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ORIGINAL ARTICLE

Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study☆

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Abstract
Objective: To describe the clinical characteristics of children and adolescents admitted to intensive care with confirmed COVID-19.
Method: Prospective, multicenter, observational study, in 19 pediatric intensive care units. Patients aged 1 month to 19 years admitted consecutively (March–May 2020) were included. Demographic, clinical-epidemiological features, treatment, and outcomes were collected. Subgroups were compared according to comorbidities, age < 1 year, and need for invasive mechanical ventilation. A multivariable logistic regression model was used for predictors of severity.
Results: Seventy-nine patients were included (ten with multisystemic inflammatory syndrome). Median age 4 years; 54% male (multisystemic inflammatory syndrome, 80%); 41% had comorbidities (multisystemic inflammatory syndrome, 20%). Fever (76%), cough (51%), and tachypnea (50%) were common in both groups. Severe symptoms, gastrointestinal symptoms, and higher inflammatory markers were more frequent in multisystemic inflammatory syndrome. Interstitial lung infiltrates were common in both groups, but pleural effusion was more prevalent in the multisystemic inflammatory syndrome group (43% *vs.* 14%). Invasive mechanical ventilation was used in 18% (median 7.5 days); antibiotics, oseltamivir, and corticosteroids were used in 76%, 43%, and 23%, respectively, but not hydroxychloroquine. The median pediatric intensive care unit length-of-stay was five days; there were two deaths (3%) in the non- multisystemic inflammatory syndrome group. Patients with comorbidities were older, and comorbidities were independently associated with the need for invasive mechanical ventilation (OR 5.5; 95% CI, 1.43–21.12; p = 0.01).
Conclusions: In Brazilian pediatric intensive care units, COVID-19 had low mortality, age less than 1 year was not associated with a worse prognosis, and patients with multisystemic inflammatory syndrome had more severe symptoms, higher inflammatory biomarkers, and a greater predominance of males, but only comorbidities and chronic diseases were independent predictors of severity.
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Introduction

Brazil has become the epicenter of infection by the new coronavirus (SARS-CoV-2) in South America and the second country with the highest number of cases and deaths in the world. COVID-19, as this disease is termed by the World Health Organization, still represents a challenge in the pediatric population, although the number and severity

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of cases are lower when compared to the adult population. Data from several countries show that children and adolescents accounted for less than 2% of symptomatic cases, with hospitalization rates (0.6–20%) and mortality (0–4%) significantly lower than in adults.[1–5] Infants and children with previous chronic conditions represent the most vulnerable pediatric population, with greater severity.[1,2,4,5] Recently, several countries reported cases of a multisystemic inflammatory syndrome in children (MIS-C) temporarily associated with COVID-19. This syndrome is characterized by prolonged fever, gastrointestinal symptoms, and altered inflammatory markers, associated with signs of organ dysfunction, acute cardiac failure, Kawasaki disease (complete or incomplete), or toxic shock syndrome.[6–8]

The report of the Latin American experience with COVID-19 in pediatrics is still quite limited, especially concerning children admitted to intensive care settings. This study aimed to describe the clinical characteristics of a cohort of children and adolescents admitted to Brazilian pediatric intensive care units (PICUs).

Materials and methods

Study design, patient selection, and setting

This was a prospective, multicenter study, conducted in 19 PICUs associated with the Brazilian Research Network in Pediatric Intensive Care (BRnet-PIC). Pediatric patients (1 month–19 years of age) with confirmed COVID-19 were included consecutively between March 1 and May 31, 2020, after obtaining informed consent. The studywas approved by the Research Ethics Committees of all institutions.

Diagnosis and data collection

Diagnosis of COVID-19 was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) assay from oro/nasopharyngeal swabs or tracheal aspirates, and when outside the period of positivity for RT-PCR, using IgM and/or IgG antibodies positive against SARS-CoV-2. Demographic, epidemiological, clinical, and outcome data from patients were collected prospectively, using standardized case report forms (REDCap – Vanderbilt University; TN, United States). MIS and non-MIS patients were compared according to the presence of comorbidities, age less than 1 year, and the need for invasive mechanical ventilation (IMV).

