European Review for Medical and Pharmacological Sciences 2022; 26: 3342-3350

Clinical characteristics and treatments of multi-system inflammatory syndrome in children: a systematic review

K.H. LEE[1], H. LI[2], M.H. LEE[3], S.J. PARK[4], J.S. KIM[5], Y.J. HAN[6], K. CHO[3], B. HA[3], S.J. KIM[3], L. JACOB[7,8], A. KOYANAGI[7,9], J.I. SHIN[1], J.H. KIM[10], L. SMITH[11]

[1]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]University of Florida College of Medicine, Gainesville, FL, USA
[3]Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of Pediatrics, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Republic of Korea
[5]Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[6]Department of Pediatrics, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea
[7]Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Barcelona, Spain
[8]Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
[9]ICREA, Pg. Lluis Companys 23, Barcelona, Spain
[10]Department of Pediatrics, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[11]Centre for Health, Performance, and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK

Keum Hwa Lee, Han Li, Min Ho Lee, Se Jin Park, Jae Seok Kim, and Young Joo Han contributed equally to this work as the first authors

Abstract. – OBJECTIVE: Multisystem inflammatory syndrome in children (MIS-C) can occur in association with coronavirus disease 2019 (COVID-19). It is not easy to differentiate MIS-C from severe COVID-19 or Kawasaki disease based on symptoms. The aim of this study was to describe the clinical and laboratory characteristics of MIS-C.

PATIENTS AND METHODS: We searched PubMed/Medline for case series and reports of MIS-C published until June 20, 2020. From a total of nine articles involving 45 cases, various clinical and laboratory data were extracted. Each target case was evaluated by using different diagnostic criteria.

RESULTS: The average age at onset of MIS-C was 8.6 years. In 80% of cases, the age of patients ranged from 5 to 15 years. Fever (100%) and shock (82%) were the most common presenting symptoms. Sixty percent of cases met the diagnostic criteria for typical or atypical Kawasaki disease. Biomarkers indicative of inflammation, coagulopathy, or cardiac injury were characteristically elevated as follows: ferritin (mean: 1,061 ng/mL), CRP (217 mg/L), ESR (69 mm/hr), IL-6 (214.8 pg/mL), TNFα (63.4 pg/mL), D-dimer (3,220 ng/mL), PT (15.5 s), troponin I (1,006 ng/L), and BNP (12,150 pg/mL). Intravenous immunoglobulin was administered in all target cases, and inotropic agents were commonly used as well. No case of death was observed.

CONCLUSIONS: This study demonstrated that MIS-C is a serious condition that presents with fever, rash, as well as cardiovascular and gastrointestinal symptoms. Although it is challenging to differentiate MIS-C from Kawasaki disease or severe COVID-19, initiation of appropriate treatments through early diagnosis is warranted.

Key Words:
Multisystem inflammatory syndrome in children, Kawasaki disease, Intravenous immunoglobulin, Coronavirus disease 2019.

Corresponding Authors: Ji Hong Kim, MD, Ph.D; e-mail: KKKJHD@yuhs.ac
Jae Il Shin, MD, Ph.D; e-mail: shinji@yuhs.ac

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious pediatric complication associated with coronavirus disease 2019 (COVID-19), and it frequently results in intensive care unit (ICU) admission[1]. As a new syndrome, MIS-C is called by various terms: pediatric inflammatory syndrome, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS), or multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.

MIS-C presents with fever, rash, conjunctivitis, coagulopathy, and involvement of various organs, especially gastrointestinal tract and heart. It is also frequently accompanied by symptoms of simultaneous active COVID-19[2]. Laboratory findings are notable for elevated biomarkers for inflammation or coagulopathy, including erythrocyte sedimentation rate (ESR), interleukin (IL)-6, fibrinogen, and D-dimer[1-3]. In particular, it can be associated with cardiac problems, such as coronary aneurysm, myocarditis, acute heart failure, and pericardial effusion[3,4]. While prognosis is favorable, the long-term outcomes of MIS-C remain unknown, and MIS-C sometimes warrants aggressive management, including ICU admission and mechanical ventilation[3]. The fatality rate of MIS-C is reported to be about 1%, and effective treatments to prevent adverse outcomes have not yet been established. Therefore, there is a need to identify and aggregate the current treatments in clinical practice for this condition.

