



ORIGINAL ARTICLE

## Multisystem inflammatory syndrome (MIS-C) in Children on Kawasaki syndrome spectrum: What's new, Local regional experience from Pakistan.

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**ABSTRACT... Objective:** To describe the prevalence, clinical spectrum (Particularly cardiac) and treatment strategies of MIS-C. **Study Design:** Case Control study (prospective and retrospective surveillance). **Setting:** Children Hospital and Pediatric Medicine Department DHQ/Allied Hospital Faisalabad, Pakistan. **Period:** 15<sup>th</sup> March, 2017, to March 14<sup>th</sup>, 2020. **Material & Methods:** All patients with confirmed MIS-C/KD were enrolled and made two groups before and after the pandemic of SARS CoV-2. **Results:** A total of 6 patients before pandemic (group 1) and 18 patients after the pandemic (group 2) were studied over a period of 3 years. There is female dominance in group 1 and male dominance in group 2. Patients in group 2 presented at higher age (median 8y). Gastrointestinal symptoms (72.2%), Shock (11.2%) and LV dysfunction (11.1%) were more different features of MIS-C as compared to KD. There was more intense hyperinflation response was in MIS-C as compared to KD (CRP median 15.5 vs 78 and S/Ferritin median 725 vs 1889). **Conclusion:** MIS-C is on the Kawasaki disease spectrum in many ways both clinically and biochemical markers but the level of inflammation and immune response and severity of cardiac involvement were much bigger than KD. This should be in high consideration in perspective of new waves of SARS CoV-2.

**Key words:** MIS-C, Kawasaki Disease, SARS CoV-2, Pediatrics.

### INTRODUCTION

In December 2019, emergence of Coronavirus disease (COVID-19) was experienced for the first time in China which rapidly turned into a pandemic, posed a public health threat around the globe including children of all ages that raised the global concern and made a huge impact as it spread rapidly across the world involving all continents like America, Europe, Australia and Asia and effected millions of people. Although pediatric population gets infected with coronavirus but existing evidence depicts a relatively low incidence and mild severity of COVID 19. Some children who had an active infection with the coronavirus might not show any signs or symptoms at all.<sup>1</sup> Resources constrained country like Pakistan also took rigorous steps to combat the spread of virus by designing special hospitals, quarantine centers, laboratories for viral

PCR testing and effective awareness campaign through electronic, print and social media. Till August 22, 2020, there are 6255 total deaths in Pakistan with a mortality of 0.3% for those aged 10 years or younger and 0.5% for those aged 11–20 years.<sup>2</sup>

Multisystem inflammatory syndrome in children (MIS-C), also known as paediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus SARS CoV-2 (PIMS-TS) reported worldwide with much higher rates in USA.<sup>3</sup> In children, MIS-C turned out to be an important post COVID manifestation. Pathogenesis of MIS-C is not very well understood but it is thought to be more likely a post infectious abnormal immune mediated response rather than direct viral infection.<sup>4</sup> MIS-C is debated to be a new syndrome or

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just a spectrum of Kawasaki disease shock syndrome (KDSS) which is having incidence of 4-6%. This condition of systemic inflammation has varied symptoms accompanied by some similarities with Kawasaki disease (KD), and may potentially develop serious illness. Both diseases share multiple cardiac and extra cardiac clinical manifestations. In the developed countries, clinical features of myocarditis, myocardial dysfunction and overt shock requiring inotropic support were prominent. Some patients developed coronary artery aneurysm as well as Macrophage Activation Syndrome (MAS) in MIS-C.<sup>5</sup>

The aim of this study was to describe the prevalence, clinical spectrum (Particularly cardiac) in context of myocardial dysfunction and shock and treatment strategies of new cases of MIS-C (Kawasaki-like presentations) admitted during the SARS-CoV-2 epidemic locally in Pakistan.

## MATERIAL & METHODS

This Case control study (prospective and retrospective surveillance of patients with MIS-C) was conducted at the Department of Cardiology, The Children Hospital and pediatric medicine department DHQ/Allied Hospital Faisalabad, Pakistan, over a period of 3 years. We divided the patients in two groups according to the date of presentation: group 1, presenting during the 3 years preceding the local SARS-CoV-2 epidemic (ie, 15<sup>th</sup> March, 2017, to March 14<sup>th</sup>, 2020); and group 2 presenting thereafter (ie, March 15<sup>th</sup> to 15<sup>th</sup> Sep, 2020). All patients presenting to the hospital for the first time and diagnosed as Kawasaki disease, KDSS and MIS-C were evaluated for inclusion in the study. After obtaining informed consent from patient's parents, evaluation was performed with confirmation of diagnosis through laboratory investigation and echocardiography.