Data processing and statistical analysis

Categorical variables were described as frequencies and percentages, and continuous variables as medians and interquartile ranges (IQRs). Comparisons between groups were made using the chi-squared test or Fisher's exact test for categorical variables, and the Mann–Whitney test for continuous variables. A multivariable logistic regression model was used to assess the association of the covariates age less than 1 year, sex, race, and presence of comorbidities with more severe forms of the disease, characterized by the need for IMV. A significance level of 5% (two-tailed) and 95% confidence intervals were established. The software R, v. 3.6.1, (R Foundation, Vienna, Austria) was used for statistical analysis.

Results

Demographic and epidemiological features

Seventy-nine patients were included (ten with MIS). Overall, the median age was four years, 54% were male (MIS, 80%), 58% were white, and 41% had previous comorbidities (MIS, 20%), of which neuromuscular diseases predominated (28%), mainly non-progressive encephalopathy. Other comorbidities, such as chronic respiratory disease, oncohematological disease, congenital heart disease, and undernutrition were also prevalent, representing together about 27% of the total. Thirty-one patients (39%) reported contact with a suspected case (household, 87%; Table 1).

Clinical presentation

Upon admission, 47 patients (60%) had respiratory symptoms, most of them pneumonia or bronchiolitis (70%), and ten (13%) had MIS, 60% a Kawasaki-like disease. The other 22 (28%) had mostly gastrointestinal and neurological symptoms (Table 1). The median time of symptoms before hospitalization was five days in the non-MIS group and two days in the MIS group. The most common signs and symptoms at presentation were fever (76%), cough (51%), and tachypnea (50%). However, other findings were also prevalent (Table 1). In the MIS group, severe symptoms such as tachypnea (60%), low SpO_2 (40%), prostration (60%), groaning (30%), hypotension (20%), nasal flaring (20%), cyanosis (10%), and gastrointestinal symptoms (40–60%) were more frequent than in the non-MIS group (Table 1).

Q1 **Table 1** Demographic, epidemiological, and clinical features of pediatric patients with COVID-19.

Characteristic	Non-MIS, n (%)	MIS, n (%)	Total, n (%)
Total	69 (100)	10 (100)	79 (100)
Age, median (IQR), y	4 (1–10.5)	5.2 (1.5–8.4)	4 (1–10.3)
Infants (<12 m)	17 (25)	2 (20)	19 (24)
Toddler (≥12 m, <3 y)	16 (23)	2 (20)	18 (23)
Preschool (≥3 y, <5 y)	6 (9)	1 (10)	7 (9)
Grade-schooler (≥5 y, <12 y)	15 (22)	4 (40)	19 (24)
Adolescent (≥12 y, <18 y)	13 (19)	1 (10)	14 (18)
Young adult (≥18 y)	2 (3)	0 (0)	2 (3)

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Table 1 (*Continued*)

Characteristic	Non-MIS, n (%)	MIS, n (%)	Total, n (%)
Sex			
Male	35 (51)	8 (80)	43 (54)
Female	34 (49)	2 (20)	36 (46)
Race/ethnicity			
White	40 (58)	6 (60)	46 (58)
Mixed race/ethnicity	19 (28)	1 (10)	20 (25)
Black	10 (14)	2 (20)	12 (15)
Asian	0 (0)	1 (10)	1 (1)
Comorbidities	30 (43)	2 (20)	32 (41)
Neuromuscular disease[a]	9 (30)	1 (50)	10 (31)[c]
Chronic respiratory disease[b]	6 (20)	–	6 (19)[c]
Oncohematological disease	6 (20)	–	6 (19)[c]
Congenital heart defect	4 (13)	1 (50)	5 (16)[c]
Undernutrition	4 (13)	–	4 (13)[c]
Diabetes	2 (7)	–	2 (6)[c]
Prematurity	2 (7)	–	2 (6)[c]
Chronic liver disease	1 (3)	–	1 (3)[c]
Obesity	1 (3)	–	1 (3)[c]
Contact with a suspected case (n = 31)	24 (35)		31 (39)
Household	20 (83)	7	27 (87)
Other	4 (17)	3	4 (13)
Main clinical syndrome at presentation			
Respiratory[d]	47 (68)		47 (60)
MIS	–	10 (100)	10 (13)
Kawasaki-like disease	–	6 (60)	6 (60)
Acute cardiac dysfunction	–	2 (20)	2 (20)
Toxic shock syndrome	–	1 (10)	1 (10)
Macrophage activation syndrome	–	1 (10)	1 (10)
Other[e]	22 (32)	–	22 (28)
Symptoms before hospitalization, median (IQR), days	5 (2–8)	2 (1–3)	4 (2–8)
Clinical features at presentation			
Fever	51 (75)	8 (80)	59 (76)
Cough	36 (53)	4 (40)	40 (51)
Tachypnea	33 (49)	6 (60)	39 (50)
Low SpO_2 (<92%)	19 (28)	4 (40)	23 (29)
Prostration	13 (19)	6 (60)	19 (24)
Chest retraction	17 (25)	1 (10)	18 (23)
Runny nose	16 (24)	1 (10)	17 (22)
Diarrhea	12 (18)	4 (40)	16 (21)
Feed refusal	11 (16)	5 (50)	16 (21)
Vomiting	10 (15)	6 (60)	16 (21)
Dehydration	9 (13)	4 (40)	13 (17)
Nasal flaring	6 (9)	2 (20)	8 (10)
Groaning	4 (6)	3 (30)	7 (9)
Cyanosis	4 (6)	1 (10)	5 (6)
Hypotension	3 (4)	2 (20)	5 (6)
Red throat	2 (3)	1 (10)	3 (4)

