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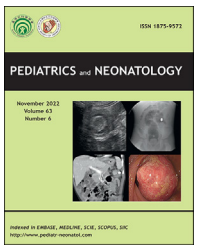

Original Article

Cardiovascular injury and clinical features of multisystem inflammatory syndrome in children (MIS-C) related to Covid-19 in Vietnam

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Key Words
cardiovascular injury;
COVID-19;
MIS-C;
SARS-CoV-2

Background: This study aimed to describe the cardiovascular injury and clinical features of multisystem inflammatory syndrome in children (MIS-C) related to coronavirus disease 2019 (COVID-19) in Ho Chi Minh City, Vietnam.
Methods: This was a retrospective cohort study of children with MIS-C (from September 1, 2021 to February 28, 2022) in Children's Hospital 1, Ho Chi Minh City. Demographics, clinical history, significant underlying conditions, clinical manifestations, laboratory investigations, and medical management were analyzed.
Results: A total of 76 patients were included (median age, 5.9 years old, 2 months—16 years). The male/female ratio was 1.6/1. Most patients (75/76) had no previous medical conditions. The mean time from acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to symptom onset was 39 days. During an acute SARS-CoV-2 infection, these patients are either asymptomatic or mildly symptomatic. In addition to fever, gastrointestinal symptoms were also prominent, as observed in our study, with 75%, 73.7%, and 72.3% of patients presenting with abdominal pain, vomiting, and loose stools, respectively. The levels of inflammatory markers increased upon admission and returned to normal levels after treatment. Echocardiography revealed decreased myocardial contractility and coronary injury in 16 (21.1%) and 32 (42.1%) patients, respectively. Most cases (72/76) had no fever within 3 days of intravenous immunoglobulin (IVIG) and methylprednisolone treatment. No deaths occurred in this study. The mean duration of hospitalization was 7.2 days.

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Conclusion: Cardiovascular involvement was observed in approximately 53.9% of the patients. Anti-inflammatory treatment with IVIG and methylprednisolone had a favorable short-term outcome. However, long-term follow-up studies on post-discharge MIS-C cases are needed to make appropriate treatment recommendations in the acute phase.

1. Introduction

Since its discovery in late December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has been declared a global pandemic, causing millions of deaths worldwide. Vietnam was also experiencing many waves of the COVID-19 pandemic, with 3,436,124 cases and 40,252 deaths as of February 28, 2022.[1] Compared with adults, the proportion of children infected with SARS-CoV-2 is lower, and the symptoms of COVID-19 are relatively milder, except in children with underlying medical conditions. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious medical condition that usually occurs 2—6 weeks after infection with SARS-CoV-2.[2] MIS-C is characterized by inflammation in different organ systems, such as the cardiovascular, respiratory, mucocutaneous, and gastrointestinal systems. The causes of MIS-C are still unknown; however, there have been many reports showing a clear association between MIS-C and COVID-19.[3] The exact incidence of MIS-C remains uncertain but is estimated to be 0.6% of COVID-19 cases in children, according to a report in New York.[4] The clinical presentation of MIS-C is diverse. Approximately 40—50% of children with MIS-C meet the criteria for typical or atypical Kawasaki disease (KD). In addition, the clinical features of MIS-C can overlap with those of toxic shock syndrome (TSS), hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS).[5,6] Inflammation of the cardiovascular system is the most severe manifestation of MIS-C cases. Many different types of cardiovascular damage have been described, including dilated heart chambers, decreased myocardial contractility, and coronary inflammation, leading to dilation or creation of coronary aneurysms.[4,5,7,8] The prognostic factors and timeframe for the onset of cardiovascular injury in patients with MIS-C are still unknown. To date, the diagnosis of MIS-C is usually based on the case definitions provided by the World Health Organization (WHO) or Center for Disease Control and Prevention (CDC).[2] The standard treatment for MIS-C is controversial. However, as the clinical presentations of MIS-C overlap with those of KD, the current treatments for MIS-C are similar to those for KD, including intravenous immunoglobulin (IVIG), aspirin, and possibly glucocorticoids.[9—11]

The majority of MIS-C cases have been reported in North America and European countries, while very few reports have been published in Asian countries.[4,5,7,12—14] Therefore, in this retrospective cohort study, we aimed to summarize and analyze the clinical features, laboratory parameters, management, and outcomes of MIS-C cases admitted to a children's hospital in Ho Chi Minh City, Vietnam, and compare them with those reported in previously published studies.

