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Characteristics and outcomes of multisystem inflammatory syndrome in children: A multicenter, retrospective, observational cohort study in Mexico

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Introduction: Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 (MIS-C), a novel hyperinflammatory condition secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is associated with severe outcomes such as coronary artery aneurysm and death.

Methods: This multicenter, retrospective, observational cohort study including eight centers in Mexico, aimed to describe the clinical characteristics and outcomes of patients with MIS-C. Patient data were evaluated using latent class analysis (LCA) to categorize patients into three phenotypes: toxic shock syndrome-like (TSSL)-MIS-C, Kawasaki disease-like (KDL)-MIS-C, and nonspecific MIS-C (NS-MIS-C). Risk factors for adverse outcomes were estimated using multilevel mixed-effects logistic regression.

Results: The study included 239 patients with MIS-C, including 61 (26%), 70 (29%), and 108 (45%) patients in the TSSL-MIS-C, KDL-MIS-C, and NS-MIS-C groups, respectively. Fifty-four percent of the patients were admitted to the intensive care unit, and 42%, 78%, and 41% received intravenous immunoglobulin, systemic glucocorticoids, and anticoagulants, respectively. Coronary artery dilatation and aneurysms were found in 5.7% and 13.2% of the patients in whom coronary artery diameter was measured, respectively. Any cause in-hospital

mortality was 5.4%. Hospitalization after ten days of symptoms was associated with coronary artery abnormalities (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.2−2.0). Age ≥10 years (OR: 5.6, 95% CI: 1.4−2.04), severe underlying condition (OR: 9.3, 95% CI: 2.8−31.0), platelet count <150,000 /mm^3 (OR: 4.2, 95% CI: 1.2−14.7), international normalized ratio >1.2 (OR: 3.8, 95% CI: 1.05−13.9), and serum ferritin concentration >1,500 mg/dl at admission (OR: 52, 95% CI: 5.9−463) were risk factors for death.

Discussion: Mortality in patients with MIS-C was higher than reported in other series, probably because of a high rate of cases with serious underlying diseases.

1. Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C), temporally associated with coronavirus disease 2019 (COVID-19), also known as pediatric multisystem inflammatory syndrome, is a novel hyperinflammatory condition secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and shares features with Kawasaki disease, toxic shock syndrome, and acute COVID-19. MIS-C was first described in April 2020 in the United Kingdom, followed by case reports in other countries (1, 2).

The clinical case definition of MIS-C varies slightly among different health agencies (2–5). Clinical features include fever, gastrointestinal symptoms, conjunctival injection, rash, and elevated inflammatory markers. Potential complications include shock, multi-organ failure, and myocardial and coronary artery involvement similar to those observed in Kawasaki disease (6–8). Many patients with MIS-C have evidence of SARS-CoV-2 infection within several weeks before disease onset (9–11). The estimated incidence of MIS-C is 3–5 per 10,000 among individuals aged <21 years who are infected with SARS-CoV2. Studies in ethnically diverse countries reported a higher incidence of MIS-C in Hispanic and Afro-descendant individuals, emphasizing the need to characterize the clinical spectrum of MIS-C in specific populations (12).

Several reports have suggested the existence of different MIS-C phenotypes, including the Kawasaki disease-like (KDL)-MIS-C, the toxic shock syndrome-like (TSSL)-MIS-C, as well as the nonspecific MIS-C with predominantly acute respiratory involvement (NS-MIS-C). Differentiating MIS-C from acute COVID-19 and other hyperinflammatory conditions can be challenging for healthcare providers. The treatment approach for MIS-C includes intravenous immunoglobulin (IVIG), systemic glucocorticoids, and anti-inflammatory biological agents; the efficacy of these treatments relies on the timely diagnosis of MIS-C.

Despite its low prevalence, MIS-C is a serious life-threatening condition. Therefore, this study aimed to examine the clinical characteristics and outcomes of KDL-MIS-C, TSSL-MIS-C, and NS-MIS-C among patients with MIS-C in eight tertiary-care pediatric centers in Mexico. We also performed exploratory analyses to identify coronary artery abnormalities and death-related factors.

2. Materials and methods

2.1. Study design

This was a multicenter, retrospective, observational cohort study including patients diagnosed with MIS-C in one of the eight participating pediatric tertiary care centers in Mexico. Four centers were located in Mexico City: Federico Gómez Mexico Children's Hospital, National Institute of Pediatrics, Siglo XXI Medical Center's Pediatrics Hospital, and. Guadalajara Civil Hospital was located in Guadalajara, Jalisco; Villa Hermosa Children's Hospital was located in Villa Hermosa, Tabasco, and one investigator collected data on cases from the state of Tamaulipas.

The study was approved by Federico Gómez Mexico Children's Hospital Institutional Review Board (approval no. HIM-2022-015) and the local ethics review board of the remaining participating centers.

Probable MIS-C cases were identified by the review of medical records of patients admitted to the emergency room, intensive care unit (ICU), or the general hospital ward for COVID-19. Patient files were evaluated to determine if they met the MIS-C case definition of the Centers for Disease Control and Prevention (Chart 1) (2).

Local investigators at participating centers collected data from the medical records using REDCap (Research Electronic Data Capture) software hosted at Federico Gómez Mexico Children's Hospital. Personal identifiers were kept confidential at participating centers and were not registered in the general database. Data were retrieved from REDCap, inconsistencies and missing data were corrected through direct communication with local investigators, units of measurement were unified, and variables were converted as necessary.

