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Multisystem inflammatory syndrome associated with SARS-CoV-2 disease in pediatric patients in Latin American countries: A systematic review.

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Abstract

Introduction: Pediatric multisystem inflammatory syndrome (PIMS) associated with COVID-19 is considered a potentially fatal complication post-COVID-19 and is characterized by a proinflammatory state affecting several organ systems of variable severity. Most of the literature published in this regard is of Anglo-Saxon origin, so it became necessary to investigate the literature reported in Latin America's Spanish and Lusophone languages.

Methods: An observational, descriptive study was developed. Scientific articles of investigations carried out with the pediatric population of Spanish-speaking and Lusophone countries were taken as sources of information, with an analytical, descriptive design of case series. Systematic reviews, case reports, and paid articles were removed. Clinical and laboratory manifestations were taken as results of interest in treating PIMS.

Results: Fifteen investigations in Latin American countries were included, with a total population of 305 pediatric patients with multisystem inflammatory syndrome associated with COVID-19 (PIMS). Clinical manifestations: fever (80-100%), abdominal pain (36-100%), diarrhea (39-100%), vomiting (40-100%), rash (47-100%), conjunctival injection (27%-100%), shock (10%-100%), Kawasaki-like disease (59%-100%), neurological manifestations (25%-60%), cardiovascular: pericardial effusion (17%-40%), and ventricular dysfunction (30%-50%). Analytical manifestations: leukocytosis, lymphopenia, thrombocytopenia; increase in acute phase reactants (C-reactive protein, procalcitonin, serum ferritin); increase in D-dimer and fibrinogen. General treatment: treatment of shock, stabilizing hemodynamics, ABC algorithm (A: airway management; B: ventilation; C: circulation. Specific treatment: intravenous immunoglobulins and corticosteroids; empirical antibiotic therapy, acetylsalicylic acid at anti-inflammatory doses or antiplatelet; and low molecular weight heparins. Management of complications.

Conclusions: In the Spanish-speaking and Lusophone-speaking countries of Latin America, the clinical and analytical presentation and management of pediatric patients with multisystem inflammatory syndrome associated with COVID-19 do not differ from the descriptions in the Anglo-Saxon literature.

Keywords: **MeSH**: Corticosteroids, Ventricular Dysfunction, Fibrinogen, Intravenous Immunoglobulins, Leukocytosis, Lymphopenia, Neurological Manifestations, Child, COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19) results from infection with the novel SARS-CoV-2 virus. After its first description in China in November 2019, the virus spread worldwide, causing millions of cases and thousands of deaths. Interestingly, the impact on children has been less in their course and outcome [1].

The number of pediatric deaths related to SARS-CoV-2 is deficient, and most of these deaths were described in children with some preexisting comorbidity [2]. Even with the optimistic panorama around the pediatric population regarding COVID-19, a more severe condition began to develop in children in the late phase of the COVID-19 pandemic. Researchers from Italy, France, the United States, and the United Kingdom described a group of children with a systemic inflammatory disorder with no diagnostic alternative, with clinical and microbiological evidence of exposure to SAR-CoV-2. Signs and symptoms overlapped with Kawasaki disease and toxic shock syndrome and were characterized by fever, abdominal pain, and cardiac involvement.

This syndrome began to be known as "Pediatric Multisystem Inflammatory Syndrome Temporarily Related to COVID-19" (PIMS-TS) and is considered a rare post-COVID-19 complication, which in a minority of cases can lead to death. Although there is significant uncertainty about the etiology of this disease and its immunological basis, there are clinical features reminiscent of other pediatric diseases. The delay between the initial SARS-CoV-2 infection and the late development of systemic inflammatory syndrome is reminiscent of acute rheumatic fever. In contrast, the sudden onset of severe systemic inflammation with shock is reminiscent of toxic shock syndrome caused by superantigens [3].

In a short period, much has been learned about this multisystem inflammatory syndrome temporally associated with COVID-19; however, numerous questions persist. Although it is a rare disease, estimated to affect two children per 100,000, it comprises a variable spectrum of symptoms, and its outcome can be fatal. The initial approach to managing pediatric patients with suspected PIMS occurs most often in the emergency department.

