

COVID-19 in a tertiary paediatric centre in Portugal: a single-centre retrospective study

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ABSTRACT

Objective To describe the demographic, clinical, laboratory and imaging features of the first 300 SARS-CoV-2-infected children presenting to a tertiary paediatric centre in Portugal.

Design Single-centre, retrospective, descriptive study of paediatric patients who had a confirmed SARS-CoV-2 infection from 7 March to 20 September 2020.

Setting Tertiary paediatric referral centre (Hospital Dona Estefânia, Lisbon, Portugal).

Patients 18 years or younger.

Main outcome measures Incidence, mortality, age of infection, clinical characteristics, treatment prescribed and outcome.

Results Three hundred patients with confirmed COVID-19 presented to the centre. One hundred and seventeen (39%) patients were admitted to the hospital: 69 with COVID-19 and 48 for other reasons. The most common symptoms in children admitted with COVID-19 were fever (49) and cough (38). Six patients required intensive care. Two children died and seven reported short-term sequelae.

Conclusions COVID-19 is usually a mild disease in children, but a small proportion of patients develop severe and critical disease. Fatal outcomes were rare and only occurred in children with severe previous medical conditions.

INTRODUCTION

COVID-19, caused by the new SARS-CoV-2,¹ was first found linked to a cluster of atypical pneumonia in Wuhan, China in December 2019.² Person-to-person transmission has resulted in the rapid spread of the disease across borders and continents. The WHO declared COVID-19 a pandemic on 11 March 2020.³ In Portugal, the first case was reported on 2 March 2020 and the first paediatric case on 7 March 2020.⁴ Our hospital was one of two national reference hospitals for paediatric patients with COVID-19 and has been responsible for the management of a major portion of paediatric severe cases in the country.⁵

Although the paediatric population seems to be less affected compared with adults⁶ and the clinical presentation and evolution seem

What is known about the subject?

- ⇒ COVID-19 is usually a mild disease in children, but a small proportion of patients develop severe and critical disease.
- ⇒ It is challenging to suspect and diagnose COVID-19 in children based on their symptoms without epidemiological information and virus testing.
- ⇒ COVID-19 in paediatric patients continues to be less characterised compared with adults.

What this study adds?

- ⇒ To our knowledge this is the largest series of paediatric patients in Portugal, one of the most affected countries in Europe.
- ⇒ A high usage of antibiotics was noted, probably related to the uncertainties regarding evolution of the disease during the first phase of the pandemic.
- ⇒ The series confirms that COVID-19 is usually mild in children, although severe and critical disease occurs, and this may have implications on vaccine recommendations in younger children.

to be generally less severe, critical cases occur nonetheless.⁷⁻¹²

COVID-19 in paediatric patients continues to be less characterised compared with adults.¹³ Aspects such as secondary transmission, ideal methods for diagnosis, and clinical and laboratory markers of worse prognosis are still being questioned.¹⁴

This study aimed to review and analyse the demographic, clinical, laboratory and imaging features of the first 300 SARS-CoV-2-infected patients accompanied to our hospital.

METHODS

This is a single-centre (Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal), retrospective, descriptive study of children and



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Table 1 Clinical respiratory syndrome associated with COVID-19 according to the WHO¹⁵

Asymptomatic	Without any symptoms, confirmed by laboratory tests.
Mild	Respiratory infection of the upper tract: fever, cough, fatigue, anorexia, myalgia, sore throat, rhinorrhoea and headache; rarely with nausea, vomiting and diarrhoea.
Moderate	Pneumonia with non-severe signs of respiratory distress: tachypnoea <2 months: ≥ 60 cpm; 2–11 months: ≥ 50 cpm; 1–5 years: ≥ 40 cpm; >5 years: > 30 cpm, moderate recession; $SpO_2 \geq 93\%$.
Severe	Pneumonia with severe signs of respiratory distress: central cyanosis or $SpO_2 < 93\%$, severe tachypnoea (70 cpm; >12 months: > 50 cpm), severe recession, grunting and nasal flaring; severe anorexia, lethargy/diminished level of consciousness and convulsions.
Critical	ARDS, sepsis and septic shock.

