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Characteristics and management of patients with SARS-CoV2 infection admitted to pediatric intensive care units: Data analysis of the Spanish national multicenter registry

María Slöcker Barrio[1,2,3] | Sylvia Belda Hofheinz PhD[3,4] | Carmina Guitart Pardellans MD[5] | Alberto García-Salido PhD[6] | Juan Carlos de Carlos Vicente MD[7] | Maite Cuervas-Mons Tejedor MD[8] | Alexandra Hernández Yuste MD[9] | Ainhoa Jiménez Olmos MD[10] | Elvira Morteruel Arizcuren MD[11] | Maria García-Besteiro MD[12] | Cristina Calvo Monge MD[13] | Miguel Rodríguez Rubio MD[14] | David Roca Pascual MD[15] | Lorena Bermúdez Barrezueta MD[16] | Carmen Martínez Padilla MD[17] | Beatriz Huidobro Labarga MD[18] | Ignacio Oulego-Erroz PhD[19] | Sonia Sanchíz Cárdenas MD[20] | Corsino Rey Galan PhD[21] | Maria Soledad Holanda Peña PhD[22] | Pablo González Navarro MD[23] | Rafael González Cortés PhD[1,2,3] | Spanish Pediatric Intensive Care Society working group on SARS-Cov2 infection

Correspondence
Rafael González Cortés, PhD, Pediatric Intensive Care Unit, Hospital General Universitario Gregorio Marañón, Calle Dr. Castelo 47, 2ª Planta Bloque D. 28009, Madrid, Spain.
Email: rgonzalezc@ucm.es

Funding information
Instituto de Salud Carlos III; Carlos III Health Institute (ISCIII)

Abstract

Introduction: The purpose of this study is to describe the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) disease characteristics and management in children admitted to the pediatric intensive care units (PICU).

Methods: The present study was based on a national multicentric prospective registry including PICU patients with SARS-CoV2 infection or symptoms of multisystem inflammatory syndrome in children (MIS-C).

Results: A total of 298 patients were admitted to 41 different Spanish PICUs. A total of 76% of them were previously healthy. The most frequent manifestation was MIS-C (69.8%). On admission, 59.4% of patients did not have respiratory distress, and only 17.4% needed conventional mechanical ventilation (MV). The need for MV was associated with age (incidence rate ratios [IRR] 1.21, $p < .012$), pediatric sequential organ failure assessment score (p-SOFA) Score (IRR 1.12,

For affiliations refer to page 2927.

María Slöcker Barrio and Sylvia Belda Hofheinz contributed equally to this study.

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$p = .001$), and need for transfusion (IRR 4.5, $p < .004$) in MIS-C patients, and with vasoactive drug use (IRR 2.73, $p = .022$) and the diagnosis of acute respiratory distress syndrome (IRR 2.83, $p = .018$) in patients admitted for other reasons. During the first day of admission, 56% of patients met shock criteria and 50.7% needed vasoactive drugs. In MIS-C patients, their use was associated with higher p-SOFA score (IRR 1.06, $p < .001$) and with the diagnosis of shock (IRR 5.78, $p < .001$). In patients without MIS-C, it was associated with higher p-SOFA score (IRR 1.05, $p = .022$). The mortality rate was 3%, being lower in MIS-C patients compared to patients admitted for other reasons (0.5% vs. 9.4%, $p < .001$). It was also lower in previously healthy patients compared to patients with previous comorbidities (0.9% vs. 9.7%, $p < .001$).

Conclusions: Severe SARS-CoV2 infection is uncommon in the pediatric population. In our series, respiratory distress was rare, being MIS-C the most frequent cause of PICU admission related to SARS-CoV2. In most cases, the course of the disease was mild except in children with previous diseases.

KEYWORDS

ARDS, mechanical ventilation, MIS-C, pediatric intensive care, SARS-COV2

1 | INTRODUCTION

The emergence of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) by the end of 2019 and its rapid development toward a pandemic constitute some of the greatest challenges of the last decades. As it is known, its high level of infectivity and morbimortality compared to other respiratory viruses has caused a global health emergency. Although the impact of this infection has been milder in the pediatric population, cases of severe SARS-CoV2 infection in children have also been reported.[1–8]

Three years since the World Health Organization declared the SARS-CoV2 pandemic state, several pandemic waves have occurred. Natural immunization, vaccination, and changes in the virulence of the circulating variants of concern have contributed to the decrease of pandemic impact in terms of public health. However, as most countries are implementing public health strategies based on tolerating a certain degree of circulating SARS-CoV2, it is very important to analyze its behavior in populations with low incidence, such as pediatric population. Medical evidence arising from the first pandemic waves might be useful to develop future strategies to face the virus in these populations.

As it is known, most children suffering from SARS-CoV2 infection develop a mild or even asymptomatic disease. However, added to severe form of disease related with respiratory symptoms, an aggressive inflammatory postinfectious syndrome affecting children was described in May 2020. It was named pediatric multisystemic inflammatory syndrome temporally associated with SARS-CoV2 infection (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C).[9–15] Symptoms include fever with severe inflammatory response involving multiple organs and causing hemodynamic instability. According to studies conducted in children suffering from SARS-CoV2 infection, MIS-C has been described as the most frequent severe manifestation in pediatric intensive care units (PICU) patients and also as a major risk factor for PICU admission.[4,15]

As the pandemic progressed, the diagnostic and therapeutic management of pediatric severe SARS-CoV2 both similar to typical adult SARS-CoV2 (COVID-19) infection as well as other clinical presentations, has gradually evolved along with the growing body of evidence.[16,17]

Related to the SARS-CoV2 disease burden in Spanish children, the data have been inaccurate. There have been disparities between the data provided by Spanish Health Ministry and the different Health Systems of the 17 Spanish autonomous communities.[18] Added to this, most Spanish governmental records describe only aggregate numbers of patients diagnosed with SARS-CoV2 infection, hospital or intensive care admissions, or death, without mentioning any specific information or subgroup analysis regarding pediatric population. By the end of data collection of our registry (30 November 2021), data from the National Network of Public Health Surveillance described approximately one million cases on the pediatric age groups since the beginning of the pandemic.[19] According to this report, approximately 0.74% required hospital admission and 0.04% were admitted to Intensive Care Units (including adult ICUs). Thirty seven deaths (0.003%) were reported, but as mentioned before, these figures (especially those regarding child mortality) have considered to be inaccurate and have subsequently been corrected.[18]

The purpose of this study is to describe the main features of SARS-CoV2 infection in pediatric patients admitted to PICUs in

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Spain. This manuscript provides data for all patients registered in the national multicentric Registry of the Spanish Society of Pediatric Intensive Care Units (SECIP) once the data collection period was completed. Further goals include describing management strategies and characterizing the short-term course and PICU prognosis of the disease.

As it is a multicenter study involving a large number of PICUs in Spain, data from some patients included in this study have been published separately as case series.[15,20–24]

2 | MATERIALS AND METHODS

A national multicenter, observational, prospective, and descriptive registry of SARS-CoV2 patients admitted to the PICU was promoted by the SECIP Critical Care Infectious Diseases task force. Patients were included between 1 March 2020 and 30 November 2021.

Patient screening, data collection, and recording were performed by one or two investigators from each PICU. The electronic registry was developed on the electronic data record platform REDcap of the Health Research Institute of Hospital General Universitario Gregorio Marañón, as the coordinating center.

