


# Pediatric Inflammatory Multisystem Syndrome or Multisystem Inflammatory Syndrome in Children: A New Thread in Pandemic Era

Global Pediatric Health  
Volume 8: 1–9  
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DOI: 10.1177/2333794X211050311  
journals.sagepub.com/home/gph  


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## Abstract

After the perturbing effects of the COVID-19 Pandemic, we observed intense public health efforts in a global-scale to prevent, control, and treat the SARS-CoV-2. Hundreds of clinical center researched for adequate treatments, other were devoted to the development the COVID-19 vaccines and other studied the nature and the effects of this mutant coronavirus SARS-CoV-2. As time goes by, the pediatric inflammatory multisystem syndrome has been recently defined and associated the COVID-19 past infection and is now considered a shot to middle-term complication of COVID-19. In this paper, we review the actual concepts of PIMS in children, the epidemiology, the clinical presentation, and evolution, the recommended laboratory and other testing. The recommended specialties interconsultation for hospitalized patients and a full discussion on the appropriate treatment of these patients. We include the Latin-American experience with PIMS and a final discussion on the outcome of this disease.

## Keywords

PIMS, Covid-19, children, adolescent

Received June 21, 2021. Accepted for publication September 14, 2021.

## Introduction

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease (COVID-19), has rapidly spread worldwide has become the new reality for everybody.<sup>1</sup>

Starting with its first confirmed case in Wuhan, China, on the 31st of December of 2019, SARS-CoV-2 virus increased to 146 689 258 confirmed cases of COVID-19 worldwide on April 26, 2021,<sup>2</sup> affecting 1.82% of global population. Only 2% of cases correspond to the pediatric population.<sup>3</sup> Some of the ongoing theories of the different incidence and different clinical aggravation in this age group might be the fewer comorbidities, the different immunological response, the lower tendency to have hyperinflammatory states<sup>4</sup> and the relatively lower presence of ACE-2 receptors.<sup>5,6</sup>

Even that few Children with COVID-19 become seriously affected, usually by respiratory involvement, but children still carry some risk of complications, during and after COVID-19 and some of them might progress to a hyperinflammatory state.

For example, in Europe and parts of North America, there were many reports of children presenting a systemic inflammatory response, resembling other pediatric conditions including Kawasaki disease (KD), toxic shock syndrome (TSS), bacterial sepsis, and macrophage activation syndrome (MAS) after recovering from COVID-19. Initial reports found that many of them have myocardial dysfunction and coronary artery involvement in addition to gastrointestinal and systemic symptoms.<sup>7-9</sup> The objective of this paper is to describe the novel disease named Pediatric Inflammatory Multisystem Syndrome (PIMS), named as well Multisystem Inflammatory Syndrome in Children (MIS-C). The aim of this work is to review this new syndrome on actual basis.

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This review do not involve direct contact with patients and we only review data from published articles. We did not required ethical approval from our IRB Committees.

## Review of Literature

### *SARS Cov-2 in Children*

An epidemiological survey in China of 72.314 cases reported only 2.2% of the children being affected and, in the USA, (2.572 cases) 1.7%, not accounting that there may be asymptomatic children.<sup>10</sup> In Canada, with overall 7.7% of COVID-19 cases being in children as of July 23, 2020. This may be due to increased community testing, which could in turn more cases of children with mild symptoms or that are asymptomatic.<sup>11</sup>

Children tend to have milder clinical presentations of SARS-CoV-2 virus infections with few complications, however, after April 2020, cases resembling Kawasaki disease (KD), toxic shock syndrome, secondary hemophagocytic lymphohistiocytosis, and macrophage activation syndrome were reported and associated to a recent infection with SARS-CoV-2 (See Table 1).<sup>12</sup> This disorder was named pediatric multisystem inflammatory syndrome (PMIS) temporally associated with COVID-19 by the NHS and Royal College of Paediatrics and Child Health (RCPCH), and other similar names came along: multisystem inflammatory syndrome in children (MIS-C) by the CDC, and multisystem inflammatory syndrome in children and adolescents with COVID-19 by WHO.<sup>13</sup> For the purpose of the discussion of this article, we will refer to all the above definitions as PIMS. The estimated incidence of PMIS is 2/100 000 children.<sup>3</sup> Unlike KD, PMIS is more frequent in children older than 5 years of age, most commonly by the age of 9 years.<sup>14</sup> PIMS can affect adolescents, and there is a race predominance in Black and Hispanic/Latino descent.<sup>15</sup>

