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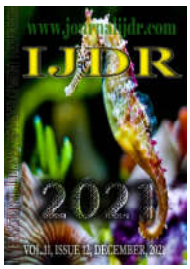

RESEARCH ARTICLE OPEN ACCESS

THE IMPACT OF COVID 19 ON CHILDREN FROM THE BRAZILIAN AMAZON REGION: CLINICAL FEATURES, OUTCOMES AND ASSOCIATED FACTORS

Emmerson C.F.de Farias[1,2], Manoel J.C.P. Junior[1], Susan C. D. de Sales[1], Luciana M.P.P. do Nascimento[1], Maria J.L. Lima[3], Ana R. G. Pedreira[4], Ana C.M. Alves[5], Mary L. F. M. F. de Mello[6] and Maria C. A. Justino[7]

[1]Fundação Santa Casa de Misericórdia do Pará, Departament of Pediatrics, Division of Pediatric Intensive Care, Belém, Pará, Brazil; [2]Departament of Child Health, Centro Universitário Metropolitano da Amazônia, Belém, Pará, Brazil; [3]Fundação Hospital das Clínicas Gaspar Viana, Departament of Pediatrics, Division of Pediatric Intensive Care, Belém, Pará, Brazil; [4]Hospital Pró-Infantil, Departament of Pediatrics, Division of Pediatric Intensive Care, Belém, Pará, Brazil; [5]Fundação Santa Casa de Misericórdia do Pará, Departament of Pediatrics, Division of Pediatric Ward, Belém, Pará, Brazil; [6]Pronto Socorro Municipal Mário Pinotti, Departament of Pediatrics, Division of Pediatric Intensive Care, Belém, Pará, Brazil; [7]Instituto Evandro Chagas, Virology Section, Health Surveillance Secretariat, Brazilian Ministry of Health, Ananindeua, Pará, Brazil

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Corresponding author:
Francinely Martins Gontijo

ABSTRACT

Objective: We aimed to describe the demographic, epidemiological, clinical, laboratory, imaging, and therapeutic characteristics of 90 pediatric coronavirus disease (COVID-19) patients, including severe cases and PMIS-TS. **Methods:** This prospective cohort study included all hospitalized children with confirmed COVID-19 admitted to four hospitals in the Brazilian Eastern Amazon. We excluded children with no molecular or serological positive test and no clinical-epidemiological presentation suggestive of SARS-CoV-2 infection. **Results:** The 90 participants were divided into three groups: ward group [18 (20%)], PMIS-TS group [30 (33.3%)] and pediatric intensive care unit (PICU) group [42 (46.7%)]. Among the PMIS-TS group, the median age was 59 months, and the most frequent age group was 2 to 5 years old [14(46.7%)]. Comorbidity had a high frequency ratio in all groups: ward [8 (44%), PMIS-TS: 22(73.3%)and PICU: 22(52%)]. Twenty-six (62%) patients had severe COVID-19. The median duration of invasive ventilation was 13 days in the PMIS-TS group. The overall mortality was 17deaths (18.9%). In the PMIS-TS group, pneumonia was diagnosed in 25 (83.3%) patients; 13 (43.3%) of them progressedtoacute respiratory distress syndrome. Additionally, male children, cutaneous rashes and longer duration of fever represented risk factors for PMIS-TS. Lymphopenia, hyperlactemia, hyperfibrinogenemia, hyperferritinemia, increased serum C-reactive protein, D-dimer and troponin levels were the main biological features in the patients with multiple organ dysfunctions. **Conclusions:** Comorbidities, cutaneous rashes and increased inflammatory markers in PMIS-TS patients indicate the subgroups that require great concern for development of severe COVID-19 in the Amazon region.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] pandemic caused unprecedented consequences for all human activities around the world. Children diagnosed with COVID-19 have an overall better prognosis and represent less than 5% of COVID-19 cases.[2,3] Notably, children under two years of age, with underlying diseases and immunocompromised are susceptible to developing severe or critical forms of the disease, with a frequency[3,4] lower than 4% and mortality ratio[3,4] around 2%. The"Pediatric Inflammatory Multisystem Syndrome temporally related with COVID-19" (PIMS-TS) was characterised for hyperinflammatory syndrome, presenting persistent fever, multiorgan dysfunction, and elevated inflammatory markers and is currently considered a rare post-COVID-19 complication, but severe, newly emerging phenotype. [5-10] In this study, we aimed to describe the demographic, epidemiological, clinical, laboratory, imaging, therapeutic characteristics of 90

children with confirmed COVID-19 and its risk factors for PMIS-TS and associated to mortality, admitted to four hospitals in the Brazilian Eastern Amazon region.