Despite the advancement and increase in information about this new pathology worldwide, especially in Europe and North America, the data from Latin America still needs to be improved. Therefore, it is necessary to conduct an exhaustive investigation that allows health professionals to develop their knowledge and guide their attention toward a diagnosis and its correct clinical management. The objective of this study is to identify the main patterns of clinical presentation, related laboratory findings, and the approach to this syndrome, taking as sources of information scientific articles on research carried out and published in the pediatric population of Latin American countries that speak Spanish and Lusophone in a period of 48 months (July 2020-July 2022).

Materials and methods

Selection of the search strategy

-Place of study: Search in search engines such as PubMed, Cochrane, plus Clinical Key in the field of Health Institutions in Latin American countries.

-Study design: Observational, descriptive study.

-Descriptors [DeCS]: The following descriptors were used. The Boolean operators "AND" and "OR" were considered to broaden the search (Table 1).

Table 1. Descriptor

Descriptor in Portuguese	Descriptor in English
Infecções por Coronavirus-19	Infection by coronavirus-19
Serviços de Saúde da Criança	Services of health pediatric
Pandemia	Pandemic
Síndrome - inflamatória – multissistêmica pediátrica	Syndrome - multisystemic - inflammatorypediatric
Doença de Kawasaki	Disease of Kawasaki

Selecting search criteria

Patients admitted to the pediatric emergency room were diagnosed with pediatric multisystem inflammatory syndrome associated with COVID-19.

Inclusion and exclusion criteria

They included:

-Publications about multisystemic inflammatory syndrome associated with SARS-CoV-2 disease in pediatric patients from Latin American countries.

-Publications made in Latin America from July 2020 to July 2022.

-Publications made in Spanish and Lusophone.

-Research with analytical, observational design, and clinical trials.

They were excluded:

-Publications made outside the period of July 2020 -July 2022.
-Literature published in languages other than Spanish and Portuguese.
-Systematic reviews, meta-analyses, conference proceedings, editorials, and degree theses.

Data extraction

This scientific essay was prepared following the procedure of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, updated in 2021 (Page et al., 2021), as shown in Figure 1.

Analysis of data

Once the eligible articles for this research were identified, the free-access reports were downloaded. After having an acceptable number of publications, we proceeded to the analytical reading of them, extracting information that allowed us to answer the research question. Once the articles included in this research were selected, according to the established selection criteria, the information for the traceability of the articles was also extracted: author/year, country, journal, volume, research design, and DOI/URL. An Excel sheet was used to collect the information, and the bibliography was managed with the Mendeley program, v19.4.1.

Bioethical aspects

For the development of this research, it was not necessary to take biological samples or carry out any interaction or intervention with patients; therefore, this work did not represent any risk for patients. Since this investigation was based on bibliographical sources, it was unnecessary to request informed consent.

Results

Study selection

In the search carried out, 254 articles were identified, of which 14 duplicates were eliminated, 204 by title and abstract, 14 for not being from Spanish-speaking or Lusophone countries in Latin America, 1 for including patients over 18 years of age, 4 for being of low quality of evidence, one letter to the editor and one editorial. At the end of the selection process, 15 articles were included in this investigation. Figure 1 shows the selection process.

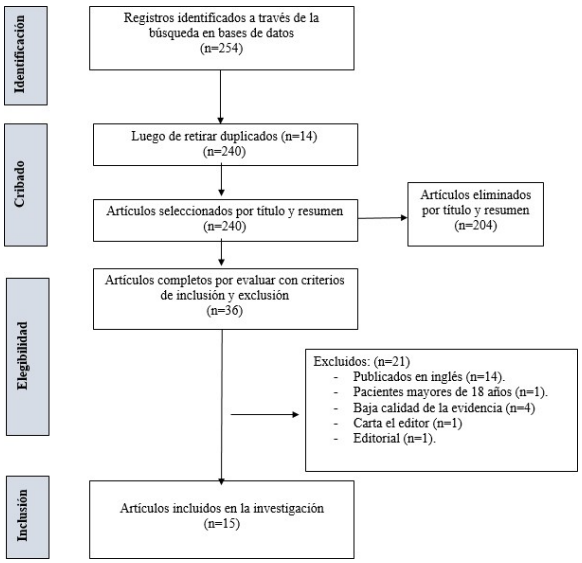

Figure 1. Diagram of article selection

Source: Prepared from Page et al. (2021). PRISMA 2020 statement: an updated guide for the publication of systematic reviews. Spanish Journal of Cardiology; 74(9): 790-799. DOI: 10.1016/j.recesp.2021.06.016

Description of selected studies

Fifteen investigations carried out in Latin American countries were included. With a total population of 1,383 pediatric patients diagnosed with COVID-19, of whom 298 were confirmed to have multisystem inflammatory syndrome associated with COVID-19 (PIMS), the median age of patients was more than eight years (8.0-8.7 years) in three studies [4-6], and a median age of 5.1 to 5.4 years was reported in three studies [7-9]. See Table 4.