Another challenge to patient care in MIS-C is its diagnosis and differentiation from other similar conditions. The diagnostic criteria for MIS-C from the Centers for Disease Control (CDC) are different from those from the World Health Organization (WHO). According to the CDC, individuals under the age of 21 years who show fever with current or recent COVID-19 are diagnosed with MIS-C when the following criteria are met: elevated inflammatory markers, such as C-reactive protein (CRP) or ESR; involvement of two or more organ systems; and no alternative competing diagnoses[5]. According to the WHO, MIS-C is diagnosed in patients with COVID-19 who are under 19 years of age when two or more of the following conditions are present: (1) rash or bilateral conjunctivitis, (2) hypotension or shock, (3) elevated cardiac markers, (4) coagulopathy, or (5) gastrointestinal problems with elevated inflammatory markers[6]. Since COVID-19 presents with fever, elevated inflammatory markers, as well as multi-organ involvement, it may be difficult to distinguish MIS-C from severe COVID-19[7]. In addition, the clinical manifestation of MIS-C is similar to that of Kawasaki disease (KD), a pediatric autoimmune disease which presents with fever, rash, and conjunctivitis[8], including atypical KD with some but not all diagnostic symptoms of KD[9]. Non-purulent conjunctivitis and skin lesions are more common in MIS-C and KD than in COVID-19, and this is what differentiates them from COVID-19. However, the differentiation of MIS-C from KD is particularly challenging. Due to the significant overlap between MIS-C and KD, their underlying pathophysiology is thought to be similar[10].

Accordingly, we performed a systematic review to investigate the clinical and laboratory characteristics of MIS-C and compare them with those of KD. We aimed to provide clinical practitioners with a summary of the currently applied treatments for MIS-C.

Patients and Methods

Search Strategy

A PubMed search was conducted for articles on COVID-19 patients with concomitant MIS-C that were published until June 20, 2020. The following search terms were used: ("COVID-19" OR "SARS-COV-2" OR "2019-nCoV" OR "novel coronavirus 2019") and ("multisystem inflammatory syndrome" OR "multi-system inflammatory syndrome"). Two investigators (MHL and JIS) separately screened the titles, abstracts, and full texts to determine whether the articles meet the inclusion criteria.

This systematic review was in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. We included the studies which met the following conditions: (1) including children and adolescents with laboratory or clinically confirmed COVID-19; and (2) describing concomitant MIS in infected patients. The exclusion criteria were as follows: (1) review articles, commentary, or letters; and (2) articles with inaccessible full text.

Data Extraction

Two investigators (MHL and JIS) independently extracted and collected the study characteristics (journal title, author names, and year of

publication), demographic characteristics, concomitant MIS or Kawasaki disease, clinical presentations, laboratory values, comorbidities, treatment methods, and clinical outcomes, if available.

Data Analysis

Based on the data extracted from the articles, we organized and summarized the information on the patients' age or sex, concomitant MIS or Kawasaki disease, clinical presentations, laboratory values, co-morbidities, treatments, and clinical outcomes. We evaluated each target case with different diagnostic criteria.

Results

A total of 77 articles were identified by title screening after duplicates were removed. Among them, 68 articles were excluded after reviewing the abstracts and/or full texts: 31 were irrelevant, eight were review articles, 26 were comments or letters, and three did not have enough information. Finally, nine eligible articles involving a total of 45 cases of MIS-C with COVID-19 were identified (Figure 1)[11-19].

