

# 1 **Gastrointestinal symptoms in severe COVID-19 children**

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## 37 **Introduction**

38 As of May, 7<sup>th</sup> the Italian National Institute of Health reported 3,752 cases of Severe Acute  
39 Respiratory Syndrome associated with Coronavirus 2 (SARS-CoV-2) in Italian children aged less  
40 than 18 years, 140 of them requiring hospital admission.

41 Since the first outbreak a global effort has been made to collect clinical and laboratory findings on  
42 patients with SARS-CoV-2 infection. The lower airway is the primary target of the infection,  
43 however the disease spectrum in adults goes from asymptomatic subjects to severe illness  
44 including 5.0% subjects requiring ICU admission, 2,3% who underwent invasive mechanical  
45 ventilation, and 1.4% who died (1). Data suggest that children are less likely to develop severe  
46 symptoms compared to adults (2). Also, there are growing evidence of clinical manifestations  
47 other than acute respiratory syndrome in paediatrics suggesting that Coronavirus Diseases-19  
48 (COVID-19) spectrum and pathogenesis in children are yet to be unravel. In this report we describe  
49 the results of our preliminary analysis of a cohort of hospitalized pediatrics COVID-19 patients  
50 focusing on mode of presentation, presence of comorbidities, severity of disease and early  
51 outcome.

## 52 **Material and Methods**

53 We conducted a multicenter retrospective analysis of clinical record of SARS-CoV-2 infected  
54 children in 23 different sites in Italy.

55 From February 21<sup>st</sup>, 2020 to May 1<sup>st</sup>, 2020 subjects aged less than 18 years with a positive result  
56 on high throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-  
57 PCR) assay of nasal/pharyngeal swab specimens were included.

58 The study was approved by the ethical committees of the coordinating center in Milan (protocol  
59 number 2020/ST/061).

60 Data regarding recent exposure history, clinical symptoms or signs, and laboratory findings on  
61 admission were extracted using a common clinical record form. Radiologic assessments and  
62 laboratory testing were performed according to the clinical care needs of the patient.

63 The Student's t test, the  $\chi^2$  method, and Fisher's exact test were used as appropriate for statistical  
64 analysis to compare continuous and categorical variables. A p value < 0.05 was chosen as cutoff  
65 for significance. Data were analyzed with StataMed (version 12.0).

## 66 **Results**

67 Overall, 127 children were included; 44 were female (34.9%) and the median age was 4.8 years  
68 (IQR 0.3-8.5); 57 (45%) aged less than 12 months.

69 Eight out 127 (6.7%) were admitted to ICU, 14 out of 127 (12%) required oxygen therapy, 5 (4%)  
70 noninvasive ventilation, and 1 patient required mechanical ventilation during the hospitalization.  
71 The severity of the COVID-19 in our children was defined using previously published criteria (3);  
72 7,9%, 48.8% and 27,7% of their clinical features were defined respectively as asymptomatic, mild  
73 or moderate accounting for 84.4% of our cohort; 8.7% was severe and 7.1% was critical.  
74 Age class, sex, and ethnic group did not show a different distribution among the severity  
75 categories ( $p=0.57$ ,  $p=0.62$ ,  $p=0.375$  Fisher exact test; table1).  
76 Twenty out 127 patients (15.7%) had at least one comorbidity. Five (3.9%) had chronic cardiac  
77 condition, 4 (3.1%) had gastrointestinal disorder, 3 (2.4%) were obese, 2 (1.6%) had chronic kidney  
78 disease, chronic neurological disorder and immunological condition respectively. Only one  
79 medically complex patient (defined as children who required long term dependence on life  
80 support) was included. Comorbidities distribution was not different among severity classes  
81 ( $p=0.08$  Fisher exact test). Moreover, the ICU admission rate was similar in patients with  
82 comorbidities and those without ( $p=0.115$  Fisher exact test).  
83 The most common symptoms reported on admission were fever (82,7%), cough (48%) and  
84 rhinorrhea (38%). Seventy-seven out of 127 (60.6%) presented with respiratory symptoms (cough,  
85 rhinorrhea, wheezing, dyspnea).  
86 Thirty-six out 127 (28,3%) had gastrointestinal symptoms (vomit, diarrhea, abdominal pain), of  
87 them twenty-eight (22%) had diarrhea, 12 (9,4%) vomit, 8 (6.3%) abdominal pain.  
88 The presence of gastrointestinal symptoms at the admission was differently distributed  
89 throughout severity classes ( $p=0.006$ ). Having gastrointestinal symptoms was more frequently  
90 associated with severe and critical phenotype ( $p=0.029$ ). Interestingly, a history of gastrointestinal  
91 symptoms was positively associated with cardiac involvement as clinical complications, in  
92 presence of other symptoms ( $p=0.007$ ) or alone ( $p=0.004$ ).  
93 Roughly, a third of the children presented lower respiratory tract complications as viral  
94 pneumonia and bronchiolitis. Viral pneumonia was more frequently reported in severe phenotype  
95 ( $p=0.004$ ), while admission rate to ICU was equally distributed among these patients. Chest X-ray  
96 was performed in 77 patients (65%) on admission and infiltrates were found in 38 out 77 (50%).  
97 Respectively 20 and 15 patients had bilateral and mono-lateral infiltrates, for 3 of them it was not  
98 specified. In 4 out of 77 (5.2%) atelectasis and pleural effusion were found. The presence of  
99 infiltrates at the chest X-Ray did not correlate with severity clinical score or ICU admission rate  
100 ( $p=0.125$  and  $p=0.71$  Fisher exact test respectively).

