ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 03 | March - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MIS-C – A NEW ENTITY IN CHILDREN : A CASE SERIES

Paediatric Medicine

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a new clinical condition characterized by signs of inflammation and multi-organ dysfunction due to cytokine storm associated with SARS-CoV-2. The clinical spectrum of MIS-C ranges from mild to severe, and even to mortal multisystem involvement. To guide clinicians, we evaluated detailed clinical features, laboratory findings, and outcomes of MIS-C cases.

KEYWORDS

Multi-organ dysfunction, cytokine storm,SARS-CoV-2

INTRODUCTION

Cases of coronavirus disease 2019 (COVID-19) among children have been less severe than those in adults. However, since late April 2020, multiple institutions have reported paediatric cases with clinical similarities to toxic shock syndrome, Kawasaki disease (KD) or severe sepsis. This new life-threatening condition has been defined as multisystem inflammatory syndrome in children (MIS-C), which is related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The mortality and morbidity in patients with MIS-C are vastly different from the benign course of COVID-19 in children [2]. The majority of patients have either known family exposures or serologic evidence of SARS-CoV-2, specifically positive IgG and negative IgM, supporting the thesis that MIS-C represents an immune-mediated com plication rather than an acute infection [2]. The underly ing pathological mechanisms of MIS-C are considered a dysregulated inflammatory response, possibly triggered by SARS-CoV-2, rather than direct viral toxicity. A cytokine storm can result from ability of SARS-CoV-2 to block types I and III interferon responses [3, 4].Although MIS-C is a multisystemic disease, cardio-vascular manifestations are most prominent [5]. Other common clinical findings of MIS-C are persistent fever, gastrointestinal (vomiting, diarrhoea, abdominal pain) symptoms, mucocutaneous rash reminiscent of KD, and respiratory symptoms. MIS-C cases present with a wide clinical spectrum, overlapping with the KD spectrum (persistent fever, polymorphic rash, mucosal changes, and conjunctivitis) or with severe acute COVID-19. Most of MIS-C cases with respiratory symptoms, such as cough, shortness of breath, pneumonia, and acute respiratory distress syndrome, have a high mortality rate and positive SARS-CoV-2 polymerase chain reaction (PCR) without seropositivity [6, 7].

Aim of the study

As MIS-C is described as a life-threatening multisystem condition, treatment options are needed urgently. The aim of MIS-C treatment is to supress systemic inflammation, improve cardiac function, and prevent long-term sequel. Current treatment regimens derived from experience with KD and adult experience with COVID-19 consist of cardiac support, immune modulation, and anticoagulation therapy [2].We retrospectively investigated clinical, laboratory features, cardiac involvement, and treatment modalities of MIS-C cases, in order to compile and disseminate information needed at present by the medical community.

METHODS AND PARTICIPANTS

Methods

We reviewed the medical records of 23 patients treated with MIS-C at the Department of Paediatrics in D Y Patil Hospital, Nerul ,Navi Mumbai . The study protocols were approved by our hospital's ethics committee . Patients were included for study based on the terms of the case definition by the Centres for Disease Control and Prevention (CDC):

Characteristics principles for diagnosis as follows:

- Age <19 years
- Clinical presentation consistent with MIS-C, including all of the following:
  Fever:
  Documented fever> 38.0 °C (100,4 °F) for> 24 hours or report of subjective fever lasting> 24 hours
- Laboratory evidence of inflammation, including any of the following:
  Elevated C-reactive protein (CRP), erythro cyte sedimentation rate (ESR), pro calcitonin, D- dimer, ferritin, LDH, Neutrophilia, lymphocytopenia
- Multisystem (≥2) organ involvement
  Cardiovascular (eg, shock,elevated brain type natriuretic peptide , abnormal echocardiography, arrhythmia)
  Respiratory (eg, pneumonia, ARDS, pulmonary embolism)
  Renal (renal failure)
  Neurologic (eg, seizure, stroke, aseptic meningi tis)
  Hematologic (eg, coagulopathy)
  Gastrointestinal (eg, abdominal pain, vomiting, diarrhoea, elevated liver enzymes, ileus)
  Severe illness requiring hospitalization
- No alternative possible diagnosis
- Evidence of infection with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2)

Any of the following
Positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR)
Positive serology
COVID-19 exposure to persons in the past 3 months [8].