The demographic profile, residence, area alert in the pandemic and family history of the person involved with COVID-19 were recorded through a specially designed questionnaire proforma through interview-based information by the author (UR) from direct caregiver including mother,

father, or the guardian.

Patients with Kawasaki-like presentations were defined according to the 2017 criteria of the American Heart Association, including both the classic type (fever for  $\geq 5$  days plus four or more clinical criteria, including bilateral bulbar non-exudative conjunctivitis, changes of the lips or oral cavity, non-suppurative laterocervical lymphadenopathy, polymorphic rash, erythema of the palms and soles, firm induration of the hands or feet, or both) and incomplete types. In incomplete types (fever for  $\geq 5$  days plus two or three of the aforementioned clinical criteria), the values of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), or both, were taken as an additional diagnostic criterion in association with the presence of anemia, thrombocytosis after 7 days of fever, hypoalbuminaemia, hypertransaminasaemia, leukocytosis, sterile pyuria, or an echocardiogram showing coronary aneurysms or cardiac dysfunction (ie, left ventricular function depression, mitral valve regurgitation, or pericardial effusion).<sup>8</sup> MIS-C was defined by criteria like serious illness leading to hospitalization, an age of less than 19 years, fever (body temperature,  $>38.0^{\circ}\text{C}$ ) or report of subjective fever lasting at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement (i.e., involving at least two systems), and laboratory-confirmed 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.<sup>5</sup> Clinical myocarditis was defined as cardiac dysfunction on echocardiography (defined as any ventricular dysfunction or hypokinesia or decreased contractility or ejection fraction) Coronary-artery aneurysm were reported on the basis of echocardiographic findings and z scores (Boston criteria, when available). We defined values for tachycardia, tachypnea, hypotension, lymphopenia, neutropenia, TropT, ECG ventricular hypertrophy or arrhythmia, on the basis of age standards.<sup>9,10</sup> Patients and caregivers had nasopharyngeal and oropharyngeal swab sampling, testing SARS-CoV-2 nucleic acid using reverse-transcriptase quantitative PCR

assay; patients with a positive nasopharyngeal and oropharyngeal swab sampling test were considered confirmed cases of SARS-CoV-2 infection. The patients diagnosed more recently had a test for the qualitative detection of SARS-CoV-2 antibodies (IgM and IgG) through a lateral flow chromatographic immuno-assay. The outcome is based on normalization of the clinical parameters and normalization of acute phase reactant and other laboratory parameter of MIS-C that come in normal reference range of that age group.

The student t test, Fisher's exact test and the  $\chi^2$  method were done for statistical analysis to compare continuous and categorical variables. Data were calculated and analyzed with SPSS (version 20.0) software. A p value of  $<0.05$  was chosen as cutoff for significance. Institutional Review Board of the hospital approved the study protocol and ethical aspects of the study with the letter no 15371/CHF.

## RESULTS

Between March 15<sup>th</sup> 2017, to March 14<sup>th</sup>, 2020, in a 3 year period, six patients age range of 3-5.6 Years with a median age of 4 years. There were 4 girls and 2 boys with girls to boys ratio of 2:1, were diagnosed as Kawasaki disease with an incidence of one patient after every six month. These were comprised as group 1. All these six patients they got admitted to the hospital on 5<sup>th</sup> day of illness (range 2-7days). Four patients (66%) admitted with the classical type and two (34%) admitted with atypical form. Patients admitted with the typical form having high grade fever (100%), hand and feet edema (33.3%), cervical lymphadenopathy (50.%), non-purulent conjunctivitis (33.3%) and strawberry tongue in five patients (83.3%). The Chest X ray and electrocardiography (ECG) is normal in all typical and atypical cases. Two patient (34%) in all the six patients having abnormal echocardiography in the form of coronary artery dilatation of left main coronary artery (LMCA) (Z score  $>2.5$ ) with no aneurysmal dilatation.

