Clinical Characteristics and Factors Associated with Unfavorable Outcomes of Pediatric Inflammatory Multisystem Syndrome Related to COVID-19 in Lima-Peru

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Research Article

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Abstract

Objective: Describe the clinical-epidemiological profile and determine the factors associated with unfavorable outcomes of pediatrics multisystemic inflammatory syndrome (SIM-P) related to COVID-19 at Edgardo Rebagliati Martins National Hospital (HNERM), Lima-Perú, from April to September 2020.

Materials and methods: Retrospective cohort in children under 14 years of age. The current criteria were used for the diagnosis of SIM-P. The effect size was estimated with relative risk (RR) and 95% confidence intervals, using a generalized linear Poisson family model with robust variance.

Results: 43 patients were included, 22 (51.2%) Kawasaki Disease (EK), 10 (23.3%) shock, and 11(25.6%) fever with inflammatory markers. The median age was 8 years, most men, without comorbidity, with negative molecular test and positive IgG. Gastrointestinal and mucocutaneous manifestations predominated, with altered inflammatory markers and myocardial injury. Most required intravenous immunoglobulin (IVIG), aspirin (AAS), corticosteroids and antibiotics. More than a third required VMI, ICU and developed organic dysfunction, with a lethality of 4.6% (2/43). Increasing lethality to 20% (2/10) in the shock subgroup. Five were found (14.7%) coronary aneurysm. Having some comorbidity (RR 1.79; IC95%1.02-3.14), C-reactive protein ≥ 10 mg/dL (RR 2.09; IC95%1.15-3.79), and SatO2 ≤92 in emergency (RR 2.84; IC95%1.47-5.50) was morelikely to betransferred to ICU. In addition, those with some comorability (RR 2.23; IC95%1.04-4.79), with lymphopenia <500cel/mL (RR 2.8; IC95%1.24-6.30), and with d≥ 3 mg/L (RR 3.57; IC95%1.23-10.38) were more likely to require VMI.

Conclusion: Active monitoringis an eye to make early diagnosis and management in order to improve the prognosis.

Introduction

The clinical spectrum of SARS-CoV-2 infection in pediatrics is broad and with characteristics that differ in adults. Most develop asymptomatic infection or mild-moderate symptoms, a lower percentage develop severe involvement (5%) critical (< 1%) [(1)]. Commitment can be acute, with predominant respiratory commitment. Lower frequency describes pediatric multisistmic inflammatory syndrome(SIM-P) related to COVID-19. For diagnosis it is necessary to have fever, altered inflammatory markers, organic dysfunction and exclude other causes. All this according to the criteria of the World Health Organization, "Royal College of Pediatrics and Child Health" of the United Kingdom, and/or "Centers for Disease Control and Prevention" of the United States[(2)]. However, there are phenotypes and severity grades in the SIM-P. The best known is the one that causes shock and multiorgan commitment. We also haveone that meets criteria for complete or incomplete Kawasaki disease (EK). In addition, fever is described with very altered inflammatory markers, but without shock, and without criteria for EK. Probably regardless of type, SIM-Pcan cause multiorgan failure and death [(1.2)].

The physiopathology of SIM-P is not yet clear. It is probably secondary to a post-viral immune reaction not mediated by direct viral invasion but with development of immune responses acquired to SARS-CoV-2, with increased cases at 4 to 6 weeks after peak sarS-CoV-2. It was initially reported in England and the United States, then in other European countries. Requiring management in an intensive care unit (ICU) and use of invasive mechanical ventilation (VMI), with a variable letality [(2)]. In Latin America there are few reports [(3.4)]. In our country there are several centers that serve SIM-P, but so far an eight-case report has been published with SIM-P[(5),] and the preliminary report of the first 37 casos at Edgardo Rebagliati Martins National Hospital (HNERM) [(6)].

Therefore, in order to describe the clinical-epidemiological profile, and to determine the factors associated with unfavorable outcomes of SIM-P, we report the results of 43 cases ofSIM-P in HNERM, Lima-Peru, from April to September 2020.

Materials And Methods

Design and population

A retrospective cohort study was conducted of patients diagnosed with SIM-P under the age of 14 from April toSeptember 2020 hospitalized at HNERM located in Lima-Peru.

For the diagnosis of SIM-P, the criteria of the World Health Organization, "Royal College of Paediatrics and Child Health" of the United Kingdom, and/or "Centers for Disease Control and Prevention" of the United States [(2)] were used. Those with SARS-CoV-2 infection and criteria for EK were excluded but did not meet CRITERIA for SIM-P.

The data were collected from the medical history (physical and electronic) of the enlisted pacientes, who were followed from entry to discharge or death.

Study variables

Patients with SIM-P were categorized into three groups. With EK criteria (complete or incomplete) according to the "American Heart Association", with shock (need for support with inotropic/vasopressor or fluid resuscitation >20 ml/kg, excluding patientswith EK and shock), and with fever and alteredinflammatory markers (and that does not meet shock or EK criteria).

