Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Cardiac Manifestations of Multisystem Inflammatory Syndrome in Children Following COVID-19

Behnaz Hatami (MD)[1], Omid Shoraka (MD)[1], Asef Younesi (MD)[1], Gelayol Bavafa (MD)[1], Melika Zamanian (MD)[1], Niloofar Nikpasand (MD)[1], Amirhossein Mohammadzade (MD)[1], Sara Naghizadehkashani (MD) [2], Anoush Azarfar (MD) [3], Mojtaba Yousefi Zoshk (MD) [4]*

[1]*Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2] *Medical Doctor, Thomas Jefferson University, Philadelphia, USA.*
[3] *Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[4] *Department of Pediatrics, Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Article type
Review article

Article history
Received: 06 Dec 2022
Revised: 06 Mar 2023
Accepted: 20 Mar 2023

Keywords
Multisystem Inflammatory Syndrome in Children
COVID-19
SARS-CoV-2
Cardiac Involvement

ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a novel syndrome in children following the coronavirus disease 2019 (COVID-19) pandemic. It has similar symptoms to Kawasaki disease or toxic shock syndrome. The most prevalent symptoms in MIS-C patients are fever and gastrointestinal symptoms with substantial cardiac complications. Cardiac involvement is frequently reported in MIS-C patients and includes arrhythmia, coronary artery aneurysm and dilation, conduction abnormalities, and ventricular dysfunction. Cardiogenic or vasodilatory shock may develop in patients with severe MIS-C, necessitating inotropic support, fluid resuscitation, mechanical ventilation, and extracorporeal membrane oxygenation. Empirical therapies have attempted to reverse the inflammatory response, and steroids or intravenous immunoglobulin have all commonly been used. Most children will survive with prompt diagnosis and appropriate treatment, but since the disease's outcomes are unclear, long-term follow-ups are necessary. This narrative review summarizes the available studies regarding cardiac involvement in MIS-C cases as well as clinical considerations for cardiac examination and follow-up.

Please cite this paper as:
Hatami B, Shoraka O, Younesi A, Bavafa G, Zamanian M, Nikpasand N, Mohammadzade A, Naghizadehkashani S, Azarfar A, Yousefi Zoshk M. Cardiac Manifestations of Multisystem Inflammatory Syndrome in Children Following COVID-19. Rev Clin Med. 2023;10(1): 41-50.

Introduction

The coronavirus disease 2019 (COVID-19) was initially discovered in China and eventually expanded to other countries (1,2). The COVID-19 pandemic had a significant load on the healthcare system and caused a substantial number of hospitalizations (3). Besides, patients who are admitted for COVID-19 might have complications after leaving the hospital and need to be readmitted (4,5). People of all ages, including newborns and children, are affected by the COVID-19 infection (6,7). According to preliminary results, children with COVID-19 infection exhibited milder symptoms and a lower fatality rate in comparison with adults who contracted COVID-19 infection (8,9). In April 2020, a new syndrome with a systemic hyperinflammatory state that is thought to be related to the COVID-19 infection was described. This disorder is known as multisystem inflammatory syndrome in children (MIS-C), and various similarities have been found between this syndrome and Kawasaki disease (KD) (10,11). Children infected with COVID-19 can develop MIS-C, a potentially fatal hyperinflammatory

Corresponding author:** **Mojtaba Yousefi Zoshk,
Department of Pediatrics, Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran
***E-mail:** dr.yousefi.md@gmail.com*
***Tel:** 9126049702*

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

condition that affects several organ systems, such as the gastrointestinal tract, heart, lungs, brain, kidneys, skin, and eyes (12). According to studies, MIS-C appears 4 to 6 weeks following the COVID-19 infection, suggesting that the virus may act as a trigger in people with certain genetic predispositions (10,13,14). While some typical symptoms are noted in both MIS-C and KD, such as strawberry tongue, lymphadenopathy, skin rash, and an increase in inflammatory markers, MIS-C has certain distinct characteristics (15) (16).

