ORIGINAL ARTICLE

Pediatric patients with COVID-19 admitted to a PICU in Southern Brazil, excluding MIS-C

Cristiane Traiber *, **Fernanda Umpierre Bueno, Luiz Roberto Braun Filho, Guilherme Unchalo Eckert, Marcelo Almeida Azambuja** ◊, **Gabrielle Segatto Gras** ◊

Hospital Criança Conceição, Porto Alegre, RS, Brazil

Abstract
Objective: To describe pediatric patients admitted to a PICU with a diagnosis of COVID-19 and to compare some variables in relation to severely ill patients and critically ill children, excluding patients with MIS-C.
Method: Retrospective case series of patients aged 24 days to 15 years with a diagnosis of COVID-19 admitted to a PICU from April 1, 2020, to April 1, 2021. We describe data regarding epidemiological characteristics, clinical manifestations, laboratory, and imaging tests, treatment, and outcome. We also divided the patients into two groups: severely ill patients and critically ill patients (those who required invasive mechanical ventilation (IMV), non-invasive ventilation or shock), and we compared some variables to determine possible predictors of greater severity.
Results: 32 children were admitted with severe COVID-19; 20 of them were considered critical. The median age was 2 years. Of the patients, 50% were male and 81% had comorbidities, and 44% had 3 or more comorbidities. Respiratory failure was the main cause of hospitalization. Fifty-six percent required IMV, and 37% used vasoactive drugs. Bacterial or viral co-infection occurred in 41%. A total of 81% of our patients received antimicrobials, 53% patients received low-dose corticoids, and 25% received enoxaparin. Patients with 3 or more comorbidities were significantly more frequent in the critically ill group.
Conclusion: Most of the children admitted to PICU had comorbidities, and children under 1 year of age made up almost half of the sample. In our study, the presence of three or more comorbidities was more frequent in pediatric patients with critical COVID-19.
© 2021 Published by Elsevier España, S.L.U. on behalf of Asociación Colombiana de Medicina Crítica y Cuidado lntensivo.

---

* Corresponding author.
  E-mail address: cristraiber@gmail.com (C. Traiber).
◊ Resident in pediactric intensive care medicine.

Pacientes pediátricos con COVID-19 ingresados en una UCI en el sur de Brasil, excluyendo MIS-C

Resumen

Objetivo: Describir a los pacientes pediátricos ingresados en una UCIP con diagnóstico de COVID-19 y comparar algunas variables en relación con los pacientes gravemente enfermos y los niños críticamente enfermos, excluyendo a los pacientes con MIS-C.

Método: Serie de casos retrospectiva de pacientes de 24 días a 15 años con diagnóstico de COVID-19 ingresados en una UCIP desde el 1 de abril de 2020 al 1 de abril de 2021. Describimos datos sobre características epidemiológicas, manifestaciones clínicas, pruebas de laboratorio y de imagen, tratamiento y resultado. También dividimos a los pacientes en 2 grupos: los gravemente enfermos y los críticos (aquellos que requirieron ventilación mecánica invasiva, ventilación no invasiva o choque), y comparamos algunas variables para determinar posibles predictores de mayor gravedad.

Resultados: Treinta y dos niños ingresaron con COVID-19 grave; 20 de ellos fueron considerados críticos. La mediana de edad fue de 2 años. El 50% de los pacientes eran varones y el 81% presentaba comorbilidades, y el 44% presentaba 3 o más comorbilidades. La insuficiencia respiratoria fue la principal causa de hospitalización. El 56% requirió ventilación mecánica invasiva y el 37% utilizó fármacos vasoactivos. La coinfección bacteriana o viral ocurrió en el 41%. El 81% de nuestros pacientes recibió antimicrobianos, el 53% de los pacientes recibió corticoides en dosis bajas y el 25% recibió enoxaparina. Los pacientes con 3 o más comorbilidades fueron significativamente más frecuentes en el grupo de enfermos críticos.

Conclusión: La mayoría de los niños ingresados en la UCIP presentaba comorbilidades, y los menores de 1 año eran casi la mitad de la muestra. En nuestro estudio la presencia de 3 o más comorbilidades fue más frecuente en pacientes pediátricos con COVID-19 crítica.

© 2021 Publicado por Elsevier España, S.L.U. en nombre de Asociación Colombiana de Medicina Crítica y Cuidado lntensivo.