METHODS

Ethical considerations: This study was approved by the Ethics Committee for Institutional Research and required the signed consent of the parents and/or legal guardians. All hospitals were instructed to inform patients with the standardised patient information sheet about their right to refuse participation.

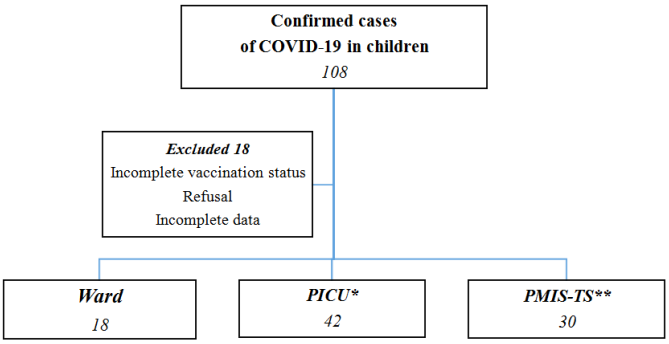
Patients and specimens collection: This was a prospective nested case-cohort study, hospital-based study involving children that were diagnosed with COVID-19 between April 1, 2020 and November 30, 2021 and admitted to four hospitals (three public and one private) in Belém, northern Brazil. These hospitals share the same clinical analysis laboratory network (Central Laboratory of the state of Pará/LACEN-PA) and accounted for over 60% of all hospital admissions of pediatric COVID-19 patients in the Belém area. We included children (aged 29 days to 12 years) admitted to any of the 4 hospitals with COVID-19 infection confirmed by a positive molecular or serological test and with a clinical-epidemiological presentation suggestive of COVID-19 or with a clinical-epidemiological presentation suggestive[5] of Pediatric Multisystem Inflammatory Syndrome-temporally associated with SARS-CoV-2 (PIMS-TS). We categorized the children with confirmed COVID-19 into case group, all patients included with PIMS-TS, and two control groups, ward and PICU group, in both groups the children had had confirmed COVID-19, but did not have met the PIMS-TS criteria according to the definition[5]. Children without confirmed COVID-19 infection were excluded from the analysis, as well as children with incomplete vaccination status.

The reverse transcription polymerase chain reaction (RT-PCR) and qualitative serology tests for IgG and IgM by immunochromatography (ONE STEP COVID-19 TEST®, Celer Biotecnologia S/A, Belo Horizonte, Minas Gerais) were performed using kits from the LACEN-PA. Based on the hospitalization sector and clinical manifestations, patients were stratified into three groups: as control group, the ward and pediatric intensive unit care (PICU) patients, while case group was the patients with PMIS-TS. According to experts' consensus statement on diagnosis,[11] patients were classified into 5 infection types: asymptomatic, mild, moderate, severe, and critical. Children were prospectively followed from the date of hospital admission until ward or PICU discharge, death, or 28th day of hospitalization, whichever occurs first. A collaborating researcher independently reviewed the collected data. Baseline information (sex, age, weight, time of onset, time of diagnosis by SARS-CoV-2 test, and dates of admission and discharge); epidemiological history; clinical manifestations; serological, microbiological, laboratory, and imaging findings; treatment; and outcome (death) were recorded using standardized data collection forms. In addition to the epidemiological data, we evaluated the clinical course, associated diagnosis of MODS,[12] ventilator settings, arterial gasometry (blood gases were measured at admission and their most critical values during the clinical course were recorded), modality and duration of mechanical ventilation (MV) support [non-invasive mechanical ventilation and invasive MV], ventilator-free days,[13] weaning failures,[14] progression to ventilator-associated pneumonia (VAP),[15] and development of acute respiratory distress syndrome (ARDS).[16] Laboratory results were recorded at admission and the most critical days until 28th day of hospitalization, before PICU or ward discharge. The presence of PMIS-TS disease was the primary outcome, as secondary outcome mortality 28th days.