2. Methods

We performed a retrospective cohort study at the Children's Hospital 1 (CH 1) from September 1, 2021 to February 28, 2022. All patients who met the WHO case definition of MIS-C and were admitted to CH 1 will be included in the study.

A standardized form was used to collect data on patient's demographics, clinical history, significant underlying conditions, clinical manifestations, laboratory investigations, and medical management. We recorded the clinical symptoms and laboratory results at the time of admission and 48—72 h after starting treatment.

Biochemical tests were performed using a BECKMAN COULTER AU-680 machine at the Department of Biochemistry, CH 1. The total blood count and coagulation test were performed using the Sysmex XN-2000 and STA R-Max machines, respectively, at the Department of Hematology Laboratory, CH 1. Chest X-ray results were evaluated by the radiologists of CH 1. Cardiac and abdominal ultrasonography were performed by the sonographers of CH 1. The degree of coronary dilatation was assessed using the Boston Classification System.

Descriptive statistics were calculated and presented as mean and standard deviation (±SD) for continuous variables or as numbers and percentages for nominal/categorical variables. Statistical analysis was conducted using STATA 14, and a two-tailed $P < 0.05$ was considered statistically significant.

Ethical considerations: This study was approved by the ethics committee of CH 1.

3. Results

Our study included 76 patients with a median of 5.9 years old (the youngest being 2 months old and the oldest being 16 years old). The most common age group was 5—11 years old (55.3%), followed by < 5 (39.4%) and 12—16 years old (5.3%). The male/female ratio was 1.6/1. Most patients had no previous medical conditions. One patient had an underlying medical condition, which was tuberous sclerosis complex. A history of SARS-CoV-2 infection was identified by the SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR), SARS-CoV-2 antigen, and SARS-CoV-2 immunoglobulin G (IgG) tests in 3, 43, and 11 patients,

respectively. The remaining 19 patients had a history of close contact with confirmed patients with COVID-19. During an acute SARS-CoV-2 infection, these patients are either asymptomatic or mildly symptomatic. None of the patients required respiratory support or anti-inflammatory or anticoagulant therapy. At the time of admission, all patients had negative RT-PCR SARS-CoV-2 results. The mean time from acute SARS-CoV-2 infection to symptom onset was 39 days. Three patients received the vaccine before the onset of MIS-C. All patients were aged >12 years. One case had a Kawasaki-like phenotype, and two had an undefined phenotype.

Most patients (71/76) were admitted because of fever. The remaining five patients were hospitalized due to palpitations, convulsions, skin rashes, vomiting, and neck lymph nodes. Fever was present in all cases. Other symptoms in typical KD, such as conjunctivitis, red lips, skin rash, limb edema, and neck lymph nodes, were also recorded in the cases of our study (Fig. 1). As observed in our study, gastrointestinal symptoms were also prominent, with 75%, 73.7%, and 72.3% of patients presenting with abdominal pain, vomiting, and loose stools, respectively. Five patients had severe abdominal pain associated with appendicitis-like symptoms; thus, they were diagnosed with appendicitis at the time of admission.

At the time of diagnosis, the average white blood cell count was 11.59 k/mm^3, and 42 of 76 patients had lymphocytopenia, with an average lymphocyte count of 1.84 k/mm^3. Six patients had hypochromic microcytic anemia. There were 16 of 76 cases that had platelet (PLT) count below 100 k/mm^3, but only 1 case had a PLT count below 50 k/mm^3. Abnormalities in the total blood count returned to normal after treatment. Other parameters reflecting inflammation, such as C-reactive protein (CRP), ferritin, and procalcitonin, also showed a strong increase, all of which improved after treatment. Four of the 76 patients had elevated liver enzyme levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) above 100 U/L. Renal function and electrolyte levels were normal in all the patients. D-dimer increased over 0.5 μg/mL in all cases, with the highest concentration being 20 μg/mL.

Chest radiography was performed in all cases, and most showed no remarkable abnormalities. Only one patient had an enlarged heart on chest radiography, and three had interstitial lesions in the left lung base. In addition, the patients had various non-specific findings on abdominal ultrasound, including 4 cases of intestinal wall edema and thickening, 5 cases of mild pleural effusions, and 13 cases of mild ascites.

