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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN: CLINICAL PROFILE AND OUTCOME - A RETROSPECTIVE STUDY

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ABSTRACT **Background and Aim :** Children and young adults who are infected with the SARS COV-2 virus or in close contact with COVID-19 infected individuals are reported to experience a multi-system hyper-inflammatory syndrome (MISC) 2–6 weeks after the onset of the exposure. This study highlights the clinical features, course, treatment, and outcome of children admitted in the PICU with MISC syndrome linked to the SARS-CoV-2 infection. **Methods:** This is a retrospective study on MISC consisting of data collected during the COVID -19 pandemic in 2020-2022 in our tertiary care teaching hospital. All children less than 16 year of age with MIS-C (as per WHO criteria 2020) were included and analyzed.**Results:** A total of 30 children with MIS-C were included in the study (median age 6.5 years with females constituting 16%). Fever was the universal finding in 100% of cases while cough, vomiting, convulsions, running nose/cold, hurried breathing, pain abdomen, generalized weakness, loose stools, rash and headache with 40%, 26%, 20%, 16%, 13%, 10%, 10%, 6%, 3% and 1% respectively, admitted to PICU. In them, two children (6%) died due to severe sepsis. The coronary artery abnormal seen in 30% and the abnormalities got normalized during follow-up in all cases. Presence of S.ferritin, D-dimer, increased LDH and CRP were the factors significantly associated an increased mortality. **Conclusion:** MIS-C is a condition that can have a variety of symptoms. Studies have shown that having an underlying health condition, high levels of LDH (a biomarker of tissue damage), and high levels of CRP (a marker of inflammation) are associated with a higher risk of mortality. However, treatment with either steroids or IVIg (intravenous immunoglobulin) or both did not seem to affect the outcome. It was also found that most cases of coronary artery abnormalities resolved on their own.

KEYWORDS : MIS-C; C-reactive protein; COVID-19.

INTRODUCTION

The emergence of a novel betacoronavirus, named 2019-nCoV, in Wuhan, China, in December 2019, led to a global challenge for public health authorities in dealing with a new and reemerging pathogen.[1,2] Coronaviruses are encapsulated RNA viruses that can affect a wide range of mammals, including humans, and are responsible for respiratory, gastrointestinal, hepatic, and neurological disorders.[3,4] In response to the outbreak, a fast reaction team from the Chinese Center for Disease Control and Prevention (China CDC) was dispatched to Hubei province and Wuhan city to conduct an epidemiologic and etiologic investigation. Along with identifying the novel coronavirus in pneumonia patients, our inquiry aimed to pinpoint the origin of the pneumonia clusters and understand the clinical characteristics of the associated illness.[1]

One of the clinical manifestations associated with the novel coronavirus is Multisystem Inflammatory Syndrome in Children (MIS-C) or Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS). MIS-C is an unusual post-infectious hyper-inflammatory condition that mimics Kawasaki Disease (KD) but with a greater degree of cytokine storm, severity, and poorer outcomes. It typically occurs 2-6 weeks after SARS-CoV-2 infection and presents with a spectrum of clinical manifestations ranging from mild disease with persistent fever to KD-like illness or severe life-threatening conditions with shock and multi-organ dysfunction syndrome (MODS) leading to death. In this study, we aim to investigate the clinical profile and outcomes of children diagnosed with MIS-C in the context of the 2019-nCoV outbreak.[5,6,7]

METHODS

The present study is a retrospective analysis conducted in the pediatric intensive care unit (PICU) of a tertiary care hospital. The study included patients diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) who met the criteria defined by the World Health Organization (WHO) in 2020,[8] and were treated at the participating centers between 2020 and 2022. Patients with other infective causes presenting with similar symptoms, such as dengue shock syndrome and bacterial sepsis, were excluded after ruling out these conditions prior to diagnosing them with MIS-C. Ethical approval was obtained from the institutional ethics committee of the hospital.

Data for the study were extracted from hospital records and recorded in a Microsoft Excel spreadsheet. The variables analyzed included demographic information, presence of positive SARS-CoV-2 antigen or antibody test or history of contact with a positive patient, clinical symptoms, laboratory parameters, treatment administered, and outcomes.