Statistical analysis: All statistical analyses were performed using the SPSS software package for Windows (version 16.0, IBM, Armonk, NY). Categorical data were expressed as number (%) and continuous data were expressed as median [interquartile range (IQR)], if it is non-parametric variables. Comparisons between groups were made using the chi-square test or Fisher exact test for categorical variables, while Student t test was used for parametric and the Mann-Whitney U test for nonparametric continuous variables. Logistic regression was used to estimate risk ratios for factors predicting PMIS-TS or associated mortality, models were built using a backward-stepwise approach. All variables with P≤ 0.05 in univariate analysis were considered for entry into a multivariate logistic regression model.

RESULTS

Characteristics of study selection, epidemiology, and outcomes: From the study period, 205 children with suspected cases of COVID-19 were admitted to four hospitals in the Brazilian Amazon region. Among them 108 (52.7%) had a positive RT-PCR or serology (IgG) test result for SARS-CoV-2, a random subsample of the original cohort (subcohort) using age-matched distribution. Of these, 18 pediatric patients were excluded from this study due to participation refusal, incomplete data, incomplete vaccination status for age and other reasons. The final analysis included 90 patients divided into the ward [18(20%)], PMIS-TS group [30(33.3%)] and PICU [42(46.7%)] groups (Figure 1).



**PICU: pediatric intensive unitcare;*
***PMIS-TS: pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2*

Figure 1. Fluxogram describing the study design and selection of participantsadmitted to four hospitals in Belém, northern Brazil, from April to November, 2021

Among the PICU patients, the median age was 26.7 months (about 2 years) and the most frequent age group was ≤ 24 months [20 (48%)], while the ward patients the median age was 54.3 months (about 4.5 years). In the PMIS-TS group the median age was 59 months (about 5 years), and the most frequent age group was between 2- and 5-years old months [14 (46.7%)]. There was a male predominance in the PMIS-TS group [24(80%)]. Regarding body mass index (kg/m²), a lower value was found in the PICU group with a median of 15.3. Comorbidity had a high frequency in PMIS-TS group with 22(73.3%) [ward: 8 cases (44%) versus PICU: 22 cases (52%)]; respiratory disorders were the most prevalent in all groups (Table 1). In the PICU and PMIS-TS groups, critical clinical presentation was the most common clinical presentation with 26 (62%) and 15 (50%) cases, respectively, whereas moderate COVID-19 predominated in the ward group with 13 (72%) cases. In the patients admitted to the PICU, the most frequent symptoms at disease onset were dyspnea [39 cases (93%)], gastrointestinal distress [34 cases (81%)], and fever [31 cases (74%)]. In the PMIS-TS group in addition to these symptoms, the presence of cutaneous rashes was significantly relevant (OR 7.68; IC95%:3.14-18.75; *p*: 0.008). In the ward group, the most common symptom was fever [13 cases (81%)] (Table 1). The median time elapsed between exposure to SARS-CoV-2 and clinical manifestation and fever duration were higher among patients in the PMIS-TS group with a median of 15 and 11 days, respectively. The median length of PICU stay was 13.5 days, while the median duration of oxygen therapy was 3.5 days among patients in the PMIS-TS groups. The median duration of invasive MV and ventilator-free period were 13 and 1.5 days, respectively in the PMIS-TS group. The overall mortality was 17 deaths (18.9%) [PICU group 13(30.9%) versus PMIS-TS 4(13.3%)] (Table 1).

