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Review

Systematic review on the clinical presentation and management of the COVID-19 associated multisystem inflammatory syndrome in children (MIS-C)

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Abstract: Firstly, we collated the vast repository of MIS-C cases and presented them in a simplified, condensed, and comprehensive format. Secondly, we explored the clinical presentation, and efficacy of the management options. Additionally, we briefly discussed the pathophysiology and addressed the variance in the jargon and criteria relating to this condition. *Methods:* A systematic literature review was conducted on the 17th of October 2020 in accordance with PRISMA (2015) guidelines. The search terms: 'MIS-C', 'Kawasaki-like Disease', 'PIMS-TS', and 'COVID-19' were queried on Medline and Embase databases. Publications that fulfilled the inclusion criteria were included and were assessed for parameters pertaining to the clinical course and management. *Results:* From December 2019 to October 2020, 131 publications were identified. Of these, 56 publications (n = 646 patients) fit the inclusion criteria. Median age was 10 years (range: 0.5–17 years), 52.2% (n = 337/646) were male, and 33.5% (n = 128/382) were of African ethnicity. SARS-CoV-2 reverse transcriptase PCR and serology were positive in 42% (n = 142/426), and 85.3% (n = 300/352) of cases respectively. Presenting complaint(s) were predominately gastrointestinal: 77.6% (n = 436/562) generalized abdominal pain, 76.4% (n = 386/505) vomiting, and 63.2% (n = 203/321) diarrhea. Hypotensive shock was also commonly observed at admission. Additionally, laboratory data revealed elevated neutrophils and inflammatory markers. Echocardiogram findings indicated reduced left ventricular ejection fraction and myocarditis in 22.6% (n = 85/376) and 22.3% (n = 84/376) of cases, respectively. Immunoglobulins and intravenous steroids were predominantly used in 76% (n = 433/571) and 51% (n = 317/618) of cases, respectively. Majority of the patients (97%, n = 418/431) were discharged home. A combination treatment of tocilizumab and IVIG had a mean length of stay of 7 ± 3 days and 95.5% (n = 21/22) discharge rate with low complications in

comparison to either of the treatments alone. *Conclusion:* MIC-S syndrome is a pediatric hyperinflammatory condition that has an association with COVID-19 background exposure. MIS-C has a heterogeneous multisystem presentation that can be associated with life threatening cardiac complications. There is a need to further explore its long-term morbidity.

Keywords: COVID-19; pediatrics; multisystem inflammatory syndrome in children (MIS-C); pediatric inflammatory multisystem syndrome (PIMS); Kawasaki like disease

Abbreviations: CRP: C-reactive protein; GI: gastrointestinal; PCR: polymerase chain reaction; IL: interleukin; CK: creatine kinase; LDH: lactate dehydrogenase; ECHO: echocardiogram; ECG: electrocardiogram; CXR: chest x-ray; Abdo U/S: abdominal ultrasound; CT: computed tomography; ESR: erythrocyte sedimentation rate; pro-BNP: pro-b-type natriuretic peptide; BNP: b-type natriuretic peptide; IL-6: Interleukin-6; IL-8: Interleukin-8; TNF Alpha: tumor necrosis factor alpha; INR: international normalized ratio; BUN: blood urea nitrogen; AST: aspartate transaminase; ALT: alanine transaminase; LOS: length of stay; SD: standard deviation; ICH: intracerebral hemorrhage; HF: heart failure; MOF: multi-organ failure; RF: respiratory failure; N/A: not available; HCQ: hydroxychloroquine

1. Introduction

1.1. Background of the COVID-19 pandemic

The first case of COVID-19 was identified in Wuhan, December 2019, after several patients presented with pneumonias of unknown etiology. Subsequently, it rapidly spread across the globe with epicenters identified in both Europe and the United States of America (USA) [1]. On the 11th of March 2020, the World Health Organization declared it as a global pandemic. As of the 17th of November 2020, there are 54826773 million confirmed cases with a global death toll of 1323093 [2]. Initial reports revealed a more severe disease manifestation in adults, particularly in those with underlying co-morbidities, relative to the pediatrics cohort [3,4]. Several theories were proposed to postulate this variance in presentation such as the protective function of the non-atrophied thymus, and the reduced angiotensin converting enzyme (ACE) 2 receptor density in their alveoli [5].

At the advent of April 2020, amidst the rising incidence and prevalence of COVID-19, there emerged new reports of a syndrome characterised by a severe hyperinflammatory reaction in the pediatrics cohort, predominately in Europe and the USA. These patients' clinical presentation mimicked Kawasaki disease and many required admission to intensive care units (ICU) due to shock and multi-organ failure [6]. These findings challenged the initial belief that COVID-19 causes merely a mild respiratory infection in the pediatric population.

1.2. Overlap between Kawasaki disease and the hyperinflammatory syndrome

Kawasaki disease is a medium vessel vasculitis that presents mainly in Asian children less than 5 years of age. The etiology and pathophysiology of Kawasaki disease have not been fully identified to date; proposed hypothesis exist however they are not necessarily universally accepted. It is

postulated to be a post-viral manifestation, where plasma cells produce IgA autoantibodies as part of an immune response to a viral infection. This is thought to be coupled with an imbalance between T-cell subtypes, particularly regulatory T-cells and interleukin (IL)-17 producing T-cells, and an initial CD14+/CD16+ neutrophilic infiltrate followed by dendritic cells, CD163+ monocytes, and CD3/8+ T-cells invasion of coronary vessels contributing to the production of cytokines, coronary artery vasculitis and the formation of coronary artery aneurysms [5,7].

