A hospital based comparative study of the first and second waves of Covid-19 related multi-system inflammatory syndrome in children

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Abstract

Introduction: Studies have shown the differential impact of the second surge of acute Covid-19 infection, across age, clinical outcome and ethnicity. How these factors impact the clinical characteristics and outcome of multisystem inflammatory syndrome in children (MIS-C) is largely unknown.

Objectives: This hospital based comparative study was undertaken to analyse the clinical characteristics and outcomes of patients admitted with MIS-C during the two waves of Covid-19 infection in a tertiary care teaching hospital in South India.

Method: Patients admitted between September 2020 and October 2021 with MIS-C were included in this study. Patient demographics, laboratory values and treatment details were compared between the two surges of COVID 19 related MIS-C.

Results: Sixty-five children were admitted with MIS-C in the first wave and 73 in the second wave. More children were referred with a diagnosis of MIS-C in the second wave (p=0.001). There was no significant difference in the mean age or male-female ratio between the two waves. A significantly higher proportion of children in the second wave had cervical lymphadenitis (p=0.02). Need for intensive care unit (ICU) admission (p<0.001), shock (p<0.001), respiratory support (p<0.001) and multi-organ involvement (p<0.001) were significantly lower in the second wave.

Conclusions: A significantly higher proportion of children with MIS-C in the second wave of Covid-19 infection had cervical lymphadenitis. The need for ICU admission, shock, respiratory support and multi-organ involvement were significantly lower in children with MIS-C in the second wave of Covid-19 infection.

(Key words: MIS-C, SARS-CoV-2, PIMS-TS, Coronary aneurysm)

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Introduction

Many countries, including India, as of November 2021, experienced two waves of coronavirus disease 2019 (Covid-19)[1,2]. MIS-C peaks have been reported to follow Covid-19 peaks by 4-6 weeks. Studies have shown the differential impact of the second surge of acute Covid-19 infection, across age, clinical outcome and ethnicity[3,4]. The differences in clinical characteristics and outcomes of acute Covid-19 infection may be due to the impact of viral variants on immunization and better treatment modalities. How these factors impact the clinical characteristics and outcomes of MIS-C is largely unknown. As there is a high chance of future resurgence of infection with the virus and its variants, it is crucial to understand the impact of different Covid-19 surges on clinical presentations of MIS-C.

Objectives

This hospital based comparative study was undertaken to analyse the clinical characteristics, laboratory profile and outcomes of patients admitted with Covid-19 related MIS-C during the two waves of Covid-19 infection in a tertiary care teaching hospital in South India.

Method

This observational study was conducted at tertiary care teaching hospital in Kerala, India.

Children aged 1 month to 12 years, admitted with MIS-C between September 2020 and October 2021, were included in the study.

Retrospective data of patients admitted with MIS-C from September 2020 to January 15, 2021, were collected from hospital records using pre-defined proforma and prospective data were collected from January to October 2021.

The period from September 2020 to April 2021 was considered as the first wave and that from May 2021 to October 2021 was considered as the second wave based on reported data of Covid-19 infection in Kerala. This is the interim analysis of an ongoing study in the department.

Case definitions: Children fulfilling the CDC criteria for diagnosis of MIS-C[5] were included in the study. Fever (body temperature >38°C) or report of subjective fever lasting at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement (involving at least two systems), and laboratory-confirmed evidence of SARS-CoV-2 infection (positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction [RT-PCR] or antibody test during hospitalization) or an epidemiologic link to a person with Covid-19.

The main outcome measures studied were the need for critical care, the number of organs involved and mortality.

Patient demographics, comorbidities, laboratory values and treatment details were also collected and compared between the two waves.

All children were treated according to the Kerala state treatment guidelines for children with Covid-19 related MIS-C[6].

Children, more than 5 years of age with features of shock and abdominal symptoms were preferentially treated with pulsed methylprednisolone, while children less than 5 years of age with features of Kawasaki Disease without shock were treated with intravenous (IV) immunoglobulin.

Children with a febrile inflammatory syndrome without shock, and cardiac involvement were either offered oral steroids or observed without steroids according to the discretion of the treating physician.

The need for IV fluids more than 20ml/kg or inotropes to maintain blood pressure above the 5th centile was taken as shock.

