

# Clinical and Epidemiological Features of Pediatric Patients with COVID-19 in a Tertiary Pediatric Hospital

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**Abstract.** *Background:* Coronavirus disease 2019 (COVID-19) affects people of any age with high mortality and morbidity in adults older than 65 years. Reports on pediatric cases highlighted those children generally develop milder symptoms than adults or are asymptomatic. We aimed to assess the epidemiological and clinical data of children and adolescents with SARS-CoV-2 infection to improve pediatric COVID-19. *Methods:* We retrospectively analyzed clinical and epidemiological features of patients with SARS-CoV-2 infection hospitalized at the Pediatric Hospital of Pavia, Italy, between February 1, 2020, to April 30, 2021. *Results:* 71 patients aged 0-16 years were included; 33 (46%) females and 38 (54 %) males. Thirty-three (46%) patients had comorbidities, such as obesity and hematological diseases. Thirty-one children (44%) were exposed to COVID-19-positive household members. Nine (12.7 %) patients were asymptomatic, whereas 57 (80.3%) had a mild-moderate disease. Only five (7%) showed a severe or critical disease, and two patients required ICU admission. The most frequent symptoms were fever (76%), loss of appetite (26%), gastrointestinal symptoms (19%), and cough (19%). Chest X-ray was performed in 42 patients showing lung abnormalities in more than half of symptomatic patients. The most common laboratory features were lymphopenia and eosinopenia associated with high levels of inflammation markers. *Conclusions:* This study confirmed that COVID-19 has a mild course in children compared to adults. Most of the enrolled children were asymptomatic or had a mild-moderate disease. Patients with comorbidities were more prone to develop clinical complications. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Keywords:** COVID-19, children, SARS-CoV-2 infection, comorbidities, eosinopenia.

## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease that has spread worldwide since December 2019, starting from a Chinese outbreak in Wuhan, in the Ubei region. The causative agent of the infection, declared a pandemic by the World Health Organization (WHO) on March 11, 2020, was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). The first Italian case of COVID-19 was detected on February 21 in Codogno, a little town near Milan in Lombardy (3). Recent data

show that children and adolescents younger than 19 years with COVID-19 constitute 22,7% (2.966.901 patients) of the total population in Italy on March 9, 2022, with a mortality rate < 0,1% (4). The most frequent symptoms of COVID-19 are related to the respiratory system and include fever, sneezing, rhinitis, cough, dyspnea, chest pain, and respiratory distress. However, asthenia, myalgia, abdominal pain, nausea, diarrhea, vomiting, ageusia, anosmia, and headache are also common among infected patients. According to current literature, COVID-19 is more severe in adults older than 60 with a history of comorbidities (4-8).

Moreover, COVID-19 tends to manifest in milder forms and more rarely with severe or critical manifestations in children. The reactive immune system, the lower expression of ACE 2 receptor, and the balance between inflammatory response and immune tolerance are some hypotheses explaining these epidemiological characteristics in children (9-11). Affected children often present an upper airway infection, while bilateral pneumonia is a common clinical manifestation in adults (7,12-14).

WHO recently identified a new pediatric consequence defined as a multisystem inflammatory syndrome of children (MIS-C). This critical form of COVID-19 has been reported in different areas, including Italy, and shows many features common to other inflammatory diseases, such as Kawasaki syndrome (15-17).

To date, only a few pediatric studies have focused on the hospital course of the infection. Therefore, this study aims to describe demographic, epidemiologic, and clinical features (symptoms, laboratory, and radiological data) of children hospitalized for COVID-19, evaluating the disease course.

## Materials and methods

### *Study design and data collection*

A retrospective, monocentric, and observational study was realized at the Pediatric Clinic of "IRCCS Policlinico San Matteo" Pavia, Italy, from February 1, 2020, to April 30, 2021. The study included patients younger than 18 years with a laboratory-confirmed diagnosis of COVID-19. Diagnosis of COVID-19 was confirmed by performing the reverse-transcription polymerase chain reaction (RT-PCR) test to detect viral nucleic acid from nasopharyngeal swabs. Patients were then hospitalized according to their clinical conditions, age, and social background. At the admission, patients were isolated in a dedicated hospital department, according to standard prevention protocol. The clinical picture was evaluated according to the classification of severity proposed by the WHO (Table 1) (17).

