

A Systematic Review of Gastrointestinal Manifestations in Children Presenting with COVID-19

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Abstract: SARS-CoV-2 infection commonly presents with mild to severe respiratory symptoms and possibly other organs involvement. Gastrointestinal manifestations have been frequently documented in adult patients whilst their occurrence in children is uncertain. This study aimed to perform a Systematic Review of gastrointestinal symptoms in children with Coronavirus disease (COVID-19) and to compare these clinical findings with those reported in a cohort of Italian children in the early phase of pandemic.

Methods: Literature search was conducted using the Cochrane Library and MEDLINE (via Pubmed) databases from 1st December 2019 to 28th April 2020, according to the PRISMA guidelines. The following search terms were inserted: "Coronavirus" OR "COVID-19" OR "SARS-CoV-2" AND "gastrointestinal" or "diarrhea". Only papers including children (0-18 years) and gastrointestinal symptoms were considered as eligible. Data records of children living in Lombardy, Italy, with infection of SARS-CoV-2 diagnosed by rRT-PCR on pharyngeal swabs, from 1st March to 28th April were also collected, analyzed and compared.

Results: The Systematic Review showed that only a minority of studies assessed gastrointestinal symptoms in children. However, diarrhea accounted for 0-50%, vomit 5-67% and abdominal pain 5.8-33.3% of infected children and gastrointestinal symptoms may represent the sole feature of COVID-19. Gastrointestinal symptoms were reported in 51/116 (44%) Italian children with SARS-CoV-2 infection. Poor feeding was present in 23.3% of children, diarrhea (median duration 2.3 days, range 1-5 days) in 22.4%, vomit in 10.4% and abdominal pain in 6.9% of cases. Respiratory symptoms were reported in 35.3% of children with gastrointestinal symptoms that represented the first clinical manifestation of COVID-19 in 25% of all patients.

Conclusions: We found that gastrointestinal symptoms are common in children with COVID-19 and, in some cases, they may represent the first and the sole clinical manifestation of SARS-CoV-2 infection. Health care professionals must be aware of the frequent gastrointestinal involvement in children to assure an accurate diagnosis and therapeutic management. The correct identification of children with COVID-19 is also crucial to adopt preventive measures and to limit the transmission of the virus.

Keywords: SARS-CoV-2, COVID-19, Coronavirus, Gastrointestinal, Diarrhea, Vomit, Abdominal pain, Poor feeding, Children.

INTRODUCTION

In December 2019 an outbreak of atypical pneumonia, later related to a new Coronavirus (SARS-

CoV-2), emerged in Wuhan city, in China (Zhu N, NEJM) [1]. Since February 2020 the infection has progressively spread in Italy [2] (Task force ISS) and throughout most world countries with hundred thousands of new patients and deaths in the following weeks [3, 4]. The Coronavirus disease-19 (COVID-19) is usually characterized by mild to severe respiratory syndrome showing ground-glass and bilateral consolidative opacities at chest imaging [5]. Associated manifestations may involve different organs and include sore throat, myalgia, fatigue, general weakness, headache, loss of taste or smell, abdominal pain, nausea, vomiting and diarrhea. Complications,

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such as cardiac and renal injuries, coagulopathy presenting as thrombosis, septic shock and eventual fatality have been worldwide reported particularly in the elderly and at risk patients [1-5]. Children of all ages can be infected by SARS-CoV-2 but are often asymptomatic or with mild COVID-19, uncommon severe presentation and extremely rare fatality [2-4].

Gastrointestinal (GI) symptoms may precede or accompany respiratory features and have been shown in 1.7% to 79% of adult patients [3, 5-10].

The prevalence and characteristics of GI manifestations in children with SARS-CoV-2 is more uncertain and reported as case reports or series or mixed cohorts of adult and pediatric patients. However, awareness and clarification of gastrointestinal involvement in the young patients is important to assure both an accurate diagnosis and management and also to limit the transmission of the virus.

The aim of this study was to perform a Systematic Review of all gastrointestinal symptoms, and particularly of diarrhea, vomiting and abdominal pain, reported in children with Coronavirus disease (COVID-19), including a cohort of Italian children from the highest endemic area.

METHODS

Study Design

This is a Systematic Review of gastrointestinal symptoms, and specifically of diarrhea, vomiting and abdominal pain, reported in the early phase of pandemic, in children with Coronavirus disease (COVID-19). Because SARS-CoV-2 infection rapidly spread to Italy and Lombardy was one of the first and most affected European Region, we also collected and analysed the data from children referred to local different pediatric hospitals and compared to those reported in the literature.