Table 1. ***Epidemiological and Clinical outcomes features of hospitalized children with confirmed SARS-CoV-2 infection (n=90)***

Variables*	Ward control group (N=18)	PICU* control group (N=42)	PMIS-TS case group (N=30)	*p* value
Age in months[a]	54.3 (17-94.3)	26.7 (10.7-98.3)	59 (53.5-101)	0.028
Age groups[b] (years)				
< 2	6 (33.3)	20 (47.6)	3 (10)	
2--5	6 (33.3)	7 (16.7)	14 (46.7)	0.013
6--10	5 (27.8)	10 (23.8)	7 (23.3)	
>11	1 (5.5)	5 (11.9)	6 (20)	
Male/ Female[b]	9 (50)/ 9 (50)	21 (50)/ 21 (50)	24 (80)/6 (20)	0.02
BMI **(kg/m^2)[a]	18.9 (17.9-22.8)	15.3 (13.9-16.6)	17.5 (15-19.5)	0.002
Comorbidity[b]	8 (44.4)***	22 (52.4)***	22 (73.3)***	0.09
Form of presentation[b]				
Mild	5 (27.8)	6 (14.3)	0 (0)	
Moderate	13 (72.2)	4 (9.5)	3 (10)	
Severe	0	6 (14.3)	12 (40)	
Critical	0	26 (61.9)	15 (50)	<0.0001
Most prevalent clinical manifestations[b]				
Dyspnea	9 (50)	39 (92.9)	22 (73.3)	
Gastrointestinal symptoms (diarrhea, vomiting)	10 (55.5)	34 (81)	30 (100)	
Fever	13 (81.25)	31 (73.8)	30 (100)	
Cutaneous rashes	3 (16.7)	12 (28.6)	25 (83.3)	<0.0001
Productive cough	3 (16.7)	11 (26.2)	16 (53.3)	
Contagion form, Home/ Hospital [b]	14 (77.8)/ 4 (22.2)	31 (73.8)/ 11 (26.2)	25 (83.3) / 5 (16.7)	0.636
Exposure interval (days)[a]	5 (3.25-11.75)	7 (5-11)	15 (14-37.5)	<0.0001
Fever duration (days)[a]	5.5 (4.25-8.75)	8.5 (6-11.75)	11 (9-12)	<0.0001
Clinical Outcomes[b]				
Length of PICU stay (days)[a]	0	5 (4-9.5)	13.5 (9-20.3)	0.015
Length of Hospital Stay (days)[a]	12 (9-14)	19 (13-32)	17 (14.5-26)	0.546
Oxigen time (days)[a]	4 (4-6.5)	5.5 (3-12.75)	3.5 (3-5.25)	0.003
Noninvasive ventilation time (days)[a]	--	3 (2-4)	2 (1-2)	0.238
Invasive ventilation time (days)[a]	--	5 (4.25-6.25)	13 (9.25-16)	0.028
Ventilator-free days	--	1(0-10)	1.5 (0-3.5)	
Died[b]	0 (0)	13 (31)	4 (13.3)	0.023
Discharge[b]	13 (72.2)	26 (61.9)	18 (60)	
Remained in hospital[b]	5 (27.8)	3 (7.1)	8 (26.7)	

[a] *Median (Interquartile range);* [b] *N (%); * Paediatric Intensive Unit Care; **Body mass index; *** Comorbity: Ward group: respiratory diseases 5 (62,5%), neurologic, cardiovascular and gastrointestinal diseases: one for each (12,5%); PICU group: respiratory diseases: 12 (54,5%) and prematurity 4(18,2%); PMIS-TS group: respiratory disease 6 (20%), neurologic diseases 6 (20%) and prematurity 4 (18.2%)*

Table 2. ***Clinical, imaging ventilatory support and treatment features of hospitalized children with confirmed SARS-CoV-2 infection (n=90)***

