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BRIEF REPORT

Clinical-laboratory profile of children and adolescents with multisystem inflammatory syndrome temporarily associated with COVID-19 in Goiás, Brazil

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Abstract

Here, we describe the clinical and laboratory characteristics of patients diagnosed with multisystem inflammatory syndrome in children (MIS-C) in the state of Goiás, Brazil, and its possible association with COVID-19. The study subjects were individuals aged between 0 and 19 years, selected from private and public institutions from May 2020 to April 2022. Thirty-five cases of MIS-C were confirmed. Four progressed to death. Most of the patients were 0–9 years old. All had fever, and 71.4% had abdominal pain. All had elevated levels of inflammatory markers, and 40.0% were positive for SARS-CoV-2 by RT-PCR. This study demonstrates a broad relationship between MIS-C and SARS-CoV-2 infection. Further studies are needed to confirm this association.

Keywords: COVID-19 · Kawasaki disease · Multisystem inflammatory syndrome in children · SARS-CoV-2

On April 26, 2020, at the height of the COVID-19 pandemic, the English National Health Service (NHS) [1] published an alert on a new clinical presentation in children, characterized by fever and multisystem inflammation, possibly associated with SARS-CoV-2 infection [1]. The clinical features of these pediatric cases were similar to those of other well-described inflammatory syndromes in children, including complete or incomplete Kawasaki disease (KD) and KD shock syndrome. Some of these children developed toxic shock syndrome and multiple organ failure [2, 3]. Those affected also had fever and unusual symptoms, such as abdominal pain, gastrointestinal symptoms with diarrhea, hypotension, and conjunctival congestion and had high levels of inflammatory markers such as C-reactive protein and interleukin 6 (IL-6) in their serum, as well as biochemical evidence of myocardial dysfunction [2–4]. Similar cases were later reported in Europe and the USA, and these were temporally and geographically associated with outbreaks of COVID-19. Most of the affected children were negative for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) but were positive for specific antibodies against the virus, indicating previous infection [5].

The cause of the clinical syndrome has been postulated to be a post-infectious inflammatory response, manifested days or weeks after SARS-CoV-2 infection. This clinical condition was called "multisystemic inflammatory syndrome associated with COVID-19 in children and adolescents", also referred to as "pediatric inflammatory multisystemic syndrome temporarily associated with SARS-CoV-2" (PIMS-TS) [6]. The World Health Organization (WHO) has referred to it as “multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19" to describe the disease, and here, it will also be referred to as such [7].

In epidemiological week (EW) 20 (05/10 to 05/16/2020), the US Centers for Disease Control and Prevention (CDC) and WHO recommended reporting suspected cases of MIS-C. In Brazil, an alert was released to the pediatric community

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on May 20 of the same year by the Ministry of Health (MH) in partnership with the Pan American Health Organization (PAHO) and the Brazilian Society of Pediatrics (BSP) [3, 7]. In view of this emergency situation and with the emergence of a series of case reports from the United Kingdom, Spain, Italy, France, Switzerland, the USA, and Brazil [8], a technical note (no. 14/2020) was published by the MH on July 24, 2020, in which criteria for defining cases were established and mandatory notification of MIS-C cases in Brazil was announced.

We describe here the clinical and laboratory characteristics of patients with MIS-C, identified in the State of Goiás, Brazil, between 2020 and 2022, which were registered in the RedCap/MS (Research Electronic Data Capture) system and notified in the Influenza Epidemiological Surveillance System (IESS; in Portuguese, SIVEP-Gripe), a system managed by the MH/Health Department together with the State and Municipal Health Departments. The inclusion criteria for the study were as follows: [i] being a resident of the State of Goiás; [ii] experiencing symptoms compatible with MIS-C, and [iii] being between 0 and 19 years old. Patients were selected from private and public institutions. The criteria were proposed by the MH based on the case definition established by the PAHO/WHO [3]. These include high (at least 38°C) and persistent (≥3 days) fever in children or adolescents (between 0 and 19 years old) accompanied by at least two of the signs and/or symptoms listed below:

1. non-purulent conjunctivitis or bilateral rash or signs of mucocutaneous inflammation (oral, hands or feet);
2. arterial hypotension or shock;
3. manifestations of myocardial dysfunction, valvulitis, pericarditis, or coronary abnormalities (including echocardiogram findings);
4. acute gastrointestinal manifestations (diarrhea, vomiting or abdominal pain);
5. evidence of coagulopathy (prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT); elevated D-dimer)

These signs and symptoms must be associated with increased levels of inflammation markers in the bloodstream, such as ferritin, C-reactive protein, or fibrinogen; an increased erythrocyte sedimentation rate (ESR); and evidence of COVID-19 (diagnosed by molecular assay, antigen detection test or positive serological test), or having a history of contact with a confirmed case of COVID-19. Additionally, other causes of infectious origin, such as bacterial sepsis, staphylococcal shock syndrome, or streptococcal infection must be ruled out. Children and adolescents who meet some or all of the criteria for Kawasaki syndrome or toxic shock, with evidence of SARS-CoV-2 infection, may be included.

The first confirmed case in Goiás, Brazil, was reported on October 22, 2020, after carrying out retrospective searches by epidemiological surveillance and evaluation by the technical group for analysis of death by COVID-19. In the period from May 17 to April 2, 2022, 86 cases were reported. MIS-C was confirmed in 35 of these cases and ruled out in 29. Twenty-two cases were still under investigation while this article was being written (Fig. 1). Four patients (aged 13, 11, and 2 years and < 1 year of age) died, giving a fatality rate of 11.4%.

The largest number of cases occurred in the age group from 0 to 4 years (15 cases), corresponding to 42.9% of the total. The mean age was 5 years (ranging from 0 to 14 years), and the majority of the patients were males (57.1%). Fever was the most frequent sign/symptom, present in 100% of the reported cases. In addition, 71.4% of individuals had abdominal pain and nausea/vomiting, 65.7% had O_2 saturation < 95% and cyanosis or pallor, 60.0% showed lethargy, and 54.3% had tachycardia. Lymphadenopathy was observed in 40% of the cases. Other signs and symptoms were reported less frequently and are listed in Fig. 2.

The most frequent laboratory findings were a significant increase in brain natriuretic peptide (BNP) and C-reactive protein levels (seen in 100% of reported cases). An increase in ERS was observed in 96.3% of cases, D-dimer in 93.1%, IL-6 in 83.3%, and fibrinogen in 81.0%. A decrease in platelet count (thrombocytopenia) was observed in just over half of MIS-C cases. Other laboratory findings are listed in Fig. 3.

Biological samples (nasopharyngeal swab and blood samples) were collected from 30 individuals and subjected to genomic amplification testing (RT-PCR) and antibody detection assays for SARS-CoV-2. For SARS-COV-2 genome detection, the molecular kit SARS-CoV-2 Bio-Manguinhos of the Berlim Protocol (Bio-Manguinhos, Rio de Janeiro, Brazil) was used. This is a target-specific amplification technique with fluorescence-labeled probes used to detect the presence of the SARS-CoV-2 envelope gene. For antibody detection, the Wondfo® SARS-CoV-2 Antibody Test (Lateral Flow Method) (Guangzhou Wondfo Biotech Co., Guangzhou, PR China) was used. This is an immunochromatographic assay for rapid, qualitative detection of SARS-CoV-2 IgG/IgM antibody in human whole blood, serum, or plasma samples.

All of the samples were tested by RT-PCR; 12 (40%) were positive and 18 (60%) were negative. In serological tests, 16 out of 18 samples tested (88.9%) were positive for IgG antibodies, and two (11.1%) were negative. Five individuals underwent rapid tests for antibody detection, and three were positive. For 10 patients, MIS-C was ruled out based on clinical and epidemiological criteria.

