SARS-COV-2 Infection in Children in Emergency Departments in Spain
A Multicenter Study

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Objectives: The first cases of infection by SARS-CoV-2 in the Spanish pediatric population were reported on early March 2020. Although most were mild or asymptomatic, new forms of clinical presentation and severity were reported with the evolution of the pandemic. We aimed to describe demographics, clinical features, and management of children with COVID-19 treated in Spanish emergency departments (EDs).

Methods: A multicenter registry including 15 pediatric EDs was carried out. Patients younger than 18 years with confirmed acute SARS-CoV2 infection diagnosed between March and August 2020 were included.

Results: Three hundred ninety-five patients were analyzed (median age, 4.3 years). Fifty-five (13.9%) had comorbidities, and 141 (35.7%) a household contact with confirmed COVID-19. The most reported symptoms were fever (85.2%) and cough (41.7%). Fifty (12.5%) were asymptomatic. Seventeen (4.9%) were not well-appearing at presentation. Children underwent a blood test in 26.7% and a chest X-ray in 21.4%; findings were often unremarkable. Symptomatic treatment was prescribed to 80%; 6 (1.7%) received antiviral treatment. Seventy-one (20.6%) were hospitalized, and 3 (0.9%) were admitted to the intensive care unit; no patient died. The main clinical diagnoses were fever without a source (38%) and upper respiratory tract infection (32.2%); 4 (1.1%) presented a multisystem inflammatory syndrome.

Conclusions: Most pediatric COVID-19 cases in EDs during the first months of the pandemic were healthy, well-appearing children, presenting with fever +/− respiratory symptoms. In a significant number of cases, there was household transmission. Most children were managed as outpatients with symptomatic treatment, being exceptional the evolution to a serious illness.

Key Words: COVID-19, SARS-CoV-2, 2019 novel coronavirus

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At the end of December 2019, a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan city, China. This virus causes the coronavirus disease 2019 (COVID-19), and its rapid spread led to the declaration of pandemic by the World Health Organization (WHO) on March 11, 2020.[1] The first large studies of COVID-19 in children in China[2,3] described that most children had mild symptoms or were asymptomatic when infected with SARS-CoV-2 and generally had better outcomes than adult population. Series published in the next months were consistent with these findings.[4,5] However, since late April 2020, several scientific societies and pediatricians from different European countries and the United States warned about a novel and often severe presentation of SARS-CoV-2 infection in children, known as multisystem inflammatory syndrome temporally associated with COVID-19 (MIS-C).[6–9]

In Spain, the first cases of pediatric COVID-19 were reported on March 4, 2020. Although several case series, including a limited number of patients, were published during the first peak of the pandemics,[10,11] global data regarding the epidemiologic and clinical characteristics, as well as the management of infected children diagnosed at the emergency departments (EDs) in Spain are still scarce.[12]

The main objectives of the study were as follows: (1) to describe the demographics and clinical features of COVID-19 in pediatric population presenting to ED in Spain and (2) to describe their management and evolution.

METHODS

Study Design and Setting

The Infectious Diseases Working Group of the Spanish Society of Pediatric Emergencies promoted the creation of a multicentric registry of pediatric patients with confirmed SARS-CoV-2 infection diagnosed at the Spanish EDs. Patients were enrolled starting from March 1, 2020.

Patient Identification and Inclusion Criteria

Patients younger than 18 years with confirmed acute SARS-CoV-2 infection diagnosed at the participating EDs from March 1, 2020, to August 31, 2020, were included. For patients with recurrent visits at the ED after SARS-CoV-2 infection diagnosis, only the initial visit was included.

Confirmed acute SARS-CoV-2 infection was defined as follows: (1) positive nucleic acid test by real-time polymerase chain reaction (RT-PCR) in nasopharyngeal or oropharyngeal swabs/aspirates and/or (2) positive result for IgM in conventional or rapid serological tests.

Data Collection

Researchers at each participating ED were responsible for identifying those patients who fulfilled inclusion criteria during

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the study period. Specific electronic questionnaires were completed on-line for all children included. Data were deidentified. Before the initiation of the study questionnaires were distributed to the site researchers who checked them for clarity and content. The completed questionnaires were then sent electronically to the principal investigator.