### *Physiopathology (PIMS vs Kawasaki Disease)*

Kawasaki disease is an acute, self-limiting vasculitis affecting medium-sized vessels, especially the coronary arteries.<sup>16</sup> Thus, the body confronted with a pro-inflammatory state can lead to various complications if left untreated. Frequently affects children under 5 years old, and is more frequent in East Asian or Pacific Islander descent, reason to which there is significant number of cases of this disease in Asian Americans or in the Japanese population.<sup>17</sup> Kawasaki disease is the primary cause of acquired heart disease in children living in the developed countries, which is one of the main concerns in this disease.<sup>18</sup> A possible explanation of the cardiac

involvement in KD is the earlier maturation of lung entry ports, with a higher number of ACE2 receptors, and/or a diet deficient in vitamin D that leads to hyperinflammation.<sup>19</sup>

PMIS, in the other hand, affects predominantly previously healthy children,<sup>12</sup> although some presented comorbidities such as obesity or overweight, chronic lung disease such as asthma.<sup>20</sup>

PMIS is associated to SARS-CoV-2 virus or to the post-infection inflammatory effects of the disease, considering that these types of disease appear after the peak of SARS-CoV-2 infection. Some patients have shown to be positive with the SARS-CoV-2 virus, confirmed by either polymerase chain reaction (PCR) or serology or have had a history of contact with a person with a confirmed or suspected case of SARS-CoV-2 virus.<sup>18</sup>

There is a lack of understanding to why these cases appear more in Europe, United States, Italy, France, and not in China or Japan<sup>21</sup> where COVID-19 first started. One reason may be the lack of reports of PMIS or that most hospitalized children with COVID-19 had a non-severe clinical course.<sup>12</sup>

In a study 186 patients with PIMS, from 26 states of the US, only 14 patients were reported with COVID-19 symptoms before the onset of PMIS, although 131 (70%) had either a positive RT-PCR or antibody test for SARS-CoV-2 virus and 55 (30%) an epidemiologic history of contact with a confirmed patient with COVID-19. This shows the intense association with the COVID-19 infection (temporal and serologic association) and development of a hyperinflammation pattern. The scarce number of cases of PMIS in adolescents and children can be attributed to something inherent to the individual's immune system or their ACE2 expression.<sup>12</sup>

As previously stated, not all children with PMIS present a positive PCR test for SARS-CoV-2 infection and this clinical manifestation appear later after peak incidence of COVID-19 cases. PMIS, considered a post infectious complication, it is a primary complication from a recent infection with SARS-CoV-2 virus.<sup>22</sup> There are many theories around the pathophysiology of PMIS, the more accepted ones are 2: (1) IgG antibody-dependent enhancement (ADE) of the disease and (2) cytokine storm.<sup>23</sup> The ADE has the ability to activate monocytes and produce persistent cytopenia and a greater activation of CD8+ T cells.<sup>24</sup> The ADE mediated by autoantibodies, autoantibodies such as anti-La and anti-Jo-1 commonly detected in PIMS patients.<sup>20</sup> In the case of the cytokine storm, induced by the coronavirus that has the capacity to block type I and type III interferon responses provoking a delayed cytokine storm in patients that have either a high viral load of SARS-CoV-2 or difficulty controlling viral replication.<sup>21</sup>

KD and PMIS have overlapping features, which poses a challenge in distinguishing the 2 when making a diagnosis. Unfortunately, there is no definite line or criteria to distinguish with absolute certainty between KD and PMIS. This leads to either underestimation or overestimation of the true conditions.<sup>25</sup> Part of the blame is that PIMS is a rare and new defined condition with only few reported cases in each country. In the United States, there are 3185 reported cases of PIMS since March 29, 2021.<sup>26</sup> Additionally, it is a relatively new syndrome, so the etiology, pathophysiology, diagnostic criteria, and treatment are in an ongoing research and discussion. Most of the management this syndrome has been based on the management KD and other similar entities, highlighting the importance of further investigation to have better and faster diagnosis, a more favorable prognosis, better prevention and more understanding of the pathophysiology of PIMS.

### *Diagnosis and Clinical Features*

The lack of complete understanding of the pathophysiology and etiology of PIMS has made diagnosing difficult due to its nonspecific clinical presentation.<sup>27</sup> WHO, RCPCH, and CDC have provided their own case definition criteria for PMIS.