Data Sources

Literature Search Strategy

We conducted a systematic literature search of the Cochrane Library and MEDLINE (via Pubmed) databases from 1st December 2019 to 28th April 2020, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. The following search terms were inserted: "Coronavirus" OR "COVID-19" OR "SARS-CoV-2" AND "gastrointestinal" or "diarrhea". No geographical restrictions were applied but only papers written in

English or Italian languages were included. The electronic search, the eligibility and bias of the studies were assessed independently by 2 of the authors (S.S., S. A.). Differences were discussed, and consensus reached.

Selection Criteria

For inclusion, studies had to meet *all* the following criteria: 1) include humans, 2) report GI symptoms (any or specified as diarrhea, vomiting, abdominal pain, nausea), 3) enrol patients with suspected or confirmed SARS-CoV-2 infection, 4) report pediatric cases (age limit "child: Birth -18 years"). Due to the expected paucity of studies, besides all prospective and retrospective case report or case series or case-control studies, we included narrative and systematic reviews and pooled data. In addition, the reference lists of all identified articles were manually examined to retrieve studies not captured by electronic searches. Exclusion criteria were lack of detailed population characteristics, in terms of ages, number of patients, GI symptoms; languages other than English or Italian; other virus than SARS-CoV-2.

Data Extraction

Two investigators (S.S. and S.E.) independently examined, summarized and completed a data extraction from all eligible studies without modification of original data onto custom-made data collection containing items on age and number of patients, GI characteristics of participants, geographical origin, and outcomes. Disagreements were resolved by consensus with a third reviewer (M.A.).

Italian Pediatric Population from Lombardy Region

We conducted a retrospective multi-centric study on the GI manifestations of 116 cases of COVID-19 in children (0-18 years) diagnosed in 22 different sites located in the Lombardy region from 1st March to April 30th. All subjects less than 18 years with a positive result for SARS-CoV-2 on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens were included. All cases were tested on the basis of suspected symptoms or exposed history as per Italian guidelines. The demographic and clinical characteristics of confirmed cases were collected by means of a clinical record form.

Data Analysis

Continuous variables were expressed as median and range. The prevalence of gastrointestinal

symptoms was categorically expressed as proportions and 95% Confidence Interval (95% CI) using the random effects model and was presented as Forest plot. Symptomatic variables were adopted categorically (symptom present or absent). Pooled risks estimate was considered as statistically significant when a $p < 0.05$ was observed. We used Cochrane Q test to detect heterogeneity among studies, with significant heterogeneity when $p < 0.10$. I^2 was calculated to measure heterogeneity in study estimates, with values $< 25\%$, $25-75\%$, and $> 75\%$ indicating low, moderate and high heterogeneity. Statistical analysis was performed using *Jamovi* Software version 1.1.9.0 (Sydney, Australia; 2019).

RESULTS

Literature Data

A total of 296 articles were identified in the initial search, 25 reports were added through other sources. After removing duplicates, 305 articles were screened by title and abstract, and of those, 74 articles were excluded (other viral agents, animal studies, no gastrointestinal topic); 231 full texts were assessed for eligibility, with 211 excluded based on article type (editorials, viewpoints, guidelines, experimental research letter), content (no data patients included), topic (endoscopy or other procedures), and population (only adult patients with COVID-19)(Figure 1). Among

