Article 6

PAMJ Clinical Medicine

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Received: 05 Jan 2024 - **Accepted:** 05 Mar 2024 - **Published:** 21 Mar 2024

Keywords: COVID-19, child, acute respiratory distress syndrome, mild pneumonia

Cite this article: Fatma Khalsi et al. Respiratory forms of COVID-19 in children: clinical characteristics and outcomes in a Tunisian hospital. PAMJ Clinical Medicine. 2024;14(29). 10.11604/pamj-cm.2024.14.29.42593

Available online at: https://www.clinical-medicine.panafrican-med-journal.com//content/article/14/29/full

Respiratory forms of COVID-19 in children: clinical characteristics and outcomes in a Tunisian hospital

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Abstract

Coronavirus disease 2019 (COVID-19) is a zoonosis that emerged in China in December 2019. Understanding the clinical presentation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and prognosis in children is a major issue. Children often present mild symptoms, and some severe forms require pediatric intensive care, with in some cases a fatal prognosis. We aimed to describe respiratory forms of novel coronavirus disease 2019 in children, including patient characteristics, clinical, laboratory, and imaging findings, as well as the disease management and outcomes. Our study was a retrospective, single-center, and descriptive study conducted for 18 months and carried out in the pediatric departments of the Children's Hospital in Tunis. The epidemiological, clinical, radiological, and therapeutic features and the outcome of respiratory forms were detailed from medical records. Fifty-one children were hospitalized for a respiratory form of COVID-19. Sixty-two-point-seven percent (n=32) of the enrolled patients were male. The average age was 49.3 months. Medical comorbidities reported were essentially respiratory, neurological, and cardiological. A history of asthma was found in 12 cases. Biologically, hyperleukocytosis was found in 41.2% of cases (n=21). C-reactive protein was increased in 19 children. Chest X-ray was performed in 42 patients and was pathological in 32 cases. A chest computed tomography scan was performed on 5 children. It showed moderate to severe SARS-CoV-2 disease. Thirty-one patients benefited from a high-flow nasal cannula. Oxygen therapy by nasal cannula was the most used mode (45.1%, n=23). Eight patients were put on Optiflow Junior. Five patients were ventilated mechanically in the pediatric intensive care unit. Nine patients presented with acute respiratory distress syndrome and 7 children required transfer to the intensive care unit. Five patients were ventilated mechanically in the pediatric intensive care unit. We had a total of 5 deaths in our study with a mortality rate of 9.8% (n=5). These deaths occurred in fragile children with comorbidities. Children with COVID-19 mainly become infected within their families, and children of all ages are generally susceptible. The disease in children is mostly mild and the prognosis is good.

Introduction

Coronaviruses are a large family of enveloped, single-stranded ribonucleic acid (RNA) viruses which can infect humans and animals. At the end of 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in China and multiple other countries, threatening to cause a global pandemic. Clinical manifestations of SARS-CoV-2 range from a common cold to more severe diseases such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multi-organ failure, and even death. SARS-CoV-2 seems to affect children less commonly. It was found that children constituted only a small proportion (2%) of infected patients [1]. This low percentage of confirmed infections in infants and young children probably results from the fact that the majority of children present with milder symptoms and are at lower risk of hospitalization and life-threatening complications [2]. To our knowledge, few Tunisian studies describing COVID-19 disease in children have been published, and even fewer have focused on the respiratory manifestations of this virus in children. This study aimed to describe respiratory forms of novel coronavirus disease 2019 in children, including patient characteristics, clinical, laboratory, and imaging findings, as well as the disease management and outcomes.

Methods

Study design and setting: our study was a retrospective, single-center, and descriptive study covering the period from March 1, 2020, to August 31, 2021 and carried out in the pediatric departments of the Children's Hospital in Tunis.