Variables*	Ward control group (N=18)	PICU* control group (N=42)	PMIS-TS case group (N=30)	*p* value
Respiratory Support [a]	14 (77.8)	42 (100)	30 (100)	--
Oxygen nasal cannula or simple mask	14 (77.8)	14 (33.3)	14 (46.7)	0.007
BIPAP**	--	4 (9.5)	5 (16.7)	0.476
Invasive mechanical ventilation	--	24 (57.2)	11 (36.7)	0.10
Ventilator mode, ACP[a]	--	19 (79.2)	9 (90)	--
Pneumonia [b]	6 (33.3)	33 (78.6)	25 (83.3)	0.001
ARDS[a]	0	17 (40.5)	13 (43.3)	0.103
ARDS forms: Mild/ Moderate/ Severe[a,f]	--	11 (64.7)/ 6 (35.3)/ 0	3 (23)/5 (38.5)/5 (38.5)	0.009
Ventilator-associated pneumonia[a]	0	6 (14.3)	4 (40)	0.689
Circulatory shock[a]	0	24 (57.1)	25 (83.3)	0.023
Shock type: Mixed/ Cardiogenic/ Septic[a,g]		2 (8.3)/ 4 (16.7)/ 18 (75)	5 (20)/14 (56)/6 (24)	0.007
MODS/ More than 3[a]	1 (5.5)/ 0	25 (59.5)/ 15 (60)	30 (100)/ 22(73.3)	--
Drugs[a]				
Methylprednisolone	4 (22.2)	15 (37.1)	30 (100)	--
IVIg	2 (11.1)	10 (23.8)	28 (93.3)	--
LMWHs[a]	6 (33.3)	21 (50)	25 (83.3)	--
Vasoactive support	0 (0)	22 (52.4)	25 (83.3)	--
Thoracic computed tomography findings[a]				
Ground-glass opacities [c]	3 (50)	21 (63.6)	23 (76.7)	0.0001
Focal consolidations and mixed opacities	3 (50)	10 (30.3)	3 (10)	--
Echocardiography[a]	14 (77.8)	22 (52.4)	30 (100)	
LVEDD[b] (mm)	31.5 (21.75-35.5)	25 (18-35.5)	38 (31.5-42)	--
LVESD[b] (mm)	21.5 (14-25.75)	15 (12.5-23)	20 (16-23.5)	--
EF[b, d, e] (%)	66 (62.5-69)	59.8 (52.5-66)	62 (60-66.5)	--

*Paediatric Intensive Unit Care. BIPAP: bi-level positive airway pressure. ACP: assisted/controlled pressure ventilation. ARDS: acute respiratory distress syndrome. IVIg: high-dose intravenous immunoglobulin. LMWHs: low-molecular-weight heparins. LVEDD: Left ventricular size End-diastolic dimension. LVESD: Left ventricular size End-systolic dimension. EF: ejection fraction. [a] N (%), [b] Median (Interquartile range), [c] peripheral and bilateral ground-glass opacities in the upper and lower segments; [d] all patients were using vasoactive drugs; [e] Left ventricular ejection fraction was estimated using Simpson's biplane method. The classification of ARDS was based on current pediatric criteria, according to PALICC, 2015[18], [f] comparison between with or without servere ARDS, [g] comparison between with or without cardiogenic shock

Clinical, imaging, and treatment characteristics: Respiratory support was required in the PMIS-TS, PICU and ward groups for 30 (100%), 42 (100%) and 14 (78%) patients, respectively. In our study, 24 (57.2%) *versus* 11 (36.7%) patients in the PICU and PMIS-TS groups, respectively, were submitted to MV. Of these, 7 patients (29%) required reintubation and were considered weaning failures, all in the PICU group. Echocardiography was performed in 30 (100%), 14 (78%) and 22 (52%) patients from the PMIS-TS, ward and PICU groups, respectively. The ejection fraction was moderately affected or had lower values (median, 62%) among patients of the PMIS-TS group despite 25 (83.3%) of them requiring the administration of vasoactive drugs (Table 2). Cardiovascular involvement was common, with 25 (83.3%) patients requiring vasoactive agents [cardiogenic shock (14, 56%), septic shock (6, 24%), and mixed shock (5, 20%)] in the PMIS-TS group. MODS was observed in 30 (100%) patients with PMIS-TS. Among them, 22 (73.3%) had three or more organs involved. Methylprednisolone, IVIg and low-molecular-weight heparins were administered in 30 (100%), 28 (93.3%) and 25 (83.3%) patients with PMIS-TS, respectively (Table 2).

