

Gastrointestinal Manifestations, Clinical Characteristics and Outcomes of COVID-19 in Adult and Pediatric Patients

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Abstract

Background: Italy was the first country in Europe to report a SARS-CoV-2 case. Since then, the country has suffered a large number of COVID-19 infections both in adults and children. This disease has been shown to lead to different outcomes in these two groups, which often present varying symptoms and comorbidities.

Aim: Therefore, we aimed to evaluate the symptoms, comorbidities and laboratory values in adults and children.

Methods: We present the characteristics of 1,324 adults and 563 pediatric COVID-19 Italian patients. The data was retrieved from studies published in Italy and found via PubMed and Google Scholar.

Results: The virus appeared to affect adults more than children and men more than women, and to result in more severe outcomes in patients with abnormal laboratory values and a higher number of comorbidities. Adults are at higher risk for complications and death, and they usually present with fever, respiratory symptoms, cough, fatigue, diarrhea, myalgia, and/or loss of taste, smell, or appetite. Children usually have a milder disease progression and usually present with fever, cough, rhinorrhea, pharyngitis, sore throat, pneumonia, GI symptoms (diarrhea, vomiting, abdominal pain), fatigue, and dyspnea.

Conclusion: Our findings support early reports that showed that SARS-CoV-2 is associated with more common asymptomatic cases and milder clinical outcome in children than in adults. Acute respiratory distress syndrome and Multisystem inflammatory syndrome in children (systemic vasculitis) are the most severe disease progressions for adults and children, respectively.

Keywords: Coronavirus Disease-19; Pandemic; Gastrointestinal Manifestation; Italy; Adults; Pediatrics

Abbreviations: COVID-19: Coronavirus Disease-19; GI: Gastrointestinal; RT-PCR: Real-time Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2

Introduction

Towards the end of 2019, several cases of a novel “viral pneumonia” were detected in Wuhan, China [1]. The disease was later found to be caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and quickly spread to the rest of the world, with 170,812,850 confirmed cases and 3,557,586 deaths as of June 2nd, 2021 (<https://covid19.who.int/>). The disease was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020 [2]. Italy was the first European country that

had to deal with a SARS-CoV-2 [3]. Until recently, it was thought that the first Italian COVID-19 case was diagnosed in Codogno, Lombardy, on February 20th, 2020. There is now evidence of a positive oropharyngeal COVID-19 swab test in the same region in early December 2019 [3]. This patient was a 4-year old boy from Milan, Lombardy, who developed respiratory symptoms, vomiting, and a measles-like rash, which led him to be mistakenly diagnosed with measles [3]. Several more infections were detected in the country in the next few days, especially in the northern regions [4].

Italy counts 4,220,304 cases of COVID-19 since the beginning of the pandemic, with 126,221 deaths (<https://covid19.who.int/region/euro/country/it>, accessed June 2nd, 2021). The country is using a color-coding system (white, yellow, orange, red) to reflect the COVID-19 situation in each individual region and the respective restrictions adopted.

With respect to the most common presentation of the disease, early reports from China showed SARS-CoV-2 to present mostly with fever, cough, fatigue, myalgia, and gastrointestinal symptoms, with acute respiratory distress syndrome as a complication of the disease [1,5,6]. The virus also appeared to affect adults more than children and men more than women, and to result in more severe outcomes in patients with comorbidities [1,5]. Early reports also showed that SARS-CoV-2 is associated with a milder clinical outcome in children than adults [7,8]. Infants, however, are particularly vulnerable to infections [8]. Common signs and symptoms in children are fever, cough, diarrhea, vomiting, erythema, rhinorrhea, and nasal congestion [7].

A more severe presentation has also been reported in pediatric populations and called Multi-Inflammatory Syndrome in Children (MIS-C) [9]. MIS-C patients usually develop fever and gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain [9]. Due to similarities in signs and symptoms and severity, this clinical feature has often been misdiagnosed as Kawasaki Disease (KD), a vasculitis disease which usually presents with fever and mucocutaneous rash and affects children below 5 years old [9]. MIS-C patients, however, are usually older and present some characteristics that are not recognized in KD patients [9].

Even though COVID-19 has been shown to be more prevalent and severe in adult patients, it is important to differentiate presentations of SARS-CoV-2 among adults and children. Most studies published in Italy since the beginning of the pandemic have looked at adult patients, and only a few have provided an in-depth analysis of pediatric cases. In this narrative review, we compared the clinical characteristics of adult and pediatric patients in Italy, with a focus on gastrointestinal manifestations. In particular, we evaluated differences in presentation, signs, symptoms, outcome, and severity of the disease, to understand how to effectively identify and manage different age groups patients, and how GI symptoms associate with age differences and outcomes.

Methods

Search strategy and selection criteria: We conducted a systematic literature search of published articles using electronic databases such as PubMed and Google Scholar, and other resources from official health organizations of Italy from January 1st, 2020, to April 30th, 2021. We searched using the following words: COVID-19 Italy, COVID-19 Europe, COVID-19 Pediatrics Italy, COVID-19 children Italy, COVID-19 adults Italy, COVID-19 clinical characteristics. Case characteristics were described, including demographics, exposures, comorbidities and symptoms. The protocol of this systematic review and analysis

for COVID-19 patients' data from Italy is in the accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidance.

Selection and identification of relevant literature: Using the listed inclusion and exclusion criteria, we first sorted the Italian COVID-19 studies by title and abstract; then we assessed the papers by relevance and conducted a new selection process by a thorough review of the data. Based on detailed insights derived from relevant papers [10,11], we incorporated studies that reported patients' characteristics and symptoms of interest. From the selected papers, tables were generated for each dataset on Microsoft Excel. These tables included the following information for extracted data of each study (when available): study author (year, location, hospital or city, state and country), date of the report, location, confirmed cases, deaths, lethality rate, median age, sex, fever, shortness of breath, cough, fatigue, myalgia, pneumonia, febrile convulsions, low oxygenation, loss of appetite, ageusia, anosmia, sore throat, rhinorrhea, abdominal pain, nausea, vomiting, diarrhea, supplemental oxygen, non-invasive ventilation, intubation, hospitalization, ICU transfer, disease severity (asymptomatic, mild, moderate, severe, critical), respiratory disease, hypertension, cardiac disease, diabetes, obesity, smoking, atrial fibrillation, liver disease, chronic gastrointestinal disease, immunosuppression, cancer, epilepsy, pre-term, congenital malformations/complex genetic syndromes, chronic kidney disease, malignancy, dyslipidemia, benign prostate hyperplasia, other comorbidities, positive chest x-ray, laboratory values, administration of Remdesivir, Tocilizumab, Hydroxychloroquine, Ritonavir/Lopinavir, antibiotics.

Inclusion criteria: The following inclusion criteria were adopted to validate article selection: Confirmed diagnosis of COVID-19 (PCR positive) with at least one gastrointestinal manifestation as reported by each country and referenced by WHO or cross-checked *via* world-meter or Johns Hopkins University COVID-19 dashboard; no distinction with regard to the number of diagnosed cases; no distinction with regard to sex, age, severity of disease, inpatient or outpatient management, data collection date, treatment and outcome.

Exclusion criteria: The following exclusion criteria were adopted to filter out incomplete or ambiguous data: Studies where the cohort was not from Italy, studies where the cases were not confirmed by RT-PCR, and studies with incomplete symptoms or comorbidities report. Papers focusing only on patients who died or had specific comorbidities (i.e. cancer patients, hematologic patients) were excluded as well.

Statistical analysis: The collected data was used to calculate COVID-19 inpatients from February 21st to May 26th Or April 30th, 2020. The common symptoms and comorbidities were combined and analyzed by weighted analysis methods when applicable. Signs and symptoms reported in only one study were excluded from statistical analysis. Comorbidities and lab values reported in pediatric studies were reported even if analyzed in only one of the sources, because the availability of this kind of information was scarce. Correlation coefficients were calculated to establish

associations between comorbidities and mortality. The effect of symptoms was reported using weighted analysis where weights were related to the size of the reported study. SPSS version 26 (SPSS Inc., Chicago, IL, USA) was used for this analysis.