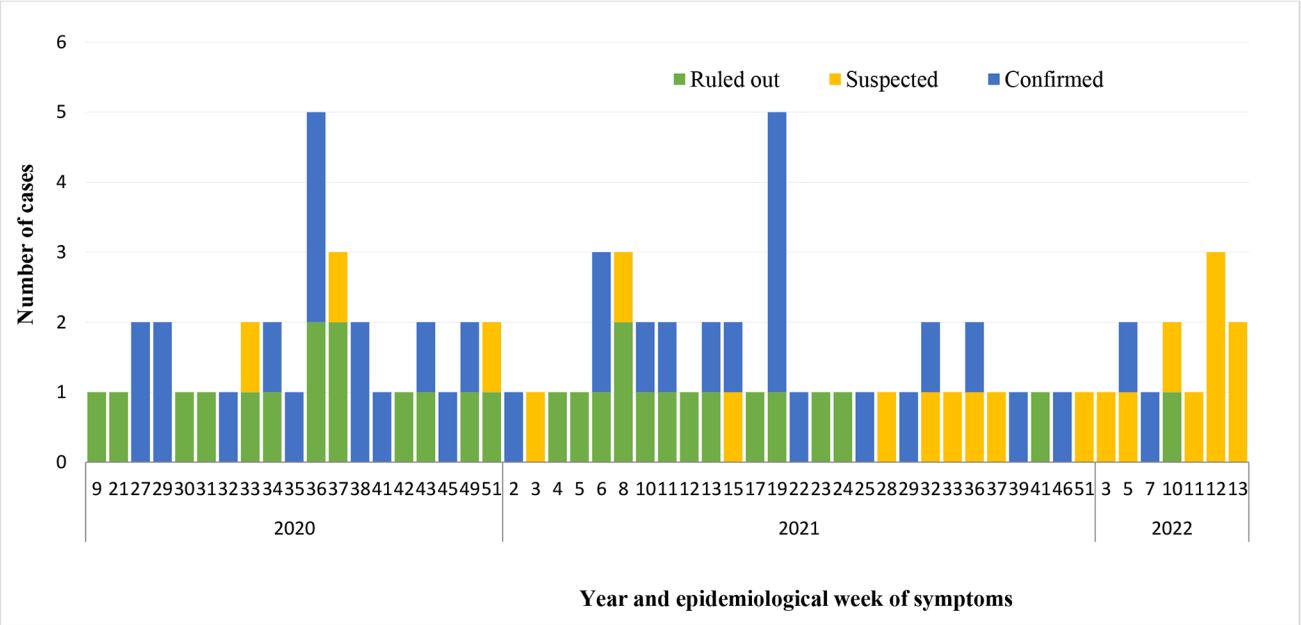

Fig. 1 Notified cases of MIS-C according to final classification and epidemiological week of symptom onset, Goiás-Brazil, 2020–2022 **N = 35**
Source: **IESS [SIVEP-Gripe]**

The 35 confirmed MIS-C patients were hospitalized, 26 (74.2%) in an intensive care unit (ICU), with a mean length of stay of 10 days (ranging from 1 to 35 days). Corticosteroid therapy was used in 88.5% of the cases, and immunotherapy with immunoglobulins was used in 85.7%. Anticoagulants were used in 60.0% of cases, and antivirals were used in 14.3%. Of the four individuals (11.4%) who died, three (75%) were male. Confusion and fever were observed in all four of these patients. O_2 saturation of < 95%, nausea, vomiting, and cyanosis or pallor was observed in three patients, two had spots on the body, myalgia, abdominal pain, and dyspnea, and one had lethargy, irritability, edema of the hands and feet, diarrhea, conjunctivitis, coryza, and headache. The four patients who died were hospitalized, two of them in the ICU. The mean length of stay in the ward or ICU was 6.75 days, with a median of 2.5 days (max, 21; min, 1). Two of them (50%) were treated with steroids and immunoglobulin. One was treated only with antivirals (25%), and one was treated only with anticoagulants (25%). One of them required a blood transfusion.

Of the 30 patients who underwent echocardiography, 23.3% had signs of valvulitis, 40.0% had signs of pericarditis, 20.0% had signs of myocardial dysfunction, and 10.0% had a coronary abnormality. Other findings were reported less frequently, including pneumonia and thromboembolism. The most frequent clinical complication was hypotension (42.9%), followed by acute renal failure (20.0%) and septicemia/pneumonia, lung edema, and convulsion (17.1%).