It included epidemiological characteristics, clinical manifestations, laboratory test findings, and therapeuticcharacteristics. RT-PCR and rapid serological test results (IgM, IgG or both) were recorded. Comorbidity includes primary immunodeficiency, end-stage kidney disease, acute leukemia, obesity, uncontrolled asthma, moderate prematurity, corticorresistent nephrotic syndrome, and chronic liver disease.

Unfavorable outcomes were recorded in the follow-up: SatO2 ≤92 in emergency, emergency intubation, ICU management, ventilatory support, macrophage activation syndrome (SAM), shock, organic dysfunction, and the onset of coronary aneurysms.

Ethical aspects

The project was approved by the Social Health Security Research Ethics Committee for COVID-19. No informed consent was requested because the information was collected directly from the medical records and the confidentiality of the data was respected using a numerical code.

Statistical analysis

The data obtained entered an Excel Microsoft 2016 program database, and then exported it to the STATA version 16 program. The data were reviewed, the possible errors were corrected after a new review of the medical history. Frequencies and percentages were used to summarize categorical variables, while mean with standard or median deviation with their intercutartyl ranges was used for quantitative variables.

To evaluate association between adverse outcomes and clinical characteristics hypothesis tests were performed according to the nature of the independent variables; for categorical variables chi squared or exact Fisher test was used, while for quantitative variables Mann-Whitney Student or U was used. The effect size was estimated with relative risk (RR) and confidence intervals at 95% using a generalized linear Poisson family model withrobust zavarian, adjusted by all variables that obtained a p-value less than 0.05 in crude analysis. A statistical significance level of 0.05 was used for all statistical tests.

Results

Epidemiological characteristics and clinical manifestations

A total of 43 patients diagnosed with SIM-P were hospitalized during the study period, 22 (51.2%) EK criteria, 10 (23.3%) shock, and 11(25.6%) fever with altered inflammatory markers but no shock or EK. Median age was 8 years and 30 (69.8%) they were male; 10 (23,3%) had comorability reaching 70% in the shock subgroup. Nearly half of the cases had intradomiciliary contact. Most had negative molecular and positive IgG testing, and belonged to the O-positive blood group. Gastrointestinal symptoms (vomiting, nausea, diarrhea, abdominal pain) and mucocutaneous involvement predominated in all subgroups. Two (1.7%) patients were diagnosed as acute abdomen requiring surgical management. Four (18.4%) patients had shortness of breath in the shock subgroup. The median disease time was 4 days, and 3 days for the duration of the fever, similar in subgroups (Table 1).

Lab test findings

Mild anemia is evident in subgroups. In addition, moderate lymphopenia is evident in the shock subgroup, with increased C-reactive protein (29.6 mg/dL), ferritina(831ng/Ml), D-dimer (7.14 mg/L), and increased hypoalbuminemia (2.9 g/dL) in this group. Also, increased commitment of myocardial injury markers (Troponin C, CPK-MB, NT-proBNP) in the shock subgroup (Table 2).

Therapeutic characteristics

Total ,42 (97.7%) required intravenous immunoglobulin (IVIG) at 2g/kg, and 12 (27.9%) a second dose. In the subgroup with EK a higher percentage (36.4%) required a second dose of IVIG. Of the total, most received aspirin (ASA) (37; 86.1%), and antibiotics (33; 76.7%) initially. The most commonly used combination was ceftriaxone or vancomycin/meropenem in all groups. 27(62.8%) received corticosteroids (methylprednisolone at 2mg/kg/day in most). Enoxaparin, ivermectin and hydroxychloroquine were administered in a smaller percentage, the latter two at the beginning of the pandemic (Table 3).

Unfavorable outcomes

A quarter of patients had SatO2 ≤92 in emergency (increasing to 50% in the shock subgroup), requiring 6 (13.9%) emergency intubation patients. 17 (39,5%) required ICU with a median of 5 days stay, and 14 (32.7%) VMI with a median of 4.5 days until extubation. A lower percentage initially used high flow cannula (CAF) and developed SAM. Organic dysfunction developed at 21 (48.8%) predominantly cardiovascular and respiratory failure; most with commitment of 2 and 3 organs/target system. Organic dysfunction, admission to ICU and VMI was more common in the shock subgroup. Echocardiography was performed at 34 (79.1%) coronary aneurysm is evident in 5 (14.7%). Two patients died, the fatality was 4.6%. These patients were from the shock subgroup, increasing lethality to 20% in this subgroup (Table 4).

Factors associated with unfavorable outcomes.

In assessing the association using Poisson regression models, it was shown that patients with some comorability (RR 1.79; IC95%1.02-3.14), with C-reactive protein ≥ 10 mg/dL (RR 2.09; IC95%1.15-3.79), and SatO2 ≤92 in emergency (RR 2.84; IC95%1.47-5.50) were more likely to be transferred to ICU. In addition, those with some comorability (RR 2.23; IC95%1.04-4.79), with lymphopenia <500cel/mL (RR 2.8; IC95%1.24-6.30), and with d≥ 3 mg/L (RR 3.57; IC95%1.23-10.38) weremore likely to requerir VMI. No factors associated with a higher incidence of shock and organ dysfunction were found (Table 5).