COVID-19, coronavirus disease 2019; IQR, interquartile range; MIS, multisystemic inflammatory syndrome; PICU, pediatric intensive care unit; SpO_2, pulse oximeter oxygen saturation.

[a] Non-progressive encephalopathy (n = 7), other causes (n = 2).

[b] Asthma (n = 3), bronchopulmonary dysplasia (n = 1), tracheomalacia (n = 1), other (n = 3)[d].

[c] Some patients presented more than one comorbidity.

[d] Pneumonia, 23; bronchiolitis, 10; other, 14.

[e] Gastrointestinal, 8; neurological, 4; miscellaneous, 10.

Diagnosis confirmation; laboratory and radiological findings

The diagnosis was confirmed by RT-PCR in 72 patients (all 79 tested, 91% positive). The others confirmed the diagnosis by detection of IgM and/or IgG antibodies (five in the MIS group; Table 2). Co-detection with other viruses occurred in about 15% tested (two respiratory syncytial virus, one human rhinovirus, and one association of parainfluenza 4 with *Bordetella pertussis*; Table 2).

Lymphopenia was present in 36% of patients in the non-MIS group (MIS, 50%). C-reactive protein (CRP) was 3 mg/dL or greater in 50% of 63 patients in the non-MIS group, compared to 10 mg/dL or greater in 50% of all ten patients in the MIS group. Erythrocyte sedimentation rate (ESR), lactic dehydrogenase (LDH), and D-dimer were tested in five, 30, and 22 patients, respectively, in the non-MIS group, and in almost all patients in the MIS group. They were increased in at least 75% of all patients, but much higher in the MIS group. In contrast, renal and hepatic functions were tested in most patients and were preserved in at least 75% of them in both groups. Ferritin and troponin were tested in only 24 and 17 patients, respectively, most of them in the MIS group. Ferritin was elevated in at least 50% of patients, and was higher in the non-MIS group. Troponin was elevated in at least 50% of patients in the non-MIS group, but not in the MIS group. Of the other cardiac injury markers, creatinine kinase (CK) was abnormal in five of 22 patients (408–2345 U/L), and the myocardial creatinine kinase band (CK–MB) was elevated in eight out of 15 patients (25 and 89 U/L). Only one of these patients was in the MIS group (toxic shock syndrome, CK 1389 U/L, CK–MB 28 U/L). The pro-b-type natriuretic peptide (proBNP) was increased in six of seven (86%) patients tested, all in the MIS group, with a median value of 5829 (range, 222—16,996 pg/mL). Procalcitonin was investigated in only three patients and was elevated in all (one in the non-MIS group, 0.4 ng/mL; two in the MIS group: an acute cardiac dysfunction, 0.37 ng/mL, and a toxic shock syndrome, 31 ng/mL). Finally, interleukin-6 was measured in only two patients in the MIS group, both with very high values: a patient with acute cardiac dysfunction (711 pg/mL) and a patient with toxic shock syndrome (194 pg/mL; Table 2).

Chest radiography was abnormal in 60–70% of patients in both groups, predominantly bilateral diffuse interstitial infiltrate (57–60%). Remarkably, pleural effusion was present in seven patients (43%) in the MIS group and in only three patients (9%) in the non-MIS group. Thirty-eight patients underwent computed tomography (CT) of the chest and ground-glass opacities were present in 58% in the non-MIS group and in only 14% in the MIS group (Table 2).