Laboratorial and microbiological characteristics: Troponin, C-reactive protein (CRP) (mg/dL), lactate (mmoL/L), LDH, ferritin and D-dimer (ng/mL) serum levels were higher among patients in the PMIS-TS group than those among patients in the PICU group. Lymphocytes were severely decreased (median, 1.03 x 10^9 /L) among patients in the PMIS-TS group (Table 3). In the PICU group, abnormal laboratorial findings included decreased total calcium and fibrinogen levels. Albumin levels were markedly lower among patients in the PMIS-TS group compared with those in the PICU group (median, 2.1 g/dL *versus* 2.7), whereas the anion gap was higher among patients with PMIS-TS group than those among patients in the PICU group (median 22.9 *versus* 13.9). Arterial gasometry showed a lower level of bicarbonate among patients in the PMIS-TS group compared with those in the PICU group (median 18.1 *versus* 19.4).

Table 3. Laboratory and microbiological features at admission of hospitalized children with confirmed SARS-Co-2 infection (n=90)

Variables*,[a]	Ward control group (N=18)	PICU* control group (N=42)	PMIS-TS case group (N=30)	*p* value
Haemoglobin g/dL	11.7 (10.7-12.6)	10.5 (9.4-11.6)	9.6 (9.4-10.7)	0.025
Leukocytes x 10^9/L	9.95 (7.6-15.87)	11.91 (7.62-14.28)	9.34 (6.78-17.94)	0.087
Neutrophils x 10^9/mL	6.39 (4.65-11.39)	6.43 (4.19-9.56)	10.36 (7.12-15.3)	0.057
Lymphocytes × 10^9/L	2.6 (1.61-3.46)	2.45 (1.39-5.28)	1.03 (0.806-1.42)	<0.0001
Platelets × 10^9/L	220.15 (146.4-355.9)	175.2 (128.6-364.2)	172 (119.5-278.8)	0.90
Troponin I (ng/mL)	0.02 (0.01-0.12)	0.1 (0.011-0.246)	0.28 (0.1-1.65)	0.002
CPK/ CK-MB (IU/L)	26.4 (20.3-46.1)/ 19 (10.7-47.8)	49.4 (20-80.5)/ 19 (9.65-52)	27(20-110.5)/ 38.8 (31.9-127.5)	0.72/0.419
CRP (mg/dl)	5.5 (1.3-20.2)	7 (1.25-42)	45 (20.7-127.5)	<0.0001
Ferritin (ng/mL)	327.2 (136.5-547.7)	418.9 (294.4-596.7)	555.15 (309.9-669)	0.002
PT/ APTT in seconds	12.1 (11.2-19.8)/ 36.6 (27.9-43.7)	12.4 (11.4-14.2)/ 35.7 (29.3-43.4)	11.7 (11.4-14.3)/ 28.2 (26-43)	0.436/0.158
INR	1.12(1-1.8)	1.2 (1.1-1.6)	1.2 (1.07-1.38)	0.11
D-dimer (ng/mL)	1282.2 (679.2-3833.8)	1796.7 (568-4165.7)	2011.5 (820-4796.5)	0.887
Fibrinogen (mg/dL)	129.1 (100.5-195.7)	116.5 (51.5-179)	453 (377-679)	<0.0001
Albumin (g/dL)	2.7 (2.6-3.2)	2.7 (2.2-3)	2.1 (2-2.2)	0.01
Lactate (mmol/L)	2.2 (1.3-2.8)	2.85 (1.7-3.4)	3.1 (2.8-3.3)	0.056
ALT (IU/L)/ AST (IU/L)	34.4 (18.6-49.7)/ 43.5 (39-60.75)	38.5 (20.9-68.1)/ 40 (27.8-76.6)	36 (17.5-44.5)/ 42 (19.5-62)	0.629/0.183
Total calcium (mg/dL)	8.7 (7.8-9.2)	8.5 (7.1-9)	8.5 (7.7-9.6)	0.661
Phosphorus (mg/dL)	2.9 (2.3-4.1)	2.8 (1.9-3.6)	2,75 (2,33-3,95)	0.864
Creatinine (mg/dL)	0.3 (0.2-0.4)	0.4 (0.27-0.6)	0,43 (0,39-0,46)	0.383
LDH (IU/L)	445 (231.3-678.5)	500.5 (222.3-599.8)	1119,0 (280,5-1208,5)	0.152
Arterial gasometry*,[a]				
BIC/ O_2 Sat (%)	22.6 (18.9-25.6)/ 98.6 (95.9-99.2)	19.4 (16.5-25.9)/ 96.9 (90.3-98.9)	18.1 (14-22.8)/ 94.9 (90-97.9)	0.389/0.209
AG/ SIG	13.6 (10.1-19.38)/ 6.16 (3.5-15.6)	13.9 (8.9-20.7)/ 7.37 (3.3-14.2)	22.9 (10.2-28.2)/ 8.7 (4.2-18.2)	0.015/<0.0001
Microbiological [b]				
RT-PCR + / IgG +	10 (55.6)/ 8 (44.4)	15 (35.7)/ 27 (64.3)	4 (13.3)/ 26 (86.7)	--
Other viruses	3 (16.7)	1 (2.4)	1 (3.3)	--
Blood/ Urine culture	1 (6.7)/ 1 (6.7)	2 (4.4)/ 0 (0)	0 (0)/ 0 (0)	--

