Egyptian Journal of Medical Research

Print ISSN: 2682-4396 / Online ISSN: 2682-440X

Original article

Short-Term Outcomes in Children with multisystem inflammatory syndrome associated with SARS-COV2 Infection

Aida Mohamed Said Salem[1], Nada Soliman Gaber[1], Eman Hamdy Mohamed[2], Dalia Saber Morgan[1]

[1] *Pediatrics Department, Faculty of Medicine, Beni-Suef University, Egypt*

[2] *Clinical pathology department, Faculty of Medicine, Beni-Suef University, Egypt*

Article Info

Article history:

Received 12 June 2023

Accepted 28 July 2023

Corresponding Author:

Nada Soliman Gaber

nadasliman111111@gmail.com

Keywords:

Short outcome,

Multisystem inflammatory syndrome in children,

COVID-19,

Kawasaki disease.

Abstract

Background and aims: Signs of inflammation and multi organ dysfunction describe a novel clinical disorder called multisystem inflammatory syndrome in children (MIS-C), which is caused by the cytokine storm correlated with SARS-CoV-2. This study aimed to follow up with children with MIS- C correlated with SARS-COV2 infection to determine any sequalae or delayed manifestation of MIS-C. **Methods:** Children less than 18 years old with a diagnosis of MIS-C were included in this prospective research at the Beni-Suef University Hospital. Comparative analyses of admission and po st discharge clinical and laboratory parameters were performed. **Results:** Fifty-three children were involved in the research from March 2022 to July 2022 with a mean age of 5.08 ±4.05 years. Fourteen o f the youngsters already had chronic systemic comorbidity. The presence of fever was observed in every case. The hematological (92.45%), GIT, and neurological (56.6%) systems were the most affected. Mo rtality is significantly higher among children with young age, chronic

illness, and MIS- C clinical presentation overlapping with COVID-19 infection. Lymphopenia and thrombocytopenia were more common among dead than survivor patients. **Conclusions:** The prognosis is good for children with no underlying medical conditions. Low lymp hocyte counts and elevated troponin levels may be unfavorable indicators of survival. Positive follow-up results in coronary care were reported.

1. Introduction:

The coronavirus pandemic has sparked a new issue: COVID-19-associated multi-system inflammatory syndrome in children (MIS-C). This disease has developed as an issue for children and adolescents since it was first diagnosed in April 2020 in England **[1].**

As a febrile pediatric inflammatory disorder, MIS-C can appear weeks after the first SARS-CoV-2 infection or exposure **[2].** Many novel ideas are emerging from recent research since the illness is so novel. Symptoms of MIS-C can range from quite minor to extremely life-threatening, making intensive care a need for certain patients. The illness, assumed to be immune-mediated, often manifests itself 6- 8 weeks following the viral infection. Compared to acute COVID-19, the inflammatory response in MIS-C is unique **[3].**

Kawasaki disease (KD) has several clinical characteristics with MIS-C, including a high temperature that doesn't go away, rashes, conjunctivitis, and changes to the oral mucosa (such as cracked, red lips and a strawberry tongue). Toxic shock syndrome (TSS), which is caused by bacterial superantigens (SAgs), and MIS-C have eerily similar clinical presentations **[4].** Improving the definition and diagnostic criteria for this inflammatory disease associated with COVID-19 is now crucial. The whole clinical, epidemiological, immunological, and prognostic spectrum cannot be adequately understood from the currently available case reports due to their dispersed nature. In order to identify any sequelae or delayed manifestation of MIS-C, we sought to conduct a follow-up study of children who had recovered from MIS-C correlated with SARS-COV2 infection.

2. Patients and Methods:

This prospective descriptive research was conducted in the inpatient pediatric department and pediatric intensive care unit (ICU) at Beni - Suef University Hospital. The study was performed starting from March 2022 to July 2022. Children less than 18 years old who were diagnosed with MIS-C were enrolled Patients included in the research were fulfilling the

criteria for the diagnosis of MIS-C according to the following criteria: Age < 18 years old, a clinical manifestation consistent with MIS-C, encompassing each of the following: **Fever:** Documented fever > 38 degrees Celsius for > 24 hrs or subjective fever enduring > 24 hrs. **Symptoms of inflammation detected in the lab can involve:**

An increased level of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, pro-calcitonin, D-dimer, ferritin, LDH, an elevated level of interleukin 6 (IL6), Neutrophilia, lymphopenia, hypoalbuminemia.