Study population: children with a respiratory form of SARS-CoV-2 were admitted to the COVID-19 isolation unit directly from the emergency department or transferred secondary from the pediatric wards. The following were included: i) children who presented with one or more respiratory signs: cough, dyspnea, chest pain, rhinorrhea, cyanosis; ii) any child presenting with an acute respiratory infection (fever + cough +/- respiratory distress) within the framework of clustered cases (in time and space); iii) any child of any age presenting with acute respiratory distress unexplained by another pathology (bronchiolitis, asthma attack, pneumonia, heart failure, etc.). In association with virological arguments based on laboratory confirmation of SARS-CoV-2 infection by polymerase chain reaction reverse transcriptase (RT-PCR) or by rapid antigenic test. The following were excluded: i) children who met the World Health Organization (WHO) definition of multisystemic inflammatory syndrome (MIS-C syndrome); ii) children who presented with the following signs in isolation, were not associated with respiratory involvement [3]: headache, asthenia, myalgia, fever, odynophagia, ageusia, anosmia, and digestive disorders (diarrhea).

Laboratory analysis: real-time polymerase chain reaction (RT-PCR) was used to diagnose COVID-19, testing nasopharyngeal and lower respiratory tract secretions. Other laboratory investigations (hemogram, natremia, C-reactive protein (CRP), renal assessment) were performed.

Data collection: data collected were age, sex, comorbidity, body weight, respiratory rate, heart rate, pulse oximetry (SpO_2), blood pressure, biology (haemogram, natraemia, C-Reactive Protein (CRP), renal assessment), chest X-ray, chest computed tomography (CT) scan, therapeutic measures, and outcomes. SARS-CoV-2 infection was confirmed by polymerase chain reaction reverse transcriptase (RT-PCR) or rapid antigen test.

Definitions

Respiratory forms of COVID-19: severe acute respiratory syndrome coronavirus-2 appears to cause predominantly respiratory disease in the form of viral pneumonia. Severe cases of severe acute respiratory syndrome coronavirus-2 infection can lead to hypoxemic respiratory failure with features of acute respiratory distress syndrome.

Acute respiratory distress syndrome (SDRA): according to the latest recommendations of the Pediatric Acute Lung Injury Consensus Conference (PALICC 2015) (Table 1) [4].

Chest computed tomography findings of COVID-19 in children: ground-glass opacities (GGO) were found to be the most prevalent chest CT manifestation, followed by peri bronchial thickening, linear or band-shaped opacities, consolidation, nodule, and effusion [5].

Statistics: data analysis was performed using SPSS (version 25). The comparison of two percentages on independent series was carried out using Pearson's Chi-square test and, in the event of non-validity of this test, Fisher's two-tailed exact test. The Student's T-test was used for a comparison of two means and the ANOVA test for a comparison of several means. If this test was invalid, we used the non-parametric U-Mann-Whitney test. The correlation between two quantitative variables was studied using the Pearson correlation test in the case of a Gaussian distribution and the Spearman test in the opposite case. For all statistical tests, the significance level was set at 0.05.

Ethical consideration: informed consent was obtained on privacy from all the parents of the infants included in the study. They were all informed of the scientific interest of this work. Data confidentiality was respected. Ethical approval was obtained from the local Ethical committee of the hospital.

Results

General characteristics of the study population: between March 1, 2020, and August 31, 2021, 224 children with COVID-19 were hospitalized at the Bechir Hamza Children's Hospital in Tunis. During this period, we recorded 51 cases hospitalized for a respiratory form of COVID-19, with a prevalence of 21.3%. Sixty-two-point-seven percent of the enrolled patients were male. The average age was 49.3 months with extremes ranging from 17 days to 182 months. The population under 12 months of age is the most affected by COVID-19 infection in its respiratory form and represents 50% of the study population (Table 2). Medical comorbidities reported were essentially respiratory (n=14), neurological (n=14), and cardiological (n=4). A history of asthma was found in 12 cases. Thirty-three children were reported to have had close contact with COVID-19-diagnosed relatives. Five patients were infected in the hospital while hospitalized for other reasons. Polymerase chain reaction (PCR) testing for SARS-CoV-2 in nasopharyngeal swabs was performed in 34 children (66.7%). Sixteen patients had a rapid nasopharyngeal antigen test (31.4%).