The study was approved by the Institutional Review Board of the coordinating center and complied with all applicable laws and regulations. Informed consent from patients or legal guardians was obtained for data collection.

Inclusion criteria:

- Age 0–18 years.
- Admission to the pediatric intensive care unit.
- Diagnosis of active SARS-CoV2 infection through real-time reverse-transcriptase polymerase chain reaction (RT-PCR).
- Informed consent provided by the patient or legal guardians.

After the first cases of pediatric MIS-C associated with SARS-CoV2 infection were reported in May 2022,[10] inclusion criteria were expanded to include patients who met MIS-C criteria, as defined by the Royal College of Pediatrics and Child Health. To minimize the loss of MIS-C patients, the participating units were asked to retrospectively identify and include patients who may have met MIS-C criteria during March and May 2020.

Spanish National Pediatrics Association has published and repeatedly updated different guidelines regarding management of pediatric patients with SARS-CoV2 acute infection and MIS-C. Those guidelines include specific PICU admission criteria.[16,25] According to these guidelines, PICU admission should be considered if the patient had lower respiratory tract infection meeting severe disease criteria or extrapulmonary manifestations associated with severe illness and/or progressive worsening. In patients with suspected MIS-C, hemodynamic instability, signs of hypoperfusion, need for vasoactive support, evidence of myocardial damage, altered consciousness, need for noninvasive ventilation or mechanical ventilation or evidence of progressive organ dysfunction were defined as recommended PICU admission criteria.

The following variables were collected:

- Demographic and anthropometric data.
- Medical history.
- Epidemiological information, clinical manifestations, and treatment before admission.
- Clinical status and complementary studies on admission and at Days 1, 2, 3, 4, 5, 7, 14 after admission, and at discharge.
- Treatment received during PICU admission.
- Isolation and self-protection measures adopted during PICU stay.

2.1 | Data processing and analysis

All data collected in the study were processed and anonymized following applicable laws and regulations. The database was analyzed using the IBM SPSS 26.0 for OsX (IBM Corp.) DataGraph 5.0 for OsX (Visual Data Tools Inc.). Quantitative variables without normal distribution were expressed as median value and interquartile range (IQR) as measures of central tendency and dispersion. Categorical variables were described as the number of subjects present in each category (n) with respect to the total number (N) and percentage of subjects. Cross-group comparison of quantitative variables was performed using Wilcoxon rank sum test. Cross-group comparison of qualitative variables was performed using χ^2 test and Fishers 39; test when the number of cases or expected cases in a category was <5.

Risk of mechanical ventilation and vasoactive drugs use was modeled using multivariate Poisson regression models for each subgroup of patients (those presenting with MIS-C and those admitted due to other causes). Initial set of variables was chosen according to clinical criteria, previously published evidence, and interdependency between variables. Subsequently, the most efficient set of variables was sought using the criterion of lowest Akaike Information Criterion. Incidence rate ratios and 95% confidence intervals were provided as risk measures for multivariate models. Variance inflation factor was used to evaluate collinearity. Statistical significance was set at $p < .05$.

3 | RESULTS

During the inclusion period, 298 patients were admitted to 41 PICU. Three centers recorded more than 20 cases; six centers recorded 10–20; 11 recorded 5–9; and 21 centers recorded <5 cases. The evolution in the number of weekly SARS-CoV2 cases among children and weekly PICU admissions is shown in Supporting Information: Figure 1. Baseline characteristics and previous comorbidities of the patients included in the Registry are described in Table 1 and in Supporting Information: Table 1. A total of 208 (69.8%) patients were admitted with suspected MIS-C.

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TABLE 1 Characteristics of patients included in the registry comparing patients admitted due to MIS-C and those patients admitted by other reasons.

	Total, *N* = 298[a]	Non-MIS-C, *N* = 90[a]	MIS-C, *N* = 208[a]	*p* Value
Positive RT-CRP	155 (53%)	83 (93%)	72 (36%)	**<.001**[b]
Sex (female)	112 (38%)	34 (38%)	78 (38%)	>.9[b]
Previously healthy	225 (76%)	48 (53%)	177 (85%)	**<.001**[b]
Respiratory difficulty[c]	121 (41%)	61 (68%)	60 (29%)	**<.001**[b]
ARDS[c]	25 (8.7%)	19 (22%)	6 (3.0%)	**<.001**[b]
Shock[c]	167 (57%)	7 (8.0%)	160 (78%)	**<.001**[b]
AKI[c]	50 (17%)	4 (4.5%)	46 (23%)	**<.001**[b]
Cardiac dysfunction[c]	101 (34%)	5 (5.7%)	96 (47%)	**<.001**[b]
Liver failure[c]	37 (13%)	6 (6.8%)	31 (15%)	**.047**[b]
Coagulopathy[c]	96 (35%)	8 (9.4%)	88 (47%)	**<.001**[b]
Fever[c]	264 (90%)	64 (73%)	200 (98%)	**<.001**[b]
Oxygen administration	203 (71%)	57 (66%)	146 (73%)	.3[b]
HFNC	65 (23%)	32 (37%)	33 (16%)	**<.001**[b]
NIV	49 (17%)	32 (38%)	17 (8.6%)	**<.001**[b]
CRRT	6 (2.1%)	2 (2.4%)	4 (2.0%)	>.9[d]
Transfusion	49 (18%)	25 (30%)	24 (12%)	**<.001**[b]
Abnormal chest *x*-ray	129 (51%)	61 (78%)	68 (39%)	**<.001**[b]
Abnormal cardiac US	70 (30%)	5 (10%)	65 (35%)	**.001**[b]
Vasoactive drugs use	151 (53%)	18 (21%)	133 (66%)	**<.001**[b]
Mechanical ventilation	52 (18%)	30 (34%)	22 (11%)	**<.001**[b]
Age (years)	8.9 (4.5, 12.1)	5.4 (0.5, 11.2)	9.3 (6.4, 12.4)	**<.001**[e]
Weight (kg)	32 (18, 50)	19 (7, 44)	35 (23, 50)	**<.001**[e]
PRISM III (Score)	7.0 (4.0, 11.0)	6.0 (2.5, 9.0)	7.0 (4.0, 12.0)	**.005**[e]
p-SOFA (Score)	4.0 (2.0, 6.0)	3.0 (0.0, 5.0)	5.0 (3.0, 7.0)	**<.001**[e]
PELOD (Score)	4.0 (2.0, 6.0)	2.0 (0.0, 5.0)	4.0 (2.0, 6.0)	**.003**[e]
Hemoglobin (gr/dL)	11.40 (10.30, 12.80)	12.00 (10.35, 13.15)	11.00 (10.30, 12.50)	**.045**[e]
Leukocytes (/mcL)	8080 (5500, 11,640)	7100 (4600, 10,875)	8635 (5720, 12,600)	**.009**[e]
Neutrophils (/mcL)	6200 (3670, 9826)	4080 (2404, 7064)	6820 (4624, 10,434)	**<.001**[e]
Lymphocytes (/mcL)	794 (507, 1535)	1752 (828, 3308)	688 (469, 1132)	**<.001**[e]
Platelets (1000/mcL)	157.5 (101, 239.2)	237 (176.5, 345)	125 (95.5, 192.3)	**<.001**[e]
NL ratio	7 (3, 14)	2 (1, 5)	10 (6, 17)	**<.001**[e]
D-Dimer (ng/mL)	2599 (1396, 5140)	1200 (627, 2100)	3308 (1982, 6031)	**<.001**[e]
CRP (mg/dL)	18 (8, 27)	2 (0, 14)	22 (15, 29)	**<.001**[e]
PCT (mcg/L)	3 (1, 12)	0 (0, 2)	6 (2, 16)	**<.001**[e]
Lactate (mmol/L)	1.60 (1.08, 2.23)	1.30 (0.90, 2.30)	1.60 (1.20, 2.20)	.093[e]

