Original article

# Multisystem inflammatory syndrome in children: a cross-sectional study of cases and factors associated with deaths during the COVID-19 pandemic in Brazil, 2020*

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## Abstract

**Objective:** To characterize the clinical-epidemiological profile of multisystem inflammatory syndrome in children temporally associated with COVID-19 (MIS-C), and to identify factors associated with MIS-C deaths in Brazil, 2020. **Methods:** This was a cross-sectional study, using national MIS-C monitoring data. Logistical regression was performed to estimate crude and adjusted odds ratios (OR). **Results:** Median case (n=652) age was 5 years, 57.1% were male, 52.0% were of brown race/skin color and 6.4% died. Likelihood of death was greater among those who presented O2 saturation <95% (ORa=4.35 – 95%CI 1.69;11.20) and altered urea results (ORa=5.18 – 95%CI 1.91;14.04); likelihood of death was lower when red skin blotches were not present (ORa=0.23 – 95%CI 0.09;0.62), when anticoagulants were used (ORa=0.32 – 95%CI 0.12;0.89) and when immunoglobulins were used (ORa=0.38 – 95%CI 0.15;1.01). **Conclusion:** Fatality ratios were higher among cases that presented O2 saturation <95% and altered urea results. Fatality ratios were lower among those with red skin blotches, and those who used immunoglobulins and anticoagulants.

**Keywords:** Coronavirus Infections; Pediatrics; Systemic Inflammatory Response Syndrome; Death; Epidemiological Monitoring; Cross-Sectional Studies.

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## Introduction

At the beginning of the COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, it was consensus that children had mild symptoms and that most of them were asymptomatic and not included in the conditions and risk factors for COVID-19 complications.[1,2] Early studies on COVID-19 also reported low incidence and low fatality ratios among children and adolescents.[1,2]

In April 2020, during the peak of the pandemic in Europe, an increase in the hospitalization of children/adolescents with severe multisystemic inflammation similar to Kawasaki syndrome, possibly associated with prior SARS-CoV-2 infection, was identified.[3] Following an alert issued by the United Kingdom, several countries recorded an increase in similar cases,[2,4,5] later called multisystem inflammatory syndrome in children (MIS-C).[6]

Although rare, the syndrome has drawn attention worldwide. It is a condition characterized by high and persistent fever, with a spectrum of signs and symptoms affecting several systems (gastrointestinal, dermatocutaneous, and circulatory manifestations, among others).[2,4-6] Respiratory symptoms are not always present, but there is a significant increase in inflammatory markers and the clinical picture can evolve to shock and coagulopathy.[2,5]

> *MIS-C is a condition characterized by high and persistent fever, with a spectrum of signs and symptoms affecting several systems (gastrointestinal, dermatocutaneous and circulatory manifestations, among others).*

In Brazil, systematic monitoring of MIS-C was implemented on July 24, 2020 by the Health Surveillance Secretariat of the Ministry of Health, throughout the national territory, allowing retroactive notification of cases identified prior to its implementation.[7,8] The objectives of this study were to characterize the clinical-epidemiological profile of MIS-C cases and to identify factors associated with deaths caused by MIS-C in Brazil in 2020.

## Methods

A cross-sectional study was conducted, based on notified suspected cases of MIS-C in Brazil, taking the date of symptom onset between February 26, 2020 (date of confirmation of the first COVID-19 case in the country) and December 31, 2020.

Duplicate notifications were excluded by the deterministic method, comparing name and date of birth, mother's name, and Federative Unit of residence. The records were then classified according to the definition adopted by the Ministry of Health,[7] taking a 'confirmed case' to be an individual under 20 years old, hospitalized, and with presence of:

a) High (minimum: 38ºC) and persistent fever (for 3 or more days).

b) Evidence of COVID-19 (molecular biology, positive antigenic test or serology) or history of contact with people with COVID-19.

c) Elevated inflammatory markers, such as altered laboratory results for erythrocyte sedimentation rate (ESR), C-reactive protein or procalcitonin, among others.

d) At least two of the following signs/symptoms:

– Non-purulent conjunctivitis or bilateral skin rash or signs of mucocutaneous inflammation (oral, on hands or feet).

– Arterial hypotension or shock.

– Manifestations of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities, including echocardiogram findings or troponin elevation or N-terminal pro-B-type natriuretic peptide (NT-proBNP).

– Evidence of coagulopathy by thrombin time (TT), activated partial thromboplastin time (aPTT) or elevated D-dimer levels.

– Acute gastrointestinal manifestations (diarrhea, vomiting or abdominal pain).

e) After ruling out any other causes of obvious infectious origin of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndrome.

The MIS-C case epidemic curve was compared to the COVID-19 curve for individuals under 20 years of age in Brazil, considering the moving average of the last three epidemiological weeks (EW) of symptom onset. Cases of severe acute respiratory syndrome (SARS) and flu-like syndrome confirmed as COVID-19 cases by laboratory, clinical, clinical-epidemiological, or clinical-imaging criteria were included.

MIS-C cases and crude incidence rates were presented according to Federative Unit of residence. Incidence was calculated by dividing the number of confirmed cases by the number of people under 20 years old, multiplied by 100,000. We also calculated

the case fatality ratio of SIM-P in Brazil by dividing the number of deaths, by the number of total cases, multiplied by 100.

The MIS-C data were taken from the national monitoring database [online notification on the REDCap® platform, hosted and under the domain of the Brazilian National Health System Information Technology Department (DATASUS)]. With regard to COVID-19 cases, data on SARS were taken from the Influenza Epidemiological Surveillance Information System, while data on flu-like syndrome were taken from the *e-SUS Notifica* system, both of which are available on the OpenDATASUS platform.[9] Brazilian Institute of Geography and Statistics (IBGE) population projections for the year 2020 were used to calculate incidence.[10] All the data used were retrieved on February 4, 2021, considering notifications as at January 14, 2021.

