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Critical disease related to SARS-CoV-2 infection in children from the Amazon region: an observational study

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Keywords:	COVID-19, Epidemiology, Virology

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ABSTRACT

This is a multicenter prospective cohort including critically ill children and adolescents, with confirmed critical disease related to SARS-CoV-2, admitted to three tertiary Pediatric Intensive Care Units in the Brazilian Amazon, between April 2020 and July 2022. 208 patients were included (median age was 3.5 years). The majority had malnutrition (62%) and comorbidities (60.6%). Mechanical ventilation support, cardiogenic shock and acute respiratory distress syndrome occurred in 47%, 30% and 37% of patients, respectively. There were 37 (18%) deaths. A poor outcome of severe COVID-19 and multisystem inflammatory syndrome (MIS-C) was observed in children and adolescents from the Brazilian Amazon.

Keywords: SARS-CoV-2; Intensive Care Unit, Pediatric, Epidemiologic Factors, Care Outcome, Critical, pediatric multisystem inflammatory disease, COVID-19 related.

Main text

SARS-CoV-2 related-disease in children usually has a good prognosis, especially in those from high income countries [1,2]. Studies in resource-restricted regions reveal higher mortality rates of severe COVID-19 in children and of MIS-C, however, there is a scarcity of studies in these regions [3,4]. Our study evaluated children and adolescents from urban and rural areas, of a wide geographic region, characterized by social inequality and poverty, and consequently, reduced access to health services.

We aimed to describe features and outcomes of children and adolescents with severe COVID-19 and MIS-C admitted to Pediatric Intensive Care Units (PICU) from the Eastern Brazilian Amazon region.

This multicenter prospective cohort included critically ill pediatric patients (1 month to 18 years of age), with confirmed critical disease related to SARS-CoV-2, admitted to three tertiary PICU in the Brazilian Amazon, between April 2020 and July 2022.

All participants and their legal guardians provided written informed assent and/or consent and were split into two groups: MIS-C, defined by the World Health Organization (WHO) criteria [5], with positive molecular or serological test, and severe COVID-19, defined by the presence of confirmed SARS-CoV-2 infection, with acute involvement of at least one organ system, and who did not fulfill the MIS-C criteria [5]. Patients with coinfection by other agents, on immunosuppression or at end-of-life decision stage, were excluded. Patients and the public were not involved in any way in the planning, management, design, or carrying out of this research.

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52 adolescents with critical disease related to SARS-CoV-2 from the Amazon region. This
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Ethics approval and consent to participate

The study was approved by the institutional review board of the coordinating center (the other centers were co-participants). The parents or guardians of the children, or, when applicable, the children themselves, provided written informed consent before being included in the study. Besides this, confidentiality was achieved by maintaining privacy at all levels of the study. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Committee of FSCMPA under number 0361/2017, opinion n° 4.060.894, CAAE 31513320.0.0000.5171

Consent for publication

Not applicable.

Availability of data and materials

All the datasets during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no competing interest to the final content of the manuscript.

Supplemental material

Not applicable.

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Authors' contributions/ [Contributorship Statement](#)

ECFF, MTT, and GC designed research, conceptualized the study, analyzed the data, and wrote the manuscript. MCAJ, MLFMFM, LMPPN, SCDS and PBC assisted with the concept, interpretation of data, and reviewed the manuscript. All authors, ECFF, MTT, GC, MCAJ, MLFMFM, LMPPN, SCDS and PBC conducted data collection, interpretation of data, and edited the manuscript. All authors have read, reviewed, and approved the manuscript.

