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Multisystem inflammatory syndrome in children across 16 Latin American countries: A multicenter study from the REKAMLATINA Network

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ABSTRACT

Objectives: Our aim was to describe the epidemiology and outcomes of multisystem inflammatory syndrome in children (MIS-C) in Latin America.

Methods: We conducted an observational, retrospective, and prospective multicenter study that gathered information from 84 participating centers across 16 Latin American countries between August 1, 2020 and June 30, 2022.

Results: Of the 1239 reported children with MIS-C, 84.18% were previously healthy. The most frequent clinical manifestation in our studied population was abdominal pain (N = 804, 64.9%), followed by conjunctival injection (N = 784, 63.3%). The median duration of fever at the time of hospital admission was 5 days and a significant number of subjects required admission to an intensive care unit (N = 589, 47.5%). Most of the subjects (N = 1096, 88.7%) were treated with intravenous immunoglobulin, whereas 76.7% (N = 947) were treated with steroids, of whom 10.6% (N = 100) did not receive intravenous immunoglobulin. The death rate attributed to MIS-C was 4.88%, with a rate of 3.39% for those initially diagnosed with MIS-C and 8.85% for those whose admission diagnosis was not MIS-C (P <0.001, odds ratio 2.76, 95% confidence interval 1.6-4.6).

Conclusions: One of the most significant findings from our study was the death rate, especially in those not initially diagnosed with MIS-C, in whom the rate was higher. This highlights the importance of increasing awareness and making an earlier diagnosis of MIS-C in Latin America.

Introduction

During the early stage of the pandemic, it was suggested that children might be less susceptible to SARS-CoV-2 infection and be either asymptomatic or develop only a mild infection [2,3]. However, in April 2020, there were initial reports in the pediatric population of a severe clinical condition in children with recent SARS-CoV-2 exposure or infection, named multisystem inflammatory syndrome in children (MIS-C). Although infrequent, MIS-C caused cardiovascular dysfunction requiring admission to the intensive care unit (ICU) in around 60% and, ultimately, death in 2% of cases [4]. Two independent studies have described this syndrome more severe and frequently in Afro-Caribbean and Latino/Hispanic populations [5,6]. There have been initial clinical reports of MIS-C in Latin America, including Mexico [7], Peru [8], Colombia [9], and Brazil [10], as well as a compilation of cases across five Latin American countries [6]. In August 2020, we pivoted our Latin American Kawasaki Disease Network (Red de la Enfermedad de Kawasaki en America Latina [REKAMLATINA]) to collect prospective and retrospective data on patients with MIS-C throughout the Latin American region. This presented us with the opportunity to provide a comprehensive evaluation of MIS-C in Latin American children. Our aim was to understand the epidemiology and outcomes of MIS-C in Latin America. The secondary objective was to identify whether a difference exists in the mortality between the patients who were earlier diagnosed with MIS-C and patients who received another diagnosis at admission.

Methods

Data collection

This is an observational, retrospective, prospective, multicenter study that gathered information from 84 participating centers across 16 Latin American countries: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, El Salvador, and Uruguay. All the data used in this study were obtained from the REKAMLATINA-3 Research Electronic Data Capture (REDCap) database, housed at the University of California San Diego KD Research Center [11]. Written approval by an institutional review board or bioethics and research committee was required for each participant center before enrollment of the patients. Data were abstracted from the subjects' medical records and uploaded to the REDCap database by team members at each individual site. This database received institutional review board approval at the University of California, San Diego (La Jolla, CA, USA).

The information collected from each patient included demographic and clinical characteristics, laboratory results, echocardiographic data, treatments, and patient outcome. Hemoglobin concentrations were age-adjusted, and the values were expressed as SDs from the mean according to the following formula: ([observed hemoglobin] − [mean hemoglobin for age] ÷ SD for age) [12].

Study definitions

The case definition of MIS-C used in this study included the following criteria: an individual aged <21 years presenting with fever (body temperature ≥ 38.0°C or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (including but not limited to one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin-6, elevated neutrophils, reduced lymphocytes, and low albumin), evidence of clinically severe illness requiring hospitalization, with multisystem (two or more) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), and laboratory-confirmed SARS-CoV-2 infection (positive SARS-CoV-2 real-time reverse transcription–polymerase chain reaction or antibody test during hospitalization) or an epidemiologic linkage (close contact with a confirmed or probable case of COVID-19 within the 4 weeks before the onset of symptoms) [3].

Statistical analysis

Categorical variables were described as frequencies and percentages and continuous variables with median and interquartile range. Chi square and Fisher's exact tests were used to determine whether the medians of two groups were statistically different (Epi Info v.7.0 software, Centers for Disease Control). We performed an odds ratio analysis to evaluate the differences in mortality between the patients who had an initial diagnosis of MIS-C and patients who had an alternative diagnosis upon admission. We considered P <0.05 as statistically significant.

