ORIGINAL ARTICLE

https://doi.org/10.1590/1984-0462/2023/41/2021267

Multisystem Inflammatory Syndrome in Children (MIS-C) temporally related to COVID-19: the experience at a pediatric reference hospital in Colombia

Síndrome inflamatória multissistêmica em criança associada à COVID-19: experiência em um hospital pediátrico de referência na Colômbia

Diego Alejandro Lozano-Espinosa[a]*, Germán Camacho-Moreno[a,b], Juan Francisco López-Cubillos[a], Adriana Soraya Díaz-Maldonado[a], Oscar Javier León-Guerra[c], Diego Mauricio Galvis-Trujillo[a], Roy Sanguino-Lobo[a], Oscar Guillermo Arévalo-Leal[a], Ana María Eraso-Díaz del Castillo[a], María Fernanda Reina-Ávila[a], Vicky Carolina Cárdenas-Hernández[b], Gabriela Ivankovich-Escoto[d], Adriana H Tremoulet[e], Rolando Ulloa-Gutiérrez[d]

ABSTRACT

Objective: This study aimed to describe the clinical characteristics and the different phenotypes of children with multisystem inflammatory syndrome in children (MIS-C) temporally related to COVID-19 and to evaluate the risk conditions that favored a greater severity of the disease during a 12-month period at a pediatric reference hospital in Colombia.

Methods: A 12-month retrospective observational study of children under the age of 18 years who met criteria for MIS-C.

Results: A total of 28 children presented MIS-C criteria. The median age was 7 years. Other than fever (100%) (onset 4 days prior to admission), the most frequent clinical features were gastrointestinal (86%) and mucocutaneous (61%). Notably, 14 (50%) children had Kawasaki-like symptoms. The most frequent echocardiographic abnormalities were pericardial effusion (64%), valvular involvement (68%), ventricular dysfunction (39%), and coronary artery

RESUMO

Objetivo: Descrever as características clínicas e os diferentes fenótipos de crianças com síndrome inflamatória multissistêmica na criança temporalmente relacionada com a COVID-19 (do inglês *multisystem inflammatory syndrome in children* — MIS-C) e avaliar as condições de risco que favorecem a maior gravidade da doença durante um período de 12 meses em um hospital pediátrico de referência na Colômbia.

Métodos: Estudo retrospectivo de 12 meses de observação de crianças menores de 18 anos que cumprem os critérios para o MIS-C.

Resultados: Vinte e oito crianças foram apresentadas com os critérios do MIS-C. A idade média era de sete anos, e 54% eram do sexo masculino. Para além da febre (100%) (com início quatro dias antes da admissão), as características clínicas mais frequentes eram gastrointestinais (86%) e mucocutâneas (61%). Quatorze crianças (50%) apresentavam sintomas semelhantes aos

*Corresponding author. E-mail: dialoes26@gmail.com (D. A. Lozano-Espinosa).
[a]Fundación Hospital Pediátrico La Misericordia, Bogotá, Colombia.
[b]Universidad Nacional de Colombia, Bogotá, Colombia.
[c]Hospital Cardiovascular de Cundinamarca, Bogotá, Colombia.
[d]Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", San José, Costa Rica.
[e]University of California San Diego, Kawasaki Disease Research Center, San Diego, CA, United States.
Received on August 12, 2021; approved on April 14, 2022.

abnormalities (29%). In addition, 75% had lymphopenia. All had at least one abnormal coagulation test. Most received intravenous immunoglobulin (89%), glucocorticoids (82%), vasopressors (54%), and antibiotics (64%). Notably, 61% had a more severe form of the disease and were admitted to an intensive care unit (median 4 days, mean 6 days); the severity predictors were patients with the inflammatory/MIS-C phenotype (OR 26.5; 95%CI 1.40–503.7; p=0.029) and rash (OR 14.7; 95%CI 1.2–178.7; p=0.034). Two patients had macrophage activation syndrome.
Conclusions: Coronary artery abnormalities, ventricular dysfunction, and intensive care unit admission were frequent, which needs to highlight the importance of early clinical suspicion.
Keywords: COVID-19; Multisystem inflammatory syndrome; Kawasaki disease; Ventricular dysfunction; Multiple organ failure; Child.

de Kawasaki. As anomalias ecocardiográficas mais frequentes foram derrame pericárdico (64%), envolvimento valvar (68%), disfunção ventricular (39%) e anomalias coronárias (29%). Tinham linfopenia 75% das crianças. Todas tinham algum teste de coagulação anormal. A maioria recebeu imunoglobulina intravenosa (89%), glucocorticoides (82%), vasopressores (54%) e antibióticos (64%). Tiveram envolvimento mais grave 61% dos pacientes, que precisaram ser internados em unidade de terapia intensiva (mediana de quatro dias, média de seis dias); os preditores de gravidade foram pacientes com fenótipo inflamatório/ MIS-C (*odds ratio* — OR 26,5; intervalo de confiança — IC95% 1,4–503,7; p=0,029) e erupção cutânea (OR 14,7; IC95% 1,2–178,7; p=0,034). Dois pacientes (7%) apresentavam síndrome de ativação macrofágica.
Conclusões: Alteração da artéria coronária, disfunção ventricular e internação na unidade de terapia intensiva foram frequentes, o que nos alerta sobre a importância da suspeita clínica precoce.
Palavras-chave: COVID-19; Síndrome inflamatória multissistêmica; Doença de Kawasaki; Disfunção ventricular; Falência de múltiplos órgãos; Crianças.

INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic has affected children less severely than adults.[1] However, some pediatric cases have required admission to the pediatric intensive care unit (PICU), mechanical ventilation (MV), and cardiorespiratory support.[2] The first cases in Italy, the United Kingdom, and Spain were raised toward the end of April 2020, and in May, researchers in the United Kingdom declared the first eight pediatric patients epidemiologically related to SARS-CoV-2 who presented a more severe illness requiring admission to the PICU.[3] Later on, other cases were reported in the United States and Europe among children with SARS-CoV-2 infection, fever, elevated inflammatory markers, and organ dysfunction, who had Kawasaki disease-like features, toxic shock syndrome (TSS), and macrophage activation syndrome (MAS) described in rheumatic entities.[2-7] The Centers for Disease Control and Prevention (CDC-USA), World Health Organization (WHO), and Royal College of Paediatrics and Child Health (RCPCH) defined this entity as multisystem inflammatory syndrome in children (MIS-C) temporally associated with SARS-CoV-2.[8-10] A cytokine storm following SARS-CoV-2 infection, associated with immunoglobulin G (IgG) and endothelial involvement, has been related to the physiology of this entity.[11] While it is true that there are fewer Latin American publications, an increasing number of cases have been reported in the region.[12-19]

The objective of this study was to describe the clinical and epidemiological characteristics and the different phenotypes of children with MIS-C and to evaluate the risk conditions associated with the worst prognosis and disease severity over a 12-month period at a pediatric reference hospital of a Latin American country with middle income (Colombia).

METHOD

A retrospective chart review was performed of patients under the age of 18 years who met the WHO criteria for MIS-C and were seen between April 1, 2020, and March 31, 2021, at a pediatric reference hospital in Bogotá, Colombia, South America (Fundación Hospital Pediátrico La Misericordia [HOMI]). The clinical variables included in the analysis were age, nutritional status (malnutrition or overweight/obesity), comorbidities, duration of fever, gastrointestinal and respiratory symptoms, mucocutaneous characteristics (e.g., erythema and chapping of the lips, strawberry tongue and/or erythema of the oral and pharyngeal mucosa, conjunctival injection, erythema and edema of hands and feet, periungual desquamation, and cervical adenopathy), and the MIS-C phenotype. Cases with Kawasaki-like symptoms and MAS were identified. Laboratory findings included the results of SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) and antigen tests (nasopharyngeal aspirate; STANDARD Q Test),

as well as IgG/IgM antibodies (immunodiffusion and chromatography) and laboratory tests. The chest X-ray and echocardiogram findings were described, as well as the treatment and degree of severity, defining those patients with greater severity of the disease when they presented shock, the need for invasive mechanical ventilation (IMV), noninvasive ventilation (NIV), or vasopressor support requiring admission to the PICU. The research protocol was presented to the Research Committee of the HOMI-Fundación Hospital Pediátrico La Misericordia for review and approval.

MIS-C was defined according to current WHO criteria.[9] Some authors have tried to classify MIS-C into phenotypes according to the predominant clinical characteristics. Harwood et al proposed classifying MIS-C cases into a Kawasaki-like phenotype and other nonspecific inflammatory phenotypes.[20] Whittaker et al proposed a strategy of subdivision into an inflammatory febrile phenotype, a Kawasaki-like disease phenotype, and an inflammatory phenotype with shock.[2] A third strategy defined by Godfred-Cato et al subdivides into three groups: Class 1: greater multiorgan involvement; Class 2: predominantly respiratory symptoms; and Class 3: similar to Kawasaki disease.[21] In this study, the MIS-C cases were classified into three distinct clusters of clinical phenotypes: inflammatory/MIS-C phenotype (characterized by a cytokine storm, with greater organ involvement shock, gastrointestinal symptoms, elevated inflammatory markers, and cardiovascular compromise), a predominantly respiratory phenotype, and a Kawasaki-like phenotype.

Secondary hemophagocytic lymphohistiocytosis (sHLH), known in literature more commonly as macrophage activation syndrome (MAS), was defined according to the following findings: persistent fever; hepatosplenomegaly; generalized lymphadenopathy; neurological involvement; hemorrhagic features; pancytopenia; elevated ferritin, hepatic enzymes, lactate dehydrogenase (LDH), and triglycerides, with reduced levels of fibrinogen; and possible hemophagocytic macrophages on bone marrow biopsy or aspiration,[22] based on the criteria proposed in 2004 and the availability of resources at our hospital.[23] Left ventricular systolic function was evaluated using the left ventricular ejection fraction (LVEF) estimated by the Simpson Biplane Method, with a value <54% considered to be low.[24] To facilitate comparisons with other published series,[25] LVEF was classified as >50% and ≤50%. Coronary artery dilation was defined as a Z-score between 2.0 and 2.4, and coronary aneurysm as a Z-score ≥2.5.[26] Patients with Kawasaki-like symptoms were defined according to the 2017 American Heart Association (AHA) criteria.[26] Two devices were used for the echocardiographic study: the Philips Affiniti 70cv and the Philips CX50 for portable studies.