Characterization of MIS-C cases included simple and relative frequencies, and measures of central tendency of the following independent variables:

a) Sociodemographic variables: age (in years: under 1; 1-9; under 20); sex (female; male); race/skin color (white; black; brown; indigenous; yellow).

b) Prior presence of comorbidities (yes; no).

c) Signs/symptoms presented in large and detailed groups (yes; no):

– Gastrointestinal – abdominal pain, nausea or vomiting, diarrhea;

– Dermatocutaneous – conjunctivitis, red blotches on body (such as rash and exanthema);

– Respiratory – dyspnea, $O_2$ saturation <95%, cough, runny nose, sore throat;

– Neurological – headache, lethargy, irritability, mental confusion;

– Circulatory and hemodynamic – tachycardia, hypotension/shock, skin color alterations (such as paleness and cyanosis);

– Edema – hand or foot edema, lymphadenopathy;

– Myalgia;

– Oliguria.

d) Altered results for inflammation markers, coagulopathy or organ dysfunction (yes; no) – C-reactive protein, D-dimer, erythrocyte sedimentation rate (ESR), ferritin, lactate dehydrogenase, albumin, aspartate transaminase (AST), alanine transaminase (ALT), thrombin time, troponin, activated partial thromboplastin time, urea, creatinine, sodium, potassium.

e) Use in treatment (yes; no) – immunoglobulin, corticoid, anticoagulant, antiviral therapy.

f) COVID-19 confirmation criterion – laboratory evidence of SARS-CoV-2 infection (serology; molecular) or clinical-epidemiological criterion (temporally associated with a laboratory confirmed COVID-19 case in the last 30 days).

g) Occurrence of complications (yes; no).

h) Hospitalization in intensive care unit (ICU) (yes; no).

i) Time (in days: between symptom onset and hospitalization; length of inpatient stay; time spent in ICU).

j) Case progression (death; hospital discharge).

When analyzing factors associated with death, the dependent variable analyzed was case progression: MIS-C cases having 'death' as the outcome were compared to those having 'hospital discharge' as the outcome; records not showing progression were discarded.

A hierarchical theoretical model[11] was built in order to process the independent variables, using the first five blocks of variables described above. First, simple logistic regression models were used to study the relationships between the independent variables and death, using variables that had at least 90% completeness in both comparison groups (death and hospital discharge).

Following this, the hierarchical approach to data modeling was adopted,[11] using a multiple logistic regression model with variables that had a significance level of up to 10% (p-value<0.10) in the simple regression. The distal block was comprised of sociodemographic variables and prior presence of comorbidities (Model 1); on the intermediate levels, Model 2 included presence of signs and symptoms and Model 3, included altered results for markers of inflammatory activity, coagulopathy or organ dysfunction, while the proximal level included treatment (Model 4).

Inclusion of independent variables in the hierarchical multiple regression model was carried out in an ordered and sequential manner, moving in the distal-proximal direction (Models 1 to 4). At each level, variables that had a significance level of up to 5% (p-value<0.05) were kept in the model, so that all levels were adjusted by the variables from the same level and the previous levels. Association between death and the independent variables studied was expressed as crude odds ratios (ORc) and

adjusted odds ratios (ORa) and their respective 95% confidence intervals (95%CI).

We opted to include specific sign/symptom variables in the regression models, rather than organizing them into large groups, since high or absolute frequency of the large groups was found among MIS-C cases that progressed to death, so that it was not possible to establish a comparison group. Multicollinearity diagnosis was also performed between specific sign/symptom variables identified in the simple regression, through the correlation matrix; for multiple regression, one specific sign/symptom variable was selected for each pair of variables that demonstrated a correlation coefficient ≥0.4 (moderate to high correlation).

MIS-C case records with missing data in any selected independent variable were considered to be losses for the multiple regression model. Taking the sample of cases included in the model, an odds ratio equal to 2.0, and a 10% difference in the outcome distribution between groups with or without the variable of interest, minimum power was estimated at 64.2%.

R 4.0.0 software was used for duplicate cleaning, data treatment and analysis, while Microsoft/Excel and QGIS3.[12] software were employed for data visualization.

The study design was submitted to the National Research Ethics Committee/National Health Council and approved on January 14, 2021 [Certificate of Submission for Ethical Appraisal No. 40867220.5.0000.0008].

## Results

Brazil recorded 1,082 notifications of suspected MIS-C cases in 2020. Forty-three (4.0%) were duplicate records and 387 (35.8%) did not meet the case definition criteria, leaving 652 (60.2%) cases classified as confirmed MIS-C cases. Of these, 525 (80.6%) were discharged from hospital and 42 (6.4%) died. There were 85 (13.0%) records with no information on case progression on the notification form (Figure 1).

The behavior of the MIS-C epidemic curve in Brazil was similar to that of the COVID-19 curve in children under 20 years of age; however, the curves showed differences in their temporal distributions. The peak in the moving average of MIS-C cases occurrence occurred five weeks after the COVID-19 peak in the pediatric age group (EW 30). The highest number of MIS-C case deaths (n=5) was recorded in EW 42 (Figure 2).

The Federative Units of São Paulo (n=142; 21.8%), Federal District (n=58; 8.9%), Minas Gerais (n=57; 8.7%), Bahia (n=50; 7.7%) and Pará (n=50; 7.7%) accounted for more than 50% of the country's MIS-C cases (Supplementary Material 1). MIS-C incidence in Brazil was 1.1 case per 100,000 population under 20 years of age. The states of Alagoas (2.2), Rio Grande do Norte (1.6), Pará (1.6), Ceará (1.2), São Paulo (1.2), Santa Catarina (1.2) and the Federal District (6.7) had incidences rates above the national average (Supplementary Material 1).

