

## SUPPLEMENT ARTICLE

## Defining the clinical phenotype of COVID-19 in children

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## Abstract

On January 7, 2020, a novel coronavirus (SARS-CoV-2) was identified as the causative agent of a cluster of pneumonia of unknown origin detected in Wuhan City by Chinese authorities. Since SARS-CoV-2 discovery, the corresponding disease (COVID-19) has rapidly expanded throughout the globe, making as a consequence the World Health Organization (WHO) declaring a pandemic. As of May 19, 2020, over 4.806.299 cases of COVID-19 had been confirmed worldwide, with more than 318.599 deaths.

## KEYWORDS

children, COVID-19, Italy, SARS-CoV-2

## 1 | INTRODUCTION

On January 7, 2020, a novel coronavirus (SARS-CoV-2) was identified as the causative agent of a cluster of pneumonia of unknown origin detected in Wuhan City by Chinese authorities. Since SARS-CoV-2 discovery, the corresponding disease (COVID-19) has rapidly expanded throughout the globe, making as a consequence the World Health Organization (WHO) declaring a pandemic.

As of May 19, 2020, over 4.806.299 cases of COVID-19 had been confirmed worldwide, with more than 318.599 deaths.<sup>1</sup>

A global effort has been made to collect clinical and laboratory findings on patients with SARS-CoV-2 infection. The lower airway is the primary target of the infection; however, the disease spectrum goes from asymptomatic subjects to severe illness, including 5.0% subjects requiring ICU admission, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died.<sup>2</sup>

Available reports show that children are less likely than other age groups to develop severe symptoms when infected by SARS-CoV-2.<sup>3-7</sup>

Although there is some evidence of differences in the infection prevalence between adults and children, data gathered from contact tracing investigation on a large cohort show that the secondary infection rate after exposure to the virus is no different in children

and they are just as likely to become infected as other age groups.<sup>8</sup> In the early phase of the infection outbreak, transmission source in children was not easily identifiable; during the last period, virus exposure has been caused by household contact. Preliminary clinical findings in China showed that infected children tend to be asymptomatic or paucisymptomatic compared to adult cases, whereas their role in the transmission dynamics is still unclear.<sup>9</sup>

The most common symptoms reported were fever, cough, and rhinorrhea. Gastrointestinal symptoms as hypoalimentation, vomiting, abdominal pain, and diarrhea were also common.<sup>3,6</sup> Estimated asymptomatic infection rates range from 1.3% to 12.9%<sup>4-10</sup>; 60%-67%<sup>3,6,7</sup> of SARS-CoV-2-infected children needed hospitalization, and all available reports agree with a higher hospital admission rate in children aged less than 12 months. Preexisting medical conditions were present in 19.6%-27% of patients.<sup>3,7,10</sup> Of note, 83% of pediatric intensive care unit (PICU)-admitted children had comorbidities.<sup>5</sup> This finding was not confirmed in other pediatric cohorts. Garazzino et al recently found that the hospitalization rate was similar between children with or without comorbidities.<sup>3</sup>

Regarding risk factors of severe phenotype in SARS-CoV-2-infected children, we highlight obesity as already reported by Simmonet A. et al in adult patients and in the pediatric population as Brambilla I. et al have found.<sup>11</sup>

Chest X-ray or chest TC was generally performed on admission and usually found infiltrates bilateral or mono-lateral, and sometimes atelectasis or pleural effusion. Of note, not all symptomatic patients had radiologic signs of pneumonia. Many authors report that the main radiologic features are bronchial thickening, ground-glass opacity, or inflammatory lung lesions, suggestive of pneumonia. These pulmonary findings were also found in patients with mild symptoms or asymptomatic, suggesting that COVID-19 induces a primary inflammation of the lower respiratory tract airways. An essential role in children diagnostics could be played by lung ultrasound (LUS). Preliminary data suggest high concordance between radiologic and LUS findings in detecting lung abnormalities in children with COVID-19.<sup>12</sup>

Few laboratory abnormalities were observed in COVID-19 children,<sup>3-13</sup> unlike in adults, where increased leukocyte and neutrophil below the normal range were commonly found in patients with unfavorable COVID-19 progression; this may be due to the few data present in the literature about severe cases in the pediatric population. Inflammatory biomarkers as C-reactive protein, procalcitonin, and IL-6 are not altered, and further data are needed to use it as prognostic markers; as in other respiratory infections in children, these laboratory findings could be suggestive of bacterial co-infection.

Usually, no treatment is needed in pediatric patients with mild-to-moderate disease. Antibiotics are often used in clinical practice to cover bacterial co-infection. It has been recognized that macrolides have immunomodulatory effects that are beneficial for those suffering from chronic pulmonary inflammatory syndromes; however, little is known about the use of azithromycin as an anti-inflammatory factor in patients with respiratory failure or mild lung impairment oxygen therapy, noninvasive, and invasive ventilation during the hospitalization.

