Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Gastrointestinal manifestations are associated with severe pediatric COVID-19: A study in tertiary hospital

Dear editor,

It is already known that the spectrum of signs and symptoms of coronavirus disease 2019 (COVID- 19) ranges from asymptomatic infection to fatal illness in children and adolescent.[1] The most common signs and symptoms of pediatric COVID-19 are milder as cough, sore throat and fever. In fact, Dr. Bin Zhang and colleagues reported in the Journal of Infection characteristics of 46 children hospitalized with COVID-19 and none of them had severe disease.[2] We have noticed that these children had no gastrointestinal symptoms identified. Nonetheless, manifestations as diarrhea, vomiting and abdominal pain have been described in COVID pediatric patients in up to 50% of the cases.[3–6] Furthermore, a systematic review[7] showed that the gastrointestinal tract was the system more frequently associated to the multisystem inflammatory syndrome in children (MIS-C), a severe spectrum of disease in children. We evaluated 83 patients with laboratory-confirmed COVID-19, both by real-time RT-PCR exam and serological test and we aimed to compare demographic and anthropometric data, underlying conditions, clinical characteristics, exams, treatments, and outcomes in laboratory-confirmed pediatric COVID-19 patients with and without gastrointestinal signs and symptoms. Patients were enrolled from April to September of 2020, in a tertiary and university hospital in São Paulo, Brazil.

We defined gastrointestinal involvement of pediatric COVID-19 required at least one of the following manifestations: diarrhea, abdominal pain or vomiting.[8] Stool culture and *Clostridioides difficile* stool toxin were also evaluated in patients with diarrhea. Nausea, upper and lower gastrointestinal bleeding were recorded. Gastrointestinal endoscopy, colonoscopy, abdominal computed tomography and abdominal ultrasonography were also analyzed. None of pediatric COVID-19 patients with diarrhea reported recent antibiotic use. MIS-C was diagnosed according to Center for Disease Control (CDC) criteria.[9] In six patients, stool samples were obtained, and a molecular method was performed to assess the presence of SARS-CoV-2 in feces.

Gastrointestinal signs/symptoms were evidenced in 25/83 (30.1%) of children and adolescents with COVID-19 confirmed by molecular or serological methods. Gastrointestinal involvement without any respiratory symptoms was observed in 6/25 (24%). Isolated vomiting was the most important symptom occurring in 9/25 (36%) pediatric COVID-19 patients. None of them had upper or lower gastrointestinal bleeding and required gastrointestinal endoscopy or colonoscopy. *Clostridioides difficile* stool toxin (n=5) and stool culture (n=4) were negative in pediatric COVID-patient with diarrhea. Severe abdominal pain with right lower quadrant tenderness mimicking acute appendicitis was observed in 2/25 (8%). Both had abdominal ultrasonography that confirmed mesenteric adenitis and none of them needed surgical procedure. Two adolescents with inflammatory bowel disease had laboratory-confirmed COVID-19 without MIS-C and without gastrointestinal involvement. They presented mild symptoms, one of them had fever and respiratory manifestations, and another patient had fever and sore throat.

Table 1 includes demographic and anthropometric data, clinical features, underlying conditions, outcomes and treatments of pediatric COVID-19 patients with and without gastrointestinal signs/symptoms. The median number of organs and systems involvement [3 (1-5) vs. 1 (0-5), $p<0.001$] and the involvement of the cardiac system (64% vs. 31%, $p=0.007$) were significantly higher in patients with gastrointestinal signs/symptoms compared to those without these manifestations (Table 1). Fibrinogen (465.9 ± 184.2 vs. 304.6 ± 170.1 mg/L, $p=0.01$) and the number of patients with D-dimer > 1000 ng/ml (67% vs 38%, $p=0.04$) were also significantly higher in the former group (Table 2). Pericarditis or myocarditis confirmed by echocardiogram (69% vs. 19%, $p=0.003$) were significantly higher in patients with versus without gastrointestinal signs/symptoms, as well as arterial hypotension (20% vs. 4%, $p=0.03$) and aspirin use (16% vs. 2%, $p=0.03$) (Table 2).

Logistic regression analysis identified that laboratory-confirmed COVID-19 pediatric patients with gastrointestinal signs/symptoms increased risk of cardiac abnormalities confirmed by echocardiogram [odds ratio (OR) 6.316; 95% confidence interval (CI) 1.717-79.043; $p=0.012$].

