


RESEARCH

Open Access



Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain

Alberto García-Salido^{1†}, Juan Carlos de Carlos Vicente^{2†}, Sylvia Belda Hofheinz³, Joan Balcells Ramírez⁴, María Slöcker Barrio⁵, Inés Leóz Gordillo¹, Alexandra Hernández Yuste⁶, Carmina Guitart Pardellans⁷, Maite Cuervas-Mons Tejedor⁸, Beatriz Huidobro Labarga⁹, José Luís Vázquez Martínez¹⁰, Míriam Gutiérrez Jimeno¹¹, Ignacio Oulego-Erróz¹², Javier Trastoy Quintela¹³, Carmen Medina Monzón¹⁴, Laura Medina Ramos¹⁵, María Soledad Holanda Peña¹⁶, Javier Gil-Antón¹⁷, Clara Sorribes Ortí¹⁸, José Carlos Flores González¹⁹, Rosa María Hernández Palomo²⁰, Inma Sánchez Ganfornina²¹, Emilia Fernández Romero²², María García-Besteiro²³, Jesús López-Herce Cid⁵, Rafael González Cortés^{5*}  and the Spanish Pediatric Intensive Care Society working group on SARS-CoV-2 infection

Abstract

Background: Multisystem inflammatory syndrome temporally associated with COVID-19 (MIS-C) has been described as a novel and often severe presentation of SARS-CoV-2 infection in children. We aimed to describe the characteristics of children admitted to Pediatric Intensive Care Units (PICUs) presenting with MIS-C in comparison with those admitted with SARS-CoV-2 infection with other features such as COVID-19 pneumonia.

Methods: A multicentric prospective national registry including 47 PICUs was carried out. Data from children admitted with confirmed SARS-CoV-2 infection or fulfilling MIS-C criteria (with or without SARS-CoV-2 PCR confirmation) were collected. Clinical, laboratory and therapeutic features between MIS-C and non-MIS-C patients were compared.

Results: Seventy-four children were recruited. Sixty-one percent met MIS-C definition. MIS-C patients were older than non-MIS-C patients ($p = 0.002$): 9.4 years (IQR 5.5–11.8) vs 3.4 years (IQR 0.4–9.4). A higher proportion of them had no previous medical history of interest (88.2% vs 51.7%, $p = 0.005$). Non-MIS-C patients presented more frequently with respiratory distress (60.7% vs 13.3%, $p < 0.001$). MIS-C patients showed higher prevalence of fever (95.6% vs 64.3%, $p < 0.001$), diarrhea (66.7% vs 11.5%, $p < 0.001$), vomits (71.1% vs 23.1%, $p = 0.001$), fatigue (65.9% vs 36%, $p = 0.016$), shock (84.4% vs 13.8%, $p < 0.001$) and cardiac dysfunction (53.3% vs 10.3%, $p = 0.001$). MIS-C group had a

*Correspondence: rafa_gonzalez_cortes@hotmail.com

[†]Alberto García-Salido and Juan Carlos de Carlos Vicente contributed equally to this work

⁵ Paediatric Intensive Care Unit, Hospital General Universitario Gregorio Marañón, Calle Doctor Castelo 47, 28007 Madrid, Spain
Full list of author information is available at the end of the article



© The Author(s) 2020. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

lower lymphocyte count ($p < 0.001$) and LDH ($p = 0.001$) but higher neutrophil count ($p = 0.045$), neutrophil/lymphocyte ratio ($p < 0.001$), C-reactive protein ($p < 0.001$) and procalcitonin ($p < 0.001$). Patients in the MIS-C group were less likely to receive invasive ventilation (13.3% vs 41.4%, $p = 0.005$) but were more often treated with vasoactive drugs (66.7% vs 24.1%, $p < 0.001$), corticosteroids (80% vs 44.8%, $p = 0.003$) and immunoglobulins (51.1% vs 6.9%, $p < 0.001$). Most patients were discharged from PICU by the end of data collection with a median length of stay of 5 days (IQR 2.5–8 days) in the MIS-C group. Three patients died, none of them belonged to the MIS-C group.

Conclusions: MIS-C seems to be the most frequent presentation among critically ill children with SARS-CoV-2 infection. MIS-C patients are older and usually healthy. They show a higher prevalence of gastrointestinal symptoms and shock and are more likely to receive vasoactive drugs and immunomodulators and less likely to need mechanical ventilation than non-MIS-C patients.

Keywords: SARS-CoV-2, Pediatric multisystem inflammatory syndrome temporally associated with COVID-19, Kawasaki disease, Toxic shock syndrome, Children, Critical care, Shock

Background

In January 2020 a novel coronavirus (SARS-CoV-2) was described in Wuhan, China. This virus produces the coronavirus disease 2019 (COVID-19), and its rapid spread has led to the declaration of a global health emergency and pandemic by the World Health Organization [1, 2]. The infection affects adults more frequently than children and the clinical manifestations of the infection are generally less severe in pediatric patients than in adults [3–7].

To date, the scarce literature on pediatric patients with SARS-CoV-2 infection shows that it most commonly affects short-age children in the form of respiratory problems [3, 4, 6–10], although severe respiratory symptoms are significantly more frequent in adults than in children [11]. Indeed, only a low proportion of pediatric patients with SARS-CoV-2 infection require intensive care [12, 13], and mortality is lower in children than in adults [12].

By the end of April 2020 and the beginning of May, several scientific societies reported a new clinical presentation related to SARS-CoV-2 infection [14–17]. This syndrome, known as *multisystem inflammatory syndrome temporally associated with COVID-19* (MIS-C), is characterized by fever, abdominal pain, gastrointestinal and cutaneous symptoms, and hemodynamic alterations. As described in these reports, MIS-C has similar features to those of Kawasaki disease (KD), toxic shock syndrome (TSS), bacterial sepsis, and macrophage-activation syndrome. To date, several publications have reported clusters of patients with different severity in the UK [10, 18–21], Italy [22], France [23–25], and the USA [26–28]. In Spain, 5 cases of children presenting with suspected acute abdomen and SARS-CoV-2 infection were initially reported in a single-center study [29]. General data of patients with SARS-CoV-2 admitted to Spanish PICUs have been published with no differentiation of those presenting with MIS-C in a previous report [30].

Although the presence of KD symptoms has been previously described in patients with infections by other coronaviruses [31, 32], the evidence provided on KD in pediatric patients with SARS-CoV-2 in the scientific literature is very limited.

The purpose of this prospective multicenter registry carried out in Spain, is to compare the cases of pediatric patients with SARS-CoV-2 infection and clinical symptoms consistent with MIS-C to those with SARS-CoV-2 infection not fulfilling MIS-C criteria.

Methods

The Spanish Society of Pediatric Intensive Care promoted the creation of a multicentric prospective registry of pediatric patients with SARS-CoV-2 infection admitted to PICUs in Spain. The Registry was approved by the Institutional Review Board of the coordinating center (Hospital General Universitario Gregorio Marañón). The Registry is fed by 47 PICUs, which account for more than 90% of the PICUs of the Spanish health system. Researchers at each participating PICU were responsible for identifying those who fulfilled inclusion criteria among every admitted patient during the study period. Written informed consent was obtained from patients or their parents before data collection. Data about patients who met inclusion criteria were collected by an electronic data collection form and entered into the Registry by researchers at each site. Data were collected between the 1st of March 2020 and the 15th of June 2020. Partial data from patients included in the study have been previously published as case series elsewhere [29, 30].

Inclusion criteria

All patients younger than 18 years admitted to a PICU with a diagnosis of SARS-CoV-2 infection were included. Patients who met the case definition for MIS-C according to the criteria of the Royal College of Paediatrics and Child Health (RCPCH) [14] were also included, even

lacking a confirmed microbiological diagnosis of SARS-CoV-2 infection.

