Gastrointestinal symptoms in severe COVID-19 children

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Introduction

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

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

Material and Methods

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

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

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

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

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

Results

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

Eight out 127 (6.7%) were admitted to ICU, 14 out of 127 (12%) required oxygen therapy, 5 (4%) noninvasive ventilation, and 1 patient required mechanical ventilation during the hospitalization.

The severity of the COVID-19 in our children was defined using previously published criteria (3); 7,9%, 48.8% and 27,7% of their clinical features were defined respectively as asymptomatic, mild or moderate accounting for 84.4% of our cohort; 8.7% was severe and 7.1% was critical.

Age class, sex, and ethnic group did not show a different distribution among the severity categories (p= 0.57, p=0.62, p=0.375 Fisher exact test; table1).

Twenty out 127 patients (15.7%) had at least one comorbidity. Five (3.9%) had chronic cardiac condition, 4 (3.1%) had gastrointestinal disorder, 3 (2.4%) were obese, 2 (1.6%) had chronic kidney disease, chronic neurological disorder and immunological condition respectively. Only one medically complex patient (defined as children who required long term dependence on life support) was included. Comorbidities distribution was not different among severity classes (p=0.08 Fisher exact test). Moreover, the ICU admission rate was similar in patients with comorbidities and those without (p=0.115 Fisher exact test).

The most common symptoms reported on admission were fever (82,7%), cough (48%) and rhinorrhea (38%). Seventy-seven out of 127 (60.6%) presented with respiratory symptoms (cough, rhinorrhea, wheezing, dyspnea).

Thirty-six out 127 (28,3%) had gastrointestinal symptoms (vomit, diarrhea, abdominal pain), of them twenty-eight (22%) had diarrhea, 12 (9,4%) vomit, 8 (6.3%) abdominal pain.

The presence of gastrointestinal symptoms at the admission was differently distributed throughout severity classes (p=0.006). Having gastrointestinal symptoms was more frequently associated with severe and critical phenotype (p=0.029). Interestingly, a history of gastrointestinal symptoms was positively associated with cardiac involvement as clinical complications, in presence of other symptoms (p=0.007) or alone (p=0.004).

Roughly, a third of the children presented lower respiratory tract complications as viral pneumonia and bronchiolitis. Viral pneumonia was more frequently reported in severe phenotype (p=0.004), while admission rate to ICU was equally distributed among these patients. Chest X-ray was performed in 77 patients (65%) on admission and infiltrates were found in 38 out 77 (50%). Respectively 20 and 15 patients had bilateral and mono-lateral infiltrates, for 3 of them it was not specified. In 4 out of 77 (5.2%) atelectasis and pleural effusion were found. The presence of infiltrates at the chest X-Ray did not correlate with severity clinical score or ICU admission rate (p=0.125 and p=0.71 Fisher exact test respectively).

Discussion

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

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

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

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

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

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

Conclusions

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

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

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

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

	ASYMPTOMATIC, MILD or MODERATE N=107		SEVERE or CRITICAL N=20			not ICU N=111		ICU N=8		
CHARACTERISTICS	**N**	**%**	**n**	**%**	***p* Value[a]**	**N**	**%**	**n**	**%**	***p* Value[a]**
AGE MEDIAN (IQR, y)	1.6 (0.3, 7.9)		4.3 (0.3, 10.1)		0.393[b]	1.6 (0.3, 7.9)		5.5 (0.4, 10.1)		0.497[b]
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 SYMTOMPS	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