Clinical features: the medical reasons for emergency unit visits for patients who subsequently tested positive were varied, dominated by fever and/or respiratory symptoms. These signs were often associated with the same patient. Some children develop these signs during hospitalization. Fever was reported in 28 patients (54.9%). The average duration of fever before admission was 2.3 days, with extremes of 1 day and 7 days. Cough was present in 23 children (45.1%). The average duration of cough before hospitalization was 2.9 days. Dyspnea was noted in 40 children (78.4%). Digestive symptoms were also observed in 15.7% of patients and the classic anosmia-ageusia association was found only once, clinical presentation on admission showed polypnea in 37 patients (72.5%). It was associated with desaturation (68.6%). The minimum saturation during hospitalizations was 20% on room air in patients with acute respiratory distress syndrome (ARDS). Saturation above 94% was noted in 16 patients (31.4%). Shock with hypotension was reported in a patient being followed for chronic liver disease, secondary to extensive digestive hemorrhage (Table 3).

Laboratory and radiological features: white blood cell count was increased in 26 (41.2%) patients. Lymphopenia (lymphocyte count < 1500 elements/mm^3) was noted in 14 patients (27.5%). The lowest level was 320 elements/mm^3. C-reactive protein was increased in 19 children. Hyponatremia (< 130 mmol/l) was found in 1 patient (2%). This hyponatremia was related to inappropriate ADH secretion. Chest radiology on admission identified diffuse alveolar opacities in 15 patients and was normal in 10 cases. Chest radiology was checked in 5 patients. In one patient, a pneumothorax appeared on the 6thday of evolution (Figure 1, Figure 2). Chest CT scans were performed on 5 patients. They showed lesions consistent with COVID-19 involvement (Figure 3, Figure 4). One patient had a negative PCR test, but the CT scan was consistent with COVID-19 infection (Table 4).

Treatment and outcome: all children received treatment involving isolation, adequate rest, and nutritional support. All patients were treated with azithromycin and vitamins. Twelve patients were treated with corticosteroids. Thirty-one patients (60.8%) received oxygen therapy with a mean duration of 7.6 days (1-34 days). Oxygen therapy by nasal cannula was the most used mode (45.1%). Eight patients were put on Optiflow Junior. Nine patients presented with acute respiratory distress syndrome and 7 children required transfer to the intensive care unit. Non-invasive ventilation was used in 3 patients. Five patients were ventilated mechanically. The average duration of the mechanical ventilation was 7.6 days, with extremes ranging from 3 days to 21 days. Length of hospital stay ranged from 1-34 days (mean: 7 days). The outcome was favorable in 46 children (90.2%). We had a total of 5 deaths in our series

with a mortality rate of 9.8%. These deaths occurred in fragile children with comorbidities.

Discussion

COVID-19 has become a pandemic. Children´s cases are less than adult cases. Our study included 51 patients. The mean age of our study population was 49.3 months. The sex ratio was 1.68. In our cohort, 31 children (60.7%) had a pathological history, including 12 with known asthma. The most frequent reasons for hospitalization were fever (54.9%), cough (45.1%), and dyspnea (69.7%). Treatment was symptomatic. Thirty-one patients (60.8%) received oxygen therapy. Five patients were mechanically ventilated in the intensive care unit. Five patients died because of severe comorbidities, giving a mortality rate of 9.8%. Our study is, to our knowledge, the first Tunisian study that has described the respiratory forms of COVID-19 in children.