Discussion

A temporality relationship between SIM-P and SARS-CoV-2 infection has been described with the advance of the pandemic. A full understanding of the pathological mechanisms that this virus uses to develop SIM-P is needed. The formation of autoantibodys by cell and humoral recognition of autoantigens, celland humoral recognition of viralantigens expressed in infected cells, formation of immune complexes that activate inflammation, and sequences of viral superantigens that activate immune cells [(2)] have been described. In addition, inhibition of interferon typel and type III responses hasbeen reported, causing longer and more severe disease. There are also the presence of autoantiantibodys involved in the activation of lymphocytes, and in intracellular signaling pathways. Finally, increased IL-18 and IL-6 con increased chemotaxis and lymphocytic/myeloid activation, and immunological deregulation of mucous

membranes have been reported. Thus, hyperinflation differs from acute COVID-19 and EK, and the cytokine storm in SIM-P is different from that observed in adults with COVID-19 [7].

All systematic reviews [8, 9, 10, 11] found and most large sample case series ([12, 13, 14, 15, 16, 17] were conducted in Europe, the United States, and some Asian countries. There are few reports from Latin America [4, 18, 19, 20, 21]. Most systematic reviews describe predominance in school and men's age (above 50%), most ofthem sanos, of Hispanic and black origin. Fever, gastrointestinal and cardiovascular symptoms are the most frequently reported. With noticeably altered inflammatory, coagulation and cardiac markers [8, 9, 10, 11]. In Latin America,he has published a multinational study reporting 95 cases, with similar characteristics (most schoolchildren, men, healthy, predominating gastrointestinal symptoms). In addition, it preliminaryly determined that the diagnosis of SIM-P was associated with older tener, gastrointestinal symptoms, low socioeconomic status, and with increased use of inotropics, IVIG and corticosteroids [4]. Similar characteristics are described in Chile [18] and Brazil [19, 20, 21], similar characteristics are described at the Latin American and global levels. A caringbra study [19] suggests that the onset of SIM-P could be associated with gastrointestinal manifestations and hypoxemia. In this study the most common filing age was in schoolchildren, with men predominating in all three phenotypes, most of them exceptin the shocksubgroup. Most had proof negative molecular and positive lgG, only 6.9% (3/43) presented positive molecular test but 30% (3/10) were positive in the shock subgroup. Other studies have reported positivemolecular prueb in one third of cases [2]. In addition, the positive O group, intradomyciliary contact (up to half of cases in the shock subgroup), gastrointestinal and mucocutaneus manifestations, has predominated. The median time ofillness and days with fever was four and three days, respectively. There was also a greater increase in inflammatory markers (lymphopenia, C-reactive protein, ferritin, D-dimer, hypoalbuminemia), and increased commitment of markers of myocardial injury (Troponin C, CPK-MB, NT-proBNP) in subgroup shock.

Therapeutic recommendations are aimed at intervening early, providing respiratory, hemodynamic support, and treatment of the underlying inflammatory process [22.23]. In ourstudy, IVIG (97.7%), AAS (86.1%) corticosteroids (62.8%) in most patients. More than a quarter required a second dose of IVIG, and more than three-quarters in the subgroup with EK. No second-line immunomodulators were used. More thanthree-quarters received antibiotic coverage at first for possibility of bacterial infection explaining the clinical picture or overinfection. A lower percentage received anticoagulation. Other studies also used IVIG, corticosteroids, AAS,antibiotics, anticoagulation and second-line immunomodulators; with a variable frequency of use [8, 9, 10, 11]. A systematic review describes that 76.4% used IVIG, 52.3% corticosteroids, and 16.8% AAS, requiring second-line immunomodulators such as anakinra and infliximab in a lower percentage, 8.5% and 6%, respectively. In addition, antibiotics were administered less frequently than this study (16.3%) [8]. Other studies report 6.2% of patients who required second doses of IGIV [10]. Other systematic reviewsreport IVIG use of 63–78.1%, corticosteroids from 44–57.6%, and AAS use by 46.2% [9.11]. With use of infliximab (6%), anakinra (12%), and tocilizumab (6.3%) [11]. A Latin American multicenter study reporteduse of IVI G by40%, corticosteroids by 28.4%, and tocilizumab by 2.1% ([4]. In Brazil, the use of IVIG was reported at 89%, and corticosteroids, antibiotics and enoxaparin by about 50%. In addition, AAS by 45% [20]. In Chile, 89% used antibiotics, 63% AAS, orn 70% IGIV, and 63% corticosteroids [18]. In Lima, out of a series of eight cases, it was reported that they all received IGIV, corticosteroids and ASS, and two patients required a second dose of IGIV. This is because most (87.5%) belonged to the EK sub-group [5]. In this study 51.2% had criteria for EK, but it was mostly used IVIG, corticosteroids and AAS.