Clinical severity was defined as follows:
1. mild MIS-C with no vasoactive requirement or respiratory support and minimal organ injury
2. moderate MIS-C with mild or isolated organ injury
3. severe MIS-C with moderate or severe organ injury, including moderate to severe ventricular dysfunction [9].

Children were also separated into three age groups (< 5 years, 5–10 years, > 10 years).

Patients were evaluated for presenting symptoms, clinical and laboratory features, radiological findings, cardiac involvement, treatment modalities, and outcomes.

Laboratory data was collected, including complete blood count with differential, routine biochemical tests, inflammatory markers (CRP, ESR, procalcitonin, IL-6, ferritin), D-dimer, pro-brain-type natriuretic peptide (NT pro-BNP).

All cases underwent antibody testing and naso- pharyngeal RT-PCR

testing for SARS-CoV-2. An enzyme- linked immunosorbent assay (ELISA) was used to identify serum anti-SARS-CoV-2 IgM and IgG (upper limit: 1 ng/ mL).

The echocardiography (ECHO) for the patients was recorded .

The therapeutics included intravenous immunoglobulin (IVIG), glucocorticoids, enoxaparin, aspirin, vasoactive drugs and antibiotics.

Participants

This study was conducted at in D Y Patil Hospital, Navi Mumbai, Maharashtra. There were a total of 23 patients. Among these 22 patients survived and 1 patient died. Inclusion criteria for the study were all the patients admitted to paediatric ward or PICU who met criteria for MIS-C.

Statistics

Descriptive statistics were done. The data is represented in number and percentages.

RESULTS

A total of 23 subjects fulfilling the criteria were enrolled for study. The mean age in our case series was 3.3 years with range from 0-19 years, of which 60.8% were males. All patients were previously healthy but had a history of COVID-19 infection. All (100%) patients had positive covid antibody. Fever was most common symptom in 86.9% of the patients followed by cough and cold in 56.5%, respiratory distress in 34.7%. Loose stool and abdominal pain was present in 21.7% of the patients. In laboratory findings, loe Hemoglobin was found in 74% of the patients. Total leucocyte counts were high in 17.3% and low in 13% of the patients. CRP was positive in 78.2 %. D-Dimer was elevated in 60%, suggestive of coagulopathy. 2D echo was abnormal in 17.4% of the patients, suggestive of LV dysfunction, pericardial effusion, Left ventricular thrombus. NT-Pro BNP was elevated in 2 patients. Steroid was given to 34.7% of the patients while anti-coagulant therapy was given to 26% of the patients. 56.5 % patients required respiratory support and intensive care unit admission. 13% patients required treatment with intravenous immunoglobulin. Out of 23 patients, 1 patient died due to cardiac complication.

Table 1: Age And Gender Of Participants

Age group in years	Gender		Total
	Boys	Girls	
less than 5	10 (55.5%)	8 (44.6%)	18 (78.2%)
5 to 10	3 (75%)	1 (25%)	4 (17.3%)
More than 10	1 (100%)	0 (0%)	1 (4.3%)
Total	14 (60.8%)	9 (39.2%)	23 (100%)

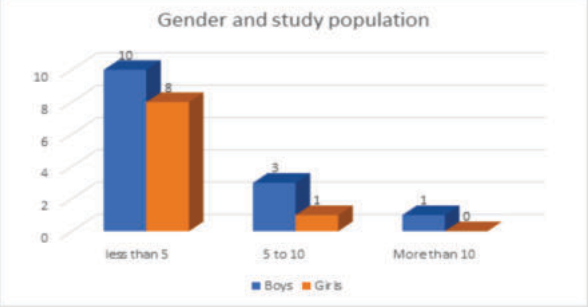


Figure 1: Age and gender of participants

Table 2: Details Of Symptoms Seen In The Study Population

Complaints (multiple option)*	Gender		
	Boys	Girls	Total
Fever	11 (55%)	9 (45%)	20 (86.9%)
Cough, cold	7 (53.8%)	6 (46.1%)	13 (56.5%)
Respiratory distress	4 (50%)	4 (50%)	8 (34.7%)
Loose stool	3 (60%)	2 (40%)	5 (21.7%)
Abdominal pain	3 (60%)	2 (40%)	5 (21.7%)
Convulsion	2 (66.6%)	1 (33.3%)	3 (13%)
Rash	2 (66.6%)	1 (33.3%)	3 (13%)
Others	0(0)	2 (22%)	2 (8.6%)