Collected data included patient demographics, associated comorbidities, exposure history, onset and clinical signs and symptoms at presentation, general appearance in the ED, microbiological SARS-CoV-2 tests performed, additional laboratory and imaging investigations performed in the ED, treatments received at the ED, hospitalization status, final clinical diagnosis, and outcomes data. General appearance was systematically evaluated using the Pediatric Assessment Triangle[13] in all the participating EDs; children were considered not well-appearing if they had an abnormal Pediatric Assessment Triangle at the ED. Criteria for SARS-CoV-2 testing and additional complementary examinations were according to the protocol of each participating center.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics for Windows (version 25.0, Armonk, NY). Descriptive statistics were reported in terms of absolute frequencies or rates for categorical variables and in terms of median value with an interquartile range (IQR: 25th percentile-75th percentile) for continuous variables. Statistical comparisons were carried out using the Pearson χ^2 test or Fisher exact test for categorical variables and the Student's t-test or Mann-Whitney *U* test for continuous variables. The confidence interval was calculated at 95%. The *P* values <0.05 were considered significant.

The registry was approved by the ethical committee of the coordinating center (Hospital Sant Joan de Déu Barcelona; PIC-152-20). Approval for the study and for data sharing with the coordinating institution and with the centralized data center was granted by the institutional review board at each participating institution. Because identities remained anonymous and no intervention was performed on patients, informed consent was not required.

RESULTS

During the study period 15 pediatric EDs, including secondary and tertiary levels of care, from 9 regions of Spain participated in the Registry. Patients were attended up to 18 years old in 3 participating EDs, up to 16 years old in 2, up to 15 years old in 8, and up to 14 years old in the remaining 2 EDs. A total of 395 children younger than 18 years with confirmed acute SARS-CoV-2 infection diagnosed at the participating EDs were included between March 1, 2020, and August 31, 2020. Real-time polymerase chain reaction was the test used for diagnosis in all cases except 5 who underwent a serological test (Fig. 1). Demographic and clinical characteristics of the study subjects are reported in Table 1.

Among the 395 included patients, 345 (87.3%) had SARS-CoV-2 suggestive symptoms with a median duration of 24 hours (IQR, 12–48 hours) at diagnosis. In relation to the 50 asymptomatic children, the test was indicated before surgery or admission for 28 (56%) and because close contact with a confirmed COVID-19 case for the remaining 22 (44%). One hundred forty-one (35.7%) patients had 1 or more household contacts with confirmed COVID-19, mainly one of the parents (103, 73.1%). In addition, 60 (15.2%) children had a symptomatic household contact with no diagnostic test performed.

Chest x-ray (CXR) was performed in the ED for 74 (21.4%) of 345 children with COVID-19 and blood tests to 92 (26.7%). The main radiology and laboratory findings are detailed in Table 2. Additional microbiological tests were indicated for 105 (30.4%) children: blood culture (76; 22%) and urine culture (56; 16.2%) were the main bacterial tests performed and 33 (9.6%) children were tested for several viruses in nasopharyngeal specimens.