In relation to unfavorable outcomes, in this study 39.5% required ICU, and 32.7% VMI. Organic dysfunction developed by 48.8%. Another study in Peru reported SAM in 50% of cases, and only one patient had cardiomyocarditis, shockandrequisitioned admission to ICU [5]. In other studies, immediate unfavorable events were variable. Systematic reviews report ICU needs 68.2 to 70%, and VMI from 12.6 to 26.1% [8.10.11]. In Latin America, there is a lower income to ICU (12.5%-21%) [4.5] and a variable VMI requirement (11–44.4%) [18.20],probably due to the reduced availability of ICU beds and specialized medical personnel. On the other hand, in this study the majority (51.2%) they had criteria for EK, 23.3% shock, and 25.6% fever with altered inflammatory markers (but no shock or EK). SatO2 ≤ 92 in emergency, organ dysfunction, ICU and VMI admission were more common in the shock subgroup. However, the other subgroups alsorequisitioned VMI and had white organ damage but in less proportion, with a stay in ICU and similar VMI time in all subgroups. In a systematic review, 28% (186/655) had hypotension, 36%(235/655) classic or atypical EK, and the rest (36%, 234/655) belonged to the subgroup with fever and inflammatory markers [10]. Unfortunately, it does not describe clinical characteristics or unfavorable outcomes by subgroups. It is necessary to be vigilant in all clinical forms of SIM-P, the shock subgroup is the one with thegreatest short-term involvement, but also the other subgroups required ICU with the use of VMI and vasoactive drugs. On the other hand, there is no medium- and long-term evidence of SIM-P complications. In this way, the pediatrician plays a transcendental role for an accurate diagnosis of the entire SIM-P spectrum.

Also worrying is the lethality found (4.6%), increased to 20% in the shock subgroup. Systematic reviews and larger sample series describe a lethality of 1.4 to 2.1% [8.9,10,11,12,13], describing in some cases comorbidity, malnutrition, shock, and shorter time between exposure to the virus and clinical manifestations [21]. On the other hand, coronary aneurysm was evident in 5 patients (14.7%). A systematic review describes abnormalities in echocardiography by up to 54% [8], including in a 11.5–61% in Latin America [4.20]. Coronary aneurysm is also described at 5.4-8% in anumber of systematic reviews [8.11]. In addition, they describe other alterations such as decreased left ventricle ejection fraction, myocarditis, pericardial effusion, mainly ([8, 10, 11, 13, 18]. In Peru, none of the eight reported casesdeveloped coronary aneurysm. Only one had myocarditis, and shock [5]. SIM-P also has a negative impact on health, it is necessary to report that SARS-CoV-2 infection in the paediatric population canalso have a sfavorable evolution and cause complications. There is a significant percentage of SIM-P with severe involvement, even causing death. On the other hand, when performing the multivariate analysis, it was shown that patients with some comobility, protein C reactive ≥ 10 mg/dL, and SatO2 ≤ 92 in emergency were more likely to be transferred to ICU. In addition, those with some comorbidity, with lymphopenia < 500cel/mL, and with D ≥ 3 mg/L were more likely to require VMI. We have not founde studios on factors associated with unfavorable outcomes in the SIM-P. Therefore, in the paediatric population it is also necessary to constantly monitor SatO2, inflammatory markers and recognition of comorities in order to improve their morbidity.

The strengths of the study are that the included cohort represents the largest number of patients with SIM-P reported in Peru so far. In addition, a thorough review of the data was carried out, using the electronicmedical history and corroborating with physics, being reviewed and corrected when finding inconsistent

values. Likewise, the selection of the cohort was based on international criteria [(2)] and a consensus among the authors of the study (pediatricians, pediatric infectologist and intensivist pediatricians). On the other hand, this study has limitations related to the origin of secondary source data (medical records) and collection retrospectively, with the possibility of greater selection bias, informationand confusion. Finally, a multivariate analysis was performed in order to adjust confusing ones, but because the SIM-P is a new and rare entity a small sample was obtained obtaining a low statistical power. Therefore, theconclusions are preliminary, especially those related to the study of factors associated with adverse outcomes. Multicenter studies are needed in order to increase the number of cases and have more accurate and straight conclusions.

In conclusion, in this study SIM-P predominated in male and healthy school children, presenting gastrointestinal and mucocutaneous symptoms. More than half presented criteria for EK, with negative molecular testing and positive IgG. With aumento of inflammatory markers and increased commitment of markers of myocardial injury, especially in the shock subgroup. More than a third required ICU, VMI and developed organic dysfunction, with a lethality of 4.6%. Likewise, the coronaries aneurysm was presented at 14.7%. In the shock subgroup, lethality increased to 20% and unfavorable outcomes dominated. Monitoring of SatO2, inflammatory markers and recognition of comobility is important. Therefore, active monitoringfor early diagnosis and management is necessary to improve the prognosis.

Thanks

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Declarations

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STATEMENT OF CONFLICTS OF INTEREST:

The authors declare that they have no conflicts of interest.

