that 27 patients (54%) presented in shock requiring inotropic support and tachycardia for age was present in 49 patients (98%).

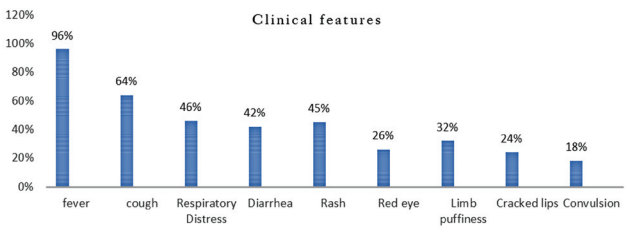

Figure 2: Figure showing percentages of presenting clinical features among the study population.

Inflammatory markers were notably high. Coagulopathy was seen with substantially deranged PT, INR requiring FFP transfusion in 41 children (82%). 21 patients (42%) had anemia for age, 40 patients (80%) had leucocytosis in terms of leucocyte count >11,000/cumm with median

of 15,000/cumm (3500 - 44000), one patient had lymphophenia in terms of absolute lymphocyte count <1000, most presented with reduced thrombocytes; there were 25 (50%) patients with thrombocytopenia and 4 of them had severe thrombocytopenia with platelet count below 20,000/cumm. Thrombocytosis (platelet count >4,00,000) was found in 7 patients (Table 1).

Table 1: Table showing the frequency and percentages of deranged haematological variables.

Variable	*N (%)*
Hemoglobin <10 gm/dl	21 (42%)
WBC >11,000/cumm	40 (80%)
Platelet count < 1,50,000	25 (50%)
Platelet count> 4,00,000	7 (14%)
Serum albumin <3.5 gm/dl	16 (32%)
SGOT > 35 SGPT>45	23 (46%)
Serum sodium <135 meq/l	24 (48%)

Hypoalbuminemia (serum albumin<3.5mg/dl) is seen in 16(32%), median albumin was 2.8mg/dl (IQR= 1.5- 4.2). Transaminitis is seen in 23 patients (46%). Hyponatremia (serum sodium <135meq/l) is seen in 24 (48%) (Table 2) and hypernatremia (>155) is seen in one patient. Respiratory support was provided by face mask and NRBM in 22 children (44%), NIV in 9 children (18%) and invasive ventilation was needed in 11 children (22%). There was evidence of Bilateral chest X-ray changes in 28 children (56%) and HRCT evidence of GGO was found in 9 of them (Table 2).

Table 2: Table showing frequency of patients receiving different management modalities.

Management	*N (%)*
Face mask oxygen	22 (44%)
NIV	9(18%)
Invasive ventilation	11 (22%)
PICU admission	21 (42%)
Inotropic support	27 (54%)
IVIG	44 (88%)
Methyl prednisolone	34 (68%)
Combined IVIG and methylprednisolone	32 (64%)

The antibody titer in 50 children by Siemens antibody test was >1AU/ml. Only two of our children had history of exposure to COVID positive patients at home. Three children had antibody titer>200AU/ml. The statistical association between antibody titer and severity of disease could not be established.

21 patients out of 50(42%) who were shifted to PICU required mechanical ventilation (either NIV or invasive ventilation), and inotropic support was required in 27 children (54%) (Table 3).

Twenty-three children (46%) had global hypokinesia of the heart detected in echocardiography with moderate to severe LV dysfunction (EF ranged from 28% to 45%). Nineteen children (38%) had coronary artery aneurysms (CAA). In MISC with undifferentiated fever 12 (50%) of them had CAA out of 24, in Kawasaki phenotype 4(33%) had CAA out of 12, and in MISC with shock 3(21.6%) out of 14 had CAA. Mild pericardial effusion is seen in many of our study population (27 children) (Table 3).

Table 3: Table showing frequency of abnormal Echocardiographic findings.

Echocardiographic findings	*N (%)*
Global hypokinesia (EF 28% - 45%)	23 (46%)
Coronary artery aneurysms	19 (38%)
In undifferentiated fever	12
Kawasaki disease like	4
Misc with shock	3
Mild pericardial effusion	27 (54%)

IVIG (Intravenous immunoglobulin) was given in 44 children (88%) and methylprednisolone was given in 34 children (68%) out of which combined IVIG and methylprednisolone was given in 32 children (Table 3). There is a significant drop in inflammatory markers post-treatment. The median CRP before the treatment is 39.6mg/L (IQR 1.6 - 275), the median CRP post-treatment was 9.1mg/L (IQR 0.3- 102) (P = 0.019). The median ESR pre-treatment was 70mm 1sthr (IQR 12- 180) and post-treatment it was 32mm 1sthr (IQR 6 - 125) (p = 0.000). The median procalcitonin pre-treatment was 8.2 ng/ml (IQR 0.02 - 400) and post-treatment it was 1.1 ng/ml (IQR 0.02 to 13) (p = 0.016). The median pre-treatment ferritin was 935 ug/dl (IQR 229 – 24,000) and post-treatment 380 ug/dl (IQR 210 - 4090) (p = 0.072). Median LDH pre-treatment is 930 U/l (IQR 200 – 10,000) and post-treatment was 855.5 U/l (IQR 130 - 1522) (p= 0.002). (Table 4).