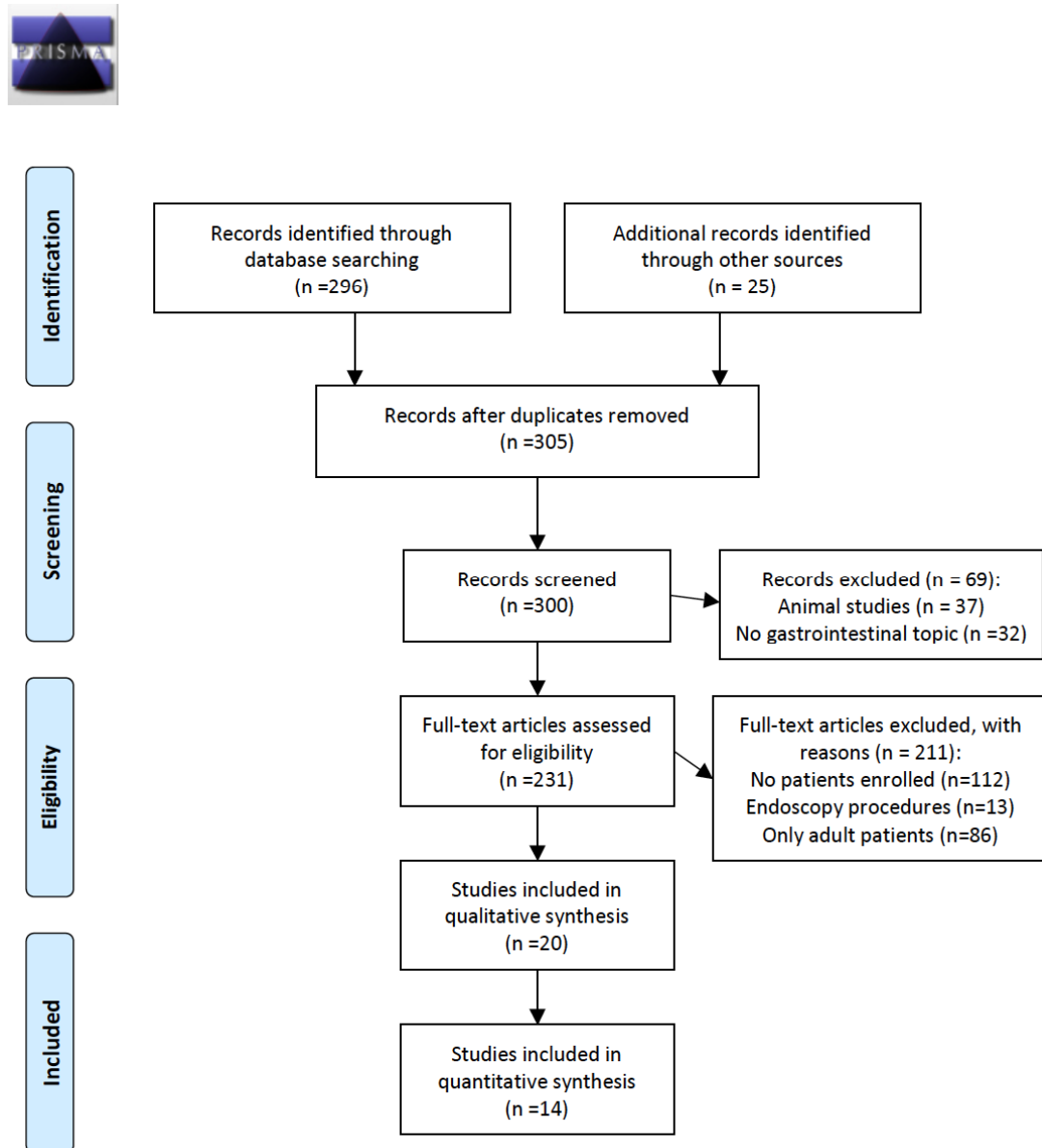


Figure 1: Flow Diagram of Study Selection.

20 pediatric articles that met the inclusion criteria and were analyzed for the systematic review: 3 were case reports [11-13], 3 included Chinese children (14, 20 and 731 COVID-19 patients) but the occurrence rate of GI symptoms was not available [14-16], one described a combined population of adult and pediatric patients [17] and 13 were case series or selected pediatric population (range 2-291 children) (Table 1) [4, 18-29].

Diarrhea was reported in 0-50% of cases (median 13%) and vomit in 5-67% (median 8%), with the highest prevalence in small case series (2 and 6 patients); abdominal pain occurred in 1 out of 3 children in one study [19] and in 17 out of 291 (5.8%) US children [4] (Figure 2). Pooled prevalence of different GI symptoms (diarrhea, vomit and abdominal pain) from included pediatric studies are represented, as Forest plot, in Figure 3, Figure 4 and Figure 5.

The pooled estimate risk of diarrhea calculated according to the random effect model was 0.115 (CI 0.074-0.155; $p < 0.001$), with moderate heterogeneity among studies ($I^2 \% = 49.84$; $Q = 18.630$). Furthermore, the pooled estimate risk of vomit was 0.086 (CI 0.056-0.116; $p < 0.001$), with low heterogeneity among studies ($I^2 \% = 22.53$; $Q = 14.643$). Finally, the pooled estimate risk of abdominal pain was 0.061 (CI 0.038-0.085; $p < 0.001$), with low heterogeneity among studies ($I^2 \% = 0$; $Q = 1.148$).

COVID-19 affects all ages and vomiting or diarrhea may represent the primary clinical manifestation [12, 13, 15, 29]. In one neonate 17-day-old severe vomiting and intravenous rehydration was necessary [13]. One children 13 month old developed vomiting and diarrhea six days before a severe pneumonia, requiring mechanical ventilation, complicated by shock with metabolic acidosis and kidney failure [12]. In another

Table 1: Summary of the Included Studies Reporting Prevalence of Gastrointestinal Symptoms in Children from China, Italy, Spain and US, with Diagnosed COVID-19 from JANUARY 2020 to April 2020