Multisystem (≥2) organ involvement: Cardiovascular conditions, such as shock, an increased level of troponin, a raised level of brain-type natriuretic peptide, abnormal echocardiogram, arrhythmia, Diseases of the lungs (such as pneumonia, ARDS, or pulmonary embolism), Renal (renal failure), disorders of the nervous system, such as convulsions, strokes, and bacterial meningitis, conditions related to the blood (such as coagulopathy), disorders of the digestive tract, such as stomach discomfort, nausea, vomiting, diarrhea, increased liver enzyme levels, and ileus.

Critical illness necessitating hospitalization No alternative plausible diagnosis.

Signs pointing to an infection with the severe acute respiratory syndrome coronavirus (SARS-CoV-2)

One of the following: A successful SARS-CoV2 reverse-transcriptase polymerase chain reaction (RT-PCR), a successful serology (both IgM and IgG), and COVID-19 infection in people within the last month**.**

Exclusion criteria: Age > 18 years and lack of paternal consent.

The sample size was determined using G power for sample size calculation size**.** The calculation was based on findings from **Sperotto et al., [5]** for pediatric admitted to the pediatric ICU with MIS_C a sample size of 35 patients should be enrolled in the study.

All patients were subjected to the following:

History taking: Full history was taken from the patients or their close relatives including Personal data, detailed medical history, and history of chronic disease if any, history of fever, abdominal pain, vomiting, diarrhea, respiratory distress, conjunctivitis, rash, disturbed consciousness level.

2- Clinical assessment: Complete physical examination including vital signs, anthropometric measurement, and complete chest, cardiology, abdominal and neurological examination. After discharge, children were followed up monthly for persistent clinical features or the emergence of any new symptoms.

3-Investigations: All labs (CBC with differential, D. dimer, ferritin, COVID-19 antibodies) and imagining(Echo, CT chest) were

conducted on admission, 4 months after discharge, and in between if clinically indicated. **Laboratory:** Rapid test for identification of antiSARS-CoV-2 IgM and IgG (only on admittance) (Antron U.K, London) and nasopharyngeal RTPCR testing for SARS-CoV-2 Specimens comprised oro/nasopharyngeal swabs (dry and in viral transport media). Specimen processing was done in a class II biological safety cabinet employing biosafety level three (BSL3) work standards at the clinical pathology laboratory of Beni-self Hospital. CBC with differential, Inflammatory markers (CRP, ESR, ferritin), D. dimer and troponin, Kidney functions (urea, creatinine, Na, k), Liver functions (ALT, AST, Albumin), and coagulation profile (Pt, Pc, INR). **Radiological: CT Chest without contrast:** [Scoring according to CoRad score] **[6], Echocardiogram:** Classification of a coronary aneurysm according to Z-Score **[7].**

Ethical considerations: The study was explained to the parents. Once the research has been approved by the local ethical committee and the cases' parents have given their written informed permission, the research can begin.

Approval No: FMBSURE/01022022/Gaber.

Statistical Methods: Analysis of the data was done using a statistical program for social science (SPSS). The quantitative variables were described in the form of mean standard deviation, median, and range. When appropriate the qualitative variables were described in the form of frequency and percentages. Person correlation
was used to correlate qualitative variables fulfilling normal distribution. P value was calculated which is either non-significant if >0.05 or significant if <0.05 or highly significant if < 0.01.

3. Results:

The current study was a prospective descriptive study conducted on 53 children and designed to follow up with children cured of the multisystem inflammatory syndrome correlated with SARSCOV2 infection to determine any sequel or delayed manifestation of MIS-C.