101 **Discussion**

102 In the present study we reported that most SARS-COV-2 infected children had fever and  
103 respiratory symptoms. Similarly, Shekerdemian et al. reported that most of the patients included  
104 in the North American Pediatric Intensive Care Unit (PICU) cohort presented respiratory  
105 symptoms, but they also state that only one child of their cohort presented gastrointestinal  
106 symptoms, speculating that these may be associated with milder clinical presentation (4).

107 In children, common circulating HCoVs can cause gastrointestinal symptoms in up to 57% of cases,  
108 and this presentation is more common in children than adults (5). Increasing evidence showed  
109 that the gastrointestinal tract may represent a target for SARS-CoV-2 due to the expression of the  
110 angiotensin-converting enzyme 2 (ACE2), a major virus receptor. We reported, differently to  
111 published data, that a history of GS was positively correlated with a worst severity score (severe  
112 and critical) and a higher ICU admission rate. The same result was found, in an pooled analyses of  
113 adult cohorts, where GS were correlated to increased odds of critical disease and higher  
114 prevalence of complications (6).

115 Interestingly, in our cohort having GS was more frequently reported in patients who developed  
116 cardiac impairment as complications of SARS-CoV-2 infection. The development of  
117 hyperinflammatory syndromes and Kawasaki-like disease in children exposed to SARS-CoV-2  
118 infection has been recently brought to attention. Riphagen et al. reported eight cases of  
119 hyperinflammatory syndrome with cardiac involvement, all of them presenting with fever and  
120 significant gastrointestinal symptoms (diarrhea, vomit, abdominal pain) (7), according to our  
121 current results and to what we have previously reported (8).

122 In recent studies (4,9) comorbidities have been frequently reported in patients requiring  
123 admission to ICU. In the North American PICU cohort, authors reported that up to the 80% of  
124 patients included had comorbidities. The most common comorbidity reported was medically  
125 complex defined as long term dependence on technological support(4). In agreement with this  
126 cohort, Parri and colleagues, in a SARS-COV-2 positive cohort of pediatric patients admitted at  
127 Italian Emergency Departments, reported that 9 patients out of 100 need mechanical ventilation  
128 and, among them, 6 (66%) had comorbidities (9).

129 In the present study only 20 (16%) children with previous medical condition were included, 3 of  
130 them required ICU. The presence of preexisting medical conditions was not different in severe and  
131 critical patients when compared to mild, moderate and asymptomatic ones. Moreover, the ICU  
132 admission rate was similar in patients with and without comorbidities.

133 There are several limitations to our study. First, the limited sample size. Second, children have  
134 been classified using a severity score previously applied to other pediatric cohorts, which is mainly  
135 designed on respiratory symptoms and lung involvement. The score criteria could explain the  
136 higher frequency of viral pneumonia among severe phenotype but not among patients requiring  
137 ICU admission. However, critical cases are defined not only by the progression to respiratory  
138 failure (ARDS) but also to life threatening organ dysfunction (shock, myocardial injury, acute kidney  
139 injury). Therefore, in the present study the subset of critical patients includes not only patients  
140 with respiratory failure but also with other life-threatening conditions. Finally, there are evidences  
141 that COVID-19 related multisystemic inflammatory syndrome could be a complication in the  
142 disease spectrum. Although a better understanding of timing between GS and its onset would be  
143 of great interest, we could not provide such information in the current study.

#### 144 **Conclusions**

145 The intention of this short report is to bring to attention that COVID-19 disease spectrum in  
146 children is far from been described in a universally shared way. Other manifestations from  
147 respiratory are often the cause of severe illness, as we reported. Having preexisted medical  
148 conditions is not associated with worse outcome and consequently, severe clinical presentation  
149 must be considering also in previously healthy children.