ARDS, acute respiratory distress syndrome; cpm, cycles per minute; SpO_2 , peripheral capillary oxygen saturation.

adolescents, 18 years or younger, who presented to the centre and had a confirmed SARS-CoV-2 infection from 7 March to 20 September 2020 (timing of the 300th diagnosed paediatric patient). Age, sex, underlying disease, date of diagnosis, route of exposure, clinical, laboratory and radiographic findings, treatment, and outcome were analysed. Cases were diagnosed by real-time reverse transcription-PCR (rRT-PCR) in a combined nasopharyngeal and oropharyngeal swab or respiratory secretions or by confirmation of antibodies to SARS-CoV-2. Patients were diagnosed at the emergency room of our hospital or were transferred from other referring centres.

Patients were considered to have mild, moderate, severe or critical disease according to the WHO guidelines (table 1).¹⁵

All antiviral therapies were administered after informed consent was signed by parents or caretakers, and approval by the pharmacy commission of our hospital was obtained.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

Three hundred patients who had confirmed COVID-19 presented to the centre. One hundred and seventeen (39%) patients were admitted to the hospital: 69 with COVID-19 and 48 for other reasons.

May was the month with a higher count of new diagnoses (81). The number of pediatric cases accompanied, with some delay, the Portuguese epidemiological curve (figure 1). The median age was 5 years (IQR 1–11), with 73 children younger than 1 year and 12 children younger than 1 month, with a male to female ratio of 1.11 (table 2). A known contact was identified in 201 (67%) patients. The most common source of infection was a household contact (158): 123 had at least one parent infected and 35 another adult cohabitant. In 13 children, infection was nosocomial. Fifty-six (18.7%) patients had a pre-existing chronic medical condition: chronic pulmonary disease (18), congenital heart disease (9), chronic neurological disease (7), chromosomal abnormalities (5), chronic

haematological disease (4), short bowel syndrome (3), chronic renal disease with end-stage kidney failure (3) and type 1 diabetes (2). Four patients were receiving immunosuppressive therapy. Among the 300 children, 57 (19%) were asymptomatic. The demographic and clinical characteristics of the patients are shown in table 2.

The mode of the time between symptom appearance and diagnosis was 3 days (IQR 1–4).

Admitted patients

One hundred and seventeen (39%) patients were admitted to the hospital: 69 with COVID-19 and 48 for other reasons, namely diagnosis during the containment phase (8), social motives (2) and other conditions requiring hospitalisation not related to COVID-19 (38), such as surgical conditions, infections with a need for intravenous antibiotics and psychiatric conditions.

COVID-19 admissions

Admitted patients with COVID-19 were classified as having mild disease in 27 cases (39.1%), moderate in 21 (30.4%), severe in 12 (17.4%) and critical in 9 (13%) (table 3).

In children admitted with COVID-19, the most frequent findings were leucocytosis (33), lymphocytosis (33), elevated lactate dehydrogenase (LDH) (50), and elevated inflammatory markers such as procalcitonin

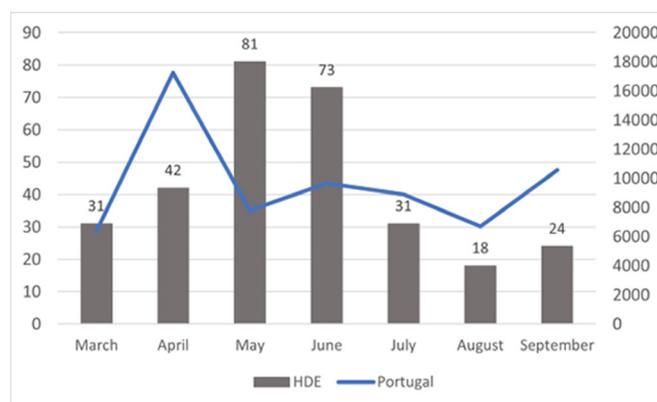


Figure 1 Monthly distribution of new diagnosis at Hospital Dona Estefânia (HDE) and new diagnosis in the Portuguese population.