Table (1): Demographic data of the examined Children; (N= 53):

			Descriptive Statistics	
General History	**Age**	**Mean ±SD**	5.08	±4.05
	Sex	**Male**	39	73.6%
		Female	14	26.4%
Measurements	**BMI**	**Below normal**	2	3.8%
		Normal wt.	46	86.8%
		Overweight	5	9.4%
Vital Signs	**Heart Rate**	**Mean ±SD**	118.74	±26.59
	RR	**Mean ±SD**	32.83	±14.38
	Temperature	**Mean ±SD**	38.98	±0.71
	Blood pressure	**Hypotension**	29	54.7%
		Normal	16	30.2%
		Hypertension	8	15.1%
History of chronic illness		**No**	39	73.6%
		CKD	5	9.4%
		Nephrotic syndrome	3	5.7%
		Others	6	11.3%

The age of our study children varied from 2 months to 14 years with 5.08 ±4.05 years old, they were 39 (73.6%) males and 14 (26.4%) females. The majority of our studied children had normal weight 46 (86.8%), two children were below normal (3.8%) and five children (9.4%) were overweight. Hypotension was found in 29 patients (54.7%) and while hypertension was found in 8 patients (15%), ,4 cases with CKD, 2 cases with nephrotic syndrome, one case with HUS, and one case with nephritic).14 children had a chronic illness (5 children with CKD (9.4%), 3children with Nephrotic syndrome (5.7%) and 6 children with other chronic illnesses (one case with SLE, one case with Epilepsy, one case with Myopathy, one case with Mild sensory hearing loss, one case with GDD and one case with H.I.E.) as revealed in a table (1)

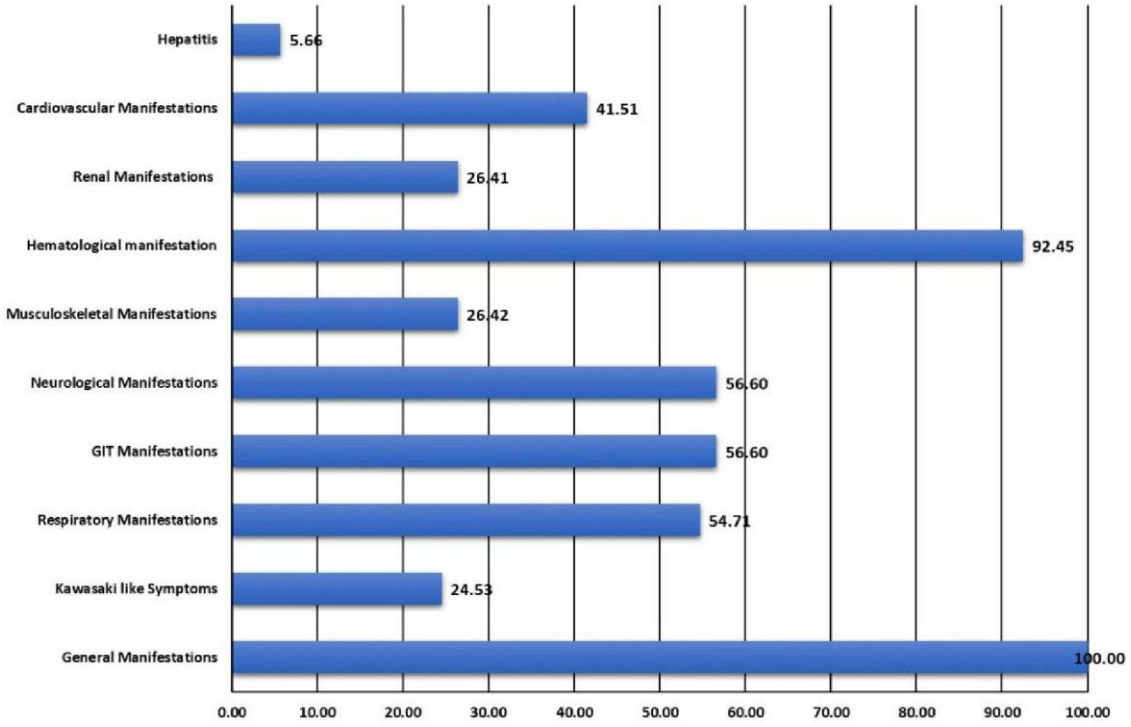

Figure (1): Systems affected among examined Children

All the studied cases showed fever on admission, hematological manifestations were most common among 92.45% of cases **(figure 1).**