The cardiac injury was observed in 41 patients (53.9%), of which 25 had a coronary injury, 9 had decreased ejection fraction (EF), and 7 had both. There were a total of 32 cases (42.1%) of coronary injury in the first week of the disease, 12 had mild coronary dilation (+2 → +5 SD), 10 presented manifestations of coronary inflammation, and 10 had both. The patient with the largest coronary dilation was a 16 years old male. The Z-score index of the left main and right coronary artery diameters were 3.88 and 3.39, respectively (according to the Boston classification). This patient had a high fever and gastrointestinal symptoms but no mucocutaneous symptoms. The patient was treated with methylprednisolone at a dose of 30 mg/kg/day for 3 days and tapered thereafter. The patient had no fever after 24 h of treatment with methylprednisolone, and the echocardiogram result at the time of discharge showed complete recovery of myocardial contractility.

Sixteen patients (21.1%) had decreased EF, of which mild and moderate decreases of EF were observed in 12 and 4 patients, respectively. The lowest EF recorded was 35%; this case presented with shock and required an inotrope (dobutamine). Elevation of troponin I was detected in five patients, of whom four had a slightly increased level, except for one patient who had a significantly increased level. Vasopressors/inotropes were used in four of the five cases of troponin elevation. Electrocardiography was performed on 23 patients; 20 had no remarkable abnormalities, and 3 had first-degree atrioventricular (AV) block and scattered premature ventricular beat.

Table 2 describes the echocardiographic features and treatment characteristics according to the clinical phenotype. Patients presenting with shock and the need for inotropes or vasopressors were classified as having a shock-like

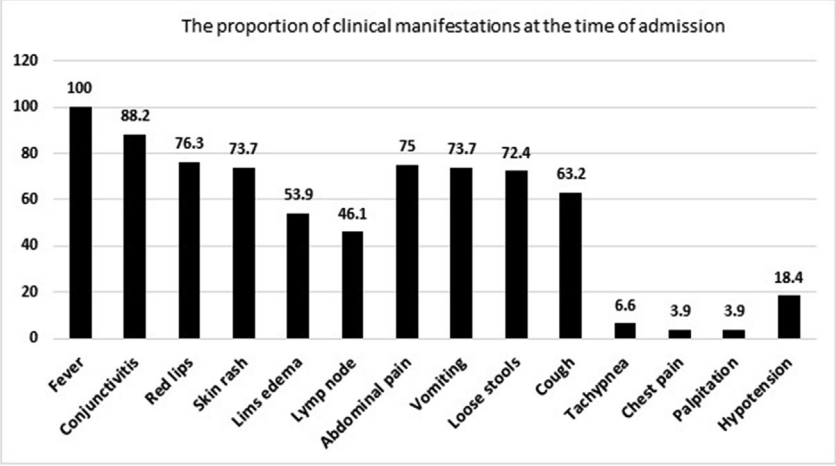

Figure 1 Proportion of clinical manifestations at the time of admission.

Table 1 Laboratory parameters before and after treatment of the study group.

Parameters	Reference range	Before treatments	After treatments	*P*-value
WBC (k/mm^3)	4.0—12.0	11.6	15.2	**< 0.001**
NEU (k/mm^3)	3.0—5.8	8.9	10.1	0.157
LYM (k/mm^3)	1.5—3.0	1.8	3.6	**< 0.001**
Hb (g/dL)	11.5—4.5	10.9	10.8	0.084
PLT (k/mm^3)	150—400	179.0	407.7	**< 0.001**
CRP (mg/L)	<5	144.9	32.9	**< 0.001**
Ferritin (μg/L)	6—320	1563.6	692.2	**0.003**
D-dimer (μg/mL)	0—0.5	4.55	1.41	**< 0.001**
VS (mm, n = 53)	0—20	51.4	33.8	**0.001**

phenotype. Patients with clinical features that met the criteria for typical or atypical KD were classified as having KD-like phenotypes. The remainder is an undefined phenotype. The rates of coronary injury and decreased EF in the shock-like group were higher than those in the other two groups. The rates of treatment escalation and length of hospital stay were also higher in the shock-like group, but these differences were not statistically significant. In addition, patients in the shock-like group had mild-to-moderate decreases in myocardial contractility. Furthermore, three patients had mild coronary dilation, and three had coronary inflammation. Patients in this group received intensive treatment, with five cases using IVIG combined with methylprednisolone and nine cases using methylprednisolone alone at a dose of 20—30 mg/kg/day. All of these patients had normal echocardiogram results at the time of discharge.