Although there are no shared therapeutic protocols, in the most severe cases, antiviral therapy has been used, such as ritonavir/lopinavir and remdesivir as compassionate use; if a hyperinflammatory clinical picture similar to those seen in adults was found, tocilizumab was used in children and adolescents to contrast the cytokine cascade famously called "cytokine storm."

However, data collected so far on therapies for COVID-19 treatment in children are purely descriptive, safe, and effective treatments of COVID-19 remain to be demonstrated by rigorous clinical trials.

All these data are far from being scientifically established, they remain anecdotal, and need to be systematically organized according to a clinical severity score.

Admission to PICU has occurred between 1.8% and 9.7% of patients according to available recent data<sup>3-7</sup>; the most significant cohort of severe and critical SARS-CoV-2-infected children included 48 PICU-admitted patients in United States and Canada<sup>5</sup>; among this, authors reported 2 deaths (4% of subjects analyzed) in contrast with previously published children fatality rate calculated on 2143 Chinese children, with only one reported death.<sup>14</sup>

### Key Message

Children are less likely than other age groups to develop severe symptoms when infected by SARS-CoV-2. Estimated asymptomatic infection rates range from 1.3% to 12.9%; 60%-67% of SARS-CoV-2-infected children needed hospitalization. Preexisting medical conditions were present in 19.6%-27% of patients. Of note, 83% of pediatric intensive care unit (PICU)-admitted children had comorbidities. According to clinical score established by Dong et al, severe and critical pediatric cases could amount from 5.9%, but further investigation is needed to evaluate real proportion of asymptomatic infection and the distribution of SARS-CoV-2-infected children among different severity clinical category. In the early phase of the COVID-19 outbreak, many authors suggested that children were less likely susceptible to SARS-CoV-2 infection; subsequently we understood that children could be infected in similar rates when compared to the adult population. Now, as many reports and clinical data are being published, we become aware of possible severe and critical cases among children, but with clinical manifestations different from what has been seen in adults. More studies are needed in order to better understand the pathogenetic pathways of SARS-CoV-2 infection in children and the clinical spectrum of this new emerging disease.

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The "Dong" severity scale is based on respiratory clinical manifestation, while recent data on different clinical phenotypes of SARS-CoV-2 in children showed that worse clinical picture is far from considering an exclusive lung involvement.

A recently published correspondence on *Lancet*<sup>15</sup> reported that children could develop systemic hyper inflammation that could lead to an atypical Kawasaki disease; interestingly, this clinical manifestation appears not to be associated with respiratory symptoms: "unrelenting fever, variable rash, conjunctivitis, peripheral edema, and generalized extremity pain with gastrointestinal symptoms."

In an Italian case report,<sup>16</sup> authors confirm these new concerns about a novel severe Kawasaki-like disease in children related to COVID-19, reporting a monthly incidence some 30-fold higher than observed for Kawasaki disease in the last 5 years.

Debates among pediatricians, infectious disease specialists, rheumatologists, immunologists, and cardiologists regard how this new phenotype could be interpreted: Is it a "pediatric inflammatory

multisystem temporally associated with SARS-CoV-2 (PIMS-TS)",<sup>17</sup> requiring critical care and underlining a severe spectrum of the disease or a "postinfectious inflammatory syndrome, maybe due to antibody or immune-complex-mediated process" as we see in the Italian cohort?

As we can see, we are far from understanding the clinical spectrum of this new emerging disease.

Investigating the pediatric population could be challenging to study for different reasons. In the early phase of the COVID-19 outbreak, many authors suggested that children were less likely susceptible to SARS-CoV-2 infection, assuming immunopathogenic theories that are yet to be confirmed; subsequently, we understood that children could be infected in similar rates when compared to the adult population. Now, as many reports and clinical data are being published, we become aware of possible severe and critical cases among children, but with clinical manifestations different from what has been seen in adults.

More studies are needed in order to understand the pathogenetic pathways of SARS-CoV-2 infection in children.

#### CONFLICT OF INTEREST

The authors have no competing interests to declare.

#### AUTHOR CONTRIBUTION

**Vania Giacommet:** Conceptualization (equal); Data curation (equal).

**Marta Stracuzzi:** Formal analysis (equal); Methodology (equal).

**Laura Paradiso:** Funding acquisition (equal); Visualization (equal).

**Maria Elisabetta Di Cosimo:** Methodology (equal); Visualization.

**Valeria Rubinacci:** Data curation; Resources (equal). **Gian Vincenzo Zuccotti:** Writing-review & editing (equal).

#### PEER REVIEW

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