There are similarities in the cytokine storm of both Kawasaki disease and the hyperinflammatory condition that temporally emerged during the current pandemic, however differences in the T-cell subtypes and associated interleukins were documented [5]. Additionally, immune complexes formation and their interaction with the Fcγ receptors on immune cells are thought to play a major role in Kawasaki disease. They promote tissue inflammation and consequent complement depletion and organ failure. To date, no data on the role of immune complex formation in patients with COVID-19 exposure has been published [7].

1.3. Jargon clarification of 'multisystem inflammatory syndrome in children' (MIS-C)

This hyperinflammatory condition is yet to be granted a universally accepted definition and was initially termed 'Kawasaki-like disease'. Currently, it is defined as 'multisystem inflammatory syndrome in children' (MIS-C), by the Centers for Disease Control and Prevention (CDC) in the USA. It is also known as 'Pediatric Multisystem inflammatory syndrome' by the Royal College of Pediatrics and Child Health (RCPCH) in Europe, and as 'Multisystem inflammatory syndrome (MIS) in children and adolescents temporally related to COVID-19' by the World Health Organization [8].

1.4. Diagnostic criteria for the pediatric multisystem inflammatory syndrome (PIMS) and MIS-C

The diagnostic criteria of these conditions are thought to be broad and overlaps with several inflammatory conditions including Kawasaki disease [9]. The main differences between these definitions include: the duration of fever, the means of assessment of exposure to SARS-CoV-2, and the different organs involved as shown in Figures 1 and 2.

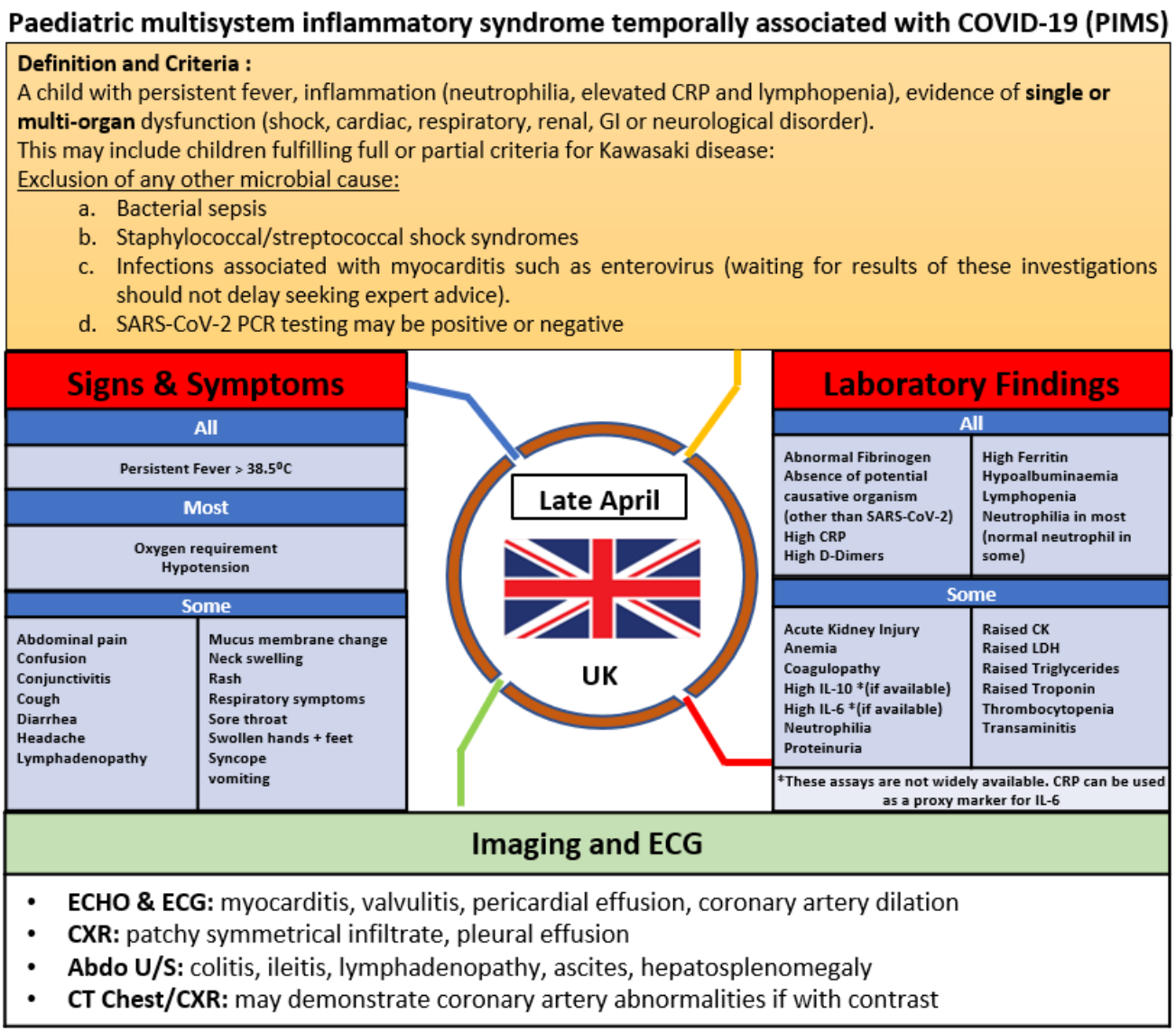

Figure 1. Summary of definitions and diagnostic criteria for the pediatric multisystem inflammatory syndrome (PIMS).