Introduction

In December 2019, in Wuan, China, a group of patients with a new type of pneumonia was described. This outbreak was caused by a beta-coronavirus, identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The disease caused by this virus was named 2019 coronavirus disease (COVID-19) by the World Health Organization (WHO). The virus quickly spread to all continents, causing a pandemic.[1]

SARS-Cov-2 infection affects children less severely than adults.[1–4] Although most infected children and youngsters are asymptomatic or present a mild to moderate illness, some manifest a severe disease, in addition to the so-called multisystem inflammatory syndrome in children (MIS-C), requiring admission to a Pediatric Intensive Care Unit (PICU).[3,5–8]

Several studies, including multicenter studies, describe a small number of pediatric patients admitted to PICU due to COVID-19.[1,3,9–13] Different ages are described in the pediatric studies, with patients up to 21 years old being included. Some studies compare patients in PICU who underwent invasive mechanical ventilation (IMV) and those who did not require IMV.[5] Other studies considered critical patients those who needed respiratory support with non-invasive ventilation (NIV) or IMV, as well, as those who evolved with shock and/or multiple organ failure.[6,8,13] Some case series describe patients with severe COVID-19 and MIS-C cases together,

others separate these two groups of patients.[4,5,7,12] Thus, the factors associated with disease severity and mortality, as well as treatment in pediatrics, are still under investigation.

Brazil is one of the countries most affected by the pandemic. The first confirmed case of COVID-19 in our country was registered on 02/26/2020. Until 03/27/2021 Brazil was the second country with the highest number of accumulated cases, totaling 12,490,362 and 310,550 deaths.[14]

In this study, we describe pediatric patients admitted to a PICU in southern Brazil with a diagnosis of COVID-19 and compare some variables in relation to severely ill patients and critically ill children, excluding patients with a diagnosis of MIS-C from the comparison.

Method

A retrospective case series study of pediatric patients admitted to the one PICU from April 1, 2020 to April 1, 2021 with a diagnosis of COVID-19. The diagnosis of infection was made by positive SARS-Cov-2 reverse transcriptase-polymerase chain reaction (RT-PCR) testing, using nasopharyngeal swabs. The included patients ranged in age from 24 days to 15 years.

We describe data regarding epidemiological attributes, clinical manifestations, laboratory and imaging tests, treatment, evolution and outcome. We also divided the patients into two groups, considering severely ill patients those cases that were admitted to the PICU, and critically ill

patients those who presented shock or needed respiratory support through invasive mechanical ventilation (IMV) or non-invasive ventilation (NIV). We compared some variables between the two groups to determine possible predictors of greater severity.

Data were collected from electronic medical records and recorded in a Microsoft office Excel 2013 spreadsheet. Categorical variables were presented as proportion (%), and continuous data were expressed as median and interquartile range (IQR) or mean and standard deviation. We used the Shapiro–Wilk normality test. Fisher's exact t-test was used to compare categorical variables. The Mann–Whitney test was used to compare median of continuous variables without normal distribution, and the T-test was used for continuous variables with normal distribution. The analyses were performed using the Statistical Product and Service Solution (SPSS 25.0).

The Research Ethics Committee of our institution approved the study.

Results

During the study period, 40 critically ill patients were diagnosed with SARS-CoV-2 infection. Of these, 32 children were diagnosed with COVID-19. Eight children were excluded from the study because they were diagnosed with MIS-C. Of the 32 patients, 18 required invasive mechanical ventilation, 1 non-invasive ventilation, and 1 child had shock, without requiring IMV; these cases were described as critical patients. The clinical and epidemiological characteristics and evolution of COVID-19 patients, both critical and non-critical, are presented in Table 1. The median age was 2 years (2 months–8.6 years). 50% of patients were male, and 81% were white. Reports of contact with a confirmed person were described in only 14 (44%) cases.

Twenty-six (81%) patients had comorbidities, with 14 (44%) having 3 or more comorbidities. Prematurity was the most common 8 (25%), still 6 (19%) children had genetic syndromes (3 with Down Syndrome) and 6 (19%) patients had oncologic disease. Two patients were on chemotherapy (one critical and one non-critical), and one was chronically using corticosteroids (non-critical). Two patients had only obesity as a comorbidity, and one child had only asthma (all three were non-critical patients). The presence of 3 or more comorbidities was significantly more frequent in critically ill patients (Table 1).

The time of symptom onset at admission was 3 days (1–6 days), with the most common symptoms being tachypnea, cough, and rhinorrhea. Only 50% of the patients had a history of fever. No patient had mucocutaneous symptoms.