Baseline Characteristics of Patients with MIS-C

Baseline characteristics of patients with MIS-C are summarized in Table I. The age at onset was between 5 and 15 years in 80% of cases, with a mean age of 8.6 years. MIS-C occurred at similar frequencies in males (24 cases) and females (21 cases). COVID-19 infection was confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and/or serology. Twenty cases were retrieved from France, 13 from the United States, 10 from Italy, and one each from India and Turkey. When different diagnostic criteria for MIS-C were applied, the CDC criteria were met in all cases and the WHO criteria were met in 43 cases (96%). 27 (60%) cases met the criteria for either typical (n = 6) or atypical (n = 21) KD.

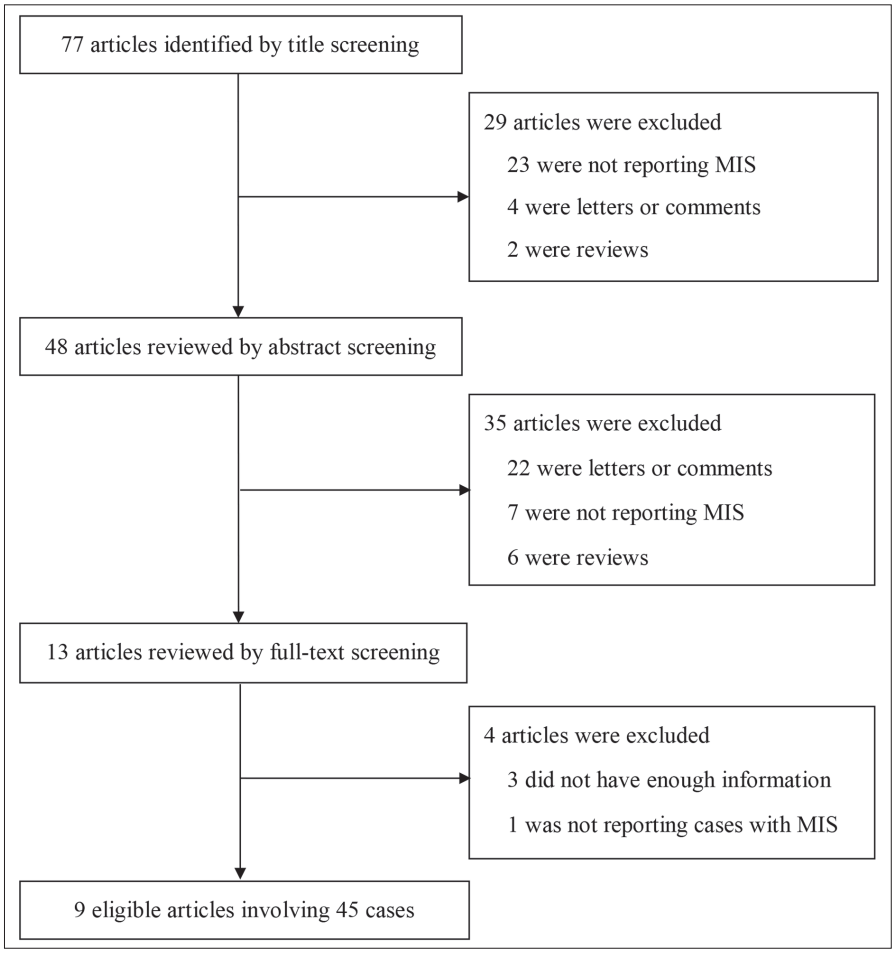

Figure 1. PRISMA flow chart of literature search. MIS, multisystem inflammatory syndrome.

Table I. Baseline characteristics of patients diagnosed with multisystem inflammatory syndrome in children.