The worst value measured within the first three days of hospitalization was obtained for laboratory parameters with more than one measurement. Life support measures (respiratory support and vasopressor utilization) and the use of IVIG, systemic glucocorticoids, and anticoagulant therapy were documented as primary therapeutic interventions. Outcomes of interest were admission, length of ICU stay and hospitalization, need for invasive mechanical ventilation, vasopressor support, myocardial depression (left ventricular ejection fraction <55%),

TABLE 1 Clinical presentation of cases with MIS-C.

	Total population (N = 239)[a]	Group 1 Toxic shock syndrome like (N = 61)	Group 2 Kawasaki like (N = 70)	Group 3 Nonspenspecific (N = 108)	p-value[b]
Female sex - no. (%)	103 (43.1%)	29 (47.5%)	30 (43.5%)	44 (40.7%)	0.68
Age median (IQR)	7.8 (2.6–13.2)	11.0 (7.1–14.4)	6.8 (2.4–10.5)	6.2 (1.9–13.4)	<0.001
<1 year	30 (12.6%)	2 (6.7%)	6 (20%)	22 (73.3%)	
1–4 years	57 (23.9%)	7 (12.3%)	26 (45.6%)	24 (42.1%)	
5–9 years	54 (22.6%)	14 (25.9%)	19 (35.2%)	21 (38.9%)	
10–14 years	67 (28.03%)	28 (41.8%)	17 (25.4%)	22 (32.8%)	
15–18 years	31 (13.0%)	10 (32.3%)	2 (6.5%)	19 (61.3%)	
Days with symptoms before admission	6 (4–9)	7 (4–8)	4 (2–6)	7 (4–10)	<0.001
SARS-CoV2 infection evidence					
Positive RT- PCR test	105/182 (57.7%)	40/57 (70%)	16/54 (29.6%)	49/71 (69%)	<0.001
Positive rapid antigen test	46/129 (35.7%)	14/34 (41.2%)	9/44 (20%)	23/51 (45.1%)	0.03
Positive RT-PCR or rapid antigen test	130/213 (61.0%)	47/60 (78%)	23/65 (35.4%)	60/88 (68.2%)	<0.001
Positive serology[c]	114/160 (71.3%)	24/37 (64.9%)	43/52 (82.7%)	47/71 (66.2%)	0.08
Previous comorbidities					
Obesity (BMI > 95th percentile)	38 (15.9%)	5 (8.6%)	12 ((17.6%)	21 (19.4%)	0.17
Respiratory	11 (4.6%)	3 (6.7%)	2 (10.5%)	6 (9.8%)	0.76
Neuromuscular	14 (15.9%)	5 (11.1%)	3 (15.8%)	6 (9.8%)	0.69
Cardiovascular	6 (2.5%)	1 (2.2%)	0	5 (8.2%)	0.25
Cancer	16 (6.7%)	7 (15.6%)	0	9 (14.8%)	0.18
Immunosuppression	3 (1.3%)	2 (4.4%)	0	1 (1.6%)	0.74
At least one underlying condition	83 (34.7%)	24 (39.3%)	17 (24.3%)	42 (38.9%)	0.09
Severe underlying condition	41 (17.5%)	15 (24.6%)	4 (5.7%)	22 (20.4%)	0.004
Clinical presentation					
Rash	98 (41%)	30 (49.2%)	49 (70%)	19 (17.6%)	<0.001
Conjunctivitis	118 (49.4%)	32 (52.5%)	59 (84.3%)	27 (25%)	<0.001
Diarrhea	80 (33.5%)	25 (41.0%)	23 (32.9%)	32 (29.6%)	0.31
Emesis	86 (36.0%)	29 (47.5%)	29 (41.4%)	28 (25.9%)	0.01
Abdominal pain	91 (38.1%)	43 (70.5%)	33 (47.1%)	15 (13.9%)	<0.001
Rhinorrhea	57 (23.8%)	22 (36.1%)	21 (30%)	14 (13%)	0.001
Respiratory dysfunction	150 (62.8%)	54 (88.5%)	25 (35.7%)	71 (65.7%)	<0.001
Anosmia/Dysgeusia	11 (4.6%)	5 (8.2%)	2 (2.9%)	4 (3.7%)	0.33
Arthralgias/Myalgias	48 (20.1%)	13 (21.3%)	22 (31.4%)	13 (12.0%)	0.007
Laboratory findings					
Neutrophil count ×10⁶ cells/mcl	8.1 (4.2–13.6)	6.5 (1.7–12.2)	9.5 (6.3–14.9)	7.7 (3.7–12.5)	0.02
Neutrophilia (>7,500 cells/mcl)	130/238 (54.6%)	30 (49.2%)	46/69 (66.7%)	54 (50%)	0.06
Neutropenia (<1,000 cells/mcl)	22/239 (9.2%)	7 (11.5%)	2 (2.9%)	13 (12%)	0.07
Lymphocyte count ×10⁶ cells/mcl	1.4 (0.6–2.6)	0.8 (0.4–1.7)	1.3 (0.9–2.2)	1.8 (0.9–3.4)	<0.001
Lymphopenia[d]	165/237 (69.6%)	44/60 (73.3%)	56/69 (81.2%)	65 (60.2%)	0.01
Lymphocite count <1,000 cells/mcl	82/237 (34.6%)	35 (57.4%)	19 (27.5%)	28 (25.9%)	<0.001
Platelets ×10³ cells/mcl	173 (96–315)	104 (64–165)	193 (99–329)	216 (148–365)	<0.001
Platelets <150 × 10³ cells/mcl	93/239 (38.9%)	41 (67.2%)	25 (35.7%)	27 (25%)	<0.001
Fibrinogen, mg/dl	427 (298–559)	508 (348–617)	401 (306–549)	391 (256–531)	0.24
Fibrinogen >400 mg/dl	104/183 (56.8%)	39/58 (67.2%)	24/51 (47.1%)	41/74 (55.4%)	0.10
Ferritin, mcg/L	557 (304–1,209)	828 (508–1,956)	437 (213–793)	530 (252–1,209)	<0.001
Ferritin >300 mg/dl	144/191 (75.4%)	50/54 (92.6%)	39/59 (66.1%)	55/78 (70.5%)	0.001
Ferritin >1,500 mg/dl	32/191 (16.7%)	14/54 (25.9%)	2/59 (3.4%)	16/78 (20.5%)	0.001
D-Dimer ng/ml	2.2 (1–5)	4.3 (1.7–9.2)	2.1 (1.0–3.8)	1.6 (0.8–4.0)	<0.001
D-Dimer >560 ng/ml (0.56 ng/L)	194/219 (88.6%)	55/58 (94.8%)	57/67 (85.1%)	82/94 (87.2%)	0.178
C-reactive protein (mg/L)	60 (17–180)	15 (7–31.5)	38.7 (14.6–179.5)	22.5 (7.3–86.9)	0.85
C-reactive protein >5 mg/L	200/225 (88.9%)	50/56 (89.3%)	62/68 (91.2%)	88/101 (87.1%)	0.71
Procalcitonin ng/ml	0.85 (0.14–3.6)	1.9 (0.5–4.8)	0.5 (0.0–2.5)	0.5 (0.1–2.5)	0.005
Procalcitonin >0.15 ng/ml	126/171 (73.7%)	49/55 (89.1%)	27/41 (65.9%)	50/75 (66.7%)	0.005
Albumin <3 g/dl	133/222 (59.9%)	51/61 (83.6%)	40/66 (60.6%)	42/95 (44.2%)	<0.001