MIS-C is a syndrome that occurs especially in children and adolescents, and health services have been alerted to its occurrence in the current pandemic scenario because of its impact on health and its still uncertain origin. It is characterized by clinical signs that are similar to those of KD, including fever, conjunctival blood vessel dilation, rash, and redness of the oropharynx, and has been observed to occur after infection with SARS-CoV-2, resulting in death in 1.8–18% of cases [8–13]. However, the global incidence of MIS-C and its frequency in a specific population remains unknown. Furthermore, the causal relationships among the syndrome, SARS-CoV-2 infection, and KD pathogenesis remain unclear [6].

MIS-C has been observed in the population of Goiás, and the analysis of the current scenario suggests that the disease is expanding, following a trend similar to that observed in several countries around the world, including Brazil, and with a median mortality rate of 11.4%. The incidence appears to be slightly higher in males than in females (54% and 46%, respectively, according to a recent meta-analysis) [14], although the difference observed in this study was not considered statistically significant.

MIS-C cases are confirmed based on a constellation of clinical signs and symptoms in addition to laboratory findings that demonstrate immunological, hematological, and biochemical changes. Among these signs and symptoms, fever, abdominal pain accompanied by diarrhea, and skin rash were the most prevalent in the cases diagnosed here. These findings coincide with those most frequently observed in cases of MIS-C described in the literature, and, taken as a whole, they resemble the description of KS cases [15]. It is important to note, however, that there are several