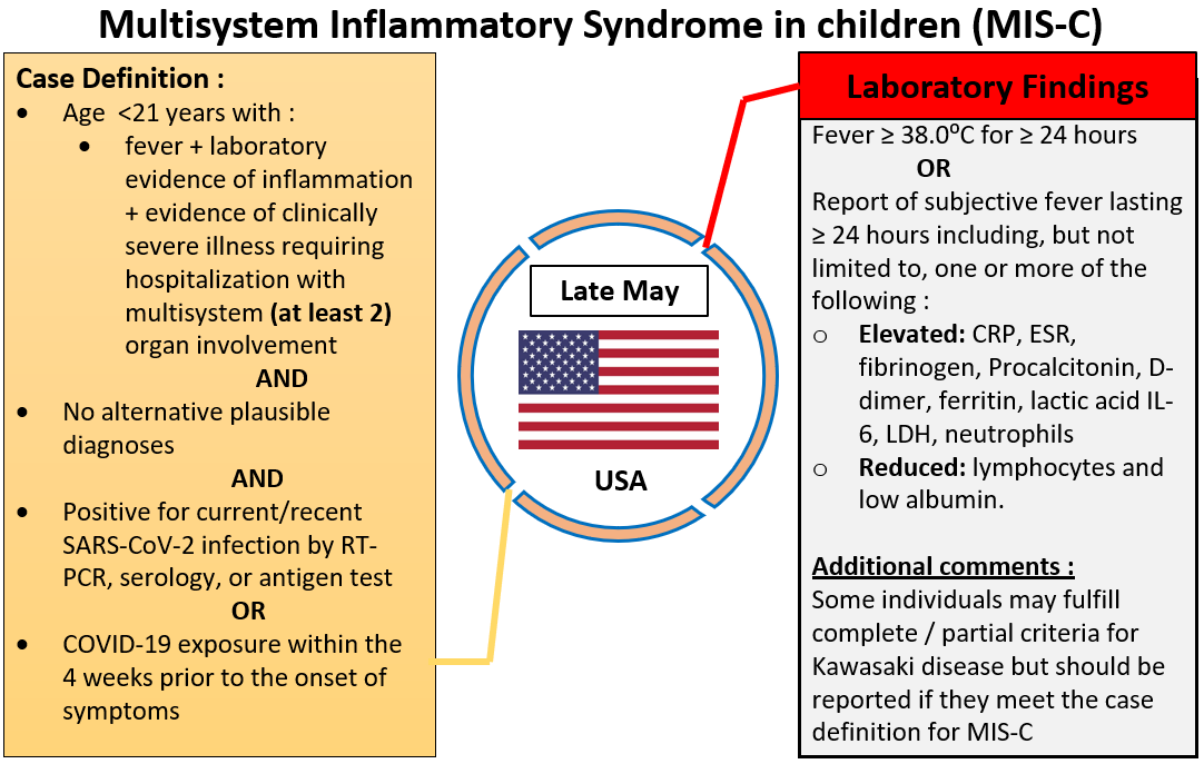

Figure 2. Summary of definitions and diagnostic criteria for the multisystem inflammatory syndrome in children (MIS-C).

The overlap in both the clinical and laboratory features, of atypical Kawasaki and MIS-C resulted in diagnostic uncertainty. This was further complicated by a lack of a diagnostic test for Kawasaki disease and a vast majority of asymptomatic COVID-19 presentations in children implying that a positive SARS-CoV-2 antibody serology or a reverse transcriptase polymerase chain reaction (RT-PCR) does not confirm that the children's presentation is secondary to SARS-CoV-2. Consequently, incorrect diagnosis can potentially be made. However, given the available epidemiological data, SARS-CoV-2 is likely involved with MIS-C but a causality relationship is yet to be confirmed [10].

Therefore, it is prudent to identify and understand the differences in the pathophysiology, clinical presentation, and laboratory investigations between the two conditions to manage patients in the most optimal way possible. Amidst the pandemic, there is a large underlying fear of misdiagnosis, within the pediatrics cohort, of a very serious condition called 'MIS-C'. Major variables influencing the propensity of misdiagnosis are a constant evolution in the definition of the disease and its criteria, the burden on the economic system, and the huge number of papers, that are only case reports, that are not compiled in an easy manner. Hence, we propose, this review to collate all the clinical variables spanning from the history of presentation, observation and physical examination, laboratory investigations, and efficacy of management. This review aims to present clarifications on the immunological understating of the disease and promote the clinical knowledge to identify this serious condition to treat it aptly to reduce morbidity, mortality, and mitigate the burden on the healthcare system.

2. Methods

A systematic literature review was conducted on 17th October 2020 by authors NSI and MSY in accordance with PRISMA (2015) guidelines as shown in Figure 3. This systematic review was independently verified by the authors AAA, CY, and PK. The review was restricted to publications between December 2019 to October 2020. The search terms utilized were 'MIS-C' OR 'Kawasaki-like Disease' OR 'PIMS-TS' AND 'COVID-19' were queried on Medline and Embase databases.