[a]N in the column heading was used to calculate proportions if not otherwise specified. For variables with missing data, denominators are reported in each cell.
[b]One-sided Fisher exact test/Mann−Whitney test for comparison between groups 1, 2, and 3.
[c]Nucleocapsid antibody in all cases.
[d]Lymphopenia: <2 years: <4,000, 2−3 years: <3,000, >4 years: <1,500 cells/mcl.

coronary aneurysm (coronary artery diameter z-score ≥2.5) and coronary artery dilatation (diameter z-score >2 to <2.5) on the echocardiographic evaluation performed during hospitalization, and in-hospital mortality.

In the present study, severe respiratory involvement was defined as the presence of infiltrates on chest x-ray or computed tomography plus the need for either oxygen therapy at 80% or higher concentration or positive pressure ventilation. Additionally, "gastrointestinal symptoms" was defined as the presence of at least one of the following: abdominal pain, diarrhea, and emesis. Severe underlying conditions included cancer and other immunosuppressive states, neuromuscular disability, chronic respiratory diseases except for asthma, congenital cardiac disorders, and chronic kidney failure.

Centers involved had different capacities to perform echocardiograms. When performed, echocardiograms were done either by a trained cardiologist who made an extensive heart evaluation, including the diameter of coronary arteries, or by emergency staff where the main aim was measurement of ventricular function for life support-oriented purposes.

2.2. Statistical analysis

Descriptive analyses were conducted using STATA v.14.0 (StataCorp, Houston, TX, USA). Categorical variables were reported as frequencies, and continuous variables were reported as medians with interquartile ranges.

In the present study, we utilized latent class analysis (LCA) to classify 239 patients into the TSSL-PIMS, KDL-PIMS, and U-PIM groups, congruent with the phenotypes identified in previous studies (13–15). LCA is a probabilistic modeling algorithm that allows clustering cases by associating indicator categorical variables. Three-class LCA was conducted using the R software package "poLCA" with 100 iterations to identify the clusters. The fit of each model was assessed using the Bayesian information criterion score. Indicator variables used in the final LCA model were the 20 features of Kawasaki disease, KDL-MIS-C, NS-MIS-C-TS, and TSSL-MIS-C (Table 1 and Supplementary Chart S1).

Potential heterogeneity among the participating centers was addressed by determining 95% confidence intervals (CIs) of the frequencies of measured outcomes using random-effects meta-analysis. Odds ratios (ORs) with 95% CIs of pooled data were calculated using clustered-robust standard error adjustment. ORs adjusted for the participating centers were calculated using multilevel mixed-effects logistic regression.

3. Results

Of the 264 identified patients, 6, 11, and 8 were excluded due to duplicate records, lack of evidence on multi-organ involvement, and lack of evidence of previous SARS-CoV-2 infection or confirmed epidemiological contact, respectively. Tables 1, 2 summarize the clinical characteristics and outcomes of the remaining 239 patients included in the final analysis.