In the descriptive analysis of the quantitative data, the following were calculated for each variable: median, average, interquartile range (IQR 25–75), and range, as applicable. Qualitative variables were presented as frequencies or percentages. The data were collected on Excel spreadsheets. The differential analysis sought to explain a greater severity of the disease, understood as those patients with shock, need for IVM and NIV or vasopressor support requiring admission to the PICU (dependent variable), using binary logistic regression models. The differences between frequencies were evaluated using chi-square or Fisher's exact test, as applicable. Differential analysis used 95% confidence intervals (CI). A logistic regression model was performed from the construction of the multivariate model after identifying significant variables that were entered into a multivariate model based on a methodology that assembles the best model according to the importance of each variable and clinical coherence, in addition to the decision criteria AIC (Akaike Information Criterion) and BIC (Bayesian Information Criteria) that compare and choose the best model that makes fewer errors in the projection of the results. Sensitivity and specificity (ROC curve) were then evaluated. An odds ratio (OR) was calculated as a measure of association between the independent variables and the dependent variable. All the statistical tests were two-tailed, with a significance level of $p<0.05$. The data were analyzed using the Stata 14 statistical package (StataCorp LP., USA).

RESULTS

A total of 672 children with a laboratory-confirmed diagnosis of SARS-CoV-2 infection were hospitalized between April 1, 2020, and March 31, 2021 (12 months). In the study period, 28 (4.2%) cases were diagnosed with MIS-C, with an average of 2.3 cases per month. The median age of the study population was 7 years (mean 8 years), most of the children were between 6 and 17 years of age (64%), and 3 (11%) cases were under 1 year old. Notably, 54% were male patients (Table 1). The main comorbidities found were overweight (18%), obesity (7%), malnutrition (14%), and systemic lupus erythematosus (7%). All had fever, with a median duration of 4 days prior to admission (mean 5 days). Notably, 24 (86%) children had gastrointestinal symptoms and 13 (46%) had some respiratory symptoms, of whom 8 (29%) had pneumonia. Mucocutaneous features were common (61%). Again, 14 (50%) patients had Kawasaki-like symptoms (median 6 years, mean 7.9 years; incomplete criteria 11/14, 79%), of whom 4 (28%) had coronary abnormalities. In addition, 17 (61%) cases had shock and 2 (7%) patients met the criteria for MAS. With regard to the MIS-C classification, 36% of the cases had inflammatory/

Table 1. Social and clinical characteristics of MIS-C cases (n=28).

Characteristics	Median (IQR) or n (%)
Age in years	7 (4–12.7)
Age classification (years)	
<2	3 (11)
2–5	7 (25)
6–11	9 (32)
>11	9 (32)
Sex	
Male	15 (54)
Female	13 (46)
Comorbidities	
Malnutrition	4 (14)
Overweight	5 (18)
Obesity	2 (7)
Prematurity (history of)	1 (4)
Asthma	1 (4)
Systemic lupus erythematosus	2 (7)
Purpura fulminans	1 (4)
Symptoms	
Fever	28 (100)
Fever on admission (days)	4 (3–5)
Total duration of fever (days)	5 (4–6)
Gastrintestinal symptoms	24 (86)
Abdominal pain	18 (64)
Vomiting	20 (71)
Diarrhea	10 (36)
Mucocutaneous symptoms	17 (61)
Rash	15 (54)
Edemas/desquamation	10 (36)
Conjunctival injection	11 (39)
Changes in the oral mucosa	6 (21)
Cervical adenopathy	1 (4)
Respiratory symptoms	13 (46)
Cough	12 (43)
Dyspnea	8 (29)
Rhinorrhea	4 (14)
Pneumonia	8 (29)
Joint features	5 (18)
Arthritis	2 (7)
Arthralgias	5 (18)
Kawasaki-like symptoms	14 (50)
Macrophage Activation Syndrome	2 (7)
Inflammatory/MIS-C phenotype	10 (36)
Respiratory phenotype	8 (28)
Kawasaki-like phenotype	10 (36)

MIS-C phenotype, 26% had predominantly respiratory phenotype, and 36% had Kawasaki-like phenotype (median 8, 10.5, and 5.5 years; mean of 8.7, 8.8, and 6.4 years, respectively). Inflammatory/MIS-C phenotype had shock (90%), abdominal pain (90%), and ventricular dysfunction (50%). Notably, 88% of the cases in predominantly respiratory phenotype had cough and 50% had pneumonia. In addition, 70% of the patients in Kawasaki-like phenotype had mucocutaneous features and 30% had ventricular dysfunction (Figure 1).

In this study, 24 RT-PCR samples and 10 anti-SARS-CoV-2 IgG samples were analyzed, of which 67% (16/24) and 90% (9/10) were positive, respectively. Seven children had both RT-PCR and antibody tests; three had positive results on both tests, and three had a negative RT-PCR and a positive IgG. An 8-year-old patient had negative results in both tests; however, due to the high suspicion for the age greater than 5 years, the anomalies of the coronary arteries and ventricular dysfunction, and the recent epidemiological contact with a family member with COVID-19, he was considered suspicious of MIS-C, although it could also have been a case of Kawasaki disease. Altogether, 54% of the D-dimer levels (15/28) were higher than 3,000 ng/mL. Of note, 89% (25/28) of the fibrinogen results were elevated. Also, 100% of the children had at least one elevated inflammatory marker, such as CRP, procalcitonin, and ferritin, and 17% (4/24) of the troponins and 57% (4/7) of the brain natriuretic peptides (BNP) were elevated. In addition, 75% (21/28) of the cases had lymphopenia (Tables 2–4).