This investigation addressed three outcomes of interest (clinical, biochemical, and PIMS treatment criteria) [4,5,7,9-13]. In two studies, only the clinical and biochemical aspects were described [6, 14]. Clinical manifestations and treatment are reported in two articles [8, 15]; two only

explain treatment [16, 17], and one study only refers to clinical manifestations [18].

The frequency of PIMS in the different series analyzed ranged from 4.7% [6] to 63.7% [18]. Twenty percent of the selected articles were in Argentina [6, 16, 17] and Chile [12, 13, 15]. All of these were published in Spanish. Two investigations from Brazil were included [9, 18], both in Portuguese (see Table 2).

Table 2. Research selected.

Author/s	Year	Country	Journal	Vol	Design	Population studied	(PIMS)	patients with confirmation from PIMS	Age	Criteria analysis
Rosanova et al.	2021	Argentina	MedicineChildish	28	cohorts	100	25	4.7%	8.7 years	Biochemical Clinic
Munaico et al.	2021	Peru	Underground Science	29	Descriptive	27	26	**	8.4 years	Biochemical Clinic Treatment
Verdugo et al.	2021	Chili	Pediatric Andes	92	cohorts	32	32	**	6.8 years	Biochemical Clinic Treatment
Yagnam et al.	2021	Chili	Pediatric Andes	92	prospective	twenty	twenty	26.20%	6.0 years	Biochemical Clinic Treatment
Prata et al.	2020	Brazil	J Pediatric (Rio J)	96	prospective	79	10	12.70%	5.2 years	Biochemical Clinic Treatment
De Coll et al.	2020	Peru	Rev. Peru Med . Exp . Public health	37	Descriptive	8	8		5.1 years	Biochemical Clinic Treatment
Eisink et al.	2021	Argentina	Arch . Argent Pediatr	119	Consensus	**	**	**	**	Treatment
Rawson et al.	2021	Argentina	Arch . Argent Pediatric	118	Consensus	**	**	**	**	Treatment
Luna et al	2021	Peru	medwave	twenty-one	Descriptive	10	10	**	6.7 years	Biochemical Clinic Treatment
Fortich et al.	2020	Colombia	Rev. Enferm infection pediatric	33	Descriptive	eleven	eleven	**	6.7 years	Biochemical Clinic Treatment
Cieza et al.	2021	Peru	Rev. Body Med . HNAAA	14	Descriptive	18	18	10.80%	8.8 years	Clinic, Biochemistry, Treatment
Lona et al.	2021	Mexico	Rev. Chil . infectol .	18	cohorts	375	39	10.40%		Clinic, Biochemistry
Fontes et al.	2021	Brazil	Rev. Baiana public health	Four. Five	cohorts	66	42	63.70%	8 years	Clinic
Domínguez et al.	2021	Peru	medwave	twenty-one	cohorts	100	31	31%	5.4 years	Clinic, Treatment
Cofré et al.	2020	Chili	Rev - Chilean infectol	37	cohorts	537	26	20.40%	6.4 years	Clinic Treatment

Clinical manifestations of pediatric multisystem inflammatory syndrome associated with COVID-19.

With the clinical manifestations in patients being PIMS, the research consulted agrees that it is a broad spectrum of symptoms and signs, in which the predominant manifestations are not of respiratory origin but rather systemic, digestive, cardiovascular, and cutaneous, with variable figures [4-15, 18].

High fever is common in all the research consulted, as are abdominal pain, nausea, vomiting, rash, conjunctivitis, affections of cardiovascular origin, and hemodynamic instability. Table 3 summarizes the figures reported for these case series' most frequent clinical manifestations.

In the research by Rosanova et al. (2021), the factors associated with the presentation of PIMS were age greater than two years (OR: 24.7; 95% CI: 1.03-592.4), lymphopenia (OR: 9.03; 95% CI: 2.05-39.7), thrombocytopenia (OR: 11.7; 95% CI: 1.88-75.2) and the absence of underlying pathologies (OR: 0.06; 95% CI: 0.01-0.03).