A case of MIS-C was defined as persistent fever (for longer than 4 days), laboratory data showing inflammation (neutrophilia, lymphopenia, or elevated C-reactive protein) and evidence of organ dysfunction (as described in the variables section) with other additional symptoms such as cutaneous–mucosal or abdominal involvement. Patients with other infections explaining their symptoms were excluded. Polymerase chain reaction (PCR) testing for SARS-CoV-2 in patients with MIS-C may be positive or negative [14].

As cases consistent with MIS-C may have been overlooked before the definition of this entity was published, researchers at every participating PICU were asked to perform a retrospective review of all admissions since the Registry's inception. None of the participating PICUs identified any patient who met the established criteria and had not been previously included in the Registry.

Variables collected

Collected data included the date of admission to and discharge from PICU, demographic variables; any medical history of interest; and the main reason for PICU admission. Other data included were clinical diagnosis within the first 24 h of admission, severity scores (PRISM III) and multi-organ failure scores (P-SOFA), and other clinical and analytical parameters recorded on admission and during the hospital stay. A clinical diagnosis of shock was established in the presence of arterial hypotension with mean blood pressure values below the 5th percentile of the reference values for age, need for vasoactive therapy to maintain normal blood pressure, or presence of signs of hypoperfusion despite adequate fluid resuscitation. Acute cardiac dysfunction was defined as the appearance of any of the following echocardiographic alterations: global or segmental contractility alterations, ventricular dilatation, reduced ejection fraction and/or presence of pericardial effusion.

Additional data included the presence or absence of the following symptoms: fever, cough, respiratory distress, odynophagia, rhinorrhea, diarrhea, nausea, vomiting, refusal to eat, headache, irritability, altered level of consciousness, seizures, fatigue, myalgia or abdominal pain.

Additionally, symptoms consistent with hyperinflammatory syndromes such as KD and TSS were recorded in patients who met the MIS-C case definition. Possible symptoms of hyperinflammatory syndromes included fever; persistent fever (more than 4 days of duration); ocular manifestations such as non-exudative conjunctivitis; oral mucosa lesions; cutaneous manifestations (palmar or plantar erythema, edema, swelling, desquamation, erythroderma, or polymorphic erythema in

the hands and feet); cervical lymphadenopathy; arterial hypotension; renal, hematological, or hepatic involvement; presence of Acute Respiratory Distress Syndrome (ARDS); neurological involvement, or soft tissue necrosis. The presence of ARDS was defined following the Pediatric Acute Lung Injury Consensus Conference criteria [33]. For renal involvement, the definition employed was an increase in creatinine levels of double the normal limits for the age of the patient or twice as baseline creatinine levels. The considered definition of hematologic involvement included the presence of coagulopathy (aPTT or PT above normal limits) or thrombocytopenia (<100,000 platelets/mcl). Liver involvement was defined as an increase in transaminase or bilirubin levels twice above baseline or normal values for the age of the patient.

Laboratory data on admission and during hospital stay were also collected, including hemoglobin, leukocyte and platelet counts, coagulation tests, D-dimer, creatinine, urea, liver function markers, LDH, and ions. Inflammatory markers such as C reactive protein (CRP), procalcitonin (PCT), and IL-6 were recorded. In patients with hyperinflammatory symptoms, NT-ProBNP, and serum troponin levels were also included. Microbiologically confirmed diagnosis of SARS-CoV-2 infection (PCR and serology) was also recorded. PCR testing was performed on nasopharyngeal swab samples. The microbiological tests were carried out according to the established practice at each participating center.

Besides, antibiotic, antiviral, and immunomodulatory therapies administered during PICU stay, respiratory and cardiovascular support (administration of vasoactive drugs and/or ECMO) or need for renal replacement therapy were obtained.

Statistical analysis

Data were entered into a database that was analyzed using the SPSS statistical package (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp). Continuous quantitative variables were expressed as median values and interquartile ranges as measures of central tendency. Comparison of continuous quantitative variables was performed using the Wilcoxon rank-sum test. Comparison of proportions between subgroups of patients was carried out by Chi-squared test and Fisher's test when the first method could not be used due to the small number of cases. Heatmap and dendrogram were performed using Jaccard distance and Jaccard index to describe clusters of co-occurring symptoms. Dendrogram was built using Jaccard distance as metric and complete linkage as adjustment method. Heatmap and dendrogram were drawn using Datagraph for MacOS version 4.5.1 (Visual Data Tools Inc. Chapel Hill, NC). When some data were

missing, the number of patients whose data were available for each variable is stated.

Results

Forty-seven PICUs, including 1st, 2nd and 3rd level of care, from every region of Spain participated in the Registry. Between March 1st and June 15th, 2020, a total of 74 children admitted to the participating PICUs were included in the Registry, with ages ranging from 15 days to 16.5 years. Forty-five patients (61%) were male, and 52 (70.3%) had no previous disease. Forty-five patients (61%) met the case definition for MIS-C proposed by the RCPCH.

SARS-CoV-2 infection was confirmed microbiologically in 61 of 74 patients (82.4%). Viral RNA was detected by PCR in 44 of 74 patients (59.5%). Serologic tests were done in 37 patients (50%) being positive in 27 of them (73%). The diagnosis was not confirmed microbiologically in thirteen patients (17.6%) with high suspicion of SARS-CoV-2 infection (according to clinical, epidemiological, or radiologic findings) or meeting MIS-C criteria. Among patients not presenting with MIS-C, viral RNA was detected using PCR in 26 of 29 (89.7%) while in the MIS-C group, PCR was positive in 18 out of 45 (40%) ($p < 0.001$). Seventeen of the 27 (63%) patients with negative PCR testing in the MIS-C group had serological confirmation of SARS-CoV-2 infection.

Table 1 compares the baseline characteristics, symptoms prior to admission, and clinical diagnoses established within the first 24 h of admission of the group of patients meeting the case definition for MIS-C vs the remainder of patients with SARS-CoV-2 infection admitted to the PICU. The group of patients with MIS-C had an older age and higher weight. The proportion of patients with a previous medical history of interest was lower in the group of patients meeting MIS-C criteria. Respiratory symptoms were less frequent in the MIS-C patients, whereas the incidence of gastrointestinal symptoms and fatigue was higher in this group. The MIS-C group presented a higher prevalence of symptoms of shock and acute cardiac dysfunction. Clusters of symptoms were identified using heatmap and dendrogram analysis (Fig. 1). Figure 2 shows the count of new SARS-CoV-2 positives admitted to the PICU every day separating patients with MIS-C from the remainder of patients. Table 2 displays the incidence of KD and TSS symptoms in the 45 patients with MIS-C.

Figure 3 compares the laboratory parameters of patients with and without MIS-C. Patients with MIS-C exhibited lower levels of lymphocytes and LDH, higher levels of CRP and PCT, neutrophils, and a higher lymphocyte/neutrophil ratio. Troponin-T was determined in 34 of the 45 MIS-C patients (75.6%) with a median value of

55.4 ng/L (IQR 13.3–204.7 ng/L) (normal value < 19 ng/L) [34] and NT-ProBNP was determined in 22 patients with MIS-C (48.9%) with a median value of 5,532 pg/ml (IQR 1582–12,783 pg/ml) (normal value < 450 pg/ml) [35]. Twenty-two patients in the MIS-C group (48.9%) exhibited echocardiographic signs of ventricular dysfunction. Coronary arteries abnormalities were reported in 3 patients in the MIS-C group (6.7%): two patients had a homogeneously dilated anterior descendent artery along its entire length, and one patient had a dilated left coronary artery with an aneurism in the anterior descendent artery.