Intravenous immunoglobulin (IVIG) was administered to 25 (89%) of 28 patients (2 g/kg), and 2 of them required a second dose due to persistent fever. A total of 23 (82%) children received glucocorticoids, of which 19 (83%) received dexamethasone (median 0.15 mg/kg/day and 7 days, mean 0.17 mg/kg/day and 6.5 days) and 5 (22%) received methylprednisolone (30 mg/kg/dose for 3 days). Two patients received dexamethasone and methylprednisolone and four children received prednisolone. Notably, 64% were anticoagulated with dalteparin (median 100 IU/kg/dose, mean 122 IU/kg/dose), taking a more than five-fold elevation of D-dimer above the reference value as a criterion. In addition, 11 (39%) children received antiplatelet drugs such as acetylsalicylic acid (ASA) and 18 (64%) patients received antibiotics. The median length of hospital stay was 10 days (mean 14 days). Also, 61% of the cases had a more severe disease involvement for which they were admitted to the PICU (median 4 days, mean 6 days). Three (11%) patients required IMV and four (14%) required NIV. Also, 54% required some type of vasopressor. One patient died (4%) (Table 3).

The most frequent findings on chest X-rays included ground-glass opacities (48%) and bilateral opacities (40%). A total of

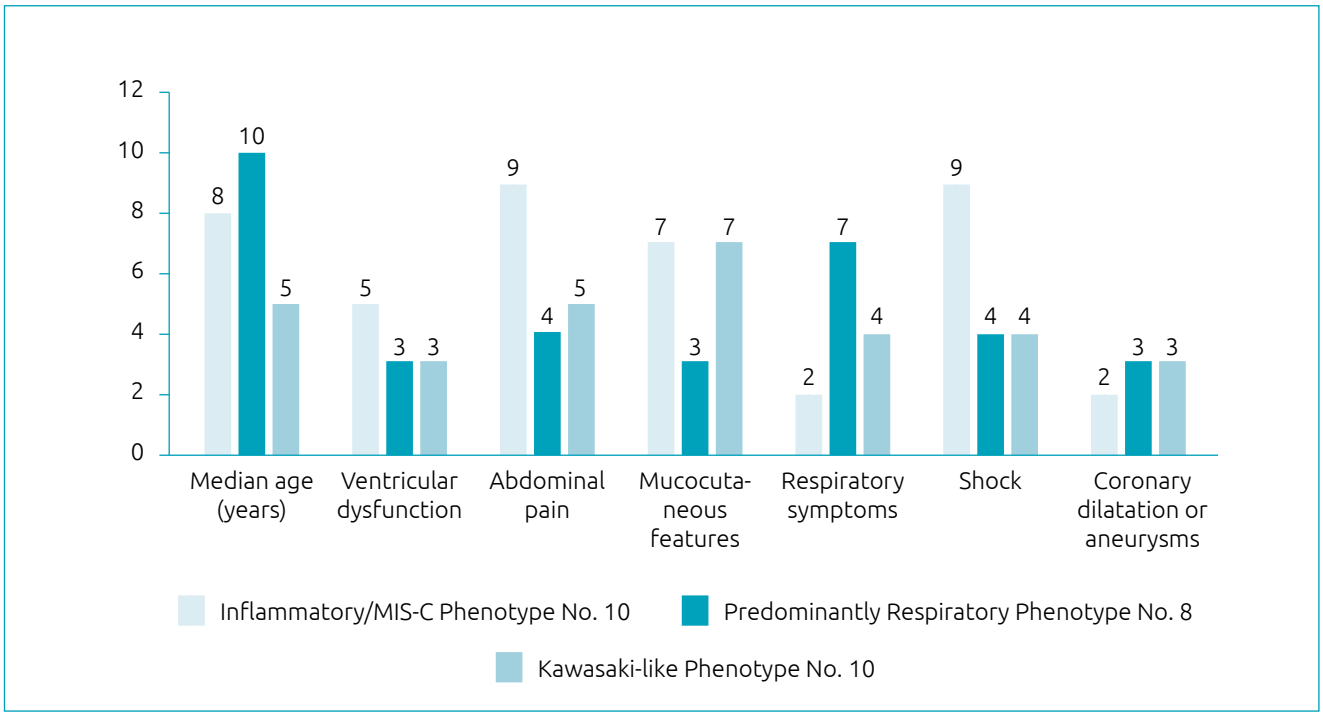

Figure 1. Multisystem inflammatory syndrome in children (MIS-C) temporally related to COVID-19: phenotypes and clinical features (n=28).

8 (29%) patients had abnormal coronary arteries: 5 (18%) had aneurysms, 6 (21%) had coronary dilation, and 3 (11%) had both abnormalities. The most frequently affected coronary arteries were the circumflex artery, left coronary artery, and proximal right coronary artery. Of the 8 children with coronary artery involvement, 7 (88%) had echocardiographic resolution at discharge. In addition, 68% had valvular involvement and 64% had pericardial effusion. The median LVEF in all patients (including those admitted to the PICU) was 60.5% (mean 58%). Notably, 39% developed left ventricular dysfunction (median LVEF 48%, mean 45%). Patients with an LVEF ≤50% made up 39% of the whole series and 58% of those with echocardiographic abnormalities. Sinus tachycardia was the most frequent electrocardiographic disorder (36%) (Table 3).