Table 2 Demographic and clinical characteristics on admission

	Admitted due to COVID-19-related causes (n=69)	Admitted for other causes (n=48)	Non-admitted patients (n=183)
Age, years, n (%)			
<1	30 (43.5)	7 (14.6)	36 (19.7)
1–5	14 (20.3)	12 (25)	57 (31.1)
6–10	10 (14.5)	10 (20.8)	33 (18)
≥11	15 (21.7)	19 (39.6)	57 (31.1)
Sex, n (%)			
Male	37 (53.6)	29 (60.4)	92 (50.3)
Female	32	19	91
Comorbidities, n (%)			
Yes	33 (47.8)	14	27
No	36 (52.2)	34 (70.8)	156 (85.2)
Symptoms at presentation, n (%)			
Fever	49 (71.0)	12	106 (57.9)
Cough	38 (55.1)	7	70 (38.3)
Rhinorrhoea	23 (33.3)	4	45 (24.6)
Odynophagia	7 (10.1)	6	31
Headache	9 (13.0)	3	27
Myalgia	3 (4.4)	1	18
Diarrhoea/abdominal pain	21 (30.4)	4	33
Nausea/vomiting	17 (24.6)	5	25
Asthenia	17 (24.6)	0	14
Anosmia	3 (4.4)	0	7
Ageusia	2 (2.9)	0	5
Thoracalgia	7 (10.1)	0	5
Seizures	1 (1.5)	0	0
Anorexia	16 (23.2)	1	13
Dyspnoea	20 (29.0)	0	7
Skin lesions	6 (8.7)	0	11
Tachycardia	20 (29.0)	0	0
Tachypnoea	23 (33.3)	0	0
Hypoxaemia	18 (26.1)	0	0

(PCT) (49), ferritin (39) and C-reactive protein (CRP) (15). Lymphopaenia was present in nine children.

Chest X-ray was performed in all admitted patients, 41 of whom had abnormal findings. Chest CT was performed in 31 of 69 (44.9%) patients, with abnormal findings in 25 of 31 (80.6%). According to the British Society of Thoracic Imaging codes,¹⁶ the classic COVID-19 findings with bilateral ground glass opacities were present in 11 patients, peripheral consolidations in 8, reverse halo in 1 and perilobular pattern in 1. Nine patients had indetermined findings with unilateral ground glass opacities and three patients had findings non-typical of COVID-19 (2 lobar pneumonia, 2 pleural effusion and 1 lymphadenopathy).

Respiratory coinfections occurred in 19 admitted patients, with rhinovirus (9), adenovirus (3), enterovirus (3), influenza B (2) and *Pneumocystis jiroveci* (2) being the most common. Other respiratory pathogens included syncytial respiratory virus, metapneumovirus, coronavirus 43, parainfluenza 3, bocavirus and *Mycoplasma pneumoniae*.

Four patients fulfilled the criteria for multisystem inflammatory syndrome in children (MIS-C) (three male, mean age 7.3 years, range 4–14 years). One patient had a congenital cardiopathy and the others were previously healthy. All of them presented with fever, abdominal pain, exanthema and non-exudative conjunctivitis. Laboratory evidence of the inflammatory state was

Table 3 COVID-19 disease classification and diagnosis of admitted patients

COVID-19 classification and diagnosis	n
Mild cases	27
Mild illness without comorbidities	16
Mild illness with comorbidities	11
Moderate cases	21
Pneumonia	21
Severe cases	12
Pneumonia	10
MIS-C without haemodynamic instability	2
Critical cases	9
MIS-C	2
Pneumonia	1
ARDS	2
Myocarditis	2
Sepsis	2

ARDS, acute respiratory distress syndrome; MIS-C, multisystem inflammatory syndrome in children.

particularly marked: CRP 234.5 (78.1–399.3) mg/L, PCT 3.17 (0.37–9.88) ng/mL, Interleukine-6 112 (56.2–456.7), LDH 559.5 (267–1220) U/L and ferritin 2615 (406–6894) ng/mL. Moreover, all patients had coagulopathy (D-dimer 866 (631–1555) µg/L), myositis (Creatine kinase 402 (129–455) U/L) and myocarditis (N-terminal pro Brain Natriuretic Peptide 13 055 (559–23 156) pg/mL and troponin I 280.5 (80.8–4632.9) pg/mL). Only two presented lymphopaenia. rRT-PCR was positive in the oropharynx/nasopharynx swabs in two patients and the other two had positive anti-SARS-CoV-2.