Support measures and antibiotic, antiviral, and immunomodulatory therapies administered during PICU hospitalization are shown in Table 3. Invasive and non-invasive mechanical ventilation were less used in patients with MIS-C, whereas the use of antibiotics and vasoactive and immunomodulatory therapies was more common in these patients.

Among 18 patients requiring intubation in 11 (61.1%) the main reason for intubation was respiratory failure while in 7 (38.9%) it was due to hemodynamic failure. Patients requiring invasive ventilation were younger (2.9 years [IQR 0.4–9.5]) than those who did not (9.1 years [IQR 4.2–11.9]), $p = 0.007$. They also had higher PRISM-III score (13 points [IQR 8–16]) than non-ventilated patients (6.5 points [IQR 4–9.3]), $p = 0.005$, and higher p-SOFA scores (6 points [IQR 4–10.5] vs 3 points [IQR 2–5]), $p < 0.001$. On the contrary, patients requiring ventilation had lower CRP levels (7.1 mg/dl [IQR 0.9–21.6]) than non-ventilated patients (20.5 mg/dl [IQR 10.3–27.6]), $p = 0.017$. Among 18 patients requiring invasive ventilation, 15 (83.3%) had radiologic alterations in the chest x-ray.

Radiologic alterations in the chest-x-ray were present in 20 patients (55.6%) with MIS-C features and in 27 patients (93.1%) without ($p = 0.001$). The existence of an abnormal chest-x-ray was observed in 36 of 44 patients (81.8%) with positive PCR for SARS-CoV-2 in the nasopharyngeal swab samples and in 16 of 30 patients (53.3%) of patients with negative nasopharyngeal swab SARS-CoV-2 PCR ($p = 0.008$). Twenty-two patients of 74 (29.7%) showed normal chest-x-ray at admission. Patients with normal chest-x-ray had higher PCT 7.9 mcg/L (3.1–55.7) than patients with chest-x-ray alterations (1.9 mcg/L [0.3–7.4]), $p = 0.006$.

Thirty-seven patients required vasoactive drugs, among them, 15 (40%) showed conserved cardiac function. Noradrenaline and dopamine were used in more patients in the MIS-C group (35.5% and 25.8%) compared to the non-MIS-C group (7.7% and 4%), $p = 0.024$ and $p = 0.033$, respectively. Fluid balance per kilogram during the first day of admission was 9.2 ml/kg (IQR –7.1 to 28) in the

Table 1 Clinical manifestations of SARS-CoV-2 in critical pediatric patients

	Total patients (N = 74)	Patients with MIS-C (N = 45)	Patients without MIS-C (N = 29)	p
Gender (male) n/N (%)	46/74 (62.2)	39/45 (66.7)	16/29 (55.2)	0.320
Age (years) Median (IQR)	8.1 (3–11.5)	9.4 (5.5–11.8)	3.4 (0.4–9.4)	0.002
0–5 years n/N (%)	30 (40.5)	12 (26.7)	18 (62.1)	0.003
6–12 years n/N (%)	33 (44.6)	27 (60)	6 (20.7)	
> 13 years n/N (%)	11 (14.9)	6 (13.3)	5 (17.2)	
Weight (kg) Median (IQR)	29.5 (15–43.5)	36 (22.5–50)	15.5 (6.5–32.5)	< 0.001
Previously healthy n/N (%)	52/74 (70.3)	37/45 (82.2)	15/29 (51.7)	0.005
PRISM III Median (IQR)	7 (4–13.5)	7 (5–14)	7 (3–13)	0.544
p-SOFA Median (IQR)	4 (2–6)	4 (3–6)	3 (1–5)	0.135
<i>Symptoms prior to PICU admission</i>				
Fever n/N (%)	61/73 (83.6)	43/45 (95.6)	18/28 (64.3)	< 0.001
Cough n/N (%)	26/73 (35.6)	12/45 (26.7)	14/28 (50)	0.043
Respiratory distress n/N (%)	23/73 (31.5)	6/45 (13.3)	17/28 (60.7)	< 0.001
Odynophagia n/N (%)	12/68 (17.6)	9/43 (20.9)	3/25 (12)	0.352
Rhinorrhea n/N (%)	11/71 (15.5)	2/43 (4.7)	9/28 (32.1)	0.002
Diarrhea n/N (%)	33/71 (46.5)	30/45 (66.7)	3/26 (11.5)	< 0.001
Nausea n/N (%)	22/53 (41.5)	18/30 (60)	4/23 (17.4)	0.002
Vomits n/N (%)	38/71 (53.5)	32/45 (71.1)	6/26 (23.1)	< 0.001
Refusal to eat n/N (%)	48/69 (69.6)	33/43 (76.7)	15/26 (57.7)	0.096
Headache n/N (%)	16/68 (23.5)	13/44 (29.5)	3/24 (12.5)	0.113
Irritability n/N (%)	15/71 (21.8)	9/45 (20)	6/26 (23.1)	0.760
Altered consciousness n/N (%)	5/72 (6.9)	2/45 (4.4)	3/27 (11.1)	0.281
Seizures n/N (%)	1/72 (1.4)	1/45 (2.2)	0/27 (0)	0.435
Fatigue n/N (%)	38/69 (55.1)	29/44 (65.9)	9/25 (36)	0.016
Myalgias n/N (%)	8/67 (11.9)	7/43 (16.3)	1/24 (4.2)	0.143
<i>Diagnoses within the first 24 h of admission</i>				
ARDS n/N (%)	11/74 (14.9)	3/45 (6.7)	8/29 (27.6)	0.014
Shock n/N (%)	42/74 (56.8)	38/45 (84.4)	4/29 (13.8)	< 0.001
Acute kidney injury n/N (%)	12/74 (16.2)	9/45 (20)	3/29 (10.3)	0.271
Acute cardiac dysfunction n/N (%)	27/74 (36.5)	24/45 (53.3)	3/29 (10.3)	0.001
Acute liver dysfunction n/N (%)	14/74 (18.9)	11/45 (24.4)	3/29 (10.3)	0.131

Comparison of patients with MIS-C and without MIS-C. Quantitative values are expressed as median values and interquartile range. Qualitative variables are expressed as number of cases with respect to the total number of cases in each group and percentages