Regarding the causes of admission, most patients had admitted for respiratory failure (72%). The second reason for admission was convulsive status epilepticus 5 (16%). Among the 5 patients who presented convulsive status was a 29-day-old girl, 36 weeks premature, with abdominal presentation and bacterial sepsis; another patient was a 9-month-old boy, healthy, viral cerebrospinal fluid and extensive bilateral ischemic stroke. In this group, there were also a 32-day-old boy with pneumococcal meningitis and two children aged 1 and 10 years with prior epilepsy. Among the other reasons for admission was a patient with decompensated

nephrotic syndrome associated with a mild viral condition (COVID-19). Of the 3 patients with shock as a cause for admission, one was a 24-day-old previously healthy infant who presented cardiogenic shock secondary to refractory supraventricular tachycardia to manage; another was a previously healthy 2-year-old girl with severe diarrhea and vomiting who required volume resuscitation several times for poor perfusion and hypotension; and a 7 year old boy with multiple liver abscesses and staphylococcus infection.

Thirteen (41%) patients had bacterial or viral co-infection diagnosed together with SARS-CoV-2 infection. Of these, only three cases were non-critical patients (Table 2).

The laboratory tests, the most altered value in the first 48 h of admission, as well as the results of the imaging tests of COVID-19 patients, both critical and non-critical, are presented in Table 3. The median alanine aminotransferase (AST) was significantly higher in critical patients (62 × 30 U/L). Twenty-four (75%) patients had altered chest radiography on admission, with bilateral infiltrate being the most common finding. Only 5 patients had chest computed tomography scan; all had ground-glass opacities bilaterally. Echocardiogram was performed in 14 (44%) patients; three patients had biventricular systolic alteration with decreased ejection fraction, two of them with pulmonary hypertension, and another patient had moderate pulmonary hypertension. Four (12%) patients had electrocardiograms, only one of which was altered, showing supraventricular tachycardia, altered ventricular repolarization and overload of the right atrium and ventricle.

The evolution, therapies and outcome of the patients are presented in Table 4. Although 19 children required respiratory support, only 9 developed acute respiratory distress syndrome (ARDS), and 8 of these required neuromuscular blockade with intermittent pancuronium or continuous atracurium. All ARDS patients were submitted to prone position and lung protective strategies. The duration of mechanical ventilation was 8.5 days (median). Two patients with severe pulmonary hypertension were ventilated with nitric oxide. Thirteen (40%) patients presented shock, 12 (37%) received, according to the characteristics of shock, adrenaline or noradrenaline, and in some cases there was an association with milrinone. Twenty-six (81%) children received antibiotics, and 17 (53%) received corticoids (dexamethasone or prednisolone). No patients received antiviral drugs or immunomodulatory biologic agents. Eight received prophylactic enoxaparin or treatment. No patient required dialysis support, although 25% of cases had altered creatinine within 48 h of admission. The PICU length of stay was 7.5 days (median), being 3 days for non-critical patients and 13.5 days for critical ones ($P = 0.01$).

Three patients had thromboembolic events, a healthy boy with acute cerebrovascular accident, a 7-year-old boy with liver abscesses and thrombosis of the portal and inferior vena cava, and a 2-year-old girl with several comorbidities, shock and ARDS, evolved with thrombosis of the jugular and subclavian veins associated with the presence of a venous catheter, even in the presence of enoxaparin in prophylactic doses. There were no hemorrhagic events in our series of cases.

There were 3 deaths during the study period. One healthy 7-year-old girl arrived in shock, without peripheral pulse, with cyanotic extremities, oxygen saturation of 80% on a

Table 1 Clinical and epidemiological characteristics.