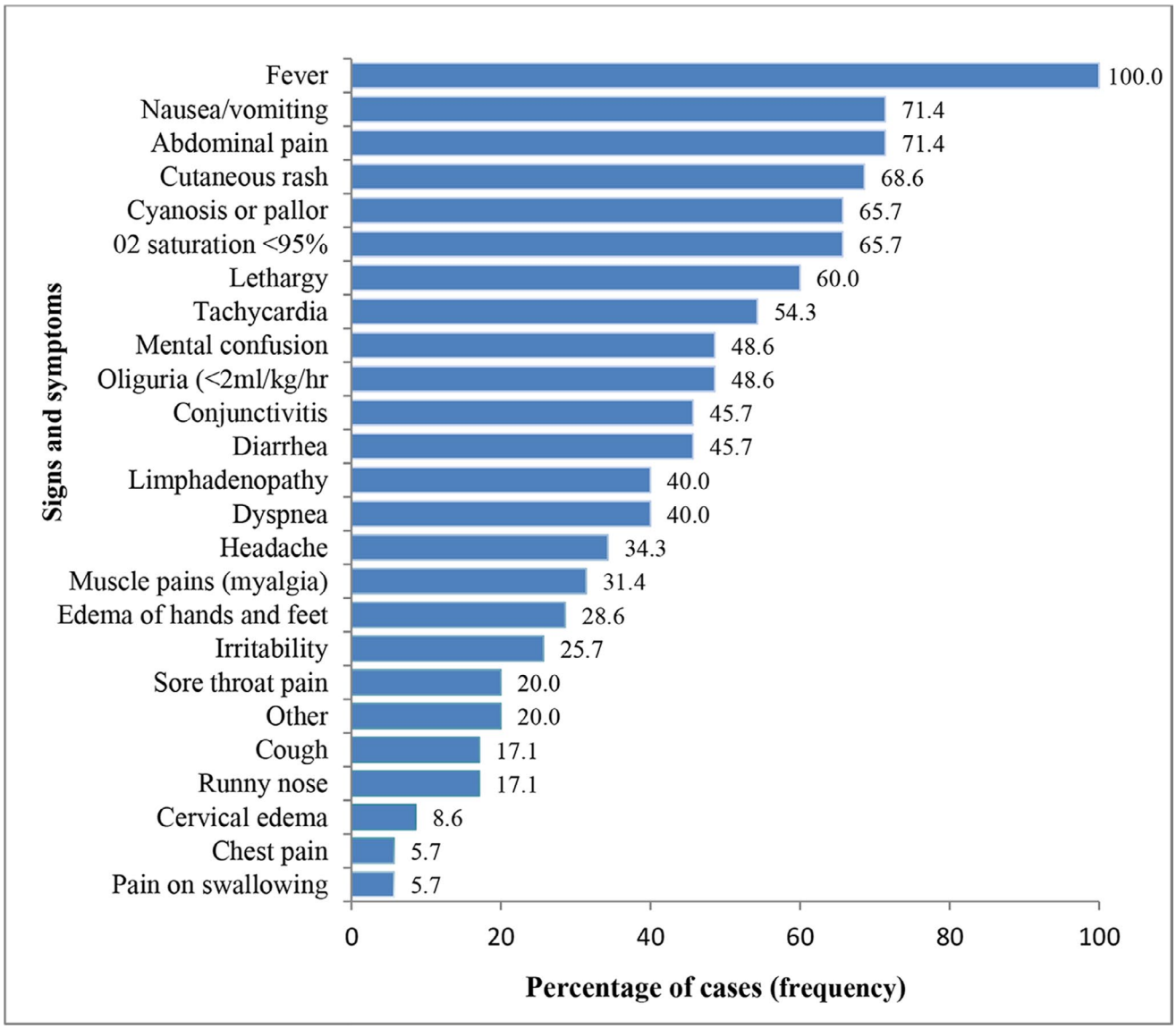

Fig. 2 Confirmed cases of MIS-C, according to signs and symptoms, Goiás, Brazil, 2020 to 2022
N = 35
Source: IESS [SIVEP-Gripe]

clinical and laboratory peculiarities that can distinguish this syndrome from KS. These include prominent cardiac dysfunction with increased troponin and elevated BNPs, and frequent (and often severe) enteropathy, in contrast to severity rates of 15%-26% among patients diagnosed with KD [15, 16], and relative thrombocytopenia rather than thrombocytosis [15]. Thus, considering the overlapping of symptoms, laboratory tests seem to be essential for differentiating the two syndromes.

The laboratory data presented here are also sufficient to support the diagnosis of MIS-C. Elevated levels of inflammatory markers and evidence of hyperinflammation have been widely reported and are found consistently in patients with this syndrome [17]. Overall, C-reactive protein, procalcitonin, and ESR are highly elevated, as are ferritin and IL-6 levels in serum. A significant increase in D-dimer and fibrinogen are the main features of the coagulation profile, while the hematological features of the disease are leukocytosis, neutrophilia, lymphopenia, and normal or decreased red blood cell and platelet counts [18, 19]. These data are in agreement with the findings presented here. Importantly, high levels of D-dimer and procalcitonin and lymphopenia have been demonstrated to be markers of worse outcomes in adult COVID-19 patients. IL-6 has been associated with the "cytokine storm" phenomenon and may also play a role in the pathogenesis of MIS-C [19].