Coronary artery involvement with a Z-score between 2 and 2.5 was taken as coronary artery dilatation (CAD) and those with coronary artery diameter with a Z-score of more than 2.5 was taken as coronary artery aneurysm (CAA)[7].

Ethical issues: Ethical approval was obtained from the Human Ethics Committee, Government Medical College, Thiruvananthapuram. Kerala, India (No. 01/32/2021/MCT Dated 15/1/2021). In the prospective part of the study from January 2021 written informed consent was obtained from the parents/guardians of the participating children.

Statistical analysis

Continuous data are described with mean ± SD for parametric data and median (IQR) for non-parametric data. Categorical data are expressed as numbers and proportions.

The two MIS-C cohorts were compared in relation to clinical presentation, demographics, laboratory parameters, treatment and clinical outcomes.

The differences between the two groups were assessed using Chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables using SPSS software version 20. $p<0.05$ was considered statistically significant.

Results

Table I shows the clinical presentation of children admitted with MIS-C during the study period.

The male: female ratio was 1.4: 1. The only death occurred in the second wave.

Table 2 shows the laboratory parameters of patients with MIS-C during the two waves.

Table 3 shows the treatment and outcome of patients with MIS-C during the two waves.

There was no significant difference in the proportion of patients receiving intravenous immunoglobulin and pulse methylprednisolone therapy between the two waves.

A higher proportion of patients were treated with oral steroids during the second wave.

Need for ICU admission ($p<0.001$), shock ($p<0.001$), clinical myocarditis ($p<0.001$), respiratory support ($p<0.001$) and involvement of 5 or more organs were significantly lower in the second wave ($p<0.001$).

Table I: ***Clinical presentation of children admitted with MIS-C during the two waves***

Characteristic	Total *(n=138)*	Wave 1 *(n=65)*	Wave 2 *(n=73)*	p value
PICU admission – n (%)	72 (52.0)	55 (85.0)	17 (23.0)	<0.001
Male: female ratio	80:57	40:24	40:33	0.389
Age (years) - Mean± SD	6.4±3.29	7.0±3.19	5.9±3.3	0.068
Fever duration - Mean± SD	5.33±5.4	4.7±2.2	5.8±7.0	0.269
PCR positive – n (%)	30 (22.0)	15 (23.0)	15 (20.0)	0.8367
Covid-19 antibody positive – n (%)	94 (68.0)	42 (65.0)	52 (71.0)	0.408
History of (H/O) Covid-19 contact – n (%)	14 (10.0)	08 (12.0)	06 (08.0)	0.574
H/O fever or URI preceding 4 weeks – n (%)	50 (36.0)	24 (37.0)	26 (36.0)	0.591
Personal H/O Covid-19 – n (%)	27 (20.0)	03 (05.0)	24 (33.0)	0.000
Referred as MIS-C – n (%)	56 (41.0)	09 (14.0)	47 (64.0)	0.001
Gastrointestinal – n (%)	108 (78.0)	55 (85.0)	53 (73.0)	0.063
Abdominal pain	67 (49.0)	36 (55.0)	31 (42.0)	0.125
Loose stools	63 (46.0)	34 (52.0)	29 (40.0)	0.126
Vomiting	79 (57.0)	43 (66.0)	36 (49.0)	0.039
Transaminitis	34 (25.0)	29 (45.0)	05 (07.0)	<0.001
Respiratory – n (%)	47 (34.0)	32 (49.0)	15 (20.0)	<0.001
Cough	14 (10.0)	05 (08.0)	09 (12.0)	0.414
Breathlessness	35 (25.0)	30 (46.0)	05 (07.0)	<0.001
Muco-cutaneous – n (%)	88 (64.0)	55 (85.0)	33 (45.0)	<0.001
Rash	67 (49.0)	41 (63.0)	26 (36.0)	0.001
Conjunctivitis	88 (64.0)	47 (72.0)	41 (56.0)	0.049
Oral mucosa	55 (40.0)	37 (57.0)	18 (25.0)	<0.001
Conjunctival haemorrhage	19 (14.0)	13 (20.0)	06 (08.0)	0.049
Oedema	41 (30.0)	33 (51.0)	08 (11.0)	<0.001
Cervical lymphadenitis	31 (23.0)	09 (14.0)	22 (30.0)	0.025
Serositis	18 (13.0)	12 (18.0)	06 (08.0)	0.08
Central nervous system	36 (26.0)	21 (32.0)	15 (21.0)	0.122
Cardiac involvement – n (%)	108 (78.0)	56 (65.0)	52 (71.0)	0.022
Shock	70 (51.0)	46 (71.0)	24 (33.0)	0.001
Myocarditis	45 (33.0)	39 (60.0)	06 (08.0)	<0.001
Ejection Fraction < 55%	26 (19.0)	19 (29.0)	07 (10.0)	0.004
Arrhythmia	21 (15.0)	15 (23.0)	06 (08.0)	0.018
CAA/CAD	46 (33.0)	22 (34.0)	24 (33.0)	1.00
Involvement of 5 or more organs – n (%)	63	48 (74.0)	15 (21.0)	0.00
Thrombosis – n (%)	12	09 (14.0)	03 (04.0)	0.046
Lymphocytopenia (<1000 /cu mm) – n (%)	26	14 (22.0)	12 (14.0)	0.292
Platelet count <150,000/cu mm – n (%)	60	37 (57.0)	23 (32.0)	0.002
ESR > 40mm in 1st hour – n (%)	79	31(48.0)	48 (66.0)	0.024
CRP >60mg/L – n (%)	87	58 (89.0)	29 (40.0)	0.000
Serum ferritin >500 ng/L – n (%)	37	21 (32.0)	16 (22.0)	0.118
D Dimer >1.5 ng/L – n (%)	106	53 (82.0)	53 (82.0)	0.149
Serum albumin <3.5g/dl – n (%)	81	46 (71.0)	35 (48.0)	0.005
Sodium <135meq/L – n (%)	66	38 (58.0)	28 (38.0)	0.014
Lactate > 2mmol/L – n (%)	26	17 (26.0)	09 (12.0)	0.032