	Total $n = 32$ n (%) or median (IQR)	Critical patients $n = 20$ n (%) or median (IQR)	Non-critical patients $n = 12$ n (%) or median (IQR)	P value
Age, months distribution by age, years	24.8 (2.7–103.8)	24.8 (2.5–117.7)	42.7 (3.7–103.8)	0.89
<1	14 (44%)	8 (40%)	5 (42%)	
1–5	5 (16%)	4 (20%)	2 (17%)	
6–10	9 (28%)	5 (25%)	4 (33%)	
11–15	4 (12%)	3 (15%)	1 (8%)	
Gender				
Male	16 (50%)	10 (50%)	6 (50%)	1.0
Ethnicity				
White	26 (81%)	17 (85%)	9 (75%)	0.65
Non-white	6 (19%)	3 (15%)	3 (25%)	
Comorbidity	26 (81%)	15 (75%)	11 (92%)	0.37
No	6 (19%)			
1	6 (19%)			
2	6 (19%)			
3 or more	14 (44%)	12 (60%)	2 (17%)	**0.028**
Contact with person with COVID-19				
Yes	14 (44%)	11 (55%)	3 (25%)	0.15
Symptoms before admission				
Tachypnea	19 (59%)	10 (50%)	9 (75%)	
Cough	17 (53%)	10 (50%)	7 (58%)	
Rhinorrohea	17 (53%)	11 (55%)	6 (50%)	
Fever	16 (50%)	9 (45%)	7 (58%)	
Prostration	8 (25%)	5 (25%)	3 (25%)	
Abdominal pain	6 (19%)	3 (15%)	3 (25%)	
Diarrhea	5 (15%)	2 (10%)	3 (25%)	
Vomiting	5 (15%)	3 (15%)	2 (17%)	
Cyanosis	5 (15%)	5 (25%)	0	
Convulsions	5 (15%)	3 (15%)	2 (10%)	
Duration of symptoms before admission, days	3 (1–6)	2 (1–6)	4 (2–7)	0.20
Admission causes				–
Respiratory failure	23 (72%)	14 (70%)	9 (75%)	
Convulsive status	5 (16%)	3 (15%)	2 (17%)	
Shock	3 (9%)	3 (15%)	0	
Other	1 (3%)	0	1 (8%)	

Significant P value < 0.05.

Hudson face mask, that evolved to death 10 h after admission. Another patient, who had an inoperable brainstem tumor and respiratory failure, progressed to death a few hours after admission, and the third was a 2-year-old girl, with Down syndrome, hypothyroidism, corrected duodenal atresia, laryngomalacia, tracheostomy and late postoperative correction of atrioventricular septal defect, who was treating endocarditis, having evolved with ARDS, pulmonary hypertension and shock. In addition to the 3 deaths, one previously healthy patient had severe neurological sequelae at the PICU discharge. At the end of the study period, a 15-year-old girl with Down syndrome and a recent diagnosis of brain tumor was still on mechanical ventilation for 39 days.

Discussion

To date, the number of children requiring PICU admission for COVID-19 is low, and the number of severe pediatric patients is much lower than that of adult patients.[2,7,9,10,13] In a cohort study that observed, within 24 days, an infection by COVID-19 in children, only 48 patients who required the PICU were evolved. This survey included 82 institutions from 25 countries in Europe.[3] Another study that included 90% of the PICUs in the Public Health System in Spain identified 50 pediatric patients admitted by COVID-19 to the PICU within a 2-month observation period.[5] It is not yet known

Table 2 Cases of co-infection (14 patients).

Pathogen	Laboratory culture sample	Age, comorbidities and admission diagnosis (critical or non-critical patient)
Staphylococcus aureus	Blood culture and hepatic collection aspirate	7 years old, previously healthy, multiple liver abscesses (**critical-IMV and shock**)
Streptococcus pneumonia	Aspirated tracheal secretion	2 years old, oxygen dependent on home with tracheostomy, pneumonia (**critical-IMV**)
Staphilococcus epidermidis Enterococcus specie	Blood culture Uroculture	29 days old, premature 36 weeks sepsis and seizures (**critical-IMV and shock**)
Staphilococcus warneri	Blood culture	1 month old, hydrocephalus, surgical wound infection, after repair of ruptured meningomyelocele. (**critical-IMV**)
Proteus miribilis	Uroculture	10 years old, extreme prematurity, neurological sequelae, prior epilepsy convulsive status (**critical-IMV**)
Streptococcus pneumoniae	Cerebrospinal fluid	1 month old, previously healthy, convulsive status (**non-critical**)
Respiratory syncytial virus	Direct immunofluorescence	3 months old, premature 37 weeks, small atrial septal defect bronchiolitis (**non-critical**)
Respiratory syncytial virus	Direct immunofluorescence	1 month old, neonatal anoxia, prior seizure, prior IMV bronchiolitis (**critical-IMV and shock**)
Staphilococcus epidermidis	Blood culture	2 months old, Down syndrome, atrial septal defect bronchiolitis (**non-critical**)
Escherichia coli	Uroculture	24 days old, previously healthy supraventricular tachycardia and cardiogenic shock (**critical-IMV and shock**)
Staphylococcus haemolyticus	Blood culture	2 years old, Down Syndrome, hypothyroidism, corrected duodenal atresia, corrected atrioventricular septal defect ARDS and shock (**critical-IMV and shock**)
Escherichia coli	Uroculture	2 months old, premature 28 weeks, bronchopulmonary dysplasia, oxygen dependent ARDS and shock (**critical-IMV and shock**)
Staphilococcus capitis	Blood culture	15 years, Down Syndrome, brain tumor ARDS (**critical-IMV and shock**)