Table 1 presents the profile of the MIS-C cases: 64.3% of the children/adolescents were between 1 and 9 years old (median: 5 years), 57.1% were male, 52.0% were of brown race/skin color and approximately 80% had no comorbidities prior to MIS-C. Presence of some signs/symptoms of the gastrointestinal group was recorded in 87.6% of MIS-C cases, followed by dermatocutaneous signs/symptoms in 72.4% and respiratory signs/symptoms in 66.0%. As a mandatory case definition criterion, high and persistent fever was present in all cases.

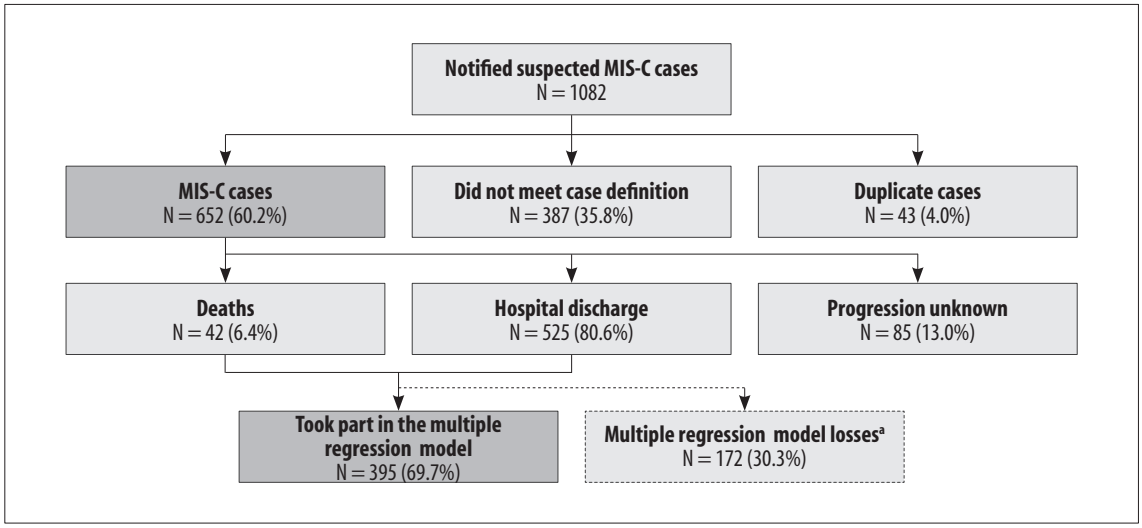
A high frequency of altered results for markers of inflammation, coagulopathy, and organ dysfunction was found among MIS-C cases, with altered C-reactive protein, D-dimer and ESR standing out in more than 80% of cases (excluding tests not performed/unknown). Use of immunoglobulins and anticoagulants was recorded in 67.9% and 55.7% of MIS-C cases, respectively. Most children/adolescents were laboratory confirmed as having COVID-19 (78.4%), and 61.2% had serology results (Table 1).

Median time elapsed between onset of signs/symptoms and hospitalization was 4 days, and median length of inpatient stay was 9 days. ICU hospitalization occurred in 44.5% of cases, with a median length of stay of 6 days (excluding cases with unknown information). The 42 cases of MIS-C that died were distributed over 15 Federative Units, among which Pará and São Paulo recorded the highest absolute number: 7 cases each.

Table 2 presents the characteristics of the MIS-C cases analyzed according to progression (death/hospital discharge) in crude regression. The <1 and <20 year-old age groups and presence of comorbidity prior to MIS-C were significantly associated with death. Regarding the clinical characteristics of deaths, we found a higher frequency of dyspnea, $O_2$ saturation <95%, tachycardia, hypotension/shock, skin color

alterations (such as paleness and cyanosis) and oliguria, and a lower frequency of conjunctivitis, red blotches on body (such as rash and exanthema), hand or foot edema and lymphadenopathy, in relation to those who were discharged from hospital.

We also found a higher frequency of altered AST, urea and creatinine results among MIS-C cases that died, when compared to those that were discharged from hospital. Use of immunoglobulins and anticoagulants was significantly associated with lower fatality, while the use of corticosteroids and antiviral therapy, was significantly associated with higher fatality. Supplementary Material 2 presents the analysis of P-PSI cases, according to additional characteristics.




Note: a) Losses occurred due to missing data in the variables studied.

**Figure 1 – Flowchart of notified suspected cases of multisystemic inflammatory syndrome in children temporally associated with COVID-19 (MIS-C), selection of confirmed cases and definition of groups having 'death' or 'hospital discharge' as their outcome and taking part in the study of association with death, Brazil, 2020**