Table (2): Association between children outcome and demographic Data

		Outcome		
		Survived N= 41	**Died N= 12**	**p-value**
Age	**Years (mean ±SD)**	5.61 ±3.64	3.26 ±4.97	0.044*
Weight	**Kg (mean ±SD)**	19.74 ±9.91	12.50 ±10.65	**0.033***
BMI	**below normal**	1 (2.4%)	1 (8.3%)	0.307
	Normal wt.	35 (85.4%)	11 (91.7%)	
	Overweight	5 (12.2%)	0 (0.0%)	
RR	**Rate/min (mean ±SD)**	28.63 ±11.80	47.17 ±13.44	**<0.001***
Temperature	**°C (mean ±SD)**	39.06 ±0.77	38.92 ±0.69	0.139
History of chronic illness	**No**	27 (81.8%)	7 (58.3%)	**0.005***
	CKD	2 (6.1%)	3 (25.0%)	
	Nephrotic syndrome	0 (0.0%)	0 (0.0%)	
	Others	4 (12.1%)	2 (16.7%)	

41 children (76.4 %) were surviving, and 12 children (22.6%) died. Children's age was significantly younger among dead vs. survived children, body weight was significantly lowest among dead children, Respiratory rate and temperature were significantly highest among dead children (p-values= 0.001, 0.010 respectively), while HR showed non-statistically significant association with children outcome (p-values >0.05). There was a statistically significant association with a history of chronic illness, especially with CKD and mortality **(Table 2).**

Table (3): Association between Children Outcomes and Laboratory investigations:

	Children Outcome		
	Survived N= 41	**Died N= 12**	***p-value***
TLC	8.73 ±5.95	6.55 ±3.95	0.239
Lymphocytes	18.05 ±9.09	12.92 ±5.02	0.068
PLT	416.73 ±304.43	253.58 ±289.08	0.105
CRP	132.85 ±74.01	133.00 ±53.54	0.995
ESR	90.37 ±33.09	88.58 ±42.06	0.879
Ferritin	840.44 ±822.45	969.00 ±668.51	0.623
D-Dimer	2.62 ±2.77	3.89 ±5.50	0.280
Troponin	9.78 ±51.59	191.84 ±508.69	**0.025***
Albumin	3.33 ±0.73	2.78 ±0.73	**0.025***

Troponin was significantly higher in dead children, and serum albumin is significantly lower in dead children with (P-Value 0.025), (Table 3). No substantial variance amongst dead and survived children regarding CT chest and echo findings. 91.7% of dead children were on mechanical ventilation and 91.7% of dead children needed inotropic support and 66.7% of dead children were on Anticoagulants which was significant with (p-value <0.001, =0.002, p-value= 0.010 respectively).Figure 2.