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Tables

Table 1. Epidemilogical characteristics and clinical manifestations of SIM-P. Edgardo Rebagliati Martins National Hospital. Lima-Peru, April-September 2020.

characteristics	No (%)*			
	SIM-P (n=43)	Fever and inflammation (No.11) *	With shock (No.10)†	Con EK (n=22) ‡
Age, median (IQR)	8(4-10)	8(3-10)	8,5(6-10)	7,5(4-11)
Sex				
Male	30(69,8)	6(54,6)	8(80,0)	16(72,7)
female	13(30,2)	5(45,4)	2(20,0)	6(27,3)
virology				
RT-PCR COVID-19	3(6,9)	0(0)	3(30,0)	0(0)
IgG COVID-19	31(72,1)	7(63,6)	9(90,0)	15(68,2)
IgM COVID-19	7(16,3)	2(18,2)	3(30,0)	2(9,1)
No RT-PCR was performed	5(11,6)	1(9,1)	0(0)	4(18,2)
Comobility ‖	10(23,3)	3(27,3)	7(70,0)	0(0)
Intradomyciliary contact	19(44,2)	4(36,4)	5(50,0)	10(45,5)
blood group	No.21	No.4	No.5	No.12
The positive	17(80,9)	2(50,0)	4(80,0)	11(91,7)
A positive	3(14,3)	2(50,0)	1(20,0)	0(0)
B positive	1(4,8)	0(0)	0(0)	1(8,3)
Sick time ·median (IQR)	4(3-6)	3(2-6)	3(2-3)	5(4-7)
Days with fever, median (IQR)	3(2-6)	3(2-8)	3(2-3)	4(3-5)
Manifestations clinics ††	No.115	No.31	No.22	No.62
Gastrointestinal	35(30,4)	10(32,3)	8(36,4)	17(27,4)
Mucocutáneo	31(26,9)	6(19,4)	3(13,6)	22(35,5)
conjunctivitis	16(13,9)	3(9,7)	2(9,1)	11(17,7)
High respiratory symptoms	9(7,8)	4(12,9)	1(4,5)	4(6,5)
difficulty Respiratory	8(7)	1(3,2)	4(18,3)	3(4,9)
Urinary discomfort	4(3,5)	2(6,5)	0(0)	2(3,2)
Pains osteoarticulars	3(2,6)	1(3,2)	0(0)	2(3,2)
Consciousness disorder	3(2,6)	1(3,2)	2(9,1)	0(0)
Myalgias	2(1,7)	1(3,2)	0(0)	1(1,6)
Surgical abdomen	2(1,7)	1 (3,2)	1(4,5)	0(0)
headache	1(0,9)	1(3,2)	0(0)	0(0)
Disgeusia	1(0,9)	0(0)	1(4,5)	0(0)

Abbreviations: SIM-P, pediatric multisistmic inflammatory chondrome associated with COVID-19; EK, Kawasaki Disease; IQR, interquartile range; RT-PCR, real-time polymerase chain reaction.

*Features are summarized in absolute frequenciess and percentages. Dividing SIM-Pin patients with fever and inflammation, shock and EK.

**Includes SIM-P that does not meet shock or EK criteria.

† Shock was defined as the need for support with inotropic/vasopressor or fluid resuscitation >20 ml/kg. Seven patients with EK and shock were excluded.

Includes complete and incomplete EK case according to the American Heart Association.

Years.

ll Includes: primary immunodeficiency, end-stage kidney disease, acute leukemia, obesity, uncontrolled asthma, moderate prematurity, corticorresistent nephrotic syndrome, chronic liver disease.

- Days.

†† It is included in the gastrointestinnal manifestations: vomiting, nausea, abdominal pain and/or diarrhea In mucocutaneous: exanthema, changes in lips, mucosa and oral cavity, erythema with or without oedema in palms and plants, and/or flaking of finger pulps.

Table 2. Findings ofSIM-P laboratory e- Edgardo Rebagliati Martins National Hospital. Lima-Peru, April-September 2020.

Finds	SIM-P (n=43)	Fever and inflammation (No.11)**	Con shock (n=10)†	Con EK (n=22) ‡
Leukocytes , x 103 /mm3 ǀ	12 (5,29-15,67)	12,3(7,04-12,85)	10,565(4,69-15,67)	12,615(6,82-16,08)
Neutrophils ,x 103 /mm3 ǀ	7,9(4,13-10,7)	7,375(3,18-10,83)	6,31(4,126-9,409)	8,195(4,45-11,5)
Lymphocytes ,x 103 /mm3 ǀ	1,3(0,79-2,1)	1,55(0,795-2,239)	0,87(0,611-1,2)	1,485(0,83-3,04)
Platelets ,x 103 /mm3	178(95-250)	226(187-351)	135,5(54-231)	163,5(95-247)
hemoglobin §, g/dL	10,8(9,5-11,7)	11,2(9,5-12,4)	9,7(8,4-11,7)	10,85(9,9-11,4)
VSG §, mm/h	22(20-36)	21(14,5-31)	26,5(23-30)	23(20-40)
Protein C reactive §, mg/dL	22,7(11-27,6)	23(12,2-27)	29,6(24,5-34)	26,15(7,4-25,5)
Ferritin §, ng/mL	434(286-1066)	434(261-1422)	831(555-1210,5)	344(286-575)
D-mero , mg/L	3,5(2,4-7,4)	2,71(2,29-4)	7,14(3,41-9,6)	3,54(2,1-8,09)
Albumin , g/dL	3(2,7-3,8)	3,5(2,6-4,1)	2,9(2,8-3,4)	2,9(2,7-3,8)
Sodium §, mmol/L	135(133-137)	135(133-137)	137,5(134-142)	134(132,5-136)
triglycerides §, mg/dL	162(101-271,5)	196(136-477)	93(88-161)	163(101,5-258,5)
LDH §, U/L	272(206,5-403)	292(211-403)	304(202-516)	256,5(207-382,5)
TP §, s	12,3(11,9-13)	11,2(11-12,49)	14,065(12,63-17,2)	12,32(12-12,98)
TTPA §, s	34,7(29,5-40,6)	32(29-40,6)	35,13(34,4-42,01)	34,93(28,6-39,06)
fibrinogen §, mg/dL	525,5(324,7-617,6)	542(445,75-617,57)	404,65(274-607)	532,47(324,7-631)
TGO §, U/L	42(26-80)	27(21-107)	45(37,5-74)	43(28-90)
TGP §, U/L	56(21-91)	43(14-88)	45,5(20,5-85,5)	58(29-96)
Troponin C §, ng/ml	0,018(0,005-0,035)	0,003(0,003-0,022)	0,035(0,014-0,29)	0,012(0,005-0,034)
CPK-MB §, U/L	1,9(0,8-29,9)	1,5(0,7-15)	9,8(2,5-32,5)	1,5(0,8-33)
NT-proBNP §, pg/mL	767(201,7-7258)	767(117-2350)	17 762(362,8-35 498)	1 596,3(158-7258)