Age, sex, and comorbidities		N / Total (%)
Age (years)	0 ~ < 1	1 / 45 (2.2)
	1 ~ < 5	5 / 45 (11)
	5 ~ < 10	23 / 45 (51)
	10 ~ < 15	13 / 45 (29)
	15 ~ 21	3 / 45 (6.7)
Sex	Male	24 / 45 (53)
	Female	21 / 45 (47)
Comorbidities	Hypothyroidism	1 / 1 (100)
	Asthma	1 / 1 (100)
	Crohn's disease	1 / 1 (100)
	Congenital adrenal hyperplasia	1 / 1 (100)
SARS-CoV-2 tests positivity		
Total diagnostic tests	40/45 (89)	
RT-PCR	Total	19 / 42 (45)
	Nasopharynx	16 / 40 (40)
	Stool	2 / 12 (17)
Antibody tests	Total	32 / 34 (94)
	IgA	15 / 15 (100)
	IgG	32 / 34 (94)
	IgM	3 / 10 (30)
Clinical diagnosis by different diagnostic criteria		
MIS-C	By CDC	45 / 45 (100)
	By WHO	43 / 45 (96)
Kawasaki disease	Typical	6 / 45 (13)
	Atypical	21 / 45 (47)

Data are presented as the number of reported cases (N) compared to total cases. RT-PCR: real-time polymerase chain reaction, MIS-C: multisystem inflammatory syndrome in children, CDC: Centers for Disease Control and Prevention, WHO: World Health Organization.

Clinical and Laboratory Characteristics of Patients with MIS-C

Fever was the most common symptom in MIS-C patients. The prominent symptoms other than fever were rash, conjunctivitis, abdominal pain, tachycardia, hypotension, or shock. Lip or tongue symptoms (14 out of 17) and oropharyngeal hyperemia (4 out of 4) were observed in a large proportion of cases reporting the presence of these symptoms. Neurological signs, including headache, altered mental status, and fatigue or pulmonary symptoms, were presented in some cases (Table II).

Abnormal results were frequently observed with routine laboratory measurements and tests for inflammatory and cytokine markers. Each mean value of complete blood count components (CBC) showed anemia, leukocytosis, neutrophilia, or lymphopenia. The mean serum concentrations of creatinine, sodium, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and lactic acid were all elevated. An increase in the mean levels of D-dimer, fibrinogen, and prothrombin time suggested coagulopathy or disseminated intravascular coagulation. The mean levels of biomarkers for acute inflammatory responses, such as ferritin, procalcitonin, C-reactive protein, and erythrocyte sedimentation rate, were all increased. The mean levels of interleukin-6, tumor necrosis factor-α, and natural killer cell count were markedly increased among cases reporting their levels (Table III).

Cardiac Characteristics of Patients with MIS-C

The mean concentrations of cardiac markers, such as troponin T and I and brain-type natriuretic peptide (BNP) or pro-BNP, were all elevated. Thoracic echocardiography demonstrated mitral valve regurgitation (n = 5), pericardial effusion (n = 4), and coronary artery dilatation (n = 5) or aneurysm (n = 2). The mean ejection fraction of

Table II. Clinical characteristics of patients diagnosed with multisystem inflammatory syndrome in children.

Clinical symptoms		N / Total (%) or Mean ± SD (n)
Shock		37 / 45 (82)
Lymphadenopathy		5 / 30 (17)
Fever		45 / 45 (100)
Skin	Rash	24 / 42 (57)
	Edema	5 / 9 (56)
Oral cavity	Lip or tongue symptoms	14 / 17 (82)
	Oropharyngeal hyperemia	4 / 4 (100)
Eye	Conjunctivitis	22 / 40 (55)
GI tract	Abdominal pain	30 / 31 (97)
	Diarrhea	14 / 21 (67)
	Emesis	8 / 9 (89)
	Poor oral intake	3 / 3 (100)
Heart	Tachycardia	25 / 25 (100)
	Hypotension	29 / 34 (85)
CNS	Glasgow Coma Scale	13.5 ± 2.7 (20)
	Meningeal irritation signs	4 / 10 (40)
	Headache	2 / 7 (29)
	Altered mental states	3 / 7 (43)
	Fatigue or drowsiness	4 / 4 (100)
Lungs	Respiratory distress	5 / 7 (71)
	Dry cough	3 / 4 (75)

Data are presented as the number of reported cases (N) compared to total cases, or mean values with standard deviation (SD) and the number of reported cases (n). GI: gastrointestinal, CNS: central nervous system.

the left ventricle was 30.5%. Abnormalities on chest radiograph were also observed in 14 out of 21 cases (Table IV).