In a cohort of cases in Chile [15], they described a predominance of digestive and cardiovascular manifestations among patients who developed PIMS. These researchers classify this syndrome into four different clinical categories:

PIMS without shock or Kawasaki disease-like symptoms. PIMS is associated with shock.

PIMS with cardiovascular involvement, specifically dysfunction of the myocardium, heart valves, pericardium, or coronary arteries.

Table 3. Reported signs and symptoms.

Author (year)	Fever	Pain abdominal	Diarrhea	vomiting	Exanthema	Injection conjunctival	shock	Kawasaki- like	neurological	cardiac	other
Rosanova, et al (2021)	100%	36%	56%	48%	64%	36%	32%	**	**	**	Myalgias (12%), odynophagia (16%), pneumonia (20%)
Munaico et al., (2021)	100%	73%	**	60%	47%	27%	63%	**	53%	**	Hemodynamic instability (73%), Edema (60%)
Verdugo et al. (2021)	100%	84%	84%	84%	**	**	100%	59%		Leak pericardial or (40%) , Insult myocardial(66%), Myocarditis (53%)	
Yagnam et al., (2021)	100%	70%	45%	60%	60%	fifty%	90%		25%	Disturbancecoronary (11%), Ventricular dysfunction (30%)	
Prata et al., (2020).	80%	**	40%	60%	**	**	10%	60%	60%	Dysfunctionventricularacute (twenty%)	Tachypnea (60%), Anorexia (50%), Dehydration (40%), Hypotension (20%), Cyanosis (10%) Macrophage activation syndrome (10%)
DeColl et al., (2020).	87.5%	**	**	**	100%	100%	**	100%	**	**	Tachypnea (50%)
Luna et al. (2021).	100%	70%	50%	40%	50%	30%	**	**	**	**/	**
Fortitch et al. (2020).	100%	100%	100%	100%	79%	90%	**	**	**	Dysfunctionventricular(36.3%) Myocarditis (9.1%)	Acute renal failure (9.1%)
Cieza et al. (2021)	100%	89%	39%	67%	fifty%	61%	78%			Tachycardiato (78%) Leak pericardial or (17%)	Tachypnea (94%), Pleural effusion (22%)
Lona, et al., (2021)	92%	38.5%	**	41%	51.3%	35.9%	25%	**	**	**	Chills (30.8%), Sore throat (38.5%)
Fontes et al. (2021)	**	61.9%	37.5%	45.2%	40.5%	42.9%	**	**	**	Tachycardiato (50%)	Headache (28.6%)
Domínguez et al., (2021)	90.3%	25.8%	**	14.9%	**	**	29%	38.70%	6.5%	**	Respiratory (32.3%)
chest, etal ., (2021)	100%	**	**	**	**	**	42%	50.0%		Myocarditis s (7.7%), Spill pericardial (27%)	

Kawasaki-like PIMS: Refers to a clinical syndrome similar to Kawasaki disease, manifested by fever, nonoozing injection of both conjunctivae, nonvesicular, generalized, fine, confluent rash, desquamation of palms and soles, oropharyngeal erythema, cervical adenopathies, glossitis and manifestations of cardiovascular damage. This

presentation is described in ten consulted investigations [4, 8, 10-13, 15,16, 18].

In the investigation by [4], it is described that the debut of the patients was with a Kawasaki-like disease, which, with the passing of the days, behaved similarly to a toxic shock, accompanied by a deterioration in the function of several organs and systems. In most cases, these researchers describe the need to use vasoactive drugs due to the refractoriness of the clinical and hemodynamic manifestations.

Fever was reported with a prevalence of 80% to 100% of the cases. Abdominal pain (36-100%), diarrhea (39-100%), vomiting (40-100%), rash (47-100%), conjunctival injection (27-100%), shock (10%-100%), Kawasaki-like disease (59%-100%), neurological manifestations (25%-60%), cardiovascular: pericardial effusion (17%-40%), and ventricular dysfunction (30%-50%). See Table 3.

Analytical manifestations

Laboratory results were not described in three of the selected investigations [8, 15, 18].

On the other hand, in the rest of the consulted works, an analytical pattern is described that indicates severe acute inflammation, which is accompanied in a characteristic way by leukocytosis, lymphopenia, thrombocytopenia, and increased tests for acute phase reactants (procalcitonin, C-reactive protein, and serum ferritin) [6, 12].

