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ORIGINAL ARTICLE

Clinical phenotypes of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19

Fenotipos clínicos del síndrome inflamatorio multisistémico pediátrico asociado a COVID-19 (SIM-C)

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What do we know about the subject matter of this study?

COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) is a heterogeneous, rare, but potentially fatal clinical entity related to SARS-CoV-2. Hispanic ethnicity has been reported as a risk factor for severity, but in Latin America, there is still scarce information on the different phenotypes of this disease.

What does this study contribute to what is already known?

In our case series, we identified the shock phenotype as the most frequent and severe one. This group presented greater hematologic dysfunction, greater alteration of inflammatory markers, and myocardial injury, with a higher frequency of unfavorable clinical outcomes. Active surveillance of clinical and laboratory markers, typical of multiorgan dysfunction, is necessary for a syndromic diagnosis of phenotypes, especially identifying the shock phenotype for early management and to improve prognosis.

Abstract

The multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) is infrequent but potentially lethal. There are few reports of this disease and its phenotypes in Latin America. **Objective:** To describe the characteristics of the clinical phenotypes of MIS-C in hospitalized patients in Lima, Peru. **Patients and Method:** A descriptive and retrospective study in patients under 14 years old with a diagnosis of MIS-C at the Hospital Nacional Edgardo Rebagliati Martins (Lima, Perú),

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from April 2020 to August 2021. Clinical-demographic and microbiological variables were recorded. According to these, patients with MIS-C were classified into the shock phenotype, Kawasaki disease (KD) without shock, and the fever and inflammation phenotype, analyzing their clinical outcomes. **Results:** 58 patients were analyzed. 32 (55.2%) presented the shock phenotype, 15 (25.8%) Kawasaki disease (KD) phenotype without shock, and 11 (19%) fever and inflammation phenotype. In the shock phenotype, 17 had KD. The mean age was 7 ± 3.5 years and 67.2% were males. Gastrointestinal and mucocutaneous manifestations predominated in all phenotypes. The mortality was 3.5%. The frequency of coronary aneurysms was 10.2%. Most patients received immunomodulatory and antiplatelet treatment. Patients with shock phenotype showed greater involvement in inflammatory markers, hematological dysfunction, and myocardial injury, with a higher frequency of respiratory failure and invasive mechanical ventilation. **Conclusions:** In our case series, patients with shock phenotype were the most frequent and had worse clinical outcomes. Active surveillance of clinical phenotypes is needed to make an early diagnosis and management to improve the prognosis in these patients.

Introduction

The clinical spectrum of SARS-CoV-2 infection in pediatrics is broad with features that differ from adults. Most children develop an asymptomatic infection or mild symptoms. A smaller percentage develop severe (5%) and critical (< 1%) involvement[1]. In these cases, the involvement may be acute and with predominantly respiratory symptoms. Less frequently, the COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) is described, which is also known as "Pediatric Inflammatory Multisystem Syndrome" (PIMS). For its diagnosis, it is necessary the presence of fever, altered inflammatory markers, multiorgan involvement, and the exclusion of other causes. All this is according to the diagnostic criteria proposed independently by the World Health Organization (WHO), the Royal College of Paediatrics and Child Health, and the Centers for Disease Control and Prevention (CDC)[2]. In addition, within this syndrome, some clinical phenotypes have been proposed to guide therapy and define risk groups[3,4]. Regardless of the clinical phenotype, MIS-C can cause multiorgan failure and death[2].

Clinical series have been reported in Latin America, but the information is still insufficient and there are few publications describing the different phenotypes of this disease[5-12]. The objective of this study is to describe the characteristics of the clinical phenotypes of MIS-C in a pediatric referral hospital in Lima, Peru.

Patients and Method

Design and population

Retrospective analytical study of patients under 14 years of age with a diagnosis of MIS-C hospitalized from April 2020 to August 2021 at the *Hospital Nacional Edgardo Rebagliati Martins* (HNERM), in Lima, Peru. This center is the most important high-complexity public hospital in Peru, with 124 pediatric and 160 neonatal beds. It has a 13-bed pediatric ICU, an 8-bed pediatric special care unit, and a 55-bed neonatal intermediate care unit. The hospital covers all pediatric clinical and surgical subspecialties, including extracorporeal membrane oxygenation (ECMO) if necessary. It also has pediatric equipment for liver, kidney, and bone marrow transplantation.

The CDC diagnostic criteria were used for the diagnosis of MIS-C[2]. Patients with SARS-CoV-2 infection with Kawasaki Disease (KD) criteria, but who did not meet the criteria for MIS-C, and those who completed management at another hospital were excluded.

Data were collected from the clinical history (physical and electronic). Given the retrospective descriptive nature of the study, no sample size calculation was performed. To avoid bias, missing data, or excluded medical records, each medical record was evaluated independently by two investigators (KCM, JDR), and when there were discrepancies, a third investigator performed a review (GAG).