Results

Overall males were predominantly more affected by COVID-19 independently of the age:

From the 1,324 adults and 563 children we analyzed (Table 1,2), the median age for adults was 64.9 years old and for children 3.6 years old. As for gender, for both adults and children, male was the most frequent gender affected by COVID-19. The ratio of men to women in adults was much higher than the ratio of boys to girls in children. In adults, 64.8% of the total population were male and only 35.1% were female. As for children, male quota was about 53.4% of cases, relatively lower than adults and closer

to equal ratios. Consequently, female pediatric patients amounted to 46.5% of the cases versus the smaller 35.1% in adult women.

Adults and children presented several common symptoms:

Our data-analysis reported fever as the most common symptom in both adult and pediatric patients (Table 1,2), with 80.7% and 66.8%, retrospectively. Other general symptoms shared in both adult and pediatric patients were shortness of breath (43.0% vs 8.5%), cough (55.1% vs 40.1%), sore throat (9.5% vs 14.0%), fatigue (24.0% vs 8.3%), and headache (10.3% vs 7.1%). The majority of adults (60.0%) developed pneumonia, which was not as common in children (12%) (Figure 1).

Symptoms that were only reported in adults were the following:

Myalgia (15.7%), loss of appetite, taste, or smell (44.2%),

Table 1: Characteristics of adult patients included in this study.

Study (N = 1324)	Schettino, et al.	Colanei, et al.	Massironi, et al.	Cattela, et al.	Aghemo et al.	Temperoni, et al.	Vena, et al.	Total
Total Patient Number% (N)	14.35 (190)	3.32 (44)	3.1 (41)	22.89 (303)	24.55 (325)	7.85 (104)	23.94 (317)	100 (1324)
Collection date% (N)	March 23 - April 20, 2020	February 21- February 28, 2020	February 21- April 20, 2020	February 22 - May 20, 2020	February 22 - March 30, 2020	February 28 - April 8, 2020	February 25 - March 25, 2020	February 21 - May 20, 2020
Age range% (N)	49-80	10-94	43-91	50-74	27-92	33.7-48.5	60-82	10-94
Median age% (N)	67	67.5	71	62	67	41.4	71	64.94
Male% (N)	66.84 (127)	63.64 (28)	70.73 (29)	60.06 (182)	68.62 (223)	53.85 (56)	67.19 (213)	64.8 (858)
Female% (N)	33.16 (63)	36.36 (16)	29.27 (12)	39.94 (121)	31.38 (102)	46.15 (48)	32.81 (104)	35.2 (466)
Fever% (N)	90.53 (172)	90.91 (40)	73.17 (30)	80.2 (243)	62.77 (204)	90.38 (94)	89.91 (285)	80.7 (1068)
SOB/respiratory syndrome% (N)	49.47 (94)	22.73 (10)	67.5 (28)	31.68 (96)	-	33.65 (35)	52.68 (167)	43 (430)
Cough% (N)	60.53 (115)	34.09 (15)	41.46 (17)	39.93 (121)	76.06 (247)	55.77 (58)	49.21 (156)	55.1 (729)
Fatigue/weakness/ malaise% (N)	53.16 (101)	4.55 (2)	51.22 (21)	13.53 (41)	-	17.31 (18)	17.98 (57)	24 (240)
Myalgia% (N)	43.16 (82)	2.27 (1)	15 (6)	7.59 (23)	10.82 (35)	10.58 (11)	-	15.7 (158)
Pneumonia% (N)	-	70.45 (31)	48.72 (20)	-	-	-	-	60 (51)
Loss of appetite% (N)	50.53 (96)	-	15 (6)	-	-	-	-	44.2 (102)
Loss of taste (ageusia)% (N)	30 (57)	-	-	16.17 (49)	-	-	-	19.8 (106)
Loss of smell (anosmia)% (N)	28.95 (55)	-	-	-	5.96 (19)	16.35 (17)	-	14.8 (91)
Headache% (N)	21.58 (41)	-	-	-	-	7.69 (8)	4.42 (14)	10.3 (63)
Sore throat% (N)	16.84 (32)	-	-	5.28 (16)	-	8.65 (9)	-	9.5 (57)

Chest pain% (N)	-	2.27 (1)	-	-	-	14.42 (15)	-	10.8 (16)
Respiratory failure% (N)	-	2.27 (1)	-	-	-	-	64.19 (203)	56.6 (204)
Confusion% (N)	-	2.27 (1)	-	-	-	-	9.15 (29)	8.3 (30)
Abdominal pain% (N)	3.68 (7)	-	-	-	-	-	-	3.7 (7)
Nausea% (N)	17.37 (33)	-	12.12 (5)	-	17.24 (56)	-	4.42 (14)	12.4 (108)
Vomiting% (N)	10.58 (20)	-	14.71 (6)	-	3.63 (12)	4.81 (5)	4.42 (14)	5.8 (57)
Diarrhea% (N)	38.42 (73)	6.82 (3)	29.27 (12)	6.93 (21)	24.38 (79)	15.38 (16)	5.68 (18)	16.8 (222)
Supplemental Oxygen (NC/VM/NRB)% (N)	80.95 (154)	38.64 (17)	26.83 (11)	55.45 (168)	45.99 (149)	-	-	55.3 (499)
Non-invasive ventilation/CPAP% (N)	40 (76)	-	21.95 (9)	20.13 (61)	7.69 (25)	-	35.02 (111)	24 (282)
Intubated (invasive ventilation)% (N)	11.05 (21)	-	21.95 (9)	9.9 (30)	34.59 (112)	-	18.93 (60)	19.8 (232)
Hospitalized% (N)	88.57 (168)	100 (44)	95.1 (39)	100 (303)	100 (325)	31.73 (33)	86.75 (275)	89.7 (1187)
ICU Transfer% (N)	13.21 (25)	6.82 (3)	21.05 (9)	22.77 (69)	17.85 (58)	5.77 (6)	20.5 (65)	17.7 (235)
Death% (N)	21.58 (41)	4.5 (2)	19.5 (8)	6.8 (21)	21.85 (71)	4.81 (5)	43.64 (138)	21.6 (286)
Positive Chest X Ray% (N)	-	70.45 (31)	-	66.34 (201)	-	74.04 (77)	88.1 (279)	76.6 (588)
Low WBC% (N)	-	50 (22)	-	-	11.08 (36)	-	-	15.7 (58)
High WBC% (N)	-	-	-	-	22.77 (74)	-	-	22.8 (74)
Low Hb% (N)	-	-	-	-	36 (117)	-	-	36 (117)
High Hb% (N)	-	-	-	-	6.77 (22)	-	-	6.8 (22)
Low Platelet% (N)	-	43.18 (19)	-	-	21.85 (71)	-	41.9 (133)	32.5 (223)
High Platelet% (N)	-	-	-	-	4.92 (16)	-	-	4.9 (16)
Low Lymphocyte% (N)	-	88.64 (39)	-	-	52 (169)	-	68.3 (217)	61.9 (425)
High Lymphocyte% (N)	-	-	-	-	0.92 (3)	-	-	0.9 (3)
Low LDH% (N)	4.21 (8)	-	-	-	76.25 (248)	-	-	49.7 (256)
High LDH% (N)	72.63 (138)	34.09 (15)	-	-	-	-	-	65.4 (153)
Low Leukocyte% (N)	-	-	-	-	-	-	17.4 (55)	17.4 (55)
Low Fibrinogen% (N)	-	-	-	-	0.31 (1)	-	-	0.2 (1)
High Fibrinogen% (N)	60.71 (115)	-	-	-	81.85 (266)	-	-	74.1 (381)
High C Reactive Protein% (N)	90.53 (172)	18.18 (8)	-	-	96 (312)	-	-	88 (492)
High Procalcitonin% (N)	-	-	-	-	22.15 (72)	-	-	22.2 (72)
Low Creatinine% (N)	-	-	-	-	14.15 (46)	-	-	14.2 (46)
High Creatinine% (N)	-	4.55 (2)	-	-	27.69 (90)	-	-	24.9 (92)
High AST% (N)	53.97 (103)	-	-	-	29.23 (95)	-	32.2 (102)	36 (300)
High ALT% (N)	37.89 (72)	-	-	-	20.62 (67)	-	34.7 (110)	29.9 (249)