Studies on children with MIS-C revealed that cardiac involvement in these children included arrhythmia, coronary artery dilation or aneurysm, myocardial dysfunction, ventricular dysfunction, hemodynamic instability, and cardiogenic shock, indicating that cardiac involvement. is a significant risk factor for severe cases (17). However, there is still scant data on the cardiac involvement of MIS-C, and the majority of the literature on the subject is comprised of case reports and case series. Therefore, we conducted this narrative review to characterize the current information on probable cardiac manifestations in MIS-C in order to provide a good understanding of their management and treatment.

Definition of MIS-C

There are three MIS-C definitions provided by the Centers for Disease Control and Prevention (CDC) (18), the World Health Organization (WHO) (19), and the Royal College of Pediatrics and Child Health (RCPCH) (20). As illustrated in Table 1, fever, inflammation, organ dysfunction without other probable diagnoses, and recent exposures to a patient or confirmation of COVID-19 are all included in these three definitions. However, there are some differences between these three definitions, such as the criterion for organ involvement, fever duration, and the requirement for documentation of COVID-19 infection.

Table 1. Case definition of MIS-C by WHO, CDC, and RCPCH.

	WHO (19)	CDC (18)	RCPCH (20)
Age (years)	0 – 19	< 21	Children
Clinical features	There must be at least 2 of the following: (Hypotension/ Coagulopathy/ Characteristics of valvulitis, pericarditis, myocardial dysfunction, or coronary abnormalities/ GI symptoms, including vomiting, diarrhea, and abdominal pain/ mucocutaneous inflammation/ bilateral non-purulent conjunctivitis/ Rash	• Multi-organ (≥ 2 organs) involvement: (Gastrointestinal/ /Renal/ Dermatologic/ Respiratory/ Neurologic/ Hematologic) • Features of a clinically significant illness that requires hospital admission.	• Multi-organ failure: (Cardiovascular/ Gastrointestinal/ Respiratory/ Hematologic/ Neurologic/ Renal) • The following symptoms are experienced by some of the patients: (Abdominal pain/ Vomiting/ Conjunctivitis/ Diarrhea/ Cough/ Rash/ Neck swelling/ Sore throat/ Lymphadenopathy/ Mucus membrane changes/ Swollen hands and feet/ Syncope/ Confusion/ Headache) • The majority of children have hypotension and need oxygen treatment.
Fever	≥ three days	• A subjective fever that lasts more than 24 hours • Documented fever of >38.0°C for more than 24 hours	> 38.5 °C
Evidence of COVID-19	• A positive RT-PCR, serology, or antigen test result • Contact with COVID-19 patients	• A positive serology, RT-PCR, or antigen test result indicating recent or current COVID-19. • Contact with patients with COVID-19 infection 4 weeks prior to the development of symptoms	• Testing for SARS-CoV-2 by RT-PCR could yield either positive or negative.
Laboratory findings	• Raised inflammatory markers such as ESR, procalcitonin, or CRP • Coagulopathy (INR, D-dimer, PT, or PTT)	o Hypoalbuminemia o Neutrophilia o Raised LDH o Elevated procalcitonin o High fibrinogen o High CRP o Lymphopenia o High IL-6 o High ferritin o High D-dimer o Elevated ESR	• All of the children would have the following test findings: (Abnormal Fibrinogen/ High CRP/ Hypoalbuminemia/ High ferritin/ Lymphopenia/ Neutrophilia/ High D-dimer) • The following test findings might be relevant to some of the patients: (Raised LDH/ Raised triglyceride/ Raised CK/ Thrombocytopenia/ Neutrophilia/ High IL-10/ High IL-6/ Anemia/ Proteinuria/ Raised troponin/ Coagulopathy)
Exclusion of other microbial causes	o Staphylococcal/Streptococcal shock syndromes o Bacterial sepsis	No other diagnoses.	o Infectious myocarditis o Streptococcal/Staphylococcal shock syndromes o Bacterial sepsis

Clinical manifestations

As noted, MIS-C is a systemic inflammation characterized by severe inflammation, prolonged fever, and multi-organ failure that is related to the COVID-19 infection (18,20). In published case reports and case series, persistent fever, non-purulent conjunctivitis, erythematous polymorphic rash, asthenia, and gastrointestinal symptoms were noted as the most prevalent symptoms in children with MIS-C (11,14,21–30). According to studies, persistent fever lasts an average of four days at the time of diagnosis, and gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting affect 60%-97% of children with MIS-C (18,19,31).