Study variables

Patients with MIS-C were categorized into three clinical phenotypes: phenotype with KD (complete or incomplete) without shock according to American Heart Association criteria[13], shock phenotype (need for inotrope/vasopressor or fluid resuscitation > 20 ml/kg, including KD phenotype with shock)[14], and phenotype with fever and inflammation (MIS-C not meeting shock or KD phenotype criteria, and clinically stable)[4]. Epidemiological characteristics, clinical manifestations on admission, laboratory tests (the most altered during hospitalization were considered), and treatment were included. The results of RT-PCR and serological tests (IgM and IgG) for SARS-COV-2 were also recorded. In

addition, unfavorable outcomes such as death, oxygen saturation ≤ 92% and emergency intubation, intensive care unit (ICU) admission, use of invasive mechanical ventilation (IMV), macrophage activation syndrome (MAS), and the presence of coronary artery aneurysms were recorded. Diagnostic criteria for MAS[15] were ferritin > 684 ng/mL plus two of the following: platelets ≤ 181 000/mm^3, glutamic oxaloacetic transaminase (GOT) > 48 U/l, triglycerides ≥ 156 mg/dL, and fibrinogen ≤ 360 mg/dL.

Statistical analysis

The data obtained were entered into a database in a Microsoft® Excel spreadsheet (Windows 2016 version). The STATA® v.16 software (StataCorp LP, College Station, Texas, United States) was used for data analysis. A descriptive analysis of categorical variables was performed using absolute and relative frequencies. Quantitative variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) according to the previous evaluation of the normality assumption with the Shapiro-Wilk test. Due to the limited number of patients, statistical tests were not performed for each MIS-C phenotype. A bivariate analysis was performed according to the presence of shock phenotype, with the Mann-Whitney test for continuous variables and the chi-square or Fisher exact test (according to the expected values) for categorical variables. For all statistical tests, the significance level was a p-value < 0.05.

Ethical aspects

The project was approved by the Research Ethics Committee for COVID-19 of the Social Health Insurance. Informed consent was not requested because the information was collected directly from the medical records and the confidentiality of the data was respected by using a numerical code. Some characteristics of the first 37 patients in this series were included in a letter to the editor in the *Revista Peruana de Medicina Experimental y Salud Pública*[12].

Results

Epidemiological characteristics and clinical manifestations

58 patients with diagnosis of MIS-C were studied. Two patients with atypical KD were excluded from the analysis because they did not meet the diagnostic criteria for MIS-C. 32 (55.2%) presented the shock phenotype, 15 (25.8%) the KD phenotype without shock, and 11 (19%) the fever with inflammation phenotype. Of the shock phenotype, 17 presented KD criteria (Figure 1).

The age was 7 ± 3.5 years and 39 (67.2%) were male. 13 patients (22.4%) had previous comorbidity, including primary immunodeficiency, chronic kidney disease, and acute lymphoblastic leukemia. More than 50% had household contact with COVID-19 cases. Within the SARS-CoV-2 testing, 37 of 50 (74%) screened patients had positive IgG results, and three of 40 (7.5%) had positive RT-PCR. Gastrointestinal symptoms (vomiting, nausea, diarrhea, abdominal pain) and mucocutaneous involvement predominated in all subgroups, 48 (82.7%) and 42 (72.4%) patients, respectively. 2 patients (1.7%) were diagnosed with acute abdomen requiring surgical management, one of the shock phenotype and the other of the fever with inflammation one. The median time of illness was 5 days (IQR 3-6), and 4 days (IQR 3-5) for fever duration (Table 1). Neurological symptoms (impaired consciousness, headache) were present in 4 (6.9%) patients, and severe respiratory distress (pneumonia) in 9 (15.5%) patients. During hospitalization, three (5.2%) patients developed acute kidney failure and one patient presented peripheral vascular involvement with necrosis.

In the bivariate analysis, patients with shock phenotype had a significantly higher frequency of epidemiological contact within the home and diagnosis of non-acute exposure to SARS-CoV-2. Acute respiratory distress occurred more frequently in patients with the shock phenotype (Table 2).

Laboratory tests

Median hemoglobin was 10.2 g/dL (IQR 8.9-11.2), with neutrophilia (9405.5/mm^3; IQR 4550-14055), mild thrombocytopenia (138,000/mm^3; IQR 7000-216000), increased C-reactive protein (24.8 mg/dL; IQR 13-29.9), elevated D-dimer (3.81 mg/L; IQR 2.68-6.31), moderate hypoalbuminemia (2.89 g/dL; IQR 2.5-3.5), hyperferritinemia (532 ng/mL; IQR 306-1.066), and elevated myocardial injury markers (CPK-MB and NT-proBNP; Table 3).

