COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy

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OBJECTIVES: To describe the epidemiological and clinical characteristics of coronavirus disease (COVID-19) pediatric patients aged <18 years in Italy.

METHODS: Data from the national case-based surveillance system of confirmed COVID-19 infections until May 8, 2020, were analyzed. Demographic and clinical characteristics of subjects were summarized by age groups (0–1, 2–6, 7–12, 13–18 years), and risk factors for disease severity were evaluated by using a multilevel (clustered by region) multivariable logistic regression model. Furthermore, a comparison among children, adults, and elderly was performed.

RESULTS: Pediatric patients (3836) accounted for 1.8% of total infections (216 305); the median age was 11 years, 51.4% were male, 13.3% were hospitalized, and 5.4% presented underlying medical conditions. The disease was mild in 32.4% of cases and severe in 4.3%, particularly in children ≤6 years old (10.8%); among 511 hospitalized patients, 3.5% were admitted in ICU, and 4 deaths occurred. Lower risk of disease severity was associated with increasing age and calendar time, whereas a higher risk was associated with preexisting underlying medical conditions (odds ratio = 2.80, 95% confidence interval = 1.74–4.48). Hospitalization rate, admission in ICU, disease severity, and days from symptoms onset to recovery significantly increased with age among children, adults, and elderly.

CONCLUSIONS: Data suggest that pediatric cases of COVID-19 are less severe than adults; however, age ≤1 year and the presence of underlying conditions represent severity risk factors. A better understanding of the infection in children may give important insights into disease pathogenesis, health care practices, and public health policies.

WHAT’S KNOWN ON THIS SUBJECT: Although coronavirus disease is less frequent and often less severe in children compared with adults, limited data exist on risk factors for disease severity and death in pediatric patients.

WHAT THIS STUDY ADDS: In the current study, we describe pediatric cases (persons aged <18 years) of severe acute respiratory syndrome coronavirus 2 infection in Italy and compare them with adult and elderly patients. Underlying medical conditions and younger age represent risk factors for disease severity among children and adolescents.


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Dr Bellino performed the statistical analyses and drafted the manuscript; Dr Punzo contributed to collect the clinical data and drafted the manuscript; Drs Rota, Filia, Rezza, and Prof Villani critically reviewed the manuscript; Drs Del Manso, Mateo Urdiales, Andrianou, Fabiani, Vescio, and Mr Boros contributed to collect the data and conducted the final database; Dr Riccardo contributed to the coordination of the coronavirus disease national surveillance; Dr Bella coordinated and supervised the surveillance data collection; Dr Pezzotti is the head of the Italian coronavirus disease surveillance system and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The infection caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), associated to coronavirus disease (COVID-19), characterized by severe pneumonia in a variable proportion of cases, was first reported in the city of Wuhan, China, in December 2019 and then spread across continents; first cases were initially diagnosed in Italy in late January in people coming from China.

After the detection of the first locally acquired case of SARS-CoV-2 infection in the Lombardia region (Northern Italy) on February 20, the number of cases and deaths during the subsequent weeks increased rapidly. Despite the high number of diagnosed subjects, children are still a small proportion of the cases in Italy. This is likely due to several factors; children are expected to experience a milder disease, and testing strategies privileged frankly symptomatic cases, especially in the intensely hit northern regions in Italy.

The Chinese Center for Disease Control and Prevention reports that, of the 72314 cases reported as of February 11, 2020, in China, only 2% were in individuals of <19 years of age. Children appear to be less commonly affected by SARS-CoV-2 infection than adults, and to be more commonly asymptomatic; however, in some cases, they can develop complications, particularly infants. To date, data on clinical features and risk factors for disease severity and death in infants, children, and adolescents are still limited, as well as a comparison with adults for differences in clinical characteristics, disease progression, and outcome.

Our objective with the current study is to describe the epidemiological and clinical characteristics of COVID-19 in individuals <18 years old in Italy and compare them with adults and the elderly.

