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Original Article

A retrospective study of children with multisystem inflammatory syndrome and intravenous immunoglobulin treatment

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Abstract

Objectives
To compare the outcomes of multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 infection treated with intravenous immunoglobulin (IVIG) and without IVIG.

Patients and methods
A retrospective observational study was conducted over a period of 2 months. We enrolled all children (1–18 years, both sexes) who presented with coronavirus disease 2019-associated MIS-C (as per WHO definition). The patient classification and treatment were done as per the PGIMER Chandigarh protocol (IVIG along with corticosteroids and aspirin was given in all cases with moderate, severe disease, and Kawasaki disease phenotype). Mild cases did not receive IVIG but received corticosteroids and aspirin. Respiratory support was given in cases with breathing difficulty. The primary outcomes of the children were noted in terms of ICU stay, requirement of ventilation, requirement of High flow nasal cannula (HFNC), and nasal oxygen. Response with respect to inflammatory parameters and coronary diameters were also assessed as secondary outcomes.

Results
Among 52 patients enrolled in the study, 25 had mild, 17 had moderate, eight had severe disease, and two had Kawasaki disease phenotype. Among 27 cases requiring IVIG, seven cases did not receive IVIG. In children who received IVIG (n = 20), there were higher odds of ICU stay [odds ratio (OR) 1.185], ventilation (OR 8.784), need for CPAP (OR 5), and HFNC (OR 3.75) but all of these were statistically insignificant ($P > 0.05$). Among the inflammatory markers, there was a significant reduction in the C-reactive protein levels (23.3 vs. 5, $P = 0.004$, OR 1.028) with the use of IVIG. There was no significant difference in the change in the D-dimer levels (1480 vs. 449.38, $P = 0.148$) and coronary artery diameter after the treatment.

Conclusion
The changing evidence about the use of IVIG producing similar outcomes to those not using IVIG suggests that corticosteroids and aspirin can alone be used in cases of MIS-C irrespective of the severity of the disease. However, considering the significant reduction in the inflammatory marker (C-reactive protein) after the use of IVIG in moderate to severe cases, its administration may not totally be negated.

Keywords: Coronavirus disease 2019, intravenous immunoglobulin, multisystem inflammatory syndrome in children

Introduction

In 2019, only 1–2% of hospitalized patients [coronavirus disease 2019 (COVID-19)] were children https://www.who.int/news-room/*commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19*. In April 2020, in Europe and the United States, children got affected with the severe systemic hyperinflammatory disease,

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as a consequence (2–4 weeks after) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1,2]. This condition was called 'multisystem inflammatory syndrome in children (MIS-C) or pediatric multisystem inflammatory syndrome' [3]. Its symptoms include digestive symptoms, persistent fever, rash, mucocutaneous inflammation signs, bilateral nonpurulent conjunctivitis, and frequent cardiovascular involvement [4].

SARS-CoV-2 causes inflammatory disorders, which have similar features to Kawasaki disease (KD; it can cause coronary aneurysms). This finding shows that the immune system gets triggered by the virus, causing damage to heart and coronary arteries similar to KD. MIS-C and hemodynamic failure are often associated with acute dysfunction of the cardiac system requiring the use of hemodynamic support in 60–75% cases [5]; it can even lead to death in some cases [6].

The treatment is based on the guidelines of KD for children with MIS-C. The treatment consisted of intravenous immunoglobulin (IVIG) either alone or in combination with corticosteroids [5]. Some children were also given a second line of treatment, which included interleukin 1 inhibitor or tumor necrosis factor inhibitor, which suggests that an optimal initial therapy still needs to be discovered [7,8].