In group 2 (i-e, March 15<sup>th</sup> to 15<sup>th</sup> Sep, 2020), in seven month there are 18 patients were

diagnosed as MISC (Kawasaki like disease spectrum) in the era of pandemic of SARS-CoV-2. Age ranges from 5-11 years with median age of 8y. There are 15 boys and 3 girls with boys to girl ratio of 5:1. In the pandemic incidence per month is fairly high almost 3 patients per month. 13 (72%) patients presented with typical features and 5 (28%) patients with atypical features. In both types all patients presented with high grade fever and presented on 3<sup>rd</sup> day of fever (Range 2-6 days). Non purulent conjunctivitis and rash is the most consistent features in all patients. In patients having MISC typical presentation 62% (n=8) patients having rash, 85% (n=11) having non purulent conjunctivitis, 62% (n=8) having strawberry tongue, 54 % (n=7) swelling of hand and feet, 18% (n=2) having lymphadenopathy. In Atypical presentation 80% (n=4) having rash and conjunctivitis, 40% (n=2) having strawberry tongue, 20% (n=1) having swelling of hand and feet and no patient having lymphadenopathy.

Among Patients presented with MISC 11.1% (n=2) presented with shock (like KDSS). Serum ferritin having a median of 698 (range 151- 4654), D Dimer was having median of 382 (range 216- 512), WBC count having median of 13200 (range 6300- 21000) with predominant neutrophils (median 75.5%) in almost all cases. CRP having median of 590 (range 10-600). There is no significant association of serum ferritin and shock (p=0.38). There is significant association of shock and cardiac involvement in the form of both coronary artery involvement and LV dysfunction (p  $<0.001$ ). There is no significant association between value of CRP and associated shock (p=0.3). out of 18 total patients 77.8% (n=14) having no cardiac involvement. 11.1% (n=2) patients presented with coronary artery involvement (both the cases having LMCA involvement z score  $>2.5$ ).11.1% (n=2) presented with LV dysfunction and both are boys with age 10 and 8 years with EF of 42% and 46% respectively. The patients admitted with mild LV dysfunction presented with IVIG and steroids and their dysfunction improved at discharge. All the patient were admitted in group 2 were negative for real time PCR for SARS-CoV-2. 94.4% (n=17) were positive for IgM antibodies and 5.6% (n=1) patient is having positive for both IgM and IgG.

(Table-I).

From Jun 15, 2017, to March 14th, 2020 (start of epidemic in Pakistan) six patients were diagnosed as Kawasaki disease with a median age of 4 years with the incidence of 0.2 patients per month. There was a female predominance (M: F=0.5:1) and majority (66%) were typical Kawasaki disease which have classical features

of KD. In these patients nobody presented with shock like condition or KDSS. There were no signs of poor perfusion clinically or features of Macrophage activation syndrome (MAS) or KDSS. Complete comparison of clinical, biochemical and laboratory parameters of both group 1 and 2 were given in Table-II. Only two patients (having coronary artery involvement) got the treatment of IVIG and completely recovered.

		Group 1		Group 2	
		N=6	Percent	N=18	Percent
Clinical Features	Fever	6	100.0%	18	100.0%
	Rash	5	83.3%	14	77.8%
	Tongue	5	83.3%	10	55.6%
	Conjunctivitis	2	33.3%	15	83.3%
	Swelling	2	33.3%	8	44.4%
	Lymphadenopathy	3	50.0%	2	11.1%
	Body aches	1	16.7%	5	27.8%
	cough	2	33.3%	9	50.0%
	Shock	0	0%	2	11.1%
GI Symptoms	0	0%	13	72.2%	

**Table-I. Clinical features in both the groups in both typical and atypical form. Group 1 (Pre- SARS-CoV-2 epidemic), Group 2 (During SARS-CoV-2 epidemic)**

	Group 1	Group 2	P-Value
Time of presentation			NA
Total patients	6	18	--
Age	4 (3- 5.6)	8 (5- 11)	P<0.003
Incidence /month	0.2	3	P<0.0001
Gender	M:F= 0.5 : 1	M:F= 5:1	NA
Incomplete Kawasaki (MISC)	2 (34%)	5 (28%)	P= 0.213
CRP (mg/dl)	15.5 (12-316)	78(10-600)	P<0.004
WBC (x 10 <sup>9</sup> per L)	14116 (12634-19264)	13200 (6300-21000)	P<0.002
Neutros (%)	81.5% (75-91)	75.5% (63-91)	P=0.249
Lymphos (%)	11.5% (5-18)	15.5 % (5-32)	P= 0.650
ALT (U/L)	45 (32-53)	48.5 (24- 322)	P= 0.412
S/Ferratin (ng/ml)	725 (529-3216)	1889 (863- 5214)	P=0.389
D Dimer (ng/ml)	395(128-659)	382 (216- 512)	P=0.671
S/LDH	372 (128-659)	315 (214- 421)	P=0.690
KDSS	0/6 (0%)	2/18 (11.1%)	P<0.0001
Abnormal echocardiography	2/6 (34%)	4/18 (22.2%)	P<0.001
LV Dysfunction	0/6 (0%)	2/18 (11.1%)	P<0.0004
Steroid treatment	0/6 (0%)	4/18 (22.2%)	P<0.0021
Inotropes	0/6 (0%)	4/18 (22.2%)	P<0.038
IVIG	2/6 (34%)	6/18 (33.3%)	P<0.016
Response to treatment	6/6 (100%)	18/18 (100%)	P=1