**METHODS**

**Study Population**

The study population included children aged <18 years with laboratory-confirmed COVID-19, reported to the Italian integrated COVID-19 surveillance system. According to the Italian case definition, all patients presenting to the health care system with symptoms compatible with COVID-19 infection or with an epidemiological link (close contact with a confirmed COVID-19 case in the 14 days before onset of symptoms, or having been a resident or a staff member, in the 14 days before onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed), hospitalized patients with severe acute respiratory infections, and high-risk health care workers should be tested for SARS-CoV-2 virus. The case definition considers as a confirmed case any person with laboratory confirmation of SARS-CoV-2 virus, irrespective of clinical signs and symptoms.

**Study Outcomes**

The primary outcomes of the study were to outline the epidemiological and clinical characteristics of COVID-19 pediatric patients in Italy, investigate the disease severity risk factors, and compare children and adolescents with adults and the elderly.

The clinical state was defined according to the following classification: asymptomatic (no apparent signs or symptoms of disease); paucisymptomatic (dry cough, general malaise, low-grade fever, tiredness); mild (uncomplicated upper respiratory tract viral infection [eg, fever, cough, sore throat, malaise, headache, muscle pain] without shortness of breath, dyspnea, or abnormal chest imaging); severe (eg, pneumonia, hypoxia dyspnea, tachypnea requiring hospitalization); and critical (eg, severe pneumonia, acute respiratory distress syndrome, septic shock, and/or multiple organ dysfunction requiring hospitalization in intensive care). However, in several cases, the information about the severity of the disease was missing or the case was reported by the Regions as “symptomatic.” Recovery was defined as resolution of clinical symptoms with 2 negative reverse transcription polymerase chain reaction (RT-PCR) results from respiratory specimens at 24-hour intervals.

**The Italian Integrated COVID-19 Surveillance System**

With the aim to monitor the epidemic in Italy and support the planning of public health actions, a case-based surveillance system was established on February 27, 2020. The system contains case-based data on all laboratory-confirmed cases of COVID-19 as per the case definition by the European Centre for Disease Prevention and Control regularly updated. From the beginning of the outbreak until March, all nasopharyngeal swabs tested positive by RT-PCR at regional level were sent for confirmation to the National Reference Laboratory at the Istituto Superiore di Sanità and retested according to the World Health Organization and Centers for Disease Control and Prevention protocols. Because of the high concordance (99%) of results with the regional laboratories, the policy was then changed, allowing selected reference regional laboratories, with demonstrated capacity, to directly confirm COVID-19 suspected cases, using a selected number of RT-PCR–based commercial diagnostic tests for SARS-CoV-2.

**Data Sources**

Data from the Italian case-based surveillance system of confirmed SARS-CoV-2 infections until May 8, 2020, collected from all 21 regions and autonomous provinces, were
analyzed, considering patients aged <18 years who tested positive for SARSCoV-2. The national surveillance system is coordinated by the Istituto Superiore di Sanità, and data were collected by using a secure online platform or received as individual data sets (from 3 regions) to be included in a single database. Data collected on all laboratory-confirmed cases include information on demographics, clinical severity, underlying medical conditions, date of symptoms onset, date of diagnosis, date of hospitalization, clinical outcome, region of diagnosis, and province of residence. Information on underlying conditions was collected based on anamnestic data, according to the following categories: cardiovascular, respiratory, oncologic, neurologic, liver, and renal diseases; metabolic disorders; diabetes; immunodeficiency; and obesity. Details on the 4 deaths that occurred in children were retrieved from the medical records.

The study was conducted as part of public health and surveillance activities for the COVID-19 emergency, which were entrusted to Istituto Superiore di Sanità. Because of the nature of aggregated data and the ongoing public health response to control the outbreak, as well as the importance of sharing the research findings, full ethical approval was not juridically required for surveillance activities. However, the Istituto Superiore di Sanità Research Ethics Committee was informed.

**Statistical Analysis**

The \( \chi^2 \) test for categorical variables and Kruskal–Wallis test for continuous variables were used to compare cases among age groups for demographic and clinical characteristics.