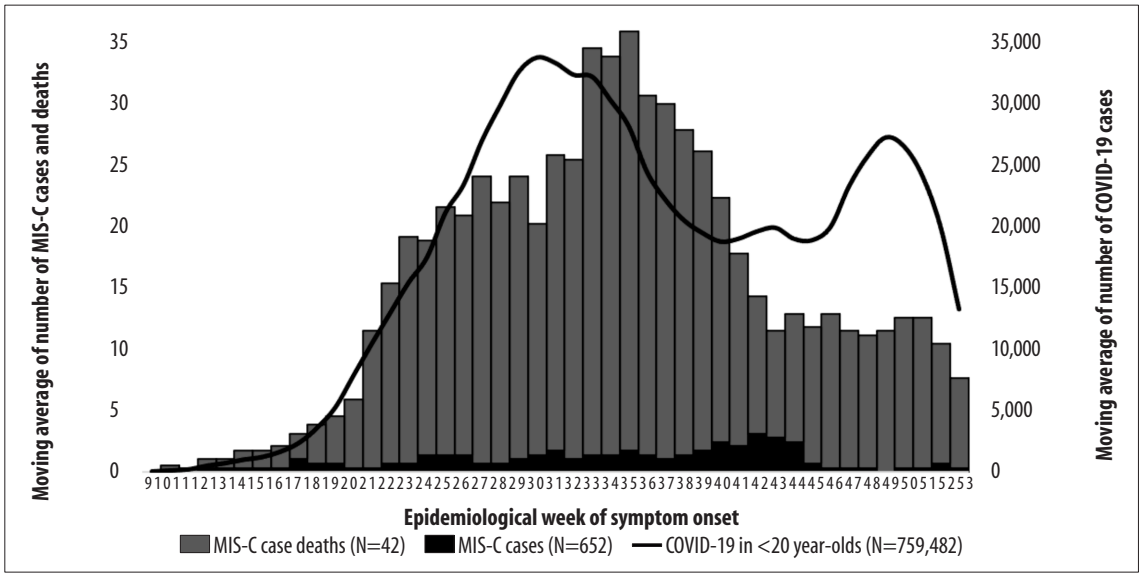



**Figure 2 – Moving average of multisystemic inflammatory syndrome cases and deaths in children temporally associated with COVID-19 (MIS-C) and of COVID-19 cases in under 20 year-olds, by epidemiological week of symptom onset, Brazil, 2020**

**Table 1 – Cases of multisystemic inflammatory syndrome in children temporally associated with COVID-19 (MIS-C) (N=652) according to personal, clinical and hospitalization characteristics, Brazil, 2020**

| Characteristics | N | % |
|---|---|---|
| **Age group (in years)** | | |
| <1 | 70 | 10.7 |
| 1-9 | 419 | 64.3 |
| <20 | 163 | 25.0 |
| **Sex** | | |
| Male | 372 | 57.1 |
| Female | 280 | 42.9 |
| **Race/skin color (N=517)** | | |
| Brown | 269 | 52.0 |
| White | 215 | 41.6 |
| Black | 31 | 6.0 |
| Indigenous | 2 | 0.4 |
| **Presence of prior comorbidity** | | |
| Yes | 131 | 20.1 |
| **Signs and symptoms presented** | | |
| Gastrointestinal | 571 | 87.6 |
| Dermatocutaneous | 472 | 72.4 |
| Respiratory | 430 | 66.0 |
| Circulatory and hemodynamic | 402 | 61.7 |
| Neurological | 366 | 56.1 |
| Edema | 295 | 45.1 |
| Myalgia | 152 | 22.3 |
| Oliguria | 129 | 19.8 |
| **Altered markers of inflammation, coagulopathy or organ dysfunction** | | |
| C-reactive protein (N=622) | 590 | 94.9 |
| D-dimer (N=526) | 493 | 93.7 |
| ESR[a] (N=427) | 379 | 88.8 |
| Ferritin (N=404) | 303 | 75.0 |
| LDH[b] (N=424) | 258 | 60.8 |
| Albumin (N=454) | 269 | 59.3 |
| AST[c] (N=588) | 301 | 51.2 |
| ALT[d] (N=590) | 273 | 46.3 |
| TT[e] (N=529) | 226 | 42.7 |
| Troponin (N=454) | 190 | 41.9 |
| aPTT[f] (N=523) | 203 | 38.8 |
| Urea (N=588) | 151 | 25.7 |
| Creatinine (N=592) | 150 | 25.3 |
| Sodium (N=559) | 142 | 25.4 |
| Potassium (N=556) | 117 | 21.0 |

a) ESR: erythrocyte sedimentation rate; b) LDH: lactate dehydrogenase; c) AST: aspartate transaminase; d) ALT: alanine transaminase; e) TT: thrombin time; f) aPTT: activated partial thromboplastin time; g) ICU: intensive care unit.

To be continued

Continuation

**Table 1 – Cases of multisystemic inflammatory syndrome in children temporally associated with COVID-19 (MIS-C) (N=652) according to personal, clinical and hospitalization characteristics, Brazil, 2020**

| Characteristics | N | % |
|---|---|---|
| **Treatment** | | |
| Immunoglobulins (N=616) | 418 | 67.9 |
| Corticoids (N=603) | 376 | 62.3 |
| Anticoagulants (N=601) | 335 | 55.7 |
| Antiviral therapy (N=600) | 96 | 16.0 |
| **COVID-19 confirmation criterion** | | |
| Clinical-epidemiological | 141 | 21.6 |
| Laboratory | 511 | 78.4 |
| Serology | 399 | 61.2 |
| Molecular | 145 | 22.2 |
| **Complications** | | |
| Hypotension (need for vasoactive drugs) | 181 | 27.8 |
| Need for invasive ventilation | 128 | 19.6 |
| Pneumonia | 126 | 19.3 |
| Need for non-invasive ventilation | 72 | 11.0 |
| Kidney failure | 62 | 9.5 |
| Convulsions | 34 | 5.2 |
| **Hospitalized in ICU[g] (N=563)** | | |
| Yes | 290 | 44.5 |
| **Progression** | | |
| Hospital discharge | 525 | 80.5 |
| Death | 42 | 6.4 |
| Unknown | 85 | 13.1 |

a) ESR: erythrocyte sedimentation rate; b) LDH: lactate dehydrogenase; c) AST: aspartate transaminase; d) ALT: alanine transaminase; e) TT: thrombin time; f) aPTT: activated partial thromboplastin time; g) ICU: intensive care unit.

**Table 2 – Frequency distribution of demographic, clinical and laboratory characteristics, according to case progression during hospitalization (death or discharge from hospital), in cases of multisystem inflammatory syndrome in children temporally associated with COVID-19, Brazil, 2020**

| Characteristics | Deaths (N=42) n | Hospital discharge (N=525) n (%) | p-value[a] |
|---|---|---|---|
| **Age group (in years)** | | | |
| <1 | 10 | 44 (8.4) | |
| 1-9 | 17 | 352 (67.0) | 0.001 |
| <20 | 15 | 129 (24.6) | |
| **Sex** | | | |
| Male | 19 | 307 (58.5) | 0.101 |
| Female | 23 | 218 (41.5) | |
| **Presence of prior comorbidity** | | | |
| Yes | 16 | 105 (20.0) | 0.007 |

a) Likelihood ratio test p-value; b) Such as rash and exanthema; c) Such as paleness and cyanosis; d) AST: aspartate transaminase; e) ALT: alanine transaminase.