Urea §, mg/dL	27,9(18,1-40,9)	25(21-34)	36,4(30-49,2)	24,3(17,1-40)
Creatinine §, mg/dL	0,47(0,37-0,67)	0,57(0,46-0,67)	0,405(0,36-0,74)	0,46(0,34-0,61)
Acidosis ǁ	12/19*(63,2)	2/2*(63,2)	7(70,0)	3/7*(42,9)

Leve ǁ, pH <7,3	2(16,7)	2(100)	4(57,1)	0(0)
Moderate ǁ, pH <7,2	4(33,3)	0(0)	1(14,3)	3(100)
Severa ǁ,pH <7,1	6(50,0)	0(0)	2(28,6)	0(0)
Co2 §	33(29-43,7)	31(30-32)	35,9(25-49)	33(29,5-43,7)
HCO3 §, mEq/L	18,4(14-20,7)	20,5(20-21)	18,2(14-20,9)	17,2(12,7-20,4)
Lactate , mmol/L	2(1,6-3,4)	1,5(1,2-2,6)	2,7(1,6-3,9)	2(1,7-3)

Abbreviations: SIM-P, pediatric multisistmic inflammatory chondrome associated with COVID-19; EK, Kawasaki Disease; VSG, globular sedimentation rate; LDH, lactate dehydrogenase; TP, prothrombin time; TTPA, time from partial thromboplastin to activate; TGO, oxalacetic glutamic transaminase; TGP; pyruvate glutamic transaminase; CPK-MB, myocardial creatine phosphokinase; NT-proBNP, cerebral natriuretic pro peptide; Co2, carbon dioxide; HC03, baking soda;

**Includes SIM-P that does not meet shock or EK criteria.

† With shock phenotype, it was defined as the need for support with inotropic/vasopressor or fluid resuscitation >20 ml/kg. Seven patients with EK and shock were excluded.

Includes complete and incomplete EK case according to the American Heart Association.

§Mediana (IQR).

ǁ absolute frequency (percentage).

Table 3. Characteristics of therapeutics in SIM-P. Edgardo Rebagliati Martins National Hospital. Lima-Peru, April-September 2020.

Characteristics	No (%)*			
	SIM-P (n=43)	Fever and inflammation (No.11) *	With shock (No.10)†	Con EK (n=22) ‡
IVIG	42(97,7)	11(100)	9(90,0)	22(100)
Second IVIG infusion	12(27,9)	1(9,1)	2(20,0)	8(36,4)
Corticoids	27(62,8)	5(45,5)	8(80,0)	14(63,6)
AAS	37(86,1)	10(90,9)	5(50,0)	22(100)
Antibiotics	33(76,7)	8(72,7)	10(100)	15(68,2)
Ceftriaxone	10(30,3)	3(37,5)	1(10,0)	6(40,0)
Meropenem+vancomicina	10(30,3)	2(25,0)	4(40,0)	4(26,67)
Ceftriaxone+metronidazole	5(15,2)	3(37,5)	1(10,0)	1(6,7)
Ceftriaxone+vancomycin	2(6,2)	0(0)	1(10,0)	1(6,7)
Cefepima	1(3,0)	0(0)	0(0)	1(6,7)
Cefepima+vancomycin	1(3,0)	0(0)	1(10,0)	0(0)
Ceftriaxone+metronidazole	1(3,0)	0(0)	1(10,0)	0(0)
Ceftriaxone+azithromycin	1(3,0)	0(0)	0(0)	1(6,7)
Meropenem+clindamicina	1(3,0)	0(0)	0(0)	1(6,7)
Ceftriaxone+vancomycin +azithromycin	1(3,0)	0(0)	1(10,0)	0(0)
Enoxaparina	5(11,6)	1(9,1)	1(10,0)	3(13,6)
prophylaxis	1(2,3)	0(0)	0(0)	1(4,5)
treatment	4(9,3)	1(9,1)	1(10,0)	2(9,1)
Ivermectin	7(16,3)	2(18,2)	4(40,0)	1(4,6)
Hidroxicloroquina	4(9,3)	1(9,1)	2(20,0)	1(4,6)

Abbreviations: SIM-P, pediatric multisistmic inflammatory chondrome associated with COVID-19; EK, Kawasaki Disease; IVIG, intravenous immunoglobulin; AAS, aspirin.