High D-Dimer% (N)	-	-	-	-	59.69 (194)	-	-	59.7 (194)
Low pH% (N)	-	15.91 (7)	-	-	-	-	-	15.9 (7)
Low CO2% (N)	-	36.36 (16)	-	-	-	-	-	36.4 (16)
Low PF ratio% (N)	-	22.73 (10)	-	-	-	-	-	22.7 (10)
Low CD4+ T-cell count% (N)	-	31.82 (14)	-	-	-	-	-	31.8 (14)
25ng/mL% (N)	-	18.18 (8)	-	-	-	-	-	18.2 (8)
High Troponin% (N)	-	-	-	-	29.67 (96)	-	-	29.7 (96)
Low Total bilirubin% (N)	-	-	-	-	1.23 (33)			
High Total bilirubin% (N)	-	-	-	-	11.07 (36)	-	-	11.1 (36)
High Direct bilirubin% (N)	-	-	-	-	27.53 (89)	-	-	27.5 (89)
Low Ferritin% (N)	-	-	-	-	0.615 (2)	-	-	0.6 (2)
High ferritin% (N)	-	-	-	-	57.53 (187)	-	-	57.5 (187)
High Triglycerides% (N)	-	-	-	-	26.15 (85)	-	-	26.2 (85)
Low CPK% (N)	-	-	-	-	35.07 (114)	-	-	35.1 (114)
Interleukin-6% (N)	-	-	-	-	94.06 (306)	-	-	94.1 (306)
High Gamma glutamyl transferase% (N)	-	-	-	-	38.87 (126)	-	-	38.9 (126)
Low Amylase% (N)	-	-	-	-	4.62 (15)	-	-	4.6 (15)
High Amylase% (N)	-	-	-	-	15.69 (51)	-	-	15.7 (51)
Low ALP% (N)	-	-	-	-	1.23 (33)	-	-	1.2 (33)
High ALP% (N)	-	-	-	-	8.92 (29)	-	-	8.9 (29)
Low Potassium% (N)	-	-	-	-	-	-	25.8 (82)	25.8 (82)
High Lipase% (N)	-	-	-	-	12.36 (40)	-	-	12.4 (40)
Respiratory disease% (N)	-	4.55 (2)	12.9 (5)	8.58 (26)	10.15 (33)	1.92 (2)	5.68 (18)	7.6 (86)
Hypertension% (N)	58.95 (112)	34.09 (15)	47.5 (19)	50.5 (153)	51.38 (167)	10.58 (11)	47 (149)	47.3 (626)
Cardiac disease% (N)	19.47 (37)	25 (11)	41.46 (17)	14.52 (44)	17.85 (58)	-	-	18.5 (167)
Metabolic, Diabetes% (N)	21.58 (41)	15.91 (7)	29.27 (12)	23.43 (71)	22.46 (73)	3.85 (33)	15.46 (49)	19.4 (257)
Obesity% (N)	18.52 (35)	8.5 (33)	22.86 (9)	16.83 (51)	25.1 (82)	-	-	20 (181)
Smoking% (N)	-	-	25.71 (11)	-	87.23 (283)	10.58 (11)	-	64.9 (305)
A fib/arrhythmia% (N)	6.32 (12)	-	12.9 (5)	-	10.46 (34)	-	-	9.2 (51)
H/O Liver disease% (N)	-	4.55 (2)	20 (8)	-	-	2.88 (3)	-	7 (13)
Chronic GI disease% (N)	-	-	3.23 (1)	8.58 (26)	-	-	-	7.9 (27)
Immunosuppressed/ Immunocompromised% (N)	2.63 (5)	-	-	-	-	-	-	2.2 (5)

Chronic Kidney Disease% (N)	3.16 (6)	2.27 (1)	29.03 (12)	4.95 (15)	8.95 (29)	-	6.94 (22)	7 (85)
Malignancy% (N)	3.16 (6)	-	-	8.58 (26)	-	2.88 (3)	3.47 (11)	5 (46)
Stroke% (N)	6.84 (13)	-	-	-	-	0.96 (1)	-	4.8 (14)
Oncologic% (N)	-	13.64 (6)	19.35 (8)	-	-	-	3.79 (12)	6.5 (26)
Dyslipidemia% (N)	18.42 (35)	-	12.9 (5)	-	-	-	-	17.4 (40)
Benign prostatic hyperplasia% (N)	7.37 (14)	-	6.45 (3)	-	-	-	-	7.2 (17)
Thyroid disorder% (N)	6.84 (13)	-	-	-	-	7.69 (8)	-	7.1 (21)
Neurological disease and mental disorder% (N)	6.32 (12)	-	-	-	-	5.77 (6)	8.83 (28)	7.5 (46)
Remdesivir% (N)	-	-	13.04 (5)	6.27 (19)	-	-	0.63 (2)	4 (26)
Tocilizumab% (N)	-	-	37.5 (15)	5.94 (18)	-	-	19.24 (61)	14.3 (94)
Hydroxychloroquine/Chloroquine% (N)	61.08 (116)	-	77.78 (32)	60.4 (183)	-	-	70.98 (225)	65.3 (556)
Ritonavir/Lopinavir% (N)	-	-	10 (33)	29.04 (88)	-	-	1.26 (33)	29.04 (88)
Antibiotics% (N)	-	72.73 (32)	-	53.8 (163)	-	-	64.04 (203)	59.9 (398)
Reference	[34]	[35]	[36]	[37]	[12]	[38]	[39]	

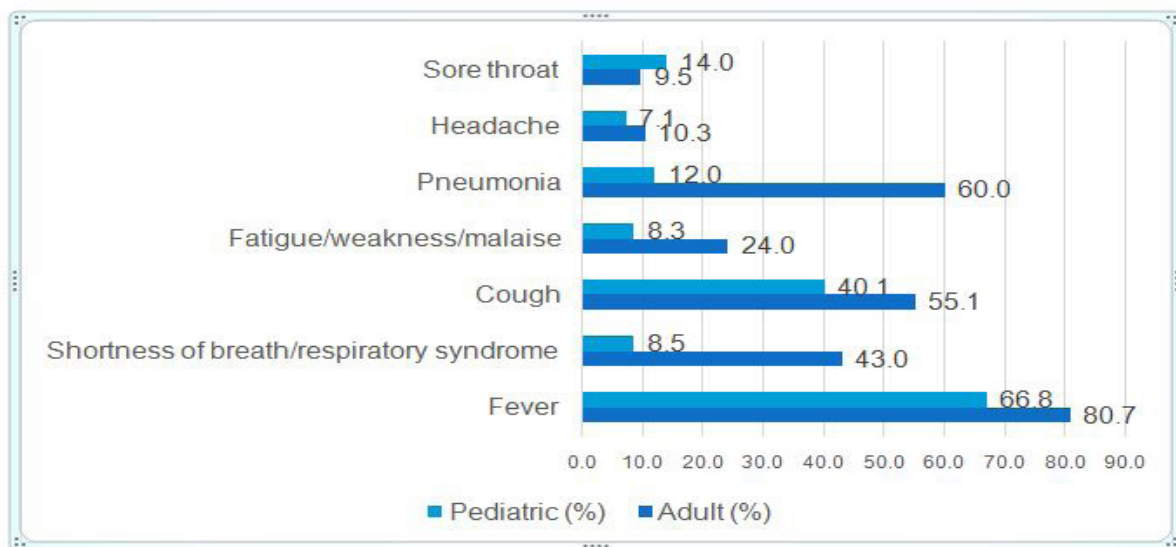


Figure 1: General signs and symptoms shared between adults and children.

19.8%, 14.8%), chest pain (10.8%), and confusion (8.3%). Respiratory failure was also reported in the majority of adult patients (56.6%) (Figure 2A). Among symptoms only identified in children we report rhinorrhea (22.3%), pharyngitis (3.4%), febrile convulsions (2.3%), and skin rash (4.9%) (Figure 2B).

Diarrhea and nausea were more common in adults, while vomiting and abdominal pain were more common in children:

Among both adults and children, diarrhea was a common GI symptom, with respective incidences of 16.8% and 11.9% (Table 1,2). In adults, this was followed by nausea at 12.4%, vomiting at 5.8%, and abdominal pain at 3.7%. In children, vomiting was in second place at 9.2%, followed by abdominal pain at 7.3% and nausea at 3.6%. While diarrhea and nausea were more commonly reported in adults, a greater percentage of children displayed vomiting and abdominal pain (Figure 3A).