* CPK, creatinophosphokinase. CK-MB, creatine kinase MB fraction. CRP, C-reactive protein. PT, prothrombin time. APPT, activated partial thromboplastin time. INR, international normalized ratio. ALT, alanine transaminase. AST, aspartate transaminase. LDH, lactate dehydrogenase. pH, potential for hydrogen. pCO_2, partial pressure of carbon dioxide. pO_2, partial pressure of oxygen. BIC, sodium bicarbonate, BE, base excess; O_2 Sat, oxygen saturation. AG, anion gap. SIG, strong ion gap. RT-PCR, reverse transcription polymerase chain reaction positive nasopharyngea for SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, and positive nasopharyngeal PCR for other viruses. IgG, immunoglobulin G. [a]Median, (Interquartile range). [b]N (%). All tests were performed according to the protocols described by the manufacturers.

Table 4. Multiple Logistic Regression Analyses related to PMIS-TS disease presence and 28th mortality

Outcomes	Model		
PMIS-TS disease presence	*OR*	CI 95%	*p* value
Exposure interval (days)	2.00	1.25-3.02	0.004
Lymphophenia	1.06	0.99-1.01	0.017
Hiperfibrinogenemia	1.03	0.99-1.06	0.047
Cutaneuos rash	7.68	3.14-18.75	0.008
28th mortality in PMIS-TS	*OR*	CI 95%	*p* value
Fever duration (days)	1.83	0.97-1.95	0.007
Shock presence	18.35	2.31-145.70	0.006

* Outcomes Odds Ratios with 95% CI

The chest computed tomography (CT) features most common was peripheral and bilateral ground-glass opacities in the upper and lower segments were observed in the CT scan of 23 (76.7%) and 21 (63.6%) patients of the PMIS-TS and PICU groups, respectively. In the PMIS-TS group, 25 (83.3%) patients were diagnosed with pneumonia caused by COVID-19 and 13 (43.3%) of them progressed to ARDS.

The number of positive serological tests for SARS-CoV-2 was higher in the PICU and PMIS-TS groups than that in the ward group [27 cases (64%) and 26 (86.7%) versus 8 cases (44%)]. No other major

differences in laboratory and microbiological results were observed between groups at baseline (Tables 3 and 4).

DISCUSSION

To our knowledge, this study represents the first large case series of sequentially hospitalized children with confirmed COVID-19 in northern Brazil. This study included clinical, laboratory, and imaging data, as well as therapeutic measures regarding pediatric COVID-19 patients in the metropolitan region of Belém. The disease presented with common symptoms—high fever, and respiratory and gastrointestinal distress—and had an unfavorable evolution, i.e., death, in 18.9% (17/90) of patients. Similar to other studies, we noted that fever, dyspnea, and gastrointestinal manifestations, such as vomiting and diarrhea, were the most common symptoms in critical pediatric COVID-19 and PMIS-TS patients. However, in our study, critical COVID-19 and PMIS-TS occurred in patients under 2 and 5 years of age, respectively, lower body mass index, high prevalence of comorbidities, cardiovascular involvement and pneumonia caused by COVID-19. Interestingly, cutaneous rashes proved to be a statistically significant finding, eight times more in PMIS-TS children in the Amazon region. Increased requirement for MV, and likely progression to ARDS and MODS were observed in this group and consequently, a higher mortality rate than others studies.[3,4, 6,7, 8] This reinforces the need for strict monitoring to effectively treat these children,[17-21] regardless of previous exposure to the virus. Studies suggest that COVID-19 pathogenesis differ depending on exposure[22]; nasal expression of angiotensin-converting enzyme 2 (ACE2),[23] the receptor used by SARS-CoV-2 for cell entry; exploration of potential host factors, such as mitochondria and microbiota dysfunction[24,25,26] and signaling pathways and genetic variants.[27]