The absolute number of pediatric cases was aggregated by regions and autonomous provinces as well as the cumulative incidence (per 100 000 inhabitants), calculated by using population estimates aged <18 years for 2019 available from the Italian National Institute of Statistics; 4 areas were detected on the basis of the quartiles of the national distribution of the pediatric population (low, medium, high, very high). In addition, on the basis of the severity of COVID-19 (considering the highest severity between baseline and follow-up), risk factors for mild, severe, or critical outcome versus asymptomatic or paucisymptomatic clinical state were evaluated by using a multilevel (clustered by region) multivariable logistic regression model, including sex, age groups (0–1, 2–6, 7–12, 13–18 years), presence of pre-existing underlying medical conditions, and calendar time: February 20 to March 23 (the first month of the epidemic), March 24 to April 15 (3 weeks after the peak of the epidemic), and April 16 to May 8 (the last 3 weeks of observation during the declining phase). Finally, a comparison for demographic and clinical characteristics was performed among children (<18 years), adults (18–64 years), and elderly (≥65 years) by using the \( \chi^2 \) test for categorical variables and Kruskal–Wallis test for continuous variables.

Statistical analysis was conducted by using the Stata software, version 16 (Stata Corporation, College Station, TX).

**RESULTS**

**COVID-19 Epidemiology in Children and Adolescents**

In Italy, 16% of the residents are made up of infants, children, and adolescents aged <18 years. As of May 8, 2020, this pediatric population accounted for 1.8% (3836 of 216305) of all COVID-19–reported cases at the national level, with a variable percentage across the Italian regions. Considering all
patients aged <18 years with an available date of diagnosis (3720, 97%), a continuous daily increase of the diagnosed cases from February 23 (the first reported pediatric case) until the peak of the outbreak (March 24–26) was found (2 weeks after the national lockdown), whereas since then, a gradual and steady decrease was observed until the first week of May (Fig 1A). An interregional variation for pediatric COVID-19 patients was observed in Italy; the highest absolute number of patients was reported in the Northern regions (Lombardia, Emilia-Romagna, Veneto, and Piemonte), the most hit by the epidemic (Fig 2A), whereas major incidence rates were detected in Autonomous Province of Trento (180.6 per 100 000), Valle d’Aosta (115.1 per 100 000 population), Emilia-Romagna (75.5 per 100 000), Abruzzo (73.8 per 100 000), and Autonomous Province of Bolzano (62.5 per 100 000) (Fig 2B).

Demographic and Clinical Characteristics of Pediatric Patients

The epidemiological history most frequently reported was a relationship with a familial cluster, followed by a contact with a confirmed case. Most cases of COVID-19 occurred in adolescents aged 13 to 17 years (40.1%), followed by those in children 7 to 12 (28.9%), 2 to 6 (17.2%), and 0 to 1 (13.8%) years old; the median age was 11 years, and 51.4% of them were male (Table 1). The median time from symptoms onset to diagnosis increased with age, from 3 days among infants to 6 days among adolescents ($P < .001$) as well as the median time from symptoms onset to hospitalization, from 1 day among infants to 4 days among adolescents ($P = .001$). Overall, the hospitalization rate was 13.3%, and the highest percentage of hospital admission occurred in infants aged ≤1 year (36.6%), followed by children aged 2 to 6 years (12.8%), 13 to 17 years (8.9%), and 7 to 12 years (8.8%) ($P < .001$); the admission rate in ICU was 3.5%, with the highest value among children aged 2 to 6 years (9.5%) ($P = .010$). Preexisting underlying medical conditions increased with age, from 3.6% in infants ≤1 year old to 6.0% in adolescents 13 to 17 years old ($P < .001$), and were particularly high (9.8%) among hospitalized patients; the most common were respiratory, cardiovascular, and oncologic.

**FIGURE 2**

Absolute number (A) and incidence rates per 100 000 population (B) of COVID-19 cases aged <18 years by Italian regions and autonomous provinces of diagnosis. IR, incidence rate.
diseases. Among patients with available clinical state classification (2015, 52% of the total), younger children, particularly infants, showed the highest proportion of severe infections ($P < .001$); specifically, the proportions of severe or critical state were 10.8%, 6.5%, 2.4%, and 3.0% for age groups 0 to 1, 2 to 6, 7 to 12, and 13 to 17 years old, respectively (Table 1).