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRP, C reactive protein; CRRT, continuous renal replacement therapy; HFNC, high flow oxygen nasal cannula; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NIV, noninvasive ventilation; NL, neutrophil lymphocyte; PCT, procalcitonin; PELOD, pediatric logistic organ dysfunction score; PRISM-III, pediatric risk of mortality III score; p-SOFA, pediatric sequential organ failure assessment score; RT-CRP, reverse transcription polymerase chain reaction; US, ultrasound.

[a]*n* (%); Median (IQR).

[b]Pearson's χ^2 test.

[c]Clinical diagnosis established within the first 24 h of admission.

[d]Fisher's exact test.

[e]Wilcoxon rank sum test.

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One hundred and sixteen patients (38.9%) were referred to the PICU from other hospitals. A total of 69 patients (23.2%) were referred from the emergency department, whereas 61 patients (20.5%) were transferred from pediatric wards.

In 91.3% of the cases (272 patients), SARS-CoV2 infection was microbiologically confirmed, with 155 patients (52%) having a positive RT-PCR test for SARS-CoV2 in a nasopharyngeal swab or tracheal aspirate; and 180 patients (60.4%) having a positive serology test. Patients with MIS-C were less likely to have a positive RT-PCR compared to patients admitted for other reasons (35.8% vs. 93.3%, $p < .001$). Likewise, the MIS-C group of patients was more likely to have a positive serology test for SARS-CoV2 than patients admitted for other reasons (80.7% vs. 27.6%, $p < .001$).

In most cases, patients were isolated during PICU stay. Sixty three patients (21.1%) were isolated in single rooms with negative pressure and airlock. Forty patients (13.4%) were isolated in single rooms with negative pressure without airlock and 110 patients (36.9%) were isolated in closed single rooms. A total of 45 patients (15.1%) were admitted to semiopen wards. A total of 234 patients (78.5%) of all the children admitted were always accompanied by one of their parents during their PICU stay.

3.1 | Respiratory manifestations of SARS-CoV2 infection

A total of 82 patients (27.5%) presented with respiratory difficulty before PICU admission, and 97 (32.6%) had a cough. During physical examination at PICU admission, 177 patients (59.4%) did not present any signs of respiratory distress, 48 patients (16.1%) had moderate or severe respiratory distress and two patients (0.7%) were intubated and ventilated on admission.

Table 2 shows the radiologic examinations made at PICU admission. From the 52 patients (17.4%) in which chest *x*-ray (CXR) was not performed on admission, 38 (12.8%) received a thoracic ultrasound. One patient in which no CXR or thoracic ultrasound were performed received a CT scan. Two patients with no CXR abnormalities showed abnormal CT scan patterns. In 37 patients (12.4%), no radiologic examinations were performed. The need for radiologic examinations was associated with the presence of respiratory difficulty (97.6% vs. 86.2%, $p = .003$) and fever (92% vs. 64.3%, $p < .001$). There were no differences in the use of radiologic tests between patients presenting with MIS-C and those with other clinical presentations. The need for mechanical ventilation was greater in patients with abnormal CXR compared to patients without radiologic abnormalities (30.5% vs. 10.8%, $p < .001$).

Univariate analysis of factors associated with the need for mechanical ventilation is described for patients presenting with MIS-C (Table 3) and for patients admitted for other reasons (Table 4). The risk of needing mechanical ventilation was modeled for both groups using multivariate Poisson regression models (Table 5 and Supporting Information: Figure 2).

TABLE 2 Radiologic examinations performed at PICU admission.

Image modality	Findings	*n* (%)
Thoracic *x*-ray 246 (82.6%)	Normal	124 (41.6%)
	Interstitial pattern	46(15.4%)
	Unilateral alveolar infiltrates	26 (8.7%)
	Bilateral alveolar infiltrates	50 (16.8%)
	Not performed	52 (17.4%)
Thoracic CT scan 17 (5.7%)	Normal	4 (1.3%)
	Ground-glass patterns	3 (1%)
	Interstitial pattern	2 (0.7%)
	Subpleural consolidations	1 (0.3%)
	Bilateral consolidations	7 (2.3%)
	Not performed	281 (94.3%)
Thoracic ultrasound 100 (33.6%)	Pneumothorax	1 (0.3%)
	Pleural effusion	30 (10.1%)
	Atelectasis	6 (2%)
	Increased unilateral B-lines	5 (1.7%)
	Increased bilateral B-lines	54 (17.8%)
	Isolated consolidation	5 (1.7%)
	Multiple consolidations	5 (1.7%)
	Not performed	198 (66.4%)

Abbreviation: PICU, pediatric intensive care unit.

In patients requiring mechanical ventilation, the most common technique for endotracheal intubation was standard laryngoscopy (40 patients, 13.4%), whereas video-laryngoscopy was only used in nine patients (3%). Self-inflating bag and mask ventilation was used in 29 patients (55.8%) who required mechanical ventilation initiation. The majority of patients were intubated using cuffed endotracheal tubes (50/52; 96.2%) and closed suction systems for airway secretion drainage (45/52; 86.5%).

3.2 | Hemodynamic impact of SARS-CoV2 infection

On the first day of admission, 167 (56%) patients received a shock diagnosis. An echocardiogram was performed in 114 patients (38.2%), showing ventricular dysfunction in 70 (23.5%) and coronary alterations in 25 (8.4%). A total of 151 patients (50.7%) needed vasoactive drugs, with noradrenaline being the most frequently used agent (95 patients—31.9%) followed by adrenaline (57 patients—19.1%).

The univariate analysis for the risk factors associated with the use of vasoactive drugs in MIS-C patients and in patients admitted due to other reasons are described in Tables 3 and 4. Multivariate

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TABLE 3 Characteristics of MIS-C patients comparing mechanical ventilation use and need of vasoactive drugs.