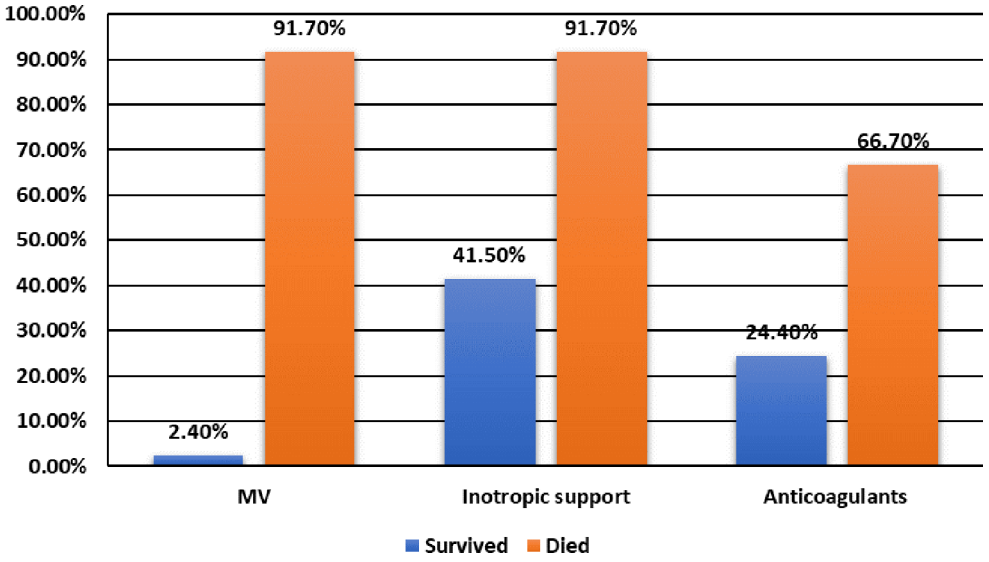

Figure (2): Association between children outcome and management

Most of the clinical symptoms were improved at follow-up among our studied participants, fatigue was reported by 15 cases (37.5%), Palpitation by one patient (2.5%), Cardiac coronary dilatation by two patients (5%), convulsions by two patients (5%) and Psychiatric manifestations by one patient (2.5%). Other clinical symptoms were completely improved as reported by our studied patients. Regarding cardiac findings on follow-up, all patients presented with impaired EF, pericardial effusion, and mitral MR became normal after 4 weeks from admission, 4 cases presented with coronary dilatation on admission, and on follow-up at 2 weeks 2 cases became normal coronary artery. On follow-up, at 6 weeks 2 cases had echo findings. Mild coronary artery and only one of them had mild coronary dilatation after 4 months. Table 4

Table (5): comparison between ECHO findings on Admission and on follow-up

ECHO findings on admission		**On admission**	**At 2 weeks**	**At 4-6weeks**
Impaired EF		9	9	-
LV Dysfunction		5	5	
Pericardial effusion	**Mild**	1	1	-
	Moderate	1	1	-
Coronary dilatation		4	2	1
MR	**Mild**	2	2	-
	Moderate	2	2	-

4. Discussion:

In most cases, the symptoms of COVID-19 in children are minimal or nonexistent. There are very few reported instances of severe or deadly COVID-19 in children. The reason why children have a less severe COVID-19 phenotype is not explained; however several immunological ideas are provided **[3].**

A novel clinical manifestation associated with SARS-CoV-2 infection was reported by many scientific organisations between the end of April 2020 and the beginning of May 2020. Multisystem inflammatory syndrome concurrent with COVID-19 (MIS-C) is a collection of symptoms including fever, stomach discomfort, gastrointestinal and cutaneous symptoms, and hemodynamic abnormalities. KD, TSS, bacterial sepsis, and macrophage-activation syndrome (MAS) are all identified as having similarities to MIS-C **[8].**

The current study was a prospective descriptive study conducted on 53 children and designed to follow up with children who have MIS-C because of SARS-COPV2 infection to find out whether there are any long-term effects.

Analysis of our findings revealed that Children's age ranged from (0.2y) to (14y) with a median age of 5.08 ±4.05 years old, they were 39 (73.6%) males and 14 (26.4%) females. The majority of our studied children had normal weight 46 (86.8%), two children were below normal (3.8%) and five children (9.4%) were overweight. Hypotension was found in 29 patients (54.7%) on admission and fluid resuscitation was done and needed inotropic support while hypertension was found in 8 patients (15%) ,4 cases with comorbid CKD, 2 cases with nephrotic syndrome, one case with HUS as a manifestation of MIS-C and one case with nephritic a manifestation of MIS-C). Furthermore, the majority of the studied children were feverish at admission 51 (96.2%). Regarding the history of chronic illness, most of our studied children had no history of chronic illness (73.6%), five children were with CKD (9.4%), three children were with Nephrotic syndrome (5.7%) and six children were with other chronic illnesses. 28 children requiring critical care and inotropic support for a duration ranging from 2 to 14 days with an average of (5.56 ±3.0), majority of the studied children needed steroids (98.1%), and immunoglobulins (94.3%). Forty-five (84.9%) children had a high titer of COVID-19 antibodies. Eight of the children tested positive for the virus using RT-PCR as well as antibody testing.