Results

We collected data on 1239 subjects aged less than 18 years ultimately diagnosed with MIS-C at participating sites between August 1, 2020 and June 30, 2022. Most children included in this study were previously healthy (N = 1043, 84.18%).

Most of our subjects and guardians self-identified as *mestizo* (64.6%) (Table 1). The most frequent clinical manifestation in our studied population was abdominal pain (N = 804, 64.9%), followed by conjunctival injection (N = 784, 63.3%). The median duration of fever at the time of hospital admission was 5 days. Although the median white blood cell count was within normal limits, there was a preponderance of lymphopenia (median 1260 μL). The median laboratory values reflecting

Table 1
Demographic and clinical characteristics of children in Latin America diagnosed with multisystem inflammatory syndrome in children.

Characteristic[a]	N (%) or median (interquartile range)
Age, years	6.5 (2.8,10.6)
Sex	
Male	699 (56.4%)
Ethnicity	
Mestizo	800 (64.6%)
White	304 (24.5%)
Unknown	98 (7.9%)
Afro-Latino	25 (2.0%)
Indigenous	12 (1.0%)
Clinical characteristics	
Abdominal pain	804 (64.9%)
Conjunctival injection	784 (63.3%)
Rash	759 (61.3%)
Emesis	692 (55.9%)
Diarrhea	573 (46.2%)
Extremity changes	513 (41.5%)
Cervical lymphadenopathy	360 (29.1%)
Strawberry tongue	325 (26.2%)
Myalgia	290 (23.4%)
Arthralgia	200 (16.2%)
Arthritis	87 (7.0%)
Days of fever on admission	5 (4, 7)
Laboratory data	
White blood cells, cells/μL	11,300 (7,400, 16,100)
Neutrophils, cells/μL	7720 (4,209, 11,920)
Lymphocytes, cells/μL	1260 (680, 2,380)
Bands, cells/μL	40 (0, 376)
Platelet count, platelets/μL	190,000 (112,000, 293,750)
Z-hemoglobin	−1.7 (−3.2, 0.3)
ESR, mm/hour	39 (22, 60)
CRP, mg/dL	14.0 (6.4, 24.4)
Sodium, mEq/L	135 (132, 138)
ALT, IU/L	40 (22, 79)
AST, IU/L	43 (28, 80)
GGT, IU/L	52 (22, 131.8)
Albumin, g/dL	3.0 (2.6, 3.6)
Procalcitonin, ng/mL	3.6 (0.8, 14.0)
Creatinine, mg/dL	0.5 (0.3, 0.7)
Globulins, g/dL	2.7 (2.2, 3.2)
Total bilirubin, mg/dL	0.5 (0.3, 0.7)
Direct bilirubin, mg/dL	0.2 (0.1, 0.5)
Indirect bilirubin, mg/dL	0.3 (0.2, 0.5)
ALP, U/L	168 (126, 245)
CPK, U/L	61 (32, 142)
LDH, U/L	317 (249, 468)
Triglycerides, mg/dL	180 (123, 268)
Ferritin, ng/mL	440 (226, 927)
ProBNP, pg/mL	1275 (304, 6689.3)
Troponin, ng/mL	0.05 (0.01, 0.27)
Cortisol, ug/dL	22.1 (14.7, 60.1)
Prothrombin, sec	14 (12.6, 15.9)
Thromboplastin, sec	32.9 (28.2, 38.5)
INR	1.2 (1.1, 1.3)
Fibrinogen, g/L	5.2 (3.8, 7.2)
Dimer D, mg/L	2.7 (1.5, 4.9)

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma glutamyl-transferase; INR, international normalized value; LDH, dehydrogenase lactic; proBNP, pro B-type natriuretic peptide.

[a] Total number of subjects for whom each characteristic was available was available: age: 1238; sex: 1239; ethnicity: 1239; abdominal pain: 1239; conjunctival injection: 1239; rash: 1239; vomit: 1239; diarrhea: 1239; extremity changes: 1236; cervical lymphadenopathy: 1239; strawberry tongue: 1239; myalgia: 1238; arthralgia: 1237; arthritis: 1238; days of fever on admission: 1226; white blood cells: 1231; neutrophils: 1068; lymphocytes: 1213; bands: 430; platelet count: 1230; Z-hemoglobin: 1234; ESR: 922; CRP: 1169; sodium: 1171; ALT: 1208; AST: 1209; GGT: 535; albumin: 1161; procalcitonin: 599; creatinine: 1189; globulins: 549; total bilirubin: 1012; direct bilirubin: 963; indirect bilirubin: 917; ALP: 697; CPK: 547; LDH: 1001; triglycerides: 553; ferritin: 1041; proBNP: 566; troponin: 806; cortisol: 18; prothrombin: 1132; thromboplastin: 1103; INR: 927; fibrinogen: 1043; D dimer: 1138.