Early pediatric epidemiological data from China showed that only a minority of Covid-19 cases were children. A review of 72314 cases showed that less than 1% of cases involved children under 9 years of age and less than 1% involved children under 18 years of age [1]. The first pediatric case of COVID-19 in the world was reported in Shenzhen, China in January 2020 [6]. Since then, several cases have been reported and published in different parts of the world. In Tunisia, out of all confirmed cases reported to the National Observatory of New and Emerging Diseases (ONMNE), subjects under 20 years of age represented 6.8% of confirmed cases [3]. The clinical presentation in children is non-specific. Furthermore, it is known that a significant proportion of children may be completely asymptomatic [7]. Our study focused on the respiratory forms of COVID-19, which represented 22.8% of children hospitalized at the Bechir Hamza Children's Hospital in Tunis. Similar figures were found in the European series where respiratory forms represented 25% of cases (143/582 children included) [7]. In the Chinese series by Xiaoxia Lu, 33 children had only respiratory manifestations of COVID-19 (19.3% of cases) [9]. The most frequently reported respiratory signs are cough and dyspnea [6,8]. In our study, cough was present in 23 children (45.1%). Dyspnea was noted in 40 children (78.4%). Most of the publications showed fever and cough as major symptoms in children [9,10]. In our cohort, fever was present in 50.9% of cases, which is consistent with the literature.

Imaging techniques have been used in adults to diagnose SARS-CoV-2 pneumonia. Children have milder clinical presentations. Indications of chest imaging are limited and may differ from adults [11,12]. Fewer studies have been performed on the pediatric population and the peripheral bilateral diffuse infiltrates widely described in adult cases, seem to be less marked in children [13]. Chest tomography (CT) in initial studies was normal in pediatric series [14]. In this study, CT was performed in 5 children (9.8%). It was pathological in all 5 patients. It showed severe involvement of more than 50% in 2 cases. A clinic-radiological correlation was observed in our study.

Worldwide, death associated with SARS-CoV-2 infection in children has been very rarely reported [15]. A fatal outcome was observed in five patients with underlying disease. However, in a study conducted in a pediatric intensive and high-dependency care unit in an urban hospital in Paris, five children died, of whom three were without past medical history [16]. The symptoms of surviving children varied from an isolated cough and minor hypoxia to severe pneumonia with a need for invasive and prolonged mechanical ventilation. The asthmatic children had a good outcome. Data from 66 children admitted to a New York hospital showed that asthma was the most common comorbidity (24%) but was not associated with the need for intensive care treatment [17].

The World Health Organization and the US Centers for Disease Control and Prevention do not recommend specific drug treatment for children

with COVID-19 [18,19]. Symptomatic treatment alone was used in most cases [20]. In our study, thirty-one patients (60.8%) received oxygen therapy. Five patients required mechanical ventilation. All our patients received oral antibiotic therapy with azithromycin. Seventeen of our patients (33.33%) received intravenous antibiotic therapy. Thirteen patients received corticosteroid therapy, mainly methylprednisolone. The prognosis of the children with COVID-19 was good in the present study.

For the strength of our study, to our knowledge, our study is the first nationwide study to describe the respiratory forms of COVID-19 in children, including a representative sample. Our results are consistent with the literature. Among the weaknesses of our study, the retrospective nature of our study, several data were missing from the files, and the medium- and long-term follow-up of patients. The emergence of numerous variants of SARS-CoV-2 had an impact on the characteristics of the epidemic (increased transmissibility and severity of infection).

Conclusion

Children of all ages can be affected by COVID-19, with a high number of clinical presentations and circumstances of diagnosis. In this population, SARS-CoV-2 infection has very different clinical presentations, ranging from a mild common cold to a severe respiratory illness and death. Despite the severity of some initial clinical pictures, mortality was not high. Co-morbidities can affect the outcome. Respiratory forms of COVID-19 are milder in children.

What is known about this topic

- *COVID-19 occurs in children of all ages;*
- *Pediatric forms differ greatly from what is observed in adults;*
- *At present, there is no specific treatment for COVID-19 in adults or children; management is usually supportive.*

What this study adds

- *This study highlighted the large spectrum of clinical presentation and time course of disease progression as well as the non-negligible occurrence of pediatric life-threatening and fatal cases of COVID-19 mostly in patients with comorbidities;*
- *Children with underlying diseases need to be protected from high-risk infection environments.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Fatma Khalsi and Neila Ben Aba collected the data. Fatma Khalsi and Soumaya Kbaier wrote the manuscript. Imen Belhadj and Khadija Boussetta revised the manuscript. Khawla Meftah and Hanen Smaoui performed and collected the laboratory exams. All the authors have read and agreed to the final manuscript.