This agreed with the study of **Patnaik et al., [9]** in which there were a total of 21 children; 13 (62 percent) were males, and their average presenting age was 8.48 (±4.3) years. The most prevalent symptom was a high body temperature, followed by a rash. Symptoms involving the children's digestive, respiratory, and cardiovascular systems were present. There were nine (43 percent of the total) cases of shock needing intensive care and inotropic support among hospitalized youngsters. Encephalitis symptoms

were only seen in one youngster. A high titer of antibodies against COVID-19 was found in 20 (95 percent) of the children. The RTPCR and antibody tests were both positive for two children. Fewer than a third of the parents (28.6%) reported having had recent, direct interaction with a COVID-19 patient within the preceding 68 weeks.

In the current study, all the studied cases showed general fever patients on admission and during hospitalization, respiratory manifestations especially RD in 49%, hematological manifestations among 92.45% of cases, renal manifestations among 26% of cases(3 children with HUS, 2 children with nephrotic syndrome and 2 children with the nephritic syndrome), GIT manifestations mostly abdominal pain (29/53; 54.7%), vomiting (28/53; 52.8%), and diarrhea (26/53; 49.1%)., as well as neurological manifestations, were among 56.6% of cases mostly seizures(18/54;34%), Kawasaki like Symptoms were among 24.53% and only three cases have hepatitis (5.66%).

Hoste et al. [3] systematic study lends credence to our findings; they found that fever was reported by virtually all patients (922/928; 99.4%), most often for at least 5 days (258/928; 27.0%). Abdominal discomfort (315/539; 58.4%), vomiting (306/532; 57.5%), and diarrhea (268/532; 50.5%) were the most common gastrointestinal symptoms reported by the majority (598/699; 85.6%). A total of 37 percent (307/387) of individuals were reported to have cardiovascular symptoms. Numerous cardiovascular abnormalities were recorded, including tachycardia (194/253; 76.7%), hemodynamic shock or hypotension (416/695; 59.9%), myocarditis (128/309; 41.4%), and mild or severe reduced left ventricular ejection fraction (LVEF between 30 and 55%; 211/522; 40.4%). Extremely rare occurrences of coronary dilatation (74/638; 11.6%), aneurysms (59/572; 10.3%), and LVEF below 30% (36/506; 7.1%) were identified. The incidence of pericardial effusion was high, measuring 22.3% (114/511). There were respiratory symptoms in 50% of the patients (295/587; 50.3%), including problems with the upper respiratory tract (95/397; 23.9%), difficulty breathing (101/378; 26.7%), and radiological infiltrates (114/321; 35.5%).

In addition to the above findings, we found that according to their outcome, 33 children (62.3%) were free from any complications while eight children (15.1%) were complicated, and 12 children (22.6%) died. Of deaths with reported ages, 6/12 (50%) cases were fewer than 6 months old one of them had acute hemorrhagic encephalitis. All reported fatalities that were accompanied by shock and/or myocardial failure and required the administration of inotropes and/or mechanical circulatory support. 6/12 (50%) of fatal cases had comorbidities (3 children with CKD and 3 children with neurological disease one with HIE, one with myopathy and one with epilepsy). Interestingly, in the current study, the

association between mortality and overlapping with KD or COVID-19, there was a statistically substantial correlation between mortality & overlapping with COVID-19 infection.