Table 2
Admission diagnosis of children in Latin America with final diagnosis of MIS-C.

Admission diagnosis	N (%)
MIS-C	892 (72.1%)
Other diagnosis[a]	346 (27.9%)
Acute COVID-19	137 (40.4%)
Acute abdomen	126 (36.8%)
Kawasaki disease	108 (31.5%)
Gastroenteritis	104 (30.3%)
Sepsis	87 (25.6%)
Septic shock	70 (20.4%)
Pneumonia	52 (15.2%)
Distributive shock	31 (9.1%)
Cardiogenic shock	15 (4.4%)
Kawasaki disease shock syndrome	6 (1.8%)
Other kind of shock	5 (1.5%)
Toxic shock syndrome	4 (1.2%)

MIS-C, multisystemic inflammatory syndrome in children.

[a] These are the diagnoses of the subjects who, upon admission, were not diagnosed with MIS-C; all subjects were ultimately diagnosed with MIS-C.Total number of subjects for whom we have the admission diagnosis: MIS-C: 1238; other diagnosis: 1238; acute COVID-19: 339; acute abdomen: 342; Kawasaki disease: 343; gastroenteritis: 343; sepsis: 340; septic shock: 343; pneumonia: 341; distributive shock: 341; cardiogenic shock: 341; Kawasaki disease shock syndrome: 342; other kind of shock: 341; toxic shock syndrome: 343.

Table 3
Treatment of multisystemic inflammatory syndrome in children in Latin America.

Treatment[a]	N (%)
Anti-inflammatory	
IVIG	1096 (88.7%)
Second dose of IVIG	162 (14.8%)
Steroid therapy	947 (76.7%)
Biologics	53 (4.3%)
Antibiotics	820 (66.7%)
Antiplatelets	
Aspirin	796 (64.5%)
Additional antiplatelet therapy	34 (2.8%)
Anticoagulants	605 (49.0%)
Inotropes	497 (40.3%)
Antivirals	26 (2.1%)

IVIG, intravenous immunoglobulin.

[a] Total number of subjects for whom we have treatment information: IVIG therapy: 1236; second dose of IVIG: 1094; steroid therapy: 1235; biologics: 1233 (the most widely used biologic was tocilizumab); antibiotics: 1229; aspirin: 1235; additional antiplatelet therapy: 1232; anticoagulants: 1234; inotropes: 1234; antivirals: 1234.

the inflammatory process that were outside of the normal range included platelet count (190,000 μL), Z-hemoglobin, (−1.7), erythrocyte sedimentation rate (39 mm/hour), C-reactive protein (14.0 mg/dL), albumin (3.0 g/dL), procalcitonin (3.6 ng/mL), ferritin (440 ng/mL), fibrinogen (5.2 g/L), and D-dimer (2.7 mg/L). Cardiovascular markers that were elevated included pro B-type natriuretic peptide (1275 pg/mL) and troponin (0.05 ng/mL).

The most common admission diagnosis was MIS-C (72.1%) (Table 2). The most common admission diagnosis of the groups of patients who were not diagnosed with MIS-C upon admission was COVID-19 in 40.4%, with 64.9% having had either a positive SARS-CoV-2 antigen test or polymerase chain reaction at the time of admission. Given the gastrointestinal manifestations of MIS-C, an additional common admission diagnosis included acute abdomen in 38.8%. All subjects were ultimately diagnosed with MIS-C.

Most of the subjects (88.7%) were treated with 2 g/kg of intravenous immune globulin (IVIG) (Table 3). In addition, 76.7% of patients were treated with steroids, of whom 10.6% did not receive IVIG. Antibiotics were administered to 66.7% of patients. A significant percentage of sub-

Table 4
Outcomes in children diagnosed with multisystemic inflammatory syndrome in children in Latin America.

Characteristic[a]	N (%) or median (interquartile range)
Total days of hospitalization	8 (6, 12)
Admitted to the ICU	589 (47.8%)
Days in the ICU	5 (3, 8)
Number of patients who died	60 (4.9%)

ICU, intensive care unit.
[a] Total reported observations for each characteristic are total days of hospitalization: 1199; admitted to the ICU: 1233; days in the ICU: 571; number of patients who died: 1230.

jects were treated with anti-platelet medications and anticoagulants: 67.3% with aspirin and 49.0% with enoxaparin.