Laboratory abnormalities indicating a predisposition to hypercoagulable states are also described, with increased values of D-dimer and fibrinogen [4, 7, 9, 13]. The consulted authors also reported increased liver enzymes [6, 7, 9, 13].

Regarding the diagnosis of COVID-19, it has been reported that PCr-TR is hostile in some cases and is identified only by history, epidemiological suspicion, or an increase in immunoglobulins (IgM, IgG) [6].

One point to highlight is that in all the works consulted, mention is made that, apart from the characteristic inflammatory state, various laboratory findings may occur during PIMS in correspondence with the symptoms or complications presented by the patient. Thus, it can be accompanied by an increase in lactic acid, creatinine, and enzymes that translate heart and muscle involvement (CK, CK-MB), an increase in renal function parameters (creatinine, urea), and alterations in the acid-base and hydroelectrolytic balance, depending on the clinical profile of the patient [13].

Table 4 summarizes the main laboratory findings described in the consulted literature.

Table 4. They summarize the main laboratory findings described in the consulted literature.

Author/s	demonstrations Laboratory
Rosanova et al., (2021)	lymphopenia Thrombocytopenia liver enzymesPCR positive (60%) IgG (96%) IgM (28%)
Munaico et al., (2021).	Elevated lactate Elevated D-dimer Elevated serum ferritin Elevated C-Reactive Protein Hypoalbuminemia Thrombocytopenia
Verdugo et al., (2021)	Thrombocytopenia Elevated C-reactive protein Neutropenia
Yagnam et al., (2021)	Leukocytosis Neutrophilia Lymphopenia Elevated C-reactive protein Elevated Procalcitonin Elevated Interleukin 6 (IL-6) Elevated D-dimer Elevated Fibrinogen creatine kinase (CK) elevated ProNB Elevation of liver function enzymes
Prata et al., (2020)	Leukocytosis Thrombocytopenia Lymphopenia Elevated C-reactive protein Elevated D-dimer Elevated IL-6 Elevated LDH elevated procalcitonin Elevated liver enzymes
De Coll et al., (2020).	Anemia Leukocytosis Neutrophilia Lymphopenia Thrombocytopenia Elevated CRP Elevated serum ferritin Elevated D-dimer Elevated fibrinogen Elevated liver enzymes
Luna et al., (2021).	Leukocytosis Lymphopenia Thrombocytopenia Elevated D-dimer elevated fibrinogen
Fortich et al., (2020).	Elevated C-reactive protein Elevated serum ferritin Elevated D-dimer
Cieza et al., (2021).	Leukocytosis Lymphopenia Thrombocytopenia Elevated fibrinogen Elevated D-dimer Elevated C-reactive protein
Lona et al., (2021).	Lymphopenia Thrombocytopenia Hypoproteinemia Elevated D-dimer

Nonpharmacological treatment

According to a consensus document of Argentine specialists, the initial management of PIMS includes the appropriate diagnosis, differentiating if it is only a PIMS or if it is associated with Kawasaki disease, with patient hospitalization and referral to specialized centers. The

first therapeutic objective is the treatment of shock, stabilizing the hemodynamic parameters. The PIMS approach, as in any severe condition, includes the ABC algorithm [16]; [17]. Table 5 summarizes the general measures to consider when caring for patients with PIMS.

Table 5. General treatment in the first hour.

Measures general in the first hour
1. Oxygenation: according to the needs of the patient, with mask, ventilation mechanics invasive either Noinvasive.
2. Obtain access vascular (intravenous either intraosseous) and obtain sample for exams of laboratory: ▪ Generals: crops, biometrics, gasometry, lactate be rich, protein C. reactive,coagulogram . ▪ Yeah there is availability: ferritin, LDH, CPK, troponin, NT- ProBNP , Dimer d,Fibrinogen, Procalcitonin. ▪ Others: test of Covid-19, bone scan of chest, electrocardiogram, echocardiogram, according to criterion doctor.
3. Assess he use of empiric antibiotics, by administration intravenous.
4. Administration of volume, according to state hemodynamic: ▪ In case of hypoperfusion, with either without hypotension: Bowling: From 10-20 ml/kg until 40 ml/kg,in the PICU ▪ In case of hypoperfusion without hypotension: crystalloids of maintenance. ▪ In case of hypoperfusion with hypotension, without evidence of volume overload: Boluses:From 10-20 ml/kg to 40 ml/kg. ▪ Surveillance constant of the overload of volume
5. Interconsultation with medicine intensive, infectology, and cardiology, according to the patient's needs.
6. Appreciate the need for treatment with inotropes and monitoring cardiovascular constant: ▪ If there is failed cardiac: epinephrine, dopamine, levosimendan. ▪ Without cardiac failure, norepinephrine is the first option.
7. Control of symptoms associated: fever, pain, vomiting

Source: (Rawson, et al., 2020).