Management and clinical outcomes

Fifty-one patients (65%) needed some type of ventilatory support: 32 (41%) used only oxygen therapy, five (6%) needed only noninvasive ventilation (NIV), and 14 (18%) needed IMV. In those requiring IMV, ten (71%) had acute respiratory distress syndrome (ARDS), of whom six were classified as severe, requiring neuromuscular blocking (n = 6), alveolar recruitment maneuver (n = 4), and intermittent prone position (n = 3). Two of these patients developed pulmonary arterial hypertension. The median duration of IMV was 7.5 days (IQR 5–10) and the median highest positive end-expiratory pressure (PEEP) was 9.5 cmH_2O (IQR 7–12). One of those severe cases of ARDS was in the MIS group (Table 3).

Antibiotics were used in 76% of all patients, oseltamivir in 43%, and corticosteroids in 23%. No patient used hydroxychloroquine (Table 3). The median PICU length of stay (LOS) was five days (IQR 2.2–10), and most patients were discharged (90%). The only two deaths (3% mortality) occurred in the non-MIS group, both patients with severe comorbidities and chronic use of corticosteroids (Table 3). One was a 14-year-old girl with chronic liver disease and the other a 1-year-old girl with chronic lung disease and short bowel syndrome.

Specific subgroups

The subgroup of patients with comorbidities was significantly older (median age: 7.5 *vs.* 1.8 years, p = 0.01), had a greater need for oxygen therapy (56% *vs.* 31%, p = 0.05) and IMV (31% *vs.* 9%, p = 0.01), and more frequent ARDS diagnosis (25% *vs.* 4%, p = 0.01), but there were no differences regarding the duration of respiratory support and PICU LOS. In patients who required IMV, the PICU LOS was significantly longer (12.0 *vs.* 5.0 days, p = 0.01). Age less than 1 year did not determine a different clinical presentation. In patients with MIS, no significant differences were observed among patients with comorbidities, age less than 1 year, and the need for IMV (Table 4a). The authors also compared these three specific groups, considering only patients who did not have MIS, but the results were quite similar (Tables S1 and S2, supplementary material).

The multivariate analysis showed that only the presence of comorbidities was significantly associated with severity, represented by the need for IMV (adjusted OR, 5.5; 95% CI, 1.43–21.12; p = 0.01) (Table 4b).

Discussion

To the best of the authors' knowledge, this is the first prospective, multicenter study to report characteristics and outcomes of children with COVID-19 admitted to PICUs in Brazil, the current epicenter of the disease in Latin America and the second in the world, after the United States. Although most children and adolescents have a benign course of the disease, it has been shown that some patients can develop severe acute clinical conditions, especially those with previous comorbidities, and later on, also present MIS.

In the present cohort, although the median age was 4 years and a quarter were infants, 44% were school-age children, adolescents, and young adults, a higher percentage than is generally observed in Brazilian PICUs for this age group, usually around 25%.[9] This is similar to that reported by a large European study[10] and by North American PICUs, which reported an even higher percentage of admissions in this age group (about 70%).[2,11] The present study did not observe a large difference between the median ages of the MIS and non-MIS groups, although the number of patients with MIS was small. As for sex, there were no differ-

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Table 2 Diagnosis confirmation, laboratory and radiological findings of pediatric patients with COVID-19.