Table 2: Characteristics of pediatric patients included in this study.

Study (N = 563)	Parri, et al.	Garazzino, et al.	De Jacobis, et al.	Lazzerini, et al.	Total
Total Patient Number% (N)	30.19 (170)	29.84 (168)	11.72 (66)	28.24 (159)	100 (563)
Collection date	March 3 - May 22, 2020	March 25 - April 10, 2020	End February - July, 2020	February 23 -March 24, 2020	February 23 - July, 2020
Age range% (N)	0-17	-	0.1-16	0-18	0-18
Median age% (N)	3.75 (6)	2.3 (33)	6.8 (33)	-	6.8 (33)
Male% (N)	55.88 (95)	55.95 (94)	53.03 (35)	48.43 (77)	53.5 (301)
Female% (N)	44.12 (75)	44.05 (74)	46.97 (31)	51.57 (82)	46.5 (262)
Fever% (N)	48.24 (82)	82.14 (138)	37.88 (25)	82.39 (131)	66.8 (376)
SOB/respiratory syndrome% (N)	8.24 (14)	9.52 (16)	-	7.55 (12)	8.5 (42)
Cough% (N)	42.94 (73)	48.81 (82)	19.7 (13)	36.48 (58)	40.1 (226)
Fatigue/weakness% (N)	14.71 (25)	1.79 (3)	-	-	8.3 (28)
Pneumonia% (N)	-	15.48 (26)	3.03 (2)	-	12 (28)
Rhinorrhea/Rhinopharyngitis% (N)	20 (34)	26.79 (45)	-	20.13 (32)	22.3 (111)
Pharyngitis% (N)	-	5.36 (9)	-	1.26 (2)	3.4 (11)
Headache% (N)	4.71 (8)	-	10.61 (7)	8.18 (13)	7.1 (28)
Sore throat% (N)	5.88 (10)	-	-	22.64 (36)	14 (46)
Febrile convulsions% (N)	-	1.19 (2)	7.58 (5)	1.26 (2)	2.3 (9)
Skin rash% (N)	5.88 (10)	-	-	3.77 (6)	4.9 (16)
Abdominal pain% (N)	7.65 (13)	-	-	6.92 (11)	7.3 (24)
Nausea% (N)	7.06 (12)	-	-	-	3.6 (12)
Vomiting% (N)	14.12 (24)	5.36 (9)	4.55 (3)	10.06 (16)	9.2 (52)
Diarrhea% (N)	11.18 (19)	13.1 (22)	12.12 (8)	11.32 (18)	11.9 (67)
Supplemental Oxygen (NC/VM/ NRB)% (N)	6.47 (11)	9.52 (16)	4.55 (3)	2.52 (33)	6 (34)
Non-invasive ventilation/CPAP% (N)	0.59 (1)	-	-	0.63 (1)	0.6 (2)
Intubated (invasive ventilation)% (N)	0.59 (1)	1.19 (2)	-	-	0.6 (3)
Asymptomatic% (N)	21 (36)	2.5 (33)	21.21 (14)	5.03 (8)	11 (62)
Mild% (N)	58 (99)	-	-	77.99 (124)	67.7 (223)
Moderate% (N)	19 (32)	-	-	12.58 (20)	15.9 (52)
Severe% (N)	1 (2)	10.12 (17)	-	3.14 (5)	4.8 (24)
Critical% (N)	1 (2)	-	-	1.26 (2)	1.1 (33)
Hospitalized% (N)	25.29 (43)	67.9 (114)	100 (66)	28.3 (45)	47.6 (268)
ICU Transfer% (N)	0.59 (1)	1.19 (2)	-	1.26 (2)	1 (5)
Death% (N)	-	-	-	-	0 (0)
Positive lung ultrasound% (N)	92.31 (157)	-	-	60 (95)	76.7 (252)
Positive Chest CT scan% (N)	66.66 (113)	-	-	80 (127)	73.1 (241)
Positive Chest X Ray% (N)	51.61 (88)	-	34.78 (23)	70.37 (112)	56.3 (223)
Low WBC% (N)	-	-	-	34 (54)	34 (54)
Low Lymphocyte% (N)	-	-	-	19.5 (31)	19.5 (31)
Low neutrophils% (N)	-	-	-	12.8 (20)	12.8 (20)
High AST% (N)	-	-	-	20 (32)	20 (32)

High ALT% (N)	-	-	-	8.7 (14)	8.7 (14)
High CRP% (N)	-	-	-	58 (92)	58 (92)
High D-dimer% (N)	-	-	-	50 (80)	50 (80)
High Erythrocyte sedimentation rate% (N)	-	-	-	50 (80)	50 (80)
Respiratory disease% (N)	-	4.17 (7)	-	3.77 (6)	4 (13)
Cardiac disease% (N)	-	-	-	5.66 (9)	5.7 (9)
Metabolic, Diabetes% (N)	-	0.6 (1)	-	0.63 (1)	0.6 (2)
Obesity% (N)	-	-	-	0.63 (1)	0.6 (1)
Chronic GI disease% (N)	-	1.19 (2)	-	-	1.2 (2)
Immunosuppressed/ immunocompromised% (N)	-	4.17 (7)	-	1.26 (2)	2.8 (9)
Oncologic% (N)	-	2.38 (33)	-	-	2.4 (33)
Epilepsy% (N)	-	2.98 (5)	-	-	3 (5)
Congenital malformations/complex genetic syndromes% (N)	-	8.33 (14)	-	-	8.3 (14)
Malformation, disability, neuromuscular disease% (N)	-	-	-	3.14 (5)	3.1 (5)
Psychiatric disorder% (N)	-	-	-	0.63 (1)	0.6 (1)
Other comorbidity% (N)	-	-	-	5.66 (9)	5.7 (9)
Antibiotics% (N)	-	-	9.09 (6)	-	9.1 (6)
Paracetamol% (N)	-	-	27.27 (18)	-	27.3 (18)
Paracetamol + antibiotics% (N)	-	-	16.67 (11)	-	16.7 (11)
Corticosteroids% (N)	-	-	3.03 (2)	-	3 (2)
Anti-rheumatic drugs% (N)	-	-	1.52 (1)	-	1.5 (1)
Anti-inflammatory% (N)	-	-	4.55 (3)	-	4.6 (3)
Heparin% (N)	-	-	3.03 (2)	-	3 (2)
Reference	[26]	[40]	[41]	[17]	

Adult patients required more oxygen support and intensive care:

Looking at general outcomes, we can see that 89.7% of adult and 47.6% of pediatric patients were hospitalized, while 17.7% of adult and 1.0% of pediatric patients required transfer to the ICU (Table 1,2). Respiratory support was also significantly more prevalent in the adult population. Indeed, 55.3% of adults were administered supplemental oxygen (*via* nasal cannula, venture mask, or non-rebreather), 24.0% were given non-invasive ventilation or CPAP, and 19.8% were intubated. The numbers for children are much lower, with 6.0% supplemental oxygen, 0.6% non-invasive ventilation/CPAP, and 0.6% intubated. Among the adult patients, there was a 21.6% incidence of death, while none of the pediatric patients died. A detailed classification of disease severity was only reported in pediatric studies (Table 2). Based on directions outlined by the National Institute of Health, 11.0% of patients were deemed asymptomatic, 67.7% were mild, 15.9% were moderate, 4.8% were severe, and 1.1% were critical.

Presence of comorbidities was significantly higher in adults:

Several comorbidities were shared between adults and children (Table 1,2), and all of them were considerably more prevalent in adults except for immunocompromised/ immunosuppressed patients, with an incidence of 2.2% in adults and 2.8% in children (Figure 3B). The other shared comorbidities are cardiac disease (18.5% vs 5.7%), metabolic disease/diabetes (19.4% vs 0.6%), obesity (20.0% vs 0.6%), respiratory disease (7.6% vs 4.0%), chronic GI disease (7.9% vs 1.2%), oncologic (6.5% vs 2.4%), and neurological/mental disorder (7.5% vs 0.6%). Other risk factors and comorbidities only recorded among adult patients were smoking (64.9%), dyslipidemia (17.4%), atrial fibrillation/arrhythmia (9.2%), benign prostatic hyperplasia (7.2%), thyroid disorder (7.1%), liver disease (7%), chronic kidney disease (7%), malignancy (5%). On the pediatric side, we also report congenital malformation/complex genetic syndromes (8.3%), malformation/disability/neuromuscular disease (3.1%), epilepsy (3%), psychiatric disorder (0.6%), and other unspecified comorbidities (5.7%).