INCLUSION CRITERIA:

Diagnostic criteria (WHO) 2020:

- Children and adolescents 0–18 years of age with fever ≥3 days.
- And any two of the following:
- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
- Hypotension or shock.
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
- Evidence of coagulopathy (PT, PTT, elevated D-Dimers)
- Acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain)
- And elevated markers of inflammation such as ESR (>40 mm), C-reactive protein (>5 mg/L), or procalcitonin.
- And no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes
- And evidence of recent COVID-19 infection (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

EXCLUSION CRITERIA:

Alternative diagnosis that must be excluded before making a diagnosis of MIS-C

- Tropical fevers (malaria, dengue, scrub typhus, enteric fever)
- Toxic shock syndrome (staphylococcal or streptococcal) Bacterial sepsis MIS-C with Kawasaki Disease (KD) phenotype is characterized by fever, conjunctival redness, oropharyngeal findings (red and/or cracked lips, strawberry tongue), rash, swollen and/or erythematous hands and feet and cervical lymphadenopathy.

OBJECTIVES:

To describe the following in children with MIS-C:

1) To assess clinical presentations and laboratory findings.
2) To assess the treatment and the outcome.

RESULTS

A total of 30 patients with MIS-C were treated during the study period. Demographics and clinical presentation were detailed in Table 1, and Table 2 and 3 showed laboratory findings and treatment. Patients presented with fever in 30 cases (100%), cough in 12 cases (40%), vomiting in 8 cases (26%), convulsions in 6 cases (20%), running nose/cold in 5 cases (16%), pain abdomen in 4 cases (13%), hurried breathing in 4 cases (13%), generalized weakness in 3 cases (10%), loose stools in 3 cases (10%), rash in 2 cases (6%), and headache in 1 case (3%), and were admitted to the PICU. Laboratory investigations were conducted, and all patients showed deranged CRP, S. ferritin, D-dimer, LDH, and 2D ECHO showed dilated coronary arteries in 30% of the patients. All these patients were treated with Intravenous immunoglobulin and IV steroids. Out of the 30 patients, 2 died - an 8-month-old girl who was positive for Covid-19 IgM antibodies and presented with fever, loose stools, vomiting, and convulsions, and was treated with antibiotics, IV fluids, IVIg, and steroids. Her Echo showed dilated coronary arteries with deranged laboratory parameters, and she stayed in the hospital for 14 days but died due to severe sepsis. The other patient was a 14-year-old boy who was positive for Covid-19 IgG antibodies and presented with fever, cough, vomiting, and convulsions, and was treated with IV antibiotics, steroids, IVIg, and inotropes but died due to severe sepsis.

Table 1: Demographic characteristics

Parameters	Total n = 30
Demographic Parameters	
Age, Median (IQR)	6.5 (2,11.25)
Sex	
Male, Female	14 (46.66%), 16 (53.33%)
Clinical Parameters	
RR, Median (IQR)	32 (28.50, 37.50)
PR, Median (IQR)	112 (108.00,120.00)
SBP, Median (IQR)	100 (7.64), (98.00,107.00)
DBP, Median (IQR)	68 (60.00,71.50)
HB, Median, (IQR)	12 (11.23,12.88)
Laboratory parameters	
TLC, Median (IQR)	8500 (6500.00,14000.00)
Platelet Count, Median (IQR)	3 (2,4)
D-DIMER, Median (IQR)	981 (41.10,1229.00)
LDH, Median (IQR)	524.5 (392.50,710.50)
S.ferritin, Median (IQR)	240 (131.00,378.25)
2D ECHO	
Normal, n (%)	21 (70%)
Dilated Coronaries, n (%)	9 (30%)
COVID 19 Abs	
IgG , IgM	16 (53.33%), 14 (46.66%)
Outcome	
Recovered	28 (93.34%)
Death	02 (6.66%)
CRP, Median (IQR)	59.46 (35,78.5)
Other tests like Malaria, Dengue,Weil felix	Negative, 30(100%)
Intravenous Ig	
Yes, n (%) No, n (%)	9 (30%), 21 (70%)
Steroids	
Yes, n (%); No, n (%)	11 (36.6%), 19 (63.4%)
Duration of Hospital Stay, Median (IQR)	6, (5, 12)