After adjusting for sex, age groups, underlying medical conditions, and calendar time of diagnosis, a lower risk of disease severity (mild, severe, or critical as compared with asymptomatic or paucisymptomatic) was detected with increasing age compared with infants $\leq$ 1 year old (2–6 years, odds ratio [OR] = 0.30, 95% confidence interval [CI] = 0.20–0.46; 7 to 12 years, OR = 0.22, 95% CI = 0.15–0.33; 13 to 17 years, OR = 0.26, 95% CI = 0.18–0.37), whereas a higher risk was associated with the presence of $\geq$1 preexisting underlying medical condition (OR = 2.80, 95% CI = 1.74–4.48). The second period after the peak of the outbreak was associated with a lower risk of disease severity as compared with the first month (February 23 to March 23) of the epidemic (OR = 0.61, 95% CI = 0.47–0.80, March 24 to April 15; OR = 0.33, 95% CI 0.23–0.46, April 16 to May 8); moreover, high interregional variation was observed, and approximately half of the disease severity variability was attributable to the region effect (Table 2).

COVID-19–Related Deaths in Children

Four deaths were reported in children, and clinical details are described below.

The first case was of a 5-year-old girl who died in hospital with SARS-CoV-2 pneumonia. The patient had a type-2 mucolipidosis (an inherited metabolic disease) associated with hypertrophic cardiomyopathy, with thickening of the mitral and aortic valves and sleep apnea syndrome. The patient was treated with antibiotics and corticosteroids, then oxygen was added, but when the general conditions deteriorated, a palliative care protocol was started. The second case was of an infant aged 2 months with Williams syndrome, a rare multisystemic genetic disease of neurologic development, characterized by typical facial features, heart disease (especially supravalvular aortic stenosis), and cognitive, developmental, and connective tissue abnormalities (joint laxity). The infant presented stenosis and hypoplasia of the pulmonary arteries and supravalvular aortic stenosis. He was admitted for cardiac surgery and underwent a complex surgical procedure. Although he survived the procedure, he remained on extracorporeal membrane oxygenation and could never be weaned from that in the following days and finally died 10 days after the surgery. The third case was of an infant aged 6 months with a rare and aggressive form of cancer (ie, an extrarenal malignant rhabdoid tumor) who underwent 10 cycles of chemotherapy and developed fever associated to neutropenia and pneumonia. The last case was of a 6-year-old girl who suffered from heart

### TABLE 1 Demographic and Epidemiological Characteristics of Individuals <18 Years of Age With COVID-19 in Italy, February 23 to May 8, 2020