To date, no standard guidelines have been accepted for the management of MIS-C, but many guidelines have been published by several organizations individually. Physicians have used parameters like specific symptoms, COVID-19 treatment guidelines for adult patients, or earlier treatment of similar conditions like KD to make treatment protocols. In case of the diagnosis of MIS-C, a multidisciplinary team approach is best suited, which includes a cardiology, rheumatology, immunology, and ICU team; a pediatric infectious diseases unit to consider immunotherapy or antiviral therapy (in case of a positive PCR for SARS-CoV-2); or both. It is critical to provide general supportive care, particularly monitoring vital signs, electrolytes, hydration, and metabolic status. Symptoms like hypoxia or respiratory compromise are rare, but careful monitoring is required for the children [9].

A British Delphi consensus study suggested the use of IVIG as initial therapy for the treatment of MIS-C [10]; however, its role in mild cases and moderate to severe cases of MIS-C needs to be compared to come to a consensus for its use. It must be kept in mind that IVIG is a costly treatment, and in India, all patients may not afford it. Besides being a day care therapy, the insurance companies usually keep terms of its exclusion. Thus, it becomes an absolute essentiality to determine the appropriate use of IVIG in the treatment of MIS-C cases as a preparatory measure for the third wave of COVID-19 [10].

The present retrospective cohort study was conducted with an aim to compare the results of MIS-C cases associated with SARS-CoV-2 infection treated with IVIG and without IVIG.

Patients and methods

A retrospective observational study was conducted in the Department of Pediatrics at SRCDH over a period of 2 months from April 16 to June 15, 2021. We enrolled all children (1–18 years, both sexes) who presented with COVID-19-associated MIS-C as per WHO definition https://www.who.int/news-room/*commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19*.

Preliminary case definition

Children and adolescents 0–19 years of age with fever more than 3 days and two of the following were included:

Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet).

Hypotension or shock.

Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-pro-BNP).

Evidence of coagulopathy (by Prothrombin time (PT), activated partial thromboplastin time (aPTT), and elevated D-dimers).

Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test, or serology positive) or likely contact with patients with COVID-19.

Children who did not conform with COVID-19 were excluded from the study. A written informed consent was obtained from the parents or guardians of the children. The study did not affect the treatment of the patients in any way in case of nonconsent. As the study was retrospective in nature, no ethical clearance was obtained.

Sample size

The study of Ouldali *et al.* [11] observed that 9% in IVIG + methylprednisolone group and 51% in IVIG alone group did not respond to treatment. Taking these values as reference, the minimum required sample size with 90% power of study and 5% level of significance was 20 patients in each study group. So, the sample size taken was 52 (20 patients in one group and 32 in another group).

From the database, the demographic details of the children were noted, which included age and sex. The clinical details

included the number of organs involved, the primary organ, and chief complaints. All of the children underwent investigations, which included the inflammatory markers such as CRP, D-dimer, ferritin, procalcitonin, Lactate dehydrogenase (LDH), fibrinogen, interleukin 6, troponin T, Pro-BNP, serum albumin, and COVID-19 antibodies IgM and IgG. The severity of the disease was classified into KD phenotype, mild, moderate, and severe disease [12] (as per PGI protocol).

The patient's treatment was done as per the PGI protocol [13] where KD phenotype and severe cases of MIS-C were treated with IVIG 2 g/kg along with dexamethasone 0.15 mg/kg body weight and aspirin 3–5 mg per kg per day. Moderate cases of MIS-C were treated with IVIG 2 g/kg along with dexamethasone 0.15 mg/kg body weight and aspirin 3–5 mg/kg per day. Mild cases of MIS-C were given only a combination of dexamethasone 0.15 mg/kg body weight and aspirin. Anticoagulation was given in selected cases.

Respiratory support was given in cases with breathing difficulty. The primary outcomes of the children were noted in terms of ICU stay, requirement of ventilation, requirement of HFNC, and nasal oxygen. The secondary outcomes were changes in the inflammatory levels of CRP and D-dimer and coronary artery dilation.

