BMJ Paediatrics Open

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

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To cite: Farias ECF, Pavão Júnior MJC, de Sales SCD, *et al*. Critical disease related to SARS-CoV-2 infection in children from the Amazon region: an observational study. *BMJ Paediatrics Open* 2023;**7**:e001865. doi:10.1136/bmjpo-2023-001865

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjpo-2023-001865).

Received 12 January 2023
Accepted 19 March 2023

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ABSTRACT

This is a multicentre prospective cohort including critically ill children and adolescents, with confirmed critical disease related to SARS-CoV-2, admitted to three tertiary paediatric 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 34.1% of patients, respectively. There were 37 (18%) deaths. A poor outcome of severe COVID-19 and multisystem inflammatory syndrome in children was observed in children and adolescents from the Brazilian Amazon.

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 multisystem inflammatory syndrome in children (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, characterised 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 paediatric intensive care units (PICU) from the Eastern Brazilian Amazon region.

This multicentre prospective cohort included critically ill paediatric 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 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 fulfil 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.

Data included demographic information, clinical, therapeutic and outcomes. Laboratory and ventilatory parameters were evaluated on the first and third day of hospitalisation. Nutritional status was defined according to WHO criteria.

A total of 208 patients were included, split into 67 (32.2%) patients in MIS-C group, and 141 (67.8%) patients in the severe COVID-19 group. The median age was 3.5 years, and 117 (56.2%) were male. There was a high frequency of malnutrition and comorbidity, present in 129 (62%) and 126 (60.6%) patients, respectively. Mechanical ventilation support was needed in 98 (47.1%) of patients. Cardiogenic shock occurred in 54 (30%) patients, and acute respiratory distress syndrome occurred in 71 (34.1%). Deaths occurred in 37 (17.8%) patients. Comorbidities and low weight were present in 34 (91.9%) and 35 (94.6%) of deceased patients, respectively. Tables 1 and 2 show the main characteristics of the patients and according to the groups. Laboratory and ventilator parameters were analysed on the first and third day as illustrated in online supplemental table. All patients were unvaccinated against COVID-19 due to the age limit allowed to receive COVID-19 vaccination, at the time of data collection.

This study in a poor Brazilian region revealed higher in-hospital mortality

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		
Demographics and epidemiological	**Severe COVID-19 (n=141)**	**MIS-C (n=67)**	**All patients (n=208)**
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 28th, 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 2 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.
MIS-C, multisystem inflammatory syndrome in children; PICU, paediatric intensive care unit.

compared with other limited-resources regions (2%–15%).[3 4] These studies included critical/non-critical children with COVID-19 and MIS-C and demonstrated a large variability of presence of comorbidities (10%–65%) and malnutrition (8%–60%).[3 4 6] Possible reasons for the higher mortality observed in our cohort are the inclusion of only critical patients hospitalised in PICU, the high frequency of comorbidities and malnutrition and the long distance to reference healthcare.

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)
Haematologic non-immunological 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: neurological 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.
MIS-C, multisystem inflammatory syndrome in children.

This finding alerts us to a possible paediatric subgroup at greater risk for mortality, and the multifactorial causes for this poor prognosis, such as malnutrition and presence of comorbidities, emphasising the need for better public health policies in low-income and high-income countries.

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Acknowledgements We would like to thank Fundação Santa Casa de Misericórdia do Pará for providing us with the opportunity to conduct this research. Our special thanks go to all the children, parents and participating PICUs.

Contributors ECFdF, MTT and GC designed research, conceptualised the study, analysed the data and wrote the manuscript. MJCPJ, MdM, LMPPdN, SCDdS and PC assisted with the concept, interpretation of data and reviewed the manuscript. All authors, ECFdF, MTT, GC, MJCPJ, MdM, LMPPdN, SCDdS and PC conducted data collection, interpretation of data and edited the manuscript. All authors have read, reviewed and approved the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

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

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval The study was approved by the institutional review board of the coordinating center (the other centers were coparticipants). 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 no 4.060.894, CAAE 31513320.0.0000.5171. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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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_2O	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_2O	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)

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.

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