Although most of the subjects had a normal left ventricular ejection fraction (LVEF) on admission (79.0% had an ejection fraction ≥55%, with a median of 64%), 18.7 % had an ejection fraction between 30% and 55%, and 2.4% had an ejection fraction <30%. The lowest LVEF reported was 14%. The median Z-score of the left anterior descending coronary artery and right coronary artery were within normal limits (median: 0.34 and −0.02, respectively).

A significant number of subjects required admission to an ICU (N = 589, 47.8%) (Table 4). The median length of stay in the ICU and hospital were 5 and 8 days, respectively (interquartile range). The death rate attributed to MIS-C was 4.9%. For subjects initially diagnosed with MIS-C, the death rate was 3.4%. In comparison, those whose admission diagnosis was not MIS-C, the death rate was 8.9% (P <0.001, odds ratio 2.76, 95% confidence interval 1.6-4.6).

Discussion

To the best of our knowledge, this is the largest multinational study to evaluate MIS-C throughout Latin America, providing a better understanding of the impact of MIS-C in this part of the world. Compared with other regions, the most striking finding was a death rate of 4.9%, and up to 8.9% in patients were initially diagnosed with something other than MIS-C. In the first report published on MIS-C in an Italian cohort, the mortality was reported to be 0% [13]. Other studies published later in the pandemic in European pediatric cohorts showed a mortality of 2%, comparable to the one reported in the United State [4,14]. Similarly, a study in Brazil showed a death rate of 1.8% [10]. In contrast, a study of 28 patients in Peru had one death and, consequently, a death rate of 4% [8]. A multicenter study conducted in pediatric ICUs of Colombia reported a mortality of 9% [15]. Our work, therefore, provides further support that the mortality of MIS-C was worse throughout Latin America than other regions of the world.

One of the greatest cardiac complications reported in MIS-C is the reduction of the LVEF. Although the median LVEF in our study was within the normal range, 21.1% of the subjects had an LVEF <55% on admission. In comparison, reports from the United States describe a higher proportion of subjects with cardiac involvement, with a LVEF of 30% to <55% in 33% and an LVEF <30% in 5% [4]. This may have been affected by the timing of the first echocardiogram because 44.2% of patients in this study received anti-inflammatory therapy before their first echocardiogram.

Clinical characteristics, laboratory findings, treatment regimens, and ICU admission rate in this study were comparable to those reported in cohorts from Europe [13,14]. As with most of the world, the most common treatment for MIS-C in Latin America was IVIG, with the addition of steroids in more severe cases. In addition, 10.6% were treated with steroids alone, likely given the regional difficulties in acquiring IVIG. A recent retrospective study found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone [16]. If this is confirmed, this would be welcome news for parts of the world, such as Latin America, where it might be difficult to obtain IVIG, in part, given the expense of the medication.

We acknowledge that this study had certain limitations and strengths. Because MIS-C is not a mandatory reportable syndrome in Latin America, much as it is not throughout the rest of the world, we were not able to calculate the incidence rate of MIS-C based on our data collected. SARS-CoV-2 nucleocapsid or anti-spike antibody were unavailable in most of the centers and, thus, not routinely used for the diagnosis of MIS-C. Due to local availability of echocardiograms, many patients received anti-inflammatory therapy before the first echocardiogram being done, making it difficult to truly understand the rate of left ventricular dysfunction at initial presentation. Also, a number of the centers participating in this study were referral national hospitals; therefore, these data could represent the more severe spectrum of MIS-C in Latin America. In addition, the cause of death was not available in this study. Regarding strengths, to the best of our knowledge, this is the largest, multinational study of MIS-C in Latin America and one of the largest cohorts anywhere in the world. Given the high mortality rate of MIS-C throughout Latin America, this emphasizes the pediatric impact of the COVID-19 pandemic.

Conclusion

In conclusion, we are reporting the largest multinational, multicenter, observational study of MIS-C in Latin America to date. Although much of the clinical presentation and treatment of children with MIS-C in Latin America reflected what was seen throughout the rest of the world during the COVID-19 pandemic, the death rate, especially in those not initially diagnosed with MIS-C, was higher, highlighting the importance of considering MIS-C in the differential diagnosis if the disease, once again, increases in prevalence worldwide.

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Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

This database received institutional review board approval at the University of California, San Diego (La Jolla, CA, USA) and follows the principles outlined in the Declaration of Helsinki. This study was guided by ethical standards and national and international laws.

Author contributions

Drs Rolando Ulloa-Gutierrez, Gabriela Ivankovich-Escoto and Adriana H Tremoulet conceptualized and designed the study, designed the data collection instruments, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Jimena García-Silva carried out the initial analyses, and critically reviewed and revised the manuscript.

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