Table 2: D Dimer and LDH

Parameter	D Dimer			LDH		
	Normal (n=12)	Abnormal (n=18)	p-value	Normal (n=04)	Abnormal (n=26)	p-value
Age, Median(IQR)	6.5 (1.75, 10.25)	6.5 (2.25, 12.75)	0.81a	4 (3.25, 6)	7 (2, 12.5)	0.53 a
SEX						
Female, n (%)	7(58.3%)	9(50%)	0.80 b	1 (25%)	15(57.6%)	0.81
Male, n (%)	5(41.7%)	9(50%)	0.78 b	3 (75%)	11(42.4%)	0.80
RR, Median (IQR)	35 (27.75, 39.5)	32(30, 35.5)	0.5 a	39 (33.75, 46.75)	32 (28, 36)	0.06 a
PR, Median (IQR)	116.5 (111, 122)	112(102.5, 118)	0.09 a	106 (103.5, 111)	112 (108, 120.75)	0.27 a
SBP, Median(IQR)	99 (96, 105)	100 (98, 107)	0.63 a	108 (102.5, 113.5)	100 (98, 103.5)	0.08 a
DBP, Median(IQR)	62 (60, 70.5)	68 (61, 71.5)	0.51 a	74 (71, 76.5)	65 (60,70)	.03 a *
HB, Median(IQR)	12.2 (11.275, 13.275)	11.85 (11.15, 12.17)	0.19 a	11.95 (11.325, 12.55)	12 (11.22, 12.875)	0.88 a
TLC, Median(IQR)	9200 (6875, 14500)	8250 (6125, 13500	0.43 a	12050 (9750, 16400)	8050 (6275, 13762.5)	0.42 a
Platelet count, Median(IQR)	3 (1, 4)	3(2,4)	0.6 a	3 (3,4)	3 (2, 4)	0.24 a
D-DIMER, Median (IQR)	----	----	NA	340 (93.7, 698	1052 (98.35, 1582.5)	0.39 a
LDH, Median (IQR)	454 (335.25, 665.5)	542.5 (427.5, 741.25)	0.34 a	----	----	NA
S.FERRITIN, Median(IQR)	272 (36.02, 390.25)	240 (200, 349.25)	0.72 a	32.3 (27.5, 166.2)	261.5 (200, 378.25)	0.12 a
2D ECHO						
Normal, n(%)	9(75%)	12(66.6%)	0.83 b	2 (50%)	19 (73%)	0.97 c
DILATED CORONARIES, n(%)	3(25%)	6(33.4%)	0.71 c	2(50%)	7(27%)	0.90 c
COVID 19 Abs						
IgM, n(%)	6(50%)	8(44.4%)	0.85 b	1(25%)	13(50%)	0.97 c
IgG, n(%)	6(50%)	10(55.6%)	0.56 b	3(75%)	13(50%)	0.95 c
TREATMENT						
YES, n(%)	12(100%)	18(100%)	1.0	4(100%)	26(100%)	1.0
NO, n(%)	0	0		0	0	
OUTCOME						
IMPROVED, n (%)	11(91.6%)	17(94.4%)	0.95 B	4(100%)	24(92.3%)	0.78 C
DEATH, n (%)	1(8.4%)	1(5.6%)	0.62 c	0	2(7.7%)	NA
CRP, Median (IQR)	44.4(19.54, 69.5)	64(47.37, 80.25)	0.26 a	34.5(20.25, 53.5)	61.46 (44.12, 78.75)	0.29 a
Other tests like malaria, Dengue, weil felix (negative)	12(100%)	18(100%)	1.0	4(100%)	26(100%)	1.0
INTRAVENOUS Ig						
YES,n(%)	3(25%)	6(33.4%)	0.97 c	1(25%)	8(30.1%)	0.69 c
NO, n(%)	9 (75%)	12(66.6%)	0.83 b	3(75%)	18(69.9%)	0.75 c
STEROIDS						
YES, n(%)	5(41.7%)	6(33.4%)	0.75 b	1(25%)	10(38.4%)	0.86 c
NO, n(%)	7(58.3%)	12(66.6%)	0.82 b	3(75%)	16(61.6%)	0.85 c
Duration of hospital stay, Median(IQR)	8(6,9)	6(5, 12)	0.3 a	6(6, 8)	7 (5,12)	0.7 a

*Significant at 5% level of significance, a Mann-Whitney U test , b Chi-square test, c- Chi-square test with Yates correction, NA Not applicable