Statistical analysis

The presentation of the categorical variables was done in the form of number and percentage. On the contrary, the quantitative data with normal distribution were presented as the means ± SD and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). The data normality was checked using Kolmogorov–Smirnov test. The cases in which the data were not normal, we used nonparametric tests. The following statistical tests were applied for the results:

(1) The comparison of the variables such as D-dimer (ng/ml), CRP (mg/dl), and Pro-BNP (pg/ml) in KD phenotype, moderate, and severe; procalcitonin (ng/ml); LDH (IU/l); interleukin 6 (pg/ml); troponin T (pg/ml); COVID antibody IgG (S/CO); and COVID antibody IgM (S/CO) were analyzed using Mann–Whitney Test (for two groups), and Kruskal–Wallis test was used for comparison of age and number of systems involved with severity of MIS-C. CRP (mg/dl) in total study participants; ferritin (ng/ml), fibrinogen (mg/dl), and pro-BNP (pg/ml) in total study participants; and serum albumin (g/dl) were compared using independent *t* test between IVIG given and not given.

(2) The comparison of requirement of ICU stay was analyzed using χ^2 test in total study participants and Fisher's exact test was used for comparison of primary system involved, complaints, sex with severity of MIS-C, and for comparing all outcomes, except ICU stay required, in total study participants. Odds ratio with 95% confidence interval was calculated taking IVIG not given as reference for outcome.

The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was done with the use of Statistical Package for the Social Sciences (SPSS) software, IBM manufacturer, Chicago, Illinois, USA, version 21.0.

For statistical significance, *P* value of less than 0.05 was considered statistically significant.

Results

Among 52 patients enrolled in the study, 25 had mild disease, 17 had moderate disease, eight had severe disease, and two had KD phenotype. The median age of the children was 4 years and comparative analysis showed that higher age was significantly associated with moderate to severe disease and KD phenotype ($P = 0.031$).

The sex distribution showed male to female ratio of 2: 1, with no significant association of sex with severity of the disease ($P = 1$).

The median number of organs involved in all MIS-C types was 1 except for severe disease where the range was 1–3 ($P = 0.0004$).

The primary system involved in the KD phenotype was skin and CVS, whereas in the other types, a plethora of systems were involved, which included cardiovascular, central nervous system, gastrointestinal system, respiratory system, hematological, and skin.

Fever was the commonest complaint as seen in 44 children with other complaints being difficulty in breathing, abdominal pain, vomiting, loose stools, cough, edema, seizures, weakness in the limbs, rashes, and conjunctivitis. There was no significant association of any clinical symptoms with the severity of the disease ($P > 0.05$), as shown in Table 1.

IVIG along with dexamethasone and aspirin was given in all cases with moderate and severe disease and KD phenotype. However, even among those 27 cases, seven cases did not receive IVIG because of financial constraints. So, among the total 52 children, 20 received IVIG and 32 did not receive IVIG.

In comparison with children who did not receive IVIG ($n = 32$), children who received IVIG ($n = 20$) had higher odds of ICU stay [odds ratio (OR) 1.185], ventilation (OR 8.784), need for CPAP (OR 5), and HFNC (OR 3.75), but was statistically insignificant ($P > 0.05$).

The comparison showed that with the use of IVIG there was a significant reduction in the CRP levels (23.3 vs. 5, $P = 0.004$, with an OR of 1.028). Even D-dimer levels were decreased to a great extent with IVIG in comparison with patients who did not receive IVIG (1480 vs. 449.38, $P = 0.148$) but remained statistically insignificant. Moreover, there was no difference in the decrease in the coronary artery diameter after the treatment (Table 2).