Pharmacotherapy

The treatment of PIMS is organized in three phases, as described in the investigation of [13], who reported that in all cases, phase I treatment was used (100%), and mechanical ventilation was necessary in 75% of the cases. Forty percent were considered refractory to phase I treatment and proceeded to phase II. The treatment phases described are described in Table 6.

Table 6. Phases of treatment of PIMS.

Phase I: - Immunoglobulin (IV) (2 g/kg) at 12 noon - Methylprednisolone (2 mg/kg/day x 3 days) - ceftriaxone 100 mg/kg/day + Clindamycin 40 mg/kg/day - enoxaparin (1 mg/kg/day) (SC) - ASA (50 mg/kg/day) if presents Kawasaki disease
Phase II: - Immunoglobulin (IV) (2 g/kg) in 12 h + Methylprednisolone (10 mg/kg/day) IV for72 hours
Phase III: - Kawasaki like : infliximab - Cytokine storm: tocilizumab
Source:Yangman et al, (2021).

Among the pharmacological measures, the consulted authors describe immunomodulators (intravenous gamma globulin, corticosteroids); the use of ASA (at anti-inflammatory and antiplatelet doses, depending on risk) is also recommended [16, 17].

The use of intravenous immunoglobulins and corticosteroids was reported in 11 studies consulted [4, 5, 7, 8, 10-12, 15-17, 19]. Empirical use of broad-spectrum antibiotics was reported in seven articles [4, 7-9, 11, 16, 17].

Weight heparins were also described in 8 reviewed articles [4, 7, 8, 10-12, 16, 17]. Two investigations reported the use of hydroxychloroquine [4, 8]. Ivermectin was also used in two articles [8, 11]. Biological therapies, which correspond to the third phase of treatment, are described in three articles [15-17].

Table 7 summarizes the treatment reports in the research consulted.

Table 7. Treatment pharmacological of PIMS, according to authors consulted

Author/s	Treatment Pharmacological

Munaico et al. (2021).	Vasoactive antibiotics Diuretics Aspirin Immunoglobulin Corticosteroids Hydroxychloroquine+Azitomycin+Ivermectin
Verdugo et al. (2021)	Immunoglobulin intravenous (75%), Acid Acetylsalicylic acid (72%), Corticosteroids (65.6%) Enoxyparin (75%) included the worth of D-dimer of 2,445 ng/ml, on average, with the rank of 980-5,000 compared to the value average < of 250 ng/ml.
Prata et al. (2020)	Antibiotics (80%), Oseltamivir (20%), Corticosteroids (20%), Antifungals (10%).
De Coll et al. (2020)	Aspirine (100%), Immunoglobulin IV. 2 gr/kg/dose (100%), Corticosteroids 2 mg/kg/day by 5 days (100%), Antibiotics (100%), Enoxyparin (75%).
Eisink et al. (2021) Rawson et al. (2020)	immunoglobulin (IV): 2 g/kg. Second dose in case of refractoriness (> 36 hours with symptoms). Premedication with corticosteroids or antihistamines to avoid events adverse to the GICorticosteroids (IV): Methylprednisolone (IV): In cases mild: 1-2 mg/kg/day for 3-5 days. In severe cases: 30 mg/kg/day for 1-3 days (Maximum dose: 1 g).Aspirin (oral): 80-100 mg/kg/day (dose anti-inflammatory). 3-5 mg/kg/day (antiplatelet dose)Biological drugs (not first line): Tocilizumab: 12 mg/kg/dose >30 kg. 8 mg/kg/dose (<30 kg). Infliximab: 5-6 mg/kg/dose
Luna et al (2021)	Immunoglobulin (IV) (100%). Corticosteroids (70%). Antibiotics (90%). Aspirine (70%). heparin (1%). Inotropes (40%), Ivermectin (10%).
Fortich et al. (2020)	Corticosteroids (100%), Aspirine(100%), Immunoglobulin IV. (81.8%), Antibiotics (45.5%), Heparin (9.1%).
Cieza et al. (2021)	Corticosteroids (89%), Immunoglobulins (89%), Catecholamines (72%), Ventilation mechanical (72%).
Domínguez et al. (2021)	Antibiotics (87.1%), Aspirin (45.2%), Immunoglobulin (45.2%), Corticosteroids (32.3%), Vasopressors (25.8%), Ivermectin (9.7%), Anticoagulants (9.7%), Oxygen therapy (6.5%), Hydroxychloroquine (3.2%).
Munaico et al. (2021).	Immunoglobulin IV. (69%), Corticosteroids (58%), plasma convalescent (3.8%), Tocilizumab (7.6%)