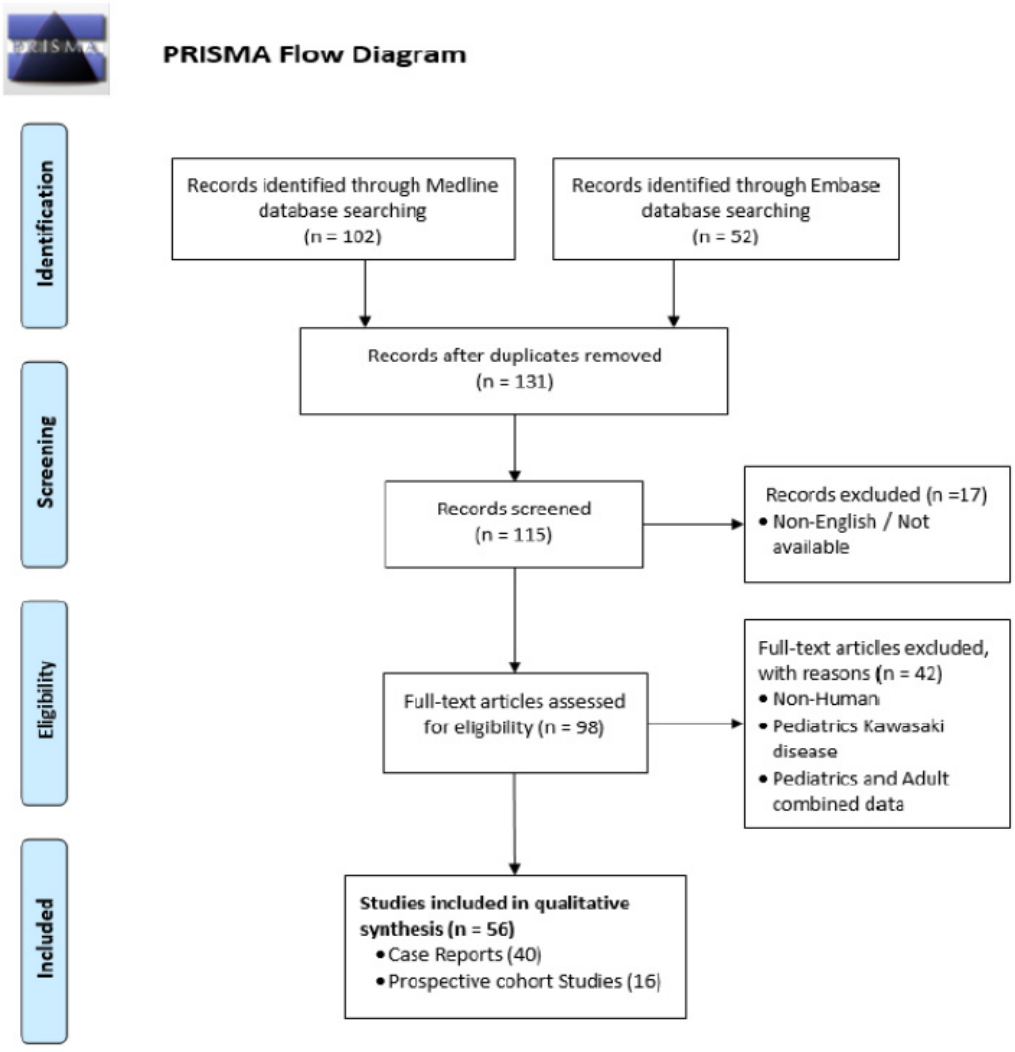

Figure 3. PRISMA flowchart outline the process of the systematic review.

Pediatric patients are defined as <18 years of age at the time of hospital presentation. Publications were excluded if not in English language, inaccessible via digital or local resource, or if the reviews lacked original patient data. Publications that combined pediatric and adult combined results without individualized data were also excluded. Each full-text article was assessed for parameters of the history of presenting complaint, the clinical observations and examination outcomes, investigations performed, and management options and strategies. Additionally, laboratory

values were collated. Short term complications specific to the treatment were analyzed when reported. The collective outcomes were evaluated quantitatively when possible and qualitatively when not.

3. Results

3.1. Demographics

Between April 2020 and October 2020, 646 pediatric patients were diagnosed with MIS-C. The median age was 10 years (range: 0.5–17 years); 52.2% (n = 337/646) were male. Of the 646, 51.1% (n = 330/646) presented in the USA, 21.4% (n = 138/646) presented in the United Kingdom (UK), 8.7% (n = 56/646) presented in France and Switzerland combined, and 18.9 % (n = 122/646) presented in 'other' country as outlined in Table S1. The predominant ethnicity (33.5%, n = 128/382) was African followed by Hispanic/Latino, (28.5%, n = 109/382).

3.2. Clinical symptoms

Among the patient cohort, 99.5% of patients presented with fever (n = 626/629) with a documented median 'max temperature' of 39.4 ℃ (range: 38.2–41 ℃). The median duration of fever before presentation to hospital was 5 days (range: 1–12 days). Predominant presenting complaints documented at the emergency department were gastrointestinal followed by respiratory symptoms. The prevalence of the different presenting complaints is described as below in Table 1.

Table 1. Summary of the analysis of the different presenting complaints (n = 646).

Clinical symptoms		Frequency % (n)*	References
Gastrointestinal	Generalized abdominal pain	77.6 (562)	[4,11–31]
system	Vomiting	76.4 (505)	[4,11–16,21–23,25,28–32]
	Diarrhea	63.2 (321)	[4,11,12,14–17,21,22,25,27,28,30,31,33]
Respiratory	Dyspnea	80 (262)	[4,12,15,16,18,22–24,30,31,34]
system	Coryza	60 (154)	[12,16,21,30,32]
	Cough	55 (177)	[12,17,18,21,26,35–37]
	Sora throat	17 (205)	[4,12,18,19,21,31,37]
	Chest pain	13.6 (155)	[12,16,21,23,34]
Neurological	Headache	30.4 (207)	[12,14,18,21,30–32,36]
system	Irritability	57.4 (21)	[14]
Others	Fatigue	61.5 (91)	[16,18,19,21,22,24,32]
	Myalgia	16.8 (143)	[12,18,19,21]

*(n): Changes indicate the prevalence in those who reported the specific findings.

3.3. Observations & physical examination findings

On physical examination, 49.7% (n = 192/368) were hypotensive; 93.5% (n = 116/124) were tachycardic and 67.3% were tachypnoeic (n = 105/156). On further assessment, several patients

exhibited features of Kawasaki disease, abdominal tenderness, meningeal signs, peripheral oedema, and bilateral crackles on auscultation. The prevalence of the different physical examination findings is described as below in Table 2.