This study was approved by the Ethical Com-

mittee (protocol number: 34401/2020). All enrolled patients provided written informed consent.

We collected the patient's characteristics, including past medical history, presenting symptoms, medications, radiological findings, and lab parameters. We also assessed age, gender, ethnic group, history of exposure to infected people, underlying comorbidities (heart diseases, chronic respiratory diseases, malignancy, immune deficiencies, obesity, prematurity, neurologic disorders). Laboratory investigations included complete blood count, reactive-C protein, procalcitonin, lactate dehydrogenase, liver function (alanine aminotransferase, aspartate aminotransferase), coagulation tests (prothrombin time, D-dimer), and cardiac enzymes. Chest X-ray was performed as a first-line evaluation. Chest CT was performed only in a minority of cases with severe-critical disease.

### *Statistical analysis*

Continuous variables were expressed as means and standard deviation, while categorical variables were reported as numbers and percentages. Frequencies were tabulated for categorical variables. Bivariate analysis of categorical variables was conducted with the chi-square test or Fisher's exact test. The Student's t-test was used to compare continuous variables. A p-value lower than 0.05 was considered significant. All analyses were performed using GraphPad Prism 8 for Mac, Version 8.4.3 (GraphPad Software, San Diego, CA, USA).

## Results

A total of 71 children hospitalized for COVID-19 were enrolled in the study. The cohort was composed of 38 (54%) males, and 73% of patients were Caucasian. Demographic characteristics are reported in Table 2. The median age was  $5.0 \pm 5.5$  years (min. one month and max. 16 years). Most hospitalized patients were younger than one year (41%). School-aged children were significantly more predisposed to asymptomatic infection ( $p = 0.04$ ). Epidemiological analysis revealed that 44% of patients had close contact with infected people at home, school, and host communities.

**Table 1.** Clinical classification of COVID-19 disease according to WHO (17).**1. ASYMPTOMATIC INFECTION**

Positive test for SARS-CoV-2.

No symptoms and radiological evidence of chest involvement.

**2. MILD DISEASE**

Mild symptoms

No radiological evidence of viral pneumonia or hypoxia.

**3. MODERATE DISEASE**

Adolescent with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia and hypoxia (SpO<sub>2</sub> ≥ 90% on room air).

Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia and hypoxia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40.

Diagnosis is based on clinical features; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

**4. SEVERE DISEASE**

Adolescent with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO<sub>2</sub> < 90% on room air.

Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:

- Central cyanosis or SpO<sub>2</sub> < 90%; severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.

- Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40.

While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

**5. CRITICAL DISEASE**

- Acute respiratory distress syndrome (ARDS);

- Sepsis in children: suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count.

- Septic Shock in children: any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.

- Acute thrombosis: acute venous thromboembolism (i.e., pulmonary embolism), acute coronary syndrome, acute stroke.

- MIS-C, preliminary case definition: children and adolescents 0–19 years of age with fever > 3 days AND two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ultrasound findings or elevated troponin/NT-proBNP); evidence of coagulopathy, acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain); AND elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

**Table 2.** Demographic features of patients with COVID-19.

Demographic characteristics	Total (n=71)	Asymptomatic cases (n= 9)	Symptomatic cases (n=62)	p value
Male, n (%)	38 (54)	4 (44)	34 (55)	0.72
Age, mean SD	5.0 5.5	8.5 5.8	4.5 5.3	<b>0.04</b>
< 1 year, n (%)	29 (41)	2 (22)	27 (44)	0.30
1-5 years, n (%)	15 (21)	0 (0)	15 (24)	0.19
6-10 years, n (%)	12 (17)	4 (44)	8 (13)	<b>0.04</b>
11-15 years, n (%)	9 (13)	1 (11)	8 (13)	>0.99
> 15 years, n (%)	6 (9)	2 (22)	4 (7)	0.16
Contact with infected people, n (%)	31 (44)	4 (44)	27 (44)	>0.99
Caucasian, n (%)	52 (73)	5 (55)	47 (76)	0.23