Treatments and Outcomes of Patients with MIS-C

Inotropic agents were frequently used in MIS-C (27 out of 38). Among anti-inflammatory agents, IVIG and corticosteroids were administered in 100% and 43% of cases, respectively, whereas agents targeting specific inflammatory cytokines were used in a small number of cases. As an anti-thrombotic or anti-coagulant agent, aspirin was more frequently used than low molecular weight heparin. In some cases, respiratory supports were needed to maintain adequate oxygenation of patients. No death was reported (Table V).

Discussion

It is known that COVID-19 infection tends to be less severe or asymptomatic in pediatric patients[20]. However, a small proportion of pediatric cases with COVID-19 may accompany MIS-C, which may result in rapid clinical deterioration requiring aggressive management[10]. This systematic review aggregated 45 cases across nine articles describing MIS-C cases in association with COVID-19. It mainly shows that MIS-C diagnosis frequently overlaps with either typical or atypical KD diagnosis. Moreover, we have identified, on a more granular level, the specific laboratory values, imaging, and treatments of MIS-C. This study supports the findings of previous systematic reviews describing MIS-C as an inflammatory syndrome characterized by cardiac and gastrointestinal dysfunction[3,8].

According to the current study, MIS-C has different characteristics compared to KD or severe COVID-19. First, MIS-C presents with higher proportions of gastrointestinal and cardiovascular symptoms than respiratory symptoms. We reported only eight cases of respiratory distress or dry cough, as compared to 30 cases with abdominal pain or 29 cases with cardiogenic hypotension. Pneumonia, a defining characteristic of symptomatic COVID-19 in children, was notably absent in all cases[21]. Second, MIS-C occurs more frequently in patients without comorbidities as opposed to COVID-19; in one study, all patients who were admitted to the ICU with COVID-19 had hydronephrosis, leukemia, or intussusception as comorbidities[22].

Although the underlying etiology of MIS-C is unknown, it is hypothesized to occur in a similar fashion to that of KD, due to the surface resemblance between the two diseases[10]. Nevertheless,

Table III. Laboratory characteristics of patients diagnosed with multisystem inflammatory syndrome in children.

Routine laboratory tests		*Mean ± SD (n)*
CBC	Hb (g/dL)	9.6 ± 2.1 (11)
	WBC (/mm^3)	15765 ± 16806 (23)
	Neutrophil (/mm^3)	12461 ± 8373 (20)
	Lymphocyte (/mm^3)	950 ± 1131 (42)
	Platelet count (/mm^3)	177238 ± 82670 (42)
Serum chemistry	Creatinine (mg/dL)	1.78 ± 1.15 (7)
	CCr (mL/min/1.73 m^2)	95.4 ± 45.1 (20)
	Sodium (mmol/L)	131.0 ± 3.7 (38)
	Triglyceride (mg/dL)	239 ± 109 (8)
	Albumin (g/L)	22.6 ± 3.6 (28)
	ALT (IU/L)	65.5 ± 111.0 (42)
	AST (IU/L)	85.6 ± 68.8 (17)
	LDH (U/L)	649 ± 297 (9)
	CPK (IU/L)	84.9 ± 64.1 (10)
	Lactate (mmol/L)	3.40 ± 2.07 (24)
Coagulation	D-dimer (ng/mL)	3220 ± 1145 (21)
	Fibrinogen (g/L)	6.67 ± 1.70 (33)
	PT (sec)	15.5 ± 0.9 (4)
	PT INR	1.49 ± 0.41 (10)
Inflammatory markers		
Acute reactants	Ferritin (ng/mL)	1061 ± 739 (21)
	Procalcitonin (ng/mL)	77.8 ± 120.0 (26)
	CRP (mg/L)	217 ± 143 (45)
	ESR (mm/hr)	69.0 ± 27.2 (16)
Cytokines	IL-1β (pg/mL)	0.8 ± 0.5 (5)
	IL-6 (pg/mL)	214.8 ± 145.5 (15)
	IL-8 (pg/mL)	67.8 ± 46.0 (5)
	TNF-α (pg/mL)	63.4 ± 21.3 (5)
Others	NK cell counts (/mm^3)	62 ± 35 (10)