<table>
<thead>
<tr>
<th>Class of Age, y</th>
<th>0–1</th>
<th>2–6</th>
<th>7–12</th>
<th>13–17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases, n (%)</td>
<td>528 (15.8)</td>
<td>659 (17.2)</td>
<td>1109 (28.9)</td>
<td>1540 (40.1)</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>245 (46.4)</td>
<td>300 (45.5)</td>
<td>542 (48.9)</td>
<td>779 (50.8)</td>
<td>.11</td>
</tr>
<tr>
<td>Male</td>
<td>283 (53.6)</td>
<td>359 (54.5)</td>
<td>567 (51.1)</td>
<td>761 (49.4)</td>
<td>—</td>
</tr>
<tr>
<td>Hospitalization, n (%)</td>
<td>183 (36.8)</td>
<td>84 (12.8)</td>
<td>97 (8.8)</td>
<td>137 (8.9)</td>
<td>.001</td>
</tr>
<tr>
<td>ICU</td>
<td>5 (2.6)</td>
<td>8 (9.5)</td>
<td>1 (1.0)</td>
<td>4 (2.9)</td>
<td>.010</td>
</tr>
<tr>
<td>Underlying conditions, n (%)</td>
<td>19 (3.5)</td>
<td>31 (4.7)</td>
<td>64 (5.8)</td>
<td>92 (6.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>0 (0.0)</td>
<td>4 (12.9)</td>
<td>9 (14.1)</td>
<td>15 (16.3)</td>
<td>.51</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2 (10.5)</td>
<td>3 (9.7)</td>
<td>5 (7.8)</td>
<td>7 (7.6)</td>
<td>.96</td>
</tr>
<tr>
<td>Oncologic</td>
<td>2 (10.5)</td>
<td>3 (9.7)</td>
<td>2 (3.1)</td>
<td>4 (4.4)</td>
<td>.40</td>
</tr>
<tr>
<td>Metabolic, diabetes</td>
<td>1 (5.3)</td>
<td>1 (5.2)</td>
<td>3 (4.7)</td>
<td>6 (6.5)</td>
<td>.90</td>
</tr>
<tr>
<td>Neurologic</td>
<td>1 (5.3)</td>
<td>0 (0.0)</td>
<td>3 (4.7)</td>
<td>2 (2.2)</td>
<td>.53</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>1 (5.3)</td>
<td>3 (9.7)</td>
<td>2 (3.1)</td>
<td>0 (0.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Disease severity, n (%)</td>
<td>43 (20.2)</td>
<td>141 (40.1)</td>
<td>267 (44.5)</td>
<td>334 (39.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>43 (20.2)</td>
<td>84 (23.9)</td>
<td>149 (24.8)</td>
<td>216 (25.4)</td>
<td>—</td>
</tr>
<tr>
<td>Paucisymptomatic</td>
<td>104 (48.8)</td>
<td>104 (29.5)</td>
<td>170 (28.3)</td>
<td>274 (32.2)</td>
<td>—</td>
</tr>
<tr>
<td>Mild</td>
<td>21 (8.9)</td>
<td>20 (5.7)</td>
<td>13 (2.2)</td>
<td>25 (2.9)</td>
<td>—</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (0.9)</td>
<td>3 (9.7)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
<td>—</td>
</tr>
<tr>
<td>Critical</td>
<td>322 (61.0)</td>
<td>412 (62.5)</td>
<td>654 (59.0)</td>
<td>968 (62.9)</td>
<td>.21</td>
</tr>
<tr>
<td>Recovery, n (%)</td>
<td>2 (0.4)</td>
<td>2 (0.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>3 (1–7)</td>
<td>4 (2–10)</td>
<td>5 (2–11)</td>
<td>8 (2–12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Days from symptoms to diagnosis, median (IQR)</td>
<td>1 (0–4)</td>
<td>2 (1–5)</td>
<td>2 (1–5)</td>
<td>4 (1–8)</td>
<td>.001</td>
</tr>
<tr>
<td>Days from symptoms to hospitalization, median (IQR)</td>
<td>28 (23–37)</td>
<td>27 (22–35)</td>
<td>29 (23–36)</td>
<td>32 (22–39)</td>
<td>.06</td>
</tr>
</tbody>
</table>

The $\chi^2$ test for categorical variables and Kruskal–Wallis test for continuous variables were used to compare the 4 age groups. IQR, interquartile range; —, not applicable.
failure and underwent a mitral annuloplasty due to severe mitral insufficiency and left ventricular dysfunction. This hospitalization was associated with a series of complications, consisting of superinfection and deterioration of cardiac failure.

Based on medical records and from the treating physicians’ notes, all 4 children died of a deterioration of very compromised conditions, and to a certain extent the impact of SARS-CoV-2 infection may have aggravated the situation but does not seem to be the underlying cause of death.

**Comparison Among Pediatric, Adult, and Elderly Populations**

Evolution of the reported COVID-19 cases in Italy followed a similar trend among children (<18 years), adults (18–64 years), and elderly (≥65 years) from February to May (Fig 1 A and B). More female individuals were affected by COVID-19, except for those aged <18 years (P < .001) (Table 3); men showed more severe symptoms compared with women (P < .001) among adults and elderly, whereas no sex difference was found among children. Hospitalization rate significantly increased with age (P < .001); indeed, 13.3% of children were hospitalized compared with adults (28.3%) and elderly (49.9%), and among hospitalized patients, adults (13.0%) were the most admitted in ICU (P < .001) as compared with children (3.5%) and elderly (10.2%) (Table 3). Disease severity also significantly increased with age (P < .001); 4.2% of children had severe or critical symptoms, compared with adults (17.2%) and elderly (41.1%), whereas 63.4% of children were asymptomatic or paucisymptomatic, compared with adults (44.0%) and elderly (27.3%). About half of patients recovered within 1 month from the onset of the disease; the recovery rate was higher in children (38.6%) and adults (41.9%) compared with the elderly (20.2%) (P < .001). Moreover, a shorter period from symptoms onset to hospitalization and recovery was found among children compared with older ages (P < .001). In general, pediatric patients with COVID-19 had a good prognosis, although 4 deaths occurred, whereas the mortality rate was 5.8% among adults with underlying medical conditions and 25.8% among the elderly.