		Mechanical ventilation			Vasoactive drugs		
	Total *N* = 200[a]	No *N* = 177[a]	Yes *N* = 22[a]	*p* Value	No *N* = 67[a]	Yes *N* = 133[a]	*p* Value
Positive RT-CRP	71 (36%)	65 (37%)	5 (23%)	.2[b]	29 (43%)	42 (32%)	.11[b]
Sex (female)	76 (38%)	66 (37%)	8 (36%)	>.9[b]	20 (30%)	56 (42%)	**.092**[b]
Previously healthy	171 (86%)	150 (85%)	19 (86%)	>.9[c]	54 (81%)	117 (88%)	.2[b]
Respiratory difficulty[d]	57 (28%)	51 (29%)	6 (27%)	.9[b]	17 (25%)	40 (30%)	.5[b]
ARDS[d]	6 (3.1%)	0 (0%)	6 (29%)	**<.001**[c]	0 (0%)	6 (4.7%)	.10[c]
Shock[d]	158 (79%)	133 (76%)	22 (100%)	**.005**[c]	29 (43%)	129 (97%)	**<.001**[b]
AKI[d]	45 (23%)	32 (18%)	13 (59%)	**<.001**[c]	4 (6.0%)	41 (31%)	**<.001**[b]
Cardiac dysfunction[d]	94 (47%)	74 (42%)	20 (91%)	**<.001**[b]	17 (25%)	77 (58%)	**<.001**[b]
Liver failure[d]	31 (16%)	24 (14%)	7 (32%)	.055[c]	9 (13%)	22 (17%)	.5[b]
Coagulopathy[d]	87 (48%)	72 (44%)	13 (65%)	.082[b]	29 (47%)	58 (48%)	.9[b]
Fever[d]	196 (98%)	174 (98%)	21 (95%)	.4[c]	65 (97%)	131 (98%)	.6[c]
Oxygen administration	144 (72%)	123 (70%)	20 (91%)	**.038**[b]	36 (55%)	108 (81%)	**<.001**[b]
HFNC	33 (17%)	27 (15%)	5 (23%)	.4[c]	8 (12%)	25 (19%)	.2[b]
NIV	17 (8.7%)	14 (8.0%)	3 (14%)	.4[c]	1 (1.5%)	16 (12%)	**.011**[b]
CRRT	3 (1.5%)	1 (0.6%)	3 (14%)	.004[c]	0 (0%)	3 (2.3%)	.6[c]
Transfusion	23 (12%)	13 (7.6%)	11 (50%)	**<.001**[c]	2 (3.0%)	21 (17%)	**.005**[b]
Abnormal chest x-ray	68 (40%)	56 (38%)	12 (55%)	.13[b]	18 (35%)	50 (42%)	.4[b]
Abnormal cardiac US	64 (35%)	52 (32%)	12 (57%)	**.022**[b]	7 (12%)	57 (45%)	**<.001**[b]
Vasoactive drugs	130 (66%)	108 (62%)	22 (100%)	**<.001**[b]	-	-	-
Mechanical ventilation	22 (11%)	-	-	-	0 (0%)	22 (17%)	**<.001**[b]
Age (years)	9.4 (6.6–12.4)	9.1(6.3–11.9)	11.4 (9.5–13.0)	**.015**[e]	7.3 (5.2–10.9)	10.0 (7.3–12.6)	**<.001**[e]
Weight (kg)	36 (23–50)	35 (22–50)	46 (38–56)	**.019**[e]	28 (18–41)	40 (26–53)	**<.001**[e]
PRISM III (Score)	7.0 (4.0–12.0)	7.0 (4.0–11.0)	14.0 (13.0–18.0)	**<.001**[e]	4.0 (2.0–9.0)	9.0 (5.0–13.2)	**<.001**[e]
p-SOFA (Score)	5.0 (3.0–7.0)	4.0 (2.0–6.0)	8.0 (7.0–10.0)	**<.001**[e]	2.0 (1.0–3.0)	6.0 (4.0–7.0)	**<.001**[e]
PELOD (Score)	4.0 (3.0–6.0)	4.0 (2.0–6.0)	7.0 (5.0–9.0)	**<.001**[e]	3.0 (1.0–4.5)	5.0 (3.0–7.0)	**<.001**[e]
Hemoglobin (gr/dL)	11.00 (10.30-12.50)	11.00 (10.22–12.50)	11.05 (10.57–12.12)	.9[e]	11.20 (10.30–12.20)	11.00 (10.30–12.57)	.7[e]
Leukocytes (/mcL)	8620 (5690-12,600)	8170 (5555–11,598)	12,850 (7600–16,450)	**.007**[e]	7530 (5050–10,350)	9100 (6655–12,812)	**.027**[e]
Neutrophils (/mcL)	6819 (4657-10,475)	6591(4416–9883)	10790 (5695–14,833)	**.005**[e]	5978 (3660–8390)	7384 (5444–10,955)	**.006**[e]
Lymphocytes (/mcL)	688 (467–1147)	715 (473–1162)	563 (357–748)	**.047**[e]	1049 (570–1520)	629 (405–900)	**<.001**[e]
Platelets (1000/mcL)	124 (94–192)	122 (96.5–189.7)	129.5 (83–198.5)	.7[e]	126 (101–217)	123 (88.7–189.2)	.14[e]
NL ratio	10 (6–18)	9 (5–16)	18 (11–26)	**<.001**[e]	6 (3–10)	12 (7–20)	**<.001**[e]
D-Dimer (ng/mL)	3315 (1965–6096)	3352 (1968–5570)	3122 (2257–11,522)	.3[e]	2710 (1710–4924)	3759 (2144–7272)	**.024**[e]
CRP (mg/dL)	22 (16–29)	22 (15–28)	24 (18–30)	.4[e]	22 (14–28)	22 (16–29)	.5[e]

(Continues)

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TABLE 3 (Continued)

		Mechanical ventilation			Vasoactive drugs		
	Total $N = 200$[a]	No $N = 177$[a]	Yes $N = 22$[a]	p Value	No $N = 67$[a]	Yes $N = 133$[a]	p Value
PCT (mcg/L)	6 (2–16)	4 (2–12)	28 (13–45)	**<.001**[e]	3 (1–7)	8 (2–27)	**<.001**[e]
Lactate (mmol/L)	1.63 (1.20–2.20)	1.55 (1.10–2.05)	2.90 (1.90–6.18)	**<.001**[e]	1.30 (1.00–1.83)	1.75 (1.20–2.42)	**.003**[e]

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRP, C reactive protein; CRRT, continuous renal replacement therapy; HFNC, high flow oxygen nasal cannula; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NIV, noninvasive ventilation; NL, neutrophil lymphocyte; PCT, procalcitonin; PELOD, pediatric logistic organ dysfunction score; PRISM-III, pediatric risk of mortality III score; p-SOFA, pediatric sequential organ failure assessment score; RT-CRP, reverse transcription polymerase chain reaction; US, ultrasound.

[a]*n* (%); Median (IQR).

[b]Pearson's χ^2 test.

[c]Fisher's exact test.

[d]Clinical diagnosis established within the first 24 h of admission.

[e]Wilcoxon rank sum test.

regression models for each group are described in Table 5 and Supporting Information: Figure 3.

3.3 | Drug therapy

During PICU stay, 87.1% of patients received intravenous antibiotics. Cefotaxime (29.2%), ceftriaxone (12.4%), and clindamycin (12.4%) were the ones most frequently used. Intravenous antibiotic therapy was more frequent in patients admitted with suspected MIS-C compared to patients admitted for other reasons (91.5% vs. 76.5%, $p = .001$).

Regarding immunomodulatory treatment, 231 patients (77.5%) were treated with corticosteroids 169 (56.7%) were treated with intravenous immunoglobulin and 149 patients (50%) received combined treatment with corticosteroids and immunoglobulins. Tocilizumab was administered to 29 patients (9.7%).

Antiviral treatments administered included lopinavir/ritonavir in 30 patients (10.1%), remdesivir in 14 (4.7%), and hydroxychloroquine in 46 (15.4%). None of the patients admitted after 1 June 2020, received hydroxychloroquine.