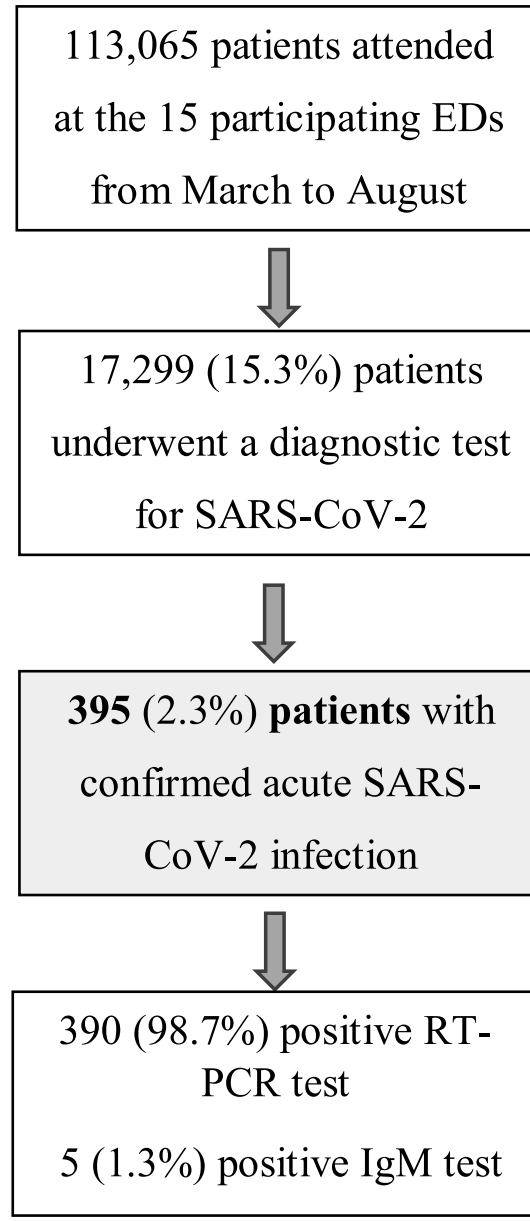

FIGURE 1. Study flowchart.

Overall, 242 (70.2%) patients with COVID-19 were given the clinical diagnosis of febrile syndrome or upper respiratory tract infection. Twenty-two (6.4%) patients were diagnosed of pneumonia; 18 (81.8%) of them were admitted to hospital, representing the 25.4% cases of inpatients. Four (1.6%) children were diagnosed of MIS-C; they were all hospitalized. In addition, 10 (2.9%) patients had a bacterial coinfection: urinary tract infection (UTI) (7 cases, one of them with associated *Escherichia coli* bacteremia) was the most prevalent; among patients under 3 months of age urine culture was performed in 29 of 38 cases and was positive in 3 (10.3%) cases. The other bacterial coinfection identified were gastroenteritis by *Campylobacter jejuni*, acute group A b-hemolytic streptococcal pharyngitis and pneumonia with a positive RT-PCR

for *Mycoplasma pneumoniae*, 1 case each. A viral coinfection was identified in 3 (0.9%) children; the viruses detected were adenovirus and enterovirus (same patient), bocavirus and respiratory syncytial virus (RSV).

Treatment other than antipyretics was prescribed at the ED to 69 (20%) patients. Antibiotics (50; 14.5%) followed by bronchodilators (21; 6.1%), steroids (14; 4.1%), and oxygen therapy (14; 4.1%) were the main treatments indicated. Only 4 (1%) children, all of them with pneumonia, were given anticoronavirus treatment at the ED: hydroxychloroquine associated with lopinavir/ritonavir (2 cases) and hydroxychloroquine or lopinavir/ritonavir alone (1 case each).

Overall, 71 (20.6%) patients were hospitalized, with a median length of stay of 4 days (IQR, 2–7 days). This percentage decreased significantly throughout the study period, from 57.7% in March to 5.5% in August (Fig. 2). Three (0.9%) children required admission to intensive care unit (ICU) (4.2% of those hospitalized): 2 patients aged 5 and 16 years with bronchopneumonia needed noninvasive ventilation and a patient aged 4 years diagnosed with MIS-C required inotropic support because of myocardial injury. None of these 3 patients had an underlying condition. No inpatients died nor had sequelae at discharge. Among the 274 (79.4%) children managed as outpatients, 5 (1.8%) required subsequent hospital admission; all did well. Significant differences were found among outpatients and inpatients (Table 3). Of note, inpatients were significantly younger than outpatients. Among hospitalized cases, 26 (36.6%) were infants younger than 3 months: 22 (84.7%) of them were diagnosed with fever without source or upper respiratory tract infection and none had a lower respiratory tract infection nor required ICU admission.