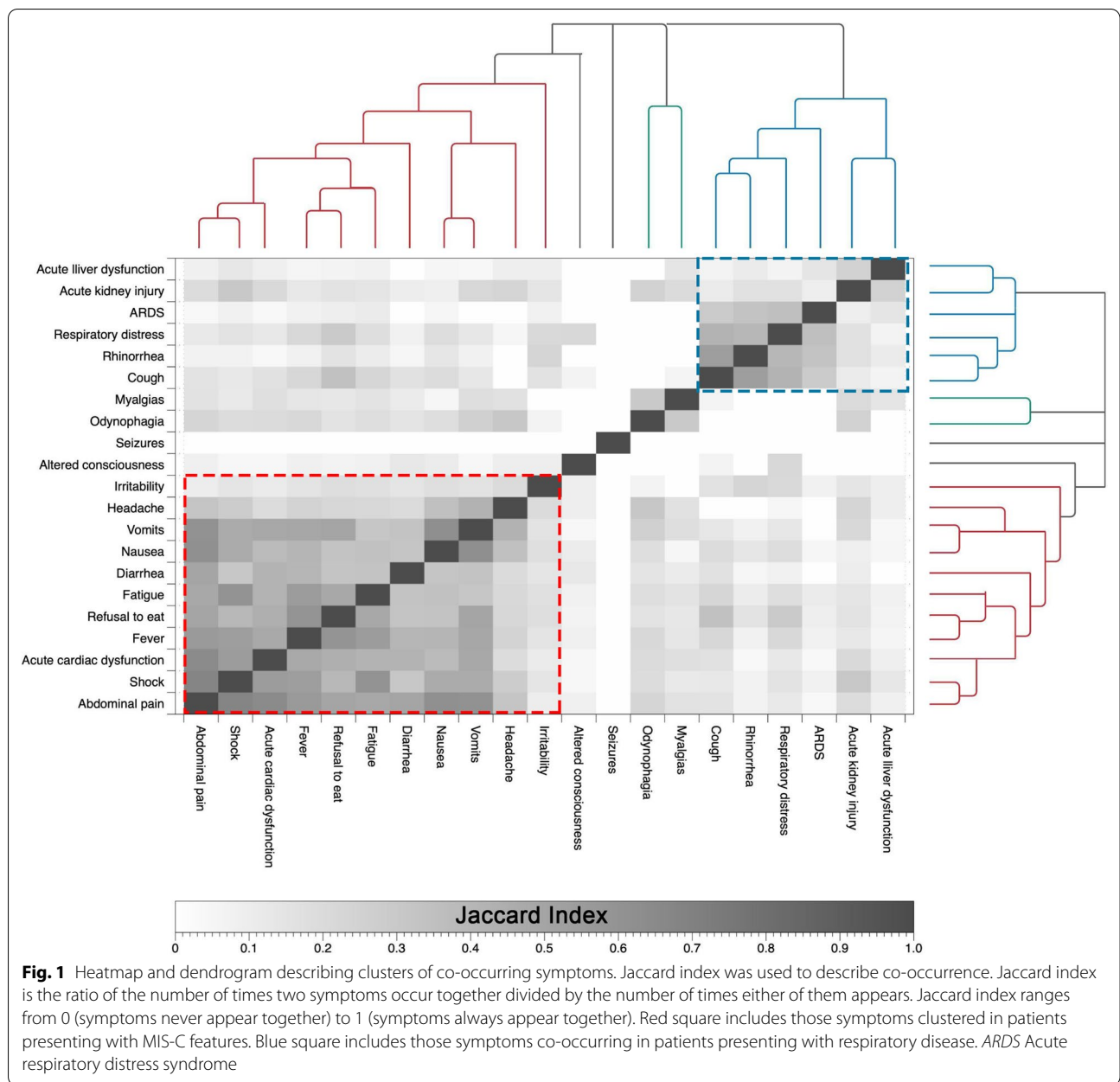
IQR Interquartile rank, p-SOFA pediatric sequential organ failure, PRISM III Pediatric risk of mortality score, ARDS Acute respiratory distress syndrome. The criteria used to define diagnostic variables within the first 24 h of admission are defined in the Materials and Methods section

group of patients without MIS-C and 21.8 ml/kg (IQR 0.2–29.7) $p = 0.450$.

The administration of antiviral treatments was similar in the two groups, except for remdesivir, which was not used in patients with MIS-C.

As of June 15, 2020, 65 of the 74 patients (87.8%) included in the Registry had been discharged from the PICU. The length of stay in patients with MIS-C was 5 days (2.5–8 days) versus 6.5 days (3.3–10.8 days) in the other group ($p = 0.523$). The patient who required

VA-ECMO was weaned and discharged to the ward. Three patients included in the registry died (4%), all of them belonged to the group of patients not presenting with MIS-C. All deceased patients previously had serious illnesses: one of them had a Niemann–Pick disease, and the other two had received hematopoietic stem cell transplantation due to acute lymphoblastic leukemia and to severe immunodeficiency. Deceased patients developed severe respiratory distress, one of them died while he was on VV-ECMO support due to massive pulmonary thromboembolism.



Discussion

In general terms, the clinical manifestations of SARS-CoV-2 infection are less severe in pediatric patients than in adults. The study published by Dong et al. revealed that only 6% of the more than 2,000 pediatric patients included, developed severe clinical symptoms [7], and only a small proportion needed intensive care. Respiratory problems are less frequent in children than in adults [3].

The occurrence of severe systemic hyperinflammatory symptoms probably associated with SARS-CoV-2 infection in children has raised concerns among scientific

societies [14–17]. This syndrome, which symptoms mimic those of sepsis, KD or TSS, has been described in different studies [18–29]. The information available on the most severe manifestation of SARS-CoV-2 in children is also very limited [12, 36]. Our multicentric Registry identified the differences between PICU patients with symptoms of hyperinflammatory syndrome and those with SARS-CoV-2 infection without symptoms of hyperinflammation. To date large series of pediatric patients suffering severe manifestations of SARS-CoV-2 infection are lacking, and our study includes an important number of them. It is the first describing characteristics of

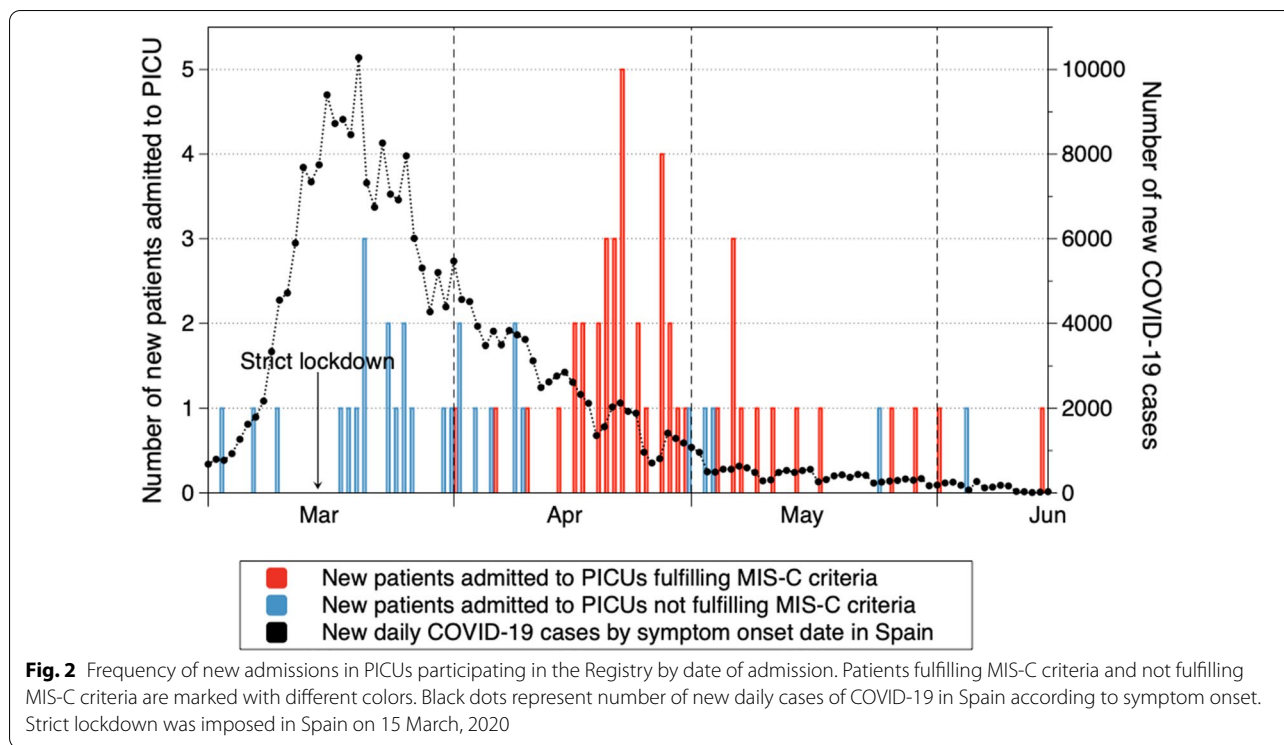


Table 2 Frequency of characteristic symptoms of other hyperinflammatory syndromes as KD and TSS in patients with MIS-C