In our study, 14 patients required vasopressors, including 12 with shock and 2 with moderately reduced EF (40%). Of the 12 patients in shock, adrenaline and dobutamine were two vasopressors, noradrenaline was used in three patients, and all of them received emergency crystalloid fluids prior to vasopressors. In the study group, 16 patients (21.1%) required respiratory support, of which 13 had cannula oxygen, 1 had a high-flow nasal cannula, and 2 had mechanical ventilation.

IVIG alone, methylprednisolone alone, and IVIG combined with methylprednisolone were administered to 5, 49, and 22 patients, respectively. Five patients who received IVIG alone had clinical presentations similar to KD and had mild coronary dilatation. The patients did not require a second dose of IVIG or corticosteroid combination. Echocardiographic results at the time of discharge in these patients completely recovered. The dose of methylprednisolone usually used was

Table 2 Cardiac ultrasound and treatment characteristics according to clinical phenotypes.

Characteristics	Shock-like phenotype (n = 14)	KD-like phenotype (n = 51)	Undefined phenotype (n = 11)	*P*-value
Coronary dilation/inflammation (n, %)	8 (57.1)	24 (47.1)	0	**0.003**
Decreased EF (n, %)	12 (85.8)	4 (7.9)	0	**< 0.001**
Mild	6 (42.9)	3 (5.9)	0	
Moderate	6 (42.9)	1 (2.0)	0	
Respiratory support (n, %)	10 (71.4)	6 (11.8)	0	**< 0.001**
Oxy cannula	8 (57.1)	5 (9.8)	0	
HFNC	0	1 (2.0)	0	
Mechanical ventilation	2 (14.3)	0	0	
Inotrope/vasopressor (n, %)	14 (100)	0	0	**< 0.001**
Primary treatment				0.063
IVIG alone	0	5 (9.8)	0	
Corticoid alone	9 (64.3)	29 (56.9)	11 (100)	
Combined	5 (35.7)	17 (33.3)	0	
Treatment escalation[a]	6 (42.9)	8 (15.7)	3 (27.3)	0.089
Anticoagulant (n, %)	6 (42.9)	11 (21.6)	1 (9.1)	0.118
Aspirin (n, %)	14 (100)	51 (100)	11 (100)	
3—5 mg/kg/d	12 (85.7)	35 (68.6)	11 (100)	0.07
30—50 mg/kg/d	2 (14.3)	16 (31.4)	0	
Antibiotic (n, %)	12 (85.7)	35 (68.6)	6 (54.5)	0.232
PPI (n, %)	12 (85.7)	9 (17.6)	3 (27.3)	**< 0.001**
Duration of fever, days (mean ± SD)	1.50 ± 0.67	2.08 ± 1.12	1.64 ± 0.62	0.814
Duration of admission, days (mean ± SD)	8.07 ± 2.53	7.24 ± 1.48	5.91 ± 1.69	0.535

[a] Increase in corticosteroid dose.

2 mg/kg/day; however, 17 cases used an additional course of 10–30 mg/kg/day of methylprednisolone for 3 days because of persistent fever and increased inflammation markers after 48 h of methylprednisolone (2 mg/kg/day) ± IVIG (2 g/kg). All patients received aspirin, of which 58 received low-dose aspirin (3–5 mg/kg/day) and 18 received a KD-like dose (30–50 mg/kg/day). Eighteen patients (23.7%) received aspirin in combination with enoxaparin. Approximately 69.7% of patients received antibiotics. Commonly used antibiotics included cephalosporin, vancomycin, aminoglycosides, and carbapenems.

Most cases (72/76) had no fever within 3 days of IVIG and methylprednisolone treatment. Complications of treatment occurred in 10 patients (2 patients had Cushing syndrome, 2 patients had gastrointestinal bleeding, and the rest had symptoms of gastritis). The mean duration of hospital stay duration was 7.2 days.