Table 2. Summary of the analysis of the observations and physical examination findings (n = 646).

Observations & physical examination findings		Frequency % (n)*	References
Observations	Hypotension	49.7 (368)	[12,13,15,16,18,19–21,23,24,30,31,33,35,37]
	Tachycardia	93.5 (124)	[12,19–24,28,34,35,37,38]
	Tachypnea	67.3 (156)	[12,13,19,21–24,32,34,35,37,38]
Features of	Polymorphic rash	57.6 (613)	[11–18,20,21,23,24,27,29–31,33,35,36–38]
Kawasaki	Non-exudative bilateral conjunctivitis	52.9 (501)	[11–13,15,21,23,24,27,29,30,34,36–38]
disease	Lip/oral cavity cracking	37 (359)	[12,14,15,21,23,29,33,36–38]
	Hand & feet anomalies	26 (462)	[11,12,14,15,23,27,29,31,33,36–38]
	Pharyngeal erythema	24.1 (137)	[11,13,19,24,31]
	Unilateral cervical lymphadenopathy	13.1 (527)	[12,14,16,29,31,33]
Others	Abdominal tenderness	51.9 (27)	[4,11–18,20,22–31,37]
	Meningeal signs	21.2 (94)	[14,22,28]
	Bilateral crackles on auscultation	15 (40)	[14,35,36]

*(n): Changes indicate the prevalence in those who reported the specific findings.

3.4. Investigations

3.4.1. Laboratory investigations and COVID-19 status

Laboratory values are useful for confirming the diagnosis as well as monitoring the disease progression in the patients. The analysis of laboratory parameters and the COVID-19 status of the patients are described as below in Tables 3 and 4 respectively.

Table 3. Summary of the COVID-19 status of patients (n = 646).

COVID-19 status	Frequency % (n)*	References
Positive SARS-CoV-2 nasopharyngeal PCR	42 (426)	[6,11–22,28–31,33,35,37,39]
Positive SARS-CoV-2 antibody	85.3 (300)	[6,11–17,21–23,25,26,30,31,33,34,38,39]
Elevated IgG only	70.7 (123)	[12,16,22,23,25,33,34]
Elevated IgA only	1.62 (2)	[12,16,33]
Elevated IgG and IgM	6.5 (123)	[12,16,33]
Elevated IgG and IgA	21.2 (123)	[12,16,33]
Exposure to COVID-19 within 4 weeks of the onset of symptoms	40.1 (182)	[13,14,16,17,33]

*(n): Changes indicate the prevelance in those who reported the specific findings.

Table 4. Summary of the quantitative and qualitative analysis of the various laboratory parameters (n = 646).

Laboratory parameters		Qualitative: frequency % (n)*	Quantitative: median (range) (n)*	References
Complete blood count	Leukocytosis (K/uL)	95% (116)	15.5 (3.6–23) (112)	[15,16,19,22,26,31,33,36–38]
	Neutrophilia (K/uL)	95% (115)	13 (4.4–19) (108)	[15,16,22,26,27,31,33,36–38]
	Lymphopenia (K/uL)	85% (235)	1.2 (0.09–16) (197)	[4,11–13,15,19,22–27,31–33,35, 37,38]
	Thrombocytopenia (K/uL)	47% (71)	153 (42–516) (47)	[11,13,21,27,30,33,36]
Inflammatory markers	CRP (mg/mL)	99% (391)	185.5 (3.19–390) (377)	[4,6,11–13,16–28,30–34,35,37–39]
	ESR (mm/hr)	82% (142)	53 (13–77.5) (108)	[4,11–13,20,22,24,27,30,32–34, 35,37,38]
	Procalcitonin (ng/L)	93% (225)	6.5 (0.11–99) (183)	[6,12,13,16,18,19,21,26,30,32]
Markers of cardiac function	Troponin (ng/mL)	77% (254)	22.6 (0–2228) (195)	[4,11–13,15,16,19,21–23,25,26, 28,30–33,35]
	Pro-BNP (pg/mL)	96% (208)	3180 (410–14255) (200)	[12,13,15,18,19,25,27,31]
	BNP (pg/mL)	77% (88)	388 (19–12166) (63)	[4,11,13,21,22,25,26,30]
Acute phase reactants	Ferritin (ng/mL)	90% (302)	596.8 (90–7791) (273)	[4,6,11–13,15,17–19,21,23,25, 26,31–34,35–37]
	LDH (U/L)	24% (103)	320 (248–1291) (24)	[11,12,19,26,32,35,36]
	D dimers (ng/mL)	96% (352)	3578 (320–24500) (328)	[4,6,12,15–23,26,26,30–34,35, 36,39]
Cytokines	IL-6 (pg/mL)	96% (197)	156 (30.5–1449) (189)	[12,13,15,16,18–21,26,27,29,33, 34,37,39]
	IL-8 (pg/mL)	100% (46)	44.6 (9.4–54.4) (45)	[13,20,21]
	TNF alpha (pg/mL)	95% (19)	30.1 (10.7–68.7) (13)	[21,21,30]
Coagulation profile	Prothrombin time (s)	67% (42)	17 (15–21) (20)	[4,11,19,30,32,35]
	Fibrinogen (mg/dL)	88% (214)	595 (22–1109) (183)	[4,11–13,19,20,22,26–28,30,31, 33]
Renal function	Creatinine (mg/dL)	23% (73)	0.6 (0.3–2) (16)	[11,13,19,22,32]
	BUN (mg/dL)	31% (35)	12 (8–143) (12)	[11,13,19,23,26,35]
	Hyponatremia (mEq/L)	73% (15)	132 (129–161) (15)	[27,33,37,38]
Liver function tests	AST (U/L)	76% (76)	48 (27–239) (58)	[4,11,13,20,26,32–33,35]
	ALT (U/L)	35% (43)	51 (21–176) (15)	[4,11,13,20,26,32–33,35]
	Hypoalbuminemia (g/dL)	53% (124)	3 (1.9–4.3) (72)	[12,20,21,22,33,35,37,38]

*(n): changes indicate the prevalence in those who reported the specific findings.