Hoste et al. [3] also found 18 fatalities, reporting a similar percentage (1.9%; 18/953), which is consistent with our own research. 2 (12) of the 12 patients who died had not yet reached their first birthday,6 (12) were between the ages of 5 and 12, and 4 (12) were above the age of 13. Although race and ethnicity were underreported, the majority of respondents were male (8/11; 72.3%). All but one of the recorded fatalities required inotropic and/or mechanical circulatory assistance due to shock and/or myocardial dysfunction. In 10/15 (66.7%) fatal instances, ECMO was started, and 5 of those cases ended in death from (hemorrhagic) cerebral infarction. Of the instances that ended in death, (n = 4 had obesity, 1 had acute leukemia, 1 had a defect in glucose-6-phosphate dehydrogenase, 1 had asthma, and 1 had numerous neurological disorders. 21 out of 287 (7.3%) patients had some form of residual cardiac dysfunction, most often a lower LVEF at discharge or follow-up. Two individuals with PIMS-TS/MIS (-C) had long-lasting neurological impairment. Other forms of persistent morbidity were not noted. Eleven patients (1.8%) died in the **Yilmaz et al. [10]** trial. Two had acute lymphoblastic leukemia, one had aplastic anemia, one had ataxia telangiectasia, and one had congenital CMV disease; these five individuals had comorbid conditions. Deaths occurred between the ages of 2.3 and 17, with a mean age of 11.5 years (±5). Two patients were treated with an extracorporeal membrane oxygenator while six others got immunomodulatory therapy.

Our findings are consistent with those of **Awasthi et al. [11],** when it is unclear how long long-term therapy will last. However, immunomodulation lasting at least two to three weeks has been proposed for particularly severe diseases. This index research had a higher death rate than studies done in industrialized nations, at 5% (N = 2). Within 24 hours of arrival, both patients died from refractory shock. This emphasizes the need for prompt diagnosis, resuscitation (with fluids and vasoactive medications), and specific immunomodulation as soon as possible after the patient arrives at the hospital.

In the current study, most of the clinical symptoms were improved at follow-up among our studied participants, fatigue was reported by 15 cases (37.5%), Palpitation by one patient (2.5%), Cardiac Manifestations by two patients (5%), convulsions by two patients (5%) and Psychiatric manifestations by one patient (2.5%). Other clinical symptoms were completely improved as reported by our studied patients. Systemic inflammation resolved in all patients. Regarding cardiac findings on follow-up, all

patients presented with impaired EF, pericardial effusion, and mitral MR became normal after 4 weeks from admission, 4 cases presented with coronary dilatation on admission, and on follow-up, at 2 weeks 2 cases became normal coronary artery. On follow-up, at 6 weeks 2 cases had echo findings. Mild coronary artery and only one of them had mild coronary dilatation after 4 months. **Penner et al., [12]** reported on a retrospective study of 46 children (18 years) with MIS-C up to 6 months after discharge. They found that all but one of the children had no signs of systemic inflammation, 90% had positive SARS-CoV-2 IgG antibodies, 87% were symptom-free from gastrointestinal issues, 96% had normal echocardiography, and only two had persistent coronary artery dilatation. In a study of 539 children with MIS-C, **Feldstein et al. [13]** found that while 34% (172/503) and 13% (57/424) of cases of left ventricular dysfunction and coronary artery aneurysm were observed during the acute phase, 99% and 100% of the children, respectively, returned to normal within 90 days. The results were consistent with the index research to a large extent. 45 New York City youngsters (younger than 21 years old) were reported to have MIS-C and were tracked for 5.8 (1.3-6.7) months by **Farooqi et al., [14]**. The majority of patients presented with moderate to severe echocardiographic abnormalities (44%), coronary artery dilatation (9%) and substantial inflammation during the acute period. After only a week to four weeks, inflammatory indicators were returned to normal, only 18% showed

moderate echocardiographic abnormalities, and all coronary arteries were normal. Mild cardiac dysfunction was present in only one patient by 4- 9 months. Concern regarding the long-term prognosis of MIS-C has been prompted by the prevalence of left ventricular dysfunction (35- 70%) and coronary artery dilatation or aneurysm (9-16%) during the acute phase of MIS-C.