GI Symptoms	Prevalence of Symptoms	Population (No. of children)	Age Range	Country	Source
Diarrhea Vomit Poor feeding Abdominal pain	22.4% 10.4% 23.3% 6.9%	116	0 mo – 17.8 y	Italy	This report
Diarrhea	50%	2	2-5 mo	Italy	Donà D, et al. ¹⁸
Abdominal pain and diarrhea	33.3%	3	1.5, 5, 6 y	China	Xing JH, et al. ¹⁹
Vomiting	66.7%	6	1y-7y	China	Liu W, et al. ²⁰
Diarrhea	22.2%	9	1y-10y	China	Shen Q, et al. ²¹
Diarrhea	0%	10	3-131mo	China	Cai J, et al. ²²
Diarrhea	30%	10	2mo-15y	China	Xu Y, et al. ²³
Diarrhea Vomiting	15% 10%	20	1d-14.7y	China	Xia W, et al. ²⁴
Diarrhea Vomiting	8.8% 6.4%	28	1mo-17 y	China	Shen and Yang. ²⁵
Diarrhea Vomiting	9.6% 6.5%	31	6mo-17y	China	Wang D, et al. ²⁶
Gastroenteritis or vomiting	5%	41	0-15 y	Spain	Tagarro A, et al. ²⁷
Diarrhea	35.6%	73 patients (children and adult)	10mo-78y	China	Xiao F, et al. ¹⁷
Not specified GI symptoms	12%	9 case series (93 children)	1d-17 y	China	Chang TH, ²⁸
Diarrhea	8.8%	171	1d-15 y	China	Lu X, et al. ²⁹
Diarrhea Nausea/vomiting Abdominal pain	13% 11% 5.8%	291	<18 y	US	CDC COVID-19 Response Team. ⁴

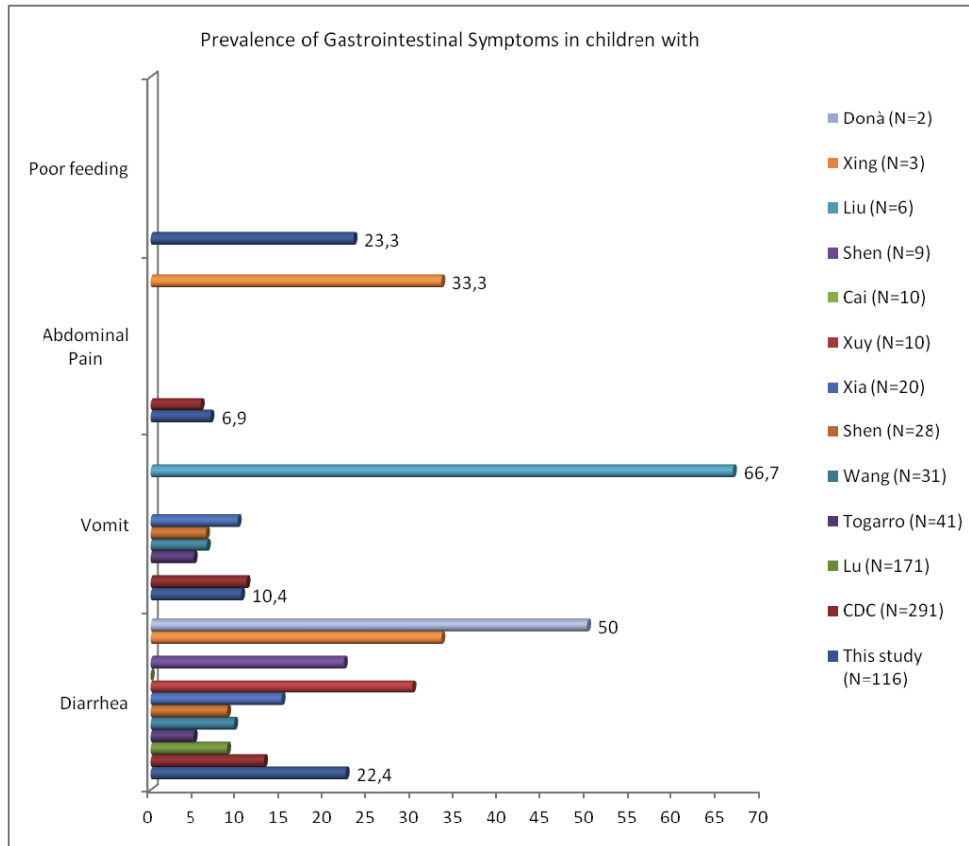


Figure 2: Summary of the reported prevalence of gastrointestinal symptoms in studies including children COVID-19. The numbers represent the maximal prevalence reported for each gastrointestinal symptom in previous studies and the rate in the Italian cohort.

Chinese case series of 31 children, 3 cases had diarrhea as the first symptom and one had vomiting with no fever or cough [26].

Remarkably, in one study 8 children had positive rectal swabs for SARS-CoV-2, even after negative nasopharyngeal test, suggesting viral shedding through

GI tract [23]. Two Italian infants tested positive for rectal swab despite only one presented diarrhea [18].