On bivariate analysis, the conditions associated with greater severity of the disease with a $p<0.05$ were rash (p=0.003), anemia (p=0.022), procalcitonin >1 ng/mL (p=0.018), use of antibiotics (p=0.003), need for oxygen (p=0.006), pericardial effusion (p=0.000), Kawasaki-like symptoms (p=0.007), and inflammatory/MIS-C phenotype (p=0.041) (Table 4). On multivariate analysis, the logistic regression model found that the following predictor variables of worse prognosis and severity of the disease: inflammatory/MIS-C phenotype (OR 26.5; 95%CI 1.4–503.7; p=0.029) and rash (OR 14.7; 95%CI 1.2–178.7; p=0.034).

DISCUSSION

This is one of the first studies on MIS-C in Colombia. Although several studies have been published on this entity since the first reports in the United States and Europe,[2-7] and more recently in Latin America,[12-19] it continues to be a diagnostic challenge in middle-income countries such as Colombia. From the beginning of the pandemic to June 26, 2021, 4,126,340 COVID-19-positive cases were reported in Colombia, 337,702 (8.1%) of whom were under the age of 18 years.[27] Up to June 19, 2021, 6,057 cases of MIS-C had been reported in the Americas, but there was significant underreporting in Colombia, with only 8 cases.[28] In contrast, in the present study, of the 672 COVID-19-positive children seen at the hospital in the 12-month period of the study, 28 (4.2%) were diagnosed with MIS-C. The highest number of cases occurred in July/August/September 2020 (15/28, 54%) and December 2020/January 2021 (7/28, 25%), coinciding with the peak of viral circulation in Colombia.

The age at onset was like to that found by Torres et al., in Santiago, Chile[12] (median 7 years vs. 6 years), as well as the length of hospital stay (median 10 days vs. 9 days). Most of the children were over the age of 5 years, similar to what Feldestein et al. reported in the United States.[5] The median duration of fever on admission was 4 days, which we consider to be relatively late and could be explained by the parents' fear of going to the emergency department during pandemic times,

Table 2. Admission lab tests and results of MIS-C cases (n=28).

Lab tests	Total	Median (IQR) or n (%)
SARS-CoV-2 RT-PCR	24	Positive 16 (67)
SARS-CoV-2 antigen	3	Positive 0 (0)
SARS-CoV-2 IgG	10	Positive 9 (90)
SARS-CoV-2 IgM	10	Positive 0 (0)
Recent contact (COVID-19)	28	Positive 11 (39)
Hemoglobin (g/dL)	28	9.7 (8.8–11.6)
Leukocytes (count ×10^9/L)	28	11 (6.1–13.6)
Lymphocytes (count ×10^9/L)	28	0.8 (0.6–2.4)
Neutrophils (count ×10^9/L)	28	7.9 (3.8–11.3)
Platelets (count ×10^9/L^3)	28	200 (100.7–343.7)
Albumin (g/dL)	25	2.5 (2.1–3)
Lactate (mg/dL)	25	2 (1.6–2.3)
LDH (U/L)	27	306 (255–421)
Triglycerides (mg/dL)	17	232 (154–339)
AST (U/L)	28	58 (42–112)
ALT (U/L)	28	62 (39–101)
Bilirubin (mg/dL)	22	0.7 (0.5–1.03)
Creatinine (mg/dL)	26	0.4 (0.3–0.7)
BUN (mg/dL)	26	15.5 (10.5–25)
CRP (mg/L)	28	275 (130–375)
ESR (mm/h)	21	40 (39–55)
Procalcitonin (ng/mL)	20	4.7 (1.4–11.6)
Ferritin (ng/mL)	27	386 (238–756)
Troponin (ng/mL)	24	100 (54–559)
BNP (pg/mL)	7	287 (67–1,260)
D-Dimer (ng/mL)	28	3,021 (1,721–6,118)
Fibrinogen (mg/dL)	28	993 (808–1,385)
PT (s)	28	14.8 (13.5–15.9)
PTT (s)	28	34 (31–38.8)

LDH: lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine transaminase (ALT); BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BNP: brain natriuretic peptide; PT: prothrombin time; PTT: partial thromboplastin time.

difficulties in accessing the healthcare system, and, possibly, a lack of recognition of the disease by primary care physicians. Overweight and obesity had a frequency similar to other studies.[5,19] Studies in the United States[5,7] reported a higher percentage of PICU admissions than our study (80% vs. 61%), although other studies published in Latin America show a lower frequency (21–59%).[12,15]

Other than fever, which presented in all cases, gastrointestinal symptoms were the most frequent. While gastrointestinal features are prevalent in MIS-C,[2,29] it is important to rule out other more frequent causes of fever, abdominal pain, vomiting, and diarrhea in children, such as gastrointestinal infection.[30] Feldestein et al.[5] reported a similar frequency of gastrointestinal and mucocutaneous involvement as our study.