In general, the criteria for PIMS include children and adolescents below 21 years old that present persistent fever with multisystem organ involvement of at least 2 organ systems gastrointestinal, hematologic, mucocutaneous, respiratory, musculoskeletal, neurological, and/or renal. The patient usually shows some of the following signs and symptoms: rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation signs in oral mucosa, hands, or feet. In addition, hypotension or shock, cardiac abnormalities such as myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, including echocardiographic findings, elevated troponin/NT-proBNP, evidence of coagulopathy, with altered PT, PTT, and elevated D-dimers. Also acute gastrointestinal problems such as diarrhea, vomiting, or abdominal pain.

In children, cardiovascular, gastrointestinal, and dermatological or mucocutaneous manifestations were more common than neurological, musculoskeletal, and respiratory symptoms.<sup>28</sup> Respiratory, neurological, and musculoskeletal features include congestion, sore throat, and cough, shortness of breath, wheezing, headache, lethargy, confusion, weakness, joint pain, and myalgia.<sup>29</sup>

Until now, there are 3 common types of PMIS clinical presentation: (1) persistent fever and gastrointestinal symptoms, (2) shock with left ventricular dysfunction, and (3) KD-like syndrome.<sup>25</sup>

Fever and gastrointestinal symptoms are the most common presentation. If PIMS is suspected and the patient presents abdominal pain, there is a need of an abdominal ultrasound scan to evaluate differential diagnosis.<sup>30</sup>

Form all patients, 50% present shock, either cardiogenic or vasoplegic, and in a lower percentage patients present respiratory distress.<sup>20</sup> Cardiac involvement encompasses a grand variety of different defects and the evaluation includes 12-lead electrocardiogram, echocardiogram, chest radiography, and cardiac biomarkers like BNP and NT-proBNP, among others (high-sensitivity troponin I, troponin I, and troponin T). Some of the possible electrocardiogram findings are ST segment abnormalities, abnormal T waves, AV block, and ventricular arrhythmia. These electrocardiographic events are not necessarily diagnostic, but prognostic of the treatment and clinical evolution. Another useful study is the echocardiogram, to be able to detect abnormal coronary arteries and aneurysms, using the Z score. Other possible defects were, in order from most common to less common, the ejection fraction less than 55%, pericardial effusion, pericarditis, and myocarditis, mitral regurgitation, left ventricular dysfunction, tricuspid regurgitation, coronary echogenicity, and right ventricular dysfunction. Chest radiography might demonstrate cardiomegaly, pericardial effusion, pleural effusion, focal or bilateral opacity, and lung edema.

### *Laboratory Findings*

Patients with PMIS must have some alteration in the inflammation markers such as ESR, CRP, procalcitonin, fibrinogen, d-dimer, ferritin, lactic acid dehydrogenase, IL-6, elevated neutrophils, reduced lymphocytes, and low albumin. The laboratory testing in Patients with suspected PIMS includes blood tests such as full blood count, CRP, urea, creatinine and electrolytes and liver function including inflammation markers before 12 hours after hospital admission.<sup>30</sup> Additionally, to discharge other etiologic causes, especially microbial, such as bacterial sepsis, staphylococcal, or streptococcal shock syndrome. After admission, the priority lab testing: respiratory viral screening and microbiological testing aimed for detecting staphylococci and streptococci through cultures and surface swabs.<sup>14,27</sup> COVID-19 need to be demonstrated through RT-PCR, antigen test, serology positive or contact with COVID-19 patients within 4 weeks before the onset of symptoms.<sup>31</sup> RT-PCR results usually come out negative most of the time rather than positive while IgG antibody against the SARS-CoV-2 virus is exactly the opposite; however, whether the results are positive or negative if there is a prior

infection to the SARS-CoV-2 virus, the association still exist.<sup>14</sup>

From the diagnostic criteria, patients that meet the criteria of typical or incomplete/partial KD are possible PMIS case until proven otherwise.<sup>27</sup>

According to the American Heart Association (AHA),<sup>14</sup> typical KD can be defined if the patient presents persist fever and 4 of the 5 following mucocutaneous features:

- erythema and cracking of lips
- strawberry tongue
- and/or erythema of oral and pharyngeal mucosa
- bilateral bulbar conjunctival injection without exudate
- rash (maculopapular, diffuse erythroderma)
- erythema and edema of the hands and feet in acute phase
- and/or periungual desquamation in subacute phase
- and/or cervical lymphadenopathy