Italian Pediatric Population from Lombardy Region

Among 116 children (median age 1.7 years, range 0-17.8 months, 75 male, 52 < 12 months) who resulted

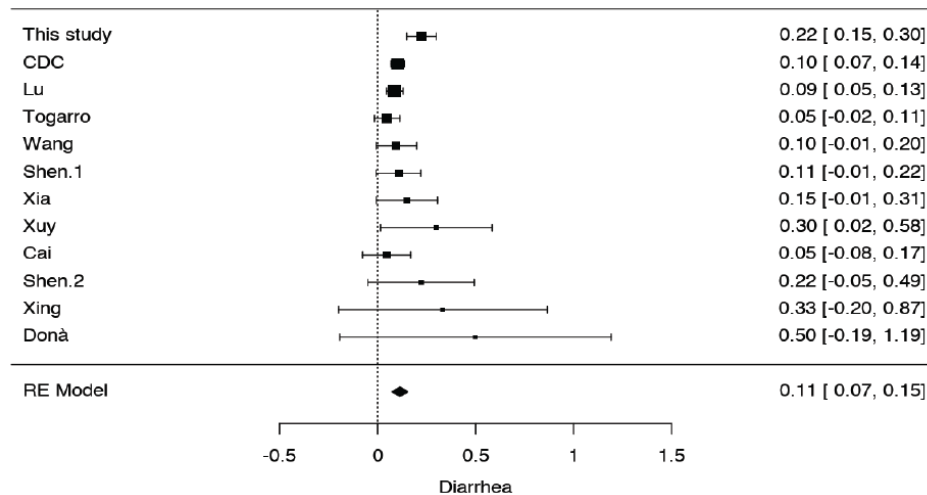


Figure 3: Pooled prevalence of Diarrhea in COVID-19 children (all studies).

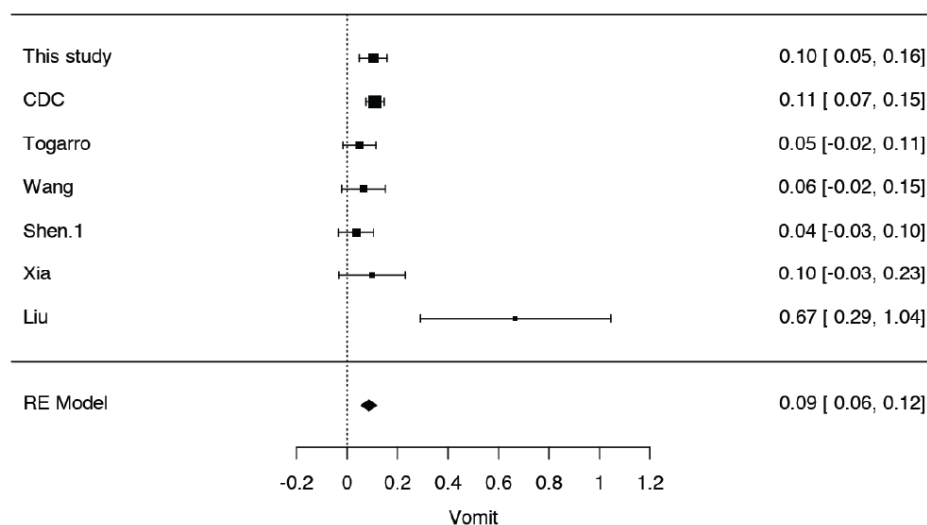


Figure 4: Pooled prevalence of Vomit in COVID-19 children (all studies).

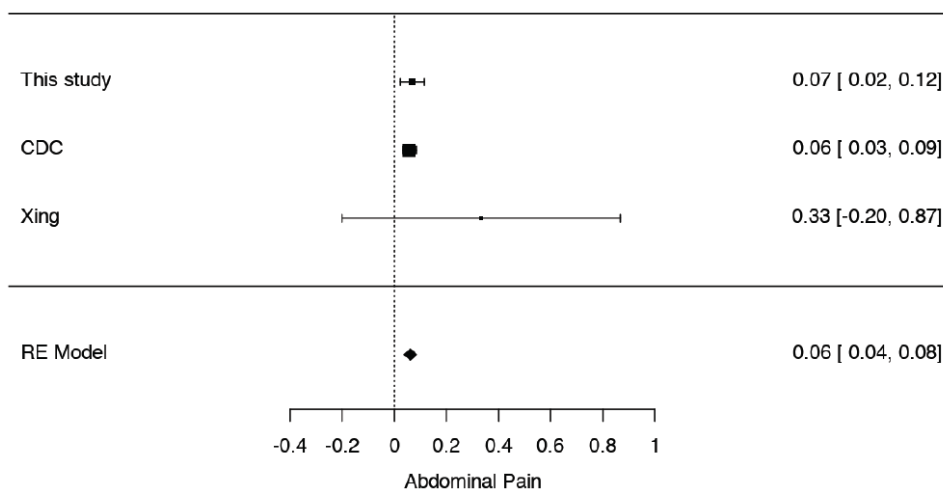


Figure 5: Pooled prevalence of Abdominal Pain in COVID-19 children (all studies).