		Non-MIS (n = 69)		MIS (n = 10)		
Etiological diagnosis, number tested (n)	n	Positive, n (%)	No.	Positive, n (%)	No.	Positive, n (%)
SARS-CoV-2 infection						
RT-PCR	69	67 (85)	10	5 (50)	79	72 (91)
Serology						
IgM	5	4 (80)	8	1 (13)	13	5 (45)
IgG	5	3 (60)	8	5 (63)	13	8 (62)
IgM and IgG	5	2 (40)	8	0 (0)	13	1 (8)
Co-detection with COVID-19						
Rapid test for respiratory syncytial virus	25	2 (8)	1	0 (0)	26	2 (8)
Other virus	18	2 (11)	3	0 (0)	21	2 (10)
Human rhinovirus	2	1 (50)	0	0 (0)	2	1 (50)
Parainfluenza 4 + *Bordetella parapertussis*	2	1 (50)	0	0 (0)	2	1 (50)
Blood test, number tested (n)	n	Worse values Median (IRQ) or		Worse values Median (IRQ) or	n	Worse values Median (IRQ)
Total leukocyte count (× 1000/μL)	66	11,850 (7933–18,075)	10	18,275 (14,293–23,868)	76	12,520 (8382–19,100)
Platelet count (× 1000/μL)	66	260,500 (159,250–374,500)	10	103,000 (78,750–177,500)	76	226,500 (136,750–367,000)
Lymphopenia n (%)	59	21 (36)	10	5 (50)	69	26 (38)
C-reactive protein (mg/dL),	63	3 (0.6–18)	10	10 (9–30)	73	5.1 (0.7–20.0)
Erythrocyte sedimentation rate (mm/1st h)	5	68 (45–85)	9	100 (49–120)	14	88 (46–115)
Lactic dehydrogenase (U/L)	30	395 (290–612)	8	630 (545–844)	38	433 (294–737)
D-dimer (ng/mL)	22	1723 (441–3966)	8	3755 (2170–5099)	30	1953 (1099–4099)
Procalcitonin (ng/mL)	1	0.4 (0.4–0.4)	2	15.7 (8–23.3)	3	0.4 (0.4–15.7)
Urea (mg/dL)	58	23 (16–35)	10	33 (22–45)	68	24 (16–38)
Creatinine (mg/dL)	59	0.4 (0.3–0.6)	10	0.5 (0.4–0.7)	69	0.5 (0.3–0.6)
Albumin (g/dL)	36	3.2 (2–4)	6	2.8 (2.4–3.2)	42	3.2 (2.3–3.8)
Alanine aminotransferase (U/L)	49	28 (15–55)	9	54 (41–70)	58	41 (15–57)
Aspartate aminotransferase (U/L)	49	40 (31–75)	10	51 (29–67)	59	42 (31–73)
Creatinine kinase, total (U/L)	14	72 (35–347)	8	67 (47–147)	22	68 (44–170)
Creatinine kinase, myocardial band (U/L)	12	27 (22–46)	3	20 (11–24)	15	26 (21–42)
Troponin (ng/mL)	9	0.4 (0–5)	8	0.0 (0.0–0.4)	17	0.1 (0.0–1.0)

Table 2 (*Continued*)

		Non-MIS (n = 69)		MIS (n = 10)		
Ferritin (ng/mL)	17	648 (198–974)	7	228 (143–1366)	24	594 (190–1030)
ProBNP (pg/mL)	0	–	7	–	7	5829 (2962–10,027)
Interleukin-6 (pg/mL)	0	–	2	453 (323–582)	2	453 (323–582)
Radiological findings upon PICU admission	n	Altered images		Altered images		Altered images
Abnormal chest radiographies	58	35 (60)	10	7 (70)	68	42 (62)
Diffuse interstitial infiltrate, bilateral	35	21 (60)	7	4 (57)	42	25 (60)
Interstitial infiltrate, localized	35	6 (17)	7	0 (0)	42	6 (14)
Consolidation	35	5 (14)	7	2 (29)	42	7 (17)
Atelectasis	35	3 (9)	7	0 (0)	42	3 (7)
Pleural effusion	35	3 (9)	7	3 (43)	42	6 (14)
Hyperinflation	35	4 (11)	7	0 (0)	42	4 (10)
Chest CT with ground-glass opacities	31	18 (58)	7	1 (14)	38	19 (50)

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; IgM, immunoglobulin M; IgG, immunoglobulin G; IQR, interquartile range; proBNP, pro-B type natriuretic peptide; PICU, pediatric intensive care unit, CT, computed tomography.

ences in the non-MIS group, while in patients with MIS there was a male predominance of 4:1, which is different from what was reported by other authors.[12,13] There was a small predominance of white patients (58–60%), which contrasts with the predominance of the Brazilian population, which is 56% non-white. However, approximately half of the patients were from private hospitals, accessible only to the middle- and upper-income population, where white patients are the majority.