Table 1: Distribution of demographic and clinical characteristics in severity of multisystem inflammatory syndrome in children

Demographic and clinical characteristics	KD phenotype (*n*=2) [*n* (%)]	Mild (*n*=25) [*n* (%)]	Moderate (*n*=17) [*n* (%)]	Severe (*n*=8) [*n* (%)]	Total	*P*
Age (years)	8 (6-10)	2 (0.92-4)	7 (3-10)	7.5 (5.5-11.25)	4 (1.75-9)	0.031†
Sex						
Female	0	8 (32)	6 (35.29)	3 (37.50)	17 (32.69)	1*
Male	2 (100)	17 (68)	11 (64.71)	5 (62.50)	35 (67.31)	
Number of systems involved	1 (1-1)	1 (1-1)	1 (1-1)	2 (1-3)	1 (1-1)	0.0004†
Primary system involved						
CVS	1 (50)	0	5 (29.41)	1 (12.50)	7 (13.46)	0.007*
CNS	0	1 (4)	1 (5.88)	3 (37.50)	5 (9.62)	0.071*
GIT	0	7 (28)	5 (29.41)	2 (25)	14 (26.92)	1*
Hematological	0	5 (20)	5 (29.41)	2 (25)	12 (23.08)	0.943*
Respiratory	0	5 (20)	0	0	5 (9.62)	0.128*
Skin	1 (50)	0	0	0	1 (1.92)	0.038*
Complaints						
Fever	2 (100)	18 (72)	17 (100)	7 (87.50)	44 (84.62)	0.088*
Breathing difficulty	0	3 (12)	0	2 (25)	5 (9.62)	0.197*
Abdominal pain	0	3 (12)	4 (23.53)	2 (25)	9 (17.31)	0.683*
Vomiting	0	1 (4)	4 (23.53)	2 (25)	7 (13.46)	0.141*
Loose stools	0	4 (16)	1 (5.88)	0	5 (9.62)	0.634*
Cough	0	6 (24)	1 (5.88)	1 (12.50)	8 (15.38)	0.46*
Edema	0	2 (8)	1 (5.88)	1 (12.50)	4 (7.69)	1*
Seizures	0	2 (8)	2 (11.76)	1 (12.50)	5 (9.62)	1*
Weakness of limbs	0	1 (4)	0	1 (12.50)	2 (3.85)	0.453*
Rash	1 (50)	1 (4)	0	0	2 (3.85)	0.097*
Conjunctivitis	0	0	3 (17.65)	0	3 (5.77)	0.13*

*Fisher's exact test. †Kruskal-Wallis test. CVS, cardiovascular system; CNS, central nervous system; GIT, gastrointestinal system

Table 2: Comparison of outcome between intravenous immunoglobulin given and not given

Outcome	IVIG given (*n*=20) [*n* (%)]	IVIG not given (*n*=32) [*n* (%)]	Total [*n* (%)]	*P*	Odds ratio (95% CI) taking IVIG not given as reference
ICU stay required	7 (35)	10 (31.25)	17 (32.69)	0.779§	1.185 (0.362-3.873)
Ventilator required	2 (10)	0	2 (3.85)	0.143*	8.784 (0.379-203.481)
HFNC required	4 (20)	2 (6.25)	6 (11.54)	0.189*	3.750 (0.618-22.744)
CPAP required	1 (5)	0	1 (1.92)	0.385*	5 (0.183-136.609)
Nasal oxygen required	2 (10)	4 (12.50)	6 (11.54)	1*	0.778 (0.129-4.694)
Decrease in CRP (mg/dl)	23.3 (14.05-60.1)	5 (0.05-11.375)	9.1 (0.2-23.3)	0.004‡	1.028 (1.004-1.053)
Decrease in D-dimer (ng/ml)	1480 (340-5745.75)	449.38 (181.622-1634.5)	847 (177.83-2660)	0.148‡	1 (1-1)
Decrease in left CAD (mm)	0.95 (0.1-1.8)	0.55 (0.1-0.75)	0.7 (0.1-1.425)	0.231	1 (1-1)
Decrease in right CAD (mm)	0.7 (0.475-1.775)	0.5 (0-0.75)	0.6 (0.375-1)	0.138	1 (1-1)

CAD, coronary arterial disease; CRP, C-reactive protein; IVIG, intravenous immunoglobulin. *Fisher's exact test. §χ^2 test. ‡Mann-Whitney test.