positive to SARS-CoV-2, 51 (44%) presented at least one GI symptom (Figure 6). Poor feeding was reported in 27 (23.3%) cases, diarrhea in 26 (22.4%), vomit in 12 (10.4%), abdominal pain in 8 (6.9%) (Table 1). Among 51 patients with GI manifestations, 18 (35.3%) children also presented respiratory symptoms and 5 (9.8%) children were admitted to Intensive Care Unit (one child with kidney failure and one with liver injury).

In 29 children (25% of the total children and 57% of the GI group), GI symptoms were the first clinical presentation. Median duration of diarrhea was 2.29 days (range 1 to 5 days). Stool testes resulted negative for common bacteria and viruses.

Antibiotic treatment was used in 46 (39.7%) children and in 14 (30%) of them diarrhea was reported.

Pre-existing health conditions were present in 9 children with GI symptoms (7.8% of the total children and 18% of the ones with GI group) and included 3 patients with chronic heart disease, 2 patients with chronic GI conditions (one with inflammatory bowel disease), 3 obese children and 1 child with neuropsychiatric condition.

DISCUSSION

To the best of our knowledge this is the first Systematic Review focused on the GI characteristics of COVID-19 in children. From the literature search including data from China, Italy, Spain and US, emerged that only a minority of studies assessed gastrointestinal symptoms in children in the early phase of pandemic. Despite most of the studies showed

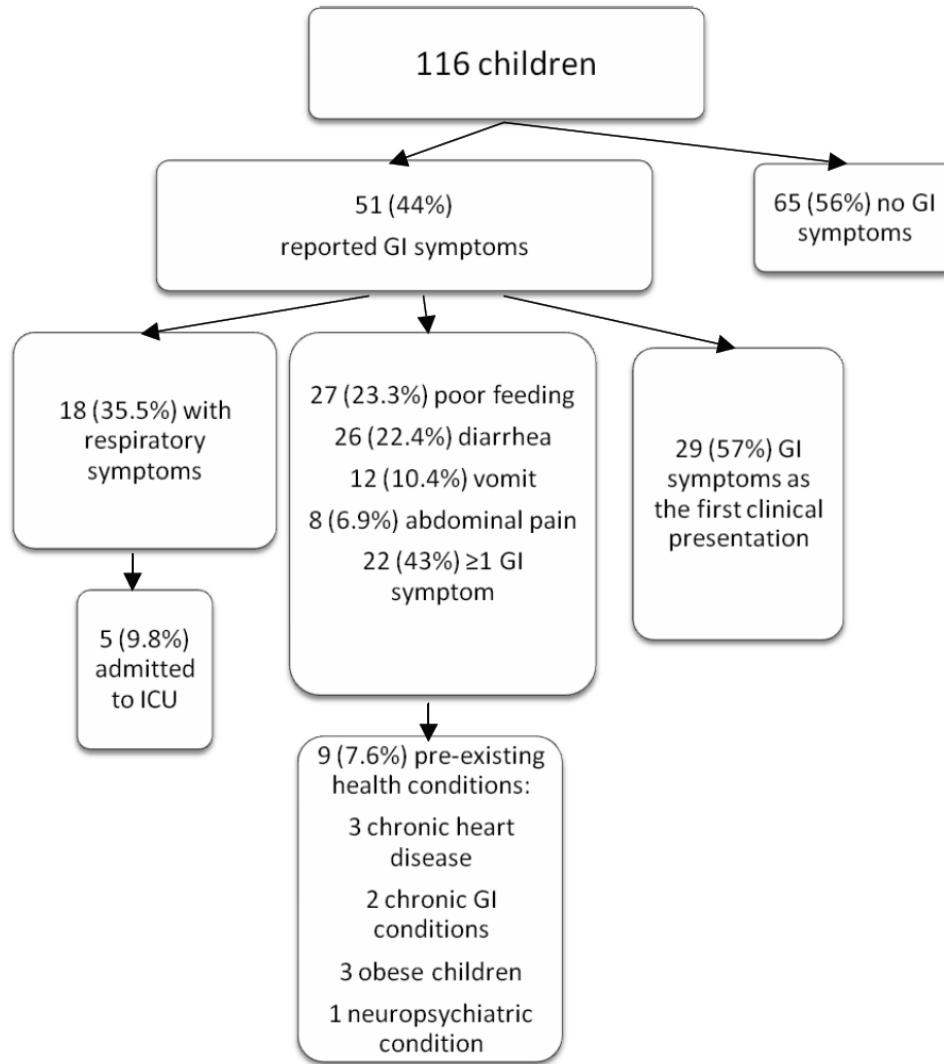


Figure 6: Flow diagram of the enrolled Italian cohort, from Lombardy Region, positive to SARS-CoV-2.