Symptom	Number of patients	%
Fever	43/45	95.6
Arterial hypotension for the age	41/45	91.1
Abdominal pain	40/45	90.9
Cutaneous manifestations	31/45	68.9
Prolonged fever (> 4 days)	27/45	60
Hematologic alterations	26/45	68.4
Ocular manifestations	18/45	40
Liver involvement	14/45	31.8
Alterations in the oral mucosa	10/45	27
Renal involvement	8/45	17.8
Neurologic involvement	6/45	13.6
Soft tissue necrosis	2/45	5.4
Lymphadenopathy	2/45	5.4
ARDS	2/45	4.7

ARDS Acute respiratory distress syndrome. The criteria used to define the different variables are defined in the Materials and Methods section

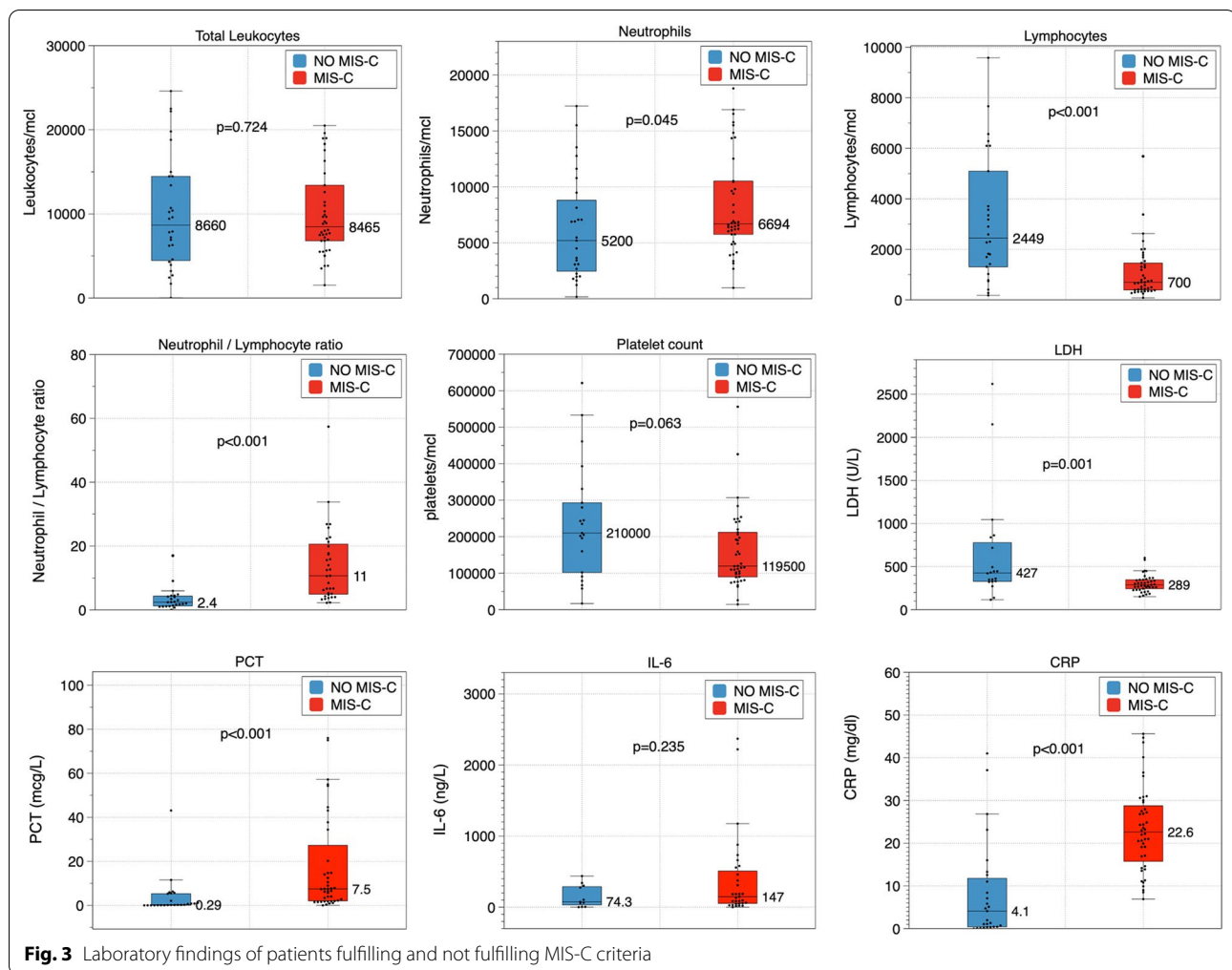
SARS-CoV-2 infection comparing the patients presenting with multisystem inflammatory symptoms with those without.

Whereas the most of COVID-19 patients in the studies performed by Shekerdeman et al. and Sachdeva et al. in

the USA and Canada [12, 36] had respiratory symptoms, inflammatory syndromes were more frequent in our series. This difference may be explained by the fact that Spain is in a more advanced stage of the pandemic, as no cases of this type were recorded in our Registry during the initial stages. Several studies in different regions have shown a delay between the peak of incidence of COVID-19 cases and the rise in the number of MIS-C cases [10, 21, 22, 27, 28]. In the same vein, the presence of previous comorbidities was higher in the sample of Shekerdeman et al. (above 80%), whereas previous comorbidities in our sample were only identified in patients without systemic inflammatory symptoms, who were prevalingly hospitalized during the first weeks of operation of the Registry. Many published studies point out that most patients presenting with MIS-C are previously healthy [19–21, 24, 26–28].

In total, 75% of pediatric patients with MIS-C were older than 6 years. This finding contrasts with KD, which is more frequent in children less than 5 years old [37]. These findings are consistent with those observed in the studies published by Whittaker et al. and Verdoni et al. where MIS-C patients are compared with previous cohorts of KD patients showing older age [19, 22].

Cluster analysis has identified two big groups of patients in our cohort, those presenting with fever, shock, acute cardiac dysfunction, and gastrointestinal symptoms (the group of patients with MIS-C features), and a second



group presenting with respiratory symptoms including ARDS that often associates also acute liver and kidney dysfunction (the group of patients with a more classical presentation of COVID-19).

In patients with MIS-C, gastrointestinal symptoms are more frequent than respiratory symptoms, whereas patients with SARS-CoV-2 typically show respiratory symptoms. This finding contradicts the data reported by Shekerdeman et al., who reported a very low incidence of gastrointestinal problems (2%) [12]. In our series, gastrointestinal symptoms were uncommon in patients without MIS-C (4% of these patients have diarrhea), whereas more than 60% of patients with inflammatory syndromes exhibited gastrointestinal symptoms. This is in line with the previously described MIS-C case series, in which abdominal symptoms as abdominal pain, diarrhea, nausea and vomiting are present in most patients [10, 18–24, 26–28].

Fever is the most frequent symptom in patients with MIS-C, with 100% of patients developing a fever, whereas

a third of the patients without MIS-C do not present a fever. Almost the totality of patients with MIS-C of our series exhibited arterial hypotension. It is worth noting that we only analyzed PICU patients. Therefore, there may have been patients with milder MIS-C symptoms who did not develop hemodynamic alterations and did not require intensive care as described in studies that include patients not requiring intensive care [19, 20, 22, 23, 27, 28].