Comorbidities have been described as an important risk factor for more severe cases of COVID-19 in children, representing between 50–80% of PICU admissions.[11,14,15] Although the present study had a slightly lower percentage of these patients (41%), they were significantly older and had a significantly more severe presentation (more ARDS, more ventilatory support, more IMV). The logistic regression model showed that comorbidities were independently associated with the need for IMV, with an adjusted odds ratio of 5.5 [95% CI, 1.4–21.1). Neuromuscular disease, chronic respiratory disease, and oncohematologic disease were the most prevalent comorbidities in this cohort, which is slightly different from others reports in pediatric critical care.[5,11,14,15]

Only about 40% of patients had a previous history of contact with a suspected case, mostly at home, which is similar to other reports.[4] Fever was the predominant symptom, followed by several respiratory and gastrointestinal signs and symptoms, which did not differ from what has been reported in other studies.[5,10,14,16] There was a higher prevalence of gastrointestinal symptoms in the MIS-group, such as diarrhea and vomiting with dehydration, which was also observed by other authors.[12,13] The interval between the onset of symptoms and hospitalization was shorter in the MIS-group (median, 2 *vs.* 5 days). This may be explained by the most severe cases in this group, some of them presenting with signs of shock and cardiorespiratory failure. Although the main clinical syndrome at hospitalization was generally of respiratory or gastrointestinal origin, there were ten patients (13%) admitted to the PICU because of MIS. This is a new phenomenon related to COVID-19 in children and it is expected that many of these patients need monitoring in the PICU, as well as by other pediatric specialties.[6]

The majority of patients had their diagnosis confirmed by RT-PCR (91%), but a greater proportion of negative results in the MIS group was observed (50% *vs.* 15%). This is compatible with previous data, showing that MIS is a late manifestation associated with COVID-19, outside the positivity window for RT-PCR. In this group, the association with a SARS-CoV-2 infection was made in half of the patients by a positive serology, mainly IgG. However, in the non-MIS group, positive IgM was detected in 80% of the few cases in which it was measured. Co-detection with other viruses was observed in 15% of the patients in which it was investigated (only in non-MIS group), which is similar to other COVID-19 studies,[5,10] and in other severe respiratory virus infections in children.[17]

Lymphopenia was observed in 38% of patients (50% in the MIS group), which has also been described in other pediatric COVID-19 studies.[5,14,15,18] Although some adult studies have associated lymphopenia with a worse prognosis,[19,20] this is still not clear in pediatrics. Inflammatory markers –

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Table 3 Management and clinical outcomes of pediatric patients with COVID-19.

	Non-MIS-C n = 69 n (%) or median (IQR)	MIS-C n = 10 n (%) or median (IQR)	Total n = 79 n (%) or median (IQR)
Management and outcomes			
Oxygen therapy only	28 (41)	4 (40)	32 (41)
Non-invasive ventilation only	4 (6)	1 (10)	5 (6)
Invasive mechanical ventilation	13 (19)	1 (10)	14 (18)
Days of use, median (IQR)	8.0 (6.0, 11.0)	5.0 (5.0, 5.0)	7.5 (5.0, 10.0)
Higher PEEP, median (IQR)	9.0 (7.0, 11.0)	12.0 (12.0, 12.0)	9.5 (7.0, 12.0)
Intermittent prone position	3 (100)	0 (0)	3 (21)
Alveolar recruitment	4 (44)	0 (0)	4 (29)
Neuromuscular blocking	5 (7)	1 (10)	6 (43)
ARDS diagnosis	9 (13)	1 (10)	10 (13)
Mild	4 (44)	0 (0)	4 (40)
Moderate	0 (0)	0 (0)	0 (0)
Severe	5 (56)	1 (100)	6 (60)
Pulmonary arterial hypertension	2 (3)	0 (0)	2 (3)
Pharmacologic treatment			
Antibiotics	52 (75)	8 (80)	60 (76)
Oseltamivir	32 (46)	2 (20)	34 (43)
Antifungal therapy	3 (4)	1 (10)	4 (5)
Corticosteroids	16 (23)	2 (20)	18 (23)
Hydroxychloroquine	0 (0)	0 (0)	0 (0)
PICU LOS, days, median (IQR)	5.0 (2.8, 10.0)	5.5 (2.8, 7.5)	5.0 (2.2, 10.0)
Outcomes			
Discharge	62 (90)	9 (90)	71 (90)
Death	2 (3)	0 (0)	2 (3)
Transfer to other hospital	5 (7)	1 (10)	6 (8)

ARDS, acute respiratory distress syndrome; IQR, interquartile range; LOS, length of stay; PEEP, positive end expiratory pressure; PICU, pediatric intensive care unit.