*Features are summarized in absolute frequencies and percentages. Dividing SIM-P in patients with fever and inflammation, shock and EK.

**Includes SIM-P that does not meet shock or EK criteria.

† With shock phenotype, it was defined as the need for support with inotropic/vasopressor or fluid resuscitation >20 ml/kg. Seven patients with EK and shock were excluded.

Includes complete and incomplete EK case according to the American Heart Association.

Table 4. Unfavorable outcomes on the SIM-P. Edgardo Rebagliati Martins National Hospital. Lima-Peru, April-September 2020.

characteristics	No (%)*			
	SIM-P (n=43)	Fever and inflammation (No.11)**	with shock (n=10)†	Con EK (n=22) ‡
SatO2 ≤92 in Emergency	11(25,6)	1(9,1)	5(50,0)	5(22,7)
SatO2 92-85	5(45,5)	1(100)	2(40,0)	2(40,0)
SatO2 84-80	5(45,5)	0(0)	2(40,0)	3(60,0)
Less than 80	1(9,0)	0(0)	1(20,0)	0(0)
Emergency intubation	6(13,9)	1(9.1)	2(20)	3(13,6)
Transferred to UCI	17(39,5)	2(18,2)	8(80,0)	7(31,8)
Days in ICU	5(4-8)	5(2-8)	6(5-8)	5(4-6)
VMI	14(32,7)	1(9,1)	8(80,0)	5(22,7)
Days in VMI	4,5(3-5)	3(3-3)	5(4-5)	4(3-5)
CAF	5(11,6)	0(0)	2(20,0)	3(13,6)
I	3(6,9)	1(9,1)	0(0)	2(9,1)
Shock II	17(39,5)	0(0)	10(100)	7(31,8)
Organic dysfunction	21(48,8)	4(36,4)	10(100)	7(31,8)
Type of organic dysfunction ··	No.55	No.6	No.31	No.18
Cardiovascular	18(32,7)	1(16,7)	10(32,3)	7(38,9)
Respiratory	13(23,6)	1(16,7)	8(25,8)	4(22,2)
Hematologic	10(18,2)	1(16,7)	4(12,9)	5(27,7)
Gastrointestinal	6(10,9)	2(33,2)	4(12,9)	0(0)
Muscular	3(5,4)	1(16,7)	1(3,1)	1(5,6)
Renal	2(3,6)	0(0)	2(6,5)	0(0)
SNC	2(3,6)	0(0)	2(6,5)	0(0)
Vascular Peripheral	1(1,8)	0(0)	0(0)	1(5,6)
Number of dysfunction organic ·	No.21	No.4	No.10	No.7
1	5(23,8)	3(75,0)	2(20,0)	0(0)
2	3(14,3)	0(0)	0(0)	3(42,9)
3	10(47,6)	1(25,0)	5(50,0)	4(57,1)
4	1(4,8)	0(0)	1(10,0)	0(0)
5	2(9,5)	0(0)	2(20,0)	0(0)
Coronary aneurysm ††	5/34*(14,7)	2/8* (25,0)	1/9*(11,1)	2/17*(11,8)
Death	2(4,6)	0(0)	2(20,0)	0(0)

Abbreviations: SIM-P, pediatric multisistmic inflammatory chondrome associated with COVID-19; EK, Kawasaki Disease; IQR, interquartile range; SatO2, oxygen saturation; ICU, intensive care unit; VMI, invasive mechanical ventilation; CAF, high flow cannula; SAM, Macrophagic Activation Syndrome.

*Features are summarized in absolute frequencies and percentages. Dividing SIM-P in patients with fever and inflammation, shock and EK.

**Includes SIM-P that does not meet shock or EK criteria.

† With shock phenotype, it was defined as the need for support with inotropic/vasopressor or fluid resuscitation >20 ml/kg. Seven patients with EK and shock were excluded.

Includes complete and incomplete EK case according to the American Heart Association.

§Mediana (IQR)

ll All shock patients were considered (includes 10 of the "shock phenotype", and 7 of the "phenotype with Kawasaki Disease").

One or more of a type of dysfunction was presented in the same patient. Cardiovascular engagement includes hypotensiveion, cardiogenic shock, myocarditis, pericarditis, pericardial effusion with or without plugging, decreased left ventricle ejection fraction and/or coronary aneurysm. Respiratory include pneumonia with or without pleural effusion. Haematological includethrombocytopenia, severe anemia, leucemoid reaction and clotting disorders. Gastrointestinal includes acute surgical abdomen, ascites, hypertransaminasemia. Muscle includes rhabdomyolysis. Kidney includes acute failure. Neurol orgicinvolvement includes intracerebral hemorrhage, necrotizing encephalitis; and peripheral vascular include vascular necrosis in the foot and hands.

