# MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH CORONAVIRUS DISEASE IN CHILDREN

*A Multi-centered Study in Belém, Pará, Brazil*

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**Abstract:** We described the characteristics of 11 children with pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2. The main clinical indications for hospital admission were vasogenic toxic shock (n = 2), Kawasaki disease (n = 4), and Kawasaki disease shock syndrome (n = 5). The echocardiography findings were abnormal in 63% of cases. All patients had 2 or more organ dysfunctions, and the mortality rate was 18%.

**Key Words:** COVID-19, coronavirus, severe acute respiratory syndrome, multiple organ failure, multisystem inflammatory syndrome

Accepted for publication August 6, 2020.

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The authors have no funding or conflicts of interest to disclose.

All authors have substantially contributed to this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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DOI: 10.1097/INF.0000000000002865



The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has impeded human activities worldwide and has no known precedent in the last 100 years.[1] In Brazil, until the end of July 2020, more than 1 million confirmed cases and over 70,000 deaths were reported.[2]

Recently, a severe inflammatory syndrome was reported in previously healthy children that tested positive for SARS-CoV-2. The clinical manifestations of this hyperinflammatory syndrome are similar to Kawasaki's disease and/or toxic shock syndrome, presenting persistent fever, multiorgan dysfunction and elevated inflammatory markers. This grouping of cases served as the basis for the description of the pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2 (PMIS-TS).[3–6]

The diagnosis of PMIS-TS should be considered in children and adolescents 0–19 years of age, with characteristics of Kawasaki disease (typical or atypical) or shock syndrome, according to the case definition proposed by the World Health Organization.[3] Currently, there is limited information on the risk factors for, pathogenesis, clinical course and treatment of PIMS-TS, and just a few cases have been reported in resource-limited settings, such as the Amazon.[7]

We described demographic, epidemiologic, clinical, laboratory, imaging and therapeutic characteristics of 11 children with PMIS-TS admitted to 4 pediatric intensive care units (PICUs) in the Eastern Amazon, Brazil.

## MATERIALS AND METHODS

### Design and Ethical Aspects of the Study

Between April 15 and June 15, 2020, a prospective observational study was carried out, which included all children with confirmed COVID-19 infection admitted to 4 PICUs located in the Eastern Amazon region, Brazil. This study was approved by the Ethics Committee for Institutional Research (#4040363; CAAE: 32150220.2.0000.5171), and the required signed consent of the parents and/or the legal guardian were obtained.

### Study Population and Groups

Children (29 days to 13 years old) admitted to any of the 4 PICUs with COVID-19 infection confirmed by a positive molecular or serological test and a clinical-epidemiological presentation suggestive of PIMS-TS, according to WHO criteria, were screened; the 4 PICUs (1 private and 3 public) share the same clinical analysis laboratory network. Children without complete vaccination status and those with associated infection characterized by any positive serologic or microbiologic tests (blood, urine and cerebrospinal fluid) for viral and/or bacterial agents were excluded from the analysis.

The reverse transcription-polymerase chain reaction and qualitative serology tests for IgG and IgM using immunochromatography (ONE STEP COVID-19 TEST, Celer Biotecnologia S/A) were performed using kits from the Central Laboratory of the state of Pará (LACEN-PA). The children were prospectively followed from the PICU admission day until hospital discharge, death, or the 28th day.

Baseline information (sex, age, weight, time of onset, time of SARS-CoV-2 diagnosis, and date of admission and discharge), epidemiologic history, clinical manifestations, the serologic, microbiologic, laboratory and imaging findings, treatment, and outcomes were recorded with standardized data collection forms.

## RESULTS

We admitted 102 children with suspected COVID-19 infection to the 4 PICUs, The diagnosis of PMIS-TS was performed in 23 (47.9%) children; we excluded 12 children from this analysis who had incomplete vaccination status (5) or associated co-infection (6 bacterial infections, 1 RSV and 1 type A influenza co-infection). The main clinical presentations of these 11 children with PMIS-TS were: Toxic shock syndrome (2 cases), Kawasaki disease shock syndrome (5 cases) and Kawasaki disease (4) (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E89).