Laboratory and test imaging findings:

GI-related laboratory findings that were shared among adult

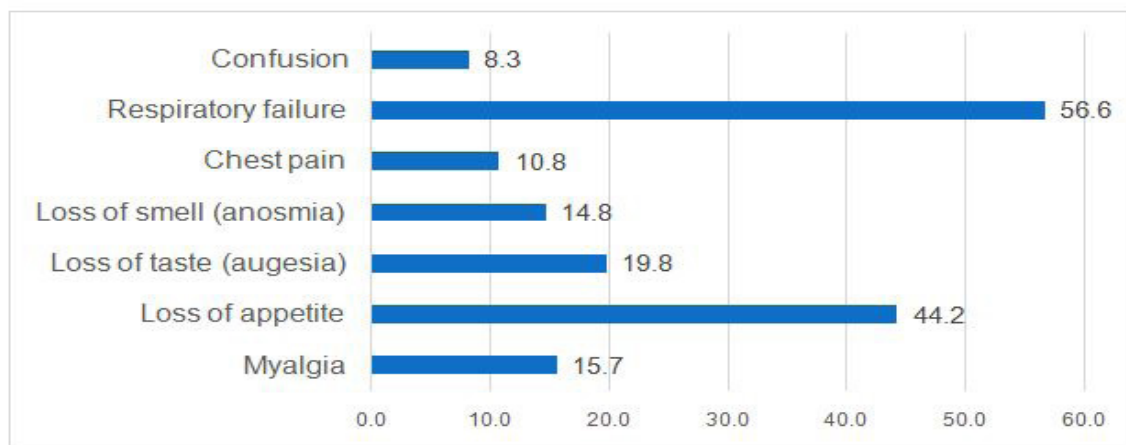


Figure 2A: Signs and symptoms only found in adults.

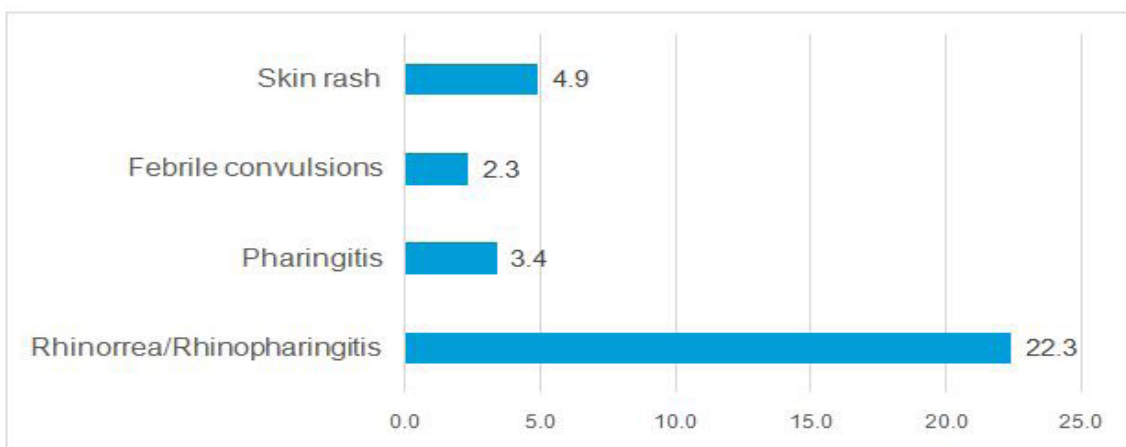


Figure 2B: Signs and symptoms only found in children.

and pediatric patients were AST and ALT (Table 1,2). Adults had a higher incidence of elevated AST and ALT than pediatric patients: 36.0% of adults and 20.0% of children had high AST, while 29.9% of adults and 8.7% of children had high ALT (Table 3).

Both adults and children had differential blood markers values and elevated D-dimer. Lymphocytopenia and high C-Reactive Protein (CRP) were more common in adults, with incidences of 61.8% vs 19.5%, and 88.0% vs 58.0%, respectively. Adults (15.7%) had low white blood cell count compared to children (34.0%) (Table 3).

Other findings in adult patients were the following:

74.1% high fibrinogen, 65.4% high LDH, 49.7% low LDH, 32.5% low platelet count, 24.9% high creatinine, and 0.2% low fibrinogen. For pediatric patients, we also report an incidence of high D-dimer of 50%, high erythrocyte sedimentation rate of 50%, and a low neutrophil count of 12.8%.

Positive chest x-ray findings were identified in 76.6% of adult and 56.3% of pediatric patients. Among children, 73.1%

were also reported to have a positive chest CT scan (for ground glass opacities, focal consolidation, interstitial abnormalities, or other descriptions) and 76.7% a positive lung ultrasound (for A-pattern, B-lines, focal consolidation, sonographic interstitial syndrome, or other description).

One of the studies (Aghemo et al), including 325 patients, presented an extensive list of laboratory test results, reporting high interleukin-6 levels in all patients [12]. Since this paper amounts to almost 25% of the total number of patients of our review, we report the following values as likely significant: 94.1% high interleukin-6, 59.7% high D-dimer, 57.5% high ferritin, 36.0% low hemoglobin, 6.8% high hemoglobin, 22.8% high white blood cell count (lymphocytosis), 35.2% low CPK, 29.7% high troponin, 26.2% high triglycerides, 25.8% low potassium, 22.2% high procalcitonin, 17.4% leukocytopenia, 14.2% low creatinine, 12.4% high lipase, 4.9% high platelet count, and 0.5% low ferritin. Looking at GI-related values reported in Aghemo et al study, we also have 38.9% high gamma glutamyl transferase, 27.5% high direct bilirubin, 15.7% high amylase, 11.2% high total bilirubin,

Table 3: Main laboratory data found in both adult and pediatric patients included in this study

Shared lab results	Adult (%)	Pediatric (%)
Low WBC	15.7	34.0
Low Lymphocyte	61.9	19.5
High AST	36.0	20.0
High ALT	29.9	8.7
High D-Dimer	59.7	50.0

8.9% high ALP and 1.2% low ALP, 4.6% low amylase, and 1.2% low total bilirubin.

Medications were administered to the majority of adults and a small number of children: Not much information was available in our sources about treatments (Table 1,2). The only shared data point between adults and children was antibiotics, which were administered to 60.0% of adults and 9.1% of children. For adults only, we report that 65.3% received hydroxychloroquine or chloroquine, 14.5% Ritonavir/Lopinavir, 14.3% Tocilizumab, and 4.0% Remdesivir. As for children, 27.3% received paracetamol, 16.7% a combination of paracetamol and antibiotics, 3.0% corticosteroids, 1.5% anti-rheumatic drugs, 4.6% anti-inflammatory drugs, and 3.0% heparin.

Shortness of breath, obesity, and smoking were significantly associated with death: Correlations between certain variables and death were found in adults. The most significant positive correlations were shortness of breath/respiratory syndrome (0.8; $p < 0.01$), obesity (0.78; $p < 0.01$), and smoking (0.9; $p < 0.01$). Other positive associations were found with cough (0.17; $p < 0.01$), cardiac disease (0.29; $p < 0.01$), and hypertension (0.27; $p < 0.01$). There are negative associations with female gender ($p < 0.01$), headache ($p < 0.01$), vomiting ($p < 0.01$), and diarrhea ($p < 0.01$).

Discussion

Italy was the first country in Europe to report a SARS-CoV-2 infection. COVID-19 has different outcome in adults vs children, as comorbidities and symptoms vary among the two groups. In this review, we present the characteristics of 1,324 adult and 563 pediatric COVID-19 Italian patients. Adults and children reported several shared symptoms, although with different prevalence (Figure 4). Pneumonia was the symptom with the greatest difference, with 60% of adults and only 12% of children. The chest x-ray, however, was positive in adults and children at 76.6% and 56.3%, respectively. Moreover, in some instances, positive imaging is also reported in asymptomatic patients [13]. These findings reflect that children display a higher resilience to the infection as many infected children were asymptomatic and a much lower number of children with positive chest x-ray presented with pneumonia than adults. This is supported by a study by Du et al [14], which reported older age (65 and older) as a predictor of mortality in COVID-19 pneumonia.