The 3 types of MISC with clinical variables for each group are shown in Table 5. It is found that there is higher chance of the presence of cracked lips and lymphadenopathy in KD group than in the other 2 groups (p=0.009 and 0.047 respectively). Also, there is higher incidence of shock in the group of MISC without life-threatening disease than the other 2 groups (p=0.007). There is also higher mean ESR and mean CRP in the MISC with shock group (p=0.016 and 0.037 respectively). There was no statistically significant difference in the means

of procalcitonin (P=0.828), LDH (P=0.33), and Ferritin (p=0.624) between the three study groups. There was also higher median antibody titre in MISC with shock group (p=0.00019). There is no significant difference among the 3 groups with respect to the median duration of response (p=0.473) (Table 5).

Table 4: Table showing Pre-treatment and Post-Treatment Inflammatory markers (median with IQR).

Inflammatory markers	*pre-treatment*	*post treatment*	*p value*
CRP	39.6 mg/L (1.6-275)	9.1 mg/L (0.3-102)	0.019
ESR	70 mm 1st hr (12-180	32mm 1st hr (6-125)	0.000
Procalcitonin	8.2 ng/ml (0.02 - 400)	1.1 ng/ml (0.02-13)	0.016
LDH	930 U/L (200-10000)	855.5 U/L (130-1522)	0.002
Ferritin	935 ug/dl (229-24000)	380 ug/dl (210-4090)	0.072

Discussion

In this prospective cohort study, we describe the clinical features, hematological and biochemical findings, echocardiographic findings, and immediate outcomes of MISC in 50 patients. Also, we categorize MISC into 3 types depicting any significant difference among the 3 groups.

Demographic characteristics in this cohort were similar to those reported in previous studies. Children with MISC are often older than 5 years of age, median age being 8.8yrs (IQR 3months -11 years), compared with children with KD who are mostly <5yrs [10-12]. Majority of the study population is constituted by males (56%) in similarity to other studies [11].

Majority of our study population are referrals from tier -1 & tier – 2 hospitals with chief complaints of unresolving fever (>5days) or KD-like symptoms which required IVIG transfusions and have responded dramatically to methylprednisolone.

Fever with respiratory symptoms take the top most position followed by GI symptoms, which are further followed by KD like symptoms, cardiovascular and CNS manifestations. A similar clinical spectrum is being sharedby other conducted studies [10, 11]. Some of the atypical findings, unique from our study include- 11 case of DVT, 2 cases of oligoarthitis and one case of acute encephalitic syndrome. DVT as a part of coagulopathy and is frequently encountered in children with indwelling central lines. There is no plausible explanation for oligoarthitis. Out of these, one child devoloped HLA B27 positive arthritis with classical sacroiliitis and involvement of hip joint; currently on DMARDS and intra-articular steroids.

Our study also includes patients with various comorbidities but no significant correlation among the incidence of MISC and severity is found. Majority of hepatomegaly seen were a part of CCF in the background, but there are also a few cases of hepatosplenomegaly without CCF. We also quote significant number of patients with lymphadenopathy. Our findings are in similarity with studies published by Shahbaznejad et al and Ramcharan et al [12, 13].

High inflammatory markers are the key pointers in the diagnosis of MISC and clinical suspicion of MISC was strengthened up by the finding of raised inflammatory markers. In our study it is observed that in severe cases, as in MISC with shock, the ESR and CRP levels were higher than in less severe cases (p<0.05). Serum procalcitonin, ferritin and LDH levels did not hold this trend and were equally high in all three groups. This finding is clearly established in various studies done by Chattopadhyay et al and Patra et al [14, 15]. Apart from this, other findings noticed are leucocytosis, thrombocytopenia, anemia, transaminitis and coagulopathy; Coagulopathy being the most frequent lab derangement [15].

PICU admission rate (42%) of our study was comparatively higher than other published studies like Davies et al and Hoste et al [16, 17]. This might be because ours is a tertiary care referral center.

As opposed to the belief that pneumonia is seen only in active COVID-19 infection, lung involvement is also seen in MISC patients which presents as pneumonia/ empyema/ground glass opacity (GGO) on HRCT. The likely explanation to this is probably inflammatory in nature [18].

As our hospital being non-COVID, only RT-PCR negative patients were undertaken, but all were subjected to antibody assay. In our study higher antibody titre is seen mostly in MISC with shock (p=0.00019) h a v i n g multiorgan dysfunction, requiring inotropes, repeat dose of IVIG and methylprednisolone. Similar findings were quoted by Harwood et al and Schlapbach et al [19, 20]. A suggested correlation between higher antibody titre with severity of disease will require higher sample size and a multicenteric study. There is no significant corelation between incidence of CAA and mortality as our study showed only one patient with CAA had succumbed.

Table 5: Table showing 3 types of MISC with their p value.