IMV = invasive mechanical ventilation, ARDS = acute respiratory distress syndrome.

why the severity and mortality in adults and children are so different, among the hypotheses are: reduced susceptibility in children due to a lower number of angiotensin 2 converting enzyme receptors in the respiratory tract, presence of cross-reaction to previous exposure to other coronaviruses, fewer comorbidities and differences in immune response.[15]

In our case series, over a 1-year period, 32 children were admitted with severe COVID-19, 20 of whom were considered critical. The factors associated with severity and higher risk of death in children are still under investigation. Some studies[1,3,5] observed a higher risk of severity in younger children, although in other case series[2,8,9,11-13] there was a predominance of severe cases in older children and adolescents. Our study found a higher number of children less than one year of age among children admitted to the PICU, but there was no significant difference regarding severity. We observed a predominance of white children in our case series, which differs from other studies.[7,9] In our region, southern Brazil, due to European colonization, there is a predominance of whites in the population (over 80%).

In our study, the gender distribution was similar, the same described in other studies.[2,7] Most patients with COVID-19 admitted to our unit had comorbidities, with 14 (44%) having more than 3 comorbidities. Unlike patients presenting with MIS-C, children with severe COVID-19 often have one or more comorbidities.[7,12] Medical complex (dependence on technological support in association with developmental delay and/or genetic abnormalities), congenital heart disease, neurological disease, chronic lung disease, oncological or hematological diseases, immunosuppressant use, and prematurity are comorbidities reported in pediatric patients with severe COVID-19.[2,3,5,10,12,16] Obesity is also described as a risk factor for more severe pictures, as in adult patients.[7-10] Although many patients admitted to PICU have comorbidities, the mortality risk and severity associated with each of them is not yet determined, and the results are controversial.[8,17] In our small sample, patients with three or more comorbidities were more frequent in the group with critical illness (Table 1).

Less than half of the pediatric patients admitted to the PICU with COVID-19 had a confirmed history of person contact, similar to that described in other studies.[4,9,12]

The median time to symptom onset on admission in our study was 3 days, with 50% of patients having 1–6 days

Table 3 Laboratory and imaging findings.

	All	Critical patients	Non-critical patients	P value
CRP mg/L median (IQR) *n* = 32	19.5 (3.5–61.5)	23 (4.5–81)	10.4 (2.6–61)	0.66
Leukocytes/μL *n* = 31 median (IQR)	12,000 (7000–16,300)	14,000 (6100–16,400)	9900 (7300–14,300)	0.50
Lymphocytes/μL median (IQR) *n* = 31	1960 (1300–5000)	1400 (993–4180)	2450 (1575–5150)	0.24
Neutrophils/μL mean (SD) *n* = 31	6868 (4087)	7090 (4300)	6516 (3870)	0.70
Platelets, μL mean (SD) *n* = 31	253,000 (128,000)	218,000 (133,000)	309,000 (101,500)	0.053
Hemoglobin g/dL, mean (SD) *n* = 31	9.8 (2.4)	9.6 (2.3)	9.9 (2.6)	0.76
LDH U/L median (IQR) *n* = 17	850 (506–1170)	920 (520–1310)	640 (400–2000)	0.46
D-Dimers median (IQR) *n* = 19	1800 (939–7400)	1910 (974–13,800)	1800 (342–2500)	0.48
Creatinine mg/dL median (IQR) *n* = 29	0.36 (0.2–0.55)	0.37 (0.2–0.6)	0.27 (0.2–0.45)	0.35
Albumin g/dL mean (SD) *n* = 11	3 (0.9)	2.8 (0.9)	3.6 (0.8)	0.49
AST median (IQR) *n* = 24	48 (28–102)	62 (35–175)	30 (17–63)	0.04
Troponin ng/L median (IQR) *n* = 19	12 (5–145)	19 (7.7–1830)	7 (5–12)	0.07
INR median (IQR) *n* = 23	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.2 (1–1.4)	0.87
Chest radiography				
Normal	8 (25%)	3 (15%)	5 (42%)	
Bilateral infiltrate	15 (47%)	9 (45%)	6 (50%)	
Consolidation	4 (12%)	4 (20%)	0	
Pleural effusion + infiltrate	3 (9%)	3 (15%)	0	
Atelectasis	2 (6%)	1 (5%)	1 (8%)	
Echocardiogram n (%)				
Normal	4 (12.5%)	2 (10%)	2 (17%)	
Previous changes	6 (19%)	5 (25%)	1 (8%)	
Biventricular dysfunction	1 (3%)	1 (5%)	0	
Biventricular dysfunction + PH	2 (6%)	2 (10%)	0	
PH	1 (3%)	1 (5%)	0	

CRP = C-reactive protein, IQR = interquartile range, LDH = lactate dehydrogenase, AST = aspartate aminotransferase, INR = international normalizad ratio, PH = pulmonary hypertension.