Echocardiographic findings were non-specific and included mild mitral valve insufficiency in two patients and coronary hyperechogenicity in another two patients. None presented with coronary dilation or aneurysms. One patient (with previous cardiopathy) showed left ventricular dysfunction and septal dyskinesia, but very similar to previous evaluations. No other patient showed ventricular or diastolic dysfunction.

Two patients presented haemodynamic instability. Both of them were treated with intravenous immunoglobulin (1 g/kg/day for 2 days) and intravenous methylprednisolone (2 mg/kg/day) for 5 days, followed by slow tapering. In both of them there was a rapid decline in IL-6 values, followed by a slow decline in C reactive protein and other inflammatory markers (leucocytosis, neutrophilia, procalcitonin) in the next days.

Six patients were admitted to the intensive care unit with an average length of stay of 10 days: two patients with MIS-C who needed inotropic support and mechanical ventilation; myocarditis in two patients with known cardiopathy; COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) in a patient with

Table 4 Antiviral therapy used in admitted patients with COVID-19

Antiviral therapy	n
Hydroxychloroquine	8
Lopinavir/ritonavir	4
Hydroxychloroquine + lopinavir/ritonavir	5
Remdesivir	4

lymphangoendotheliomatosis; and another patient with chronic respiratory insufficiency.

Treatment

Antiviral therapy was proposed in 21 (30.4%) patients (table 4), including mild disease with comorbidities (3), moderate (5), severe (6) and critical (7) disease.

Four patients with MIS-C and one case of severe ARDS were treated with intravenous immunoglobulin and systemic corticosteroids. Systemic corticosteroids were still administered in four patients with exacerbation of asthma and in one patient with chronic respiratory insufficiency.

Antibiotics were used in 30 patients: ceftriaxone, amoxicillin with clavulanate, cefuroxime and/or clindamycin when respiratory bacterial superinfection was suspected (17); ampicillin, cefotaxime and gentamicin in infants less than 3 months old (2); and vancomycin, ceftriaxone and clindamycin empirically in the admission for MIS-C (4). Two patients with *P. jiroveci* coinfection received cotrimoxazole. Others received antibiotics due to non-related COVID-19 infections, such as pyelonephritis (2), sepsis related to central venous catheter (2) and osteomyelitis (1). Azithromycin and/or oseltamivir were used when coinfections with *M. pneumoniae* and influenza were suspected.

Nineteen admitted patients needed supplemental oxygen for a mean duration of 6.9 days (range 1–38). Mechanical ventilation was needed in four patients for a mean duration of 10 days (range 5–20). Inhaled therapy with bronchodilators and corticosteroids was used in 39 patients. Prophylactic enoxaparin was used in three patients with MIS-C and in one patient with sickle cell disease and acute chest syndrome.

Adverse drug reactions were seen in three patients who received lopinavir/ritonavir, with nausea and vomiting, but without the need to discontinue therapy. Among 13 patients who received hydroxychloroquine, regular ECG was undertaken and only two had to discontinue HCQ temporarily (24 hours) due to prolonged QT interval (QTc) >500 ms. No adverse effects were seen with remdesivir.

The mean duration of hospital stay was 6.8 days (range 1–28 days), with a mean of 3.1 days in mild illness, 4.3 days in moderate illness, 6.4 days in severe illness and 17.1 days in critical illness.

Two patients had a fatal outcome, both with severe comorbidities (neurological disease and congenital cardiopathy).

The mean duration of time between the first positive and the first negative rRT-PCR was 23 days, ranging from 1 to 115 days.