Discussion

To our knowledge, this is the first study on Indian children who were admitted to the hospital with MIS-C. Although recommendations include IVIG for KD phenotype and moderate to severe disease, our findings showed that IVIG may be avoided without compromising the prognosis of the patients.

India is a developing country where IVIG is not much in use, and in addition, it is a day care procedure, which is not covered by the insurance companies. Under these circumstances, the procurement of IVIG is not as easy as in the developed countries. In our study, 27 cases needed IVIG based on the international guidelines but only 20 could be given while the rest of the seven could not avail due to financial constraints.

In contrast to the present study, previous studies have mainly focused on the subgroup analysis of IVIG with methylprednisolone versus IVIG alone. As per a recent research letter [14], a treatment, which consisted of IVIG plus corticosteroids, had a better cardiac recovery than the treatment with IVIG alone. This study included 40 children and was a single-center study. Another similar study stated that IVIG and corticosteroids also reduced the hospital stay of patients [15].

Somewhat in line with the present study, recent UK guidelines for MIS-C management [10], based on a Delphi method, with no comparative studies, preferred the use of comparative studies, IVIG only or no treatment at all in few children.

The data with the ongoing pandemic suggest revisions in the recommendations of the use of IVIG. This may be because every child has a different presentation, ethnicity, and clinical course, requiring a tailored pharmacological therapy by the individual treating doctor [13]. Like, we found a significant association of higher age with severe cases of MIS-C and KD phenotype in comparison with mild cases of MIS-C. This was similar to a recent prospective COVID-19 surveillance in children which stated that there is a higher risk in older children of severe disease development [16]. However, no major connections were seen in subgroups analysis of one study (age was the criteria for grouping, ten years or above is the eligibility) [11].

Whether age remains a prognostic factor for the outcomes of children with MIS-C needs further assessment as the sample size was small in our study and other studies. It suggested that IVIG and methylprednisolone together had better efficacy in both younger and older children. However, it needs further studies to confirm the same.

Currently, the corticosteroid is among the approved drugs used to treat respiratory problems in adults with COVID-19 [17,18]. The current study suggests the benefits of using corticosteroids in MIS-C (it is assumed that they inhibit SARS-CoV-2-induced inflammation) similar to IVIG (IVIG exerts anti-inflammatory action by saturation of Fcγ receptor binding, anti-idiotypic binding to antiviral antibodies, and binding of proinflammatory cytokines). It is thought that there are some common paths between MIS-C and severe respiratory adult forms of COVID-19 which led to similar outcomes among patients who were given IVIG and were not given IVIG [19,20]. Further studies are needed to understand that how corticosteroids benefit in severe forms of MIS-C.

It must be stressed here that the use of IVIG caused significant decrease in the inflammation than corticosteroids alone (without IVIG) in terms of CRP; however, it was not confirmed with D-dimer levels. This accounts for the slightly different immunomodulatory action of IVIG (in comparison with corticosteroids) which has led to the current use of IVIG in moderate to severe cases of MIS-C following COVID-19. As COVID-19 is mainly linked with the exuberant inflammatory burden in the acute state, a significant reduction in the inflammation may prove beneficial over long-term outcomes of the patients. This fact needs to be confirmed in the future studies with long-term follow-ups. As in the current scenario, the use of IVIG was without any adverse effects, it may be continued in severe cases of MIS-C and may be optionally avoided by the treating physician depending upon the financial state of the patients without compromising the short-term outcomes.

The study holds strength in validating the findings. as population baseline features like rate of gastrointestinal symptoms, median age, rash, mucocutaneous inflammation signs, or bilateral nonpurulent conjunctivitis were comparable to other MIS-C reports [1,5,21]. The clinical characteristics of the patients under study have been explained previously [2,6,14,22] and are in sync with the literature.