Using a molecular method, the presence of SARS-CoV-2 in feces was performed in six patients. In two stool samples the virus was detected, in two the molecular test were negative and inconclusive results were observed in another two patients. The two children that had detection of SARS-CoV-2 in feces were under the age of one year and had preexisting chronic disease (Downś syndrome and renal rhabdoid tumor, respectively). One of them presented vomiting. No one had diarrhea or abdominal pain. On the other hand, the two patients with no detection of the virus in the feces were older than 10 years and one had nausea, vomiting, diarrhea and abdominal pain.

The present study showed that laboratory-confirmed COVID-19 pediatric patients with gastrointestinal manifestations, particularly vomiting, had a severe systemic involvement and high mortality rate. Moreover, cardiac abnormalities were a relevant finding in this setting.

We extended previous report of laboratory-confirmed pediatric COVID-19 with at least one gastrointestinal sign/symptom demonstrating that cardiac abnormalities and hyperinflammation may occur in these patients.[4,7] Indeed, Belhadjer et al., reported that the vast majority of 35 pediatric COVID-19 patients with severe cardiac involvement had at least one gastrointestinal manifestation (diarrhea, abdominal pain or vomiting).[8]

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Table 1
Demographic data, anthropometric data, clinical characteristics, underlying conditions, outcomes and treatments of laboratory-confirmed pediatric coronavirus disease 2019 (COVID-19) patients with and without gastrointestinal signs/symptoms.

Variables	With gastrointestinal signs/symptoms (n=25)	Without gastrointestinal signs/symptoms (n=58)	p
Demographic data			
Male sex	15 (60)	32 (55)	0.81
Current age, years	8 (0.5-17.75)	10.75 (0-17.92)	0.78
Age < 10 years	9 (36)	31 (53)	0.16
Anthropometric data			
Body mass index, kg/m^2	16 (13-25)	18 (11-36)	0.33
Clinical characteristics			
Duration of signs/symptoms before diagnosis, days	4 (1-11)	2 (0-114)	0.11
Fever	17/25 (68)	44/58 (76)	0.59
Duration of fever, days	2 (0-11)	1 (0-15)	0.29
Nasal discharge	7/25 (28)	26/57 (46)	0.15
Sneezing	4/25 (16)	12/57 (21)	0.77
Cough	11/25 (44)	27/56 (48)	0.81
Sore throat	3/21 (14)	10/43 (23)	0.52
Anosmia	2/17 (12)	4/32 (13)	1.0
Dysgeusia	1 /13(8)	4/29 (14)	1.0
Headache	5/21 (24)	12/42 (29)	0.77
Myalgia	7/20 (35)	10/45 (22)	0.21
Arthralgia	0/20	1/43 (2.3)	-
Conjunctivitis	2/24 (8)	1/52 (2)	0.23
Dyspnea	7/25 (28)	24/56 (43)	0.23
Hypoxemia	7/25 (28)	18/56 (32)	0.80
Respiratory symptoms	19/25 (76)	42/58 (72)	0.79
Cutaneous rash	1/25 (4)	4/58 (7)	1.0
Fever without a source	0/25	12/57 (21)	-
Neurological symptoms	1/25 (4)	6/58 (10)	0.67
Pneumonia	8/25 (32)	14/56 (25)	0.59
Pediatric severe acute respiratory syndrome	6/25 (24)	12/56 (21)	0.78
Multisystem inflammatory syndrome in children (MIS-C)	5/25 (20)	3/57 (5)	0.05
Renal involvement	3/25 (12)	1/58 (2)	0.08
Dermatologic involvement	1/25 (4)	4/58 (7)	1.0
Neurological involvement	1/25 (4)	6/58 (10)	0.67
Hematologic involvement	16/24 (67)	29/54 (54)	0.33
Cardiac involvement	16/25 (64)	18/58 (31)	0.007
Respiratory involvement	9/25 (36)	17/58 (29)	0.61
Number of organs and systems involvement	3 (1-5)	1 (0-5)	<0.001
Underlying conditions			
Pediatric preexisting chronic diseases	20/25 (80)	43/57 (75)	0.78
Diabetes mellitus	0/25	1/58 (2)	-
Arterial hypertension	6/25 (24)	8/58 (14)	0.34
Immunosuppressive diseases	14/25 (56)	21/58 (36)	0.15
Primary immunodeficiency	1/25 (4)	1/58 (2)	0.51
Solid organ transplantation	1/25 (4)	2/58 (3)	1.0
Hematopoietic stem cell transplantation	0/25	2/58 (3)	-
Malignancy	8/25 (32)	12/58 (21)	0.28
Current chemotherapy	6/24 (25)	11/58 (19)	0.56
Current radiotherapy	0	0	-
Chronic kidney disease	3/25 (12)	5/58 (9)	0.69
Autoimmune chronic illnesses	1/25 (4)	4/58 (7)	1.0
Immunosuppressive therapy	8/24 (33)	19/58 (33)	1.0
Outcomes			
Hospitalization	20/25 (80)	41/58 (71)	0.43
Duration of hospitalization, days	6 (1-54)	7 (0-67)	0.46
Pediatric intensive care unit admission	9/25 (36)	14/57 (25)	0,30
Mechanical ventilation	5/25(20)	6/57 (11)	0.30
Vasoactive agents	4/25 (16)	3/57 (5)	0.19
Arterial hypotension	5/25 (20)	2/56 (4)	0.03
Shock	5/25 (20)	5/57 (9)	0.16
Disseminated intravascular coagulation	0/25	2/57 (4)	-
Thrombosis	0/25	3/57 (5)	-
Viral co-infection (rhinovirus)	0/2	4/6 (67)	-
Death	4/25 (16)	2/58 (3)	0.06