	MIS-C without life-threatening disease (n=24)	*Kawasaki type (n=12)*	*MIS-C with shock or life-threatening disease (n=14)*	*p value*
Fever	24 (100%)	12 (100%)	12 (85.7%)	0.89
Cough	14 (58.3%)	8 (66.6%)	10 (71.4%)	0.88
Respiratory distress	12 (50%)	3 (25%)	8 (57%)	0.44
Gastro-intestinal symptoms	9 (37.5%)	6 (50%)	6 (42.8%)	0.86
Rash	11 (45.8%)	7 (58.3%)	5 (35.7%)	0.69
Red eye	6 (25%)	5 (41.6%)	2 (14%)	0.39
Cracked lips	5 (20.8%)	7 (58.5%)	0	0.009
Puffiness	8 (33.3%)	6 (50%)	2 (14%)	0.27
Convulsion	4 (16.6%)	3 (25%)	2 (14%)	0.79
Liver	19 (79%)	7 (58.3%)	9 (64%)	0.74
Spleen	6 (25%)	3 (25%)	3 (21.4%)	0.97
Lymphadenopathy	11 (45.8%)	8 (66.6%)	1 (7%)	0.047
Tachycardia	24 (100%)	12 (100%)	13 (93%)	0.97
Shock	20 (83.3%)	0	9 (64%)	0.0078
Comorbidities	10 (41.6%)	2 (16.6%)	4 (28.5%)	0.44
Coagulopathy	21 (87.5%)	10 (83.3%)	10 (71.4%)	0.86
Median total leucocyte count	17,835 /cumm	13,200 /cumm	19,000 /cumm	0.09
Mean albumin	2.7 gm/dl	2.8 gm/dl	2.9 gm/dl	0.72
Median SGOT	50	50	45	0.64
Median SGPT	52.5	59.5	41.5	0.56
Median sodium	136 meq/l	134.5 meq/l	135.5 meq/l	0.47
Mean ESR (Pre-treatment)	64.9 mm1sthr	71 mm1sthr	101.1 mm1sthr	0.016
Mean CRP (Pre-treatment)	49.5 mg/L	65.4 mg/L	113.4 mg/L	0.037
Mean procalcitonin (Pre-treatment)	27.9 ng/dl	15.3 ng/dl	26.4 ng/dl	0.82
Mean LDH (Pre-treatment)	936.6 U/L	808 U/L	1536.9 U/L	0.33
Mean ferritin (Pre-treatment)	2344.5 ug/dl	1196.4 ug/dl	1677.1 ug/dl	0.624
Median antibody titre	20.45	72.25	244.4	0.00019
Coronary artery aneurysms	12 (50%)	5 (41.6%)	2 (14%)	0.22
Echocardiographic findings	12 (50%)	5 (41.6%)	2 (14%)	0.22
Inotropes	13 (54%)	6 (50%)	8 (57%)	0.96
IVIG	23 (96%)	10 (83.3%)	13 (93%)	0.93
Methylprednisolone	13 (54%)	10 (83.3%)	11 (78.5%)	0.51
Deaths	2 (8%)	0	5 (35.7%)	0.03
PICU admissions	11 (45.8%)	3 (25%)	7 (50%)	0.57
Median duration of response	36 hours (min – 6 hrs, max – 48 hrs)	58 hours (min – 12hrs, max – 48 hrs)	48 hours (min – 24 hrs, max – 96 hrs)	0.67

Our center experienced a case of typical KD which was IVIG resistant and febrile 36 hours after IVIG transfusion which subsequently found out to be COVID-19 antibody positive, hence reinforcing the idea to watch out for MISC in Kawasaki disease.

Majority (76%) of our study population belonged to 2nd wave of pandemic. Even after the study period has ended we are still experiencing scattered cases of MISC.

Our findings suggested the involvement of heart in different ways like myocarditis(evident by decreased Ejection fraction) and coronary artery abnormalities. They were strengthened from other similar studies conducted by Harwood et al and Kohli et al [19, 21].

Mortality rate of our study is 14% (7 deaths out of 50patients) which is higher than compared to other cohort studies by Carter et al, Penner et al and Toubiana et al [10, 22, 23]. This high mortality can be attributed to the presence of comorbidities and IVIG resistance. Out of 7 deaths, 2 of the patients had severe DKA, 1 case was a known case of evolving cerebral palsy, 1 was coinfected with scrub typhus and 1 case was a known case of nephrotic syndrome in relapse.

Limitations: It was conducted at a single center, possibly biasing the results in favor of more sick patients with PIMS-TS (i.e., patients who require intensive care).

Conclusion

The typical clinical features, deranged biochemical parameters and high incidence of echocardiographic abnormalities are in similarity to previous studies. Our study showed a drastic improvement in inflammatory markers after immunomodulatory therapy in all the three groups of MIS-C. This reinforces the importance of early identification and prompt treatment to prevent mortality and morbidity. Further studies are needed to identify long term complications in these cohorts. Any association between MIS-C and chronic autoimmune disorders like Juvenile Idiopathic arthritis also needs to be explored.

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Conflicts of interest

Authors declare no conflicts of interest.

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