Gastrointestinal symptoms and fecal nucleic acid testing of children with coronavirus disease 2019: a systematic review and meta-analysis

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Abstract

**Objective:** To understand the clinical manifestations and incidence of gastrointestinal symptoms of Coronavirus disease (COVID-19) in children and discuss the importance of fecal nucleic acid testing.

**Methods:** Retrospective analysis of studies of gastrointestinal symptoms and fecal nucleic acid detection in pediatric COVID-19 since the outbreak of COVID-19, as well as prospective clinical studies and case reports to understand the clinical characteristics of gastrointestinal symptoms and feces in children. Nucleic acid detection results were also analyzed.

**Results:** 1. The clinical manifestations of gastrointestinal symptoms in children with COVID-19 are mostly vomiting and diarrhea, with a total incidence rate of 21.1% (95% CI = 0.14-0.28). 2. When analyzing by country (studies from China versus studies from other countries), the pooled prevalence of gastrointestinal symptoms in studies from countries other than China was much lower at 18.2% (95% CI 0.05 to 0.31). This is in comparison to studies from China where the prevalence was higher: 23.3% (95% CI 0.153 to 0.310). 3. In Wuhan patients, the pooled prevalence was much higher at 41.2% (95% CI 0.147 to 0.678) as compared to areas outside Wuhan, China (15.1% (95% CI 0.075 to 0.227)). 4. Fecal nucleic acid detection is as accurate as respiratory specimen nucleic acid detection. The positive rate of fecal nucleic acid testing in COVID-19 patients was 92.5% (25/27). In patients where nucleic acid tests of respiratory tract specimens produced negative results, a positive fecal nucleic acid test result was present in 83.3% (20/24); one week after the respiratory tract specimen was nucleic acid-negative, 54.1% (13/24) were fecal nucleic acid-positive; two weeks after the respiratory tract nucleic acid negative test, 37.5% (9/24) were fecal nucleic acid-positive. The longest interval between a negative respiratory system result and positive fecal specimen result exceeded 19 days.

**Conclusions and Relevance:** Gastrointestinal symptoms in pediatric COVID-19 are relatively common. Attention should be paid to the detection of fecal nucleic acids in children. Fecal nucleic acid-negative status should be considered as one of the desegregation standards.

Introduction

Currently, coronavirus disease (COVID-19) is a global pandemic. There are a large number of reports of cases across the world. It mainly infects in the middle-aged and elderly, and the mortality rate is the highest in patients with comorbid diseases. Therefore, it was believed that children were not easily infected during the early stages of the pandemic. However, with the development of the pandemic, pediatric cases of COVID-19 began to emerge and even severe cases gradually appeared; therefore, people began to pay attention to the pandemic in children. The main clinical manifestations of COVID-19 are fever, dry cough, and fatigue. A small number of patients will have nasal obstruction, runny nose, pharyngalgia, muscle pain, and other symptoms. However, patients attending the clinic are often diagnosed with an upper respiratory tract infection based on their manifestation. Children with gastrointestinal symptoms as the first symptom or with gastrointestinal symptoms are not typical. The
detection of viral nucleic acid in respiratory tract specimens is a typical focus when treating children attending the clinic, while fecal nucleic acid detection is often neglected. Therefore, children with gastrointestinal symptoms as the main manifestation are often misdiagnosed. Currently, there are no large prospective double-blind controlled studies on COVID-19 gastrointestinal symptoms and fecal nucleic acid detection in children. Therefore, this study summarizes gastrointestinal symptoms and fecal nucleic acid detection in children with COVID-19.

Methods

Inclusion and exclusion criteria

Inclusion criteria: Studies of COVID-19 in children (<18 years old) published in English or Chinese between the outbreak and 15 May, 2020, referring to gastrointestinal symptoms and fecal nucleic acid testing. Without limitations to gender, race, and region.

Exclusion criteria: 1. adult studies; 2. studies in children that do not mention digestive system symptoms and fecal nucleic acid tests. 3. There may be overlapping studies of data.

Literature retrieval

The present systematic review focused on MS epidemiology in Iran based on PRISMA guidelines (S1 File). We searched the PubMed, Embase, Johns Hopkins Uni, CNKI, Wanfang, and data collected by the World Health Organization and the National Health Committee of the People's Republic of China. We conducted extensive manual searches of the reference lists of papers and reports. The following sequence of search was performed in PubMed: #1, (((covid-19) or 2019-ncov) or SARS-cov-2) or new coronavirus) or novel coronavirus; #2, ((clinical manifestation) or epidemiology) or gastrointestinal symptoms; and #1 and #2 combined. For the Chinese databases, we searched for "new coronavirus," "gastrointestinal symptoms," "epidemiology," "clinical manifestations," "feces," and "children".