TABLE 1. Demographic and Clinical Characteristics of the 395 Patients With Confirmed Acute SARS-CoV-2 Infection

Characteristics	
Age, mo	52.0 (11.0–122.1)
Male sex	201 (50.9%)
Comorbidities	55 (13.9%)
• Immunosuppression	19 (4.8%)
• Respiratory disease	15 (3.8%)
• Cardiovascular disease	12 (3.0%)
• Neuromuscular disease	8 (2.0%)
• Encephalopathy	7 (1.8%)
• Metabolic disorder	2 (0.5%)
• Other	8 (2.0%)
Confirmed case in household	141 (35.7%)
SARS-CoV-2 infection suggestive symptoms	345 (87.3%)
Signs and symptoms	
• Fever (temperature ≥37.5°C)	294 (85.2%)
• Cough	144 (41.7%)
• Nausea/vomiting/diarrhea	88 (25.5%)
• Upper respiratory symptoms/rhinorrhoea	52 (15.1%)
• Sore throat	44 (12.8%)
• Breathing difficulty	41 (11.9%)
• Headache	39 (11.3%)
• Abdominal pain	35 (10.1%)
• Fatigue	34 (9.9%)
• Myalgia	21 (6.1%)
• Refusal to eat	12 (3.5%)
• Cutaneous manifestations	10 (2.9%)
• Dysgeusia	10 (2.9%)
• Anosmia	8 (2.3%)
• Irritability	9 (2.6%)
• Thoracic pain	9 (2.6%)
• Other	20 (5.8%)
Not well-appearing at the ED	17 (4.9%)

Categorical variables are reported in terms of absolute frequencies and rates and continuous variables in terms of median value with IQR.

TABLE 2. Main Radiology and Laboratory Findings at the ED

Chest x-ray	74 (21.4%)
• Normal	52 (70.3%)
• Lobar consolidation	13 (17.6%)
• Multilobar consolidation	4 (5.4%)
• Perihiliar infiltrates	5 (6.7%)
Blood test	92 (26.7%)
• WBC count (per mm^3)	7660 (5305–10400)
• WBC >15,000/mm^3	9/92 (9.8%)
• WBC < 5,000/ mm^3	18/92 (19.6%)
• Lymphocyte count (per mm^3)	2400 (1300–4200)
• Lymphocytes <1200/mm^3	19/92 (20.6%)
• C-reactive protein (mg/L)	4.5 (1.0–38.4)
• C-reactive protein >40 mg/L	20/92 (21.7%)
• Procalcitonin (ng/mL)	0.12 (0.07–0.24)
• Procalcitonin >0.5 ng/mL	10/69 (14.5%)
• D-dimer (mg/dL)	477 (228–1104)
• D-dimer >500 mg/dL	10/23 (43.5%)
• NT-proBNP (ng/L)	1644 (264–8739)
• NT-proBNP >350 ng/L	4/6 (66.7%)

Categorical variables are reported in terms of absolute frequencies and rates and continuous variables in terms of median value with IQR.

WBC, white blood cell count; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

DISCUSSION

To our knowledge, our study including 395 patients is one of the largest case series of pediatric patients with confirmed acute SARS-CoV-2 infection in Spain. Our findings add to the current knowledge of clinical presentation, management, and evolution of COVID-19 in children diagnosed at the ED.

Median age of the included patients was 4.3 years and 50.9% were boys. In 2 systematic reviews by Patel[4] and Mantavoni et al,[14] including 2914 and 2855 pediatric patients, median age varied from 1 to 11 years with a mean age of 6.9 years, respectively, and no gender predominance was neither found. Of note, in our series inpatients were significantly younger than outpatients. This finding is consistent with the study by Desai et al,[15] including 627 pediatric patients (5.6 years vs 8.2 years; $P < 0.001$). Although in our study nearly 40% of inpatients were very young infants, most of them had mild symptoms and were probably hospitalized because of their age, so we couldn't conclude that this group of patients are more likely to have a higher severity of the disease.