Acute kidney injury occurred less frequently than in other studies (14% vs. 17–67%).[2,5,19] Most of the cases of Kawasaki-like symptoms were in children over the age of 5 years, unlike classic Kawasaki disease.[26] The proportion of coronary abnormalities in all patients and the subgroup of cases with Kawasaki-like symptoms was slightly higher than in other MIS-C studies (29% vs. 5–22%)[2,4,5,7,15,25] and close to what is reported in classic Kawasaki disease (25%).[26] The MIS-C cases in our study were classified into three groups or phenotypes, with a greater proportion of shock, abdominal pain, and ventricular dysfunction in inflammatory/MIS-C phenotype, significantly associated with greater severity of the disease given the multiorgan compromise requiring greater vasopressor support and IMV with PICU admission, while predominantly respiratory phenotype had a higher frequency of cough and pneumonia and children in Kawasaki-like phenotype had more mucocutaneous features with less ventricular dysfunction. The common findings on laboratory tests included a high proportion of lymphopenia, anemia, and neutrophilia. Thrombocytopenia was present in 39% of the series and in 64% of children with Kawasaki-like symptoms, in contrast to the higher proportion of thrombocytosis seen in classic Kawasaki disease.[26] The inflammatory, hematological, and coagulation involvement found in our study does not differ from other series.[6,16] Feldestein et al.[5] reported 70% positivity for SARS-CoV-2 (RT-PCR 39% and antibodies 31%), with a somewhat lower frequency than we found (67% and 90%, respectively). SARS-CoV-2 antibodies were run in less than half of the cases, as the hospital began to process them in October 2020.

Thus far, left ventricular dysfunction has been one of the greatest cardiac complications in MIS-C patients[3-7] and was a significant finding in our study. There were more cases with LVEF ≤50% than those found by Pignatelli et al.[25] (39% vs. 11%). A local study (Colombia) of 78 children with MIS-C in 14 PICUs found a significant frequency of shock (87%) and cardiac dysfunction (19%), with greater mortality (9%) compared to studies in higher income countries, probably explained by greater cardiovascular involvement coupled with difficulties in accessing the healthcare system in countries with limited resources like ours.[19] This study showed a greater frequency of

Table 3. Cardiac imaging, studies, treatment, and clinical outcomes of MIS-C cases (n=28).

Characteristics	Tests or patients/total	Median (IQR) or n (%)
Echocardiograms		
Abnormal echocardiogram	28	19 (68)
VEF (%)		60.5 (49–67)
VEF >50%		17 (61)
VEF ≤50%		11 (39)
Ventricular dysfunction		11 (39)
Valvular involvement		19 (68)
Pericardial effusion		18 (64)
Abnormal coronary arteries		8 (29)
Coronary aneurysms		5 (18)
Coronary dilation		6 (21)
Electrocardiograms		
Sinus tachycardia	11	4 (36)
Abnormal repolarization		2 (18)
Supraventricular tachycardia		1 (9)
Normal		4 (36)
Chest X-ray		
Ground-glass opacities	25	12 (48)
Bilateral opacities		10 (40)
Pleural effusion		8 (32)
Consolidations		5 (20)
Treatment		
Antibiotics	28	18 (64)
Antiplatelets		11 (39)
Anticoagulation		18 (64)
IVIG		25 (89)
IVIG, 2 doses		2 (8)
Glucocorticoids		23 (82)
Clinical outcomes		
Hospitalization (days)	28	10 (9–15) range 1–56
ICU admission		17 (61)
Days in ICU		4 (2–5) range 1–45
Need of oxygen		18 (64)
Invasive mechanical ventilation		3 (11)
Non-invasive ventilation		4 (14)
Shock		17 (61)
Vasopressors		15 (54)

VEF: ventricular ejection fraction; IVIG: intravenous immunoglobulin; ICU: intensive care unit.

Table 4. Characteristics of the study population and conditions associated with greater severity (PICU admission).

Characteristics	Severe/critical cases (admitted to PICU; n=17), n (%)	Non-severe cases (not admitted to PICU; n=11), n (%)	p-value
Abdominal pain	10 (59)	8 (73)	>0.05
Vomiting	10 (59)	10 (91)	>0.05
Cough	7 (41)	5 (45)	>0.05
Rash	13 (76)	2 (18)	**0.003**
Leukocytosis (according to age)	6 (35)	3 (27)	>0.05
Neutrophilia (according to age)	10 (59)	4 (36)	>0.05
Lymphopenia (<1,500 mm^3)	15 (88)	6 (55)	>0.05
Anemia (according to age)	16 (94)	6 (55)	**0.022**
Thrombocytopenia (<150,000 mm^3)	7 (41)	4 (36)	>0.05
Hypoalbuminemia (<3 g/dL)	14/15 (93)	8/10 (80)	>0.05
Lactate >2 mg/dL	8/16 (41)	2/3 (67)	>0.05
Lactate dehydrogenase (>295 U/L)	9/16 (56)	6/11 (55)	>0.05
Hypertriglyceridemia (>150 mg/dL)	8/10 (80)	5/7 (71)	>0.05
Elevated transaminases	16 (94)	7 (64)	>0.05
Acute kidney injury	4 (24)	0 (0)	
C-reactive protein >100 mg/L	16 (94)	8 (73)	>0.05
Procalcitonin >1 ng/mL	14/14 (100)	3/6 (50)	**0.018**
Ferritin >500 ng/mL	9 (53)	2/10 (20)	>0.05
D-Dimer >3,000 ng/mL	10 (59)	5 (45)	>0.05
Elevated fibrinogen >600 mg/dL	15 (88)	10 (91)	>0.05
Ground glass (chest X-ray)	10 (59)	2 (18)	>0.05
Consolidation (chest X-ray)	5 (29)	0 (0)	
Pleural effusion (chest X-ray)	7 (41)	1 (9)	>0.05
Ventricular dysfunction	11 (65)	0 (0)	
Valvular involvement	14 (82)	5 (45)	>0.05
Pericardial effusion	16 (94)	2 (18)	**0.000**
Coronary abnormalities	6 (35)	2 (18)	>0.05
Antibiotics	15 (82)	3 (27)	**0.003**
Antiplatelets	7 (41)	4 (36)	>0.05
Glucocorticoids	16 (94)	7 (64)	>0.05
Anticoagulation	13 (76)	5 (45)	>0.05
Intravenous immunoglobulin	16 (94)	9 (82)	>0.05
Shock	17 (100)	0 (0)	
Oxygen	14 (82)	3 (27)	**0.006**
Invasive mechanical ventilation	3 (18)	0 (0)	
Vasopressors	15 (88)	0 (0)	
Kawasaki-like symptoms	12 (71)	2 (18)	**0.007**
Macrophage activation syndrome	0 (0)	2 (18)	
Inflammatory/MIS-C phenotype	9 (52)	1 (9)	**0.041**
Respiratory phenotype	4 (24)	4 (36)	>0.05
Kawasaki-like phenotype	4 (24)	6 (55)	>0.05