Discussion

To identify the clinical manifestations and therapeutic management of patients with pediatric multisystem inflammatory syndrome associated with SARS-CoV-2 disease in Latin American countries, this research was carried out based on literature published in Spanish and Portuguese from countries in Latin America.

Regarding the clinical manifestations, the literature consulted indicates that it is a potentially severe condition that appears up to two weeks after developing COVID-19; therefore, in many cases, the PCR-Rt test is negative for COVID-19. -19. Additionally, it is a syndrome with a predominance of inflammatory manifestations, with a symptomatic procession that includes digestive, skin, cardiovascular, neurological, and hematological symptoms and, to a lesser extent, respiratory manifestations caused by tachypnea.

In this sense, it should be noted that the initial descriptions of PIMS exposed significant clinical heterogeneity, partially overlapping with the characteristics of Kawasaki disease (KD) or toxic shock syndrome (TSS) but distinct from these known inflammatory conditions. Unlike (acute) respiratory disease from COVID-19, it is currently known that data such as the age of presentation (3 years in KD, 8-12 years in PIMS), etiologic agent obtained by culture (S. epidermidis, S. aureus, Spyogenes, and S. pneumoniae in TSS) and specific clinical features help to distinguish the diagnosis between these three central diseases [19].

This review determined that in most patients, the presence of fever, abdominal pain, vomiting, and diarrhea is the primary clinical manifestation in case series from Latin America. These results coincide with reports in the literature in Belgium, in which [22] explained that digestive symptoms are the ones that lead to cases of PIMS in the pediatric population.

According to the cited authors, fever was documented for at least five days in almost all cases. In addition, most presented gastrointestinal symptoms, mainly abdominal pain, vomiting, and diarrhea. Cardiovascular manifestations, tachycardia, hemodynamic shock or hypotension, myocarditis, and decreased left ventricular ejection fraction (LVEF) were frequently observed as cardiovascular abnormalities. Other findings that coincide with what was obtained in this investigation are pericardial effusion, myocarditis, pneumonia, and respiratory distress [22].

Similarly, an inflammatory syndrome, characterized by a spectrum of symptoms ranging from fever to cardiogenic shock, has been reported in patients from Canada, with complications that involve at least four

organ systems: cardiovascular, renal, hematological, and neurological. The most frequent symptoms include abdominal pain, cardiomyopathies, shock, skin rash, and high fever. These symptoms are consistent with those collected in the Latin American literature. However, the mortality recorded in Latin America is between 1-7% compared to the Canadian report of 17%.

In this sense, according to the Ontario clinical guidelines, the most frequent signs and symptoms in patients with PIMS were abdominal pain, vomiting, rash, conjunctivitis, diarrhea, changes in the oral cavity (dry and cracked lips, canker sores, tongue strawberry) and lower limb edema. Less common symptoms included shortness of breath, cough, headache, lymphadenopathy, myalgia, and odynophagia, which also coincides with the results of this research [20].
Additionally, the findings of this research can also be supported by the reports by Soma et al. (2021) [21] in the New York population, in which they describe a clinical presentation characterized by the presence of fever, digestive manifestations (abdominal pain, vomiting, diarrhea), cardiovascular dysfunction, shock, and hypotension. Additionally, this paper describes the cases that develop Kawasaki-like disease, characterized by skin rash, conjunctival infusion, and systemic vasculitis of considerable severity, which also coincides with the results of this investigation.

Regarding the analytical manifestations, the evidence indicates that an acute inflammatory profile predominates, with elevation of acute phase reactants, such as ferritin, C-reactive protein, and procalcitonin. In addition, from the point of view of blood count, most of the consulted authors describe lymphopenia, leukocytosis, and thrombocytopenia.