A significant number of patients had known exposure with a confirmed or suspected COVID-19 person, mainly their parents. This result supports that most pediatric patients infected with SARSCoV-2 have been probably part of a family cluster outbreak or had a household positive contact.[2,4,10,16–18] Although most

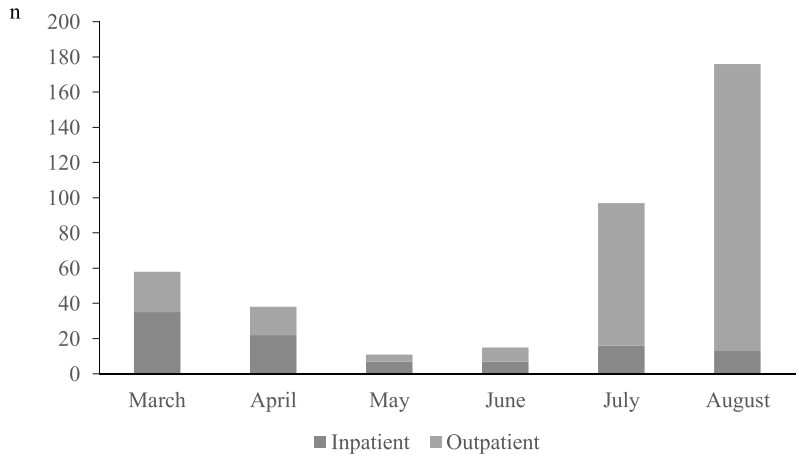

FIGURE 2. Distribution of cases and hospitalization rate during the study period.

children had no associated comorbidities, the percentage was clearly higher among inpatients, reaching 31%. Nevertheless, the lack of knowledge and fear of severe disease in those children at the beginning of the pandemic probably led to a more aggressive management, including preventive hospitalization. None of the 3 patients who required ICU admission had an underlying condition. This result must be taken with caution because of the low number of patients who were admitted to ICU. In a multicenter study carried out in 47 pediatric ICU in Spain,[19] 22 (29.7%) of the 74 included children were not previously healthy; of note, this percentage was significantly higher for those patients without MIS-C related to those with MIS-C (48.3% vs 17.8%; $P = 0.005$).

Consistent with previous studies,[4,14,20] fever associated with respiratory symptoms was the most prevalent clinical presentation at the time of COVID-19 diagnosis. In contrast, specific symptoms described in adult population, as dysgeusia or anosmia, were reported in less than 3% of patients.

A CXR was performed at the ED only to 21.4% children and a unilateral consolidation was the main presentation reported for those patients with abnormal findings. In a study carried out in a tertiary pediatric hospital in Madrid (Spain) including 44 children,[21] a consolidation was the initial finding in 18.2% of cases, whereas peri bronchial cuffing (86.3%) and ground glass opacities (50%) were the most common findings identified. Unfortunately, in our study, these categories were not included as options for radiological data question, so we cannot report about these findings. Specific data about chest computed tomography (CT) scan performance was not recorded because it was rarely used. In contrast, most of the publications regarding children were based on CT; overall, normal results (32–45.1%) and ground glass opacities (29.4%–36%) were the most frequent imaging features.[4,16,22]

Most of patients who underwent a blood test at the ED had no anomalies or were not relevant. Lymphopenia was reported in nearly 20% of our cases; this percentage is significantly higher than those reported by other authors.[3,23,24] This difference could be partially explained because these studies included predominantly asymptomatic or mild forms of COVID-19, whereas in our series, only symptomatic patients were analyzed and blood tests were mainly performed on admitted children, who were expected to have a higher proportion of moderate or severe cases. This finding is consistent with studies in adult population, where low lymphocyte count has been correlated with severity of infection, with up to 80% lymphopenia rate in infected critically ill subjects.[25,26] Similar to Henry et al[23] and Simsek Uzunoglu et al,[27] C-reactive protein and procalcitonin values were elevated in a limited number of patients; again, this result may be explained by the limited number of severe COVID-19 at presentation included and also by the low proportion of bacterial coinfection detected. Unfortunately, we could not draw conclusions from the rest of the analytical parameters recorded because they were only requested from a very limited number of patients.