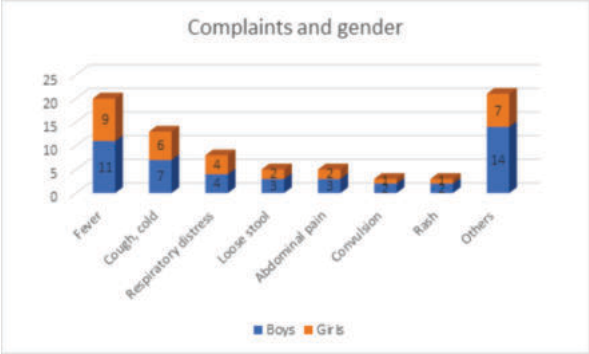


Figure 2: Details Of Symptoms Seen In The Study Population

Table 3: Complaints And Age Group

Complaints (multiple option)	Age group			Total
	less than 5	5 to 10	More than 10	
Fever	17 (85%)	3 (15%)	0 (0%)	20 (86.9%)
Cough, cold	12 (92.3%)	1 (7.6%)	0 (0%)	13 (56.5%)
Respiratory distress	6 (75%)	2 (25%)	0 (0%)	8 (34.7%)
Loose stool	4 (80%)	1 (20%)	0 (0%)	5 (21.7%)
Abdominal pain	3 (60%)	1 (20%)	1 (20%)	5 (21.7%)
Convulsion	2 (66.6%)	1 (33.3%)	0 (0%)	3 (13%)
Rash	1 (33.3%)	1(33.3%)	1(33.3%)	3 (13%)
Others	17 (91%)	3 (14.2%)	1 (4.7%)	21 (91.3%)

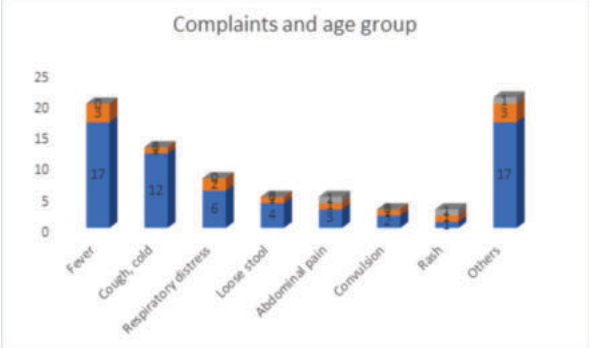


Figure 3:

Table 4 : Hemoglobin Level

Age group in years	Haemoglobin level		Total
	low	normal	
Less than 5	14 (77.7%)	4 (22.3%)	18 (78.2%)
5 to 10 years	2 (50%)	2 (50%)	4 (17.3%)
More than 10 years	1 (100%)	0 (0%)	1 (4.3%)
Total	17 (74%)	6 (26%)	23 (100%)

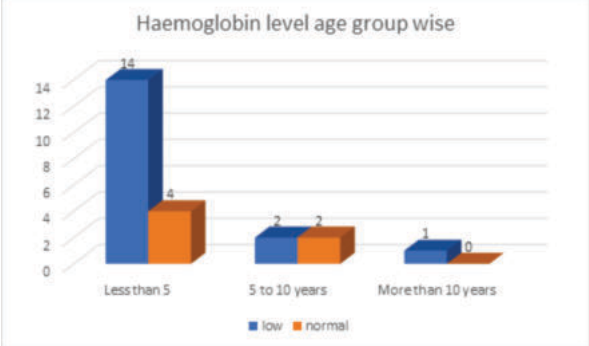


Figure 4:

Table 5: Total Leucocyte Count

Gender	Total leucocyte count			Total
	High	Low	Normal	
Boys	3 (21.4%)	1 (7.1%)	10 (71.4%)	14 (61%)
Girls	1 (11.1%)	2 (22.2%)	6 (66.6)	9 (39%)
Total	4 (17.3%)	3 (13%)	16 (69.5%)	23 (100%)

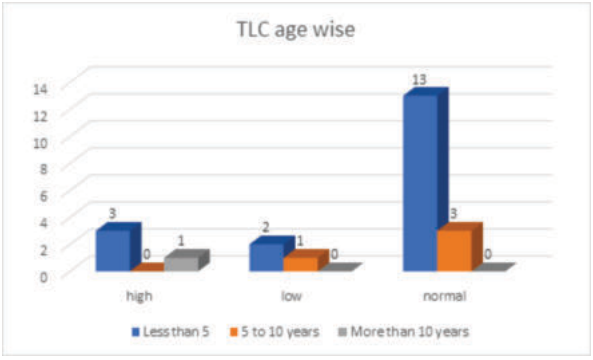


Figure 5:

Table 6: Platelet

Age group in years	Platelet			Total
	high	low	normal	
Less than 5	7 (38.8%)	2 (11.1%)	9 (50%)	18 (78.2%)
5 to 10 years	0 (0%)	0(0%)	4 (100%)	4 (17.3%)
More than 10 years	0(0%)	0(0%)	1 (100%)	1 (4.3%)
Total	7 (30.4%)	2 (8.6%)	14 (60.6%)	23 (100%)

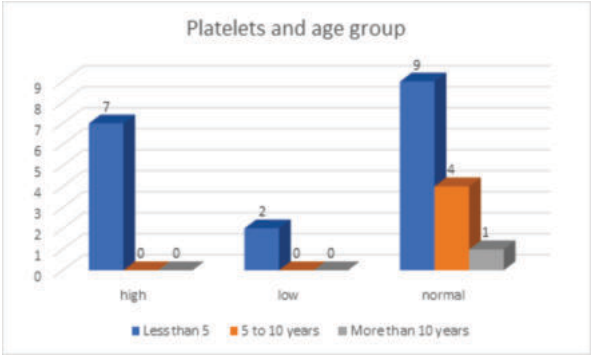


Figure 6:

Table 7: CRP

Age group in years	CRP		Total
	Negative	positive	
Less than 5	5 (27.7%)	13 (72.3%)	18 (78.2%)
5 to 10 years	0 (0%)	4 (100%)	4 (17.3%)
More than 10 years	0 (0%)	1 (100%)	1 (4.3%)
Total	5 (21.7%)	18 (78.2%)	23 (100%)

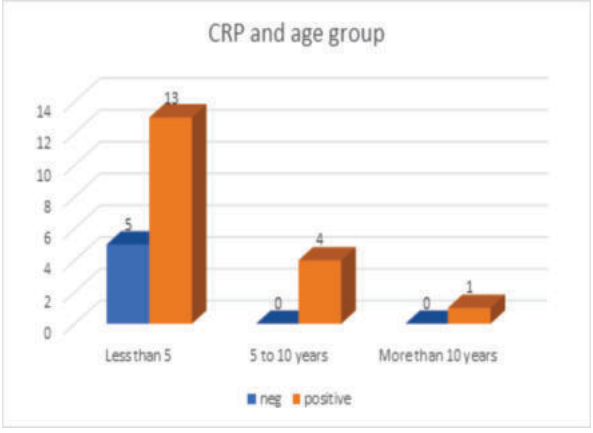


Figure 7:

Table 8: Use Of Clexane

Age group in years	clexane		Total
	Yes	No	
Less than 5	3 (16.6%)	15 (83.4%)	18 (78.2%)
5 to 10 years	2 (50%)	2 (50%)	4 (17.3%)
More than 10 years	1 (100%)	0 (0%)	1 (4.3%)
Total	6 (26%)	17 (73.9%)	23 (100%)

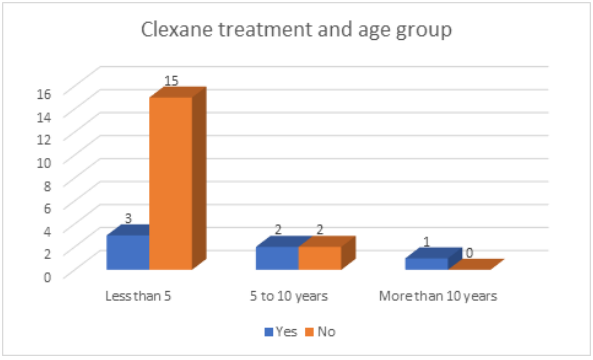


Figure 8:

Table 9: D-dimer

Age group in years	d dimer			Total
	high	normal	Not done	
Less than 5	3 (16.6%)	3 (16.6%)	12 (66.6%)	18 (78.2%)
5 to 10 years	2 (50%)	1 (25%)	1 (25%)	4 (17.3%)
More than 10 years	1 (100%)	0 (0%)	0 (0%)	1 (4.3%)
Total	6 (26%)	4 (17.3%)	13 (56.2%)	23 (100%)