As mentioned above, the clinical-laboratory manifestations of MIS-C mimic those of KD and TSS, and a high proportion of patients may meet the diagnostic criteria for both diseases [37, 38]. However, some of the typical symptoms of these diseases were very uncommon in our series, especially the typical cervical adenopathy of KD or the oral mucosa and lips lesions (only present in 1 out of 4 patients of our series) [37]. Some studies have described how the presence of cutaneous manifestations in children with MIS-C might vary according to the age, being less frequent in older patients [27, 28].

Table 3 Support measures and pharmacological treatments administered to patients admitted for SARS-COV-2

	Total patients (N = 74)	Patients with MIS-C (N = 45)	Patients without MIS-C (N = 29)	p
<i>Support measures. n/N (%)</i>				
Oxygen therapy	56/74 (79.7)	36/45 (80)	20/29 (69)	0.215
HFO	26/74 (35.1)	14/45 (31.1)	12/29 (41.4)	0.379
NIV	9/74 (12.2)	2/45 (4.4)	7/29 (24.1)	0.026
MV	18/74 (24.3)	6/45 (13.3)	12/29 (41.4)	0.005
Neuromuscular blockade	12/74 (16.2)	3/45 (6.7)	9/29 (31)	0.009
Ventilation in prone position	9/74 (12.2)	1/45 (2.2)	8/29 (27.6)	0.002
V-V-ECMO	1/74 (1.4)	0/45 (0)	1/29 (3.4)	0.394
A-V-ECMO	1/74 (1.4)	1/45 (2.2)	0/29 (0)	1
NOi	3/74 (4.1)	0/45 (0)	3/29 (10.3)	0.057
CRRT	0/74 (0)	0/45 (0)	0/29 (0)	-
Transfusion of hemoderivatives	14/74 (18.9)	5/45 (11.1)	9/29 (31)	0.034
Vasoactive drugs	37/74 (50)	30/45 (66.7)	7/29 (24.1)	<0.001
<i>Pharmacological therapies n/N (%)</i>				
Antibiotic	65/74 (87.8)	42/45 (93.3)	23/29 (79.3)	0.020
Lopinavir–ritonavir	30/74 (40.5)	18/45 (40)	12/29 (41.4)	0.857
Remdesivir	5/74 (6.8)	0/45 (0)	5/29 (17.2)	0.006
Hydroxychloroquine	43/74 (58.1)	25/45 (55.6)	18/29 (62.1)	0.550
Corticosteroids	49/74 (66.2)	36/45 (80)	13/29 (44.8)	0.003
Immunoglobulins	25/74 (33.8)	23/45 (51.1)	2/29 (6.9)	<0.001
Tocilizumab	17/74 (23)	11/45 (24.4)	6/29 (20.7)	0.871

Comparison of patients with MIS-C and without MIS-C

HFO high-flow rate oxygen, NIV noninvasive ventilation, MV invasive mechanical ventilation, V-V-ECMO veno-venous extracorporeal membrane oxygenation, V-A ECMO veno-arterial extracorporeal membrane oxygenation, NOi Inhaled nitric oxygen, CRRT continuous renal replacement therapy

Concerning the laboratory parameters, the MIS-C patients presented severe inflammation, with very elevated levels of acute-phase reactants (CRP and PCT), exceeding those of SARS-CoV-2 patients without MIS-C. Although absolute leukocyte counts were not very elevated and were similar in the two groups, patients with MIS-C exhibited severe lymphopenia, with a high neutrophils/lymphocyte ratio and a low platelet count. Special attention needs to be paid to the fact that LDH was lower in patients with MIS-C as compared to those without MIS-C, since elevated LDH levels may be associated with hemolysis or myocardial damage. The clinical interpretation of this finding is challenging. The analytical findings in our series were similar to those previously reported, i.e., lymphopenia without significant leukocytosis, thrombocytopenia, and high CRP and PCT [18–22, 27, 28].

Hyperinflammatory state has been previously reported in adults presenting with COVID-19. This hyperinflammatory state has been related to disease severity and the need for mechanical ventilation and has been described in the context of classic COVID-19 syndrome presenting with bilateral pneumonia [39, 40]. In our study, contrary to the studies in adults, patients presenting

with hyperinflammatory features such as elevated CRP, showed lower prevalence of chest x-ray abnormalities and lesser need of mechanical ventilation. Our study points out differences regarding hyperinflammatory states related to SARS-CoV-2 infection in children as compared to those described in adults. In adults, hyperinflammation is more frequent in the context of COVID-19 bilateral pneumonia and in children in patients with mild or absent respiratory symptoms presenting gastrointestinal symptoms and shock fulfilling MIS-C criteria.

Several authors have proposed a mechanism of immune dysregulation underlying MIS-C cases. In children, increased antibodies against receptor binding domain of SARS-CoV-2 have been described in patients with MIS-C compared with patients with COVID-19 without hyperinflammatory features [41]. Activation of neutrophils and monocytes has been also described in the acute phase of pediatric patients with MIS-C with normalization in the resolution and convalescent phases of the disease [42]. In adults with severe COVID-19, hyperinflammation and abnormal activation of different cell lineages have also been described widely [43]. However, it remains unclear why in children, SARS-CoV-2 related hyperinflammatory states seems to affect more

frequently cardiovascular and digestive organs instead of the lungs as seen in adults.

With regard to the treatments administered, most MIS-C patients admitted to the PICU required vasoactive therapy, whereas this therapy was less frequent in patients without this MIS-C. There was a high proportion of MIS-C patients requiring vasoactive drugs with conserved cardiac function and use of noradrenaline was also higher in this group. These facts might point out an important element of vasoplegia in MIS-C patients.

In contrast with the use of vasoactive drugs, the need of mechanical ventilation was higher amongst those patients without MIS-C. In overall terms, the use of mechanical ventilation nearly reached 30%, which is similar to the percentage reported in studies about PICU admissions including children with SARS-CoV-2 related diseases [12, 36]. In our population of patients with MIS-C, the use of mechanical ventilation was infrequent (below 15%) as described by Dufort et al. in New York State [28], and lower to the rates described in studies from other regions as U.S.A., U.K. and France where more than 30% of patients with MIS-C needed mechanical ventilation.

As to pharmacological treatments, most patients with MIS-C included in the Registry received antibiotic therapy. The use of immunomodulatory and corticosteroid treatments was also higher in the group of patients with MIS-C. No differences were observed in the use of antiviral treatments, although remdesivir was not administered to any of the patients with MIS-C. Remdesivir availability was limited in Spain during this phase of the pandemic. The distribution of remdesivir was subject to request and authorization by the ministry of health and administration in children was considered only in the context of a clinical trial. Remdesivir administration was requested in several patients in the MIS-C group but delay related to approval and favorable course in most MIS-C patients probably determined the difference in its use between groups. In view of the scant evidence available on the effectiveness of antiviral therapies in the treatment of SARS-CoV-2, further studies should be conducted to assess the efficacy of the immunomodulators used to treat similar symptoms to those described above (such as steroids and immunoglobulins) to attenuate the inflammatory mechanisms involved in the disease [44]. Treatments used in patients with MIS-C are similar to those described in studies from other regions [21, 27, 28].

The relationship observed between time and the occurrence of MIS-C cases is worthy of note. All MIS-C patients were admitted to the PICU at least 15 days after the lockdown was imposed in Spain on March 15, 2020. In the stage where the first patients with MIS-C were recorded, in early April, the number of new cases

was already decreasing. The simultaneous occurrence of similar symptoms to those described in our series in other European countries [18–24] leads us to foresee an increase in the incidence of this syndrome in more advanced stages of the epidemic in countries where the coronavirus spike occurred some weeks later than in Europe. This added to the fact that PCR was negative in more than half of MIS-C patients but serology was positive for SARS-CoV-2 in a high proportion of them suggests that MIS-C may be caused by an underlying deregulation of the immune system, with the viral infection triggering a hyperinflammatory response rather than being a direct expression of SARS-CoV-2 infection [22].