Tables and figures

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Figure 2: basal bronchoalveolar syndrome

Figure 3: infectious SARS-CoV-2 pneumonia with moderate involvement estimated at 10-15%

Figure 4: mild SARS-CoV-2 infectious lung disease

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Table 1: paediatric acute respiratory distress syndrome definition	
Age	Exclude patients with peri-natal related lung disease
Timing	Within 7 days of known clinical insult
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Chest imaging	Chest imaging findings of new infiltrate (s) consistent with acute pulmonary parenchymal disease
Oxygenation	**Non-invasive mechanical ventilation: PARDS (no severity stratification)**
	Full face-mask bi-level ventilation or CPAP ≥ 5cmH2O
	PF ratio ≤ 300
	SF ratio ≤ 264
	Invasive mechanical ventilation
	Mild
	4 ≤IO< 8
	5 ≤ OSI < 7.5
	Moderate
	8 ≤ IO <16
	7.5 ≤ OSI <12.3
	Severe
	IO ≥16
	OSI ≥ 12.3
OI = oxygenation index, OSI = oxygen saturation index	

Table 2: demographic data of patients	
Demographics	**N (%)**
Gender	
Girl	19 (37.3%)
Boy	32 (62.7%)
Age	
< 12 months	26 (51%)
1-5 years	6 (11.8%)
> 5 years	19 (37.2%)
Comorbidity	
Prematurity	2 (3.92%)
Asthma	12 (23.52%)
Cardiac disease	4 (7.84%)
Encephalopathy	4 (7.84%)
Chronic liver disease	2 (3.92%)

Table 3: clinical manifestations of patients	
Clinical manifestations	**N (%)**
Fever	28 (54.9%)
Cough	23 (45.09%)
Respiratory distress	37 (72.54%)
Cyanosis	35 (68.62%)
Hemodynamic disorders	16 (31.4%)

Table 4: chest computed tomography (CT) findings of COVID-19 in children	
Patients	**Chest CT findings**
Patient 1	Severe SARS-CoV-2 disease is estimated at 75%
Patient 2	Right basal pulmonary condensation with liquid pleural effusion
Patient 3	Right basal pulmonary condensation with liquid pleural effusion, several bilateral subpleural ground-glass areas associated with a few basal condensations in the medial segment of the middle lobe and the lower segment of the lingula suggestive of COVID-19 pneumopathy, probably with areas of bacterial superinfection in the middle lobe and lingula. 15% parenchymalinvolvement
Patient 4	Moderate parenchymal damage is estimated at between 10 and 15%
Patient 5	Severe parenchymal damage is estimated at between 50 and 85%