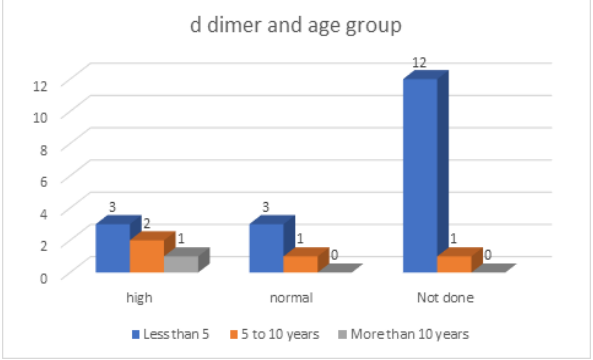


Figure 9:

Table 10: Ferritin

Age group in years	ferritin			Total
	high	normal	Not done	
Less than 5	3 (16.6%)	3 (16.6%)	12 (66.6%)	18 (78.2%)
5 to 10 years	1 (25%)	1 (25%)	2 (50%)	4 (17.3%)
More than 10 years	0 (0%)	1 (100%)	0 (0%)	1 (4.3%)
Total	4 (17.3%)	5 (21.7%)	14 (60.8%)	23 (100%)

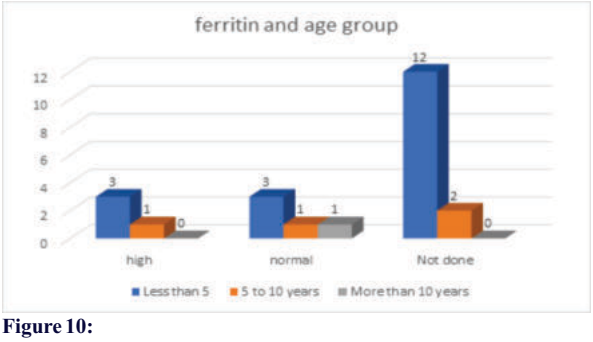


Figure 10:

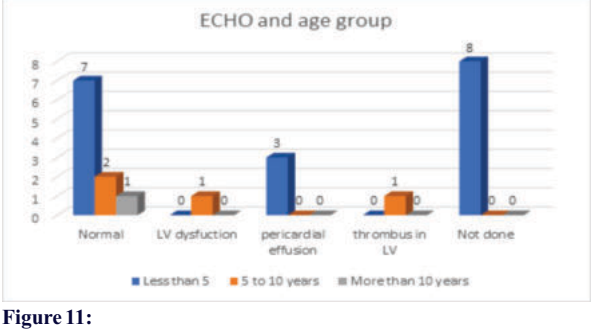


Figure 11:

Table 11 : Cardiac Dysfunction

Age group in years	ECHO finding					Total
	Normal	LV dysfunction	pericardial effusion	thrombus in LV	Not done	
Less than 5	7 (38.8%)	0 (0%)	3 (16.6%)	0 (0%)	8 (44.4%)	18 (78.2%)
5 to 10 years	2 (50%)	1 (25%)	0 (0%)	1 (25%)	0(0%)	4 (17.3%)
More than 10 years	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0(0%)	1 (4.3%)
Total	10 (43.4%)	1 (4.3%)	3 (13%)	1 (4.3%)	8 (34.7%)	23 (100%)

Table 12: Use of IVIG

Age group in years	IVIG		Total
	Yes	No	
Less than 5	1 (5.5%)	17 (94.6%)	18 (78.2%)
5 to 10 years	2 (50%)	2 (50%)	4 (17.3%)
More than 10 years	0 (0%)	1 (100%)	1 (4.3%)
Total	3 (13%)	20 (87%)	23 (100%)