A study reviewing the pathophysiology of COVID-19 claims that people with a higher expression of the ACE-2 receptor develop a more severe disease, because the virus can invade host cells more quickly [15]. According to the authors, however,

ACE-receptor expression decreases after birth up until a certain point and then starts increasing, which would explain why infants and adults, who have a higher expression of ACE-2 than pediatric patients between 1 and 18 years old, develop a more severe disease. ACE-2 is also more expressed in men than women, which would also explain why male sex is associated with worse outcomes [15]. Dhochak et al. also propose other reasons for the lower incidence of pneumonia in children. Lungs become progressively worse at regenerating with ageing [16]. This implies that children's lungs recover more quickly from infection, reducing the possibility to develop pneumonia. This might also be the reason why sore throat is the only symptom with a greater incidence in children than adults, and why pharyngitis and rhinorrhea/rhinopharyngitis were only reported in pediatric patients. Since the lungs regenerate quickly, the virus can cause infection preferentially in the upper airway, including the nasopharynx. After pneumonia, the symptom with the largest difference in the prevalence between adults and children is shortness of breath (43% vs 8.5%). Dyspnea has a large variety of causes. The higher incidence of this symptom in adults matches that of pneumonia. More adults develop lung infection, and this likely causes them to develop shortness of breath.

Other symptoms, such as fatigue and cough, were more present in adults. However, our data-analysis included a portion of asymptomatic children (11.0%), so these smaller differences could simply reflect the discrepancy in the rate of patients who actually had symptoms. These findings are in line with a study from Li et al. [13], which found a greater percentage of adult than pediatric asymptomatic patients, respectively at 13.16% and 28.57%. Loss of appetite, anosmia, ageusia, myalgia, and confusion are all manifestations that infants and toddlers might not be able to express. Thus, we can assume that these results are biased towards signs and symptoms that the patient must be able to express. It is worth mentioning that the study from Lazzerini et al. [17] reports some cases of anosmia and ageusia, and that study from Mak, et al [18] presents 3 case studies of adolescents (14, 15, and 17 years old) with these symptoms. They too hypothesize that the scarce number of children found to have anosmia/ageusia is due not to the fact that few children develop them, but to difficulty assessing them in younger patients [18].

Skin rashes and febrile convulsions were only reported in children. The latter is not uncommon in children experiencing fever and has many causes. Skin rash, on the other hand, could be considered as a sign of possible COVID-19 infection. A meta-analysis from Shah et al. reported cutaneous manifestations in patients aged 1-18 years old and found that the majority of

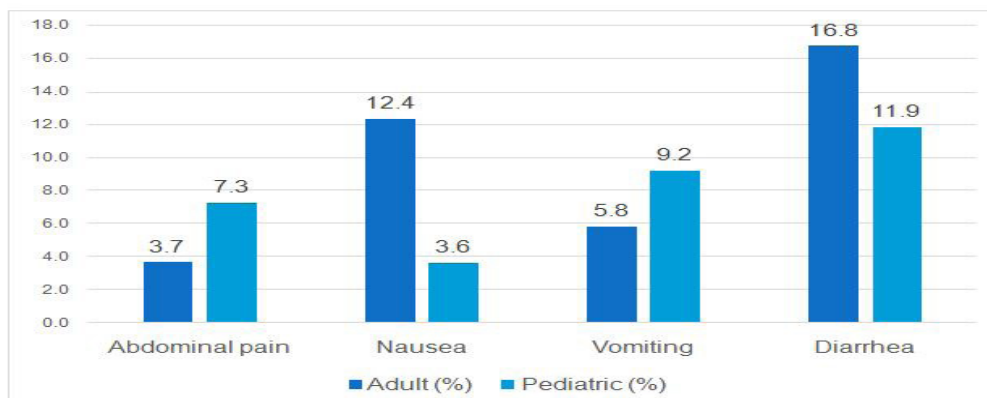


Figure 3A: Gastrointestinal symptoms shared between adults and children.

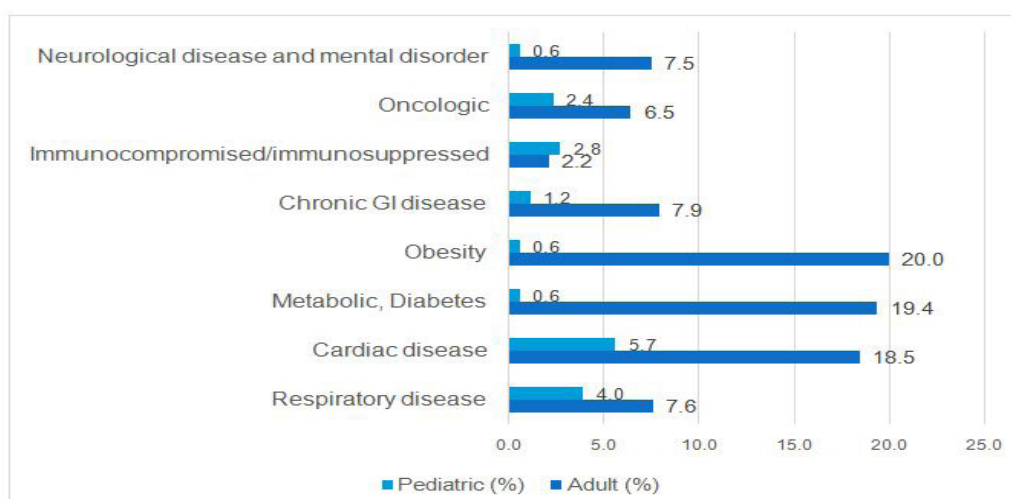


Figure 3B: Comorbidities shared between adults and children.

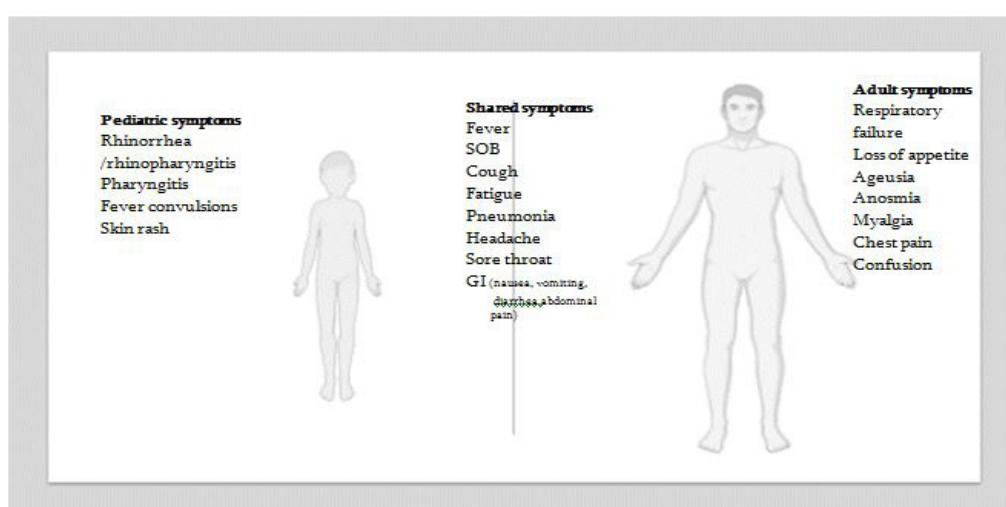


Figure 4: Covid-19 symptoms in children and adults.

patients developed some type of skin rash [19]. The authors hypothesized the high incidence of skin manifestations is the surge in interferon secondary to viral infection. According to the authors, type I interferon is released upon viral entry, activating the JAK-STAT signaling pathway. This pathway upregulates genes that inhibit proliferation and support elimination of the virus [19]. High type I IFN had been reported in patients with chilblain-like lesions, which usually affect the hands or feet [19]. This suggests that IFN first helps the body fight viral infection, and then causes mucocutaneous rashes. It is possible however that such skin manifestations be a reflection of some liver function alterations [20], in response to the viral infection.