Data are presented as mean values with standard deviation (SD) and the number of reported cases (n). CBC: complete blood count, WBC: white blood cell, CCr: creatinine clearance, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, PT: prothrombin time, INR: international normalized ratio, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IL: interleukin, TNFα: tumor necrosis factor α, NK cell: natural killer cell.

we found that a significant proportion of MIS-C patients (40%) did not meet the clinical criteria for either typical or atypical KD. This may suggest that, in some patients, MIS-C is driven by different inflammatory mechanisms compared to those observed in KD. Furthermore, our study found

Table IV. Cardiac characteristics of patients diagnosed with multisystem inflammatory syndrome in children.

Cardiology tests		*N / Total (%) or Mean ± SD (n)*
Cardiac markers	Troponin T (ng/mL)	435.4 ± 925.0 (29)
	Troponin I (ng/L)	1006 ± 1860 (9)
	BNP (pg/mL)	12150 ± 17050 (19)
	pro-BNP (ng/L)	1870 ± 2220 (11)
Echocardiography	LVEF (%)	30.5 ± 9.0 (38)
	Mitral valve regurgitation	5 / 12 (42)
	Pericardial effusion	4 / 11 (36)
	Coronary artery dilatation	5 / 7 (71)
	Coronary artery aneurysm	2 / 11 (22)
Abnormalities on chest radiograph	14 / 21 (65)	

Data are presented as the number of reported cases (N) compared to total cases, or mean values with standard deviation (SD) and the number of reported cases (n). BNP: brain-type natriuretic peptide, LVEF: left ventricular ejection fraction.

Table V. Treatment types and outcomes of patients diagnosed with multisystem inflammatory syndrome in children.

Types of treatment		N / Total (%)
Inotropic agents	Total	27 / 38 (71)
	Epinephrine	18 / 26 (69)
	Norepinephrine	6 / 22 (27)
	Dobutamine	6 / 21 (29)
	Dopamine	3 / 3 (100)
	Milrinone	13 / 23 (57)
Anti-inflammatory agents	Corticosteroids	16 / 37 (43)
	IVIG	42 / 42 (100)
	IL-1 antagonist	3 / 22 (14)
	IL-6 antagonist	4 / 23 (17)
	TNF-α antagonist	3 / 3 (100)
Anti-microbial agents	Ceftriaxone	4 / 4 (100)
	Cefepime	6 / 8 (75)
	Vancomycin	7 / 7 (100)
	Clindamycin	4 / 8 (50)
	Metronidazole	3 / 3 (100)
	Hydroxychloroquine	1 / 1 (100)
Anti-thrombotic or anti-coagulant agents	Aspirin	13 / 13 (100)
	Enoxaparin	3 / 3 (100)
Respiratory supports	Non-invasive	13 / 26 (50)
	Invasive	11 / 26 (42)
	High flow nasal oxygenation	2 / 21 (10)
Outcomes		
Death		0 / 45 (0)
Survival		45 / 45 (100)

Data are presented as the number of reported cases (N) compared to total cases. IVIG: intravenous immunoglobulin, IL: interleukin, TNFα: tumor necrosis factor α.