Peripheral edema and mucosal changes are other commonly reported syndromes that, accompanied by conjunctivitis and rash, mimic the clinical features of KD (11,22–25,32). Studies revealed that approximately 50% of MIS-C patients present with a shock that is cardiogenic, vasodilatory, or a combination of both, and most of them develop a serious disease that necessitates intensive care during their treatment (13,14,33). Cardiac manifestations in MIS-C patients differ from those reported in KD patients, which are described in more detail further below.

Cardiac involvement

Cardiac involvement affects approximately 67% to 80% of patients with MIS-C, making it more frequent than in KD (13,34–37). The cardiac manifestations in patients with MIS-C are ventricular dysfunction, arrhythmias, conduction abnormalities, and coronary artery aneurysms. The cardiac clinical manifestations of MIS-C patients might vary depending on the severity of the disease, and most of them emerge with shock and cardiovascular compromise, which could be sudden and severe (36,38,39).

On the other hand, patients might present with no signs or symptoms of cardiovascular disease. In patients with suspected MIS-C, a complete cardiac assessment, comprising an electrocardiogram, echocardiography, troponin, and brain natriuretic peptide levels, must be performed as soon as possible. Further cardiac tests, including cardiac magnetic resonance imaging or chest computed tomography, could be performed as indicated (40). Table 2 summarizes the cardiac abnormalities in children with MIS-C (10,11,13,14,21,29,30,33,41–44).

Coronary involvement

Preliminary MIS-C reports revealed a KD-like disease. Although it is becoming obvious that MIS-C is not the same as KD, there are some clinical similarities between the two disorders, such as coronary artery dilatation (11). As illustrated in Table 2, 6 to 24% of patients have been reported to develop a coronary artery aneurysm or dilation. The majority of patients had z-scores of between 2 and 2.5, with mild coronary artery dilation.

Since coronary artery z-scores are generally calculated using data from children who feel well without fever, a few of the outcomes in the acute stage could be connected to coronary vasodilation during the fever and inflammatory condition (40). Nevertheless, occurrences of massive and huge coronary artery aneurysms have also been documented (14,21), and concerns about coronary artery intimal disruption are raised by the development of a coronary aneurysm after discharge (14,21,30,41,44). The significance of ongoing follow-up for children with MIS-C is reinforced by the late onset of coronary aneurysms.

Myocardial dysfunction

In both the preliminary studies and later case series, a significant portion of MIS-C patients had left ventricular dysfunction (40). Cardiac dysfunction was found in 6 out of 8 (75%) cases in the first case series (21). According to the diagnostic and inclusion criteria used in later studies, ventricular dysfunction has already been documented in 35 to 100% of cases (40,42,43). In two studies, the inclusion criteria were stated as groups of individuals with myocardial dysfunction (10,28).

A cohort of 35 children with MIS-C suffering from acute left ventricular failure (ejection fraction < 50%) or shock, increased inflammatory markers, and fever were described by Belhadjer et al. (10). Besides, they reported that in 80% of patients, inotropic support and mechanical ventilation were used for the treatment, while 28% of them received extracorporeal membrane oxygenation support. They also stated that none of the children died as of the publication date (10).

Another study by Grimaud et al. evaluated 20 children with MIS-C who had cardiogenic or vasoplegic shock, and 19 out of 20 children needed vasopressors or inotropes but no extracorporeal membrane oxygenation support (28). They also reported that prior to being discharged, the left ventricular function had fully recovered in all patients (28). According to Table 2, most patients showed increased troponin levels or B-type natriuretic peptide (BNP)/pro-BNP that could be helpful indicators of myocardial involvement. Most MIS-C cases experienced ventricular function recovery, although 6% to 14% of them continued to suffer dysfunction after discharge (40).

The exact physiopathology of myocardial dysfunction in MIS-C is not completely understood. The probable etiologies of myocardial injury after COVID-19 in adults are stress cardiomyopathy, systemic inflammatory response syndrome, ischemic injury by microvascular damage of the heart, hypoxic injury, acute myocarditis, and right heart strain (45–49).