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Table 1 - Demographics, clinical, and outcome features of children and adolescents with critical disease related to SARS-CoV-2

Characteristics	Patients with critical disease related to SARS-CoV-2		
	Severe COVID-19 (n=141)	MIS-C (n=67)	All patients (n=208)
Demographics and epidemiological			
Age, in months, median (IQR)	28 (9-101)	53 (12-112)	41.6 (9.6-103.1)
Male sex, n (%)	65 (46.1)	52 (77.6)	117 (56.2)
Comorbidity, n (%)	74 (52.5)	51 (76.2)	126 (60.6)
Main comorbidity: Neurologic and neuromuscular, n (%)	21 (14.9)	20 (29.8)	41 (19.7)
Malnutrition, n (%)	90 (63.8)	39 (58.2)	129 (62.0)
SARS-CoV-2 infection confirmed tests, n (%)			
RT-PCR	66/85 (77.6)	21/61 (34.4)	87/146 (59.6)
Antigen	60/83 (72.3)	28/52 (53.8)	88/135 (65.2)
ELISA IgG	4/47 (8.5)	18 /23(78.3)	22/70 (31.4)
ELISA IgM	11/47 (23.4)	4 /23 (17.4)	15/70 (21.4)
Clinical and intensive support			
Cardiogenic shock, n (%)	26 (18.4)	28 (41.8)	54 (30.0)
Mechanical ventilation support, n (%)	52 (36.9)	46 (68.7)	98 (47.1)
Acute respiratory distress syndrome, n (%)	38 (26.9)	35 (52.2)	71 (34.1)
Kidney Disease: Improving Global Outcome classification system: Stage 1/Risk, n (%)	70 (49.6)	35 (52.2)	105 (50.5)
Treatment			
Low molecular weight heparin therapy, n (%)	59 (41.8)	49 (73.1)	108 (51.9)
Methylprednisolone pulse therapy, n (%)	4 (2.8)	21 (31.3)	25 (16.8)
Intravenous immunoglobulin therapy, n (%)	25 (17.7)	45 (67.2)	70 (33.6)
Outcomes			
Ventilator weaning success at first attempt, n (%)	35 (24.8)	42 (62.7)	77 (37.0)
Tracheostomy tube use, n (%)	8 (5.7)	0 (0)	8 (3.8)
Ventilator free days at 28 th , median (IQR)	1 (0-3)	3 (1-9)	3 (1-5)
Length of stay in PICU, in days, median (IQR)	7 (2-12)	5 (3-10)	5 (2-10.5)
Length of stay in hospital, in days, median (IQR)	14 (10-20)	15 (10-19)	14 (10-20)
Mechanical ventilation time, in days, median (IQR)	6 (4-12)	4 (1-7)	4 (3-9)
Death, n (%)	21 (14.9)	16 (23.9)	37 (17.8)

Table 2 - Laboratorial and ventilator parameters of children and adolescents with critical disease related to SARS-CoV-2 on first and third day from admission

Laboratorial and ventilator parameters	Patients with critical disease related to SARS-CoV-2					
	On first day			On third day		
Cardiovascular system	Severe COVID-19 (n=141)	MIS-C (n=67)	Total	Severe COVID-19 (n=141)	MIS-C (n=67)	Total
VIS	7 (6-38)	68 (17-105)	84 (39-120)	6 (2-13)	25 (8-74)	9 (5-42.5)
Troponin I (ng/L)	0.03 (0.01-0.17)	0.28 (0.02-1.8)	0.11 (0.02-0.44)	0.06 (0.01-0.9)	0.2 (0.01-13.4)	0.1 (0.01-2.25)
Respiratory system						
DP in cmH ₂ O	7 (6-8)	12 (10-16)	9 (7-12)	8 (5-10)	12 (9-16)	8 (10-14)
Tidal volume in ml/kg	7.1 (5.7-9.7)	5.7 (4.9-6.6)	7.0 (6.3-9.4)	7.2 (5.4-9.6)	6.6 (4.1-8.2)	7.3 (5.4-9.4)
PIP in cmH ₂ O	18 (15-20)	16 (14-27)	18 (15-23)	16 (12-22)	16 (12-24)	18 (12-22)
OI	3.6 (1.9-6)	8.8 (4.9-13.4)	5.3 (2.4-10.3)	2.7 (1.2-5.3)	6.8 (3.2-11)	4.2 (2-7.9)
Inflammatory markers						
CRP (mg/dL)	7 (2-18)	45 (18-85)	12 (3-36)	5 (1.3-12.2)	22 (7.3-59)	8 (2.4-20)
ESR in mm/h	17 (10-120)	55 (28-110)	33 (10-108)	9 (2-17)	20 (13-58)	17 (10-35)
Haematological system						
Lymphocytes/mm ³	2,646 (1,398-4,878)	1,249 (960-1,773)	1,874 (1,118-3,772)	2,655 (1,268-4,284)	2,266 (1,248-4,525)	2,563 (1,114-4,257)
D-Dimer (ng/dL)	1,192 (529-3,406)	2,014 (1,085-5,009)	989.6 (522.2-2790.1)	854 (406-2,851)	1,264 (609-3,861)	769.8 (350.8-2,836)
Renal system						
Creatinine(mg/dL)	0.3 (0.2-0.42)	0.39 (0.3-0.6)	0.40 (0.20-0.56)	0.49 (0.3-0.7)	0.4 (0.25-0.6)	0.5 (0.38-0.67)
Hepatic system						
Albumin (g/dL)	2.9 (2.5-3.5)	2.7 (2.2-3.6)	2.7 (2.3-3.5)	3.0 (2.5-3.6)	2.2 (1.9-3.2)	2.7 (2.3-3.5)