**Table-II. Comparison between patients with Kawasaki disease before and after the pandemic**

In comparison to group 1, after the epidemic of SARS CoV-2 (i-e, March 15th to Sep 15<sup>th</sup>, 2020) in group 2 there was 18 patients were admitted with an incidence of three patients per month (0.2/month in group 1). The median age was more in group 2 which is eight year (4y in group 1)  $P < 0.003$ . In group 1 there were girl's dominance but in group 2 older boys were more prominent. Rash and conjunctivitis was more dominant feature in group 2 in comparison to group 1 where rash and strawberry tongue was the predominant clinical features. GI symptoms were almost nil in group 1 as compared to group 2 in which almost 72.2% (n=13) of patients do develop GI symptoms in the form of abdominal pain and vomiting. Incomplete/Atypical forms of Kawasaki or MIS-C like syndrome were almost same in the both groups (34% vs 28%). The value of CRP in group 1 is median of 15.5 (range 12-316) but in group 2 it's significantly high with median of 78 (range 10-600)  $P < 0.004$ . Although serum ferritin in both the groups are high but in current epidemic of SARS CoV-2 its much higher and having a higher range as compared to group 1 {group 1 (median 725) vs group 2 (median 1889)} but it's not statistically significant  $p = 0.389$ . The level of Serum LDH and D Dimer are almost the same values in both group and are not statistically significant  $p = 0.69$  and  $p = 0.67$  respectively. In group 1 no patient was admitted with shock like or with hemodynamic ally unstable condition but in group 2 there were 2 (11.1%) patients presented with shock and required inotropes for the management of shock and Milrinone is the main drug used for the management.

Although in both groups coronary artery was involved and in both the group LMCA is the main artery that have a dimension with z score  $> 2$ . 34% patients having coronary artery involved in group 1 and 11.2 % patients involved in group 2 and its statistically significant  $p < 0.0001$ . There was LV dysfunction in group 2 in 11.1% of cases and in the both cases the ejection fraction (EF) is 43% and 46% respectively and in mild category but in group 1 no patients involved the LV dysfunction. The LV dysfunction in group 2 was managed with Immunosuppressant drugs and successfully with diuretics, ACE inhibitors and inotropes.

Steroids were used in all the patients in group 2 with cardiac involvement because in addition to their cardiac involvement all the patients have a relatively higher level of CRP and serum ferritin level. IVIG was used in 34% patients in group 1 and 6 (33.3%) patients in group 2 ( $p < 0.016$ ) which were used not only in patients with cardiac involvement but in those with clinically moderate to severe symptoms in two patients in which fever not settled with anti-inflammatory drugs. 66.7% (n=12) patients who have mild symptoms and usually not high acute phase reactant were treated with aspirin in anti-inflammatory dose and in all patients fever settled within 3 days and almost all patients in group 1 and 2 were put on antiplatelet dose of aspirin after the settlement of clinical features and laboratory parameters. Till date, all the patients in group 2 had been discharged, treatment with aspirin in antiplatelet dose is ongoing and a follow up echocardiography is planned after 6-8 weeks. (Table-II)

## DISCUSSION

Multisystem inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus SARS CoV-2 (PIMS-TS) carries a serious risk of avoidable morbidity, mortality and life threatening issues. Kawasaki disease is similar to MIS-C and both having many theories for the cause of the disease but aberrant immune response in genetically predisposing children is the widely accepted hypothesis.<sup>11</sup> However the search of infectious agent triggers this process is always disappointing. Epidemics usually make an impact on such illness because sometimes they trigger such issues at a wide level and similar things happened in the most parts of the world including Pakistan where SARS CoV-2 is triggering such diseases. Direct effect of this pandemic on children is very small as compared to adults in both burden and severity. However, they are likely to be victims of the overall impact of the pandemic on the society and of the measures to curtail it, both in the short and long term. The major impact seen when the number of cases of MIS-C (Kawasaki disease like illness) is increased in this pandemic era as compared

to the previous years. In the past it is suggested that corona virus family might have triggered many cases of Kawasaki disease but it remained a debatable issue in different part of the world as a cause.<sup>12-14</sup> But SARS CoV-2 turned out to be a virulent organism triggering an intense host immune response resulting in Kawasaki (MIS-C) like illness in different areas of both developing and developed world.