Incomplete KD is when the patient does not meet any or some of the criteria and usually is considered in patients less than 6 months with unexplained fever for more than 7 days but have no clinical findings of KD or in patients with unexplained fever of more than 5 days with 2 or 3 clinical findings.<sup>32</sup> Utilizing an echocardiogram and assessing inflammation markers help in guiding toward the likelihood that that patient has incomplete KD. PMIS and KD are very similar considering both can have persistent fever and similar mucocutaneous signs.<sup>23</sup> However, PMIS is usually associated with more prevalent gastrointestinal symptoms and frequent cardiovascular involvement leading to a necessity for vasoactive support.<sup>12</sup> These patients have a higher white blood cell count, neutrophil count and CRP, more profound lymphopenia and anemia, lower platelet counts, and higher fibrinogen and troponin levels.<sup>14</sup> They also are more likely to develop left ventricular dysfunction and shock.<sup>27</sup>

### Treatment

The most common treatment for PMIS is usually intravenous immunoglobulin IgG (IVIg) of 2 g/kg after onset of fever preferably within 5 to 7 days in order to reduce the risk of coronary artery aneurysm and low dose aspirin.<sup>33</sup> Those with persistent fever, even after the application of IVIg for at least 36 hours and less than 7 days can receive a second dose of IVIg and methylprednisolone.<sup>1</sup> Corticosteroids, interleukin-6 inhibitors (tocilizumab or siltuximab), interleukin-1Ra inhibitor (anakinra), and

anticoagulation treatment (aspirin or enoxaparin) are the general approach to reduce the inflammation process and combat the hypercoagulable state.<sup>12,23</sup> Empirical broad-spectrum antibiotics like ceftriaxone proved to be useful to PMIS's patients due to the similarity of PMIS with bacterial infections.<sup>22</sup> when the patient develop cardiac involvement vasopressor support should be started as IV fluid boluses, norepinephrine, and vasopressin to treat systemic hypotension, LV dysfunction, or refractory hypotension. Metronidazole can be added if there are GI symptoms. If the clinical course is of a severe illness or shock, vancomycin, clindamycin and cefepime or vancomycin, meropenem, and gentamicin is recommended.

If the patient has a high likelihood to be a COVID-19 infection or the patient had a positive COVID-10 PCR test, then the Remdesivir can be started, although the benefit is unknown. Some required intubation or extracorporeal membrane oxygenation (ECMO) in patients with severe cytokine storm, refractory vasoplegia, and shock.<sup>22,28</sup> Management of PIMS requires a multidisciplinary team considering the multisystem involvement of this syndrome thus when figuring out the right treatment to avoid more complications; pediatric disease experts, immunologist, cardiologists, rheumatologists, and intensivists need to be involved in the decision-making process.<sup>30</sup>

### Prognosis

Majority of PMIS cases are admitted to the ICU and stayed hospitalized for a median length of 4 to 12 days; fortunately, most are discharged alive until the inflammatory markers return to normal, when they are afebrile for at least 24 hours, normotensive, well hydrated, and do not require supplementary oxygen or inotropic help to keep cardiac function.<sup>3,12,20,30,34</sup> The mortality rate of PMIS is low, only 2% of the infected patients died from PMIS; in the US, there have been only 36 deaths from PMIS.<sup>23,26</sup> The recommended follow-up for recovering PMIS is every 1 to 2 weeks and echocardiograms 4 to 6 weeks after discharge. The follow up must include pediatrician/neonatologist, immunologists, infectious disease experts and cardiologists especially with children that required organ support during their hospitalization<sup>30</sup>

### PIMS in Latin America

The first report of case series of PIMS in Latin America came from Brazil,<sup>35</sup> comprising cases from March to May 2020. Also, in the Easter Amazon region from the same country, a prospective observational study was carried out, which included all children with confirmed SARS-CoV-2 infection admitted to 4 PICUs between