Of all phenotypes, the KD phenotype with shock had higher thrombocytopenia (95,000/mm^3; IQR 46,000-166,000), higher C-reactive protein (27.5 mg/dL; IQR 21.2-30), hypoalbuminemia (2.5 g/dL; IQR 2.3-2.81), and higher myocardial injury markers (CPK-MB 2.525 U/L, IQR 1.77-31.44; NT-proBNP 8,131.5 pg/mL, IQR 2515-13725). Also, the shock phenotype showed higher lymphopenia (846/mm^3; IQR 450-1660), higher D-dimer (4.31 mg/L; IQR 3.38-7.46), and higher hyperferritinemia (616.5 ng/mL; IQR 521.3-1,210.5) (Table 3).

In the bivariate analysis, patients with shock phenotype (with and without KD) presented significantly higher hematologic (anemia, lymphopenia, thrombocytopenia, prolonged prothrombin time), inflamma-

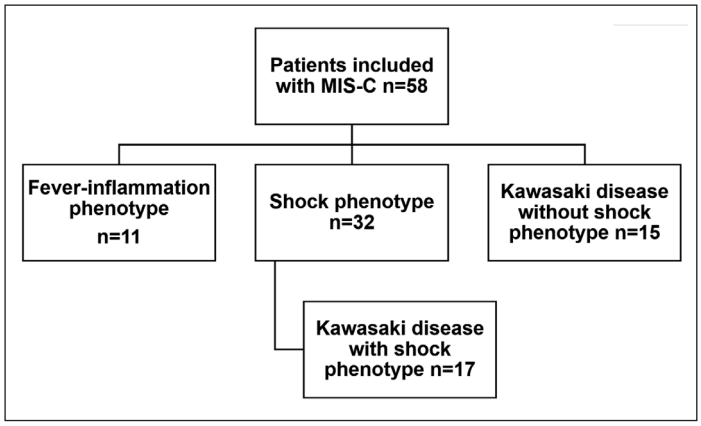

Figure 1. Flow diagram of patients with multisystem inflammatory syndrome in children (MIS-C) included in the study and their clinical phenotypes.

tory (increased C-reactive protein, D-dimer, ferritin, and hypoalbuminemia), and cardiac (increased troponin C, NT-proBNP) dysfunction (Table 2).

Treatment characteristics

57 (98.3%) patients received intravenous immunoglobulin (IVIG) at 2g/kg. 17 (29.3%) required a second dose, one with fever and inflammation phenotype, nine with shock phenotype (four of KD phenotype with shock), and seven with KD phenotype without shock. Acetylsalicylic acid (ASA) was administered in 52 (89.6%) patients, corticosteroids (methylprednisolone) in 42 (72.4%), and antibiotics in 48 (82.8%) patients. Combined therapy of corticosteroids (methylprednisolone 2 mg/kg/day) plus a first immu-

Table 1. Epidemiological, clinical and treatment characteristics in patients with multisystem inflammatory syndrome in children (MIS-C)

Characteristics	MIS-C n = 58 n (%)	Clinical phenotypes			
		Fever-Inflammation n = 11 n (%)	Shock n = 32 n (%)	KD§ without Shock n = 15 n (%)	KD§ with Shock n = 17 n (%)
Age (years)*	7.15 ± 3.54	7.09 ± 3.56	7.37 ± 3.51	6.71 ± 3.77	6.89 ± 3.72
Male sex	39 (67.24)	6 (54.5)	21 (65.6)	12 (80.0)	9 (52.9)
Home contact	31 (53.5)	4 (36.4)	21 (65.6)	6 (40.0)	12 (70.6)
SARS-COV-2 Identification, n (%)					
RT-PCR (swab)	3/40 (7.5)	0 (0.0)	3/22 (13.6)	0 (0.0)	0 (0.0)
IgG	37/50 (74.0)	7/11 (63.6)	22/24 (91.7)	8/15 (53.3)	12/13 (92.3)
IgM	9/48 (18.8)	2/11 (18.2)	5/22 (22.7)	2/15 (13.3)	2/11 (18.2)
Illness duration (days)**	5 (3-6)	3 (2-6)	5 (3-5)	5 (4-7)	5 (4-5)
Clinical manifestations on admission, n (%)					
Manifestations Gastrointestinal†	48 (82.7)	10 (90.9)	28 (87.5)	10 (66.7)	15 (88.2)
Fever	58 (100.0)	11 (100.0)	32 (100.0)	15 (100.0)	17 (100.0)
fever time **	4 (3-5)	3 (2-8)	5 (3-5)	4 (3-5)	5 (4-5)
Manifestations Mucocutaneous††	42 (72.4)	6 (54.6)	21 (65.6)	15 (100.0)	15 (88.2)
Conjunctivitis	28 (48.3)	3 (27.3)	17 (53.1)	8 (53.3)	12 (70.6)
Upper respiratory symptoms	9 (15.5)	4 (36.4)	4 (12.5)	1 (6.7)	3 (17.7)
Severe respiratory distress	9 (15.5)	1 (9.1)	8 (25.0)	0 (0.0)	4 (23.5)
Treatment, n (%)					
Corticosteroids	42 (72.4)	5 (45.5)	30 (93.8)	7 (46.7)	17 (100.0)
Vasopressors	31 (53.5)	0 (0.0)	31 (96.9)	0 (0.0)	16 (94.1)
Immunoglobulin (first dose)	57 (98.3)	11 (100.0)	31 (96.9)	15 (100.0)	17 (100.0)
Immunoglobulin (second dose)	17 (29.3)	1 (9.1)	9 (28.1)	7 (46.7)	4 (23.5)
Acetylsalicylic acid	52 (89.6)	10 (90.9)	27 (84.4)	15 (100.0)	17 (100.0)
Antifungal	1 (1.72)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)
Anticoagulation					
Treatment	4 (6.9)	1 (9.1)	2 (6.3)	1 (6.7)	1 (5.9)
Prophylaxis	1 (1.7)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Antibiotic	48 (82.8)	8 (72.7)	32 (100.0)	8 (53.3)	17 (100.0)
Ivermectin	7 (12.1)	2 (18.2)	4 (12.5)	1 (6.7)	0 (0.0)
Hydroxychloroquine	4 (6.9)	1 (9.1)	2 (6.3)	1 (6.7)	0 (0.0)