In this study patients with PMIS-TS, hemodynamic instability and cardiac dysfunction were prominent findings (high serum troponin, moderate ejection fraction despite use of vasoactives, metabolic acidosis, hypoxemia, reduced bicarbonate, and elevated anion gap and SIG). In addition, coagulopathy was a common finding in this case series (high levels of fibrinogen and D-dimer). The presence of hyperinflammation was evidenced by moderate hyperferritinemia associated with high CRP levels. The interaction between hypovolemic and hyperinflammatory shock associated with myocardial dysfunction play an important role in explaining the severity and mortality observed, as evidenced in other studies.[28-31] Other studies found more severe hyperferritinemia cases than those found in this series.[6,7,8,16,17] This divergence may be explained by differences in the pathobiological and nutritional mechanisms of ferritin production as a marker of acute inflammation.[31] It is also noteworthy that the association between high serum ferritin and CRP values are associated with worse outcomes.[32,33] This information corroborates the presence of hyperinflammation in the patients included in this study. Most pediatric patients with PMIS-TS had antibodies against the SARS-CoV-2 virus and negative RT-PCR test results associated with a reduced number of lymphocytes, which is suggestive of a postinfectious, inflammatory, and immunologically mediated pathophysiology.[33,34,35] There is a laboratorial and epidemiological evidences of other viral infections[36-38] and SARS-CoV-2[39-42] developing changes in subpopulations of T lymphocytes, such as CD^{3+}, CD^{4+} e CD^{8+}. Clinically, our region experienced two distinct stages of the COVID-19 pandemic. The first stage comprised the initial 30 days of the pandemic and was characterized by most hospitalized patients presenting positive RT-PCR test results, hospital contagion, short exposure to the virus, moderate disease, predominance of respiratory manifestations, and comorbidities. The second stage begun at the third month of the pandemic and was characterized by hospitalized patients presenting negative RT-PCR and positive serological test results, home contagion, long exposure to the virus, severe and critical disease, and predominance of gastrointestinal manifestations, dyspnea, fever and MODS. This study has some limitations. Unfortunately, there are no widely accepted diagnostic criteria to classify the severity of pediatric COVID-19 cases. Besides the small sample size, the data were collected from hospitals that did not use an uniform protocol, requiring the management and conduction of the study to be individualized by center and patient. The target population was exclusively composed of critical patients, which may be a source of selection bias. In contrast, the strengths of this study lie on the following aspects: (a) we conducted a multicenter prospective study including children with confirmed SARS-CoV-2 infection in a limited-resource setting; (b) a regional large sample of PMIS-TS cases, suggesting local variations in inflammatory markers and disease severity, thus characterizing cases of pediatric critical COVID-19 and PMIS-TS and reducing the bias associated.

CONCLUSION

We provided clinical, epidemiological, and laboratory data on hospitalized children with confirmed COVID-19 in the Amazon region. Our results indicate a variable disease with a high frequency of shock, associated MODS and higher mortality for patients with critical COVID-19 and PMIS-TS compared with those with mild and moderate disease. The evolution of organ failure and laboratory findings evidenced in our study could be used as prognostic markers for this inflammatory syndrome. Furthermore, we collected blood samples from the patients included in this study for future analysis of inflammatory cytokines at the Virology Section, Evandro Chagas Institute, Health Surveillance Secretariat, Brazilian Ministry of Health.

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