As to prognosis, the course of MIS-C patients included in our registry was generally favorable, without any mortality. Most patients were discharged to the ward in a few days. Other studies describe similar findings with low mortality in patients with MIS-C (below 3% in all series) [19, 21, 23, 24, 27, 28].

Limitations

This study has some limitations. First, it is a multicentric study that includes most—but not all—PICUs in Spain. Therefore, some patients with similar symptoms could have not been included in the study. We consider that PICUs not participating in the registry do not represent a specific region or subset of PICUs that might prevent generalizing our results to all Spanish PICUs. Secondly, the new syndrome observed led us to retrospectively review the potential cases that may have been overlooked. Although the participating PICUs reviewed their records, some patients may have not been included. Although it is a prospective Registry, some clinical or laboratory variables were missing. Beside this, each hospital had their own microbiological tests and thus differences on diagnostic precision regarding SARS-CoV-2 infection might be present. As only patients admitted to PICU were included in the registry, we consider that probably our study does not include the whole spectrum of MIS-C and some patients might develop milder manifestations. Finally, the long-term course of patients could not be analyzed, given the short period of time elapsed from the onset of the clinical symptoms and analysis. In this sense, given that KD is one of the most frequent causes of heart disease acquired in childhood, it would be very interesting to describe the incidence of coronary lesions in patients with MIS-C.

Conclusions

Although SARS-CoV-2 infection is less severe in children than in adults, some pediatric patients may present severe symptoms requiring intensive care. In Spain, most pediatric patients requiring intensive care presented

with hyperinflammatory syndrome instead of classic COVID-19 disease with severe respiratory involvement. This syndrome is characterized by fever, hypotension, gastrointestinal symptoms and cutaneous manifestations with elevation of inflammatory markers together with significant lymphopenia, requiring vasoactive therapy. The course of this syndrome is generally favorable. The number of cases of MIS-C was higher after the spike in coronavirus cases in Spain. This, and the fact that it is frequent that MIS-C patients have negative SARS-CoV-2 PCR tests supports a causal link between SARS-CoV-2 and MIS-C in which children immune response dysregulation might be involved. Larger, international, multi-centric studies are needed to characterize this syndrome more accurately and establish the optimal treatment. Health policies regarding pediatric intensive care units preparedness for SARS-CoV-2 pandemic should take into account that a high proportion of patients will present with MIS-C. Therefore, specific management protocols should be elaborated, and resource acquisition and distribution should consider the previously described patients characteristics and therapeutic needs.

Abbreviations

MIS-C: Multisystem inflammatory syndrome temporally associated with COVID-19; PICUs: Pediatric intensive care units; KD: Kawasaki disease; TSS: Toxic shock syndrome; RCPCH: Royal College of Paediatrics and Child Health; IQR: Interquartile range; PCR: Polymerase chain reaction; ARDS: Acute respiratory distress syndrome; CRP: C reactive protein; PCT: Procalcitonin; HFO: High-flow rate oxygen; NIV: Noninvasive ventilation; MV: Mechanical ventilation; VV-ECMO: Venovenous extracorporeal membrane oxygenation; VA ECMO: Venovenous arterial extracorporeal membrane oxygenation; NOi: Inhaled nitric oxide; CRRT: Continuous renal replacement therapy.

Acknowledgements

We would like to show our respect and gratitude to all the healthcare workers that are assisting the patients affected by COVID-19. They will probably not appear in the scientific publications derived from their hard work, but they are mainly the ones who are at the bedside caring of patients who are suffering this terrible disease. We would like to show our deepest respect and solidarity with all the patients and families suffering COVID-19, specially with those who have passed away all around the world. We would like to thank to all members of the Spanish Society of Pediatric Intensive Care Study group on SARS-CoV-2 in critically ill pediatric patients which should be considered as co-authors of the manuscript. Members of the SECIP Study group on SARS-CoV-2 in critically ill pediatric patients are: María Slöcker Barrio, Amaya Bustinza Arriortua, Jesús López-Herce Cid and Rafael González Cortés (Hospital General Universitario Gregorio Marañón), Juan Carlos de Carlos Vicente (Hospital Universitari Son Espases), Maite Cuervas-Mons Tejedor and Pedro Pablo Oyáguéz Ugidos (Complejo Asistencial Universitario de Burgos), Iolanda Jordan and Carmina Guitart Pardellans (Hospital Sant Joan de Déu), Sonia Sanchiz Cárdenas (Hospital Clínico Universitario Virgen de la Arrixaca), Javier Gil Antón (Hospital Universitario de Cruces), Belén Joyanes (Hospital Clínico Universitario San Carlos), Ainhoa Jiménez Olmos (Hospital Universitario Miguel Servet), Antonio Rodríguez Núñez, Javier Trastoy Quintela (Complejo Hospitalario Universitario de Santiago), Alexandra Hernández Yuste (Hospital Materno Infantil Universitario de Málaga), Laura Díaz Munilla (Complejo Hospitalario de Navarra), Carlos Solís Reyes (Hospital Universitario Nuestra Señora de Candelaria), Laura Medina Ramos (Hospital General Universitario de Alicante), David Roca Pascual and Joan Balcells Ramírez (Campus Hospitalario Vall d'Hebron de Barcelona), Mario Sánchez Fernández (Hospital Universitari Dr. Josep Trueta), Alberto García-Salido, Inés Leóz Gordillo, Montserrat Nieto Moro, Amelia Martínez de

Azagra Garde, María Ángeles García Teresa (Hospital Infantil Universitario Niño Jesús), Corsino Rey Galán (Hospital Universitario Central de Asturias), Alfredo Molina Cambra (Hospital Universitario y Policlínico La Fé), Manuel González-Ripoll Garzón (Hospital Universitario Torrecardenas), Pepe Fernández-Cantalejo Padial (Hospital Universitario Fundación Jiménez Díaz), Ignacio Oulego-Erróz (Hospital Universitario de León), Laia Vega Puyal (Hospital Universitari Dexeus), Daniel Moreno (Hospital Universitario de A Coruña), Emilia Fernández Romero (Hospital Universitario Virgen de la Macarena), María García Besteiro (Corporación Sanitaria Parc Taulí), José Carlos Flores González (Hospital Universitario Puerta del Mar), Carmen Medina Monzón (Hospital General Universitario de Albacete), Beatriz Huidobro Labarga (Complejo Hospitalario Universitario de Toledo), Rosa María Hernández Palomo (Hospital Universitario Quirónsalud), Cristina Calvo Monge (Hospital Universitario Donostia), Francisco Fernández (Hospital Universitario de Salamanca), Nieves González (Hospital Universitario de Canarias), Lorena Bermudez Barrezueta, Cesar Villa Francisco (Hospital Clínico Universitario de Valladolid), Ana Abriel Molina (Hospital Materno Infantil Virgen de las Nieves), Mónica Valeron (Complejo Hospitalario Universitario Insular Materno Infantil), Ramón Hernández Rastrollo (Hospital Universitario de Badajoz), Sylvia Belda Hofheinz and Manuel Gijón Mediavilla (Hospital Universitario Doce de Octubre), José Luis Vázquez Martínez (Hospital Universitario Ramón y Cajal), Manuel Frías and Raúl Montero Yéboles (Hospital Universitario Reina Sofía), Juan Ignacio Muñoz Bonet (Hospital Clínico Universitario de Valencia), María Velázquez (Hospital Universitario La Moraleja), Inma Sánchez Ganfornina (Hospital Universitario Virgen del Rocío), Antonio Pérez Iranzo (Hospital General Universitario de Castellón), David Lozano (Hospital General La Mancha Centro), Clara Sorribes Ortí (Hospital Universitario Joan XXIII), María Soledad Holanda Peña (Hospital Universitario Marqués de Valdecilla), Miriam Gutiérrez Jimeno (Clínica Universidad de Navarra).