4. Discussion

This retrospective cohort study reported 76 cases of MIS-C in a large Children's Hospital in Ho Chi Minh City during the fourth wave of the COVID-19 pandemic in Vietnam. Similar to recent reports, the patients were admitted to the hospital approximately 2–6 weeks after the acute episode, with a prominent symptom of prolonged fever.[5,14,15]

In our study, in addition to prolonged fever and clinical features compatible with KD, gastrointestinal symptoms were also salient. Similar findings are consistent with other reported cases.[6,15,16] Therefore, this is an important different point between the MIS-C and KD. The differential diagnosis was acute appendicitis at the time of admission in five patients presenting with severe right lower quadrant pain. The ultrasound results in all five cases showed inflammation of the ileocecal region, and two cases were accompanied by a small amount of homogeneous peritoneal fluid. However, these gastrointestinal symptoms improved significantly after treatment, and the subsequent abdominal ultrasound did not reveal any abnormalities. Chest pain is also an important symptom that requires careful consideration, particularly in older children. The three patients who presented with complaints of chest pain in our study were older children, all of whom had cardiac injury and hypotension and then received vasopressor support. Respiratory symptoms were less severe in our study and were similar to findings on chest X-rays (mostly normal or minor lung injury). Sixteen patients required respiratory support, of which only two required mechanical ventilation. Respiratory support therapies in these cases play a role as supportive therapy in shock resuscitation, not due to respiratory failure. This is consistent with previous studies, although some studies have reported a higher percentage of cases requiring respiratory support during illness.[6,16]

Although the pathophysiology of MIS-C is not fully understood, recent studies have reported an abnormal immune response in patients with MIS-C, which is manifested by elevated levels of inflammatory markers such as CRP, ferritin, procalcitonin, and coagulation abnormalities (elevated D-dimer levels).[17–19] Elevated inflammatory markers and evidence of coagulopathy are common laboratory findings and are among the most important criteria in the current case definition of MIS-C established by the CDC/WHO. All patients in this study also had an increase in at least one of many inflammatory markers or D-dimer levels, and abnormalities in these parameters returned to normal after treatment (Table 1).

The cardiovascular involvement of MIS-C varies and is often described in a manner similar to that of KD. However, depressed left ventricular function, the most common manifestation of cardiac injury, has been reported in up to 56% of patients with MIS-C.[16,20] This contrasts with KD, which rarely results in decreased myocardial function. Therefore, point-of-care ultrasonography can be beneficial in the emergency management of MIS-C to detect early ventricular function and assess fluid responsiveness. Our study showed that 21.1% of patients had mild to moderate decreased EF, and 18.4% of patients required inotrope/vasopressors. The vasopressors used were adrenaline and noradrenaline, and the inotrope used was dobutamine. Epinephrine is preferred to noradrenaline when there is evidence of left ventricular dysfunction. The use of milrinone may be helpful in children with severe left ventricular dysfunction.[8,21]

Coronary injury is a serious problem in patients with MIS-C. A total of 32 patients (42.1%) in the study had coronary dilatation or inflammation on cardiac ultrasound. Then, 21 patients recovered completely during their hospital stay, and 11 patients still had mild coronary dilatation at the time of discharge. In a report from Italy, children with MIS-C were 30 times more likely to develop coronary aneurysms than those afflicted with KD, although it is likely that other children with milder symptoms in the region were not included in this case series.[22] In addition, in children with MIS-C, the timeframe for the development of coronary aneurysms is uncertain, and coronary aneurysms can develop in children without Kawasaki-like features.[8] Finally, no clear predisposing factors were identified for MIS-C cases with a higher risk of developing coronary involvement. Therefore, echocardiography is an important tool for the diagnosis and management of patients with MIS-C. Elevated troponin I level is also a critical feature. Five of the 76 patients in our study had elevated troponin I levels, and 4 of them needed vasopressor therapy. In previous reports, elevated troponin levels were associated with poor outcomes in patients with COVID-19 and could be a reflection of the degree of systemic inflammation and myocardial effects.[23]

Even though no randomized clinical trials have been conducted to guide the treatment of MIS-C, standard therapies for KD, including high dose IVIG (2 g/kg), low-dose aspirin (3–5 mg/kg) in combination with methylprednisolone, or not have shown effectiveness in many previous studies.[9,11,15] Owing to economic reasons and the availability of IVIG, the majority of patients in our study (93.4%) used methylprednisolone, 28.9% of cases in combination with IVIG, and only five patients used IVIG alone. The short-term treatment outcomes between the IVIG alone and methylprednisolone alone groups were not significantly different. This is also consistent with previous studies.[9,11,14–16] However, the long-term outcomes of MIS-C, such as sequelae of coronary artery aneurysm formation according to treatment therapies, remain unknown.