Table 2. Demographics, clinical presentations, and cardiac abnormalities of patients with MIS-C.

Study	Patients N	Gender	Age	PMH	Clinical Presentations	Cardiac involvement					SARS-CoV-2 Test	
						Coronary Abnormalities	Ventricular Function	ECG Changes/ Arrhythmia	Elevated Troponin	Elevated ProBNP/ BNP	Positive RT-PCR	Serology
Belhadjer et al. (10)	35	17F 18M	1-16	Previously healthy: 31 Overweight: 6 SLE: 1 Asthma: 3	Fever: 35 Respiratory symptoms: 23 Cardiogenic shock: 28 GI symptoms: 29 Rash: 20 Meningism: 11 Lymphadenopathy: 21 Chest pain: 6	No aneurysm Mild coronary dilation: 6 (z-score > 2)	LVEF (<50%): 35 LVEF (<30%):10 LVEF (30-50%): 25 LV hypokinesis: 31 Segmental wall hypokinesis: 3 Takotsubo syndrome:1	ST elevation: 1 Ventricular arrhythmia: 1	35	35	14	IgG+: 28 IgM+: 2
Feldstein et al. (13)	186	71F 115M	3-12	Previously healthy: 135 Cardiac disease: 5 Obesity: 45 Respiratory disease: 33 Autoimmune/immunocompromise: 10	Fever: 186 Respiratory symptoms: 131 Conjunctivitis: 103 GI symptoms: 171 Cardiovascular symptoms: 149 Rash: 110 Peripheral edema: 69 Oral mucosal changes: 78 Lymphadenopathy: 18	Coronary aneurysm:15/170 (z-score≥2.5)	Myocardial dysfunction: 90	Arrhythmia: 12	50/128	73/173	73	IgG+/IgM+: 85
Whittaker et al. (14)	58	33F 25M	6-14	Previously healthy: 51 Asthma: 3 Epilepsy: 1 Alopecia: 1 Neuro-disability: 1	Fever: 58 Respiratory symptoms: 12 GI symptoms: 58 Rash: 30 Shock: 29	Coronary artery dilation: z-score>2.5: 7 z-score>2: 8 Giant aneurysm: 2	Left ventricular dysfunction: 18/29	AF: 1 Second-degree AV block: 1 First-degree AV block: 1 Intractable broad	58	58	15	IgG+: 40/46

				Sickle cell trait: 1	Conjunctivitis: 26 Mucosal change: 17 Lymphadenopathy: 9 Peripheral edema: 9 Sore throat: 6			complex tachycardia: 1				
Rostami-Maskopaee et al. (41)	225	91F 134M	2.1-10	Previously healthy: 152 Obesity: 44 Chronic lung disease: 12 Seizure:17 Immunosuppressive: 3 G6PD insufficient: 16 Diabetes: 3	Fever: 225 Respiratory symptoms: 121 GI symptoms: 200 Conjunctivitis: 88 Rash: 138 Lymphadenopathy: 21 Neurologic symptoms: 64 Strawberry tongue: 16	Coronary artery dilatation: 62 Coronary artery aneurysms: 2	Ventricular dysfunction: 93 Low EF: 51	Arrhythmia: 45	52	97	49	IgG+/IgM+: 79
Kaushik et al. (42)	33	13F 20M	6-13	Previously healthy: 17 Asthma: 5 Obesity: 4	Fever: 33 Respiratory symptoms: 11 GI symptoms: 23 Rash: 14 Conjunctivitis: 12 Neurologic symptoms: 4 Mucosal change: 7 Hypotension: 21	Coronary ectasia: 2 Prominent coronary arteries: 6	LVEF (<30%): 4 LVEF (<50%): 21	-	33	33	11	IgG+/IgM+: 27
Pouletty et al. (43)	16	8F 8M	5-12	Previously healthy: 10 Obesity: 4 Asthma: 2	Fever: 16 Respiratory symptoms: 2 GI symptoms: 13 Rash: 13 Mucosal changes: 14 Conjunctivitis: 15 Neurologic symptoms: 9	Coronary artery dilation: 3 (Mean z-score:2.6)	LVEF: 35% Myocarditis: 7	-	11	11	11	IgG+: 7/8