partial or incomplete report of GI manifestations, diarrhea accounted for 0-50%, vomit 5-67% and abdominal pain 5.8-33.3% of infected children. Nonetheless, in some patients, gastrointestinal symptoms may represent the sole feature of COVID-19. In our cohort of children from Lombardy Region, with proven infection of SARS-CoV-2 during the first two months of Italian endemic spread, gastrointestinal symptoms occurred in nearly half (51/116, 44%) of enrolled children. In particular, poor feeding and diarrhea were the two most frequent GI presentation, affecting 23% and 22% of cases, whilst vomit and abdominal pain were reported, respectively, in 10% and 6.9% of patients. Noteworthy, respiratory symptoms were present in slightly more than one third (35%) of children and GI symptoms were the first clinical manifestation of COVID-19 in one fourth (25%) of all patients.

In pediatric patients clinical presentation of COVID-19 varies in severity from asymptomatic, frequent mild illness, few severe cases and extremely rare fatality [2-4].

In our population diarrhea lasted one to five days, was not related to other GI pathogen and was present in 30% of concomitant antibiotic treatment. Among children with GI manifestations and associated respiratory symptoms, 9.8% children were admitted to Intensive Care Unit, no death was reported. Only a minority of reports investigated and partially described GI symptoms in pediatric patients, [4, 11-13, 18-27, 29]. The prevalence of diarrhea ranged from 0% to 50% in small case series [18-27] and from 8.8% to 13% in the two largest American and Chinese studies [4, 29].

Vomiting was present in 4 out of 6 children in one report [20], in 5-10% of children in small case series [24-27] and in 11% of American children with COVID-19 [4]. Abdominal pain was quantified as 5.8% in the US report [4] and in one out of 3 Chinese children [19]. In three pediatric case series from China, vomiting, nausea and diarrhea were reported but the prevalence rate was not specified [14-16].

Our population showed a rate of vomit and abdominal pain similar to American children, but a higher prevalence of diarrhea, that could be related to the high proportion of infants (45% of cases), who also accounted for the frequency of poor feeding, and to the frequent (40% of cases) use of antibiotics.

In adult population with COVID-19, gastrointestinal symptoms have been also documented in a wide range of 1.7-79% [3, 5-10].

According to the report of the European Center for Disease Prevention and Control, diarrhea was present only in 1.7% and unspecified pain in 6.9% out of 100233 European cases in which information on symptoms was available. Children made a very small proportion (5%) of total positive cases, were less hospitalized (15% <19 years) and expressed less severe illness (<1%). Unfortunately, a subgroup analysis of GI symptoms according to age was not available [3].

In a recent review of a mixed Chinese population of 2023 patients (adult and children): anorexia was the most frequently reported digestive symptom (39.9-50.2% of cases), diarrhea showed a range of 2-49.5%, vomiting was more common in children than in adult patients (6.5-66.7% vs. 3.6-15.9%), nausea accounted for 1-29.4%, and abdominal pain for 2.2%-6.0% [8]. Few reports presented diarrhea and vomiting without respiratory symptoms or other manifestation of COVID-19 [8].

Elevated aminotransferases were also frequently identified, especially in those with severe COVID -19 [5-10, 30].

There are contradictory results on the association of GI symptoms with disease severity in adult patients and insufficient data in children [8]. In one report of adult cases of COVID-19 nausea, vomiting and diarrhea were associated with longer disease but lower trend of admission rate to Intensive Care Unit and lower mortality [7]. Conversely, abdominal pain was more frequently reported in severely ill cases [8, 30].

Erosive esophagitis and round ulcers have been documented in few severely ill adult patients with COVID-19 submitted to endoscopy because of coffee ground vomiting or gastric contents in the gastric drainage tube or positive fecal occult blood. SARS-CoV-2 RNA was detected in the esophagus, as well as in the stomach, duodenum and rectum [31, 32]. Among 73 adult and pediatric patients, 10 (13.7%) had GI bleeding but the age of all patients was not specified [13]. In esophageal biopsies, occasional lymphocytes were found in esophageal epithelium. Numerous infiltrating plasma cells and lymphocytes with interstitial edema were seen in the mucosa of stomach, duodenum and rectum [17].

In our population, 5 (9.8%) children, with concomitant GI and respiratory symptoms, were admitted to Intensive Care Unit, but none reported GI hemorrhage and no death occurred.