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VIS, -vasoactive inotropic score. DP - drive pressure. PIP - peak inspiratory pressure. OI - oxygen index. CRP, -C-reactive protein. ESR erythrocyte sedimentation rate. All tests were performed according to the protocols described by the manufacturers. It was chosen to define reference ranges according to age and sex.

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of comorbidities, emphasizing the need for better public health policies in developing countries.

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Ethics approval and consent to participate

The study was approved by the institutional review board of the coordinating center (the other centers were co-participants). The parents or guardians of the children, or, when applicable, the children themselves, provided written informed consent before

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3 being included in the study. Besides this, confidentiality was achieved by maintaining
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5 privacy at all levels of the study. The study was conducted in accordance with the
6
7 Declaration of Helsinki. The study was approved by the Research Ethics Committee of
8
9 FSCMPA under number 0361/2017, opinion n° 4.060.894, CAAE 31513320.0.0000.5171

12 13 **Consent for publication**

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15 Not applicable.

16 17 18 **Availability of data and materials**

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20 All the datasets during and/or analyzed during the current study are available from
21
22 the corresponding author upon reasonable request.

23 24 25 **Competing interests**

26
27 All authors declare that they have no competing interest to the final content of the
28
29 manuscript.

30 31 32 **Supplemental material**

33
34 Not applicable.

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38
39 This study had no financial support.

40 41 42 **Authors' contributions/ [Contributorship Statement](#)**

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ECFF, MTT, and GC designed research, conceptualized the study, analyzed the
data, and wrote the manuscript. MCAJ, MLFMFM, LMPPN, SCDS and PBC assisted
with the concept, interpretation of data, and reviewed the manuscript. All authors, ECFF,
MTT, GC, MCAJ, MLFMFM, LMPPN, SCDS and PBC conducted data collection,
interpretation of data, and edited the manuscript. All authors have read, reviewed, and
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Table 1 - Demographics, clinical, and outcome features of children and adolescents with critical disease related to SARS-CoV-2.