that the majority of patients had gastrointestinal symptoms, as well as overall laboratory abnormalities representing coagulopathy, anemia, and major organ damages such as liver, kidney and heart, all of which are not included in the diagnostic criteria for KD. By including imaging information, we also found that MIS-C can sometimes present with chest abnormalities on X-ray. Previous studies by Hoste et al[23] reported that MIS-C patients meeting the KD criteria had higher rates of lymphopenia, thrombocytopenia, and elevated markers of cardiac injury. Furthermore, those with MIS-C who met the KD criteria had more serious illness overall, with higher rates of shock, coronary dilatation, and aneurysm formation[23]. Collectively, our study demonstrated that MIS-C is a separate etiological entity from KD and may not respond to the same treatments as KD.

We found that the current treatment for MIS-C involved supportive cardiorespiratory care combined with traditional anti-inflammatory agents that are also commonly used for acute KD, including IVIG, corticosteroids, and aspirin[24]. On the other hand, other targeted agents, such as anakinra, tocilizumab, or infliximab, were rarely used. Our study did not aim to identify which therapies are most effective in MIS-C; however, we did demonstrate that the condition is treated in a non-systematic fashion, which derives primarily from KD treatments. As up to 40% of MIS-C patients presented differently than KD, further investigation is warranted to identify effective therapies for MIS-C.

Findings from the present review should be interpreted in light of its limitations. First, we did not aim to evaluate the effectiveness of therapies on disease prognosis. As such, our study is a small retrospective collection of case series that cannot compare the efficacies of interventions. Second, details regarding the disease prognosis and long-term outcomes were also not reported; for example, duration of hospitalization, risk of relapse, and chronic cardiovascular complications were not searched or reported in this review. Third, the majority of cases were obtained from France, Italy, and the United States, with little emphasis

on India or East Asian countries. Finally, due to the small sample size, the results of this study should not be interpreted as definitive, but rather as a driving force for further research.

Conclusions

MIS-C, a serious condition associated with COVID-19 infection, presents with similar clinical features to those of KD, and is often difficult to differentiate from severe COVID-19 itself. However, MIS-C has different characteristics compared to KD or acute COVID-19; and therefore, proper treatment initiation through early diagnosis of MIS-C is recommended. Further investigation is warranted to identify the methods of accurate diagnosis and effective therapies for MIS-C.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Source of Funding

Neither financial support nor any sort of sponsorship was provided for this study.