LCA indicated that 61 (26%), 70 (29%), and 108 (45%) of the patients exhibited the clinical profiles of TSSL-MIS-C, KDL-MIS-C, and NS-MIS-C, respectively (Table 1). The median age was higher in the TSSL-MIS-C group than in the overall cohort (11 [IQR: 7.1–14.4] vs. 7.8 [IQR: 2.6–13.2] years). Duration of clinical symptoms before diagnosis was significantly shorter in the KDL-MIS-C group than in the other two clinical groups ($p <$ 0.001). Additionally, the frequency of virologic positivity for acute SARS-CoV-2 infection was lower ($p < 0.001$) and the frequency of serologic positivity tended to be higher ($p = 0.08$) in the KDL-MIS-C group than in the other two clinical groups. Only four (5.7%) children in the KDL-MIS-C group had a severe underlying condition, while it was present in 15 (24.6%) and 22 (20.4%) of the TSSL-MIS-C and NS-MIS-C, respectively. The levels of plasma inflammatory markers were highest in the TSSL-MIS-C group compared with the other two clinical groups.

Table 2 describes treatments and outcomes in the total study population and the three clinical groups. IVIG and systemic glucocorticoids were administered in 172 (42%) and 187 (78.2%) of the patients, respectively; both treatments were more frequently (93% and 91%) administered to patients in the KDL-MIS-C group. Anticoagulant therapy was prescribed in 99 (41.4%) of the whole cohort and administered more frequently (60%) in the TSSL-MIS-C group. Oxygen supplementation and vasopressor support were required in 143 (59%) and 92 (39%) of the whole cohort, respectively.

An echocardiogram was performed in 194 cases, of which 159 reported values of coronary arteries diameters. Left ventricular ejection fraction was below 55% in 61/195 (31%) of the patients, and coronary artery dilatation and aneurysm were observed in 9/159 (5.7%) and 21/159 (13.2%), respectively. The entire cohort's median in-hospital stay was eight days (IQR: 5–13), and about half (54.4%) of the patients were admitted to the ICU. There were 13 in-hospital deaths (5.4%), including eight patients with severe underlying conditions and two from causes unrelated to SARS-COV-2 infection. Most deaths (69%) occurred in the TSSL-MIS-C group, whereas none occurred in the KDL-MIS-C group.

Hematologic, neurologic, gastrointestinal, mucocutaneous, and renal dysfunction were frequently observed, with frequency variability among the clinical groups. Prolonged coagulation time based on international normalized ratio, low platelet count, gastrointestinal symptoms, and acute renal injury were more frequent in the TSSL-MIS-C group (61%, 67%, 90%, and 33% of the patients, respectively) than in the other clinical groups.

Coronary aneurysm or dilatation occurred in 27 (11.3%) patients (2). After adjustment for cluster effect, symptom duration >10 days before hospital admission was the only factor significantly associated with coronary artery abnormalities (OR: 1.6, 95% CI: 1.2–2.0) (Table 3).

There were thirteen deaths; eight of them had a severe underlying condition. Three cases with a fatal outcome were on antineoplastic chemotherapy, one case with medulloblastoma was on palliative care, and a kidney transplant recipient had a diagnosis of sepsis with a possible respiratory infection. Besides, one of the cancer patients with a germ cell tumor developed a deep vein thrombosis. A case with chronic granulomatous

TABLE 2 Treatment and outcomes of cases with MIS-C.