Table 4 Clinical outcomes and therapies in COVID-19 patients.

	All patients n = 32 n (%) or median (IQR)	Critical n = 20 n (%) or median (IQR)	Non-critical n = 12 n (%) or median (IQR)	P value
ARDS	9 (28%)	9 (45%)	0	–
Shock	13 (40%)	13 (65%)	0	–
Vasoactive support	12 (37.5%)	12 (60%)	0	–
Pulmonary hypertension	2 (6%)	2 (10%)	0	–
Co-infection	13 (41%)	10 (50%)	3 (25%)	0.27
Thromboembolic event	3 (9%)	3 (15%)	0	–
Respiratory support				–
None	1 (3%)	0	1 (8%)	
Oxygen only	12 (37.5%)	1 (5%)	11 (92%)	
NIV only	1 (3%)	1 (5%)	0	
IMV	18 (56%)	18 (90%)	0	
Neuromuscular blocker	8 (25%)	8 (40%)	0	–
iNO	2 (6%)	2 (10%)	0	–
Prone ventilation	9 (28%)	9 (45%)	0	–
Pharmacotherapy				
Antibiotics	26 (81%)	16 (80%)	10 (83%)	–
Corticosteroids	17 (53%)	10 (50%)	7 (58%)	
Enoxaparin	8 (25%)	5 (25%)	3(25%)	
Duration of IMV, days	8.5 (3.5–15.5)	8.5 (3.5–15.5)	–	–
PICU stay, days	7.5 (2.2–19.5)	13.5 (7.2–22)	3 (2–5)	0.01
Died	3 (9%)	3 (15%)	0	–
Still hospitalized	1	1	0	–

IQR = interquartile range, ARDS = acute respiratory distress syndrome, NIV = non-invasive mechanical ventilation, IMV = invasive mechanical ventilation, iNO = inhaled nitric oxide, PICU = Pediatric Intensive Care United.

of symptoms on admission. A shorter period between the onset of symptoms and the need for hospitalization was seen in children compared to adults.[2,3,9,12] An Italian study found 1 day (median) from symptom onset to hospitalization for infants and 4 days for adolescents.[2] A study, which included patients less than 21 years of age hospitalized in 66 hospitals, found a median of 3 days of symptoms pre-hospitalization for severe COVID-19 and 4 days for patients with MIS-C.[7]

Respiratory failure was the leading cause of PICU admission in children with COVID-19 in our case series, which was similar to other studies.[3,5,9–12] In a large study that described differences among 1116 patients under 21 years of age hospitalized with severe COVID-19 and MIS-C patients in 66 hospitals in the United States, 62% of patients had lower respiratory tract symptoms, 57% had gastrointestinal symptoms, 32% neurological symptoms, and only 10% mucocutaneous symptoms, unlike MIS-C patients who had 90% gastrointestinal symptoms, 66.8% mucocutaneous symptoms, and 43% lower respiratory tract symptoms.[7] In this study, of the 577 patients with severe COVID-19, 84 (14.6%) patients underwent mechanical ventilation, and 50 (8.7%) patients required vasoactive drugs.

Some studies report thrombocytopenia, lymphopenia, neutropenia, increased aspartate aminotransferase (AST), creatinine, C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase (LDH), D-dimer, interleukin 6, interleukin 10, troponin and pro-brain natriuretic peptide in

pediatric patients with COVID-19.[6,7,9,18] We compared the tests collected from children admitted to the PICU with critical children in the PICU and found a significant difference only in the median AST (Table 3). A study noted that pediatric and adolescent patients with MIS-C had more thrombocytopenia and higher inflammatory markers than patients with severe COVID-19, median CRP 152 mg/L in MIS-C and 33 mg/L in COVID-19.[7] In a French nationwide study describing 306 children hospitalized for COVID-19, the factors independently associated with severity were: age greater than or equal to 10 years, hypoxemia, and CRP > 80 mg/L.[13]

Studies describe electrocardiographic changes, arrhythmias and myocardial dysfunction in pediatric patients with MIS-C, but these changes may also occur more rarely in patients with severe COVID-19.[7,16] One patient in our study had electrocardiographic change, and four had change on echocardiogram, but most patients did not have cardiologic evaluation. Echocardiographic findings described in studies include depressed function of one or both ventricles, decreased ejection fraction, mitral valve insufficiency, pericardial effusion and coronary artery dilation or aneurysm.[7,16]