A bacterial coinfection was identified in less than 3% cases, mainly positive urine cultures, and a viral coinfection in less than 1%. This result must be interpreted with caution because of the limited number of patients who underwent microbiological tests. Of note, among urine cultures performed on patients less than 3 months of age, 10.3% were positive. This result is consistent with the study by Blázquez-Gamero et al,[28] who found a prevalence of

TABLE 3. Significant Differences Among Outpatients and Inpatients

	Outpatients (n = 274)	Inpatients (n = 71)	*P*
Age, mo	58.5 (13.5–120)	15.5 (1.3–108)	<0.001
Comorbidities	25 (9.1%)	22 (31%)	<0.001
Duration of symptoms at diagnosis, h	24 (12–48)	42 (17.2–96)	0.020
Not well-appearing at the ED	3 (1.1%)	14 (19.7%)	<0.001
Complementary examinations* at the ED	82 (29.9%)	67 (94.4%)	<0.001
Treatment prescription	26 (9.5%)	43 (60.6%)	<0.001

*Complementary examinations included chest radiography, blood tests, and/or microbiological tests.

Categorical variables are reported in terms of absolute frequencies and rates and continuous variables in terms of median value with IQR.

concomitant UTI in 7.5% of 27 infants younger than 3 months of age with COVID-19 who presented with fever without source. Accordingly, detection of SARS-CoV-2 should not lead to automatically rule out UTI in this group of patients. Different European studies carried out between March and May 2020 reported a viral coinfection in 5% to 7.5% of children; enterovirus and rhinovirus were the most frequent pathogens identified.[10,20,29,30] Although it would be expected that coinfection rates with influenza or RSV would be higher during the winter months when outbreaks of both viruses mostly occur, low levels of RSV and influenza activity were detected in Europe during the 2020/2021 season; public health measures implemented to reduce transmission of coronavirus disease and ecological niche competition were factors proposed as possible explanations.[31,32]

According with previous reviews,[15,16] symptomatic treatment alone was used in most cases, particularly in children managed as outpatients, whereas less than 1% of patients were given antiviral agents or hydroxychloroquine at the ED. During the period of the study none of the experimental treatment for SARS-CoV-2 infection had shown a clear benefit in children, so there were no specific recommended or were restricted to severe ill cases.[33,34]

Overall, 20.6% patients were admitted to hospital. According to the study by Martín Espín et al[12] carried out in Madrid during the first and second waves of pandemic, hospitalization rate decreased significantly throughout the study period, from nearly 60% in March to only 5.5% in August. The initial high percentage of admission could be justified by inclusion criteria for testing; in Spain at the beginning of the study period diagnostic tests were only performed in those children with compatible respiratory symptoms and criteria for hospitalization or underlying medical conditions.[33] Less than 1% required admission to ICU and no deaths were registered. Our data confirmed that critical illness and fatality rates in children are very low.[2,4,14–16,19,35] Unfortunately, long covid entity was not yet identified in the study period, so we couldn't monitor these cases.

Along with other authors,[2,4,10,11,36] febrile syndrome and upper respiratory tract infection accounted the final clinical diagnoses in nearly three-fourth of global patients, and pneumonia was the main reason for both hospitalization and admission to ICU. Again, this result must be interpreted with caution because only patients with confirmed acute SARS-CoV-2 infection were included; therefore, several cases of MIS-C, often associated with severe illness, had been probably missed because a significant number of them have negative SARS-CoV-2 PCR tests.[18,37,38]

This study had several limitations. First, not all regions of Spain were represented in the Registry, so the results could not be exactly extrapolated to the whole country. Secondly, because on the design of the study only patients diagnosed at hospital's ED were included, so it could be a bias of selection to moderate-severe cases; nevertheless, most cases in our series had mild disease, as they were managed as outpatients with symptomatic treatment only. Thirdly, not all participating ED attended patients up to 16–18 years of age; therefore, cases in older adolescents could be partially underestimated. Fourth, although children were mostly screened according to Spanish Public Health recommendations, criteria for SARS-CoV-2 testing differed somewhat by hospital, region and over time; however, standardization of these protocols was beyond the control of the study. Finally, because of the low number of patients who were admitted to ICU we could not explore factors associated to critical illness.

CONCLUSIONS

Our study revealed that most patients with acute SARS-CoV-2 infection diagnosed at the EDs in Spain during the first months of pandemic were well-appearing healthy children consulting with fever associated or not to respiratory symptoms. A significative number were part of a family cluster outbreak. Laboratory and radiology findings were mainly non-specific. Most cases were managed as outpatients with symptomatic treatment with a favorable outcome; nevertheless, a few patients presented severe illness, with no deaths registered.

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