To be continued

**Table 2 – Frequency distribution of demographic, clinical and laboratory characteristics, according to case progression during hospitalization (death or discharge from hospital), in cases of multisystem inflammatory syndrome in children temporally associated with COVID-19, Brazil, 2020**

| Characteristics | Deaths (N=42) n | Hospital discharge (N=525) n (%) | p-value[a] |
|---|---|---|---|
| **Signs and symptoms presented** | | | |
| Abdominal pain | 19 | 316 (60.2) | 0.056 |
| Nausea or vomiting | 22 | 290 (55.2) | 0.697 |
| Diarrhea | 18 | 255 (48.6) | 0.467 |
| Conjunctivitis | 7 | 352 (67.0) | <0.001 |
| Red blotches on body[b] | 10 | 313 (59.6) | <0.001 |
| Dyspnea | 31 | 178 (33.9) | <0.001 |
| $O_2$ saturation<95% | 29 | 152 (29.0) | <0.001 |
| Cough | 14 | 116 (22.1) | 0.105 |
| Runny nose | 7 | 79 (15.0) | 0.769 |
| Sore throat | 4 | 76 (14.5) | 0.359 |
| Headache | 11 | 132 (25.1) | 0.886 |
| Lethargy | 14 | 121 (23.0) | 0.140 |
| Irritability | 9 | 106 (20.2) | 0.881 |
| Mental confusion | 7 | 41 (7.8) | 0.071 |
| Tachycardia | 25 | 184 (35.0) | <0.001 |
| Hypotension/shock | 35 | 173 (33.0) | 0.002 |
| Skin color alterations[c] | 20 | 154 (29.3) | 0.017 |
| Hand or foot edema | 6 | 167 (31.8) | 0.010 |
| Lymphadenopathy | 2 | 113 (21.5) | 0.003 |
| Myalgia | 12 | 121 (23.0) | 0.448 |
| Oliguria | 14 | 93 (17.7) | 0.023 |
| **Altered markers of inflammation, coagulopathy or organ dysfunction** | | | |
| C-reactive protein | 39/40 | 478/502 (95.2) | 0.477 |
| AST[d] | 31/39 | 235/477 (49.3) | <0.001 |
| ALT[e] | 22/38 | 216/477 (45.3) | 0.132 |
| Urea | 25/38 | 107/481 (22.2) | <0.001 |
| Creatinine | 21/40 | 110/480 (22.9) | <0.001 |
| **Treatment** | | | |
| Immunoglobulins | 15/38 | 357/501 (71.3) | <0.001 |
| Corticoids | 30/39 | 300/493 (60.9) | 0.043 |
| Anticoagulants | 14/38 | 281/487 (57.7) | 0.013 |
| Antiviral therapy | 11/38 | 74/487 (15.2) | 0.039 |

a) Likelihood ratio test p-value; b) Such as rash and exanthema; c) Such as paleness and cyanosis; d) AST: aspartate transaminase; e) ALT: alanine transaminase.

**Table 3 – Factors associated with death in cases of multisystemic inflammatory syndrome in children temporally associated with COVID-19 (MIS-C) (N=397), according to analysis in hierarchical multiple logistic regression models, with inclusion of variables in blocks proximal to the outcome 'death', Brazil, 2020**

| Model/variables | $OR_c$ [a] (95%CI)[b] | $OR_a$ [c] (95%CI)[b] | p-value[d] |
|---|---|---|---|
| **Model 1: Sociodemographic and comorbidity variables (AIC: 204)** | | | |
| Age group (reference: 1-9 years) | | | 0.159 |
| <1 | 2.56 (0.79;8.32) | 2.57 (0.79;8.39) | |
| <20 | 2.01 (0.87;4.75) | 1.97 (0.84;4.62) | |
| Presence of any prior comorbidity | | | 0.092 |
| Yes | 2.09 (0.93;4.72) | 2.07 (0.91;4.71) | |
| **Model 2: Signs and symptoms presented (AIC: 182)** | | | |
| Presence of signs and symptoms (reference: No) | | | |
| Red blotches on body[e] | 0.19 (0.08;0.48) | 0.23 (0.09;0.62) | 0.001 |
| Skin color alterations[f] | 2.29 (1.05;4.95) | 1.31 (0.53;3.22) | 0.557 |
| $O_2$ saturation<95% | 5.10 (2.19;11.92) | 4.35 (1.69;11.20) | 0.002 |
| Mental confusion | 2.07 (0.74;5.78) | 1.59 (0.51;4.92) | 0.437 |
| Hand or foot edema | 0.34 (0.12;1.01) | 0.52 (0.16;1.68) | 0.254 |
| Lymphadenopathy | 0.26 (0.06;1.10) | 0.35 (0.08;1.60) | 0.127 |
| Oliguria | 1.88 (0.82;4.33) | 1.41 (0.55;3.57) | 0.476 |
| **Model 3: Altered test results (AIC: 163)** | | | |
| Presence of signs and symptoms (reference: No) | | | |
| Red blotches on body[e] | 0.19 (0.08;0.48) | 0.18 (0.07;0.49) | < 0.001 |
| $O_2$ saturation<95% | 5.10 (2.19;11.92) | 3.6 (1.44;8.98) | 0.004 |
| Altered markers of inflammation, coagulopathy or organ dysfunction (reference: No) | | | |
| AST[g] | 4.07 (1.61;10.26) | 2.11 (0.77;5.82) | 0.135 |
| Urea | 7.85 (3.42;18.03) | 5.18 (1.91;14.04) | < 0.001 |
| Creatinine | 3.84 (1.76;8.40) | 1.12 (0.43;2.95) | 0.817 |
| **Model 4: Treatment (AIC: 191)** | | | |
| Presence of signs and symptoms (reference: No) | | | |
| Red blotches on body[e] | 0.19 (0.08;0.48) | 0.19 (0.07;0.54) | < 0.001 |
| $O_2$ saturation<95% | 5.10 (2.19;11.92) | 4.64 (1.75;12.28) | 0.001 |
| Altered markers of inflammation, coagulopathy or organ dysfunction (reference: No) | | | |
| Urea | 7.85 (3.42;18.03) | 4.7 (1.88;11.73) | < 0.001 |
| Treatment (reference: No) | | | |
| Antiviral therapy | 1.67 (0.68;4.11) | 2.28 (0.79;6.53) | 0.137 |
| Corticoids | 2.39 (0.95;6.05) | 2.48 (0.83;7.44) | 0.091 |
| Immunoglobulin | 0.25 (0.11;0.56) | 0.38 (0.15;1.01) | 0.050 |
| Anticoagulant | 0.33 (0.14;0.74) | 0.32 (0.12;0.89) | 0.025 |