The median age was 59 months (7 months to 11 years), consisting of 9 (81%) male patients. The median time elapsed between exposure to the COVID-19 and the clinical manifestations of PMIS-TS, was 15 days (7–60 days). The fever was maintained for

4–15 days; however, among the survivors, the duration oscillated between 8 and 15 days (Table 1).

The median length of PICU stay was 5 days (3–12 days). The mortality rate was 18.2% (2 cases), which was associated with comorbidities (neurologic and respiratory diseases), marked poor nutrition, shorter length of time between virus exposition and clinical manifestations (range: 7–10 days), and toxic shock syndrome. Mechanical ventilator (MV) support was provided to 7 patients; invasive MV was initiated for 3 children (average of 4.7 days), whereas noninvasive MV was initiated for 4 children (average of 1.8 days), as shown in Table 1.

Abnormal lymphocyte count was found in 8 patients (72.7%), among whom 1 (9.1%) had an increased number of lymphocytes (highest value 5.162 × 109/L) and 7 (63.6%) had a reduced number of lymphocytes (lowest value 0.463 × 109/L) (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/E90).

Notably, all 11 patients presented with hypofibrinogenemia (median 36.9 mg/dL; range 23.7–86.4), hypoalbuminemia (median 2.2 g/dL; range 1.5–2.6), hyperlactatemia (median 2.3 mmol/L; range 2.1–2.8), C-reactive protein (median 38.8 mg/dL; range 1.5–127.5), and an elevated D-dimer level (median 1357 ng/mL; range 580.0–5228). Additionally, ferritinemia (average 619.7 ng/mL) and troponin levels (median 0.28 ng/mL; range 0.01–68.8) were elevated in 7 patients (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/E90).

Ground-glass areas in the posterior segments of the lower and upper lobes in both lungs were observed in the chest computed tomography of 7 patients. The echocardiography examination was abnormal in 7 (63%) cases, showing mild and medium aneurysms in 4 and 3 cases, respectively. All patients had 2 or more organ dysfunctions. Pneumonia caused by COVID-19 was diagnosed in 9 patients, with 4 of them progressing with ARDS. Fluid resuscitation was required in 8 patients, 7 of whom were classified as fluid refractory shock demanding vasoactive agents [cardiogenic shock (4), septic shock (2) and mixed shock (1)] (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/E91).

## DISCUSSION

The COVID-19 pandemic had a major impact in our region, not only because of the high number of confirmed cases (more than 125,000 cases and 5000 deaths) but also because of a greater demand for intensive care unit beds, and consequently, an elevated mortality rate16. Similar to other parts of the world (England, USA and France), an increased number of children with severe late manifestations of COVID-19 demanding PICU admission was observed.[4–7]

We report a cluster of PICU admissions for cardiovascular failure associated with PMIS-TS. This study showed that PMIS-TS mostly affected younger children, contrary to what was reported in other studies.[8–12] Although the available data suggest that PMIS-TS is uncommon in this age group; there is still no confirmatory explanation for this finding.[13]

Cardiovascular involvement was common, in addition to the presence of myocardial dysfunction as a prominent manifestation of COVID-19 in this cases series. An interaction of hypovolemic and hyperinflammatory shock associated with myocardial dysfunction can play an important role in determining the severity and mortality observed, as evidenced in other cases.[10–12]

The higher mortality (18.2%) in this series is in accordance with the elevated values of the PELOD2 and pediatric risk of mortality IV. Greater severity of the disease may be triggered by the limiting comorbidities, poor nutrition, facilitating the development of marked hyperinflammatory syndrome, with ferritin, d-dimer, and troponin values that are greater than in survivors, in addition to cardiac dysfunction evidenced by lower cardiac output and ejection fraction. As reported in previous studies, the evolution to worse clinical outcomes is related to the magnitude of the inflammatory response.[7–12]

In this study, the presence of hyperinflammation was evidenced by moderate hyperferritinemia associated with high C-reactive protein values. Other studies reported more marked hyperferritinemia than those found in this series.[7–12] The possible explanation for this discrepancy is based on the fact that the pathobiologic mechanisms of ferritin production are a marker of acute inflammation.[14] The finding that most patients tested negative on reverse