*Mean+/-Standard deviation. **Median (interquartile range). (†) Included in gastrointestinal manifestations: vomiting, nausea, abdominal pain and/or diarrhea. (††) In the mucocutaneous: rash, changes on the lips, mucosa and oral cavity, erythema with or without edema on the palms and soles, and/or desquamation of the pads of the fingers. (§) Includes cases of complete and incomplete KD according to the "American Heart Association". MIS-C: Multisystem inflammatory syndrome in children. KD: Kawasaki disease. RT-PCR: real-time polymerase chain reaction. Shock: Need for inotropic support or fluid resuscitation > 20 mL/kg. Includes those patients with KD phenotype and developed shock. IgG: Serum immunoglobulin G specific for SARS-CoV-2. IgM: Serum immunoglobulin M specific for SARS-CoV-2.

Table 2. Clinical-demographic, laboratory and therapeutic characteristics and unfavorable outcomes of patients with multisystem inflammatory syndrome in children (MIS-C) according to presentation with shock phenotype

Characteristics	Shock phenotype n = 32	Non-Shock Phenotype n = 26	p-value†
Age (years)*	8 (5.5-10)	7.5 (3-10)	0.689
Male sex, n (%)	21 (65.6)	18 (69.2)	0.77
Home contact, n (%)	21 (65.6)	10 (38.5)	0.039
SARS-COV-2 Identification, n (%)			
RT-PCR (swab)	3 (13.6)	0 (0)	0.136††
IgG	22 (91.6)	15 (57.0)	< 0.001
IgM	5 (23.4)	4 (15.4)	0.06††
Clinical manifestations on admission			
Manifestations Mucocutaneous **, n (%)	21 (65.6)	21 (80.8)	0.19
Upper respiratory symptoms, n (%)	4 (12.5)	5 (19.2)	0.48
Severe respiratory distress, n (%)	8 (25.0)	1 (3.8)	0.027
Laboratory characteristics *			
Hemoglobin g/dL	9.3 (8.7-10.8)	11 (9.9-11.6)	0.004
leukocytes x 10^3/mm^3	14335 (9625-23840)	12125 (6820-15670)	0.081
Neutrophils x 10^3/mm^3	10590 (6082-16655)	6643 (2140-10900)	0.066
Lymphocytes x 10^3/mm^3	846 (460-1550)	1500 (1000-3040)	0.007
Platelets x 10^3/mm^3	98500 (46000-152500)	206000 (154000-310000)	< 0.001
C-reactive protein mg/dL	27.4 (21.8-33.0)	18.5 (8.8-26.5)	0.004
GOT U/L	63 (40-95)	44 (26-101)	0.316
PT seconds	14 (13-15)	12 (11-13)	< 0.001
APTT seconds	41 (35-48)	32 (29-40)	0.003
Fibrinogen mg/dL	443 (258-606)	538 (331-618)	0.296
D-dimer mg/L	4.3 (3.4-7.3)	2.7 (2.0-4.6)	0.023
Albumin g/dL	2.71 (2.40-2.96)	3.57 (2.75-3.97)	0.001
Sodium mmol/L	135 (132-139)	135 (132-137)	0.598
Ferritin ng/mL	617 (521-1.211)	382 (261-697)	0.041
Troponin C ng/mL	0.0265 (0.015-0.073)	0.005 (0.003-0.021)	0.001
NT-proBNP pg/mL	4098 (678-13725)	158 (154-767)	0.012
CPK-MB U/L	4.24 (1.87-35.0)	1.49 (0.8-15.0)	0.084
Triglycerides mg/dL	167 (101-311)	163 (102-273)	0.807
Lactate dehydrogenase U/L	291 (232-357)	253 (218-411)	0.696
Urea mg/dL	33 (23-49)	22 (17-27)	0.027
Creatinine mg/dL	0.5 (0.4-0.7)	0.5 (0.4-0.6)	0.937
Arterial blood gases*			
$PaCO_2$	38 (31-46)	30 (29-31)	0.092
HCO_3 mEq/L	17 (16-20)	20 (19-21)	0.258
Lactate mmol/L	2.1 (1.6-3.4)	1.6 (1.4-2.1)	0.301
Treatment			
Corticosteroids, n (%)	30 (93.8)	12 (46.2)	< 0.001
Immunoglobulin (1st dose), n (%)	31 (96.9)	26 (100)	1.0††
Immunoglobulin (2nd dose), n (%)	9 (28.1)	8 (30.8)	0.82
Acetylsalicylic acid, n (%)	27 (84.4)	25 (96.2)	0.209††
Antibiotic, n (%)	32 (100)	16 (61.5)	< 0.001
Unfavorable outcomes			
Respiratory insufficiency, n (%)	26 (81.0)	4 (15.4)	0.01††
Invasive mechanical ventilation, n (%)	24 (75.0)	1 (3.8)	< 0.001
Coronary aneurysm, n (%)	2 (6.9)	3 (15.2)	0.387††
Activation síndrome macrophage, n (%)	0 (0)	3 (11.5)	0.084††
Length of ICU stay (days)	5 (4-7)	5 (3.5-6.5)	0.813
Mortality, n (%)	2 (6.2)	0 (0)	0.497††