150 Gastrointestinal symptoms seem to be a clinical warning for children evaluated in any clinical  
151 settings when SARS-CoV-2 infection is suspected, independently of comorbidities.

152 Pathogenetic mechanisms causing severe phenotypes in SARS-CoV-2 infected children need to be  
153 deepened by multidisciplinary approach as well we need more data to define a suitable clinical  
154 severity score for COVID-19 in children.

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**Table 1: Association of clinical characteristics with severity score and ICU**

CHARACTERISTICS	ASYMPTOMATIC, MILD or MODERATE N=107		SEVERE or CRITICAL N=20		P Value <sup>a</sup>	not ICU N=111		ICU N=8		P Value <sup>a</sup>
	N	%	n	%		N	%	n	%	
AGE MEDIAN (IQR, y)	1.6 (0.3, 7.9)		4.3 (0.3, 10.1)		0.393 <sup>b</sup>	1.6 (0.3, 7.9)		5.5 (0.4, 10.1)		0.497 <sup>b</sup>
AGE GROUP					0.845					0.854
Newborn	5	4.7	1	5.0		6	5.4	0	0.0	
Infant	44	41.1	7	35.0		44	39.6	3	37.5	
Children	42	39.2	8	40.0		46	41.4	3	37.5	
Adolescent	16	15.0	4	20.0		15	13.5	2	25.0	
MALE	68	64.2	14	70.0	0.799	71	64.5	5	62.5	1.000
PRESENTATION										
Fever	85	79.4	20	100.0	0.023	92	82.9	8	100.0	0.352
RESP SYMPTOMS	68	63.6	14	70.0	0.799	74	67.3	4	50.0	0.441
Respiratory Symptoms Only	46	43.0	7	35.0	0.624	44	39.6	2	25.0	0.468
Cough	52	48.6	9	45.0	0.812	57	51.4	2	25.0	0.812
Rhinorrhea	43	40.2	6	30.0	0.460	46	41.4	0	0.0	0.022
Wheezing	4	3.7	0	0.0	1.000	3	2.7	0	0.0	1.000
Dyspnea	5	4.7	5	25.0	0.009	7	6.4	2	25.0	0.114
GI SYMPTOMS	26	24.3	10	50.0	0.029	31	27.9	4	50.0	0.232
GI Symptoms Only	13	12.1	5	25.0	0.160	14	12.6	3	37.5	0.087
Vomit	6	5.6	6	30.0	0.004	6	5.4	6	75.0	0.004
Diarrhea	20	18.7	8	40.0	0.044	20	18.0	8	100	0.044
Abdominal Pain	6	5.6	2	10.0	0.611	8	7.2	0	0.0	1.000
COMORBIDITIES	14	13.1	6	30.0	0.088	16	14.4	3	37.5	0.115
Chronic Cardiac Conditions	3	2.8	2	10.0	0.176	4	3.6	1	12.5	0.298
Gastrointestinal Disorder	2	1.9	2	10.0	0.117	2	1.8	1	12.5	0.190
Obese	1	0.9	2	10.0	0.064	3	2.7	0	0.0	1.000
Chronic Kidney Disease	2	1.9	0	0.0	1.000	2	1.8	0	0.0	1.000
Chronic Neurological Disease	0	0.0	2	10.0	0.024	1	0.9	0	0.0	1.000
Immunological Condition	2	1.9	0	0.0	1.000	1	0.9	0	0.0	1.000
CXR POSITIVE	25	43.9	13	65.0	0.125	35	51.5	3	37.5	0.711
COMPLICATION	23	21.5	19	95.0	<0.001	35	31.5	7	87.5	0.003
Viral pneumonia	16	15.0	9	45.0	0.004	24	21.6	1	12.5	0.468
Bronchiolitis	8	7.5	1	5.0	0.570	9	8.1	0	0.0	0.522
Bacterial pneumonia	0	0.0	2	10.0	0.024	1	0.9	1	12.5	0.130
ARDS	0	0.0	2	10.0	0.024	1	0.9	1	12.5	0.130
Pleural effusion	0	0.0	1	5.0	0.157	0	0.0	1	12.5	0.067
Myocardial involvement	0	0.0	6	30.0	<0.001	2	1.8	4	50.0	<0.001
Bacteremia	0	0.0	1	5.0	0.157	0	0.0	1	12.5	0.067
Coagulation disorder	0	0.0	1	5.0	0.157	0	0.0	1	12.5	0.067
AKI	0	0.0	1	5.0	0.157	0	0.0	1	12.5	0.067
Liver dysfunction	0	0.0	1	5.0	0.157	0	0.0	1	12.5	0.067
Myositis	1	0.93	0	0.0	0.843	1	0.9	0	0.0	0.933