a) $OR_c$: crude odds ratio; b) 95%CI: 95% confidence interval; c) $OR_a$: adjusted odds ratio; d) likelihood ratio test p-value; e) Such as rash and exanthema; f) Such as paleness and cyanosis; g) AST: aspartate transaminase.

Table 3 shows the results of multiple regression in hierarchical modeling, which included 28 MIS-cases that died and 368 cases that were discharged from hospital (70% of the 567 cases with known progression). Losses occurred due to missing data in the variables studied.

No statistically significant association was found between the adjusted variables in Model 1 and the outcome 'death'. In Model 2, we found that the likelihood of $O_2$ saturation<95% was significantly higher (ORa=4.35 - 95%CI 1.69;11.20) and the presence of red blotches on the body (ORa=0.23 - 95%CI 0.09;0.62) was significantly lower among those who died, when compared to those who were discharged from hospital. The 'conjunctivitis', 'dyspnea', 'tachycardia' and 'hypotension/shock' variables were not included in the hierarchical model due to identification of moderate correlation with the 'red blotches on body' variable (for conjunctivitis) and the 'O2 saturation <95%' variable (for the remainder) (Supplementary Material 3).

In Model 3, which was controlled by the variables with association in the previous models, only altered urea test results showed statistically significant association with death (ORa=5.18 - 95%CI 1.91;14.04). In Model 4, after including the treatment-related variables, use of anticoagulants was associated with a significantly lower likelihood of death (ORa=0.32 - 95%CI 0.12;0.89), while the significance effect of immunoglobulin use in reducing the likelihood of death was borderline (ORa=0.38 - 95%CI 0.15;1.01).

## Discussion

MIS-C cases in Brazil in 2020 had a median age of 5 years and most occurred in children/adolescents of brown race/skin color and of the male sex, after the COVID-19 peak in the pediatric age group. Clinical manifestations were diverse and were mostly associated with elevated markers of inflammation, coagulopathy or organ dysfunction, and positive serology for SARS-CoV-2. The MIS-C fatality ratio in Brazil was 6.4% in 2020, with $O_2$ saturation <95% and altered urea results being factors associated with death. Fatality was lower among cases with no red blotches on the body and those who used anticoagulants and immunoglobulins.

Occurrence of MIS-C after the COVID-19 peak in the pediatric age group has been seen in other countries, most of which reported a 3- to 5-week difference between the curves.[2,12-14] Also consistent with the literature were the results of the frequency of SARS-CoV-2 serology test positivity and presence of inflammatory markers/coagulopathy (also described in severe COVID-19 cases).[4,5,12-14] These aspects support the hypothesis that MIS-C is a late immune response to SARS-CoV-2 infection in children/adolescents.[15-17]

The median age of MIS-C cases in Brazil was lower than that found in most studies,[2-5,12-17] and was closer to that found for Kawasaki Syndrome or acute pediatric COVID-19.[18-20] This result may indicate that health services in Brazil were more sensitive in suspecting MIS-C in younger children/adolescents, or that the study included cases of other inflammatory manifestations similar to MIS-C. The overlap with other multisystemic syndromes has been described in several papers.[2,18,20] The high frequency of children under 1 year of age also drew attention, especially among those who died, this being precisely an age group that presents an even greater challenge for diagnosis.[16]

The frequency rates of MIS-C cases in those of brown race/skin color and of the male sex were consistent with the literature;[2,4,14-16] however, the contribution of genetic factors remains poorly elucidated and it is believed that the results may be related to environmental factors such as social and racial inequities.[16,20,21] It is noteworthy that race/skin color was not recorded in more than 20% of the MIS-C cases, even though including this information is mandatory for health information systems in Brazil.[22]

The study found clinical diversity and multiple organ involvement among MIS-C cases, with important differences between those who died and those who were discharged from hospital, corroborating the current understanding of the scientific community about the existence of different phenotypes and levels of severity of the syndrome.[2,4,23,24] High fatality among MIS-C cases in the presence of respiratory signs/symptoms and absence of dermatocutaneous manifestations, for example, has been described previously.[4,24,25] Children/adolescents with mucocutaneous lesions, however, may be at increased risk for coronary abnormalities, especially among those manifesting typical or atypical Kawasaki Syndrome characteristics.[23,24]

Altered urea and creatinine tests and elevated presence of oliguria among the MIS-C cases that died indicate that kidney failure seems to play an important role in the clinical course of severe cases. Diagnosis of MIS-C has been previously associated with children/adolescents hospitalized for COVID-19 who presented acute kidney injury.[16,25,26] Urea alteration is also predictive of pneumonia severity, especially in the presence of sepsis, and can result from the administration of drugs such as corticosteroids, as well as from multiple organ involvement resulting from multisystem inflammation.[25,27]