In our sample, the duration of mechanical ventilation was 8.5 days, and the length of stay in PICU was 7.5 days. Studies describe median PICU stay of 4–7 days and mechanical ventilation time of 7–9 days.[3,7,9,10,12,13] Co-infection, especially viral, appears to be a risk factor for PICU admission.[3,8] In our series, co-infection was frequent 50% of the cases in

critically ill patients and bacterial co-infection was more frequent than viral. Twelve (37%) patients required vasoactive drugs in our study. Cardiovascular complications and shock seem to occur less frequently in pediatric patients with COVID-19 than in patients with MIS-C.[7] In our small case series, no patients required renal replacement therapy, which was similar in other studies.[9,10]

Twenty-six (81%) children received antimicrobials. Most series of critically ill patients with COVID-19 describe a high percentage of empiric antimicrobial use, due to difficulty in ruling out bacterial condition or co-infection.[9,18] No patients in our study received antiviral drugs or immunomodulatory biologic agents. Seventeen (53%) received low dose corticosteroids, and 8 (25%) received prophylactic or therapeutic enoxaparin.

To date, there is no treatment for COVID-19 in pediatric patients with proven safety and efficacy. Studies describe the use of antivirals, systemic corticosteroids, biological agents and convalescent plasma in a variable number of severely and critically ill pediatric patients.[7,9,13,18] Respiratory and cardiovascular support measures, as well as fluid and electrolyte maintenance, remain as the main management.[7,18] Low-dose corticoids have reduced mortality in adult patients with severe or critical COVID-19 without increasing adverse events.[19,20] According to current criteria, there is a group of children where the differentiation between MIS-C and COVID-19 is not clear.[7,21] In these patients, the use of anti-inflammatory drugs such as corticosteroids could be beneficial.[7] Regarding antivirals, Remdesivir, based on results from studies in adult patients, could be considered in critically ill pediatric patients requiring respiratory support or ECMO, preferably as part of a clinical trial.[8] The prophylactic use of low molecular weight heparin is suggested for pediatric patients hospitalized for COVID-19 or MIS-C who have a risk factor for thromboembolic event or elevated D-dimer levels, in the absence of contraindications.[22] The same consensus suggests an increase of D-dimer greater than 5 times the normal value to guide thromboprophylaxis indication.[22]

In relation to prognosis, one patient in our case series was left with severe neurological sequelae after a seizure disorder secondary to stroke (the reason for hospitalization). This previously healthy patient underwent extensive investigation for other causes of thromboembolic event, with all tests normal, and SARS-COv-2 infection was the only possible explanation for the event. Although rare events in children, there are reports of stroke, seizures and encephalopathy associated with SARS-CoV-2 infection.[23] Because this is a new disease, the long-term prognosis of children admitted to PICU and the critically ill is not yet known.

Our mortality was 9% (3 out of 32). Death from COVID-19 in pediatric patients is described as a rare event. Mortality described in case series of pediatric patients with COVID-19 in PICU was varied as 1 death in 13 patients, 4/48, 0/50, 4/18, 3/24, 2/69.[2–5,9,12] In some cases of patients with multiple comorbidities or co-infection, SARS-CoV-2 infection may not have been the main factor in the severity or unfavorable outcome, which happened to some of our patients and was also described in other studies.[2,5,12]

Our study has several limitations; it was a retrospective study, performed in a single center with a small number of patients, and one patient was still hospitalized on respiratory support at the end of the study. Due to the small number of patients, the power to detect significant differences between the groups of severely ill and critically ill children was small.

Conclusion

Children of all ages can have severe or critical COVID-19; in our case series, most of the admitted children had comorbidities, and the presence of three or more comorbidities was more frequent in critical patients. Under 1 year old were almost half of the sample, but there were no significant differences between severely ill and critically ill patients. Further studies are needed to determine factors associated with severity.

Authors' contributions

Cristiane Traiber, Fernanda Umpierre Bueno, Luiz Roberto Braun Filho and Guilherme Unchalo Eckert worked in the conception and design of the research, in the literature review, in the analysis and interpretation of data, in the writing and review of the article.

Marcelo Almeida Azambuja and Gabrielle Segatto Gras collaborated in the collection and review of data and in the review of the article.

All authors reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval

This study was approved by the Research Ethics Committee of Hospital Group Conceiçao CEP-GHC.

Funding

Conflict of interest

None.