GI manifestations' incidence of each individual symptom is quite similar in adults and children, ranging from about 4% to about 15%. GI symptoms are reported with large variety in published studies. For instance, a meta-analysis from China [21] reported a 12% overall incidence of GI symptoms in children, while a study from 14 states in the United States [22] recorded a 42% incidence in pediatric patients. Interestingly, this study also reported one third of hospitalized children requiring ICU admission (a rate that is similar to that of adults), but low fatality nonetheless [22]. Another meta-analysis of COVID-19 pediatric studies from 26 countries [23] only reported a 6.5% incidence of abdominal pain/diarrhea and a 5.4% incidence of vomiting/nausea. As for adults, the literature seems to share more consistent data. A large meta-analysis including patients from 60 studies and with a median age of 58.5 years old [24] reported 17.6% incidence of any GI symptom. Another meta-analysis [25], which included 52 studies, reported a 16.6% incidence of diarrhea and 9.9% nausea. This shows how important it is to pool together the data available for both adults and children for a better comparison. In adults, only diarrhea is reported as one of the top 10 symptoms, and it occupies the eighth position. In children, we have 3 GI manifestations in top 10: diarrhea, vomiting, and abdominal pain, respectively at the sixth, seventh, and tenth position. This might highlight the importance of GI symptoms in the profile of children with COVID-19, as they might attenuate the disease effect. It is once again worth noting, however, that children have difficulties reporting subtle symptoms.

In this study, elevated levels of AST and ALT were more prevalent in adults. Since these, especially ALT, are indicators of liver damage, if children were more prone to GI manifestations, these laboratory values should be higher in younger patients than adults, but this is not in line with our findings. It is worth mentioning that opposite results were presented in a paper from Li, et al. [13], which reported AST and AST/ALT ratio to be significantly higher in children than adults, indicating that children might be more prone to liver function viral-induced alterations than adults. Whether or not this reduces the possibility of developing severe respiratory symptoms is not clear yet, considering that in that same study, patients in the ICU usually had high aminotransferase levels [13].

More adults than children were hospitalized (89.7% vs 47.6%), sent to the ICU (17.7% vs 1.0%), and required respiratory support. Specifically, 55.3% of adults and 6.0% of children

required supplemental oxygen *via* nasal cannula, Venturi mask, or nonrebreather; 24% of adults and 0.6% of children required non-invasive ventilation or CPAP, and 19.8% of adults and 0.6% of children had to be intubated. Also, in our data-analysis, 21.6% of adults and none of the children died. Once again, the lower need for respiratory support in children is likely a consequence of the children's more efficient lung regeneration capacity [16] and the fact that there is a lower number of pediatric patients with respiratory disease or history of smoking. Parri et al. [26] shows, 6 of the 13 children that required respiratory support had comorbidities, which probably contributed to making their respiratory support.

Evidence suggests that COVID-19 patients might benefit from antibodies developed when fighting other coronaviruses' infections [16]. In support of this theory, a study from Consiglio et al. [27] found that pediatric COVID-19 patients often had antibodies to common coronaviruses present in their blood. However, patients who developed MIS-C, the most severe form of COVID-19 in children, were the only ones lacking such antibodies [27]. It is possible that adults who were infected by common coronaviruses at younger ages are no longer immune, which is why they develop more severe signs and symptoms. Moreover, developmental changes in immunity could also explain the difference in outcomes [16]. Children have a stronger innate immune response than the elderly due to trained immunity, as proven by the fact that adults have a lower number of NK cells, macrophages, dendritic cells, and an upregulation of pro-inflammatory cytokines [15,16,28]. Children also have a better adaptive immunity, due to a higher proportion of lymphocytes and absolute numbers of T and B cells than adults [28]. Severe COVID-19 patients, in fact, are usually found to have T cell exhaustion. The high expression of pro-inflammatory cytokines and the low number of T cells are also seen in infants, which could explain why very young children often develop a more severe disease [16]. In our data-analysis, adults were significantly more likely to have low lymphocyte count than children (61.8% vs 19.5%), in line with the literature [28].

Dzhokhar et al. [16], as well as the CDC (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html> accessed May 25th), have shown that comorbid conditions are predictors of worse outcomes in COVID-19 patients. Comorbidities and risk factors were significantly more present in adults than in children, the top being smoking (64.9%), hypertension (47.3%), obesity (20.0%), diabetes (19.4%), and cardiac disease (18.5%). Predictably, all of these can be considered acquired comorbidities, derived from lifestyle, habits, and biological ageing, while the top comorbidities in children were congenital (congenital malformations or complex genetic syndrome, 8.3%; cardiac disease, 5.7%; asthma and other respiratory disease, 4.0% malformation, disability, or neuromuscular disease, 3.1%; epilepsy, 3.0%). Notably, despite children with comorbidities typically develop a more severe disease, their outcomes are still much better than adults [28].

Even though none of the sources included in this study were directly focused on ARDS and MIS-C, our comparison of adults

and children would be incomplete if we did not mention the most severe presentations of COVID-19 in these demographic groups. In adults, critical disease progression is referred to as Acute Respiratory Distress Syndrome (ARDS), and it is caused by a cytokine storm most likely caused by a specific cytokine, Interleukin-6 (IL-6) [29]. IL-6 is produced when the virus enters the cell *via* the ACE-2 receptors and upregulates the NF- κ B signalling pathway, which is associated with inflammation. Then, once the homeostatic balance of angiotensin-2 is compromised by the reduced number of ACE-2 enzymes, more IL-6 is produced [29]. As a result, a positive feedback loop is initiated leading to a cascade of cytokines and consequent hyper inflammation. Notably, ARDS can also develop in children, but it is less common and denominated Pediatric Acute Respiratory Distress Syndrome (PARDS) [30]. In pediatric patients however, the most severe form of COVID-19 is the MIS-C- which was originally referred to as Kawasaki Disease (KD), due to the similarities in clinical presentations [31]. Both diseases target children, although MIS-C patients have a higher median age, and they are characterized by vasculitis, with MIS-C having more significant cardiac involvement [31]. Further differentiation of MIS-C and KD has been extensively covered by other studies and is out of the scope of this data-analysis [27]. It is worth mentioning that while regular COVID-19 infects children at a similar rate as adults, albeit with milder symptoms, MIS-C is very rare and can develop even 1-2 months after initial infection [27].

In conclusion, this study shows that adults are at higher risk for complications and death, and they usually present with fever, respiratory symptoms, cough, fatigue, diarrhea, myalgia, and/or loss of taste, smell, or appetite. Children usually have a milder disease progression and usually present with fever, cough, rhinorrhea, pharyngitis, sore throat, pneumonia, GI symptoms (diarrhea, vomiting, abdominal pain), fatigue, and dyspnea. Sometimes they are also subjected to skin rashes and febrile seizures. ARDS (respiratory failure) and MIS-C (systemic vasculitis) are the most severe disease progressions for adults and children respectively. The high prevalence of GI symptoms in children might play as a buffer that attenuates and mitigates the disease course [32]. However, overall adult and pediatric patients with such symptoms might benefit from continuous follow-ups to avoid suspected sequelae that associate with the virus persistence in the GI system.