3.4.2. Radiological investigations

Of the 227 patients with reported data, 86.7% (n = 197/227) had a chest x-ray (CXR) performed. Majority of the CXR findings included ground glass opacification and pleural effusions. These findings were further confirmed and validated by computed tomography of the thorax (CT-T) which was performed in 45% of patients (n = 27/60).

To assess cardiac involvement, 93.8% (n = 439/468) of patients received echocardiography (ECHO); findings mainly included: left ventricular systolic dysfunction with a median ejection

fraction of 40% (range: 30–55%), myocarditis, and coronary aneurysms. The qualitative analysis of the different CXR and ECHO findings is described as below in Table 5.

Table 5. Summary of the qualitative analysis of the various CXR and ECHO findings (n = 646).

Radiological investigations		Frequency % (n)*	References
CXR	Ground glass opacification	44.2 (104)	[11–14,21,28,33,39]
	Pleural effusion	15.4 (104)	[11–14,21,33]
	Mono/bilateral infiltrates	14.4 (104)	[11–14,33]
	Cardiomegaly	12.5 (104)	[11–14,24,30,33]
	Interstitial abnormality	7.7 (104)	[11–14,24,30,33]
	Others	5.8 (104)	[4,11–14,21,33]
ECHO	Left ventricular systolic dysfunction	22.6 (376)	[11–16,19,30,31,33,39,40]
	Myocarditis	22.3 (376)	[11–16,30,31,33,39,40]
	Coronary artery aneurysm	20.2 (376)	[11–16,30,31,33,39,40]
	Pericardial effusion	17.8 (376)	[11–16,21,30,31,33,39,40]
	Coronary artery dilation	9.3 (29)	[11–16,30,31,33,39,40]
	Mitral regurgitation	4.5 (376)	[11–16,21,24,30,31,33,39,40]
	Others	3.2 (376)	[11–16,21–23,25,30,31,33,35,39,40]

*(n): Changes indicate the prevalence in those who reported the specific findings.

3.5. Management

The management of the patients included pharmacological interventions and organ support in the Pediatric Intensive Care Unit (PICU). Generally, patients that required organ support were admitted to PICU amounting to 75% (n = 333/445) of the patients.

3.5.1. Medications

In terms of pharmacological management, majority of patients received intravenous immunoglobulins (IVIG). Furthermore, intravenous steroids were administered in 51% (n = 317/618). Further breakdown of the type of steroids used is described in Table 6.

Aspirin was used in 59% (n = 91/153) as either an anti-inflammatory or anti-platelet agent or both.

Given the overlap of the presentation of MIS-C with that of bacterial infections, 68% (n = 169/248) received empiric antibiotics; ceftriaxone was the most used antibiotic. An exhaustive list of the primary, secondary, and tertiary choices of antibiotics is available in the Tables S2–S5. Due to the prominence of hemodynamic instability, intravenous fluid boluses were administered in 48% (n = 21/44). Additionally, inotropes were administered in 51% (n = 287/571) due to refractory hypotension. Further analysis of the pharmacological management is available in Table 6.

Table 6. Summary of the pharmacological intervention in patients (n = 646).

Pharmacological therapy		Frequency % (n)*	References
-	Intravenous Immunoglobulins	76 (571)	[6,11–16,19,21–24,26–28,30–33,34,37,39]
-	Hydroxychloroquine	5 (40)	[22,36]
Anti-retroviral	Remdesivir	90 (31)	[11,13,19,21]
	Lopinavir	3 (31)	[36]
	Acyclovir	3 (31)	[32]
	Ritonavir	3 (31)	[36]
Intravenous steroids	Methylprednisolone	2 (317)	[19,22,26,27,35]
	Hydrocortisone	4 (317)	[30]
	Type not specified	9 (317)	[6,11,12,14,15,29–31,33,39,41]
Anticoagulants	Enoxaparin	86 (212)	[11,16,17,19,22,29,30,35]
	Oral anticoagulant	14 (212)	[13,19]
Antiplatelet	Aspirin	59 (153)	[6,13,14,21,24,25,27,30,33,34,37–39]
Biologics	Tocilizumab	81(62)	[13,19,21,22,29,30,36,37]
	Infliximab	19 (62)	[6,15,20,29,31,34]
	Anakinra	11 (380)	[11,13,16,21,29,31]
Inotropes and vasopressors	Dopamine	5 (287)	[6,11–14,16,21,22,29,31,33,41]
	Epinephrine	3 (287)	[6,11–14,16,21,24,29,31,33,35,41]
	Norepinephrine	7 (287)	[6,11–14,16,21,24,29,31,33,35,41]
	Phenylephrine	0.3 (287)	[6,11–14,16,24,29,31,33,41]
	Milrinone	2 (287)	[6,11–14,16,19,21,24,29,31,33,41]
	Vasopressin	2 (287)	[6,11–14,21,29,31,33,41]
	Dobutamine	4 (287)	[13]
Diuretics	Furosemide	33 (73)	[13,19,24,35]

*(n): Changes indicate the prevalence in those who reported the specific findings.

3.5.2. Respiratory support

Respiratory support played a crucial part in the management of patients. The different modes of respiratory support utilized are described in Table 7.

Table 7. Summary of the various modalities of respiratory support utilized (n = 646).