The respiratory and renal impairments found in this study may be related to a combination of hypovolemic and hyperinflammatory shock. Although the pathophysiology of MIS-C has not been completely elucidated, multiple organ failure is believed to occur due to the exacerbated delayed immune response, and not necessarily to the direct action of the virus on tissues.[5,17,18,25]

Circulatory/hemodynamic system complications have been shown to be more frequent in MIS-C than in Kawasaki Syndrome and, although there is a risk of sequelae, good prognosis has been observed.[18,24,28] These complications have also been observed in severe and fatal outcomes of COVID-19 in adults, and may be associated with myocardial impairment due to the phenomenon known as 'cytokine storm', as well as progression of acute respiratory failure.[18,24,28] Alterations in biomarkers of cardiac function and hyperinflammatory reaction have been reported as predictors of MIS-C severity, but were not included in the study of association with death due to lack of data.[18,24,28]

In Brazil, the therapy used in cases of MIS-C was varied, which may be related to nonspecific pathophysiological manifestations, the absence of a clear prognosis, and the possibility of putting life at risk.[15] However, there is no standardized treatment for MIS-C in the literature;[5,20] treatment protocols have been proposed, based on clinical management guides for other inflammatory syndromes with a similar clinical spectrum.[5,17,20,29,30] Use of immunoglobulin is usually the first choice of treatment,[17] combined or not with use of corticoids in moderate and severe cases; use of anticoagulants is indicated in cases of thromboembolic events, and plays an important role in preventing shock.[5,17,20,23,26,29,30] The results found suggest that immunoglobulins and anticoagulants may have been protective factors against a fatal outcome; the results, however, should not be viewed as measures of efficacy, given the observational nature of the study.

MIS-C fatality in Brazil was high when compared to case series published by other countries (approximately 1 to 2%),[4,14,20,25] and this may reflect differences in the dynamics of transmission, the epidemiological situation, availability of diagnostic resources, care provided by local health services, as well as underreporting of milder cases.

This study has other limitations related to the quality of the records, such as incompleteness and non-standardization. These limitations may have implications for the classification of confirmed cases, based on the variables filled out on the notification form. Regarding this aspect, it is noteworthy that all MIS-C case definition conditions were mandatorily recorded among the cases classified as confirmed; however, it was not always possible to obtain detailed data on subsequent variables, such as differential etiologic diagnoses having been carried out. The clinical-epidemiological profile presented and the selection of variables for the study of association with death may also have been influenced by under-recording or absence of variables in the database, such as race/skin color, inflammatory and cardiac function markers, and other classes of drugs.

It is also noteworthy that the losses in the hierarchical regression model occurred due to under-recording of laboratory results and treatment, which may be a consequence of differentiated access to diagnostic and therapeutic resources. Moreover, the quantitative results of laboratory markers are not available in the notification records, making it impossible to know at what stage of the syndrome the altered qualitative result was obtained. The temporality of the clinical characteristics and drug administration has not been established either. For these reasons, interpretation and comparison of the findings of factors associated with death should be viewed in an exploratory manner, also considering the possibility of residual confounding.

On the other hand, this study presents the largest MIS-C case series described in Brazil and was the first conducted based on the national monitoring database. Future studies on representativeness and data quality can qualify the interpretation of the results presented. Additional investigations that establish the temporal relationship between clinical manifestations, details of laboratory results, and treatment administered are also

necessary for better clinical-epidemiological definition and definition of factors associated with death.

This study also contributes to the understanding of the signs of MIS-C severity, in the face of which specialized care is recommended, with the joint participation of multidisciplinary teams, timely treatment, monitoring of renal function and follow-up of children/adolescents to detect possible sequelae, especially in relation to cardiac involvement, whenever possible.[24-26] We also highlight the importance of SUS care and epidemiological surveillance health workers being aware and able to recognize, notify and investigate different spectrums of clinical manifestations of MIS-C, in order to improve the understanding of the syndrome, favoring timely treatment and better prognosis for children and adolescents affected by COVID-19.

## Authors' contributions

Relvas LAB, Gava C, Camelo FS, Porto VBG, Alves RFS and De Assis DM contribution to the study concept and data analysis. All the authors contributed to discussion of the results, reviewing the literature, drafting the manuscript and critically reviewing its intellectual content. All the authors have approved the final version and declare themselves to be responsible for all aspects thereof, including the guarantee of its accuracy and integrity.