*Median +/- interquartile range. **In mucocutaneous manifestations: rash, changes on the lips, mucosa and oral cavity, erythema with or without edema on the palms and soles, and/or desquamation of the fingertips. (†) Mann-Whitney test for continuous variables and chi-square for categorical variables. (††) Fisher's exact test. Shock: Need for inotropic support or fluid resuscitation > 20 mL/kg. Includes those patients with the Kawasaki disease phenotype who developed shock. RT-PCR: real-time polymerase chain reaction. IgG: Serum immunoglobulin G specific for SARS-CoV-2. IgM: Serum immunoglobulin M specific for SARS-CoV-2. GOT: glutamic oxaloacetic transaminase, PT: prothrombin time, APTT: activated partial thromboplastin time, NT-proBNP: pro-cerebral natriuretic peptide, CPK-MB: myocardial creatinephosphokinase; $PaCO_2$: partial pressure of carbon dioxide, HCO_3: sodium bicarbonate. Macrophage activation syndrome: ferritin > 684 ng/mL plus 2 of the following parameters: platelets ≤ 181,000/mm^3, GOT > 48 U/l, triglycerides ≥ 156 mg/dL, and fibrinogen ≤ 360 mg/dL.

Table 3. Laboratory characteristics in patients with multisystem inflammatory syndrome in children (MIS-C)