(*continued on next page*)

Table 1 (*continued*)

Variables	With gastrointestinal signs/symptoms (n=25)	Without gastrointestinal signs/symptoms (n=58)	p
Treatments			
Blood products transfusion	5/25 (20)	8/57 (14)	0.52
Red blood cells transfusion	5/24 (21)	8/57 (14)	0.51
Platelets transfusion	3/24 (13)	5/57 (9)	0.70
Plasma transfusion	1/24 (4)	0/57	-
Oxygen therapy	7/25 (28)	21/57 (37)	0.61
Antibiotic	16/25 (64)	32/57 (56)	0.63
Oseltamivir	6/25 (24)	19/57 (33)	0.45
Intravenous immunoglobulin	6/25 (24)	4/57 (7)	0.06
Enoxaparin	4/25 (16)	5/57 (9)	0.45
Aspirin	4/25 (16)	1/57 (2)	0.03
Systemic glucocorticoid	6/25 (24)	8/57 (14)	0.34
Intravenous methylprednisolone pulse therapy	1/25 (4)	1/57 (2)	0.52
Dialysis for acute renal injury or shock	3/25 (12)	1/58 (2)	0.08

Results are presented in n (%), median (minimum-maximum values) and mean ± standard deviation.

Table 2
Laboratory exams and echocardiographic abnormalities of laboratory-confirmed pediatric coronavirus disease 2019 (COVID-19) patients with and without gastrointestinal signs/symptoms.