	Total sample (N = 239)[a]	OR (IC 95%[b])	Between centers heterogeneity I² (p)	Group 1 Toxic shock like (N = 61)	Group 2 Kawasaki like (N = 70)	Group 3 Nonspecific (N = 108)	p-value[c]
Treatment – no. (%)							
Intravenous immune globulin	172 (42.0%)	0.76 (0.58–0.94)	70.3% (<0.001)	49 (80%)	65 (93%)	58 (53.7%)	<0.001
Systemic steroids	187 (78.2%)	0.81 (0.67–0.94)	54.1% (<0.001)	52 (85%)	64 (91%)	71 (66%)	<0.001
Anticoagulation therapy	99 (41.4%)	0.35 (0.10–0.60)	96.4% (<0.001)	42 (69%)	16 (23%)	41 (38%)	<0.001
Ventilatory support needed - no (%)							
Any oxygen supplementation	143 (59.8%)	0.54 (0.34–0.72)	94.5% (<0.001)	57 (93.4%)	30 (43%)	56 (52%)	<0.001
Non-invasive mechanical ventilation	14 (5.9%)	0.07 (0.01–0.13)	62.5% (0.0)	8 (13%)	0	6 (5.6%)	0.006
Invasive mechanical ventilation	57 (23.9%)	0.19 (0.04–0.33)	91.7% (>0.001)	41 (67.2)	0	16 (15%)	<0.001
Any infiltrates in chest Rx or CT[d]	127/224 (56.7%)	0.46 (0.22–0.71)	94.1% (<0.001)	46 (75%)	19 (27%)	62 (57%)	<0.001
Severe respiratory involvment[e]	82/239 (34.3%)	0.32 (0.19–0.44)	75.7% (<0.001)	36 (59%)	16 (22%)	30 (27%)	<0.001
Cardiovascular involvement							
LVEF[e] <55%	61/194 (31.4%)	0.43 (0.31–0.55)	47.6% (0.13)	25 (41%)	7 (10%)	29 (27%)	<0.001
LVEF <45%	20/194 (10.3%)	0.14 (0.06–0.22)	37.8% (0.19)	7 (12%)	1 (1.4%)	12 (11%)	0.02
LVEF <35%	10/194 (5.2%)	0.04 (0.01–0.11)	–	3 (5%)	0	7 (7%)	0.05
Coronary aneurysm (z > 2.5)	21/159 (13.2%)	0.19 (0.06–0.32)	61% (0.04)	6 (10%)	6 (9%)	9 (8%)	0.87
Coronary dilatation (z: 2–2.5)	9/159 (5.7%)	0.12 (0.04–0.21)	0% (0.48)	1 (2%)	4 (6%)	4 (4%)	0.47
Vasopressor support – no (%)	92/235 (39.2%)	0.35 (0.10–0.6)	96.4% (<0.001)	48 (79%)	4 (6%)	40 (37%)	<0.001
Hematologic involvement							
INR > 1.2	104/233 (44.6%)	0.46 (0.30–0.62)	82.8% (<0.001)	37 (61%)	31 (44%)	36 (33%)	0.002
Platelets count <150,000 cell/mcl	93 (38.9%)	0.40 (0.31–0.48)	41.2% (0.12)	41 (67%)	25 (36%)	27 (25%)	<0.001
Neurologic involvement	16 (6.7%)	0.06 (0.03–0.09)	0% (0.74)	3 (5%)	4 (6%)	9 (8.3%)	0.43
Gastrointestinal involvement	175 (73%)	0.74 (0.60–0.89)	89.2% (<0.001)	55 (90%)	57 (80%)	63 (58%)	<0.001
Alanine Aminotransferase >90 U/L	53/203 (26.1%)	0.24 (0.15–0.33)	52.2% (0.06)	19 (31%)	14 (20%)	20 (19%)	0.08
Mucocutaneous involvement	192 (80.3%)	0.83 (0.72–0.93)	80.9% (<0.001)	52 (81%)	70 (100%)	70 (69%)	<0.001
Acute Kidney Injury[f]	35/226 (15.5%)	0.14 (0.09–0.20)	33.9% (0.20)	20 (33%)	6 (9%)	9 (8%)	<0.001
ICU[g] admission	130 (54.4%)	0.43 (0.17–0.69)	–	52 (85%)	42 (60%)	36 (33%)	<0.001
Length of ICU stay, days (n = 129)	4 (2–7)	–	–	5 (3–8)	3 (2–6)	4 (2–7)	0.34
Length of Hospital stay days	8 (5–13)	–	–	10 (6–17)	8 (6–12)	8 (4–13)	0.10
Any cause in-hospital deaths	13 (5.4%)	0.05 (0.01–0.09)	40.1% (0.17)	9 (15%)	0	4 (4%)	<0.001
Died from SARS COV-2	11 (4.6%)	0.04 (0.0–0.08)	54.5% (0.09)	8 (13%)	0	3 (3%)	<0.001

[a]N was used to calculate proportions if not otherwise specified. For variables with missing data, denominators are reported in each cell.
[b]Exact confidence intervals by random effects metaanalisis of eight centers data. This analysis excludes centers with frequencies =0% and 100%, which explains the difference in point estimate with the first column.
[c]Exact Fisher Kruskal Kruskal Wallis as suitable for comparison between groups 2 and 3.
[d]Rx: chest x-ray, CT: Computed tomography.
[e]LVEF, left ventricular ejection fraction.
[f]Acute Kidney Injury (AKI) was defined as an increase greater than two times the upper limit of the reference range for gender and age.
[g]ICU: intensive care unit.

TABLE 3 Coronary artery aneurism or dilatation associated factors.