Authors' contributions

AGS, JCCV, MSB, ABA, JLHC and RGC designed the study and database. Spanish pediatric intensive care society working group on SARS-CoV-2 infection were responsible of patient recruitment and data collection. RGC and MSB were responsible of data collection and analysis. Manuscript draft was elaborated by AGS, JCCV, SBH, MSB, JLHC and RGC. All authors read and approved the final version of the manuscript.

Funding

This study has been funded by the Carlos III Health Institute (ISCIII) through the COVID-19 fund. Ref. COV20-00944. The founder had no role in study design, data collection, analysis and interpretation.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Registry was approved by the Institutional Review Board of the coordinating center (Hospital General Universitario Gregorio Marañón). Written informed consent was obtained from patients or from their parents before data collection.

Consent for publication

Non applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Hospital Infantil Universitario Niño Jesús, Madrid, Spain. ² Hospital Universitario Son Espases, Palma, Spain. ³ Hospital Universitario 12 de Octubre, Madrid, Spain. ⁴ Hospital Universitario Vall D'Hebron, Barcelona, Spain. ⁵ Paediatric Intensive Care Unit, Hospital General Universitario Gregorio Marañón, Calle Doctor Castelo 47, 28007 Madrid, Spain. ⁶ Hospital Regional Universitario de Málaga, Málaga, Spain. ⁷ Hospital Universitario Sant Joan de Deu, Esplugues de Llobregat, Spain. ⁸ Hospital Universitario de Burgos, Burgos, Spain. ⁹ Hospital Universitario Virgen de La Salud, Toledo, Spain. ¹⁰ Hospital Universitario Ramón Y Cajal, Madrid, Spain. ¹¹ Clínica Universidad de Navarra, Pamplona, Spain. ¹² Complejo Asistencial Universitario de León, León, Spain. ¹³ Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain. ¹⁴ Hospital General Universitario de Albacete, Albacete, Spain. ¹⁵ Hospital General

Universitario de Alicante, Alicante, Spain. ¹⁶ Hospital Universitario Marques de Valdecilla, Santander, Spain. ¹⁷ Hospital Universitario de Cruces, Barakaldo, Spain. ¹⁸ Hospital Universitario Joan XXIII, Tarragona, Spain. ¹⁹ Hospital Universitario Puerta del Mar, Cádiz, Spain. ²⁰ Hospital Universitario Quirónsalud Madrid, Pozuelo de Alarcón, Spain. ²¹ Hospital Universitario Virgen del Rocío, Sevilla, Spain. ²² Hospital Universitario Virgen de La Macarena, Sevilla, Spain. ²³ Parc Taulí Hospital Universitari, Sabadell, Spain.

Received: 30 July 2020 Accepted: 6 October 2020
Published online: 26 November 2020

References

- Lee P-I, Hu Y-L, Chen P-Y, Huang Y-C, Hsueh P-R. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect* Wei Mian Yu Gan Ran Za Zhi. 2020;53:371–2.
- Ministerio de Sanidad, Consumo y Bienestar Social - Profesionales - Situación actual Coronavirus. <https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/situacionActual.htm>.
- Ludvigsson JF. Systematic review of COVID-19 in children show milder cases and a better prognosis than adults. *Acta Paediatr Oslo Nor*. 1992;2020(109):1088–95.
- Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382:1663–5.
- Cruz A, Zeichner S. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics*. 2020;145:e20200834.
- Parri N, Lenge M, Buonsenso D, Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in pediatric emergency departments in Italy. *N Engl J Med*. 2020;383:187–90.
- Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145:e20200702.
- Tagarro A, Epalza C, Santos M, Sanz-Santaefemia FJ, Otheo E, Moraleda C, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. 2020.
- Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. *Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull*. 2020;25:2000600.
- Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. British Medical Journal Publishing Group; 2020. <https://www.bmj.com/content/370/bmj.m3249>.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet Lond Engl*. 2020;395:1054–62.
- Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr*. 2020.
- Pathak EB, Salemi JL, Sobers N, Menard J, Hambleton IR. COVID-19 in children in the United States: intensive care admissions, estimated total infected, and projected numbers of severe pediatric cases in 2020. *J Public Health Manag Pract JPHMP*. 2020;26:325–33.
- Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. RCPCH. <https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19>.
- Multisystem inflammatory syndrome in children and adolescents with COVID-19. <https://www.who.int/news-room/commentaries/detail/multi-system-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>.
- HAN Archive - 00432 | Health Alert Network (HAN). 2020. <https://emergency.cdc.gov/han/2020/han00432.asp>.
- Kids with Kawasaki disease symptoms possibly linked to COVID-19; coronavirus infection leading to critical illness in children remains very infrequent. *Am Heart Assoc*. <https://newsroom.heart.org/news/kids-with-kawasaki-disease-symptoms-possibly-linked-to-covid-19-coronavirus-infection-leading-to-critical-illness-in-children-remains-very-infrequent>.
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395:1607–8.
- Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020.
- Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. *Pediatr Cardiol*. 2020.
- Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health*. 2020.
- Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet*. 2020;395:1771–8.
- Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094.
- Belhadj Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020.
- Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Intensive Care*. 2020;10:69.
- Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. 2020.
- Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020.
- Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020.
- Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, Alonso-Cadenas JA, Gochi-Valdovinos A, González Brabin A, et al. Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. *Pediatr Infect Dis J*. 2020.
- González Cortés R, García-Salido A, Roca Pascual D, Slöcker Barrio M, de Carlos Vicente JC, SECIP Study Group on SARS-CoV-2 in Critically Ill Pediatric Patients. A multicenter national survey of children with SARS-CoV-2 infection admitted to Spanish Pediatric Intensive Care Units. *Intensive Care Med*. 2020.
- Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis*. 2005;191:499–502.
- Turnier JL, Anderson MS, Heizer HR, Jone P-N, Glodé MP, Dominguez SR. Concurrent respiratory viruses and Kawasaki disease. *Pediatrics*. 2015;136:e609–14.
- Khemani RG, Smith LS, Zimmerman JJ, Erickson S. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology. *Pediatr Crit Care Med*. 2015;16:S23–40.
- Peacock WF, Baumann BM, Bruton D, Davis TE, Handy B, Jones CW, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. *JAMA Cardiol*. 2018;3:104–11.
- Hildebrandt P, Collinson PO, Doughty RN, Fuat A, Gaze DC, Gustafsson F, et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. *Eur Heart J*. 2010;31:1881–9.
- Sachdeva R, Rice TB, Reisner B, Brundage N, Hulbert C, Kaminski A, et al. The impact of coronavirus disease 2019 pandemic on U.S. and Canadian

- PICUs. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc.* 2020.
37. Wood LE, Tulloh RMR. Kawasaki disease in children. *Heart Br Card Soc.* 2009;95:787–92.
 38. Buchdahl R, Levin M, Wilkins B, Gould J, Jaffe P, Matthew DJ, et al. Toxic shock syndrome. *Arch Dis Child.* 1985;60:563–7.
 39. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol.* 2020;146(128–136):e4.
 40. Del Valle DM, Kim-Schulze S, Huang H-H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med.* 2020.
 41. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). *Pediatrics.* 2020.
 42. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med.* 2020.
 43. Kuri-Cervantes L, Pampena MB, Meng W, Rosenfeld AM, Ittner CAG, Weisman AR, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. *Sci Immunol.* 2020;5.
 44. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev.* 2020;102567.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