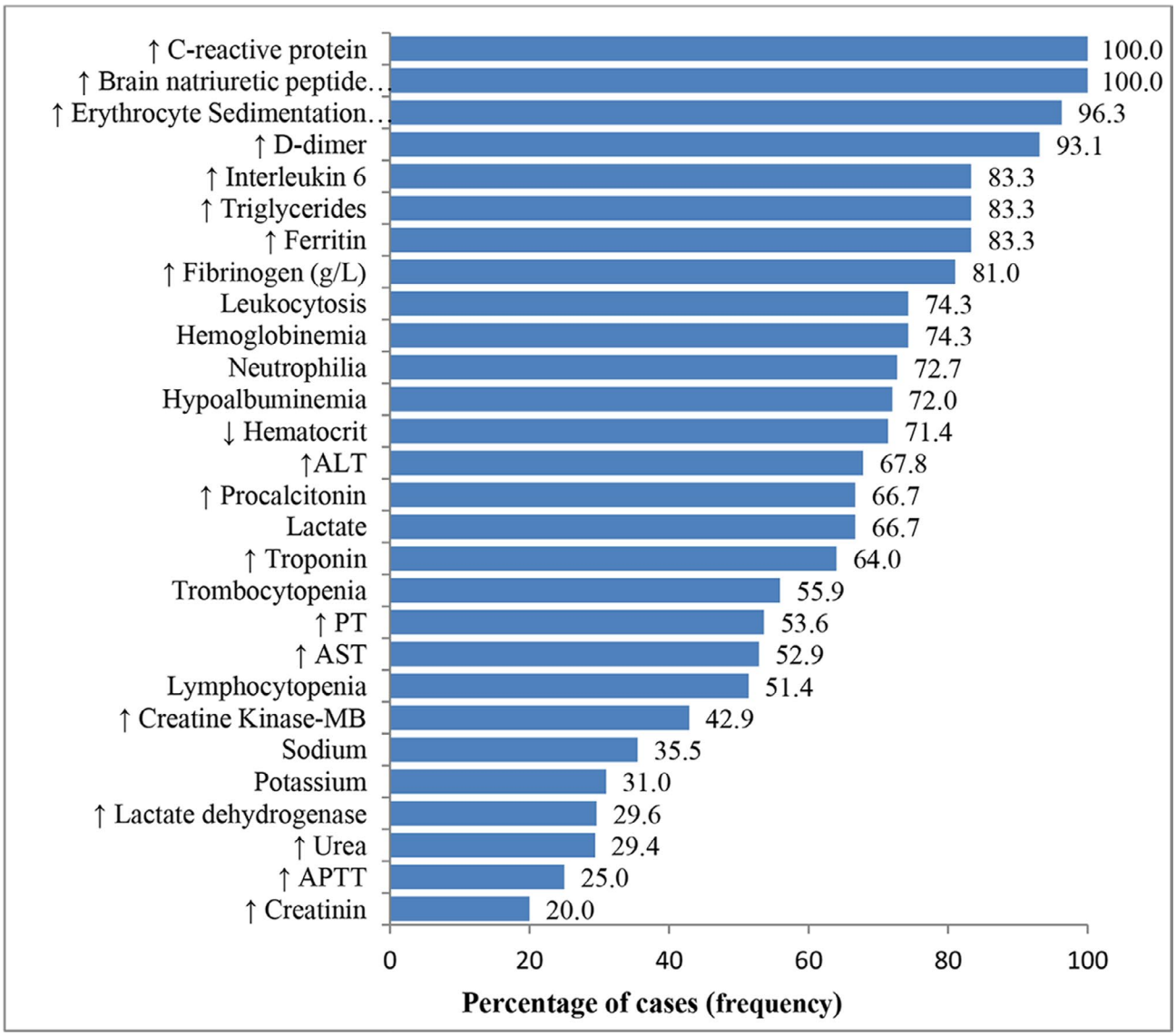

Fig. 3 Laboratory findings of confirmed cases of MIS-C, Goiás, Brazil, 2020–2022
N = 35
Source: IESS [SIVEP-Gripe]

As the correlation of COVID-19 cases with the development of MIS-C was established previously [20], in this study, biological samples from the 30 individuals were subjected to laboratory tests that could show previous exposure to SARS-CoV-2 or active infection by this agent. Of this total, 28 patients (93.3%) were shown to have been exposed to SARS-CoV-2, including 12 with active infection, confirmed by detection of viral genomic RNA. These results suggest that there is a broad correlation between MIS-C development and previous SARS-CoV-2 infection. However, it is important to note that MIS-C cases seem to develop 4 to 6 weeks after the acute stage of COVID-19 and not during active infection [21], which suggests that the pathogenic process is mediated by the immune response. Furthermore, while the definition of MIS-C given by the Royal College of Pediatrics and Child Health recognizes temporal association with COVID-19, it does not require proof of infection or exposure to SARS-CoV-2 to meet the case definition, such as the criteria defined by the CDC and WHO [22]. On the other hand, it has been reported that almost all patients with MIS-C had positive serological results for SARS-CoV-2, with some of them still in the acute phase of infection [23]. Thus, to categorically state that there is or is not a correlation may still be premature.