Seven children have shown short-term sequelae: increased oxygen necessity in an infant with bronchopulmonary dysplasia and COVID-19 pneumonia (1); myocardial scar tissue on cardiac magnetic resonance (at 6 months post admission) in a patient with MIS-C (1); worsening of cardiac function in a child with previous severe aortic valve regurgitation and MIS-C (1); and weight loss and muscular atrophy in all patients with MIS-C (4). Psychological sequelae were not analysed.

DISCUSSION

The COVID-19 pandemic has placed a high burden on the medical community.¹⁷ Children at any age are at risk of being infected.^{7–11 18 19} In our series, the median age of presentation was 5 years, in concordance with the ptbnet group study of European paediatric patients.¹⁰

In our sample, there was a significant number of children with unknown exposition (33%). This brings to light the potential role of asymptomatic, non-diagnosed patients in the transmission of the virus in the community,²⁰ outside the house environment, and the need for mass testing of the general population.²¹ The rates of asymptomatic children have varied from 4.4% to 23%^{7 8 10 11 18} and probably represent a significant underestimation as many asymptomatic children are not screened. In our population, these asymptomatic patients represent cohabitants of infected people and patients who were diagnosed during hospital preadmission screening or during control of nosocomial transmission.

We had a hospital admission rate of 39%. Patients younger than 1 year presenting with respiratory distress signs and those with pre-existing medical conditions were significantly more likely to be admitted. The high admission rate and the clinical severity reported relate to the fact that we function as a referral centre for the entire south area of the country. Nonetheless a significant percentage of admitted patients had mild disease (with or without comorbidities). This occurred during the early phase of the pandemic and probably reflects some uncertainty regarding the clinical evolution of paediatric patients.

Respiratory viral coinfection occurred in 27.5% of the admitted patients with COVID-19, which is a rate lower than what has been previously reported.²² The increased use of masks and the quarantine measures instituted (eg, closing of schools) probably explain this discrepancy.²³ The role of these coinfections in disease severity and outcome remains to be established,^{24 25} especially when co-circulation of different viruses is expected to occur as schools open and quarantine measures dwindle.

In children with SARS-CoV-2, treatment primarily consists of supportive care, including oxygen and advanced respiratory support, hydration, nutritional support, and antipyretics.^{12 26} A various number of drugs have been proposed as treatment options in children and their use has been reported and encouraged by national guidelines.¹⁰ Some of them have, since the beginning of the pandemic, been withdrawn from regular clinical use,²⁷ such as LPV/r and hydroxychloroquine. Remdesivir has emerged as the preferred agent for treating severe COVID-19 in children.^{12 23 28} Our data reflect the uncertainties regarding drug treatment options for COVID-19.

In our series, a high usage of antibiotics in the initial management of patients was noted. The percentage of severe and critical admitted patients and the uncertainties surrounding the first phase of the pandemic probably explain this finding, as has already been noted in some studies.²⁹

Rare paediatric fatal cases have been reported.¹⁰ In our study, both fatal cases had severe pre-existing medical conditions. The sequelae reported in our sample (2.3%) are probably under-rated. They do not include, for example, psychological sequelae. Exercise intolerance, reduced lung vital capacity, myocardial scars in patients with MIS-C and loss of muscle mass are just some of the possible sequelae that need to be identified as soon as possible.^{30 31}

The main limitation of the study relates to population characteristics. As mentioned above, we are a tertiary referral hospital. Our patients are likely to represent individuals at the more severe disease spectrum. It excludes a significant proportion of asymptomatic and mild patients. The follow-up period also does not permit drawing conclusions about the real incidence of medium-term and long-term sequelae of COVID-19.

CONCLUSIONS

Our findings add to the general perception that COVID-19 is usually a mild disease in children, but a small proportion of patients develop severe and critical disease. It is very challenging to suspect and diagnose COVID-19 in children based on their symptoms without epidemiological information and virus testing. A significant proportion of patients are likely to be asymptomatic and the only way of diagnosing these patients is mass testing in the community. Uncertainty remains regarding specific antiviral options as more robust studies are bound to arrive in the near future.

We hope our study clearly details our experience with these patients and adds to the general information on this global health problem.

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reviewed the manuscript for important intellectual content. TMS is the guarantor of this article.

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