†† Of the 43 cases, 34 patients were echocardiography.

Table 5. Factors associated with variable empathetic outcomes on the SIM-P. Edgardo Rebagliati Martins National Hospital. Lima-Peru, April-September 2020.

Factors*	Unfavorable outcomes on the SIM-P														
	Trasferido a UCI(n=17)				In VMI (No.14)				Shock** (n=17)				Organic dysfunction†		
	RR crudeoil (IC95 %)	P value	RR asetad ‡§ (IC95%)	Valor of p	RR crudeoil (IC95 %)	Valor of p	RR asetad ‡§ (IC95%)	Valor of p	RR crudeoil (IC95 %)	Valor of p	RR asetad ‡§ (IC95%)	Valor of p	RR crudeoil (IC95 %)	P value	R a ‡ (I
Males	0,49 (0,24-0,99)	0,045	-	-	0,58 (0,25-1,34)	0,20 3	-	-	1,04 (0,46-2,37)	0,92 6	-	-	0,58 (0,32-1,03)	0,062	-
IgM COVID-19	1,58 (0,72-3,47)	0,251	-	-	0,86 (0,24-3,06)	0,81 3	-	-	1,10 (0,42-2,88)	0,84 3	-	-	1,61 (0,88-2,93)	0,122	-
Comorbilidad	1,8 (1,19-4,49)	0,014	**1,79 (1,02-3,14)**	**0,04 4**	3,3 (1,51-7,21)	0,00 3	**2,23 (1,04-4,79)**	**0,04 0**	2,31 (1,19-4,49)	0,01 4	1,72 (0,88-3,4)	0,11 5	2,03 (1,19-3,45)	0,009	1 (2
contact intradomiciliario	1,42 (0,89-3,65)	0,103	-	-	1,68 (0,70-4,06)	0,24 6	-	-	1,42 (0,67-3,0)	0,35 6	-	-	1,68 (0,9-3,15)	0,104	-
Linfopenia <500cel/mL	2,81 (1,56-5,03)	0,001	1,17 (0,56-2,39)	0,67 6	2,86 (1,36-6,01)	0,00 6	**2,8 (1,24-6,30)**	**0,01 3**	2,14 (1,10-4,17)	0,02 5	1,6 (0,76-3,39)	0,21 5	1,61 (0,88-2,93)	0,122	-
Protein C reactive, ≥ 10 mg/dL	4,85 (0,71-32,90)	0,106	**2,09 (1,15-3,79)**	**0,01 5**	3,94 (0,57-27,13)	0,16 4	-	-	2,27 (0,61-8,42)	0,21 9	-	-	2,88 (0,79-10,45)	0,108	-
D-d, ≥ 3 mg/L	3,69 (1,22-11,15)	0,02	1,72 (0,88-3,35)	0,11 0	4,75 (1,19-19,01)	0,02 8	**3,57 (1,23-10,38)**	**0,01 9**	5,94 (1,52-23,2)	0,01	4,15 (0,96-17,87)	0,05 6	3,36 (1,34-8,43)	0,01	2 (6
Ferritin, ≥ 1066 ng/ml	1,82 (0,89-3,72)	0,099	-	-	2,43 (1,11-5,34)	0,02 7	2,08 (0,92-4,73)	0,07 8	1,35 (0,59-3,07)	0,48	-	-	1,75 (0,99-3,06)	0,05	-
Albumin, < 2,5 g/dL	1,35 (0,59-3,07)	0,480	-	-	1,19 (0,43-3,5)	0,73 7	-	-	1,35 (0,59-3,07)	0,48	-	-	1,37 (0,71-2,63)	0,349	-
Sodium, < 135 mmol/L	1,42 (0,67-2,99)	0,356	-	-	2,27 (0,9-5,72)	0,08 1	-	-	1,42 (0,67-3,0)	0,35 6	-	-	1,39 (0,75-2,57)	0,296	-
SatO2 ≤92 in emergency	4,16 (2,09-8,28)	p<0,00 01	**2,84 (1,47-5,50)**	**0,00 2**	3,87 (1,71-8,78)	0,00 1	1,47 (0,55-3,95)	0,44 1	3,27 (1,68-6,39)	0,00 1	1,66 (0,72-3,81)	0,23 5	2,64 (1,57-4,45)	p<0,00 01	1 (3

Abbreviations: SIM-P, pediatric multisistmic inflammatory chondrome associated with COVID-19; ICU, intensive care unit; VMI, invasive mechanical ventilation; RR, relative risk; IC95%, 95% confidence interval; SatO2, oxygen saturation.

*Free absolute frequency (percentage).

**Shock was defined as the need for support with inotropic/vasopressor or fluid resuscitation >20 ml/kg. Includes 10 of the "shock phenotype", and 7 of the "phenotype with Kawasaki Disease".

† With at least one organic dysfunction.

- General linear model of Poisson family with robust variance.
- Adjusted by all variables that obtained a p-value less than 0.05 in crude analysis.