Acknowledgments

References

1. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020, http://dx.doi.org/10.1542/peds.2020-0702.
2. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 disease severity risk factors for pediatric patients in Italy. Pediatrics. 2020;146, http://dx.doi.org/10.1542/peds.2020-009399, e2020009399.

3. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4:653–61, http://dx.doi.org/10.1016/S2352-4642(20)30177-2.

4. Gaborieau L, Delestrain C, Bensaid P, Vizeneux A, Blanc P, Garraffo A, et al. Epidemiology and clinical presentation of children hospitalized with SARS-CoV-2 infection in suburbs of Paris. J Clin Med. 2020;9:2227, http://dx.doi.org/10.3390/jcm9072227.

5. González Cortés R, García-Salido A, Roca Pascual D, Slöcker Barrio M, de Carlos Vicente JC, SECIP Study Group on SARS-CoV-2 in Critically Ill Pediatric Patients. A multicenter national survey of children with SARS-CoV-2 infection admitted to Spanish Pediatric Intensive Care Units. Intensive Care Med. 2020;46:1774–6, http://dx.doi.org/10.1007/s00134-020-06146-8.

6. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr. 2020;179:1029–46, http://dx.doi.org/10.1007/s00431-020-03684-7.

7. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with Multisystem Inflammatory Syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA. 2021;325:1074–87, http://dx.doi.org/10.1001/jama.2021.2091.

8. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, et al. Multicenter Interim Guidance on use of antivirals for children with Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. J Pediatric Infect Dis Soc. 2021;10:34–48, http://dx.doi.org/10.1093/jpids/piaa115.

9. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City. J Pediatrics. 2020;223:14–9, http://dx.doi.org/10.1016/j.jpeds.2020.05.006, e2.

10. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with Coronavirus Disease 2019 (COVID-19) infection admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020;174:868–73, http://dx.doi.org/10.1001/jamapediatrics.2020.1948.

11. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe Coronavirus Disease-2019 in children and young adults in the Washington, DC, Metropolitan region. J Pediatrics. 2020;223:199–203, http://dx.doi.org/10.1016/j.jpeds.2020.05.007.

12. Prata-Barbosa A, Lima-Setta F, Santos GRD, Lanziotti VS, de Castro REV, de Souza DC, et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. J Pediatr (Rio J). 2020;96:582–92, http://dx.doi.org/10.1016/j.jped.2020.07.002.

13. Ouldali N, Yang DD, Madhi F, Levy M, Gaschignard J, Craiu I, et al. Factors associated with severe SARS-CoV-2 infection. Pediatrics. 2021;147, http://dx.doi.org/10.1542/peds.2020-023432, e2020023432.

14. Ministério da Saúde Brasil. Boletim epidemiológico especial, Doença pelo Coronavirus COVID-19. https://www.gov.br/saude/pt-br/media/pdf/2021/abril/01/boletim_epidemiologico_covid_56.pdf [accessed 16.7.21].

15. Chatziparasidis G, Kantar A. COVID-19 in children with asthma. Lung. 2021;199:7–12, http://dx.doi.org/10.1007/s00408-021-00419-9.

16. Niaz T, Hope K, Fremed M, Misra N, Altman C, Glickstein J, et al. Role of a pediatric cardiologist in the COVID-19 pandemic. Pediatr Cardiol. 2021;42:19–35, http://dx.doi.org/10.1007/s00246-020-02476-y.

17. Issitt RW, Booth J, Bryant WA, Spiridou A, Taylor AM, du Pré P, et al. Children with COVID-19 at a specialist centre: initial experience and outcome. Lancet Child Adolesc Health. 2020;4:e30–1, http://dx.doi.org/10.1016/S2352-4642(20)30204-2.

18. Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021;41:19–32, http://dx.doi.org/10.1007/s00296-020-04749-4.

19. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A Meta-analysis. JAMA. 2020;324:1330–41, http://dx.doi.org/10.1001/jama.2020.17023.

20. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704, http://dx.doi.org/10.1056/NEJMoa2021436.

21. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19-associated multisystem inflammatory syndrome in Children – United States, March–July 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1074–80, http://dx.doi.org/10.15585/mmwr.mm6932e2.

22. Goldenberg NA, Sochet A, Albisetti M, Biss T, Bonduel M, Jaffray J, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. J Thromb Haemost. 2020;18:3099–105, http://dx.doi.org/10.1111/jth.15073.

23. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, et al. Neurological issues in children with COVID-19. Neurosci Lett. 2021;743:135567, http://dx.doi.org/10.1016/j.neulet.2020.135567.