Variables	With gastrointestinal signs/symptoms (n=25)	Without gastrointestinal signs/symptoms (n=58)	p
Hematological parameters			
Hemoglobin, g/dL	11.0 (± 2.2)	11.4 (± 2.2)	0.44
Hemoglobin < 10 g/dL	7/24 (29)	10/56 (18)	0.37
Leucocyte count/mm^3	6,678 (100-25,890)	6,795 (430-39,900)	0.78
Leucopenia < 4,000/mm^3	4/24 (17)	9/56 (16)	1.0
Neutrophil count/ mm^3	4,020 (0-19,500)	5,063 (0-27,900)	0.42
Neutropenia < 1,000/ mm^3	3/24 (13)	11/56 (20)	0.54
Lymphocyte count/mm^3	1,084 (0-17,860)	1,802 (0-13,300)	0.14
Lymphopenia < 1,500/ mm^3	14/24 (58)	20/56 (36)	0.08
Thrombocyte count/mm^3	219,416.7 (± 141,953.0)	234,535.7 (± 142,177.8)	0.66
Thrombocytosis > 450,000/ mm^3	2/24 (8)	5/56 (9)	1.0
Thrombocytopenia < 100,000/ mm^3	3/24 (13)	11/56 (20)	0.54
Inflammatory markers			
C-reactive protein, mg/L	30.4 (0.2-272.8)	6.4 (0.29-407)	0.08
Fibrinogen, mg/dL	465.9 (±184.2)	304.6 (±170.1)	**0.01**
D-dimer, ng/mL	1,908 (232-95,040)	1,957 (0-44,251)	**0.02**
D-dimer > 1000 ng/mL	14/21 (67)	17/45 (38)	**0.04**
Ferritin, ng/mL	447 (25-35,976)	148 (0-8,000)	0.18
Ferritin > 391 ng/mL	11/19 (58)	10/30 (33)	0.14
Other exams			
Lactate dehydrogenase, U/L	312 (159-4,476)	295 (0-2,078)	0.57
Serum albumin, g/dL	3.5 (±0.8)	3.7 (±0.7)	0.30
Aspartate aminotransferase, U/L	30 (13-2,002)	31 (10-374)	0.78
Alanine aminotransferase, U/L	20 (6-560)	24 (5-495)	0.87
Gamma-glutamyl transferase, U/L	41 (6-1,496)	35 (11-251)	0.76
Alkaline phosphatase, U/L	146 (87-1,559)	144 (69-545)	0.33
Blood urea, mg/dL	23 (8-118)	22 (8-186)	0.83
Serum creatinine, mg/dL	3.3 (±10.3)	0.8 (±1.5)	0.25
Triglycerides, mg/dL	163 (51-750)	132 (77-308)	0.94
CK, U/L	86 (13-443)	72 (14-2,291)	0.62
CK-MB, ng/ml	1.6 (0.3-15.7)	1.8 (0.3-28.9)	0.54
Troponin T, ng/mL	0.016 (0.003-1.05)	0.009 (0.002-0.08)	0.11
Prothrombin time, sec	14 (11-100)	13 (11-34)	0.16
INR	1.1 (1-7.0)	1 (1-3)	0.27
Activated partial thromboplastin time, sec	34 (12-51)	34 (22-53)	0.86
Hematuria > 5 erythrocytes/ml	3/14 (21)	4/27 (15)	0.67
Proteinuria > 0.5 g/day	1/11 (9)	2/23 (9)	1.0
Pyuria > 5 leucocytes/field	1/14 (7)	2/27 (7)	*1.0*
Chest X-ray abnormalities	11/17 (64.7)	20/42 (47.6)	0.26
Pulmonary CT abnormalities	10/11 (90.9)	9/16 (56.2)	0.09
Cardiac abnormalities confirmed by echocardiogram			
	2/16 (13)	1/25 (4)	0.55
Pericarditis or myocarditis	11/16 (69)	5/26 (19)	**0.003**

Results are presented in n (%), median (minimum-maximum values), mean (± standard deviation), CK creatine phosphokinase, INR - international normalized ratio, CT-computer tomography.

In this study the number of organs and systems involvement, intravenous immunoglobulin and aspirin were more frequently observed in patients with digestive signs/symptoms. These findings support the idea that the involvement of the gastrointestinal tract may be an expression of systemic disease and hyperinflammation.

The mortality rate in this study was 7%. The high frequency of chronic and immunosuppressed conditions in our laboratory-confirmed pediatric COVID-19 population may contribute to high lethality.

We also confirmed previous reports that gastrointestinal involvement had high levels of serum biomarkers, indicating acute inflammation, predominantly with increase of fibrinogen and D-dimer parameters. The elevated levels of these parameters have been also correlated with cytokine storm, multi-organ dysfunction and unfavorable outcome in severe patients with COVID-19.[10] Further studies with a systematic analysis of pro-inflammatory and anti-inflammatory cytokines profile, and lymphocyte subpopulations will be necessary in laboratory-confirmed pediatric COVID-19 populations to clarify these findings.

In conclusion, pediatric COVID-19 patients, mainly in those with underlying conditions and gastrointestinal manifestations, may have a severe and systemic involvement, with high mortality rate. Therefore, our study suggested that laboratory-confirmed COVID-19 pediatric patients with digestive signs/symptoms require attention for hyperinflammation condition and cardiac abnormalities.

Declaration of Competing Interest

The authors have no conflict of interest.

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