					Lymphadenopathy:6 Shock: 11							
Riphagen et al. (21)	8	3F 5M	4-14	Previously healthy: 6 Allergic rhinitis and alopecia areata: 1 Autism: 1	Fever: 8 GI symptoms: 7 Shock/hypotension: 8 Conjunctivitis: 5 Rash: 4 Headache: 2 Odynophagia: 3 Myalgia:1	Giant aneurysm:1 Echo-bright coronary arteries:8	RV dysfunction: 1 LV dysfunction (mild to moderate): 4 BiV dysfunction: 1	-	8	8	2	-
Dufort et al. (33)	99	46F 53M	0-20	Previously healthy: 63 Obesity: 29	Fever: 99 Upper respiratory symptoms:27 Lower respiratorysymptoms:40 GI symptoms: 79 Mucosal change: 60 Rash: 59 Hypotension: 61 Neurologic symptoms: 30 Swollen hands or feet: 9	Coronary artery aneurysm :9	Myocarditis: 52 Ventricular dysfunction: 51	-	63/89	74/82	50	IgM+: 3/77 IgG+: 76/77
Cheung et al. (30)	17	4F 11M	2-16	Asthma: 3	Fever: 17 Respiratory symptoms: 7 GI symptoms: 15 Rash: 12 Shock: 13 Conjunctivitis: 11 Neurologic symptoms: 8 Mucosal change: 9 Lymphadenopathy: 6	Echo-bright coronary arteries: 7 Coronary aneurysm: 1	LV dysfunction: Mild: 11 Moderate-severe: 6	Attenuated QRS voltage: 1 Non-specific ST/T-wave abnormalities: 10	14	15	8	IgG+/IgM+: 9

Toubiana et al. (29)	21	12F 9M	4-17	-	Fever: 21 GI symptoms: 21 Conjunctivitis: 17 Rash: 16 Mucosal change: 16 Shock/hypotension: 16 Neurologic symptoms: 6 Lymphadenopathy: 12	Echo-bright coronary arteries: 3 Dilated coronary arteries: 5	Myocarditis: 16	diffuse ST elevation or ventricular dysrhythmias Increased QT interval: 2	17	14/18	8	IgG+: 19
Ramcharan et al. (44)	15	4F 11M	7-11	-	Fever: 15 Myalgia: 4 Lethargy: 4 GI symptoms: 13	Coronary involvement in 14 cases: Ectasia:6 Prominent:7 Aneurysm:1	LVEF (<55%): 12 Reduced LV fractional shortening: 8	Abnormal T waves Abnormal PR interval: 9	15	15	2	IgG+/IgM+: 12/12
Verdoni et al. (11)	10	3F 7M	3-16	None	Fever: 10 GI symptoms: 6 Rash: 10 Mucosal change: 4 Meningeal signs: 4	Coronary artery aneurysm: 2	LVEF<50%: 5	-	5	10	2	IgG+: 8 IgM+: 3

Arrhythmia and conduction abnormality

According to several investigations into arrhythmic presentations, 7 to 60% of MIS-C cases experience rhythm abnormalities with varying severity (40). The most prevalent electrocardiogram (ECG) findings in MIS-C patients are T-wave abnormalities and low QRS amplitude (50). The PR interval is most often impacted; however, all ECG intervals are prolonged (50). First-degree heart block is a frequent condition that affects 6.3% to 25% of patients with MIS-C, and it has not been linked to increased cardiac enzymes (39,50,51). In 7% of MIS-C patients, second- or third-degree heart blocks were found, and these patients showed high BNP levels and ventricular dysfunction, but normal troponin levels (51). Furthermore, QT prolongation was documented in 28% of cases, and QRS prolongation in 4% of cases (39,52).

Another observation in MIS-C patients is sinus bradycardia, and severe sinus bradycardia has improved after receiving anti-inflammatory treatment (50,53,54). There have been conflicting reports about ST segment changes, with some stating that this is an uncommon finding and others indicating that it is a more frequent finding (50,55).