In this study, the clinical and laboratory parameters related to corona virus are different from the previous historic cohort of Kawasaki disease and so termed as MIS-C (Kawasaki like disease). The distribution is quite similar to the situation reported in different part of world. Male predominance found in our study has been documented in previous regional and international studies.<sup>15-17</sup> This is different from the historic cohort of Kawasaki disease which having a female dominance and its similar to our group 1 which was before the pandemic. The children in our study reported having a higher age group (median= 8y) which is similar to the data around world and also a peculiarity as compared to Kawasaki disease which usually involves the lower age group (group 1 median age =4y).<sup>15</sup> The clinical features although vary from patient to patient but high grade fever was the most consistent feature which was present in all the cases at the time of presentation. This may be due to many awareness campaigns on electronic and social media in Pakistan about the pandemic and the probable reason why children were picked up early due to early presentation of high grade fever (median 3<sup>rd</sup> day of onset, range 2-6 days).<sup>18</sup> The GI symptoms like abdominal pain and vomiting were present in 77.2% of the cases and were consistent in both typical and atypical forms. This is similar to the literature.<sup>15,19</sup> Although the atypical form was more common than the typical form of disease but in our study typical features of MIS-C were present in almost 72% of the children.<sup>18,20-21</sup> Rash and conjunctivitis were common in many children presented after the pandemic and strawberry tongue were more common before the pandemic.

The cohort of children in our study were negative

for SARS CoV-2 by molecular testing done on nasopharyngeal swab in 16 children but almost all the children were positive for the antibodies of the SARS CoV-2, which also depicts that although the disease triggered by COVID-19 but this is not the direct invasion of the virus but as a result of hyper inflammatory syndrome and hyper immune response of the body against the viral antigen. This theory is also related to the data in different parts of the world.<sup>15,17</sup> MIS-C although similar to Kawasaki disease in many ways in clinical features but the hyper inflammatory response in response to viral invasion is much stronger than the Kawasaki disease. This is the reason that acute phase reactant values turn out to be very high in MIS-C due to possible cytokine storm trigger by SARS CoV-2. In our study the value of CRP and serum ferritin were quite high as compared to pre-pandemic era and it depicts the spectrum of MIS-C is quite indifferent from the classical disease in some ways despite many other similarities. Similar observation was found in the literature in different case series.<sup>22</sup> If we consider the dissimilarities between MIS-C and Kawasaki disease then one distinguishing features were the severity of cardiovascular involvement and that's why despite other overlapping features MIS-C is a separate disease rather than lumping it into Kawasaki disease. The prominent entity for this distinguish feature is myocardial dysfunction and the shock which is more commonly related to SARS CoV-2 versus the other pathogens for Kawasaki disease. In our study 11.1% of patients were presented with shock and left ventricular dysfunction and there was mild LV dysfunction in both the cases and were treated with inotropic support (Milrinone), IVIG and they responded very well and clinically patients improved on day 4<sup>th</sup> of admission and echocardiography findings got normalized after 2 weeks follow up echocardiography. The similar observations being observed in other part of the world.<sup>23,24</sup> The incidence of shock and LV dysfunction in Kawasaki disease ranges from 1.4% to 7% in the pre-pandemic era.<sup>25</sup> One of the largest data to date reported 138 KDSS cases in 9,488 children with Kawasaki disease (1.5%) in Taiwan<sup>26</sup> and in Toronto shows an incidence of 2% for KDSS. The important characteristics of KDSS are multi organ

dysfunction and also correlation with Macrophage activation syndrome (MAS) but in our study there was no reported case of MAS. The outcome was excellent in patients in both the groups in our study and to do so in MIS-C and all the patients were discharged home with no morbidity but put on aspirin in antiplatelet dose.

### LIMITATION

There was an inherent limitation of collection of data from one or two tertiary care hospital settings in the study and it only included the patients who did reach to such facilities and may missed some patients who are atypical and either treated locally or being mild symptoms and a self-limiting disease pattern. Although majority were RT-PCR assay negative for SARS CoV-2 and all were positive for antibodies but false positive results in screening procedure cannot be ruled out completely. Also there is a need of testing of the genetically pre dispose children who are prone to such illness.

### CONCLUSION

In this study we concluded that MIS-C is on the Kawasaki disease (KD) spectrum in many ways both clinically and biochemical markers but the level of inflammation and immune response was much bigger than KD. The severity of cardiac involvement and features of shock were more prominent in MIS-C.





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No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
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