such as ESR, CRP, LDH, D-dimer, procalcitonin, and ferritin – were elevated in most tested patients, but mainly in the MIS group, which is in accordance with the diagnostic criteria for this syndrome.[21–23] In the present cohort, troponin, CK, and CK–MB were measured in less than 20% of patients; elevated levels were found in at least 50% of them. These cardiac injury biomarkers have also been reported as abnormal in other studies, especially in patients with some form of cardiac failure.[12–14] Another known sensitive marker for heart failure detection, proBNP, was elevated in all seven patients in which it was measured in the MIS group, as has also been reported in other studies.[6,24] The present study also measured interleukin-6 (IL-6) in two patients in the MIS group, both with severe cardiac dysfunction and shock; very high levels were found. Elevated levels have previously been described in critically ill pediatric patients with COVID-19.[5,8,12]

Another finding consistent with cardiac dysfunction in patients in the MIS group was pleural effusion, detected by chest radiography, a feature much less frequent in the non-MIS group. The other radiological findings of diffuse bilateral interstitial infiltrates and ground-glass opacities on chest X-rays and on CT were present in most patients, which is consistent with previous reports.[10,18,25]

As for the management of patients, the majority needed some kind of respiratory support, most of them only oxygen therapy, but about 20% needed IMV (median 7.5 days), which is within the reported range of use (18–50%) described in other studies.[5,10,11,14] Of these, 71% developed ARDS, mainly severe, requiring neuromuscular blocking, high PEEP, alveolar recruitment maneuver, and prone position in some cases. Although it was not possible to confirm bacterial infections, antibiotic therapy was used in three-quarters of patients and oseltamivir in almost half, which can be explained by the national guidelines for the treatment of SARS, which indicates the initial use of empirical oseltamivir.[26] Hydroxychloroquine was not prescribed, although some studies have reported its use in 7%–47% of patients.[5,10,11,14] Perhaps this difference can be explained by the fact that the cases in Europe and the United States started weeks or months before those in Brazil, when a more compassionate use of drugs could be explained and also fewer studies were available.

Demographic and clinical characteristics were compared according to the presence of comorbidities, age below 1 year, and the need for IMV. Although the numbers in these subgroups were small, significant differences were found, determined by the presence of comorbidities. These patients were older and needed more respiratory support, with more cases of ARDS. The only two deaths also occurred in this group. The presence of comorbidities independently increased the chance of IMV, but the factors associated with a worse prognosis need more investigation. Obesity, which is reported as the worse prognostic factor in children with

Table 4a Demographics and clinical features of pediatric patients with COVID-19 according to the presence of comorbidities, age less than 1 year, and the need for invasive mechanical ventilation, in all patients (n = 79).

Characteristic	Comorbidities			Age less than 1 year			Invasive mechanical ventilation		
	Yes	No	p-Value	Yes	No	p-Value	Yes	No	p-Value
Age, median (IQR), y	7.5 (2.1, 12.4)	1.8 (0.8, 7.0)	0.01[c]	0.5 (0.2, 0.7)	7.0 (1.9, 12.4)		5.6 (1.2, 10.3)	4.2 (1.2, 10.8)	0.94[c]
Sex, n (%)									
Male	17 (53)	26 (55)	1[a]	9 (47)	34 (57)	0.48	6 (43)	37 (57)	0.51[a]
Female	15 (47)	21 (45)		10 (53)	26 (43)		8 (57)	28 (43)	
Ethnicity, n (%)									
White	17 (53)	29 (62)	0.57[a]	8 (42)	38 (63)	0.17[a]	8 (57)	38 (58)	1[a]
Non-white	15 (47)	18 (38)		11 (58)	22 (37)		6 (43)	27 (42)	
Comorbidities, n (%)									
Yes	–	–	–	5 (26)	27 (45)	0.19[a]	10 (71)	22 (34)	0.01[a]
No	–	–	–	14 (74)	33 (55)		4 (29)	43 (66)	
Main presentation, n (%)									
Respiratory	22 (69)	25 (53)	0.11[a]	13 (68)	34 (57)	0.72[a]	11 (79)	26 (48)	0.08[a]
MIS	2 (6)	8 (17)	0.18[b]	2 (11)	8 (13)	1[b]	1 (7)	9 (17)	0.67[a]
Kawasaki-like disease	2 (100)	4 (50)	0.56[b]	2 (100)	4 (50)	0.56[b]	0 (0)	6 (67)	0.30[b]
Acute cardiac dysfunction	0 (0)	2 (25)		0 (0)	2 (25)		0 (0)	2 (22)	
Toxic shock syndrome	0 (0)	1 (13)		0 (0)	1 (12)		1 (100)	0 (0)	
Macrophage activation syndrome	0 (0)	1 (13)		0 (0)	1 (12)		0 (0)	1 (11)	
Other	8 (25)	14 (30)	0.85[a]	4 (22)	18 (30)	0.73[a]	2 (14)	20 (37)	0.12[a]
Management, n (%)									
Oxygen therapy only	18 (56)	14 (31)	0.05[a]	5 (26)	27 (45)	0.24[a]	–	32 (49)	
Non-invasive ventilation	3 (9)	2 (4)	0.39[b]	1 (5)	4 (7)	1[a]		5 (8)	
Invasive mechanical ventilation	10 (31)	4 (9)	0.01[b]	3 (16)	11 (18)	1[a]	–	–	
Days of use, median (IQR)	7.5 (5.5–9.0)	12.5 (8.8, 16.2)	0.67[c]	9.0 (9.0—9.0)	7.0 (5.0, 11.0)	0.66[c]	7.5 (5.0–10.0)	–	
ARDS diagnosis, n (%)	8 (25)	2 (4)	0.01[b]	1 (5)	9 (15)	0.44[b]	–	–	–
PICU LOS, days, median (IQR)	5.5 (2.8, 10)	5 (2—8)	0.88[c]	6 (4—11)	5 (2—9)	0.18[c]	12 (6—18)	5.0 (2—7)	0.01[c]
Outcome, n (%)									
Discharge	26 (81)	45 (96)	0.10[b]	17 (89)	54 (90)	0.79[b]	10 (71)	61 (94)	0.01[b]
Death	2 (6)	0 (0)		0 (0)	2 (3)		2 (14)	0 (0)	
Transfer to other hospital	4 (12)	2 (4)		2 (11)	4 (7)		2 14)	4 (6)	