MIS-C: Multisystem inflammatory syndrome in children, PICU: Paediatric intensive care unit, CAA: Coronary artery aneurysm, CAD: Coronary artery dilatation, CRP: C-reactive protein, PCR: Polymerase chain reaction, ESR: Erythrocyte sedimentation rate

Table 2: ***Laboratory parameters of patients with MIS-C during the two waves***

Characteristic	Total *(n=138)* Mean (SD)	Wave 1 *(n=65)* Mean (SD)	Wave 2 *(n=73)* Mean (SD)	p value
Haemoglobin (g/dl)	10.9 (1.15)	10.7 (1.19)	11.0 (1.1)	0.231
Total white cell count /cu mm	11,053 (5655)	10,825 (5811)	11,253 (5548)	0.660
Absolute lymphocyte count /cu mm	2457 (2018)	2104 (1838)	2765 (2128)	0.055
Absolute neutrophil count /cu mm	8010 (4587)	7923 (5109)	8086 (4110)	0.839
Platelet count /cu mm	198,716 (120340)	167,693(103764)	226,291(127841)	0.004
ESR (mm in 1st hour)	52 (34)	43.9 (33.6)	59.7 (33.08)	0.008
Serum ferritin (ng/L)	608 (1005)	754.2 (1251)	469 (674)	0.110
C-reactive protein (mg/L)	108 (92)	150.8 (89.6)	71.5 (77.534)	<0.001
D Dimer (ng/L)	3.85 (3.28)	3.9 (3.0)	3.8 (3.5)	0.883
NT Pro BNP (pg/ml)	3442 (5900)	4603 (6562)	2410 (5069)	0.03
Fibrinogen (mg/dl)	465 (163)	470 (168)	461 (160.6)	0.786
LDH (U/L)	362 (175)	373 (184)	351 (167)	0.484
Troponin T (ng/L)	25.6 (14.8)	42 (20.8)	9.8 (38.85)	0.238