3.4 | Clinical course

Figure 1 describes the treatments administered. The median length of PICU stay was 4 days (IQR 2–7), without any difference between patients admitted for MIS-C and other patients ($p = .732$). PICU stay was prolonged in patients requiring mechanical ventilation (9 days, IQR 6–16), compared to patients who did not (4 days, IQR 2–6), $p < .001$. Likewise, PICU stay was longer in the patients requiring vasoactive drugs (5 days, IQR 3–7.8 days), compared to those who did not (3 days, IQR 2–6 days) $p = .001$.

Nine patients died while PICU treatment (3%). No differences on age, weight, or severity score on admission were observed between the patients who died and the survivors. Mortality was higher in patients admitted for reasons other than MIS-C in comparison to those who were admitted with MIS-C (9.4% vs. 0.5% $p < .001$). Mortality was also higher in patients with pre-existing conditions than in previously healthy patients (9.7% vs. 0.9%, $p < .001$). Seven patients who died had severe pre-existing conditions and three were receiving immunosuppressive therapy. Supporting Information: Table 2 describes the features of patients who died during PICU admission.

4 | DISCUSSION

In our study, in line with previous research, severe cases occurred mostly in patients older than 4 years, unlike other respiratory viral infections, which usually affect younger patients.[26] According to our results, MIS-C was the most frequent severe manifestation of SARS-CoV2 infection in Spanish children, accounting for more than two-thirds of the patients requiring PICU. Primary respiratory manifestations appeared only in approximately a quarter of our patients. Some studies have tried to define the incidence of MIS-C among pediatric patients. However, despite its low incidence,[27] MIS-C still accounted for an important proportion of pediatric patients requiring intensive care in relation to SARS-CoV2 infection.[5,8]

This study was carried out with the participation of most of the PICU in Spain. Data collection was extensive and included detailed information about clinical presentation, laboratory and radiologic tests, management, and clinical course among others. This might provide a different point of view compared to other reports. Our study shows similar severe pediatric COVID-19 phenotypes to those described by other authors, but also some differences regarding epidemiology, patient characteristics, and management.

Prospective data analysis was useful to estimate the incidence of severe SARS-CoV2 infection among pediatric patients in Spain. As described in other countries, the incidence of severe SARS-CoV2

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TABLE 4 Characteristics of Non-MIS-C patients comparing mechanical ventilation use and need of vasoactive drugs.

		Mechanical ventilation			Vasoactive drugs		
	Total $N = 87$[a]	No $N = 57$[a]	Yes $N = 30$[a]	p Value	No $N = 67$[a]	Yes $N = 18$[a]	p Value
Positive RT-CRP	81 (93%)	54 (95%)	27 (90%)	.4[b]	65 (97%)	14 (78%)	**.017**[b]
Sex (female)	33 (38%)	24 (42%)	9 (30%)	.3[c]	26 (39%)	7 (39%)	>.9[c]
Previously healthy	46 (53%)	36 (63%)	10 (33%)	**.008**[c]	39 (58%)	6 (33%)	.060[c]
Respiratory difficulty[d]	59 (68%)	36 (63%)	23 (77%)	.2[c]	44 (66%)	14 (78%)	.3[c]
ARDS[d]	19 (22%)	3 (5.3%)	16 (55%)	**<.001**[c]	9 (13%)	10 (59%)	**<.001**[b]
Shock[d]	7 (8.2%)	3 (5.3%)	4 (14%)	.2[b]	2 (3.0%)	4 (25%)	**.011**[b]
AKI[d]	4 (4.7%)	2 (3.5%)	2 (6.9%)	.6[b]	2 (3.0%)	2 (12%)	.22
Cardiac dysfunction[d]	81 (94%)	55 (96%)	26 (90%)	.3[b]	1 (1.5%)	4 (24%)	**.005**[b]
Liver failure[d]	6 (7.0%)	4 (7.0%)	2 (6.9%)	>.9[b]	4 (6.0%)	2 (12%)	.6[b]
Coagulopathy[d]	8 (9.6%)	3 (5.6%)	5 (17%)	.12[b]	4 (6.2%)	4 (24%)	.056[b]
Fever[d]	63 (73%)	43 (77%)	20 (67%)	.3[c]	48 (72%)	14 (78%)	.8[b]
Oxygen administration	56 (66%)	36 (64%)	20 (69%)	.7[c]	45 (67%)	11 (61%)	.6[c]
HFNC	31 (36%)	17 (30%)	14 (48%)	.10[c]	22 (33%)	9 (50%)	.2[c]
NIV	32 (38%)	18 (32%)	14 (50%)	.10[c]	23 (34%)	9 (53%)	.2[c]
CRRT	2 (2.4%)	0 (0%)	2 (7.1%)	.11[b]	0 (0%)	2 (12%)	**.039**[b]
Transfusion	25 (30%)	9 (16%)	16 (57%)	**<.001**[c]	15 (22%)	10 (59%)	**.003**[c]
Abnormal chest x-ray	60 (78%)	33 (70%)	27 (90%)	**.041**[c]	44 (75%)	15 (88%)	.3[b]
Abnormal cardiac US	5 (11%)	3 (10%)	2 (11%)	>.9[b]	2 (5.9%)	3 (25%)	.10[b]
Vasoactive drugs	18 (21%)	2 (3.6%)	16 (55%)	**<.001**[c]	-	-	-
Mechanical ventilation	29 (34%)	-	-	-	13 (19%)	16 (89%)	**<.001**[c]
Age (years)	4.4 (0.4–10.6)	7.4 (0.8–11.3)	1.3 (0.4–9.9)	.4[e]	6.9 (0.7–11.1)	0.6 (0.3–9.6)	.3[e]
Weight (kg)	18 (6–41)	23 (9–42)	10 (6–35)	.4[e]	23 (8–44)	7 (5–35)	.2[e]
PRISM III (Score)	6.0 (2.0–9.0)	5.0 (0.0–8.0)	7.0 (4.0–13.0)	**.024**[e]	5.0 (0.0–8.2)	6.5 (3.0–12.2)	.11[e]
p-SOFA (Score)	3.0 (0.0–4.8)	2.0 (0.0–3.8)	4.0 (3.0–8.1)	**<.001**[e]	3.0 (0.0–4.0)	7.0 (4.0–9.0)	**.003**[e]
PELOD (Score)	2.0 (0.0–5.0)	1.0 (0.0–2.5)	5.0 (4.0–6.0)	**<.001**[e]	2.0 (0.0–4.0)	5.0 (4.5–9.0)	**.003**[e]
Hemoglobin (gr/dL)	12.00 (10.25–13.10)	12.60 (10.95–13.25)	11.20 (9.42–12.53)	**.018**[e]	12.15 (10.43–13.17)	11.10 (9.90–12.50)	.12[e]
Leukocytes (/mcL)	7100 (4600–10750)	7005 (4300–11025)	7100 (5300–10400)	.8[e]	7005 (4350–10938)	7560 (5340–10625)	.5[e]
Neutrophils (/mcL)	4056 (2377–7062)	3410 (2241–6629)	4629 (3065–7912)	.2[e]	3796 (2335–6899)	5024 (3171–8077)	.3[e]
Lymphocytes (/mcL)	1752 (821–3367)	1550 (814–3404)	1830 (876–3072)	.8[e]	1622 (854–3308)	2304 (500–3417)	>.9[e]
Platelets (1000/mcL)	237 (178.5–342.5)	239 (159.5–343)	235 (197–327)	.7[e]	238.5 (161.5–346.5)	233 (188–252)	.8[e]
NL ratio	2.1 (1.1–5.0)	1.9 (1.1–4.7)	2.5 (1.3–6.5)	.4[e]	2.1 (1.4–4.5)	2.4 (1.1–9.1)	.5[e]
D-Dimer (ng/mL)	1195 (618–2100)	1120 (600–1912)	1205 (762–2204)	.7[e]	1076 (600–1895)	1905 (1000–2518)	.2[e]
CRP (mg/dL)	2 (0–15)	3 (0–16)	2 (1–8)	.8[e]	2 (0–14)	3 (1–14)	.5[e]