**TABLE 1.** Demographic and Epidemiological Characteristics of Patients With PMIS-TS

| Characteristics | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age in months (years) | 7 (…) | 56 (4) | 137 (11) | 54 (4) | 90 (7) | 28 (2) | 112 (9) | 73 (6) | 59 (4) | 53 (4) | 127 (10) |
| Gender | Female | Male | Male | Male | Male | Female | Male | Male | Male | Male | Male |
| Nutritional status: BMI/age | Severe poor nutrition | Severe poor nutrition | Overweight | Normal | Normal | Normal | Overweight | Overweight | Obese | Obese | Obese |
| Form of presentation* | TSS | TSS | KDSS | KD | KD | Atypical KD | KDSS | KDSS | KDSS | KD | KD |
| Contagion form | Hospital | Hospital | Home | Home | Home | Home | Home | Home | Home | Home | ... |
| Exposure interval (days) | 10 | 7 | 10 | 45 | 60 | 30 | 15 | 15 | 15 | 45 | 14 |
| RT-PCR | + | + | – | – | – | – | – | – | – | – | – |
| Rapid test IgM–/IgG+ | – | – | + | + | + | + | + | + | + | + | + |
| Disease duration in days | 4 | 5 | 21 | 18 | 12 | 23 | 14 | 14 | 13 | 13 | 12 |
| Fever duration (days) | 4 | 5 | 12 | 13 | 8 | 15 | 12 | 10 | 10 | 11 | 12 |
| Length of PICU stay (days) | 4 | 5 | 8 | 5 | 4 | 8 | 12 | 8 | 6 | 3 | 5 |
| Length of Hospital Stay (days) | 180 | 60 | 16 | 30 | 12 | 22 | 17 | 18 | 14 | 15 | 13 |
| Noninvasive ventilation time in days | — | — | 2 | — | — | — | 2 | — | 1 | — | 2 |
| Invasive ventilation time in days | 4 | 5 | — | — | — | — | — | 5 | — | — | — |
| Hospital discharge | Death | Death | + | + | + | + | + | + | + | + | + |
| PIM3 (%) | 18 | 99.9 | 50.2 | 31 | 4.3 | 5.2 | 51.9 | 45.1 | 0.64 | 7 | 20.5 |
| PRISM-IV (%) | 16 | 33 | 1 | 2 | 1 | 2 | 5 | 3 | 0.94 | 3 | 5 |
| PELOD2 | 10 | 18 | 9 | 8 | 8 | 8 | 9 | 12 | 2 | 6 | 9 |

*Toxic shock syndrome; Kawasaki disease shock syndrome; Kawasaki disease.
RT-PCR, reverse transcription-polymerase chain reaction

transcription-polymerase chain reaction and positive for antibodies against SARS-CoV-2, raises the possibility that PMIS-TS may result from an acquired immunity disorder.[15,16]

This study has some limitations. The diagnostic criterion for PMIS-TS was based exclusively on the WHO case definition. The data collected is based on investigations without the use of a single protocol; therefore, management and conduction were individualized by center and by patient. The target population was exclusively critical patients, which can cause selection bias. There are no national data available on seroprevalence in children for COVID-19, and there is no national record of Kawasaki disease or toxic shock syndrome for comparison.

On the contrary, the strengths of this study lie on some relevant aspects: (1) it is a multicenter prospective study that included children with confirmed infection by SARS-CoV-2 in resource-limited scenario, and (2) it excluded the bias of any relevant associated co-infection as well as the guarantee that all children had a vaccination calendar updated.

The heterogeneity of the pro-inflammatory immune response in pediatric COVID-19 associated with different prognoses and worse clinical outcomes associated with comorbidities in infants suggest the possibility of certain subgroups in the pediatric age group being more susceptible to PMIS-TS. Blood samples were collected in these patients for future analysis of inflammatory cytokines at the Virology Section, Evandro Chagas Institute.

## ACKNOWLEDGMENTS

*The authors thank our patients for their participation in this case series.*

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