Management of MIS-C

Because of the limited number of reported patients and inadequate knowledge, the treatment of MIS-C patients has mostly been dependent on expert opinion and extrapolation from KD management, other systemic inflammatory diseases in children, and adult experience with COVID-19 (56,57) . Generally, the treatment of MIS-C involves both immunomodulatory therapy and supportive care (57). The American College of Rheumatology has published guidance statements on the treatment of MIS-C (58,59).

Supportive therapy, such as fluid resuscitation and respiratory support, is recommended for children with MIS-C who have mild symptoms. Nevertheless, children with critical conditions and hemodynamic instability often require inotropic support, which was documented in 20% to 100% of the patients (10,11,13,14,21,24–26,28–30,33,42–44,60). Children who were admitted to the PICU required veno-arterial (V-A) support in some cases (0% - 28%) (10,13,14,21,25,33,42). Although several treatments have been proposed, it is still unclear how effective they are. Moreover, there is no supporting data for these treatments, which are based on the experts' opinions.

Cardiac support

As previously discussed, a significant majority of children who presented with hemodynamic instability needed immediate resuscitation. As a result, it is essential to adhere to the pediatric resuscitation recommendations (61). Children who are at risk for cardiogenic shock and ventricular dysfunction might receive lower fluid doses, including an assessment of symptoms of fluid overload performed prior to injection. Once medical support becomes ineffective, extracorporeal membrane oxygenation must be considered (40).

Immunomodulatory therapy

Immunomodulatory therapy has a variety of well-established benefits when used to treat systemic inflammatory diseases as well as KD (62,63). Most patients received an anti-inflammatory treatment, such as corticosteroids and intravenous immunoglobulins (IVIGs), and in a few situations, they additionally received an anti-inflammatory dose of aspirin (10,11,14,21,24,26,29,30,33,60). It is crucial to keep in mind that IVIG must be administered more slowly to individuals with cardiac dysfunction to minimize the chance of fluid overload. Although administration of corticosteroids is determined by a physician's judgement, using a low dosage is advised in more severe cases (17).

According to the analysis of the cytokine storm pattern in MIS-C patients, macrophage activation is a key factor in this disorder, similar to that found in KD and other autoimmune diseases like systemic lupus erythematosus. As a result, corticosteroids are a different alternative for treating MIS-C patients because they can modulate this syndrome (11,64).

Two corticosteroid therapy approaches have been suggested. The first way is to administer 0.8 mg/kg of methylprednisolone intravenously twice daily for five to seven days, or until the CRP level is normal, before continuing with oral therapy at a dose of 2 mg/kg/day for two to three weeks.

The proposed scenario calls for administering methylprednisolone intravenously (10–30 mg/kg/day) for three days, then administering oral prednisone/prednisolone at a dose of 2 mg/kg/day for four days, or until the CRP level becomes normal, before reducing the dose over the course of two to three weeks. It's crucial to understand that administering corticosteroids during an active infection phase is not recommended (65,66).

Antiviral Therapy

Although MIS-C in children appears to be a post-infectious complication rather than an active infection, studies have shown that children with this syndrome may benefit from antiviral treatment (67,68).

Conclusion

The COVID-19-associated MIS-C is a serious, even life-threatening syndrome. Cardiac involvement is an important and common clinical manifestation

in MIS-C patients that occurs across a spectrum of severity. Cardiac pathology includes arrhythmias, ventricular dysfunction, conduction disorders, and coronary artery dilation. Many of these cardiac abnormalities have been successfully treated with current therapeutic methods, although there is still potential for improvement. Close disease monitoring is continued, and it will help describe the cardiac symptoms and possible outcomes of MIS-C.