Limitations

There are certain limitations in this study, as the study design was not of a randomized trial. Because of the severity and rarity of MIS-C, it is quite difficult to perform a randomized trial; therefore, it is safe to say such observational methods make the best choice. Second, in each treatment group, patients visited the hospital at different times in the natural run of the disease. In our study, there were limited number of cases, and mild cases did not receive IVIG, and thus larger studies need to be done to document the recommendations of IVIG.

Conclusion

MIS-C is becoming common in children after COVID-19. The changing evidence about the use of IVIG producing similar outcomes to those not using IVIG suggests that low-dose dexamethasone can alone be used in cases of MIS-C irrespective of the severity of the disease. However, considering the significant reduction in the inflammatory marker (CRP) after the use of IVIG in moderate to severe cases, its administration may not totally be negated. The present study can be considered a pilot study in this regard and thus the results need future validation to surmount the upcoming third wave of COVID-19.

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Conflicts of interest

There are no conflicts of interest.

References

1. Whittaker E, Bamford A, Kenny J, *et al.* PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020; 324:259–269.
2. 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:m2094.
3. European Centre for Disease Prevention and Control. Rapid risk assessment: paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. May 15, 2020. Available at: https://www.ecdc.*europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment*. [Accessed August 4, 2021].
4. 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.
5. Dufort EM, Koumans EH, Chow EJ, *et al.* New York State and

Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York state. N Engl J Med 2020; 383:347–358.
6. Belot A, Antona D, Renolleau S, *et al*. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Euro Surveill 2020;25:2001010.
7. 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.
8. Felsenstein S, Willis E, Lythgoe H, *et al*. Presentation, treatment response and short-term outcomes in paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS). J Clin Med 2020; 9:E3293.
9. Jiang L, Tang K, Levin M, *et al*. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020; 20:e276–e288.
10. Harwood R, Allin B, Jones CE, *et al.* PIMS-TS National Consensus Management Study Group. 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 Adolesc Health 2020; S2352-4642:30304–30307.
11. Ouldali N, Toubiana J, Antona D, *et al.* French Covid-19 Paediatric Inflammation Consortium. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA 2021; 325:855–864.
12. Chen MR, Kuo HC, Lee YJ, *et al*. Phenotype, susceptibility, autoimmunity, and immunotherapy between Kawasaki disease and coronavirus disease-19 associated multisystem inflammatory syndrome in children. Front Immunol 2021; 12:632890.
13. 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; 57:101232.
14. Belhadjer Z, Auriau J, Méot M, *et al*. Addition of corticosteroids to immunoglobulins is associated with recovery of cardiac function in multi-inflammatory syndrome in children. Circulation 2020; 142:2282–2284.
15. Jonat B, Gorelik M, Boneparth A, *et al*. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York City: patient characteristics and an institutional protocol for evaluation, management, and follow-up. Pediatr Crit Care Med 2021;22:e178-e191.
16. Ouldali N, Yang DD, Madhi F, *et al.* investigator group of the PANDOR study. Factors associated with severe SARS-CoV-2 infection. Pediatrics 2021;147:e2020023432.
17. Horby P, Lim WS, Emberson JR, *et al.* RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19: preliminary report. N Engl J Med 2021;384:693-704.
18. Sterne JAC, Murthy S, Diaz JV, *et al.* WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020; 324:1330–1341.
19. Arditi M, Bahar I. Multisystem inflammatory syndrome in children in the United States. N Engl J Med 2020; 383:1794.
20. Levin M. Childhood multisystem inflammatory syndrome: a new challenge in the pandemic. N Engl J Med 2020; 383:393–395.
21. Feldstein LR, Rose EB, Horwitz SM, *et al.* Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med 2020; 383:334–346.
22. Bordet J, Perrier S, Olexa C, *et al*. Paediatric multisystem inflammatory syndrome associated with COVID-19: filling the gap between myocarditis and Kawasaki? Eur J Pediatr 2021;180:877-884.