Figure 1: left basal pneumonia

Figure 2: basal bronchoalveolar syndrome

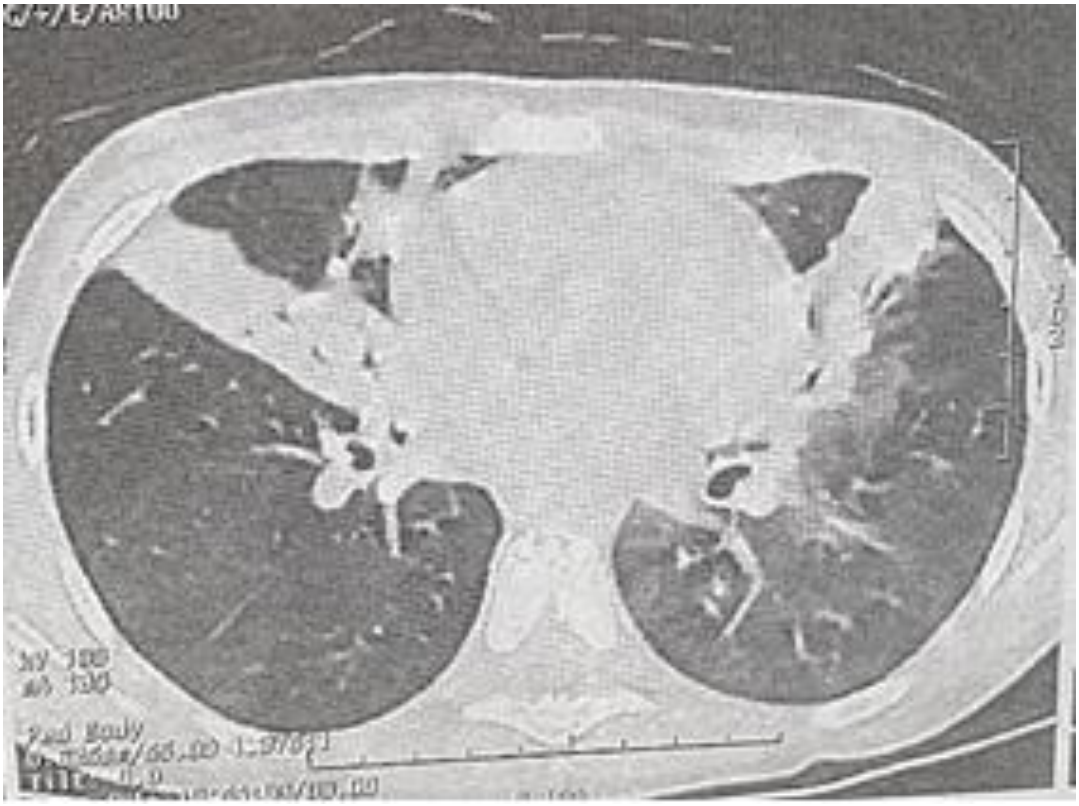

Figure 3: infectious SARS-CoV-2 pneumonia with moderate involvement estimated at 10-15%

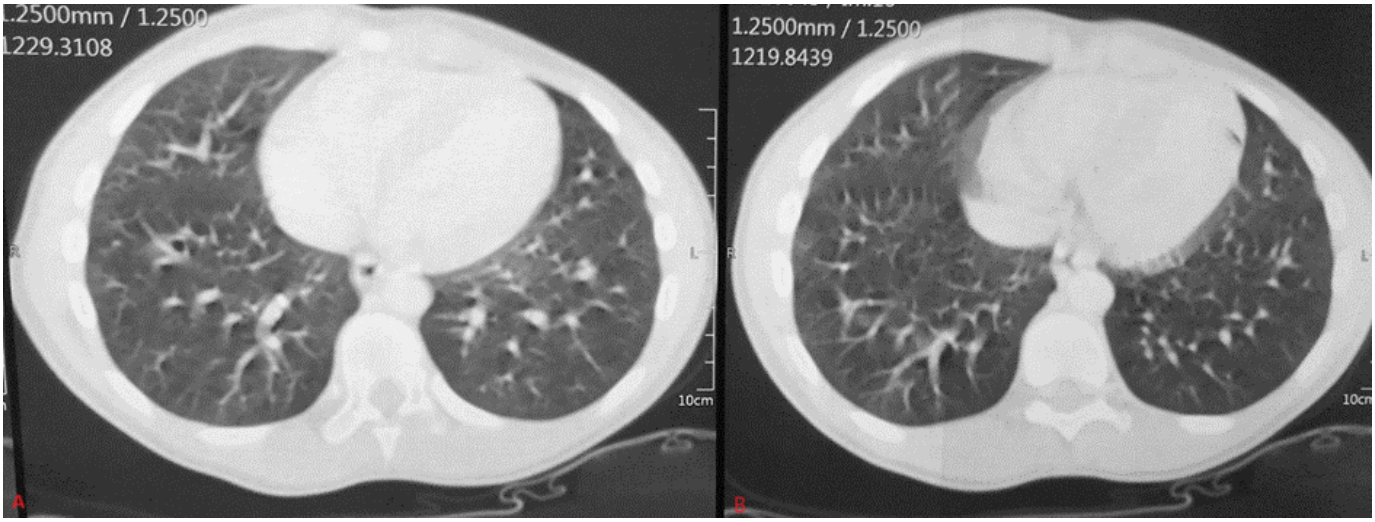

Figure 4: mild SARS-CoV-2 infectious lung disease