**Table 1.** Comparative Epidemiology of Kawasaki Disease PIMS and Toxic Shock Syndrome.

Kawasaki disease	PIMS	Toxic shock syndrome
It is an acute, self-limiting vasculitis affecting medium-sized vessels, especially the coronary arteries.	PIMS is associated to SARS-CoV-2 virus or to the post-infection inflammatory effects of the disease, considering that these types of disease appear after the peak of SARS-CoV-2 infection. Produce hyperinflammation.	It is a toxin-mediated disease that is caused by toxin-producing streptococci or <i>S. aureus</i> . These superantigens bypass the normal pathway for activation of T cells resulting in over-activation of cytokines and inflammatory cells.
Frequently affects children under 5 years old	Older children and adolescents	In non-menstrual settings occurs at any age
Its incidence in Northeast Asian countries including Japan, South Korea, China, and Taiwan is 10 to 30 times higher than that in the United States and Europe	There is a lack of understanding to why these cases appear more in Europe, United States, Italy, France, and not in China or Japan) where COVID-19 first started.	The incidence tends to be higher in the winter and is more prevalent in developing countries.
Its etiology is unclear, with no specific infectious cause.	PIMS is associated to SARS-CoV-2 virus	It is most commonly caused by a toxigenic strain of <i>Staphylococcus aureus</i> or Group A Strep ( <i>Streptococcus pyogenes</i> ).
Risk factors: To be a boys tend to develop more this disease and the entity of being from Asia or Pacific islands	Risk factor: to have a present or recent COVID-19 infection. To have comorbidities like obesity or asthma.	Risk factors include superabsorbent tampon use, nasal packing, post-operative wound infections, recent influenza infection, as well as immunocompromised states.

April and June 2020.<sup>36</sup> In the following months, from April to August 2020, other Latin American countries like Peru, Chile, Mexico and Cuba started reporting series of cases describing children with current criteria for PIMS.<sup>37,38</sup>

The first Latin American country reporting favorable clinical outcomes in children with PIMS was Chile, with a study describing a series of 27 children diagnosed and treated from May to June 2020.<sup>39</sup> In most studies, diagnosis followed the criteria for PIMS according to the Centers for Disease and Control (CDC) and microbiologic documentation of SARS-CoV-2 exposure (serology or PCR).<sup>38-40</sup> Positive serology was more common than positive PCR test in children with PIMS.<sup>41</sup> By this time, PIMS syndrome with characteristics of Kawasaki disease (typical or atypical) or shock syndrome in children and adolescents 0 to 19 years of age became accepted.

These centers included radiographic evaluation with chest radiograph as part of the patients' work-up, in a patient suspected to have COVID-19, but imaging did not influence positively the PIMS diagnosis. Computed tomography, on the other hand, showed ground-glass areas in both lungs in around 70% of patients. Nonetheless, a Mexican study reports little or no correlation between PIMS and respiratory symptoms of COVID-19,<sup>42</sup> while in other countries, like Chile, they detected recent COVID-19 infection in up to 82% of cases.<sup>39</sup>

Echocardiography examination was abnormal in approximately half of the reported cases, showing mild and medium aneurysms, myocardial, pericardial, or

coronary damage. Hepatic enzymes, bilirubin levels, renal function tests, troponins, EKG, and blood gases only for patient with aggravated condition or severe progression.<sup>35,37-40</sup>

Clinical criteria considered to establish the diagnosis included having 2 or more organ dysfunctions (2), presence of hyperinflammation, and some studies included fever  $\geq 38.0^{\circ}\text{C}$ .<sup>(6)</sup> The clinical examination includes cutaneous rash, non-purulent conjunctivitis, edema and erythema in extremities, oral mucositis and lips cheilitis, abdominal pain, and nausea/vomiting. Work up included as in other countries, measurement of inflammation markers, myocardial damage markers, serum albumin, and complete blood count, as well as echocardiography and serology for SARS-CoV-2.<sup>41</sup> Most cases showed significant increase in C-reactive protein (CRP), polymorphonuclear cells, procalcitonin, D-dimer, ferritin, and fibrinogen, as well as abnormal lymphocyte count and hypoalbuminemia.<sup>36,42</sup> Troponin levels were found significantly more elevated in PIMS patients than in those with KD (including children with shock associated to KD).<sup>41,43</sup>

### Case Series Experience in Latin America

In Latin America, hospitalized children with PIMS showed different disease patterns, with diverse outcomes according to the clinical presentation, age group, ethnicity, and especially geographic area and socioeconomic level.<sup>39</sup>

Mexican reports identified 3 main patterns:

- First group, with persistent fever and high levels of inflammation markers, but without characteristics of KD, shock, or organ dysfunction
- Second group, with criteria for KD
- Third group, with shock and clinical, echocardiographic, and laboratory evidence of myocardial injury.