**Table 3.** Symptoms.

Symptoms	All symptomatic cases n= 62	Mild cases n=50	Moderate cases n=7	Severe/Critical cases n=5
Fever, n (%)	47 (76)	36 (72)	6 (86)	5 (100)
Lack of appetite, n (%)	16 (26)	13 (26)	2 (29)	1 (20)
Rhinitis, n (%)	15 (24)	11 (22)	3 (43)	1 (20)
Cough, n (%)	12 (19)	6 (12)	4 (57)	1 (20)
Diarrhea, n (%)	12 (19)	10 (20)	1 (14)	1 (20)
Vomit, n (%)	9 (15)	7 (14)	0 (0)	1 (20)
Dyspnea, n (%)	4 (7)	3 (6)	0 (0)	1 (20)
Headache, n (%)	4 (7)	3 (6)	1 (14)	0 (0)
Abdominal pain, n (%)	4 (7)	3 (6)	0 (0)	1 (20)
Asthenia and myalgia, n (%)	6 (10)	6 (8)	0 (0)	0 (0)
Skin lesions, n (%)	4 (7)	4 (8)	0 (0)	0 (0)
Pharyngitis, n (%)	3 (5)	3 (6)	0 (0)	0 (0)
Seizures, n (%)	3 (5)	2 (4)	0 (0)	1 (20)

According to WHO guidelines, 12.7% of patients were asymptomatic, 70.4% showed mild disease, 9.9% a moderate disease, 1.4% a severe disease, and 5.6% a critical course of COVID-19. Overall, most of the cases were symptomatic (87.3%), despite extremely varied clinical presentation (Table 3). The most common symptom was fever (76%). Loss of appetite was the second most common symptom, found in 26% of symptomatic children.

Thirty-three (46,5%) patients had underlying conditions (Table 4).

A significant correlation was demonstrated between a more severe COVID-19 and previous pathologies, particularly with obesity/overweight, immune deficit, and heart disease. Patients underwent laboratory and radiological tests (Table 5 and Table 6). Lymphopenia ( $p= 0.01$ ), eosinopenia ( $p= 0.01$ ),

elevated RCP ( $p= 0.006$  and  $p= 0.03$ ), elevated procalcitonin ( $p= 0.02$ ) were significantly related to the risk of severe/critical disease. Radiological tests were normal in 30% of cases. Lung interstitial accentuation was founded in 59% of cases, bronchitis in 5%, and pneumonia in 18%, including bilateral pneumonia in 2%. Chest CT was normal in 33% of patients and pathological in 66% of cases, finding interstitial pneumonia in 33% of children. The most common chest ultrasounds findings were white lung (29%) and pleural irregularity (57%). The course of the disease varied according to the severity. 99% of patients had a complete recovery from illness and were successfully discharged. Two children (3%) needed intensive care during the admission and were transferred to ICU; of these, one died for severe respiratory complications. Less severe complications occurred during

**Table 4.** Comorbidities.

Comorbidity	Total (n=71)	Symptomatic cases n=9	Mild cases n=50	Moderate cases n=7	Severe/Critical cases n=5
Obesity/overweight, n (%)	15 (46,0)	2 (40,0)	7 (33,0)	2 (100)	4 (80,0)
Immunodeficiency, n (%)	11 (33,0)	3 (60,0)	6 (29,0)	0	2 (40,0)
Prematurity, n (%)	6 (18,0)	0	6 (29,0)	0	0
Chronic respiratory disease, n (%)	4 (12,0)	0	4 (19,0)	0	0
Heart disease, n (%)	4 (12,0)	0	2 (10,0)	0	2 (40,0)
Hemoglobinopathies, n (%)	3 (9,0)	1 (20,0)	1 (5,0)	0	1 (20,0)
Neurological disease, n (%)	3 (9,0)	1 (20,0)	2 (10,0)	0	0