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TABLE 4 (Continued)

	Total $N = 87$[a]	Mechanical ventilation			Vasoactive drugs		
		No $N = 57$[a]	Yes $N = 30$[a]	*p* Value	No $N = 67$[a]	Yes $N = 18$[a]	*p* Value
PCT (mcg/L)	0.2 (0.1–2.1)	0.2 (0.1–2.7)	0.3 (0.1–1.6)	.3[e]	0.2 (0.1–1.3)	0.4 (0.1–2.2)	.13[e]
Lactate (mmol/L)	1.30 (0.90–2.38)	1.50 (1.00–2.00)	1.10 (0.70–2.40)	.2[e]	1.37 (0.90–2.22)	1.25 (0.93–2.40)	.7[e]

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRP, C reactive protein; CRRT, continuous renal replacement therapy; HFNC, high flow oxygen nasal cannula; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NIV, noninvasive ventilation; NL, neutrophil lymphocyte; PCT, procalcitonin; PELOD, pediatric logistic organ dysfunction score; PRISM-III, pediatric risk of mortality III score; p-SOFA, pediatric sequential organ failure assessment score; RT-CRP, reverse transcription polymerase chain reaction; US, ultrasound.

[a]*n* (%); Median (IQR).

[b]Pearson';s χ^2 test.

[c]Fisher's exact test.

[d]Clinical diagnosis established within the first 24 h of admission.

[e]Wilcoxon rank sum test.

TABLE 5 Multivariate poisson regression models assessing the risk of mechanical ventilation and vasoactive drugs use in patients admitted due to MIS-C and patients admitted for other reasons.

Risk of mechanical ventilation in MIS-C patients				
Variable	**IRR**	**95% CI**	***p* Value**	**VIF**
Transfusion	4.50	1.54, 12.5	**.004**	1.4
Abnormal cardiac US	2.59	1.01, 7.28	.053	1.2
Age (years)	1.21	1.05, 1.42	**.012**	1.2
p-SOFA (Score)	1.12	1.04, 1.20	**.001**	1.3
Risk of mechanical ventilation in Non-MIS-C patients				
Variable	**IRR**	**95% CI**	***p* Value**	**VIF**
ARDS[a]	2.83	1.20, 6.82	**.018**	1.3
Vasoactive drugs use	2.73	1.16, 6.51	**.022**	1.3
Risk of vasoactive drugs use in MIS-C patients				
Variable	**IRR**	**95% CI**	***p* Value**	**VIF**
Age (years)	1.04	0.99, 1.09	.140	1.0
p-SOFA (Score)	1.06	1.02, 1.10	**<.001**	1.0
Risk of vasoactive drugs use in Non MIS-C patients				
Variable	**IRR**	**95% CI**	***p* Value**	**VIF**
Shock[a]	5.78	2,41, 19.0	**<.001**	1.0
p-SOFA (Score)	1.05	1.00, 1.09	**.022**	1.0

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; IRR, incidence rate ratio; MIS-C, multisystem inflammatory syndrome in children; p-SOFA, pediatric sequential organ failure assessment score; US, ultrasound; VIF, variance inflation factor.

[a]Clinical diagnosis established within the first 24 h of admission.

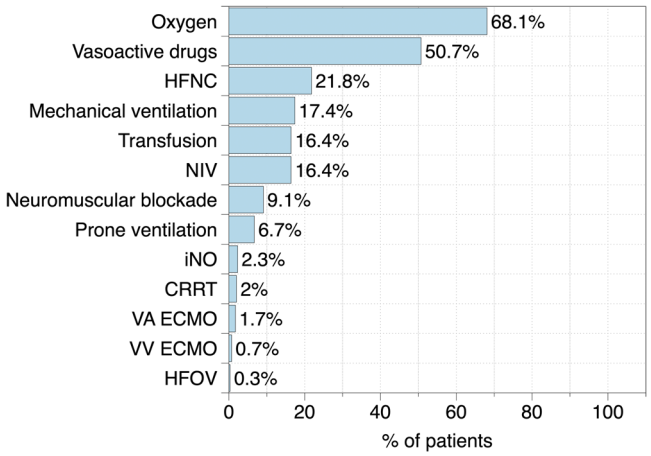

FIGURE 1 Treatments administered to the study patients during their PICU stay. CRRT, continuous renal replacement therapy; HFNC, high flow nasal cannula; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; NIV, noninvasive ventilation; VA ECMO, veno-arterial extracorporeal membrane oxygenation; VV ECMO, veno-venous extracorporeal membrane oxygenation.

infection was significantly lower in the pediatric population compared to adults.

Since the beginning of the pandemic, the presence of pre-existing comorbidities was identified as a risk factor for the development of severe disease.[28,29] Although the PICU Spanish Registry shows that previously existing comorbidities were associated with a poorer prognosis, most PICU patients in our country were previously healthy. Data from other countries such as the United Kingdom, the United States, or Canada described a higher prevalence of comorbidities (50%–85%) among patients admitted to PICU.[1,4,30–32] This difference might be explained by the high prevalence of MIS-C among our patients, which mostly occurred in previously healthy patients. Differences might also be related to other causes including different PICU admission criteria and different timeframes of data collection.

In our study, a significant proportion of children (more than a third) were transferred from their hospital to a PICU in a different hospital. This highlights the need for more efficient interhospital transfer and medical emergency systems for special situations such as potentially infectious diseases in pediatric patients.[33] However, our study also illustrates that pediatric patients who require PICU

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admission due to SARS-CoV2 infection were not always in the infectious phase, especially those presenting with MIS-C. This could influence patient isolation and accompaniment policies for PICU patients in the presence of high SARS-CoV2 prevalence rates.