Laboratory characteristics*	MIS-C	Clinical phenotypes			
	n = 58	Fever-Inflammation n = 11	Shock n = 32	KD† without Shock n = 15	KD† with Shock n = 17
Hemoglobin g/dL	10.2 (8.9-11.2)	11.2 (9.5-12.4)	9.3 (8.7-10.75)	11 (9.9-11.4)	9.3 (8.7-10.2)
Hematocrit %	31 (26.3-33.65)	33 (28.6-36.7)	28.2 (25.9-31.2)	33 (28.5-34)	28.2 (26.1-31)
Leukocytes x 10^3/mm^3	12945 (7200-18890)	12300 (7040-12850)	14335 (9625-23840)	11950 (3110-20840)	14390 (10700-23680)
Neutrophils x 10^3/mm^3	9405.5 (4550-14055)	7375 (3180-10830)	10590 (5854-19060)	6643 (1990-15720)	10590 (7900-21470)
Lymphocytes x 10^3/mm^3	1100 (604.5-2049)	1550 (795-2239)	846 (450-1660)	1500 (1000-3250)	1040 (469-1760)
Platelets x 10^3/mm^3	138000 (7000-216000)	226000 (187000-351000)	98500 (46000-152500)	181000 (130000-250000)	95000 (46000-166000)
ESR mm/h	24.5 (20-42.5)	21 (14.5-31)	33 (20-52.5)	25 (20-40)	31 (16.55-47.5)
C-reactive protein mg/dL	24.8 (13-29.9)	23 (12.2-27)	27.4 (21.75-33)	14.2 (6.7-25.5)	27.5 (21.2-30)
GOT U/L	53.5 (32.5-96.5)	27 (21-107)	62.5 (40-95)	62 (34-101)	53 (36-119)
GPT U/L	58 (31-97)	43 (14-88)	58 (35-106)	63 (29-96)	69 (43-107)
PT seconds	12.8 (12-14)	11.2 (11-12.49)	13.63 (12.83-15.07)	12.05 (11.87-12.98)	13.29 (12.8-14.4)
APTT seconds	37 (31.9-44.9)	32 (29-40.6)	40.77 (34.71-47.55)	32.96 (28-37.25)	43.4 (37.57-48.8)
INR	1.16 (1.1-1.3)	1.05 (0.99-1.12)	1.22 (1.14-1.36)	1.09 (1-1.16)	1.2 (1.15-1.3)
Fibrinogen mg/dL	511 (303-614.7)	542 (445.75-617.57)	442.85 (257.5-605.5)	530.9 (324.7-640.9)	511 (241-562)
D-dimer mg/L	3.81 (2.68-6.31)	2.71 (2.29-4)	4.31 (3.38-7.46)	2.68 (2.03-4.6)	3.9 (3.5-6.31)
Albumin g/dL	2.89 (2.5-3.5)	3.5 (2.6-4.07)	2.71 (2.4-2.96)	3.64 (2.75-3.83)	2.5 (2.3-2.81)
Sodium mmol/L	135 (132-138)	135 (133-137)	135 (132-138.5)	134 (132-137)	135 (133-136)
Ferritin ng/mL	532 (306-1 066)	434 (261-1422)	616.5 (521.3-1 210.5)	340 (268.5-544.5)	606 (510.6-692.28)
Troponin C ng/mL	0.019 (0.006-0.034)	0.003 (0.003-0.022)	0.0265 (0.015-0.0725)	0.005 (0.005-0.01)	0.024 (0.015-0.033)
NT-proBNP pg/mL	2.515 (524-11.303)	767 (117-2.350)	4097.5 (677.7-13.725)	156 (154-158)	8.131.5 (2.515-13.725)
CPK-MB U/L	2.525 (1.14-29.93)	1.55 (0.71-15)	4.24 (1.87-35)	1.34 (0.8-18)	2.525 (1.77-31.44)
Triglycerides mg/dL	163 (101-307)	196 (136-477)	167 (101-311)	163 (101-270)	247 (112-331)
LDH U/L	279 (224-361)	292 (211-403)	290.5 (232-357)	242 (227-419)	293 (232-357)
Urea mg/dL	30 (21-42.8)	25 (21-34)	33.15 (23-49)	19 (15-40)	33.15 (22.2-50.2)
Creatinine mg/dL	0.48 (0.37-0.67)	0.57 (0.46-0.67)	0.465 (0.36-0.725)	0.41 (0.355-0.535)	0.55 (0.36-0.71)
Glucose mg/dL	107 (96-132)	107.5 (107-114)	115 (91-174)	99 (92.5-105.5)	129 (94-176)
Arterial blood gases					
Acidosis**	22/34 (64.7)	2/2 (100.0)	20/31 (64.5%)	0/1 (0.0)	10/16
Moderate/severe acidosis (pH < 7,2)	6 (27.3)	0 (0.0)	6 (30)	0 (0.0)	3 (30.0)
$PaCO_2$	35.95 (30-44.8)	31 (30-32)	37.6 (30.5-46.3)	26.4	42.65 (32.6-47.4)
HCO_3 mEq/L	17.55 (15.6-20.2)	20.5 (20-21)	17.2 (15.5-20.1)	17.2	18.15 (15.35-18.15)
Lactate mmol/L	2 (1.5-3.4)	1.5 (1.2-2.6)	2.1 (1.5-3.4)	1.7	2.2 (1.65-2.9)

*Median+/-interquartile ranges. ** absolute and relative frequency. (†) Includes cases of complete and incomplete KD according to the "American Heart Association". MIS-C: multisystem inflammatory syndrome in children. KD: Kawasaki disease. RT-PCR: real-time polymerase chain reaction. Shock: Need for inotropic support or fluid resuscitation > 20 mL/kg. Includes those patients with KD phenotype and developed shock. ESR: erythrocyte sedimentation rate; PT: prothrombin time, APTT: activated partial thromboplastin time, INR: International normalized ratio, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, CPK-MB: myocardial creatine phosphokinase, LDH: lactate dehydrogenase, NT-proBNP: pro-brain natriuretic peptide, PaCO2: pressure partial carbon dioxide, HCO3: sodium bicarbonate.