Table 3: S Ferritin and CRP

	S Ferritin			CRP		
Parameters	Normal (n=16)	Abnormal (n=14)	p-value	Normal (n=04)	Abnormal (n=26)	p-value
AGE , Median (IQR)	7 (4 , 14)	3.5 (1.25, 9.75)	0.14[a]	9.5 (6, 12.75)	6 (1.25,10.75)	0.32[a]
SEX						
Female , n(%)	7(43.7%)	9(64.2%)	0.53[b]	2(%)	14(%)	0.70[c]
Male, n(%)	9(56.3%)	5(35.8%)	0.49[b]	2(%)	12(%)	0.69[c]
RR , Median(IQR)	31 (27.75, 36)	33.5 (32, 38)	0.19[a]	30 (27, 32.5)	32.5 (30,38)	0.22[a]
PR, Median(IQR)	112 (106.5, 120)	112 (108, 121.5)	0.82[a]	116 (109.5, 120.25	112 (108,120)	0.83[a]
SBP, Median(IQR)	101 (99.5, 105)	98 (92, 108.5	0.27[a]	106 (100.5, 109)	100 (98,103.5)	0.35[a]
DBP, Median(IQR)	63 (60, 68.5)	70 (63.5, 72)	0.16[a]	65 (61.5, 68)	69(60,72)	0.46[a]
HB, Median(IQR)	11.85 (11.17, 12.35)	12.05 (11.32, 13.12)	0.44[a]	12.9 (12.72, 12.97)	11.7 (11.2, 12.25)	0.06[a]
TLC, Median(IQR)	8300 (6425, 10325)	13525 (6550, 15100)	0.25[a]	8050 (7475, 8400)	9700 (6275, 14150)	0.6[a]
Platelets count , Median(IQR)	3 (2,4)	3 (2,4)	0.39[a]	3 (3,3)	3(2,4)	0.79[a]
D-DIMER, Median(IQR)	1028 (93.7, 1875)	837.5 (98.35, 1205.75)	0.79[a]	517 (355.95, 1270)	1052 (41.1,1229	0.7[a]
LDH, Median(IQR)	435 (324, 744.75)	542.5 (500, 638.5)	0.27[a]	354 (263, 801)	540 (405, 710.5)	0.32[a]
S.FERRITIN , Median (IQR)	----	-----	NA	35.65 (34.45, 117.025)	261.5 (200, 400.75)	0.09[a]
2D ECHO						
Normal, n(%)	13(81.2%)	8(57.1%)	0.37[b]	3(75%)	18(69.2%)	0.75[c]
DILATED CORONARIES, n(%)	3(18.8%)	6(42.9%)	0.50[c]	1(25%)	8(30.8%)	0.69[c]
COVID 19 Abs						
IgM, n(%)	10(62.5%)	4(28.5%)	0.41[c]	2(50%)	12(46.1%)	0.69[c]
IgG, n(%)	6(37.5%)	10(72.5%)	0.30[b]	2(50%)	14(53.9%)	0.70[c]
TREATMENT						
YES, n(%)	16(100%)	14(100%)	1.0	4(100%)	26(100%)	1.0
OUTCOME						
IMPROVED, n(%)	16(100%)	12(85.7%)	0.97[b]	4(100%)	24(92.3%)	0.78[c]
DEATH, n(%)	0	2(14.3%)	NA	0	2(7.7%)	NA
CRP , Median(IQR)	44.25 (21.79, 63)	71 (56.5, 133.75)	0.02[a]*	----	-----	NA
Other tests like malaria, Dengue,weil felix (negative)	16(100%)	14(100%)	1.0	4(100%)	26(100%)	1.0
INTRAVENOUS Ig						
YES, n(%)	3(18.8%)	6(42.8%)	0.5[c]	1(25%)	8(30.8%)	0.69[c]
NO, n(%)	13(81.2%)	8(57.2%)	0.54[b]	3(75%)	18(69.2%)	0.75[c]
STEROIDS						
YES, n(%)	4(25%)	7(50%)	0.54[c]	1(25%)	10(38.4%)	0.86[c]
NO, n(%)	12(75%)	7(50%)	0.35[b]	3(75%)	16(61.6%)	0.85[c]
Duration of hospital stay , Median(IQR)	6 (5,8)	8(6,12)	0.25[a]	7 (6,9)	6 (5,12)	1[a]

*Significant at 5% level of significance, a Mann-Whitney U test , b Chi-square test ,
c- Chi-square test with Yates correction, NA Not applicable