According to our data, severe respiratory distress secondary to SARS-CoV2 was infrequent. The need for mechanical ventilation was rare, whereas cardiovascular involvement with shock and myocardial dysfunction requiring the use of vasoactive drugs was considerably more frequent. Risk factors for mechanical ventilation and vasoactive drugs use have been described for patients presenting with MIS-C and for patients admitted for other causes. These factors were similar to those reported by other authors.[31,32]

Our study provides information about the use of respiratory support and tracheal intubation. The frequent use of conventional laryngoscopy, which could pose a high risk for the professional performing the technique, is noteworthy. Further studies are necessary to understand why most techniques used to minimize the risk for SARS-CoV2 infection during airway handling in adults have not been widely adopted during children intubation in our country, despite international recommendations.[17,34]

Half of the patients included showed hemodynamic instability on admission. Despite the high incidence of shock, ventricular dysfunction was only observed in a small proportion of patients. Distributive shock was the most important cause of hemodynamic instability in children with severe SARS-CoV2 infection, as described by other groups.[13,23,24,35]

The use of intravenous antibiotic treatment was a common practice, especially in patients admitted with suspected MIS-C. The difficulty of differentiating this syndrome from sepsis or toxic shock syndrome secondary to a bacterial infection forced the early use of antibiotic therapy for these patients, although it is not included in all recommendations.[16]

Immunomodulatory treatment has proven to be crucial for the treatment of typical manifestations of COVID-19 and MIS-C. In our series, corticosteroids were the most commonly used, followed by immunoglobulins. The use of other immunomodulatory drugs was considerably more limited. Likewise, the use of specific antiviral treatments was anecdotal, and its use was limited to very selected patients.[36] Following current recommendations, other drugs such as hydroxychloroquine or lopinavir/ritonavir are no longer indicated, given the limited scientific evidence supporting its use. In opposition to the vast evidence regarding SARS-CoV2 vaccination in children which has been described in several randomized controlled trials,[37–39] evidence related to acute management of SARS-CoV2 disease is scarce and mainly derived from observational studies like ours.[30,40–44] Considering the low prevalence of severe SARS-CoV2 infection in children, it is difficult to obtain treatment recommendations supported by large randomized clinical trials. However, further evidence regarding the best management of these patients could be based in data aggregation of multiple observational studies like the present one.

The clinical course of the patients included in our series was generally favorable, with a low mortality, as previously reported in other series of PICU patients with SARS-CoV2 infection.[1,4,45,46] As described in other pediatric and adult studies, previous comorbidities are clear risk factors for mortality due to SARS-CoV2.[29,46]

Network multicenter clinical trials promoted by scientific societies such as our study have contributed to generate a large body of knowledge about this novel coronavirus. The data obtained in this study have contributed to identify mortality report and estimation errors in our country.[18] More robust tools are needed for a standardized collection and analysis of epidemiological data both at national and international level.

5 | LIMITATIONS

Although this multicenter prospective registry contains data of most PICU patients with SARS-CoV2 infection in Spain during the first 2 years of the pandemic, small proportion of cases may be missing. Thus, some pediatric patients may have been admitted to adult ICU in the absence of a PICU. In addition, some patients may have not been included due to parental refusal to participate in the study. However, the number of patients refusing to participate in the study was minimal (four patients according to participating units). As mentioned in the results section, some centers contributed with fewer cases compared to others. A total of 15% of patients were recruited by centers participating with <5 cases. This may reflect the specific characteristics of Spain, where there are important geographic variations in the pediatric population. Patient characteristics and management should not significantly differ between different size centers except for some specific therapies that were seldom used such as extracorporeal membrane oxygenation, which might not be universally available.

The observational design of the study added to variability in clinical practice and changes in therapeutic management recommendations make drawing conclusions about the efficacy of treatments and measures difficult.

Another limitation of this study is the absence of long-term follow-up of the patients included in the Registry. Although mortality from SARS-CoV2 infection in the pediatric population is low, this study only collects data from pediatric patients who presented severe manifestations during the acute or subacute phase of infection. Understanding the long-term course of these patients, especially in relation to the development of chronic symptoms secondary to COVID-19 is a challenge that we will try to answer in the coming months.

Finally, it is worth mentioning that data collection was limited in time, as it was completed by the end of November 2021. Therefore, the impact of vaccination on the incidence and clinical manifestations of SARS-CoV2 infection is unknown.

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6 | CONCLUSIONS

Severe SARS-CoV2 infection was significantly less frequent in children than in adults in Spain. MIS-C was the most frequent presentation of SARS-CoV2 infection in children requiring intensive care, and specific respiratory involvement was infrequent. Despite the existing evidence that undesirable outcomes are more frequent in adults, the Spanish experience demonstrates that a small proportion of patients can still become very sick as a result of COVID-19 infection and its sequelae. In the pediatric population, mortality was very low and associated with the presence of severe pre-existing conditions.

Members of the SECIP Study group on SARS-COV2 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, Madrid, Spain)
- Juan Carlos de Carlos (Hospital Universitari Son Espases, Palma de Mallorca, Spain)
- Maite Cuervas-Mons Tejedor and Pedro Pablo Oyágüez Ugidos (Complejo Asistencial Universitario de Burgos, Burgos, Spain)
- Iolanda Jordan and Carmina Guitart (Hospital Sant Joan de Déu, Barcelona, Spain)
- Sonia Sanchiz Cárdenas (Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain)
- Javier Gil Antón and Elvira Morteruel Arizcuren (Hospital Universitario de Cruces, Barakaldo, Spain)
- Belén Joyanes (Hospital Clínico Universitario San Carlos, Madrid, Spain)
- Ainhoa Jiménez Olmos (Hospital Universitario Miguel Servet, Zaragoza, Spain)
- Antonio Rodríguez Núñez and Javier Trastoy Quintela (Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain)
- Alexandra Hernández Yuste (Hospital Materno Infantil Universitario de Málaga, Malaga, Spain)
- Laura Díaz Munilla (Complejo Hospitalario de Navarra, Pamplona, Spain)
- Carlos Solis Reyes (Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain)
- Laura Medina Ramos (Hospital General Universitario de Alicante, Alicante, Spain)
- David Roca Pascual and Joan Ballcels (Campus Hospitalario Vall d'Hebron de Barcelona, Spain)
- Mario Sánchez Fernández (Hospital Universitari Dr. Josep Trueta, Girona, Spain)
- Alberto García-Salido, Inés Leóz Gordillo, Montserrat Nieto Moro, Amelia Martínez de Azagra Garde, and María Ángeles García Teresa (Hospital Infantil Universitario Niño Jesús, Madrid, Spain)
- Corsino Rey Galán (Hospital Universitario Central de Asturias, Oviedo, Spain)
- Alfredo Molina Cambra (Hospital Universitario and Policllinico La Fé, Valencia, Spain)
- Manuel González-Ripoll Garzón (Hospital Universitario Torrecardenas, Almería, Spain)
- Pepe Fernández-Cantalejo Padial (Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain)
- Ignacio Oulego-Erroz (Hospital Universitario de León, León, Spain)
- Laia Vega Puyal (Hospital Universitari Dexeus, Barcelona, Spain)
- Daniel Moreno Leira and Raquel Diaz Soto (Hospital Universitario de A Coruña, A Coruña, Spain)
- Emilia Fernández Romero (Hospital Universitario Virgen de la Macarena, Sevilla, Spain)
- María García Besteiro (Corporación Sanitaria Parc Taulí, Sabadell, Spain)
- José Carlos Flores González (Hospital Universitario Puerta del Mar, Cádiz, Spain)
- Carmen Medina Monzón (Hospital General Universitario de Albacete, Albacete, Spain)
- Beatriz Huidobro Labarga (Complejo Hospitalario Universitario de Toledo, Toledo, Spain)
- Rosa María Hernández Palomo (Hospital Universitario Quirónsalud, Madrid, Spain)
- Cristina Calvo Monge (Hospital Universitario Donostia, San Sebastián, Spain)
- Francisco Fernández (Hospital Universitario de Salamanca, Salamanca, Spain)
- Nieves González (Hospital Universitario de Canarias, La Laguna, Spain)
- Lorena Bermudez Barrezueta (Hospital Clínico Universitario de Valladolid, Valladolid, Spain)
- Ana Abril Molina (Hospital Materno Infantil Virgen de las Nieves, Granada, Spain)
- Mónica Valerón (Complejo Hospitalario Universitario Insular Materno Infantil, Las Palmas de Gran Canaria, Spain)
- Ramón Hernández Rastrollo (Hospital Universitario de Badajoz, Badajoz, Spain)
- Sylvia Belda Hofheinz and Manuel Gijón Mediavilla (Hospital Universitario Doce de Octubre, Madrid, Spain)
- José Luis Vázquez Martínez (Hospital Universitario Ramón and Cajal, Madrid, Spain)
- Manuel Frias and Raúl Montero Yéboles (Hospital Universitario Reina Sofía, Córdoba, Spain)
- Juan Ignacio Muñóz Bonet (Hospital Clínico Universitario de Valencia, Valencia, Spain)
- María Velázquez (Hospital Universitario La Moraleja, Madrid, Spain)
- Inma Sánchez Ganfornina (Hospital Universitario Virgen del Rocío, Sevilla, Spain)
- Antonio Pérez Iranzo (Hospital General Universitario de Castellón, Castellón, Spain)
- David Lozano (Hospital General La Mancha Centro, Alcazar de San Juan, Spain)
- Clara Sorribes (Hospital Universitario Joan XXIII, Tarragona, Spain)