**Table 5.** Laboratory tests.

Laboratory tests	Asymptomatic cases n=50	Mild cases n=50	Moderate cases n=7	Severe/Critical cases n=5	p value	
Lymphocytes (cell/ $\mu$ l), mean SD	4 $\pm$ 3.4	3.8 $\pm$ 2.6	4.2 $\pm$ 2.9	0.9 $\pm$ 0.4	<b>0.01</b>	D-B
Eosinophil (cell/ $\mu$ l), mean SD	0.2 $\pm$ 0.1	0.1 $\pm$ 0.3	0.04 $\pm$ 0.04	0.02 $\pm$ 0.04	<b>0.01</b>	A-D
RCP (mg/dL), mean SD	0.16 $\pm$ 0.2	2.4 $\pm$ 5.0	1.2 $\pm$ 0.8	13.1 $\pm$ 17	<b>0.006, 0.03</b>	(A-D), (B-D)
Procalcitonin (ng/mL), mean SD	0.02 $\pm$ 0.01	3.0 $\pm$ 8.9	0,02	18.8 $\pm$ 7	<b>0.02</b>	
D-dimer ( $\mu$ g/L), mean SD	190	2,354 $\pm$ 4,783	349 $\pm$ 150	3,187 $\pm$ 3,847	0,8	

Patients were divided in four gravity groups: (A) asymptomatic, (B) mild, (C) moderate, (D) Severe/critical

hospitalization. 28% of patients presented co-infections (urinary, respiratory, skin, or gastrointestinal infections) caused by other microbiological agents. 3% of children had seizures, 3% myositis, 1% acute pancreatitis. MIS-C occurred in 3% of patients. The management of patients was standardized, based on clinical evidence and guidelines. Asymptomatic or mild cases were hospitalized to monitor vital signs and administrate fluids, caloric intake, antipyretics, and analgesics. Patients with moderate, severe, and critical infections needed corticosteroid and immunosuppressive therapy (IV immunoglobulins), oxygen support, antithrombotic prophylaxis, and antibiotic therapy in case of co-infections.

**Table 6.** Radiological findings.

Radiological characteristics	Total (n=71)
Chest X-ray, n (%)	44 (62)
Normal, n (%)	13 (30)
Interstitial accentuation, n (%)	26 (59)
Bronchitis, n (%)	2 (5)
Pneumonia, n (%)	8 (18)
Bilateral Pneumonia, n (%)	1 (2)
Chest CT, n (%)	3 (4)
Normal, n (%)	1 (33)
Interstitial pneumonia, n (%)	1 (33)
Bronchial thickening, n (%)	1 (33)
Pulmonary ultrasound, n (%)	7 (10)
Normal, n (%)	1 (14)
White lung, n (%)	2 (29)
Pleural irregularity, n (%)	4 (57)
Parenchymal thickening, n (%)	1 (14)
B lines, n (%)	2 (29)

CT, computed tomography.

## Discussion

COVID-19 is a pandemic that affects people of any age and involves the whole population with a high rate of interpersonal transmission. Adults are more prone to develop a severe infection, especially in elderly age, comorbidities, and male sex. Children generally report asymptomatic and mild symptoms of illness, and only a minority of patients have complications or a severe course, such as MIS-C development (15). Our data, according to the literature, confirm that children show frequently COVID-19 in asymptomatic forms or mild symptomatic forms and more rarely with severe or critical manifestations. They more often present upper respiratory airways involvement, and the gastrointestinal tract and skin are more involved in children than in adults (18-19).

When pediatric clinical data were still scarce at the beginning of the Italian outbreak, affected children were generally hospitalized for clinical monitoring and hospital management despite their good clinical conditions. Therefore, we realized a retrospective study to assess the clinical features of children hospitalized for COVID-19 in our Pediatric Clinic. Most patients acquired the infection because of close contact with other affected family members (parents, grandparents, siblings).

As already reported in the literature, COVID-19 affected 54% of male children with a mean age of 5 $\pm$ 5.5 years in our cohort (7). The youngest patient was a 1-month-old infant.