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Author Contributions

Study concept and design (HA), HA and HB wrote the paper; TR collected, and analyzed the clinical data. GO performed statistical analysis. Obtained funding (HA), material support (HA, HB, GL, SM). All authors evaluated the manuscript for intellectual content and approved the manuscript.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395: 497-506. doi: 10.1016/S0140-6736(20)30183-5.
2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020; 91: 157-160. doi: 10.23750/abm.v91i1.9397.
3. Amendola A, Bianchi S, Gori M, Colzani D, Canuti M, Borghi E, et al. Evidence of SARS-CoV-2 RNA in an Oropharyngeal Swab Specimen, Milan, Italy, Early December 2019. *Emerg Infect Dis*. 2021; 27: 648-650. doi: 10.3201/eid2702.204632.
4. Indolfi C, Spaccarotella C. The Outbreak of COVID-19 in Italy: Fighting the Pandemic. *JACC Case Rep*. 2020; 2: 1414-1418. doi: 10.1016/j.jaccas.2020.03.012.
5. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020; 75: 1730-1741. doi: 10.1111/all.14238.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020; 323: 1061-1069. doi: 10.1001/jama.2020.1585.
7. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. *N Engl J Med*. 2020; 382: 1663-1665. doi: 10.1056/NEJMc2005073.
8. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. 2020; 145: e20200702. doi: 10.1542/peds.2020-0702.
9. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine*. 2020; 26: 100527. doi: 10.1016/j.eclinm.2020.100527.
10. Ashktorab H, Pizuorno A, Oskroch G, Fierro NA, Sherif ZA, Brim H. COVID-19 in Latin America: Symptoms, Morbidities, and Gastrointestinal Manifestations. *Gastroenterology*. 2021; 160: 938-940. doi: 10.1053/j.gastro.2020.10.033.
11. Ashktorab Y, Brim A, Pizuorno A, Gayam V, Nikdel S, Brim H. COVID-19 Pediatric Patients: Gastrointestinal Symptoms, Presentations, and Disparities by Race/Ethnicity in a Large, Multicenter US Study. *Gastroenterology*. 2021; 160: 1842-1844. doi: 10.1053/j.gastro.2020.10.033.
12. Aghemo A, Piovani D, Parigi TL, Brunetta E, Pugliese N, Vespa E, et al. COVID-19 Digestive System Involvement and Clinical Outcomes in a Large Academic Hospital in Milan, Italy. *Clin Gastroenterol Hepatol*. 2020; 18: 2366-2368.e3. doi: 10.1016/j.cgh.2020.05.011.
13. Li X, Rong Y, Zhang P, Wang J, Qie L, Rong L, Xu J. Differences in Clinical Features and Laboratory Results between Adults and Children with SARS-CoV-2 Infection. *Biomed Res Int*. 2020; 2020: 6342598. doi: 10.1155/2020/6342598.
14. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020; 55: 2000524. doi: 10.1183/13993003.00524-2020.
15. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol*. 2020; 215: 108427. doi: 10.1016/j.clim.2020.108427.

16. Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: Why Children Fare Better than Adults? *Indian J Pediatr.* 2020; 87: 537-546. doi: 10.1007/s12098-020-03322-y.
17. Lazzarini M, Sforzi I, Trapani S, Biban P, Silvagni D, Villa G, et al. Characteristics and risk factors for SARS-CoV-2 in children tested in the early phase of the pandemic: a cross-sectional study, Italy, 23 February to 24 May 2020. *Euro Surveill.* 2021; 26: 2001248. doi: 10.2807/1560-7917.ES.2021.26.14.2001248.
18. Mak PQ, Chung KS, Wong JS, Shek CC, Kwan MY. Anosmia and Ageusia: Not an Uncommon Presentation of COVID-19 Infection in Children and Adolescents. *Pediatr Infect Dis J.* 2020; 39: e199-e200. doi: 10.1097/INF.0000000000002718.
19. Shah S, Akhade K, Ganguly S, Nanda R, Mohapatra E, Goel AK. Cutaneous manifestations associated with COVID-19 in children: A systematic review. *J Family Med Prim Care.* 2021; 10: 93-101. doi: 10.4103/jfmpc.jfmpc_1389_20.
20. Bergasa NV. The itch of liver disease. *Semin Cutan Med Surg.* 2011; 30: 93-98. doi: 10.1016/j.sder.2011.04.009.
21. Chang TH, Wu JL, Chang LY. Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *J Formos Med Assoc.* 2020; 119: 982-989. doi: 10.1016/j.jfma.2020.04.007.
22. Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep.* 2020; 69: 1081-1088. doi: 10.15585/mmwr.mm6932e3.
23. Hoang A, Chorath K, Moreira A, Evans M, Burmeister Morton F, Burmeister F, et al. A systematic review. *EClinicalMedicine.* 2020; 24: 100433. doi: 10.1016/j.eclinm.2020.100433.
24. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology.* 2020; 159: 81-95. doi: 10.1053/j.gastro.2020.03.065.
25. Shehab M, Alrashed F, Shuaibi S, Alajmi D, Barkun A. Gastroenterological and hepatic manifestations of patients with COVID-19, prevalence, mortality by country, and intensive care admission rate: systematic review and meta-analysis. *BMJ Open Gastroenterol.* 2021; 8: e000571. doi: 10.1136/bmjgast-2020-000571.
26. Parri N, Lenge M, Cantoni B, Arrighini A, Romanengo M, Urbino A, et al. COVID-19 in 17 Italian Pediatric Emergency Departments. *Pediatrics.* 2020; 146: e20201235. doi: 10.1542/peds.2020-1235.
27. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell.* 2020; 183: 968-981.e7. doi: 10.1016/j.cell.2020.09.016.
28. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child.* 2020; archdischild-2020-320338. doi: 10.1136/archdischild-2020-320338.
29. Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, et al. How COVID-19 induces cytokine storm with high mortality. *Inflamm Regen.* 2020; 40: 37. doi: 10.1186/s41232-020-00146-3.
30. Sinaei R, Pezeshki S, Parvaresh S, Sinaei R. Why COVID-19 is less frequent and severe in children: a narrative review. *World J Pediatr.* 2021; 17: 10-20. doi: 10.1007/s12519-020-00392-y.
31. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet.* 2020; 395: 1771-1778. doi: 10.1016/S0140-6736(20)31103-X.
32. Livanos AE, Jha D, Cossarini F, Gonzalez-Reiche AS, Tokuyama M, Aydllo T, et al. Intestinal Host Response to SARS-CoV-2 Infection and COVID-19 Outcomes in Patients With Gastrointestinal Symptoms. *Gastroenterology.* 2021; 160: 2435-2450.e34. doi: 10.1053/j.gastro.2021.02.056.
33. Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT Jr, Skanderson M, et al. Covid-19 by Race and Ethnicity: A National Cohort Study of 6 Million United States Veterans. *medRxiv [Preprint].* 2020; 2020.05.12.20099135. doi: 10.1101/2020.05.12.20099135.
34. Schettino M, Pellegrini L, Picascia D, Saibeni S, Bezzio C, Bini F, et al. Clinical Characteristics of COVID-19 Patients With Gastrointestinal Symptoms in Northern Italy: A Single-Center Cohort Study. *Am J Gastroenterol.* 2021; 116: 306-310. doi: 10.14309/ajg.0000000000000965.
35. Colaneri M, Sacchi P, Zuccaro V, Biscarini S, Sachs M, Roda S, et al. Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. *Euro Surveill.* 2020; 25: 2000460. doi: 10.2807/1560-7917.ES.2020.25.16.2000460.
36. Massironi S, Viganò C, Dioscoridi L, Filippi E, Pagliarulo M, Manfredi G, et al. Endoscopic Findings in Patients Infected With 2019 Novel Coronavirus in Lombardy, Italy. *Clin Gastroenterol Hepatol.* 2020; 18: 2375-2377. doi: 10.1016/j.cgh.2020.05.045.
37. Cattelan AM, Di Meco E, Trevenzoli M, Frater A, Ferrari A, Villano M, et al. Clinical characteristics and laboratory biomarkers changes in COVID-19 patients requiring or not intensive or sub-intensive care: a comparative study. *BMC Infect Dis.* 2020; 20: 934. doi: 10.1186/s12879-020-05647-7.
38. Temperoni C, Grieco S, Pasquini Z, Canovari B, Polenta A, Gnudi U, et al. Clinical characteristics, management and health related quality of life in young to middle age adults with COVID-19. *BMC Infect Dis.* 2021; 21: 134. doi: 10.1186/s12879-021-05841-1.
39. Vena A, Giacobbe DR, Di Biagio A, Mikulska M, Taramasso L, De Maria A, et al. Clinical characteristics, management and in-hospital mortality of patients with coronavirus disease 2019 in Genoa, Italy. *Clin Microbiol Infect.* 2020; 26: 1537-1544. doi: 10.1016/j.cmi.2020.07.049.
40. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. *Euro Surveill.* 2020; 25: 2000600. doi: 10.2807/1560-7917.ES.2020.25.18.2000600.
41. De Jacobis IT, Vona R, Cittadini C, Marchesi A, Cursi L, Gambardella L, et al. Clinical characteristics of children infected with SARS-CoV-2 in Italy. *Ital J Pediatr.* 2021; 47: 90. doi: 10.1186/s13052-021-01045-0.