	Frequency in the aneurism/dilatation group N = 27 (%)	Unadjusted OR (95% CI)[a]	p-value	OR adjusted for center[b]	p-value
Sex (male)	19/27 (70.4%)	2.20 (0.99–4.9)	0.05	1.71 (0.63–4.58)	0.29
Age ≥10 years	5/27 (18.5%)	0.31 (0.05–2.04)	0.22	0.55 (0.17–1.80)	0.32
≥10 days with symptoms before admission	10/25 (40%)	4.16 (2.61–6.23)	<0.001	1.62 (1.19–2.04)	<0.001
Positive SARS-COV-2 RT-PCR or rapid antigen test	12/20 (60%)	0.70 (0.13–3.73)	0.67	1.11 (0.31–3.96)	0.87
Positive SARS-COV-2 serology	16/20 (80%)	2.58 (0.77–8.64)	0.125	1.45 (0.36–5.89)	0.60
Obesity (BMI > 95th percentile)	16/20 (80%)	1.04 (0.53–2.04)	0.92	1.40 (0.37–5.37)	0.63
Rash	9/27 (33%)	0.49 (0.10–2.29)	0.36	0.69 (0.25–1.91)	0.48
Conjunctivitis	17/27 (63.0%)	1.5 (0.33–6.92)	0.60	1.82 (0.57–5.77)	0.31
Gastrointestinal	16/27 (59.3%)	0.39 (0.10–1.49)	0.17	0.70 (0.22–2.15)	0.54
Severe respiratory dysfunction	11/27 (40.74%)	1.53 (0.63–3.71)	0.35	1.56 (0.59–4.18)	0.37
Arthralgias/Myalgias	2/27 (4.41%)	0.21 (0.05–0.94)	0.04	0.13 (0.02–0.67)	0.015
Mucocutaneous involvement	13/27 (48.15%)	0.35 (0.17–0.70)	0.003	0.74 (0.25–2.17)	0.59
Neutrophilia (>7,500 cells/mcl)	19/27 (70.37%)	2.13 (0.82–5.58)	0.12	1.87 (0.67–5.22)	0.23
Lymphopenia[c]	15/27 (55.56%)	0.52 (0.20–1.31)	0.17	0.40 (0.15–1.10)	0.08
Platelets count <150,000 cell/mcl	7/27 (25.93%)	0.48 (0.17–1.40)	0.18	0.48 (0.16–1.37)	0.17
Fibrinogen >400 mg/dl	11/21 (52.38%)	0.68 (0.26–1.75)	0.42	0.86 (0.31–2.37)	0.77
Ferritin >300 mg/dl	18/20 (90%)	4.39 (0.81–23.89)	0.09	4.50 (0.90–22.5)	0.07
D-Dimer >560 ng/ml (0.56 ng/L)	24/26 (92.3%)	1.64 (0.41–6.47)	0.48	0.97 (0.17–5.66)	0.98
C-reactive protein >5 mg/L	26/27 (96.3%)	2.41 (0.47–12.4)	0.29	2.68 (0.28–25.31)	0.39
Procalcitonin >0.15 ng/ml	15/23 (65.2%)	0.45 (0.27–0.76)	0.003	0.84 (0.23–3.00)	0.75
Albumin <3 g/dl	20/27 (74.07%)	1.83 (0.72–4.62)	0.20	1.62 (0.57–4.63)	0.90
INR > 1.2	14/27 (51.85%)	1.37 (0.54–3.54)	0.50	2.45 (0.86–7.00)	0.093
LVEF[d] < 55%	8/25 (32%)	1.25 (0.30–5.1)	0.76	1.49 (0.50–4.47)	0.45
Alanine Aminotransferase >90 U/L	4/25 (16%)	0.53 (0.19–1.43)	0.21	0.97 (0.26–3.70)	0.97
Intravenous immune globulin	27/27 (100%)	–	–	–	–
Systemic steroids	21/27 (77.78%)	0.9 (0.16–4.93)	0.90	0.96 (0.27–3.3)	0.95
Group 1 (TSS-like)	7/27 (25.9%)	1 (reference)	–	1 (reference)	–
Group 2 (Kawasaki-like)	9/27 (33.3%)	1.14 (0.29–4.45)	0.85	0.66 (0.17–2.58)	0.55
Group 3 (Unespecific presentation)	11/27 (40.7%)	1.25 (0.25–6.15)	0.78	0.59 (0.15–2.31)	0.45

[a]Clustered robust standard error adjustment.
[b]OR adjusted for center with multilevel mixed-effects logistic regression.
[c]Lymphopenia: <2 years: <4,000, 2−3 years: <3,000, >4 years: <1,500 cells/mcl.
[d]LVEF, Left ventricular ejection fraction.

diseases, a patient with Down syndrome, and a case with a severe neuromuscular disability had diagnoses of pneumonia on admission. Of the five previously healthy cases, one presented as a nephrotic syndrome and myocarditis, and another received the diagnosis of hepatorenal syndrome on admission. The three remaining cases presented with severe respiratory distress syndrome, heart failure, and coagulopathy.

Risk factors for death were age ≥10 years (OR: 5.6, 95% CI: 1.4–2.04), presence of at least one underlying condition (OR: 5.3, 95% CI: 1.5–18.4), severe underlying condition such as cancer (OR: 9.3, 95% CI: 2.8–31.0), platelet count <150,000 /mm^{3} (OR: 4.2, 95% CI: 1.2–14.7), international normalized ratio >1.2 at admission (OR: 3.8, 95% CI: 1.05–13.9), and serum ferritin concentration >1,500 mg/dl (OR: 52, 95% CI: 5.9–463) (Table 4).

The patient population was not homogeneous among the eight participating centers. Heterogeneity was high for almost all calculated treatment and outcome frequencies, and I^2, a measure of heterogeneity, was 50% for most of the factors. Accordingly, association measures were adjusted for the center effect. A significant cluster effect of the reporting center was demonstrated

for every evaluated factor in Tables 3, 4. Disaggregated data collected from the five centers with more included cases are presented in Supplementary Tables S1, S2.

4. Discussion

MIS-C, a recently characterized clinical presentation secondary to SARS-CoV-2 infection, is closely associated with Kawasaki disease and toxic shock syndrome. In the present study, we aimed to summarize the clinical characteristics and outcomes of patients with MIS-C treated in eight pediatric tertiary care centers across Mexico. Our analyses reveal that our study shares several similarities with those reported previously while exhibiting some differences, thus highlighting the high heterogeneity in disease presentation and outcomes among the participating centers.

It is relevant and essential to examine the clinical characteristics, disease management, and outcomes of MIS-C due to the potentially severe consequences such as death (16–18), damage to coronary arteries, and the toll on healthcare resources

TABLE 4 Characteristics of deaths and associated conditions.