Median age of presentation was of 8.2 years. All patients reported presented fever of more than 3 days, and gastrointestinal involvement, significant increase in inflammatory and myocardial damage markers, and only half of the patients had myocardial involvement.<sup>38,42</sup>

Brazilian studies described the characteristics of children with the following clinical patterns: toxic-shock syndrome, Kawasaki disease, and Kawasaki disease shock syndrome. The echocardiography findings were abnormal in 63% of cases, and all patients had 2 or more organ dysfunctions. The mortality rate in this study was 18%. Contrary to other reported cases, Brazil observed more affection in younger children the median age was 4 years.<sup>35,36,44</sup>

In Chile, PIMS appeared approximately 1 month after the peak of COVID-19 cases, especially in the most vulnerable areas. Gastrointestinal symptoms were the most frequent, and inflammatory markers found increased at admission. In this country 80% of patients presented cardiac compromise, from subclinical forms to those requiring aminergic support or ECMO.<sup>39,43</sup>

Comparison between PIMS and KD in Colombia indicated that patients affected by PIMS were of older age, and had higher rates of cardiac involvement, requiring critical care in a higher percentage. Adolescents over 12 years and infants younger were the 2 age groups higher incidence, often in need of hospitalization and intensive care.<sup>45,46</sup>

Natural course of PIMS, met the criteria for viral sepsis with organ dysfunction; therefore, its initial management was very similar.<sup>47</sup> Treatment consisted of initial fluid resuscitation and vasoactive support as needed. Regarding immunomodulatory medication, 55% to 75% received intravenous immunoglobulin (IVIG) at 2 g/kg/dose and/or systemic steroids 10 to 30 mg/kg/dose. Some individuals in these groups required invasive respiratory support. Less than 1% of patients received extracorporeal membrane oxygenation (ECMO).<sup>35,39,46</sup>

Few times, there is a need for Antiviral drugs, such as hydroxychloroquine, oseltamivir, lopinavir-ritonavir. Empiric broad-spectrum antibiotics were given to prevent bacterial superinfection or treat sepsis. In addition, antiplatelet and anticoagulant therapy is useful to

prevent thrombocytosis, or altered flow in affected coronary arteries. In the presence of a cytokine storm syndrome, IL-6 inhibitors like tocilizumab are useful.<sup>38,39,46,48</sup>

## Outcome

Some studies described transient complications including but not limited to, acute kidney injury, appendicitis, pleural effusion, and resistance to initial anti-inflammatory treatment. Early coronary compromise (within first 2 weeks) was relevant in all clinical groups, including those who only presented with fever and elevated inflammatory markers.

Patients who had underlying comorbidities and/or lower socioeconomic status presented the worst outcomes. A vast majority of patients presenting the syndrome required admission to a pediatric intensive care unit. A case series report in a pediatric center in Mexico, was the only study found in Latin America in which none of the patients required mechanical ventilation and none of them died.<sup>42</sup>

The SARS-CoV-2 pandemic had a major impact in Latin America, not only because of the high number of confirmed cases but also because of a greater demand for intensive care unit beds, and consequently, an elevated mortality rate. PIMS, in contrast with KD, is associated with greater resistance to IVIG, trend toward macrophage activation syndrome (MAS), and admission to the PICU due to a much higher severity of the disease.<sup>38</sup>

Mortality rates varied from 4.2% to 25%, and most of those who died were classified as low—very low socioeconomic conditions. These data support current evidence of a more severe disease in Latin/Hispanic children.<sup>38,39,46,48</sup> (Ulloa-Gutierrez 2020)

## Conclusion

Most children with Covid-19 might remain asymptomatic, even unnoticed, less than 10% will need hospital support and only 2 in 100 000 will develop PIMS. With this new awareness we need to keep a constant vigilance on any children or adolescent with persistent fever, and more if they have the past history of COVID-19.

PIMS and KD both represent hyperinflammatory states, both capable to involve heart and its vasculature, but different from KD, PIMS has been associated to a particular virus, the SARS-CoV-2 as a trigger to the disease. We reviewed the most common clinical presentation, the most common complications, the laboratory needed and the most actual treatment for PIMS patients as well as the general outcome.

## Author Contributions

All authors contributed substantially to the research and writing of the article.

## Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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