MIS-C: Multisystem inflammatory syndrome in children, LDH: lactate dehydrogenase

Table 3: ***Treatment and outcome of patients with MIS-C during the two waves***

Treatment	Total *(n=138)* *n (%)*	Wave 1 *(n=65)* *n (%)*	Wave 2 *(n=73)* *n (%)*	p value
Intravenous immunoglobulin (IVIG)	21 (15)	13 (20)	08 (11)	0.1601
Methylprednisolone (MP)	84 (61)	43 (66)	41 (56)	0.294
IVIG + MP	18 (13)	07 (11)	11 (15)	0.6137
Oral steroids	09 (07)	01 (02)	08 (11)	0.0358
No treatment	05 (04)	0 (0)	05 (07)	0.0601
Inotrope	56 (41)	40 (62)	16 (22)	<0.001
Invasive Ventilation + NIV	17 (12)	10 (15)	07 (10)	0.3149
Mechanical ventilation	11 (08)	07 (11)	04 (05)	0.203
Chest X-ray abnormality	23 (17)	09 (14)	14 (19)	0.494
Ejection Fraction <55%	26 (19)	19 (29)	07 (10)	0.0043

NIV: non-invasive ventilation

Discussion

MIS-C due to Covid-19 often peaks 4–6 weeks after Covid-19 peaks[8]. Similar to previous observations, the incidence of admissions due to MIS-C in our hospital increased approximately 4 weeks after the Covid-19 surges in the population during both waves. Covid-19, after being reported first from Wuhan in China in December 2020, rapidly spread to most countries in the world. As of November 2021, like many countries in the world, India also experienced two surges of Covid-19 cases. The first surge peaked in September 2020, while the second surge peaked in May 2021. In India, the first wave was relatively milder, while the second wave starting in March 2021 was severe, with India accounting for more than 50% of global cases by May 2021.

In our study, there was no significant difference in the mean age, male-female ratio or duration of fever before admission between the two waves. Similar to our study, Harahsheh AS, *et al*[9] in their study also did not find any significant change in the incidence of MIS-C in various age groups in the two surges in children below 12 years of age, but they had reported a significant increase in incidence in those above 15 years of age. Our study did not include children above 12 years of age. We observed an increased incidence of cervical lymphadenitis in the second wave compared to the first, while the incidence of mucocutaneous manifestations, breathlessness and oral mucosal congestion were higher in the first wave. The incidence of gastrointestinal symptoms and CNS symptoms were similar in both waves.

In the study by Harahsheh AS, *et al*[9] nearly 100% of patients received IVIG and there was a significantly increased need for escalation to methylprednisolone in the second wave (29% vs 7%) compared to the first. In our study, in children with severe MIS-C, there was no significant difference in choice of initial immunomodulation and need for repeat immunomodulation between the two waves. Methylprednisolone was used in more than 55% of patients in both waves and the need for adding IVIG to steroids was found in 10-15% of patients. The incidence of coronary artery involvement was similar in both waves.

Belay ED, *et al*[10] also reported a higher proportion of patients with cardiac dysfunction, myocarditis, and higher pro–brain natriuretic peptide values and decreased lymphocyte values in children admitted with MIS-C before July 2020. In our study, a significantly higher proportion of patients were referred as MIS-C during the second wave compared to the first. Contrary to the observation by Harahsheh AS, *et al*[9], we report that the need for ICU admission, shock, clinical myocarditis, need for respiratory support and involvement of 5 or more organs was significantly lower in the second wave, compared to the first.

Whether early diagnosis and appropriate treatment or difference in genotypic lineage have led to the difference in severity and clinical presentation is not really known. By January 2021 in India, there was seeding and expansion of B.1.1.7 (Alpha), B.1.617.1 (Kappa) and B.1.617.2 (Delta) lineages and by April 2021 Delta became the predominant lineage[11]. However, in the study from the US in which the second wave showed an increasing severity of MIS-C there was a minimal circulation of Delta variant in the community there. Whether mutations in the Covid-19 virus or early identification and treatment contributed to the change in presentation of MIS-C is not really known. Further large-scale studies are needed to assess the factors associated with different clinical presentations and treatment outcomes.

Conclusions

MIS-C cases following the 2 Covid-19 surges exhibited certain distinctive features. Patients with MISC in the second wave exhibited a higher incidence of lymphadenitis and lower CRP levels. They also exhibited improved clinical outcome measures like less need for ICU care, respiratory support and shock.

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