However, **Patnaik et al., [9]** found that 16 children who were supposed to be followed up with between 12 and 16 weeks following discharge really did so. There were no significant health issues among the youngsters. We ran the biochemistry and blood count tests again. All patients' inflammatory and hematologic indicators have returned to normal. None of our patients showed signs of coronary dilation on follow-up echocardiography, which was performed on 15 youngsters. At 12 weeks of follow-up, a kid diagnosed with global hypokinesia on admission was found to have moderate tricuspid regurgitation. Electroencephalogram and magnetic resonance imaging of the brain studies showed no abnormalities.

In addition, after 6 weeks of follow-up, all patients who had been released were found to be clinically stable by **Tiwari et al., [15]**. In any instance, the clinical evaluation revealed no abnormalities. All patients were found to be trending upward on echocardiographic

examinations. At 6 weeks, echocardiography showed persistent coronary abnormalities in 8 (21%) individuals; 5 (13%) had hyperechoic or non-tapering thick-walled coronaries, 2 (5%) had coronary dilatation, and 1 (0.5%) had a tiny coronary aneurysm. However, compared to before the severe sickness, echocardiographic coronary abnormalities were better. One patient had persistent moderate left ventricular systolic dysfunction, while another patient had persistent pulmonary artery hypertension.

5. Conclusion:

In conclusion, MIS-C represents a novel illness within the framework of the COVID-19 pandemic, and our understanding of this clinical condition is still evolving. During the COVID-19 pandemic, MIS-C has emerged as a new threat. Major challenges in its administration include a vague case definition, a lack of defined diagnostic tests and care recommendations, and a lack of knowledge concerning long-term consequences. For kids who are symptom-free from the start, the prognosis is good. Elevated levels of troponin and lymphopenia may be unfavorable indicators of prognosis. Heart-related follow-up results were encouraging.

6. References:

1. Belhadjer Z, Méot M, Bajolle F. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation, 2020; 142:429436.
2. Patel JM. Multisystem Inflammatory Syndrome in Children (MIS-C). Curr Allergy Asthma Rep., 2022; 22(5):53-60.
3. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr, 2021;180, 2019-2034.
4. Noval Rivas M, Porritt RA, Cheng MH, Bahar I, Arditi M. Multisystem Inflammatory Syndrome in Children and Long COVID: The SARS-CoV-2 Viral Superantigen Hypothesis. Front Immunol. 2022; 7; 13:941009.
5. Sperotto F, Friedman KG, Son MBF. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr., 2021; 180:307322.
6. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, et al. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. J Med Virol., 2020;92(10):1902 1914.
7. Rowley AH, Shulman ST, Arditi M. Immune pathogenesis of COVID-19 related multisystem inflammatory syndrome in children. J Clin Invest, 2020; 130:5619 11.5621.
8. García-Salido A, de Carlos Vicente JC, Belda Hofheinz S. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicenter

study in pediatric intensive care units in Spain. Crit Care, 2020; 24, 666.

9. Patnaik S, Jain MK, Ahmed S, Dash AK, Sahoo B, Mishra R, et al. Short-term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Rheumatol Int. 2021 Nov; 41(11):1957-1962.
10. Yilmaz Ciftdogan D, Ekemen Keles Y, Cetin BS, et al. COVID-19 associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group. Eur J Pediatr, 2022; 181, 2031 2043.
11. Awasthi P, Vijay K, Sanjeev N, Karthi N, Suresh K, Arun B, et al. Multisystem Inflammatory Syndrome in Children: Follow-Up of a Cohort from North India, 2022; 106(4): 1108 1112.
12. Penner J. 6-month multidisciplinary follow-up and outcomes of patients with the pediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary pediatric hospital: a retrospective cohort study. Lancet Child Adolescent Health, 2021; 5: 473 482.
13. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB. Characteristics and outcomes of US children and adolescents with the multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA, 2021; 325: 1074 1087.
14. Farooqi KM. Longitudinal outcomes for multisystem inflammatory syndrome in children. *Pediatrics*, 2021; 148*:* e2021051155.
15. Tiwari A, Balan S, Rauf A, Kappanayil M, Kesavan S. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a hospital-based prospective cohort study from Kerala, India. BMJ Paediatr Open, 2021; 18: 5(1):001195.