Patients with MIS-C require hospitalization, and the median duration has been reported to be 6 days. More than 60 percent

need care in the ICU [20]. The percentage of ICU admissions observed in the state of Goiás, as expected, was also high. As MIS-C patients show some clinical and laboratory similarities to KD patients, the principles of therapy for KD apply, and applying this treatment protocol has been shown to result in rapid clinical improvement, reduction of inflammatory markers in most patients, and prevention of death [24].

Cardiac involvement seems to be the most frequently observed complication and sequela in patients with MIS-C. Recent studies have described coronary artery anomalies and changes in cardiac function (based on conventional echocardiographic parameters such as ejection fraction and velocity). However, detailed analysis of cardiac mechanics is needed in order to detect subtle changes in myocardial function. The major finding during the acute phase of MIS-C is a myocarditis-like clinical picture, which may remain subtle and subclinical. This has led to the hypothesis that MIS-C may be associated with reduced systolic and diastolic function, similar to other forms of viral myocarditis, and may produce coronary artery dilation similar to that found in KD [25].

Our analysis also showed that, in 16.7% of the cases analyzed, the patient was obese or overweight. Previous studies have also suggested that MIS-C may occur more frequently in obese patients, with the frequency ranging from 10 to 37% [26, 27]. Obesity results in "metainflammation", a chronic inflammatory response to excess energy substrate produced by metabolic cells, including adipocytes, hepatocytes, myocytes, pancreatic islets of Langerhans, astrocytes, and neurons. This inflammatory signaling activates immune response cells, which in turn, exacerbate tissue inflammation [28], which is already present in MIS-C cases [29, 30]. It is postulated that obesity and obesity-associated chronic inflammation may also contribute to endothelial cell activation, a phenomenon also observed in cases of MIS-C, whose occurrence has been associated with elevated plasma levels of biomarkers of arterial damage [28, 31]. Therefore, the harmful effects of the hyperinflammatory response and endothelial cell activation observed in childhood obesity are believed to contribute to poor outcomes in critically ill children.

It has been shown that MIS-C can lead to gastrointestinal manifestations, myocardial dysfunction, and coronary abnormalities – complications that can worsen and lead to death due to multiple organ failure if not properly treated. Therefore, to minimize the risk of adverse outcomes, patients with MIS-C need an early diagnosis in order for appropriate treatment to be initiated. Currently, these patients are being treated in different ways based on symptoms, using a standard KD protocol involving corticosteroids, immunoglobulins, anticoagulants, and antivirals, depending on the specific situation and the needs of the patient. However, it is important to note that KD is a disease of unknown etiology (although recent research supports the existence of an unidentified virus as the cause [6]), and despite its clinical similarity to MIS-C, there are subtle differences in the characteristics of these syndromes. Furthermore, the clinical signs of MIS-C can be seen in many infectious diseases in childhood and are not specific for any diagnosis. Therefore, a diagnosis of MIS-C should be made with caution.

Another intriguing aspect of MIS-C is its origin. Although there is some evidence that it is a post-infection immune reaction to COVID-19, it should be kept in mind that our understanding of the immune response to SARS-CoV-2 is still limited. SARS-CoV-2 is a new virus, and its association with MIS-C, despite an increasing number of case reports suggesting a relationship, is still not definitively established.

Finally, in view this scenario, healthcare professionals should be aware of the signs and symptoms of MIS-C and, when in doubt, refer the patient to a local or state healthcare facility so that the case can be properly investigated. Analysis of reported cases can increase our understanding of this syndrome and improve our ability to identify the disease for early detection and treatment.

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Author Contribution Mary Alexandra: first author and intellectual mentor of the study, data extraction, preparation of tables, and study design. Robélia Pondé: discussion and relevant critical review of the manuscript's intellectual content and design, adaptation of tables throughout the text, and revision of the manuscript. Robério Pondé: discussion, study design, writing, analysis and interpretation of data, and revision of the manuscript

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Data Availability The clinical and laboratory characteristics of patients with MIS-C, identified in the State of Goiás between 2020 and 2022, are recorded in the RedCap/MS (Research Electronic Data Capture) system, through its own form available using the link https:/is.gd/simpcovid, and notified in the SIVEP-Gripe.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could appear to have influenced the work reported in this paper.

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