Table 4. Unfavorable outcomes in patients with multisystem inflammatory syndrome in children (MIS-C).

Unfavorable outcomes	MIS-C n = 58	Clinical phenotypes			
		Fever-Inflammation n = 11	Shock n = 32	KD† without Shock n = 15	KD† with Shock n = 17
	n (%)	n (%)	n (%)	n (%)	n (%)
Deaths	2 (3.5)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)
Echocardiography	n = 49	n = 8	n = 29	n = 12	n = 15
Coronary aneurysm	5 (10.2)	2 (25.0)	2 (6.9)	1 (8.3)	1 (6.6)
Saturation in the emergency					
≤ 92%	15 (25.9)	2 (18.2)	13 (40.6)	1 (6.7)	8 (47.1)
85-92%	8 (53.3)	1 (100.0)	7 (53.8)	0 (0.0)	5 (62.5)
< 85%	7 (46.7)	0 (0.0)	6 (46.2)	1 (100.0)	3 (37.5)
Required emergency intubation	7 (12.1)	1 (9.1)	6 (18.8)	0 (0.0)	4 (23.5)
ICU admission	32 (55.2)	2 (18.2)	29 (90.6)	1 (6.7)	15 (88.2)
Length of ICU stay (days)*	5 (4-7)	5 (2-8)	5 (4-7)	5	6 (4-7)
Invasive mechanical ventilation	25 (43.1)	1 (9.1)	24 (75.0)	0 (0.0)	14 (82.4)
IMV time (days)*	4 (3-5)	3	4 (3-5)	0 (0.0)	3.5 (3-5)
High flow nasal cannula	7 (12.1)	0 (0.0)	6 (18.8)	1 (6.7)	3 (17.7)
Macrophage activation syndrome	3 (5.2)	1 (9.1)	0 (0.0)	2 (13.3)	0 (0.0)

*Median+/-interquartile ranges. MIS-C: Pediatric multisystem inflammatory syndrome associated with COVID-19. KD: Kawasaki disease. Shock: Need for inotropic support or fluid resuscitation > 20 mL/kg. Includes those patients with KD phenotype and developed shock. (†) Includes cases of complete and incomplete KD according to the "American Heart Association". ICU: intensive care unit. IMV: invasive mechanical ventilation. Macrophage activation syndrome: ferritin > 684 ng/mL plus 2 of the following parameters: platelets ≤ 181,000/mm^3, GOT > 48 U/l, triglycerides ≥ 156 mg/dL, and fibrinogen ≤ 360 mg/dL.

noglobulin dose was recorded in 42 (72.4%) patients. 12 (20.7%) patients received corticosteroid (methylprednisolone 10-30 mg/kg/day) plus a second dose of immunoglobulin. The most used antibiotics were ceftriaxone in 20 (41.7%) patients and vancomycin/meropenem in 12 (25%) patients. Anticoagulation with enoxaparin was also administered in 5 (8.6%) patients, ivermectin in 7 (12.1%) patients, and hydroxychloroquine in 4 (6.9%) patients, the latter two at the beginning of the pandemic (Table 1).

Bivariate analysis showed that patients with shock phenotype were treated with corticosteroids and antibiotics more frequently but did not require other therapies or a second dose of immunoglobulin more frequently than patients without shock (Table 2).

Unfavorable outcomes

In the emergency unit, 15 (25.9%) patients presented oxygen saturation ≤ 92% and 7 (12.1%) patients were intubated. 32 (55.2%) required ICU admission with a median stay of 5 days (IQR 4-7). High-flow nasal cannula was used in 7 (12.1%) patients. 25 (43.1%) patients required IMV with a median of 4 days (IQR 3-5) until extubation. ICU admission was more frequent in the shock phenotype (29 patients; 90.6%). Emergency room intubation (6 patients;10.3%) and IMV (24 patients;41.3%) were more frequent in the KD phenotype with shock. Echocardiography was performed in 49 (84.5%) patients, finding coronary artery aneurysm in 5 (10.2%). 2 (3.5%) patients with the shock phenotype died due to multiple organ failure (Table 4).

In the bivariate analysis, patients with the shock phenotype had a significantly higher frequency of respiratory failure and required IMV compared with patients without shock. In addition, the shock phenotype had a lower frequency of MAS (Table 2).

Discussion

In this retrospective study, we identified 58 patients with MIS-C, with the shock phenotype as the most frequent. We could identify significant laboratory alterations associated with the severity of the shock phenotype, with multiorgan involvement and a more severe course. We also reported the presence of other phenotypes (KD and fever and inflammation) with less torpid evolution but requiring early recognition and continuous monitoring during hospitalization.