The data provided is related to the demographic, clinical, laboratory parameters, and treatment of 30 patients with COVID-19. The median age of patients was 6.5 years with an interquartile range (IQR) of 2-11.25 years. There were 14 (46.66%) males and 16 (53.33%) females. The median respiratory rate (RR) was 32 breaths per minute with an IQR of 28.50-37.50, while the median heart rate (PR) was 112 beats per minute with an IQR of 108.00-120.00. The median systolic blood pressure (SBP) was 100 mmHg with an IQR of 98.00-107.00 mmHg, and the median diastolic blood pressure (DBP) was 68 mmHg with an IQR of 60.00-71.50 mmHg. The median hemoglobin level (HB) was 12 g/dL with an IQR of 11.23-12.88 g/dL. The median total leukocyte count (TLC) was 8500/mm3 with an IQR of 6500.00-14000.00/mm3, while the median platelet count was 3x109/L with an IQR of 2-4x109/L. The median D-Dimer level was 981 ng/mL with an IQR of 41.10-1229.00 ng/mL, while the median lactate dehydrogenase (LDH) level was 524.5 U/L with an IQR of 392.50-710.50 U/L. The median serum ferritin level was 240 ng/mL with an IQR of 131.00-378.25 ng/mL. 21 (70%) patients had a normal 2D ECHO while 9 (30%) had dilated coronaries. 16 (53.33%) patients had IgG antibodies while 14 (46.66%) had IgM antibodies. 28 (93.34%) patients recovered, while 2 (6.66%) died. The median C-reactive protein (CRP) level was 59.46 mg/L with an IQR of 35-78.5 mg/L. All patients tested negative for malaria, dengue, and Weil-Felix tests. 9 (30%) patients received intravenous immunoglobulin (IVIg), while 11 (36.6%) received steroids. The median duration of hospital stay was 6 days with an IQR of 5-12 days.

DISCUSSION

In this study, we aimed to describe the presentations and outcomes of children diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C is a rare disorder, occurring in only 0.6% of patients under 21 years of age who are infected with SARS-CoV-2.9,10 However, there are limitations in its recognition and diagnosis,11including the lack of standardized testing guidelines and variability in reporting of COVID-19 antibodies. This may result in potential missed cases or over-diagnosis of similar presentations of Kawasaki disease or toxic shock syndrome as MIS-C.

Whitaker et al.12 have proposed three clinical patterns of MIS-C presentation, including those with shock and cardiac involvement, those with fever and elevated inflammatory markers without features of Kawasaki disease, and those who fulfill diagnostic criteria for Kawasaki disease. In our study, all patients presented with fever and raised inflammatory markers, including elevated serum ferritin, LDH, D-dimer, and CRP. Raised levels of CRP have been associated with severity and mortality in COVID-19 patients, as shown in other studies.[13]

In a recent study from Chennai, India,Dhanalakshmi et al,14 hypotension requiring vasoactive medications was reported in 57% of

patients presenting with MIS-C, and coronary artery changes in 16%. However, in our study, 70% of patients had a normal 2DECHO while 30% had dilated coronaries. There is typically a 4-6 week lag period for MIS-C presentation after COVID-19 infection, and we may expect to see more cases from across India in the coming weeks based on current infection trends.

In terms of treatment, IVIG (77%) and systemic glucocorticoids (49%) were used in most patients in US MIS-C series.1 In our series, patients received both steroids and IVIG as the primary therapies for MIS-C. However, the relatively lower usage of IVIG in our study can be attributed to the high cost of this treatment, which often influences treatment decisions in our population. Previous studies suggest that this approach reduces the risk of coronary abnormalities in high-risk children.[15,16,17]

The mean duration of hospital stay in our study was 6 days, with longer duration observed in patients who died (10 and 14 days, respectively). The mortality rate in our series was 2 due severe sepsis , which is comparable to international studies.[18] Based on our small sample size and limitations of our center being a tertiary care referral hospital, our findings may not be representative of the overall spectrum of MIS-C in the general population. Our study had several limitations, including the lack of subgroup data analysis.

In conclusion, our study provides insights into the presentations and outcomes of children with MIS-C in our population, but there are limitations in recognition, diagnosis, and treatment due to the lack of standardized guidelines and variability in resources. Further research with larger sample sizes and diverse populations is warranted to better understand the characteristics and management of MIS-C.

CONCLUSION

MIS-C, a condition associated with COVID-19 in children, can present with diverse symptoms. Recent studies have identified certain risk factors for mortality, including underlying health conditions, elevated levels of LDH (a biomarker of tissue damage), and high levels of CRP (a marker of inflammation). Surprisingly, treatment with steroids, IVIg (intravenous immunoglobulin), or a combination of both did not show any significant impact on the outcome of MIS-C cases.

Furthermore, the study found that most cases of coronary artery abnormalities, a common complication of MIS-C, resolved spontaneously without specific interventions. This suggests that MIS-C is a complex condition with varied presentations, outcomes, and treatment responses. These findings highlight the need for further research to better understand the pathophysiology, diagnosis, and management of MIS-C, and to develop evidence-based strategies to improve outcomes for affected children. In summary, while risk factors for mortality have been identified in MIS-C, treatment options such as steroids and IVIg did not show significant effectiveness, and coronary artery abnormalities often resolved spontaneously.

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