Characteristics	Patients with critical disease related to SARS-CoV-2		
	Severe COVID-19 (n=141)	MIS-C (n=67)	All patients (n=208)
Demographics and epidemiological			
Age, in months, median (IQR)	28 (9-101)	53 (12-112)	41.6 (9.6-103.1)
Male sex, n (%)	65 (46.1)	52 (77.6)	117 (56.2)
Comorbidity*, n (%)	75 (53.2)	51 (76.2)	126 (60.6)
Malnutrition, n (%)	90 (63.8)	39 (58.2)	129 (62.0)
SARS-CoV-2 infection confirmed tests, n (%)			
RT-PCR	66/85 (77.6)	21/61 (34.4)	87/146 (59.6)
Antigen	60/83 (72.3)	28/52 (53.8)	88/135 (65.2)
ELISA IgG	4/47 (8.5)	18/23(78.3)	22/70 (31.4)
ELISA IgM	11/47 (23.4)	4/23 (17.4)	15/70 (21.4)
Clinical and intensive support			
Cardiogenic shock, n (%)	26 (18.4)	28 (41.8)	54 (30.0)
Mechanical ventilation support, n (%)	52 (36.9)	46 (68.7)	98 (47.1)
Acute respiratory distress syndrome, n (%)	38 (26.9)	35 (52.2)	71 (34.1)
Kidney Disease: Improving Global Outcome classification system: Stage 1/Risk, n (%)	70 (49.6)	35 (52.2)	105 (50.5)
Treatment			
Low molecular weight heparin therapy, n (%)	59 (41.8)	49 (73.1)	108 (51.9)
Methylprednisolone pulse therapy, n (%)	4 (2.8)	21 (31.3)	25 (16.8)
Intravenous immunoglobulin therapy, n (%)	25 (17.7)	45 (67.2)	70 (33.6)
Outcomes			
Ventilator weaning success at first attempt, n (%)	35 (24.8)	42 (62.7)	77 (37.0)
Tracheostomy tube use, n (%)	8 (5.7)	0 (0)	8 (3.8)
Ventilator free days at 28 th , median (IQR)	1 (0-3)	3 (1-9)	3 (1-5)
Length of stay in PICU, in days, median (IQR)	7 (2-12)	5 (3-10)	5 (2-10.5)
Length of stay in hospital, in days, median (IQR)	14 (10-20)	15 (10-19)	14 (10-20)
Mechanical ventilation time, in days, median (IQR)	6 (4-12)	4 (1-7)	4 (3-9)
Death, n (%)	21 (14.9)	16 (23.9)	37 (17.8)

* Comorbidities were present in 92/171 (53.8%) of survivors and in 34/37 (91.9%) of non survivors. 88/208 (42.3%) patients had more than two comorbidities, with 65/171 patients in the survivors group and 23/37 (62.2%) in the non survivors group. In the severe COVID-19 and MIS-C group 67/141 (47.5%) and 21/67 (31.3%) patients had more than 2 comorbidities, respectively.

Table 2 – Comorbidities and nutritional status in children and adolescents with critical disease related to SARS-CoV-2.

Comorbidities* and nutritional status**	Patients with critical disease related to SARS-CoV-2		
	Severe COVID-19 (n=141)	MIS-C (n=67)	All patients (n=208)
Neurologic and neuromuscular, n (%)	21 (14.9)	20 (29.8)	41 (19.7)
Gastrointestinal, n (%)	15 (10.6)	10 (14.9)	25 (12)
Respiratory, n (%)	6 (4.3)	11 (16.4)	17 (8.2)
Premature and neonatal, n (%)	6 (4.3)	4 (6.0)	10 (4.8)
Renal and urologic, n (%)	8 (5.7)	2 (3.0)	10 (4.8)
Genetic defect or other congenital disease, n (%)	7 (5.0)	2 (3.0)	9 (4.3)
Metabolic, n (%)	4 (2.8)	1 (1.5)	5 (2.4)
Cardiovascular, n (%)	3 (2.1)	1 (1.5)	4 (1.9)
Hematologic non-immunologic disease, n (%)	2 (1.4)	0 (0)	2 (1.0)
Technology dependence, n (%)	3 (2.1)	0 (0)	3 (1.4)
Transplantation, n (%)	0 (0)	0 (0)	0 (0)
Malignancy, n (%)	0 (0)	0 (0)	0 (0)
Low weight	90 (63.8)	39 (58.2)	129 (62)
Normal weight	46 (32.6)	19 (28.4)	65 (31.3)
Overweight and obesity	5 (3.6)	9 (13.4)	14 (6.7)

*Survivors and non survivors patients had as main comorbidities: neurologic and neuromuscular diseases with 31/171 (18.1%) and 10/37 (27.0%), gastrointestinal diseases 16/171 (9.4%) and 9/37 (24.3%), respiratory diseases 10/171 (5.9%) and 7/37 (18.9%), respectively. **Survivors and non survivors patients were classified as low weight 94/171 (55%) and 35/37 (94.6%), normal weight 64/171 (37.4%) and 1/37 (2.7%), and overweight/obesity 13/171 (7.6%) and 1/37 (2.7%), respectively.