References

1) Kwak JH, Lee SY, Choi J-, Korean Society of Kawasaki Disease. Clinical features, diagnosis, and outcomes of multisystem inflammatory syndrome in children associated with coronavirus disease 2019. Clin Exp Pediatr 2021; 64: 68-75.
2) Sood M, Sharma S, Sood I, Sharma K, Kaushik A. Emerging Evidence on Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 Infection: a Systematic Review with Meta-analysis. SN Compr Clin Med 2021; 1-10.
3) Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, Acosta S, Naqvi R, Burmeister-Morton F, Burmeister F, Tarriela A, Petershack M, Evans M, Hoang A, Rajasekaran K, Ahuja S, Moreira A. Multisystem inflammatory syndrome in children: A systematic review. E Clinical Medicine 2020; 26: 100527.
4) Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, Auriau J, Grimaud M, Oualha M, Beghetti M, Wacker J, Ovaert C, Hascoet S, Selegny M, Malekzadeh-Milani S, Maltret A, Bosser G, Giroux N, Bonnemains L, Bordet J, Di Filippo S, Mauran P, Falcon-Eicher S, Thambo JB, Lefort B, Moceri P, Houyel L, Renolleau S, Bonnet D. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation 2020; 142: 429-436.
5) Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) | CDC. https://www.cdc.gov/mis/ (accessed July 10, 2021).
6) Multisystem inflammatory syndrome in children and adolescents with COVID-19. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (accessed July 10, 2021).
7) Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, Soma VL, Maddux AB, Mourani PM, Bowens C, Maamari M, Hall MW, Riggs BJ, Giuliano JS Jr, Singh AR, Li S, Kong M, Schuster JE, McLaughlin GE, Schwartz SP, Walker TC, Loftis LL, Hobbs CV, Halasa NB, Doymaz S, Babbitt CJ, Hume JR, Gertz SJ, Irby K, Clouser KN, Cvijanovich NZ, Bradford TT, Smith LS, Heidemann SM, Zackai SP, Wellnitz K, Nofziger RA, Horwitz SM, Carroll RW, Rowan CM, Tarquinio KM, Mack EH, Fitzgerald JC, Coates BM, Jackson AM, Young CC, Son MBF, Patel MM, Newburger JW, Randolph AG. Overcoming COVID-19 Investigators. Characteristics and Outcomes of US Children and Adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA 2021; 325: 1074-1087.
8 Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int 2021; 41: 19-32.
9) Yu JJ. Diagnosis of incomplete Kawasaki disease. Korean J Pediatr 2012; 55: 83-87.
10) Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, Gupta A. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev 2021; 38: 51-57.
11) Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr 2020; 10: 537-540.
12) Rauf A, Vijayan A, John ST, Krishnan R, Latheef A. Multisystem Inflammatory Syndrome with Features of Atypical Kawasaki Disease during COVID-19 Pandemic. Indian J Pediatr 2020; 87: 745-747.
13) Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395: 1771-1778.
14) Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, Fitzgerald JC, Topjian A, John ARO. Multisystem Inflammatory Syndrome

in Children During the Coronavirus 2019 Pandemic: A Case Series. J Pediatric Infect Dis Soc 2020; 9: 393-398.

15) Dolinger MT, Person H, Smith R, Jarchin L, Pittman N. Dubinsky MC, Lai J. Pediatric Crohn Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated with Infliximab. J Pediatr Gastroenterol Nutr 2020; 71: 153-155.

16) Hunt M, Koziatek C. A Case of COVID-19 Pneumonia in a Young Male with Full Body Rash as a Presenting Symptom. Clin Pract Cases Emerg Med 2020; 4: 219-221.

17) Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, Leruez-Ville M, Quartier P, Léger PL, Geslain G, Semaan N, Moulin F, Bendavid M, Jean S, Poncelet G, Renolleau S, Oualha M. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020; 10: 69.

18) Waltuch T, Gill P, Zinns LE, Whitney R, Tokarski J, Tsung JW, Sanders JE. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. Am J Emerg Med 2020; 38: 2246. e3-2246.e6.

19) Yozgat CY, Uzuner S, Bursal Duramaz B, Yozgat Y, Erenberk U, Iscan A, Turel O. Dermatological Manifestation of Pediatrics Multisystem Inflammatory Syndrome Associated with COVID -19 in a 3-Year-Old Girl. Dermatol Ther 2020; 33: e13770.

20) Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. Pediatr Pulmonol 2020; 55: 2565-2575.

21) Carlotti APCP, Carvalho WB, Johnston C, Rodriguez IS, Delgado AF. COVID-19 Diagnostic and Management Protocol for Pediatric Patients. Clinics (Sao Paulo) 2020; 75: e1894.

22) Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, Zhang W, Wang Y, Bao S, Li Y, Wu C, Liu H, Liu D, Shao J, Peng X, Yang Y, Liu Z, Xiang Y, Zhang F, Silva RM, Pinkerton KE, Shen K, Xiao H, Xu S, Wong GWK, Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 Infection in Children. N Engl J Med 2020; 382: 1663-1665.

23) Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr 2021; 180: 2019-2034.

24) Ramphul K, Mejias SG. Kawasaki disease: a comprehensive review. Arch Med Sci Atheroscler Dis 2018; 3: e41-e45.