References

1. Diabetes Canada Clinical Practice Guidelines Expert C, Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol. 2020;92:401.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. jama. 2020;323:1061–1069.
3. Yeo I, Baek S, Kim J, et al. Assessment of thirty-day readmission rate, timing, causes and predictors after hospitalization with COVID-19. J Intern Med. 2021;290:157–165.
4. Uyaroğlu OA, BaŞaran NÇ, Özişik L, et al. Thirty-day readmission rate of COVID-19 patients discharged from a tertiary care university hospital in Turkey: an observational, single-center study. Int J Qual Health Care. 2021;33:mzaa144.
5. Akbari A, Fathabadi A, Razmi M, et al. Characteristics, risk factors, and outcomes associated with readmission in COVID-19 patients: A systematic review and meta-analysis. Am J Emerg Med. 2022;52:166–173.
6. Sinha IP, Harwood R, Semple MG, et al. COVID-19 infection in children. Lancet Respir Med. 2020;8:446–7.
7. Farhat AS, Sayedi SJ, Akhlaghi F, et al. Coronavirus (COVID-19) infection in newborns. Int J Pediatr. 2020;8:11513–11517.
8. DeBiasi RL, Delaney M. Symptomatic and asymptomatic viral shedding in pediatric patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): under the surface. Jama Pediatr. 2021;175:16–18.
9. Ghodsi A, Azarfar A, Ghahremani S. A Review of Coronavirus Disease (COVID-19) in Children. J Pediatr Nephrol. 2020;8.
10. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:429–436.
11. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet. 2020;395:1771–1778.
12. Ghodsi A, Malek A, Ghahremani S. A review of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. cal. 2020;12:13.
13. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383:334–346.
14. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Jama. 2020;324:259–269.
15. Lee MS, Liu YC, Tsai CC, et al. Similarities and differences between COVID-19-related multisystem inflammatory syndrome in children and Kawasaki disease. Front Pediatr. 2021;9:573.
16. Hennon TR, Penque MD, Abdul-Aziz R, et al. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines; a Western New York approach. Prog Pediatr Cardiol. 2020.
17. Ghodsi A, Mahmoudabadi E, Ghahremani S, Malek A. Cardiac manifestations of multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection. Arch Pediatr Infect Dis. 2021;16.
18. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children Associated with Coronavirus Disease 2019. Av
19. World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents Temporally Related to COVID-19. Available online at: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.
20. Royal College of Paediatrics and Child Health. Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19-Guidance for Clinicians.
21. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;395:1607–1608.
22. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020;10:537–540.
23. Rivera-Figueroa EI, Santos R, Simpson S, et al. Incomplete Kawasaki disease in a child with Covid-19. Indian Pediatr. 2020;57:680.
24. Licciardi F, Pruccoli G, Denina M, et al. SARS-CoV-2–induced Kawasaki-like hyperinflammatory syndrome: a novel COVID phenotype in children. Pediatrics. 2020;146.
25. Deza Leon MP, Redzepi A, McGrath E, et al. COVID-19–associated pediatric multisystem inflammatory syndrome. J Pediatr Infect Dis Soc. 2020;9:407–408.
26. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatr Infect Dis Soc. 2020;9:393–398.
27. Waltuch T, Gill P, Zinns LE, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. Am J Emerg Med. 2020;38:2246-e3.
28. Grimaud M, Starck J, Levy M, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care. 2020;10:1–5.
29. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. bmj. 2020;369.
30. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. Jama. 2020;324:294–296.
31. Alsaied T, Tremoulet AH, Burns JC, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation. 2021;143:78–88.
32. Malek A, Ghodsi A, Hamedi A. The Negative Predictive Value of Harada Scoring for Coronary Artery Dilatation or Aneurysm in Children with Kawasaki Disease: A Cross-sectional Study. Iran J Med Sci. 2022;
33. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347–58.
34. 34. Zhang QY, Xu BW, Du JB. Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment. World J Pediatr. 2021;17:335–340.
35. Blondiaux E, Parisot P, Redheuil A, et al. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. Radiology. 2020;297:E283–288.
36. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children—initial therapy and outcomes. N Engl J Med. 2021;385:23–34.
37. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021;180:2019–34.
38. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine. 2020;26:100527.
39. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation. 2021;143:21–32.
40. Sperotto F, Friedman KG, Son MBF, et al, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review