Patients were stratified according to WHO classification of COVID-19.<sup>17</sup> As already reported in the literature, most hospitalized children had mild disease (about 70%) with nonspecific symptoms, such as fever and loss of appetite (7). Other prevalent symptoms were cough, rhinitis, and gastrointestinal symptoms (vomiting).



School-aged children were significantly more predisposed to develop asymptomatic infection ( $p=0.04$ ). On the contrary, infants, and toddlers presented with mild disease in our cohort. This result displays the more prudent approach adopted by clinicians of our Pediatric Clinic, who preferred to hospitalize these young patients to monitor the disease progression and guarantee the best management.

Although underlying conditions prevailed in the adult population, children with chronic comorbidities have a potential risk of more severe COVID-19. About 47% of enrolled patients had some comorbidities, particularly obesity/overweight (46%) and immunodeficiencies (33%). In our cohort, the presence of other coexisting diseases is indeed related to the worst evolution of COVID-19, confirming that also children may develop a critical or severe infection (20). Moreover, only one patient with severe genetic immunodeficiency (Adenosine deaminase 2 (ADA2) deficiency) died for multiorgan failure development. For this reason, Pfizer-BioNTech COVID-19 vaccine was recently authorized in children aged 5 to 11 years old in Italy to avoid and prevent COVID-19 related complications (21).

The 99% of patients, including those with overweight/obesity or other coexisting diseases (malignancies, hemoglobinopathies), wholly recovered. Because this study only focused on hospitalized patients, we did not assess long-term complications like long-COVID. However, patients in our study showed acute complications; some were related to COVID-19. Three patients developed MIS-C and were treated with IV immunoglobulins and systemic steroids. All these children recovered, and only one needed ICU admission. This data confirms the potential severe evolution of COVID-19 in children, and hospitalization should always be considered in children with fever for more than three days and refractory to antipyretics.

Although no validated biomarkers have been included in the diagnostic work-up of children with SARS-CoV-2 infection, we found that high levels of inflammatory indexes altered coagulation parameters, lymphopenia, and eosinopenia are significantly related severe/critical course of COVID-19. These data confirm the hypothesis that specific laboratory parameters (eosinophil and lymphocyte count, serum inflammatory indexes) may predict the course of COVID-19 as al-

ready reported in adult studies (22-24). Therefore, the host antiviral immune response and the genetic predispositions play a crucial role in the prediction of COVID-19 evolution (25).

The management of patients with COVID-19 varies according to the clinical appearance of the disease. Although the mild symptoms, children were hospitalized when they were very young, and families could not safely manage them at home. In these children, supportive care (fluids, antipyretics) was offered. The therapeutic management of more severe cases also included immunosuppressive drugs, oxygen administration, antithrombotic prophylaxis, and antibiotics in co-infections. Although antiviral drugs such as remdesivir are recommended by several guidelines in some subgroups of children with severe COVID-19 because of a good drug safety profile, enrolled patients did not required antiviral drugs (26,27).

This study has some limitations. Firstly, this is a single-center retrospective study with a relatively small number of cases. Secondly, our Pediatric Clinic was a reference center for COVID-19; thus, the hospital management was susceptible to new evidence, making the clinical approach mutable during the time. For these reasons, data could appear heterogeneous and sometimes challenging to summarize. On the other hand, we included patients since the beginning of the Italian outbreak, allowing a good description of changes in pediatric COVID-19 management.

## Conclusions

This study essentially confirms published data on pediatric COVID-19, highlighting children generally develop a mild disease and completely recover, even in more severe cases. However, we also reported patients with severe/critical COVID-19, and one patient with a coexistent chronic disease died. We found that the presence of comorbidities, lymphopenia, eosinopenia, and high inflammatory indexes are predictors of a more severe COVID-19. Therefore, it is crucial to assess the risk of COVID-19 evolution, analyze the patient's history (comorbidity assessment), and perform laboratory investigations. This approach may provide a patient stratification based on their risks and a more personalized therapeutic strategy.

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**Conflict of Interest:** Each author declares that they have no commercial associations that might pose a conflict of interest in connection with the submitted article.

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