Respiratory support	Frequency % (n)*	References
Mechanical ventilation	30 (583)	[13,14,16,21,22,34,35,36]
Noninvasive ventilation	57 (109)	[11,13,16,17,21,22,41]
Nasal cannula	43 (109)	[11–13,16,17,41]
Extracorporeal membrane oxygenation (ECMO)	5 (305)	[6,13,16,21,29,31,34,36]

*(n): Changes indicate the prevelance in those who reported the specific findings.

3.6. Complications & outcome

Complications developed over the course of admission are described in Table 8. Overall, 97% (n = 418/431) progressed well and were discharged; median length of stay was 8 days (range: 3–14 days). Of the 431 patients, 3% (13/431) deceased.

Table 8. Summary of the complications developed over the course of admission (n = 646).

Complications	Frequency % (n)*	References
Heart failure	23 (75)	[16,26,35,36]
Hypoxia	15 (40)	[22,28,35,36]
Renal failure	15 (225)	[11,12,22,28,31,34–36]
Disseminated intravascular coagulation	3 (40)	[36]
Intracerebral hemorrhage	5 (4)	[32]

*(n): Changes indicate the prevelance in those who reported the specific findings.

Table 9 shows the outcomes of immunomodulation in the MIS-C patients treated with combinations of biologics (n = 24/40 tocilizumab, n = 2/40 anakinra, and n = 3/40 infliximab) and immunoglobulins (n = 31/40 IVIG, n = 2/40 convalescence plasma). Maximal data was available from the co-treatment group of biologics and immunoglobulins. Further analysis of this group did not yield any statistically significant outcomes due to low sample number (Table S6).

Table 9. The outcomes in the treatment groups with and without biologics and immunoglobulin therapy (n* = 40).

Treatments	LOS in days: mean ± SD	Outcomes	Complications	Conclusion & caveats	References
Biologics OR Immunoglobulin (n = 13)	9 ± 3	84.6% discharge, 15.4% deceased	ICH (n = 2), HF (n = 2), MOF (n = 2)	Longest LOS of the 3 treatment groups. More single organ failures. LOS data not available in 2 patients.	[4,20–22,24,26, 28,30,32,34]
Biologics AND Immunoglobulin (n = 22)	7 ± 3	95.5 % discharge, 4.5% deceased	RF (n = 1), MOF (n = 1)	Medium LOS of the 3 treatment groups. Best outcomes with the highest ratio of discharged/deceased. Low complication rates. LOS data not available in 4 patients.	[19,21–23,27, 30,30,36,37]
NEITHER Biologics OR Immunoglobulin (n = 5)	6 ± 2	80% discharge, 20% deceased	MOF (n = 2)	Lowest LOS but outcomes are poor with the lowest ratio of discharged/deceased. Sample size is the smallest.	[22,25,30,35,38]

*(n): Changes indicate the prevalence in those who reported the specific findings.

4. Discussion

In this systematic review, we describe 646 patients with MIS-C. These patients fulfilled the CDC criteria of fever, multi-organ involvement with a severe clinical presentation, and no other possible diagnosis with evidence of SARS-CoV-2 infection on RT-PCR, serological testing, or exposure to COVID-19 within 4 weeks of onset of symptoms [42].

The median age of patients was 10 years (range: 0.5–17 years). Most of the patients were of African and Hispanic ethnicity. This contrasts with the demographic distribution associated with Kawasaki disease; age <5 years, Asian ethnicity, and Pacific Island decent [9]. Epidemiological differences indicate that they have distinct aetiologies and are associated with different pathophysiological and immunological processes. MIS-C syndrome has a heterogeneous clinical presentation as evident from the frequency distribution of the various presenting symptoms. The predominant presenting complaint was of gastrointestinal symptoms and the second most common presentation was with respiratory symptoms. It is thought that the pulmonary manifestation in children is less severe than that in adults due to a relatively lower ACE-2 receptor expression. In adults, ACE-2 receptors are highly expressed on type II alveolar cells and are a target of the SARS-CoV-2 virus. These receptors act as the portal of entry for the virus facilitating the release of its RNA into lung cells [5,43]. Interestingly, ACE-2 receptors are also found in different parts of the body including the brush border membrane of the small intestine enterocytes. Given the predominant presentation with gastrointestinal symptoms in children, this raises the question as to whether children have a relatively higher level of ACE-2 receptor density on enterocytes. Despite that not being tested to date, a recent study in adults revealed differences in the expression of the receptors in the different age groups; perhaps a similar pattern exists in children [44]. A second plausible theory relates to differences in the expression of amino acid transporters between the adult and the pediatric population; this can have an impact on the proteolytic action of ACE-2 and consequently can affect the susceptibility of SARS-CoV-2 to infect enterocytes [44]. Furthermore, it is suggested that gastrointestinal symptoms are possibly due to intestinal ischemia secondary to the vasculitis of bowel vessels [14].

SARS-CoV-2 nasopharyngeal RT-PCR was positive in less than 50% of the patient cohort. On the contrary, majority tested positive for SARS-CoV-2 antibodies. Further analysis revealed that the predominating antibody was IgG and occasionally patients had dual antibody elevation (IgG and IgA or IgG and IgM) while no patient had an isolated IgM increase. Therefore, both the production of immunoglobulins by intraepithelial lymphocytes and the higher ACE-2 receptor density on gut enterocytes, relative to the alveolar cells, can possibly explain both the laboratory findings and clinical presentations. In fact, serological findings suggest that MIS-C is likely a post-viral manifestation rather than an early immune response to an acute infection. This further complicates the attempt to distinguish it from Kawasaki disease as they seem to share a similar pathophysiological timeline. Additionally, both conditions are associated with an increase in IgA antibodies; the initial immune response is likely activated in intestinal or respiratory mucosa and thus an elevated IgA antibody level is justifiable in both conditions [45].