The pathophysiological mechanisms of SARS-CoV-2 infection to trigger MIS-C are complex. Autoantibody formation by autoantigen recognition, viral antigens recognition expressed on infected cells, immune complex formation, and the presence of viral superantigen sequences that activate immune cells have been described[2]. This inflammatory response differs from that observed in acute pediatric and adult COVID-19 and KD[16].

All the systematic reviews[17-20] found and most of the case series with large sample sizes[3,21-25] were carried out in Europe, the United States, and some Asian countries. In these reports and Latin America[10,26-29], the predominance is described in school age, in males, mostly healthy, of Hispanic origin, or of African descent.

Among the clinical manifestations, fever, gastrointestinal, mucocutaneous, and cardiovascular symptoms are the most frequently reported, associated with markedly altered inflammatory, coagulation, and cardiac markers[17-20]. Regarding the report of coronary aneurysms, there is great variability among studies, from 5.4% in some systematic reviews to 24% in large series[3,17,20,21,30-32]. In addition, they describe other alterations such as decreased left ventricular ejection fraction, myocarditis, and pericardial effusion mainly[3,17,19,20,20,26].

In Latin America, a multinational study has been published reporting 95 cases[10]. There are also reports from centers in Chile[5,6] and Brazil[27-29] that describe characteristics similar to those described worldwide. Therapeutic recommendations are aimed at an early intervention, providing respiratory and hemodynamic support and immunomodulatory treatment, which includes IVIG, corticoids, and, in specific cases, biological therapy with anakinra, infliximab, or tocilizumab, whose efficacy is unknown and the level of evidence is still very low[33].

This study also presents similar characteristics to those reported, but a subclassification was made according to the clinical phenotypes of MIS-C. In our case series, a higher case fatality rate (2/58;3.5%) stands out compared with other studies (1.4 to 2.1%)[3,17-21]. The deaths occurred at the beginning of the pandemic when the diagnostic criteria for MIS-C and its management were not entirely clear. In addition, the lack of pediatric ICU and specialized personnel in Peru could explain the higher case fatality rate reported. We found coronary aneurysms in 10.2% of cases, which is within the range described by other studies[3,17,20,21,30-32,34]. All MIS-C phenotypes presented similar age (schoolchildren), and sex (male), mostly without comorbidities, and similar duration of illness, fever, ICU stay, and duration of IMV.

In patients with shock phenotype and KD phenotype with shock, there was more home contact with COVID-19 cases and a higher frequency of severe respiratory distress. In addition, they had greater alteration of hematological, inflammatory, and permeability tests, and greater involvement of myocardial injury markers compared with the other phenotypes. They also presented a higher frequency of unfavorable outcomes during hospitalization (oxygen saturation ≤ 92% and intubation in emergency, admission to ICU, and IMV) and a higher case-fatality rate (2/32; 6.3%). It is worth mentioning that also the other phenotypes presented unfavorable events but at a lower frequency.

The fever and inflammation phenotype also requires complete evaluation and continuous monitoring. Some guidelines do not suggest the initiation of immunomodulatory treatment, but aim at a multidisciplinary evaluation, ensuring a strict follow-up[33]. All patients in this study with fever and inflammation phenotype received IVIG, about half received systemic corticosteroids and most received antiplatelet therapy. This phenotype had a lower ICU admission and IVIG requirement compared with the other phenotypes. This difference could be because they are less severe and without treatment could also have had the same outcome. The development of randomized clinical trials or at least observational interventional studies with low risk of bias is needed to assess the need for first-line immunomodulatory therapy in patients with the fever and inflammation phenotype.

The KD phenotype without shock had more mucocutaneous involvement and a lower frequency of gastrointestinal symptoms. All received IVIG and antiplatelet therapy, with a higher frequency of a second dose of IVIG. The decision to administer a second dose of IVIG was based on the criterion of persistence of fever more than 36 hours after the end of the infusion of the first dose. Regarding the severity of this phenotype, one patient was admitted to the ICU without requiring IMV, and only one patient presented coronary aneurysm. In this phenotype, there was a higher frequency of MAS compared with the other phenotypes.

The main strength of this study is that it presents in detail, from a reference hospital, a significant number of patients with MIS-C, a rare disease associated with COVID-19. This allows the classification of a higher frequency and severity phenotype of this heterogeneous disease. On the other hand, this study has limitations related to the origin of secondary source data (medical records) and retrospective collection, with the possibility of greater selection and information bias. In addition, another limitation is that the results represent the clinical profile of a single hospital center.

Conclusions

In our series of MIS-C cases, the shock phenotype was the most frequent. Patients with the shock phenotype had greater hematologic dysfunction, greater involvement of inflammatory markers and myocardial injury, and a higher frequency of unfavorable clinical outcomes. Due to the potentially fatal consequences of this new and rare clinical entity, active surveillance is necessary for early diagnosis and management, as well as its clinical phenotypes, in order to identify risk groups and improve prognosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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