	Deaths (N = 13)	p[a]	OR (IC 95%)[b]
Female sex - no. (%)	4	0.26	0.57 (0.17–1.96)
Age-median (IQR)	14.4 (10.6–15.3)	0.02	–
<1 year	2		–
1–4 years	1		
5–9 years	0	–	
10–14 years	6		
15–18 years	4		
Age ≥10 years	10	0.008	5.64 (1.43–22.22)
Days of symptoms before admission	4 (2–5)	0.4	
More than 10 days since symptom onset	3	0.39	1.53 (0.36–6.47)
Positive RT-PCR test	8/10	0.11	3.13 (0.76–12.81)
Positive rapid antigen test	2/6	0.49	0.80 (0.17–3.69)
Positive RT-PCR or rapid antigen test	8/12	0.47	1.42 (0.38–5.28)
Positive SARS-CoV-2 serology	3/4	0.67	0.81 (0.05–13.62)
Obesity (BMI > 95th percentile)	0	0.09	–
Respiratory	1	0.58	1.08 (0.11–10.82)
Neuromuscular	3	0.06	3.73 (0.73–19.19)
Cardiovascular	0	0.63	–
Cancer	4	0.016	6.3 (1.3–30.6)
Immunosuppression (not oncological)	2	0.20	6.99 (0.41–119.11)
Kidney transplant recipient	1		1.69 (0.15–18.7)
At least one underlying condition	9	0.01	5.3 (1.5–18.4)
Severe underlying condition	8	<0.001	9.3 (2.8–31.0)
On palliative care	1	–	–
Lymphocyte count ×10⁶ cells/mcl - median (IQR)	0.6 (0.3–1.4)	0.01	–
Lymphopenia[d]	10	0.40	1.4 (0.4–5.5)
Platelets ×10³ cells/mcl	94 (46–191)	0.03	–
Platelets <150 × 10³ cells/mcl _median (IQR)	9	0.023	4.2 (1.2–14.7)
Fibrinogen, mg/dl	94 (46–191)	0.89	–
Fibrinogen >400 mg/dl	6/8	0.24	2.48 (0.47–13.15)
Ferritin, mcg/L median (IQR)	3,619 (2,108–4,752)	<0.001	–
Ferritin >300	9/9	0.04	–
Ferritin >1,500	8/9	<0.001	52 (5.9–463)
Intravenous immune globulin	8	0.28	0.34 (0.08–1.44)
Systemic steroids	11	0.43	1.28 (0.25–6.61)
Anticoagulation therapy	7	0.25	1.52 (0.45–5.15)
Coronary aneurysm (z score >2.5)	0/2	0.75	–
Coronary dilatation (z score >2 to <2.5)	0/2	0.89	–
INR > 1.2	9	0.06	3.8 (1.05–13.9)
ICU[c] admission	11	0.02	(1.14–37.11)
Group 1 (TSS-like)	9		1 (reference)
Group 2 (Kawasaki like)	0	0.001	–
Group 3 (Unespecific presentation)	4		0.15 (0.03–0.66)

[a]Comparison with surviving cases with one tailed exact Fisher test or Mann–Whitney U test.
[b]OR adjusted by center with multilevel mixed effects logistic regression.
[c]ICU, intensive care unit.
[d]Lymphopenia: <2 years: <4,000, 2–3 years: <3,000, >4 years: <1,500 cells/mcl.

necessary for its management. The present cohort's mortality rate was 4.6%, which exhibited high heterogeneity across the centers, ranging from 0% to 13.5%. Similarly, the rate of coronary artery abnormalities, which was 18.9% in the overall cohort, ranged from 0% to 56.3% across the participating centers. Published systematic reviews estimate mortality and a rate of coronary artery abnormalities ranging from 0% to 4% and from 11.6% to 21.7%, respectively, in patients with MIS-C, according to the systematic reviews (14, 19–22). In the present study, coronary artery abnormalities were observed in all three clinical groups, with no significant difference in frequency.

Among the factors that might explain the high heterogeneity in outcomes between the centers included in our study and the previously published case series are (i) a wide spectrum of clinical presentation in the presence of relatively nonspecific diagnostic criteria that are currently used for MIS-C, (ii) variations in ethnicity and prevalence of comorbid conditions, and (iii) variations in access, diagnostic paths, and therapeutic interventions across different healthcare systems.

Attempts have been made to classify cases according to their predominant clinical characteristics to address the lack of specific diagnostic criteria and, thus, phenotype heterogeneity. In the

Chart 1 Case definition criteria for MIS-C.

1. Fever	
2. Elevation of inflammation markers	At least one of the following: • C-Reactive Protein (CRP) >5 mg/L • Procalcitonin >0.15 ng/ml • Ferritin >300 mcg/L • Fibrinogen >400 mg/dl • D-Dimer >560 ng/ml • Neutrophils >7,500 cells/mcl • Lymphopenia: <2 years: <4,000, 2–3 years: <3,000, >4 years: <1,500 cells/mcl • Albumin <3 g/dl
3. At least two systems involved	3.1 Cardiovascular. At least one of the following: • Required vasoactive drug • Left ventricular ejection fraction <55%
	3.2 Respiratory. At least one of the following: 3.3 Supplementary oxygen with non-rebreathing mask or higher oxygen concentration device. • Oxygen saturation <90% • Pulmonary infiltrates in chest x-ray or Computed Tomography
	3.4 Neurologic. At least one of the following: 3.5 Glasgow score <14 if not sedated • Meningismus • Seizures
	3.4 Hematologic. At least one of the following: • Platelets <150,000 cells/mcl • INR > 1.2 s
	3.5 Gastrointestinal. At least one of the following: • Abdominal pain • Vomit • Diarrhea • Alanine aminotransferase (ALT) >90 U/L
	3.6 Mucocuteneous. At least one of the following: • Rash • Extremity edema • Desquamation • Mucosal inflammation • Conjunctivitis
	3.7. Renal Creatinine >twice the upper limit of the reference range for age
4. Hospitalization	
5. No alternative diagnosis	• No positive blood culture during the first 48 h in the hospital • In uncertain cases, complete file review and consensus by an expert panel.
6. Present or recent infection by SARS-COV-2	At least one of the following • Positive RT-PCR[a] for SARS-CoV-2 • Positive serology for SARS-CoV-2 • Contact with a confirmed positive COVID-19 case in the last four weeks.