and proposed clinical approach. Eur J Pediatr. 2021;180:307–322.
41. Rostami-Maskopaee F, Ladomenou F, Razavi-Amoli SK, et al. Clinical characteristics and outcomes of the multisystem inflammatory syndrome in children (MIS-C) following COVID-19 infection in Iran: A multicenter study. PLoS One. 2022;17:e0274104.
42. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr. 2020;224:24–29.
43. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79:999–1006.
44. Ramcharan T, Nolan O, Lai CY, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatr Cardiol. 2020;411391–1401.
45. Sanna G, Serrau G, Bassareo PP, et al. Children's heart and COVID-19: up-to-date evidence in the form of a systematic review. Eur J Pediatr. 2020;179:1079–1087.
46. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5:802–810.
47. Creel-Bulos C, Hockstein M, Amin N, et al. Acute cor pulmonale in critically ill patients with Covid-19. N Engl J Med. 2020;382:e70.
48. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17:259–260.
49. Tersalvi G, Vicenzi M, Calabretta D, et al. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. J Card Fail. 2020;26:470–475.
50. Regan W, O'Byrne L, Stewart K, et al. Electrocardiographic changes in children with multisystem inflammation associated with COVID-19: associated with coronavirus disease 2019. J Pediatr. 2021;234:27–32.
51. Dionne A, Mah DY, Son MBF, et al. Atrioventricular block in children with multisystem inflammatory syndrome. Pediatrics. 2020;146.
52. Dionne A, Newburger JW. The electrocardiogram in multisystem inflammatory syndrome in children: mind your Ps and Qs. J Pediatr. 2021;234:10–11.
53. Hallberg TC, Bjorklund AR, Slusher TM, et al. Sinus bradycardia in a toddler with multisystem inflammatory syndrome in children (MIS-C) related to COVID-19. BMJ Case Rep CP. 2021;14:e242058.
54. Tomlinson LG, Cohen MI, Levorson RE, et al. COVID-19-associated multisystem inflammatory syndrome in children presenting uniquely with sinus node dysfunction in the setting of shock. Cardiol Young. 2021;31:1202–1204.
55. Aski BH, Anari AM, Choobdar FA, et al. Cardiac abnormalities due to multisystem inflammatory syndrome temporally associated with Covid-19 among children: a systematic review and meta-analysis. IJC Heart Vasc. 2021;33:100764.
56. Ghodsi A, Sarabi M, Malek A, et al. Current Treatment Guidelines of SARS-CoV-2 Related Multisystem Inflammatory Syndrome in Children: A Literature Review and Expert Opinion. J Child Sci. 2021;11:e133–140.
57. McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385:11–22.
58. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated With SARS–CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol. 2020;72:1791–1805.
59. Henderson LA, Canna SW, Friedman KG, et al. American College of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS–CoV-2 and Hyperinflammation in pediatric COVID-19: version 2. Arthritis Rheumatol. 2021;73:e13–29.
60. Rauf A, Vijayan A, John ST, et al. Multisystem inflammatory syndrome with features of atypical Kawasaki disease during COVID-19 pandemic. Indian J Pediatr. 2020;87:745–747.
61. Edelson DP, Sasson C, Chan PS, et al. Interim guidance for basic and advanced life support in adults, children, and neonates with suspected or confirmed COVID-19: from the emergency cardiovascular care committee and get with the guidelines-resuscitation adult and pediatric task forces of the American Heart Association. Circulation. 2020;141:e933–943.
62. Pineton De Chambrun M, Luyt CE, B et al. The clinical picture of severe systemic capillary-leak syndrome episodes requiring ICU admission. Crit Care Med. 2017;45:1216–1223.
63. Thompson PD, Myerburg RJ, Levine BD, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 8: coronary artery disease: a scientific statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132:e310–314.
64. Ravelli A, Minoia F, Davì S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative. Arthritis Rheumatol. 2016;68:566–576.
65. Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, et al. Cardiovascular impact of COVID-19 with a focus on children: A systematic review. World J Clin Cases. 2020;8:5250.
66. Nakra NA, Blumberg DA, Herrera-Guerra A, Let al. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children. 2020;7:69.
67. Goldman JD, Lye DC, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020;383:1827–1837.
68. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19. N Engl J Med. 2020;383:1813–1826.