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Supplementary Table - Laboratorial and ventilator parameters of children and adolescents with critical disease related to SARS-CoV-2 on first and third day from admission.

Confidential: For Review Only

Laboratorial and ventilator parameters	Patients with critical disease related to SARS-CoV-2					
	On first day			On third day		
	Severe COVID-19 (n=141)	MIS-C (n=67)	Total	Severe COVID-19 (n=141)	MIS-C (n=67)	Total
Cardiovascular system						
VIS	7 (6-38)	68 (17-105)	84 (39-120)	6 (2-13)	25 (8-74)	9 (5-42.5)
Troponin I (ng/L)	0.03 (0.01-0.17)	0.28 (0.02-1.8)	0.11 (0.02-0.44)	0.06 (0.01-0.9)	0.2 (0.01-13.4)	0.1 (0.01-2.25)
Respiratory system						
DP in cmH ₂ O	7 (6-8)	12 (10-16)	9 (7-12)	8 (5-10)	12 (9-16)	8 (10-14)
Tidal volume in ml/kg	7.1 (5.7-9.7)	5.7 (4.9-6.6)	7.0 (6.3-9.4)	7.2 (5.4-9.6)	6.6 (4.1-8.2)	7.3 (5.4-9.4)
PIP in cmH ₂ O	18 (15-20)	16 (14-27)	18 (15-23)	16 (12-22)	16 (12-24)	18 (12-22)
OI	3.6 (1.9-6)	8.8 (4.9-13.4)	5.3 (2.4-10.3)	2.7 (1.2-5.3)	6.8 (3.2-11)	4.2 (2-7.9)
Inflammatory markers						
CRP (mg/dL)	7 (2-18)	45 (18-85)	12 (3-36)	5 (1.3-12.2)	22 (7.3-59)	8 (2.4-20)
ESR in mm/h	17 (10-120)	55 (28-110)	33 (10-108)	9 (2-17)	20 (13-58)	17 (10-35)
Haematological system						
Lymphocytes/mm ³	2,646 (1,398-4,878)	1,249 (960-1,773)	1,874 (1,118-3,772)	2,655 (1,268-4,284)	2,266 (1,248-4,525)	2,563 (1,114-4,257)
D-Dimer (ng/dL)	1,192 (529-3,406)	2,014 (1,085-5,009)	989.6 (522.2-2,790.1)	854 (406-2,851)	1,264 (609-3,861)	769.8 (350.8-2,836)
Renal system						
Creatinine(mg/dL)	0.3 (0.2-0.42)	0.39 (0.3-0.6)	0.40 (0.20-0.56)	0.49 (0.3-0.7)	0.4 (0.25-0.6)	0.5 (0.38-0.67)
Hepatic system						
Albumin (g/dL)	2.9 (2.5-3.5)	2.7 (2.2-3.6)	2.7 (2.3-3.5)	3.0 (2.5-3.6)	2.2 (1.9-3.2)	2.7 (2.3-3.5)

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4 VIS -vasoactive inotropic score. DP - drive pressure. PIP - peak inspiratory pressure. OI - oxygen index. CRP -C-reactive protein. ESR erythrocyte sedimentation rate. All tests were performed according to the protocols
5 described by the manufacturers. It was chosen to define reference ranges according to age and sex.
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10 Supplementary Table - Laboratorial and ventilator parameters of children and adolescents with critical disease related to SARS-CoV-2 on first and third day from admission
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