Further analysis of laboratory investigations revealed leukocytosis with neutrophilic predominance coupled with thrombocytopenia and a significant elevation in inflammatory markers. These findings were accompanied with an elevation of inflammatory cytokines, transaminases, LDH, ferritin, and D-dimers. All of which are consistent with a cytokine storm implying a possible defect

in the innate immune system contributing to the manifestation of fever, neurological signs and symptoms, polymorphic rash, and significant coagulopathy. This can escalate to multiple organ failure and death [46]. The constellation of elevated cytokines mediated an increase in vascular permeability causing fluid leakage into the extravascular compartment contributing to the distributive shock seen in our patient cohort. Furthermore, the initial activation of macrophages and the resultant stimulation of T-helper cells resulted in a significant production of pro-inflammatory cytokines perpetuating the recruitment of further monocytes, macrophages, neutrophils, B-cells/plasma cells and the production of antibodies [47]. This contributed to the evolution of the delayed hyperinflammatory syndrome seen in the pediatric population.

It is prudent to note that the cytokine storm seen in patients with MIS-C has a different profile to that associated with either Kawasaki disease or adults with acute COVID-19 infection. This is attributed to the different T-cell subpopulations and their corresponding frequencies [5].

On closer assessment of CD 4+ T-cells, the patient cohort with MIS-C and mild SARS-CoV-2 infection had a similar pattern of distribution [5]. However, when compared to the cohort with Kawasaki disease, patients with COVID-19 infection (mild or MIS-C) had a higher prevalence of the effector and central memory CD4+ T-cells and less naïve and follicular helper T-cells [5]. Additionally, pediatric patients with MIS-C were found to have fewer total T-cell frequencies when compared to healthy children [5]. This validated COVID-19 as the culprit for the differences seen relative to healthy patients.

In our review, the most common findings on ECHO were left ventricular systolic dysfunction (heart failure) and myocarditis. The extent of myocardial damage was further corroborated by an elevated troponin and pro-BNP/BNP in a large proportion of our patient cohort. The coronary arteries were spared in most of our MIS-C patients demonstrating the possibility that coronary arteries are not commonly affected in the early stages of the syndrome. Our findings mirrored the findings of key European studies by Verdoni et al and Belhadjer et al. where no aneurysms were diagnosed on presentation or during admission [33,46]. Follow up would be required to better understand the long-term impact of MIS-C on coronary arteries; due to the burden on the healthcare system during the pandemic no such studies are available. Future studies need to validate long term scope of disease. It is important to note that coronary artery aneurysms and coronary artery dilation are two distinct phenomena. The latter is merely a physiological response to increased oxygen demand implicated by a hyperinflammatory state [48]. Contrastingly, myocarditis appears to be a common early manifestation that develops secondary to the recognized COVID-19 associated systemic vasculitis [7]. The presentation with myocarditis in the context of a normal ejection fraction is subclinical and resolves as the inflammation subsides [48]. However, myocarditis, in children with reduced ejection fraction, presents severely with cardiovascular shock secondary to myocardial dysfunction and is coupled with a decrease in the peripheral vascular resistance secondary to the production of pro-inflammatory cytokines as discussed earlier [14].

In our analysis, a broad range of pharmacological therapies were used. Given the possible overlap with severe bacterial infection and septic shock, patients were empirically started on broad spectrum antibiotics, most commonly ceftriaxone. Generally, it is recommended to liaise with the microbiology team and the local antimicrobial guidelines to guide antibiotic choice. Additionally, adjunct treatment with anti-inflammatory and immunomodulatory agents, in addition to IV fluids and inotropic support, were initiated particularly in children that presented with profound shock. This included: IVIG, corticosteroids, aspirin, in addition to the IL-6 monoclonal antibody, tocilizumab,

and anakinra, an IL-1 receptor antagonist. Occasionally, some children were treated with infliximab, a TNF-alpha blocker. Studies have demonstrated that TNF-alpha levels in children with MIS-C are lower than in adults with COVID-19. Also, levels are not significantly different from healthy children [5]. Therefore, infliximab might not be the most suitable agent to suppress the hyperinflammatory state. Our data analysis revealed a TNF-alpha elevation in 95%. However, data was documented in only 19 patients, hence limited conclusions can be extrapolated. Our analysis also showed that the mean length of stay with both biologics such as tocilizumab and immunoglobulins such as IVIG was 7 ± 3 days. This combination treatment had a better outcome of 95.5% (n = 21/22) discharge and lower complications than either treatment alone. More studies with higher sample size are required to validate this observation.

Overall, the pediatric patients in our review responded to both anti-inflammatory and immunomodulatory agents indicating that the manifestation of disease is primarily secondary to the hyperinflammatory state mediated by the immune detection of the virus rather than the virus itself. Furthermore, the massive cytokine production and neutrophilic infiltration of tissue, that forms extracellular traps to control further spread of SARS-CoV-2 infection, contributes to the histopathognomic systemic microangiopathy and thrombosis exhibited in MIS-C [7]. Therefore, as was the case in our review, thromboprophylaxis use is prudent. Most of our patients were discharged home with appropriate therapy and early detection of MIS-C.

5. Conclusions

Our systematic review collated all case reports and article reviews on patients admitted with MIS-C and highlighted both its heterogeneous presentation and evaluated the management options. As the pandemic evolves, it is prudent to continue to study and collate further patient data to identify the circulating immune cells profile and better understand the significance of the varying immunoglobulin levels and their association with prognosis in the post-infection phase. Additionally, further data on the role of IL-1 receptor antagonist as a possible adjunct or replacement to IVIG in patients with acute myocarditis and hemodynamic instability is needed.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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