**DISCUSSION**

This is the first large study offering a comprehensive picture of the pediatric population diagnosed with SARS-CoV-2 infection in Italy. After the first indigenous case of COVID-19 diagnosed on February 20, the number of cases rapidly increased nationwide until the peak of the epidemic, which occurred ~2 weeks after the national lockdown declared on March 11. A steady and gradual decrease has been observed since March 26; however, data referred to the last week of observation (May 2–8) might be influenced by reporting delay of the more recently diagnosed cases. Of note, the median delay between the date of symptoms onset and the date of the positive test result in the 3 study periods was 3, 5, and 9 days, respectively.

As of May 8, 2020, just after the start of the lockdown easing in Italy, patients <18 years old accounted for 1.8% of all reported COVID-19 cases. This relatively low burden among children has also been observed in other countries, but the age distribution might reflect testing policies and case definitions, which usually include the presence of

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**TABLE 2 Risk Factors for Disease Severity (Mild, Severe, or Critical Versus Asymptomatic, Paucisymptomatic) in Individuals <18 Years of Age; Multilevel Multivariable Logistic Regression Model, Italy, February 23 to May 8, 2020**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Disease Severity</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Reference</td>
<td>0.96</td>
<td>0.77–1.20</td>
<td>.73</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class of age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>0.30</td>
<td>0.20–0.46</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>7–12</td>
<td>0.22</td>
<td>0.15–0.33</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>13–17</td>
<td>0.26</td>
<td>0.18–0.37</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Underlying conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.80</td>
<td>1.74–4.48</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Calendar time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>February 23 to March 23</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 24 to April 15</td>
<td>0.61</td>
<td>0.47–0.80</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>April 16 to May 8</td>
<td>0.33</td>
<td>0.23–0.48</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Regions (random effect)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance among regions</td>
<td>4.18</td>
<td>2.04–8.59</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>ICC (%)</td>
<td>56.0</td>
<td>38.2–72.3</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

ICC, intraclass correlation (proportion of variation that is attributable to the effect of clustering [Italian regions]); —, not applicable.
symptoms; moreover, it may be possible that the small proportion of infected children reflects a lower risk of younger subjects developing disease symptoms. Of note, a survey conducted in the municipality of Vo’ in Italy revealed a prevalence of SARS-CoV-2 infection of 2.6% in the population, and 43.2% of the confirmed cases were asymptomatic. At the national level, the disease cumulative incidence rate was 40 per 100 000 and 419 per 100 000 in subjects aged <18 years, respectively. The distribution of pediatric cases varied throughout the country, with most of them concentrated in northern Italy; however, differences in incidence rates may be due to different testing strategies implemented at the local level (ie, children with a more serious infection are more likely to be tested) or to existing specific clusters. Furthermore, children were usually diagnosed with COVID-19 after exposure to an infected adult within the family circle. Children of all ages were found positive to COVID-19, suggesting that susceptibility is always present. Clinical manifestations were less severe than in adults; however, among pediatric patients, younger children were more vulnerable, particularly infants aged ≤1 year, who were hospitalized in approximately a third of cases; instead, children aged 2 to 6 years were the most frequently admitted in ICU.

Lower risk of disease severity was detected with increasing age, whereas a higher risk was associated with the presence of pre-existing underlying medical conditions. Moreover, our study highlighted that the second period of the outbreak was associated with a lower risk of severe disease. Indeed, the percentage of pediatric patients with severe or critical symptoms slightly decreased over time, from 5.4% in the first month of the outbreak to 3.5% during the last 3 weeks of the observation period, as did the percentage of patients with mild symptoms, from 43.4% to 28.9%. Nevertheless, this seems due more to the effect of the phase of the epidemic (during the peak of the outbreak, only subjects with clear signs and symptoms of the disease were tested) and probably to a more efficient health care provision due to a decreasing number of cases in the second phase rather than to a change in the pathogenicity of the SARS-CoV-2. The shifts of COVID-19 in terms of clinical presentation and outcome as the disease moved out from China into Europe and the rest of the world is still under debate; however, our data support the hypothesis that the disease course and severity have not undergone major changes. The evolution of the virus throughout the pandemic is not occurring faster than expected compared with other viruses during an outbreak. Different clades are emerging as COVID-19 spread worldwide, and a study in which researchers performed genetic analyses of 86 complete or near-complete genomes of SARS-CoV-2 from 12 countries revealed many mutations and deletions on coding and noncoding regions. This provided evidence of the genetic diversity and evolution of this novel coronavirus, although it does not mean that the emerged new strains are more pathogenic than others circulating right now.