PIMS is also accompanied by alterations in D-dimer and fibrinogen in favor of hypercoagulability and is part of the criteria for indicating low molecular weight heparin as part of the treatment of these patients. Additionally, the consulted authors describe the possibility of an increase in lactic acid values in severe cases, with refractory shock, metabolic acidosis, hypoalbuminemia, increased liver enzymes, and nitrogen dioxide, depending on the organ system affected in the PIMS course (De Coll-Vela et al., 2020) [7]; (Prata-Barbosa et al., 2020) [9]; (Rosanova et al., 2021) [6]; (Executioner, et al., 2021) [12]; (Yagnam et al., 2021) [13].

These results coincide with those of Yasuhara et al. (2021) [23] in a systematic review in which they describe within the analytical manifestations of PIMS a significant elevation of inflammatory biomarkers, such as C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation rate, interleukin-6 (IL-6) and fibrinogen. Furthermore, according to these investigators, cardiac markers showed marked elevations, especially B-type natriuretic peptide, N-terminal proB-type natriuretic peptide, and troponin. Most patients had elevated D-dimer levels, neutrophils, low lymphocytes, and hypoalbuminemia.

At this point, it should be noted that only one of the consulted studies described elevated B-type natriuretic peptide values, the N-terminal proB-type natriuretic peptide [24], probably due to its cost and because it is not accessible in all health institutions.

Regarding management, there is a consensus that it implies a nonpharmacological approach (general measures) aimed at resuscitation with fluids, oxygenation, symptomatic relief, and sampling for laboratory tests. Within the specific pharmacological treatment, the scientific literature is clear that it is organized into three phases, starting with intravenous immunoglobulins and corticosteroids; empirical antibiotic therapy, acetylsalicylic acid at anti-inflammatory or antiplatelet doses, and low molecular weight heparins [4, 5, 7-12, 15-17].

This research also coincides with a multicenter report in hospitals in Latin America, which described a prevalence of PIMS of 23.2%, with a mean age of 3 years (lower than that obtained in this review). With treatment, the authors above describe using immunoglobulins and intravenous corticosteroids. Additionally, these authors less frequently describe the use of inotropes, tocilizumab, and hydroxychloroquine, which also coincides with the findings of this investigation [7].

Despite having clear recommendations based on evidence [25- 27], the treatment of PIMS must be individualized according to the requirements of the patients and according to the reality of the health institution in which it is located. Thus, the early detection of renal, cardiovascular, and hematological failure, among others, becomes very important to establish timely treatment actions. Beyond the recommendations for administering immunoglobulins, corticosteroids,

antibiotics, and anticoagulants, cases should be treated individually, depending on the affected organs.

In this context, the treatment recommendations in the Spanish and Portuguese literature do not differ significantly from those in the Anglo-Saxon literature; however, as it is a scientific trial, quantitative synthesis of the evidence (meta-analysis) could not be performed, which constitutes one of the main limitations of this research. In addition, another limitation is that evidence was found only from some countries in the region, so it was impossible to obtain representative information on the reality in the Spanish and Lusophone-speaking countries of the area.

Conclusions

In the Spanish-speaking and Lusophone countries of Latin America, the clinical presentation, laboratory analysis, and management of pediatric patients presenting with inflammatory syndrome multisystemic associated with COVID-19; No differences in the descriptions in Literature anglo saxon knowledge of the items clinical and analytical that characterize the PIMS are of great importance to establish the diagnosis, since it was a syndrome novel, that No counted with enough support theoretical in the beginnings of the pandemic. The average age of presentation recorded in the studies was 8-12 years; the male sex was predominant, and half of the patients presented some basic comorbidity, including respiratory, cardiac, obesity, malnutrition, and hemato-oncological illness. This scientific essay, composed of 6 cohort studies, five descriptive, two prospective types, and two advice document types, contributes to and represents the reality of Latin America; however, it is still necessary to gather more information to obtain a panoramic view of the entire continent. Therefore, we depend on published literature from other continents to update the knowledge that HE has of this pathology.

Abbreviations

PIMS: Pediatric Inflammatory Multisystem Syndrome.

Supplementary information

No supplementary materials are declared.

Thanks

Not declared.

Author contributions

Priscila Michelle Cárdenas Cárdenas: Conceptualization, data curation, formal analysis, fundraising, research, writing - original draft.
Alexis Rivas Toledo: Methodology, project administration, resources, software, supervision, validation, visualization, writing - revision and edition.
All the authors have read and approved the final version of the manuscript.

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The authors declare they have no conflicts of interest.

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