[a]Reverse transcriptase polymerase chain reaction.

present study, we utilized LCA to classify 239 patients into the TSSL-MIS-C, KDL-MIS-C, and U-PIM groups, congruent with the phenotypes identified in previous studies (13–15) In the present study, patient age differed among the clinical groups; additionally, the frequency of virologic positivity was lower, and

the frequency of serologic positivity was higher in the KDL-MIS-C group than in the other two clinical groups, suggesting different underlying pathologic mechanisms at play. Multiple pathologic mechanisms have been shown to be altered in MIS-C, including the possible involvement of superantigens and autoantibodies (23). The levels of plasma inflammatory markers were highest in the TSSL-MIS-C group. Additionally, the rate of life support measures and mortality rate were highest in this group. The vagueness of the current clinical criteria for MIS-C might be partially responsible for the wide variation in the rate of these three clinical phenotypes reported by each center, suggesting a lack of clarity among physicians for the threshold of clinical manifestations that eventually leads to the diagnosis of MIS-C (Supplementary Table S1).

Demographic and preexisting medical conditions of patients in different published series and clinical groups widely vary, likely accounting for some of the heterogeneity observed in outcomes.

In the present study, 34.7% of the cohort had underlying conditions, which was higher than that reported by Radia et al. and Antúnez et al. (24). In the present cohort, severe underlying conditions were present in 17.5% of the patients varying from 3.6% to 23.1% across the participating centers. In addition, the frequency of patients with cancer/immunosuppressive disorders or neuromuscular conditions was four to tenfold. In contrast, the observed frequency of obesity (15.9%) was not as high as that reported by other studies (25). Notably, 9 of the 13 deaths in the present cohort had a severe underlying condition, and the mortality was highest in the center with the highest rate of patients with severe underlying conditions and the highest proportion of patients with TSSL-MIS-C. These findings suggest that the high rate of severe underlying conditions might explain the relatively high mortality observed in the present cohort.

Although the centers included in the present study are tertiary care reference hospitals, they belong to different healthcare systems with different protocols for service delivery and different resources for the management of patients during the COVID-19 pandemic; the difference in frequencies of IVIG utilization (from 45% to 94%) might be a reflection of this aspect. In addition, there is evidence of an association between delayed access to health services and worst outcomes, which might explain differences in risk for bad outcomes across different geographic locations (11). Of note, the only factor that was significantly associated with the development of coronary artery abnormalities after adjustment for center effect was a delay of ≥10 days in hospital admission after the onset of symptoms, a factor likely influenced by socioeconomic and geographic factors.

Factors associated with mortality were age ≥10 years, severe underlying condition, thrombocytopenia, hyperferritinemia, and toxic shock syndrome phenotype. A study in a larger cohort might reveal an association with other factors, such as IVIG use and coagulopathy. Abrams et al. reported that older age, non-Hispanic black ethnicity, disease onset before June 1, 2020, and high levels of serum D-dimer, troponin, atrial natriuretic peptide, C-reactive protein (CRP), ferritin, and interleukin-6 were associated with ICU admission in patients with MIS-C. The authors also reported abdominal pain and shortness of breath as

clinical findings at hospitalization admission predicting subsequent ICU admission (26).

According to most systematic reviews, myocarditis is the most frequent complication observed in patients with MIS-C; however, it was not examined in the present study due to the lack of a standardized definition among the participating centers. However, left ventricular ejection fraction, which was below 55% in 31% of the cohort, might be considered a proxy for this outcome. In addition, we did not evaluate socioeconomic status, ethnicity, and the levels of D-dimer, troponin-B, natriuretic peptide, or interleukin-6, which were assessed in previous studies.

Our study has several limitations. One of them is related to the heterogeneity of participating centers, the variable reliability of data captured in the different centers, and the high frequency of missing data for some variables. Also, cardiologic outcomes are limited to a single in-hospital measurement with a lack of follow-up. Besides, data collection was started months before the publication of updated case definition criteria for multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection (5). With the updated criteria, 32 cases would not have been included in the final analysis. Of these, 19 observations would not have met the criteria regarding the involvement of two or more systems after the elimination of the respiratory, renal, and neurological criteria, and the modification of the hematological system criteria. Thirteen cases that did have two or more systems involved according to the new criteria had a CRP < 3.0 mg/dl and thus would not have been included; however, these 13 cases did have elevation of at least another inflammation marker according to definitions given in Chart 1.

In conclusion, death was an infrequent outcome in patients with MIS-C, occurring mainly in older patients with severe underlying conditions, whereas coronary aneurysms were primarily associated with delayed treatment. Extrapolation of the frequency of observed outcomes to the general population might not be valid due to the high frequency of comorbid conditions and the heterogeneity of participating centers. The causal association of risk factors with adverse outcomes should be further analyzed in longitudinal studies with sufficient statistical power to adjust for multiple confounding factors found in the present cohort.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Hospital Infantil de México Federico Gómez Ethics and Investigation Review Board del Hospital Infantil de México

Federico Gómez. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1167871/full#supplementary-material.

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