Gastrointestinal symptoms may derive from a combination of direct cytopathic effect of the virus, interaction with ACE2 receptors, inflammatory cytokine storms, and adverse effect of COVID-19 treatments. Compared to adults, children are less likely to have severe symptoms of COVID-19. Nonetheless, GI presentation of COVID-19 is frequent, is indistinguishable from that of other viral infections or other conditions, may contribute to critical evolution, and may increase the risk of viral transmission.

Single-cell transcriptom analysis showed ACE2, the entry receptor for SARS-CoV-2, highly expressed in the respiratory tract, and other organs, in the esophageal epithelium, in stomach, small bowel enterocytes and in the colon [33].

In a cohort from Hong Kong and Systematic Review of adult literature, SARS-CoV-2 RNA has been detected in feces in 48% of patients (95% CI, 38.3%-57.9%) even in absence of diarrhea and of positive respiratory samples [10]. In one study 8 children had positive rectal swabs for SARS-CoV-2, persisting after negative nasopharyngeal swabs [23]. Two Italian infants tested positive for rectal swab despite only one presented diarrhea. The authors suggested that surveillance with rectal tests might be extended to infants and children, for the implications for household contacts and isolation timing [18]. Prolonged RT PCR positivity in the stool has raised the possibility of fecal-oral transmission. However, the viability and infection potential is uncertain and rectal swabs for SARS-CoV-2 have been rarely performed in children. It is also too early to know how long post-infective GI infection and

inflammation will last, as this will require focused longitudinal studies over an extended period of time.

Considering the variety of COVID-19 presentation and the risk of contagiousness by aerosol generation, dispersion of viral particles and the feces, elective endoscopic investigations should be postponed during the epidemic period. However, as severe GI symptoms or bleeding may necessitate urgent endoscopy, staff members should follow standard operating measures for COVID-19 prevention and control regardless of patient risk stratification. Detailed guidelines for adult and pediatric endoscopic procedures have been published [34, 35].

Patients with inflammatory bowel disease (IBD) or chronic liver disease and post liver transplant children have not been reported as at increased risk of SARS-CoV-2 infection or complications and should continue their current medications and clinical monitoring [36, 37]. According to a electronic survey distributed in March among Pediatric Tertiary IBD Centers across Canada, China, Europe, Israel, and South Korea, eight IBD children reported COVID-19 (6 confirmed and 2 suspected cases) globally, all with mild infection, no occurrence of GI symptoms and no need of hospitalization despite treatment with immunomodulators and/or biologics [38]. In our cohort, only one child was an IBD patient with a household contact and had no complications.

Limitations of our study mainly include the incomplete report of GI manifestations in children with COVID-19. At present, the exact prevalence of SARS-CoV-2 infection in pediatric patients is unclear because only children with household contact or admitted to the hospital have been tested. Moreover, in many case series GI symptoms were not described. Besides, new cases are reported every week and this systematic review can provide only a partial figure of what is continuously evolving over the time. We also restricted the electronic search to English and Italian languages. However, we consider as strength of this report the extensive review of the literature search with the retrieval of Chinese and all other pediatric studies through extrapolation of the clinical data from narrative reviews and pooled analysis. In addition, the reference lists of all identified articles were manually examined to identify possible further studies of interest. Finally, the inclusion of an Italian pediatric population from a high epidemic area, provided new and detailed GI information. We also tried to interpret our results considering adult findings and suggested explanation.

Our results highlight the clinical significance of proper identification of GI symptoms in children with COVID-19. First, GI symptoms may be the first and sole manifestations of COVID-19. Second, particularly in infants and young children dehydration due to diarrhea and vomiting may aggravate the clinical status of the patient. Next, fecal shedding and transmission may occur and persist longer than in the respiratory tract and pharyngeal swabs. Finally, in case of endoscopic indications, protective measures and transmission-based precautions must be applied. Therefore, we strongly recommend that testing for SARS-CoV-2 should be performed routinely in children with GI manifestation regardless the presence of fever, severity of symptoms and respiratory involvements.

CONCLUSION

Only a minority of studies fully assessed gastrointestinal symptoms in children with SARS-CoV-2 infections. Data from China, Italy, Spain and US showed diarrhea and vomit as the most commonly reported GI symptoms but varied between null to two third of cases.

Diarrhea, vomiting, poor appetite and abdominal pain can precede, being unique or associated with other manifestations of SARS-CoV-2 and should be carefully considered by health care providers for a proper clinical management and risk of viral transmission. At present, prognostic role of GI involvement and long term gut consequences of COVID-19 are unknown.

STATEMENT OF FINANCIAL SUPPORT

No financial support from extramural sources.

DISCLOSURE STATEMENT

No conflicts of interest for all authors.

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Received on 6-10-2020

Accepted on 05-01-2021

Published on 11-03-2021

DOI: <https://doi.org/10.12974/2311-8687.2021.09.1>

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