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- María Soledad Holanda Peña (Hospital Universitario Marqués de Valdecilla, Santander, Spain)
- Miriam Gutiérrez Jimeno (Clínica Universidad de Navarra, Pamplona, Spain)
- Carmen Martínez Padilla (Hospital Universitario de Jaén, Jaén, Spain)
- Miguel Rodríguez Rubio, Guillermo Santos Simarro, and Cristina Schüffelmann (Hospital Universitario La Paz, Madrid, Spain)

AUTHOR CONTRIBUTIONS

María Slöcker Barrio: Conceptualization; data curation; formal analysis; writing—original draft; investigation; writing—review and editing; methodology. **Sylvia Belda Hofheinz**: Conceptualization; data curation; writing—original draft; investigation; writing—review and editing. **Carmina Guitart Pardellans**: Investigation; data curation; writing—review and editing. **Alberto García-Salido**: Data curation; investigation; writing—review and editing; conceptualization; writing—original draft; methodology. **Juan Carlos de Carlos Vicente**: Conceptualization; methodology; data curation; investigation; writing—original draft; writing—review and editing. **Maite Cuervas-Mons Tejedor**: Data curation; investigation; writing—review and editing. **Alexandra Hernández Yuste**: Data curation; investigation; writing—review and editing. **Ainhoa Jiménez Olmos**: Data curation; investigation; writing—review and editing. **Elvira Morteruel Arizcuren**: Data curation; investigation; writing—review and editing. **Maria García Besteiro**: Data curation; investigation; writing—review and editing. **Cristina Calvo Monge**: Data curation; investigation; writing—review and editing. **Miguel Rodríguez Rubio**: Data curation; investigation; writing—review and editing. **David Roca Pascual**: Data curation; investigation; writing—review and editing. **Lorena Bermúdez Barrezueta**: Data curation; investigation; writing—review and editing. **Carmen Martínez Padilla**: Data curation; investigation; writing—review and editing. **Beatriz Huidobro Labarga**: Data curation; investigation; writing—review and editing. **Ignacio Oulego Erroz**: Data curation; investigation; writing—review and editing. **Sonia Sanchíz Cárdenas**: Data curation; investigation; writing—review and editing. **Corsino Rey Galan**: Data curation; investigation; writing—review and editing. **Maria Soledad Holanda Peña**: Data curation; investigation; writing—review and editing. **Pablo González Navarro**: Methodology; formal analysis; data curation; writing—review and editing. **Rafael González Cortés**: Conceptualization; methodology; software; data curation; investigation; validation; formal analysis; supervision; funding acquisition; visualization; project administration; writing—original draft; writing—review and editing.

AFFILIATIONS

[1]Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Development Origin Network (RICORS) RD21/0012/0011, Instituto de Salud Carlos III, Madrid, Spain

[2]Pediatric Intensive Care Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[3]Public Health and Maternal and Child Department, Complutense University of Madrid, Madrid, Spain

[4]Pediatric Intensive Care Unit, Hospital Universitario 12 de Octubre, Madrid, Spain

[5]Pediatric Intensive Care Unit, Hospital Universitario Sant Joan de Déu, Barcelona, Spain

[6]Pediatric Intensive Care Unit, Hospital Universitario Niño Jesús, Madrid, Spain

[7]Pediatric Intensive Care Unit, Hospital Universitario Son Espases, Palma de Mallorca, Spain

[8]Pediatric Intensive Care Unit, Complejo Asistencial Universitario de Burgos, Burgos, Spain

[9]Pediatric Intensive Care Unit, Hospital Materno Infantil Universitario de Málaga, Málaga, Spain

[10]Pediatric Intensive Care Unit, Hospital Universitario Miguel Servet, Zaragoza, Spain

[11]Pediatric Intensive Care Unit, Hospital Universitario de Cruces, Baracaldo, Spain

[12]Pediatric Intensive Care Unit, Corporación Sanitaria Parc Taulí, Sabadell, Spain

[13]Pediatric Intensive Care Unit, Hospital Universitario Donostia, San Sebastián, Spain

[14]Pediatric Intensive Care Unit, Hospital Universitario La Paz, Madrid, Spain

[15]Pediatric Intensive Care Unit, Campus Hospitalario Vall d'Hebron, Barcelona, Spain

[16]Pediatric Intensive Care Unit, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

[17]Pediatric Intensive Care Unit, Hospital Universitario de Jaén, Jaén, Spain

[18]Pediatric Intensive Care Unit, Complejo Hospitalario Universitario de Toledo, Toledo, Spain

[19]Pediatric Intensive Care Unit, Complejo Asistencial Universitario de León, León, Spain

[20]Pediatric Intensive Care Unit, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

[21]Pediatric Intensive Care Unit, Hospital Universitario Central de Asturias, Oviedo, Spain

[22]Pediatric Intensive Care Unit, Hospital Universitario Marqués de Valdecilla, Santander, Spain

[23]Methodology and Biostatistics Unit, Gregorio Marañón Health Research Institute, Madrid, Spain

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Alberto García-Salido http://orcid.org/0000-0002-8038-7430
Maite Cuervas-Mons Tejedor https://orcid.org/0000-0002-8998-9534
Ainhoa Jiménez Olmos https://orcid.org/0000-0002-9965-3401
Miguel Rodríguez Rubio https://orcid.org/0000-0001-9145-4718
Lorena Bermúdez Barrezueta http://orcid.org/0000-0002-3607-0516
Ignacio Oulego-Erroz https://orcid.org/0000-0002-9653-954X
Maria Soledad Holanda Peña https://orcid.org/0000-0001-8868-8601
Pablo González Navarro https://orcid.org/0000-0002-6906-6556
Rafael González Cortés http://orcid.org/0000-0002-3259-7898

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