Our findings are in line with those in published studies in which authors describe the epidemiology of COVID-19 among pediatric patients in China and the United States, in terms of percentage of children on the overall population, clinical severity, hospitalization, and outcome. As reflected in our analysis, authors of previous studies also showed that children of all ages are susceptible to
SARS-CoV-2 infection, but they seem to be less affected than the adult population, besides presenting with milder symptoms.\textsuperscript{23,25,26} Although a minority of children with COVID-19 require hospitalization, severe cases have been reported.\textsuperscript{10,27} Moreover, although children are most commonly infected through familial clusters, they were less likely to become positive, when exposed, than adults.\textsuperscript{28}

Concerning the disease severity, especially for the more severe cases, our data were comparable with a study on 2135 children from China including 728 laboratory-confirmed cases, in which researchers found that 5% were severe (presenting hypoxemia, dyspnea, central cyanosis), and <1% were critical (with respiratory failure, acute respiratory distress syndrome, shock).\textsuperscript{23}

It is unclear why children showed milder symptoms of COVID-19. A cytokine storm has been involved in the pathogenesis of severe forms of the disease in adults\textsuperscript{29}; therefore, one possible explanation could be a weaker immune response to SARS-CoV-2 in children compared with adults. Other hypotheses take into account a possible viral “competition” in the respiratory tract of young children and the expression of the angiotensin-converting enzyme 2 receptor. In the first scenario, viral interference may lead to a lower viral load in children. As for the angiotensin-converting enzyme 2 receptor, it acts as the receptor for SARS-CoV-2 and it may be expressed differently in the respiratory tract of children compared with adults.\textsuperscript{30,31}

A recent study showed that the viral load of symptomatic and asymptomatic patients were similar, and asymptomatic patients can still infect others.\textsuperscript{32} These “silent patients” may remain undiagnosed and be able to spread the disease to large numbers of people.\textsuperscript{33} However, the extent to which children can act as sources of infection is still under debate, also because of physical distancing and the closure of schools.

Of note, the European Centre for Disease Prevention and Control is closely following the information about the emergence of a postinflammatory syndrome in children in Europe, with a possible connection to COVID-19,\textsuperscript{34} and on May 15, 2020, the World Health Organization gave a preliminary case definition because of the urgent need for the collection of standardized data describing clinical presentations, severity, outcomes, and epidemiology.\textsuperscript{35}

Unfortunately, the data reported in our database do not allow the identification of children with a multisystem inflammatory disorder. Before drawing any conclusion, some limits of the study should be mentioned. In particular, the data were collected in a continuous consolidation phase and, as foreseeable in an emergency situation, some information was incomplete. Moreover, different testing strategies may have been applied regionally because each region is responsible for planning and organizing its health services; therefore, the number of swabs per residents, as well as the ability to detect less serious cases in the period after the epidemic peak, varied in the Italian regions. Finally, we were unable to assess clinical data, such as chest radiography, pulmonary lesions, and hematologic and biochemical parameters; therefore, additional studies are required to understand clinical and laboratory findings associated with pediatric cases of COVID-19.

**CONCLUSIONS**

Pediatric cases account for a small percentage of COVID-19 patients in Italy, and disease in children was often milder than in adults. Severe disease cases in children were associated with younger age and underlying conditions. Infection control measures should be implemented to prevent COVID-19 nosocomial spread, with the need to protect vulnerable individuals and children with serious underlying conditions.

A widespread availability of testing may allow us to better understand the infection in children, giving important insights into disease pathogenesis, health care practices, and public health policies.

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**ABBREVIATIONS**

Cl: confidence interval
COVID-19: coronavirus disease
OR: odds ratio
RT-PCR: reverse transcription polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
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