It is very difficult to exclude bacterial infections because of the high prevalence of bacterial infections in Vietnam, high inflammatory response, and abnormal abdominal ultrasound and chest X-ray findings. Therefore, most patients

in our study (69.7%) were treated with antibiotics. However, the use of antibiotics for 2—3 days did not improve the clinical or inflammatory status of the patients in our study. The use of aspirin in the treatment of MIS-C has been agreed upon; however, the use of anticoagulants remains unclear. In mild to moderate cases of MIS-C, it should use prophylactic doses of enoxaparin (0.5 mg/kg every 12 h), and in severe cases, therapeutic doses may be used.[10,24,25] In addition, supportive interventions such as early respiratory support for patients with respiratory failure, adequate fluid resuscitation, and vasopressor support for patients with shock also play an important role.

5. Conclusions

Cardiovascular involvement was observed in approximately 53.9% of the patients. Early consideration and appropriate diagnostic evaluation are important, as these children are at high risk of multiple cardiovascular complications, including coronary artery aneurysms. Long-term follow-up studies on post-discharge MIS-C cases are needed to make appropriate treatment recommendations in the acute phase.

Declaration of competing interest

The authors declare no conflicts of interest.

References

1. Ministry of Health of Vietnam. *Channel of the Ministry of Health of Vietnam about covid-19 pandemic*. 2022. Available at https://covid19.gov.vn/. Accessed March 1, 2022.
2. F Son Mary Beth, Friedman Kevin. *Coronavirus disease 2019 (COVID-19): multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis*. Available at https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation-and-diagnosis?topicRef=129614&source=see_link, 2022. Accessed March 1, 2022.
3. Centers for Disease Control and Prevention. *Multisystem inflammatory syndrome (MIS-C)*. Available at https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/mis-c.html, 2022. Accessed March 1, 2022.
4. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med* 2020;**383**:347—58.
5. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. Children and adolescents. *N Engl J Med* 2020;**383**:334—46.
6. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;**324**:259—69.
7. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Asolesc Health* 2020;**4**:669—77.
8. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation* 2020;**142**:429—36.
9. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. *N Engl J Med* 2021;**385**:11—22.
10. Bansal N, Azeka E, Neunert C, Kim JS, Murray J, May L, et al. Multisystem inflammatory syndrome associated with COVID-19 anti-thrombosis guideline of care for children by action. *Pediatr Cardiol* 2021;**42**:1635—9.
11. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Asolesc Health* 2021;**5**:133—41.
12. Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. *Int J Infect Dis* 2020;**100**:75—81.
13. Almoosa ZA, Al Ameer HH, AlKadhem SM, Busaleh F, AlMuhanna FA, Kattih O. Multisystem inflammatory syndrome in children, the real disease of COVID-19 in pediatrics - a multicenter case series from Al-Ahsa, Saudi Arabia. *Cureus* 2020;**12**:e11064.
14. Hasan MR, Al Zubaidi K, Diab K, Hejazi Y, Bout-Tabaku S, Al-Adba B, et al. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a case series from a tertiary care pediatric hospital in Qatar. *BMC Pediatr* 2021;**21**:267.
15. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. *Pediatr Infect Dis J* 2020;**39**:e340—6.
16. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: a systematic review. *EClinicalMedicine* 2020;**26**:100527.
17. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell* 2020;**183**:968—81.e7.
18. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;**135**:2033—40.
19. Buonsenso D, Riitano F, Valentini P. Pediatric inflammatory multisystem syndrome temporally related with SARS-CoV-2: immunological similarities with acute rheumatic fever and toxic shock syndrome. *Front Pediatr* 2020;**8**:574.
20. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: is there a linkage to Kawasaki disease? *Trends Cardiovasc Med* 2020;**30**:389—96.
21. F Son Mary Beth, Friedman Kevin. *COVID-19: multisystem inflammatory syndrome in children (MIS-C) management and outcome*. Available at https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-management-and-outcome?search=mis-c&source=search_result&selectedTitle=1~94&usage_type=default&display_rank=1#H2249684645, 2022. Accessed March 1, 2022.
22. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;**395**:1771—8.
23. Nguyen Y, Corre F, Honsel V, Curac S, Zarrouk V, Burtz CP, et al. A nomogram to predict the risk of unfavourable outcome in COVID-19: a retrospective cohort of 279 hospitalized patients in Paris area. *Ann Med* 2020;**52**:367—75.
24. Goldenberg NA, Sochet A, Albisetti M, Biss T, Bonduel M, Jaffray J, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. *J Thromb Haemost* 2020;**18**:3099—105.
25. Whitworth H, Sartain SE, Kumar R, Armstrong K, Ballester L, Betensky M, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood* 2021;**138**:190—8.