[a] Chi-squared test.
[b] Fisher's exact test.
[c] Mann–Whitney *U* test.

Table 4b Unadjusted and adjusted[d] odds ratios and 95% confidence intervals for pediatric patients with COVID-19, according to the need for invasive mechanical ventilation (n = 79).

	Invasive mechanical ventilation			
	Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Age < 1 y	1.00 (0.99–1.01)	0.69	0.99 (0.99–1.00)	0.64
Sex, male	0.57 (0.18–1.82)	0.34	0.53 (0.15–1.84)	0.32
Race, non-white	1.06 (0.33–3.39)	0.93	0.85 (0.24–2.98)	0.80
Comorbidities	4.89 (1.37–17.37)	0.01	5.49 (1.43–21.12)	0.01

IQR, interquartile range; MIS, multisystemic inflammatory syndrome; ARDS, acute respiratory distress syndrome; PICU, pediatric intensive care unit; LOS, length of stay; OR, odds ratio; CI, confidence interval; PICU, pediatric intensive care unit.
[d] Adjusted for age < 1 year old, race, sex, and presence of comorbidities.

COVID-19,[5,11] was not frequent in the present cohort, where the main significant comorbidities were neuromuscular diseases, chronic respiratory diseases, and cancer. Age less than 1 year, sex, and race were not associated with more severe cases in the present study, although infants had a worse clinical course in China and the United States.[1,2] As MIS is a poorly understood disease that appears to occur in the subacute phase of SARS-CoV-2 infection, the authors also made the same subgroup comparisons and the assessment of predictors of severity in only the non-MIS group, but the results did not differ. As also shown in all pediatric studies on COVID-19, the vast majority of the present patients progressed well and were discharged, with a mortality rate of just 3%.

The present study has some limitations. As it involved only Brazilian patients, this may limit the generalization of the results. In addition, some details about treatment are lacking, such as the reason for the high percentage of use of antibiotics or corticosteroids. Not all patients had inflammatory markers measured, so they could not be compared depending on the severity of the disease. Despite these limitations, it is believed that this study may contribute to a better understanding of COVID-19, as it describes the first large series of patients admitted to PICUs in the Southern Hemisphere.

In conclusion, to the best of the authors' knowledge, this is the first study on COVID-19 in PICU patients in Brazil. It was shown that the characteristics of this disease in tropical and subtropical locations are similar to other countries. In this cohort, lethality was low, and chronic diseases and other comorbidities played an important role in the development of severe forms of the disease. Unlike other studies, the age less than 1 year was not associated with a worse prognosis. Patients with MIS had more severe symptoms, higher inflammatory biomarkers, and a greater predominance of males.

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Conflicts of interest

The authors declare no conflicts of interests. Q5

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Appendix A. Supplementary data

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