Data expressed in number (%). Bold indicates statistically significant values.

shock; however, these were critically ill patients exclusively hospitalized in the PICU, unlike our study. Most cases received IVIG and glucocorticoid treatment with a favorable response similar to that found by other authors[5,6,12]; however, it is important to mention that more recent studies have not found a significant difference in recovery after treatment with IVIG alone, IVIG with glucocorticoid, or glucocorticoid alone (BATS study).[31] Our study found a high level of antibiotic prescription compared to what was reported by Yock-Corrales et al.[18]

Severe cases requiring PICU admission and those with cardiac complications seem to be common in this study. The underlying causes of MIS-C are still not fully understood. The immune response in MIS-C seems different from that of acute SARS-CoV-2 infection. The acute phase is characterized by activated innate immune cells and T- and B-cell lymphopenia, but vascular inflammation and endothelial dysfunction are also important in the pathophysiology.[32] An increase in cytokines and chemokines (cytokine storm) is proposed in MIS-C, along with an activation of the innate and adaptive immune system, higher concentrations of interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), soluble complement C5b9, and deformed red blood cells, which also suggests a vascular compromise.[11,33] The incidence of MIS-C in Latino and Hispanic populations appears to be higher;[6,7,29] however, it is not yet clear if there is a greater severity of the disease in low- or middle-income countries, such as some of the Latin American countries.

This study has some limitations. First, the data were obtained from a single hospital, and we cannot extrapolate the findings to other healthcare centers in Colombia due to the paucity of national registries and local publications, although the findings are not very different from what other Latin American studies have found. Second, this was a retrospective study and so outpatient follow-up was not able to be conducted, especially echocardiographic follow-up. A strength of the study is that this is the first case series, and perhaps the largest for patients with MIS-C published in a single hospital in Colombia. The cases in this series were included in the Red de Enfermedad de Kawasaki en Latinoamérica (REKAMLATINA) [Latin American Kawasaki Disease Network] REKAMLATINA-3 study.

In conclusion, the gastrointestinal and mucocutaneous features, blood abnormalities, altered inflammatory and coagulation markers, coronary artery abnormalities, ventricular dysfunction, and intensive care unit admission were frequent, which should highlight the importance of early clinical suspicion. As we have mentioned earlier, more studies are needed in Latin America to broaden the understanding of MIS-C in low- and middle-income populations.

Funding

This study did not receive any funding.

Conflict of interests

The authors declare there is no conflict of interests.

Authors' contribution

Study design: Lozano-Espinosa DA, Camacho-Moreno G. *Data collection*: Lozano-Espinosa DA, Cárdenas-Hernández VC. *Data analysis*: Lozano-Espinosa DA, Camacho-Moreno G, León-Guerra OJ. *Manuscript writing*: Lozano-Espinosa DA, Camacho-Moreno G. *Manuscript revision*: Lozano-Espinosa DA, Camacho-Moreno G, López-Cubillos JF, Díaz-Maldonado AS, León-Guerra OJ, Galvis-Trujillo DM, Sanguino-Lobo R, Arévalo-Leal OG, Eraso-Díaz del Castillo AM, Reina-Ávila MF, Cárdenas-Hernández VC, Ivankovich-Escoto G, Tremoulet AH, Ulloa-Gutiérrez R. *Study supervision*: Camacho-Moreno G, Ulloa-Gutiérrez R.

Declaration

The database that originated the article is available with the corresponding author.

REFERENCES

1. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145:e20200702. https://doi.org/10.1542/peds.2020-0702
2. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324:259-69. https://doi.org/10.1001/jama.2020.10369
3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607-8. https://doi.org/10.1016/S0140-6736(20)31094-1
4. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395:1771-8. https://doi.org/10.1016/S0140-6736(20)31103-X

5. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-46. https://doi.org/10.1056/NEJMoa2021680
6. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York city. J Pediatr. 2020;224:24-9. https://doi.org/10.1016/j.jpeds.2020.06.045
7. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med. 2020;383:347-58. https://doi.org/10.1056/NEJMoa2021756
8. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Atlanta: CDC; 2020.
9. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Geneva: WHO; 2020.
10. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. London: RCPCH; 2020.
11. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020;183:968-81.e7. https://doi.org/10.1016/j.cell.2020.09.016
12. Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. Int J Infect Dis. 2020;100:75-81. https://doi.org/10.1016/j.ijid.2020.08.062
13. Chacon-Cruz E, Correa-Bautista Y, Urrea-Sanchez G, Lopatynsky-Reyes E, Chan-Dzib FA, Montano-Duron JG. Multisystem inflammatory syndrome in children associated with COVID-19: report of four cases in Mexico across the Mexico-US. J Infect Dis Case Rep. 2020;1:1-3.
14. Lima-Setta F, Magalhães-Barbosa MC, Rodrigues-Santos G, Figueiredo EA, Jacques ML, Zeitel RS, et al. Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: a multicenter, prospective cohort study. J Pediatr (Rio J). 2021;97:354-61. https://doi.org/10.1016/j.jped.2020.10.008
15. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, Arteaga-Menchaca E, Lavariega-Saráchaga M, Salcedo-Lozada P, et al. COVID-19 and multisystem inflammatory syndrome in Latin American children: a multinational study. Pediatr Infect Dis J. 2021;40:e1-6. https://doi.org/10.1097/INF.0000000000002949
16. Farias EC, Piva JP, Mello ML, Nascimento LM, Costa CC, Machado MM, et al. Multisystem inflammatory syndrome associated with coronavirus disease in children: a multi-centered study in Belém, Pará, Brazil. Pediatr Infect Dis J. 2020;39:e374-6. https://doi.org/10.1097/INF.0000000000002865
17. Farias EC, Justino MC, Mello ML. Multisystem inflammatory syndrome in a child associated with coronavirus disease 19 in the Brazilian Amazon: fatal outcome in an infant. Rev Paul Pediatr. 2020;38:e2020165. https://doi.org/10.1590/1984-0462/2020/38/2020165
18. Yock-Corrales A, Lenzi J, Ulloa-Gutiérrez R, Gómez-Vargas J, Antúnez-Montes OY, Rios Aida JA, et al. High rates of antibiotic prescriptions in children with COVID-19 or multisystem inflammatory syndrome: a multinational experience in 990 cases from Latin America. Acta Paediatr. 2021;110:1902-10. https://doi.org/10.1111/apa.15847
19. Acevedo L, Piñeres-Olave BE, Niño-Serna LF, Vega LM, Gomez IJ, Chacón S, et al. Mortality and clinical characteristics of multisystem inflammatory syndrome in children (MIS-C) associated with covid-19 in critically ill patients: an observational multicenter study (MISCO study). BMC Pediatr. 2021;21:516. https://doi.org/10.1186/s12887-021-02974-9
20. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2021;5:133-41. https://doi.org/10.1016/S2352-4642(20)30304-7
21. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19-associated multisystem inflammatory syndrome in children – United States, March-July 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1074-80. https://doi.org/10.15585/mmwr.mm6932e2
22. Ravelli A, Minoia F, Davì S, Horne AC, Bovis F, Pistorio A, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol. 2016;68:566-76. https://doi.org/10.1002/art.39332
23. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31. https://doi.org/10.1002/pbc.21039
24. Zhang L, Gao J, Xie M, Yin P, Liu W, Li Y, et al. Left ventricular three-dimensional global systolic strain by real-time three-dimensional speckle-tracking in children: feasibility, reproducibility, maturational changes, and normal ranges. J Am Soc Echocardiogr. 2013;26:853-9. https://doi.org/10.1016/j.echo.2013.05.002
25. Pignatelli R, Antona CV, Rivera IR, Zenteno PA, Acosta YT, Huertas-Quiñones M, et al. Pediatric multisystem SARS COV2 with versus without cardiac involvement: a multicenter study from Latin America. Eur J Pediatr. 2021;180:2879-88. https://doi.org/10.1007/s00431-021-04052-9
26. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki Disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017;135:e927-99. https://doi.org/10.1161/CIR.0000000000000484
27. Colombia. Ministerio de Tecnologías de la Información y las Comunicaciones. [homepage on the Internet]. Dados abiertos [cited 2021 Jun 26]. Available from: https://www.datos.gov.co/Salud-y-Protecci-n-Social/Casos-positivos-de-COVID-19-en-Colombia/gt2j-8ykr/data

28. World Health Organization. [homepage on the Internet]. Epidemiological update: coronavirus disease (COVID-19) [cited 2021 Jun 19]. Geneva: WHO; 2021. Available from: https://www.paho.org/en/documents/epidemiological-update-coronavirus-disease-covid-19-19-jun-2021

29. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to coronavirus disease 2019: a single center experience of 44 cases. Gastroenterology. 2020;159:1571-4.e2. https://doi.org/10.1053/j.gastro.2020.05.079

30. Dworsky ZD, Roberts JE, Son MB, Tremoulet AH, Newburger JW, Burns JC. Mistaken MIS-C: a case series of bacterial enteritis mimicking MIS-C. Pediatr Infect Dis J. 2021;40:e159-61. https://doi.org/10.1097/INF.0000000000003050

31. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385:11-22. https://doi.org/10.1056/NEJMoa2102968

32. Henderson LA, Yeung RS. MIS-C: early lessons from immune profiling. Nat Rev Rheumatol. 2021;17:75-6. https://doi.org/10.1038/s41584-020-00566-y

33. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183:982-95.e14. https://doi.org/10.1016/j.cell.2020.09.034