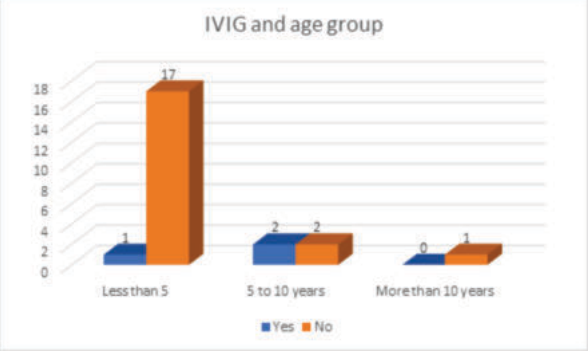
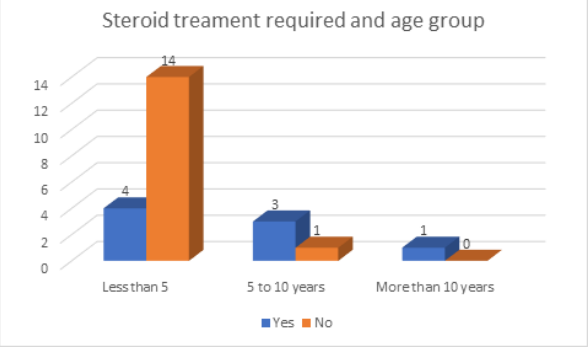


Figure 12:

Table13: Use of steroid

Age group in years	steroid		Total
	Yes	No	
Less than 5	4 (22.2%)	14 (77.8%)	18 (78.2%)
5 to 10 years	3 (75%)	1 (25%)	4 (17.3%)
More than 10 years	1 (100%)	0 (0%)	1 (4.3%)
Total	8 (34.7%)	15 (65.2%)	23 (100%)



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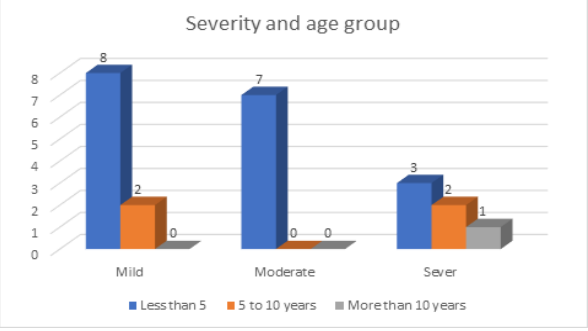

Figure 14:

Table 14: Severity

Age group in years	severity			Total
	Mild	Moderate	Sever	
Less than 5	8 (44.4%)	7 (38.8%)	3 (16.6%)	18 (78.2%)
5 to 10 years	2 (50%)	0 (0%)	2 (50%)	4 (17.3%)
More than 10 years	0 (0%)	0 (0%)	1 (100%)	1 (4.3%)
Total	10 (43.4%)	7 (30.4%)	6 (26%)	23 (100%)

DISCUSSION

In a large case series of MIS-C, 60% of the patients were male; median age of the patients with MIS-C was 9 years[8]. Consistent with the literature, we found that 60.8% of patients with MIS-C were male . And the median age was 3.3 years. Most common symptoms in our study was related to respiratory system in contrary to other studies , in which gastrointestinal symptoms predominates. In this MIS-C study , cardiac abnormality was found in 17.4%% of cases . In a study by Feldestien et al., cardiac abnormality was found in 8.8% of patients [9]. In the study by Jain et al., cardiac abnormality was found in 23% (n=6/23) of patients with MIS-C [10]. Almost 56.5% of the patients required a stay in the intensive care unit. This is lower than in the Feldstein cohort, in which 80% of patients received intensive care; in the Godfred-Cato cohort, 63% of the patients received intensive care [9]. We found that, association with low haemoglobin leads to higher grade of severity. In a recent MISC data from CDC, 0.8% of the 4196 identifed MIS-C patients died(11). In our study, the mortality rate was 4.3%(1/23).

There are two case series of MIS-C reported from India. In comparison with a series of 19 patients with MIS-C from Chennai, our cohort had less frequent GI symptomes(21.7% in our study vs 42%), a lower proportion of individuals with active COVID-19 during MIS-C (4.5%% vs 58%), and cardiac involvement was similar. (17.4% vs 16%).[12] Comparing with another case series of 23 patients with MIS-C from Mumbai, we observed a lower proportion of individuals with active COVID-19 during MIS-C (4.5%% in our study vs 39%), lower frequency of abdominal pain (21.7%% vs 52%).[13]Other available clinical and laboratory parameters from these two studies were similar to our study.

CONCLUSION

The diagnosis of MIS-C requires special attention due to its unique clinical manifestations with multi-systemic involvement . As SARS-COV-2 continues to circulate around the world, MIS-C should be considered in all children with fever. In suspected MIS-C cases, early cardiac evaluation can provide early diagnosis and favourable outcomes can be achieved with IVIG and corticosteroids.

DECLARATION

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGEMENT

We thank all participants in this study for their invaluable contribution.

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