## References


1. She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. J Med Virol. 2020 Jul;92(7):747-54. doi: https://doi.org/10.1002/jmv.25807.
2. Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021;41(1):19-32. doi: https://doi.org/10.1007/s00296-020-04749-4.
3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020 May 23;395(10237):1607-8. doi: https://doi.org/10.1016/S0140-6736(20)31094-1.
4. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19 associated multisystem inflammatory syndrome in children: United States, March-July 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug 14;69(32):1074-80. doi: https://doi.org/10.15585/mmwr.mm6932e2.
5. Tang Y, Li W, Baskota M, Zhou Q, Fu Z, Luo Z, et al. Multisystem inflammatory syndrome in children during the coronavirus disease 2019 (COVID-19) pandemic: a systematic review of published case studies. Transl Pediatr. 2021 Jan;10(1):121-35. doi: https://doi.org/10.21037/tp-20-188.
6. World Health Organization. Case Report Form for suspected cases of multisystem inflammatory syndrome (MIS) in children and adolescents temporally related to COVID-19 [Internet]. Geneva: WHO. 2020 Jun 01 [acesso 23 ago. 2021]. Disponível em: https://www.who.int/publications/i/item/WHO-2019-nCoV-MIS_Children_CRF-2020.2
7. Ministério da Saúde (BR). Nota técnica n. 16/2020 CGPNI/ DEIDT/SVS/MS: orientações sobre a notificação da síndrome inflamatória multissistêmica (SIM-P) temporalmente associada à COVID-19. [Brasília, DF: MS]; 2020 [acesso 23 ago. 2021]. Disponível em https://portaldeboaspraticas.iff.fiocruz.br/biblioteca/nota-tecnica-no-16-2020-cgpni-deidt-svs-ms.
8. Ministério da Saúde (BR). Síndrome inflamatória multissistêmica pediátrica (SIM-P), temporalmente associada à COVID-19. Boletim Epidemiológico. Jun 2021;52(23):21-6. Disponível em: https://www.gov.br/saude/pt-br/media/pdf/2021/junho/21/boletim_epidemiologico_svs_23.pdf
9. Ministério da Saúde (BR), Banco de dados do Sistema Único de Saúde. Notificações de Síndrome Gripal, sistema e-SUS VE notifica. [Rio de Janeiro]: MS; [s.d.; acesso 4 fev. 2021]. Disponível em: https://opendatasus.saude.gov.br/
10. Ministério da Saúde (BR), Banco de dados do Sistema Único de Saúde. Projeção da população das unidades da federação por sexo e grupos de idade: 2000-2030: notas técnicas. [Rio de Janeiro]: MS; [s.d.; acesso 4 fev. 2021]. Disponível em: http://tabnet.datasus.gov.br/cgi/Ibge/projpopuf.pdf
11. Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological

analysis: a hierarchical approach. Int J Epidemiol. 1997;26(1):224-7. doi: https://doi.org/10.1093/ije/26.1.224.

12. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020 Jul 23;383(4):334-46. doi: https://doi.org/10.1056/NEJMoa2021680.

13. Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. Int J Infect Dis. 2020;100:75-81. doi: https://doi.org/10.1016/j.ijid.2020.08.062.

14. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine. 2020;26:100527. doi: https://doi.org/10.1016/j.eclinm.2020.100527.

15. Felsenstein S, Willis E, Lythgoe H, McCann L, Cleary A, Mahmood K, et al. Presentation, treatment response and short-term outcomes in paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS). J Clin Med. 2020 Oct 14;9(10):3293. doi: https://doi.org/10.3390/jcm9103293.

16. Guimarães D, Pissarra R, Reis-Melo A, Guimarães H. Multisystem inflammatory syndrome in children (MISC): a systematic review. Int J Clin Pract. 2021 Jun 9:e14450. doi: https://doi.org/10.1111/ijcp.14450.

17. Zou H, Lu J, Liu J, Wong JH-W, Cheng S, Li Q, et al. Characteristics of pediatric multi-system inflammatory syndrome (PMIS) associated with COVID-19: a meta-analysis and insights into pathogenesis. Int J Infect Dis. 2021;102:319-26. doi: https://doi.org/10.1016/j.ijid.2020.11.145.

18. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA. 2021 Mar 16;325(11):1074-87. doi: https://doi.org/10.1001/jama.2021.2091.

19. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020 Jun 6;395(10239):1771-8. doi: https://doi.org/10.1016/S0140-6736(20)31103-X.

20. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol. 2021;56(5):837-48. doi: https://doi.org/10.1002/ppul.25245.

21. Oliveira RG, Cunha AP, Gadelha AGS, Carpio CG, Oliveira RB, Corrêa RM. Racial inequalities and death on the horizon: COVID-19 and structural racism.Cad Saude Publica. 2020 Sep 18:36(9):e00150120. doi: https://doi.org/10.1590/0102-311X00150120.

22. Ministério da Saúde (BR). Portaria de consolidação n. 1, de 28 de setembro de 2017. Consolidação das normas sobre os direitos e deveres dos usuários da saúde, a organização e o funcionamento do Sistema Único de Saúde. [Brasília, DF]: MS; atualizado 28 set. 2017; acesso 23 ago. 2021]. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0001_03_10_2017.html

23. Zhu F, Ang JY. 2021 update on the clinical management and diagnosis of kawasaki disease. Curr Infect Dis Rep. 2021;23(3):3. doi: https://doi.org/10.1007/s11908-021-00746-1.

24. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5(5):323-31. doi: https://doi.org/10.1016/S2352-4642(21)00050-X.

25. Sood M, Sharma S, Sood I, Sharma K, Kaushik A. Emerging evidence on multisystem inflammatory syndrome in children associated with SARS-CoV-2 Infection: a systematic review with meta-analysis. SN Compr Clin Med. 2021 Jan 7:1-10. doi: https://doi.org/10.1007/s42399-020-00690-6. Epub ahead of print.

26. Stewart DJ, Hartley JC, Johnson M, Marks SD, du Pré P, Stojanovic J. Renal dysfunction in hospitalised children with COVID-19. Lancet Child Adolesc Health. 2020;4(8):e28-9. doi: https://doi.org/10.1016/S2352-4642(20)30178-4.

27. Corrêa RA, Lundgren FLC, Pereira-Silva JL, Silva RLF, Cardoso AP, Lemos ACM, et al. Brazilian guidelines for community-acquired pneumonia in immunocompetent adults - 2009. J Bras Pneumol. 2009;35(6):574-601. doi: https://doi.org/10.1590/s1806-37132009000600011.

28. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory

syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2020;180(2):307-22 doi: https://doi.org/10.1007/s00431-020-03766-6. Epub ahead of print 2020 Aug 15.

29. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. Arthritis Rheumatol. 2021 Apr;73(4):e13-29. doi: https://doi.org/10.1002/art.41616. Epub 2021 Feb 15.

30. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2021;5(2):133-41. doi: https://doi.org/10.1016/S2352-4642(20)30304-7. Epub 2020 Sep 18. Erratum in: Lancet Child Adolesc Health. 2021 Feb;5(2):e5. doi: https://doi.org/10.1016/S2352-4642(20)30304-7.

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