Data extraction

The quality of the studies was evaluated by two reviewers, and a third researcher assessed the study in case of a difference in opinion. The following data were extracted: name of the first author, Date, Region, Total patients, Number of gastrointestinal symptoms (%), Age of patients average/median (range), Frequency of diarrhea, Disease severity of patients with GI symptoms, Patients with GI symptoms but no respiratory symptoms, The respiratory tract PCR test was negative while the stool test was positive, Time Differences between negative PCR test in stool and negative PCR test in respiratory specimens (d). Refer to the quality evaluation criteria for cross-sectional studies recommended by the United States Agency for Health Care and Research (AHRG). There are 11 items in total, with a total score of 1 ~ 11 points. The quality level of the survey will be determined according to the score.

Statistical analysis
Stata 15 performed a meta-analysis of the prevalence of gastrointestinal tract in patients. The prevalence is expressed in terms of proportion and 95% confidence interval. $I^2$ and Q tests were used to assess inter-study heterogeneity. If $I^2$ is less than 50% and $P > 0$ of Q test is 0.05, the fixed effect model is adopted; otherwise, the random effect model is adopted. In order to explore heterogeneity, we performed subgroup analysis by region of study.

**Ethics**

As this is a systematic review, ethical approval is not required.

**Results**

**Gastrointestinal symptoms in COVID-19**

Figure 1 summarizes article retrieval and abstraction using PRISMA guidelines. Most research data are concentrated in articles published by the Chinese. A total of 25 studies were included in the analysis,\(^8^{30}^{50-51}\) 18 of which described the gastrointestinal symptoms of patients (Table 1), including one by the Centers for Disease Control and Prevention (CDC)\(^8\) in the United States and one in Italian\(^50\), one in Spain.\(^20\) A total of 843 patients were included in the study, 182 of whom had digestive tract symptoms, accounting for 21.1% (95% CI = 0.14-0.28) of patients. See Figure 2. In the US, the CDC\(^8\) collected 149,082 reported cases of COVID-19 from February 2, 2020, to April 2, 2020, with a total incidence of 2572 cases under 18 years old; 291 exhibited symptoms and physical signs including: nausea and vomiting, 31 (11%); abdominal pain, 17 (5.8%); and diarrhea, 37 (13%). Out of 41 patients in Spain, two had gastroenteritis or vomiting 2 (5%). Out of 168 patients in Italian, Diarrhoea 22 (13.1%), Vomiting 9 (5.44%).

When analyzing by country (studies from China versus studies from other countries), the pooled prevalence of diarrhea in studies from countries other than China was much lower at 18.2% (95% CI 0.05 to 0.31). This is in comparison to studies from China where the prevalence was higher: 23.3% (95% CI 0.15 to 0.31). See Figure 3. In Wuhan patients, across 4 studies\(^9,^{11,^{12,^{18}}\) including 205 patients, the pooled prevalence was much higher at 41.2% (95% CI 0.15 to 0.68) as compared to areas outside Wuhan of China\(^15\) (15.1% (95% CI 0.075 to 0.227)) See Figure 4. There are two studies\(^9,^{18}\) from Wuhan Children's Hospital and the data may overlap. However, Sun D\(^18\) described severe cases of COVID-19; therefore, their study was analyzed separately. Of the eight children who required treatment in the pediatric intensive care unit, four had nausea and vomiting (50%), three had diarrhea, one had constipation, and two had diarrhea and vomiting. Among them, seven hospitalized patients had recovered and had been discharged by the time of publication. The highest incidence of vomiting was found in six children hospitalized in Wuhan Children’s Hospital from 2020/1/7 to 2020/1/15, among whom, four had vomiting (66.7%). Han YN in Xi’an, China\(^15\) included seven patients in their study, four of whom (57.1%) had diarrhea or vomiting; however, the number of cases was too small to be conclusive. Other reports come from six provinces in north China (Shaanxi, Gansu, Ningxia, Hebei, Henan, and Shandong).\(^10\) In the Zhejiang province of
China,\textsuperscript{13} Changsha city,\textsuperscript{14} Guangdong province,\textsuperscript{17,19} and Jiangxi province,\textsuperscript{21} the incidence of gastrointestinal symptoms was between 8.6\% and 22\%.

Most studies did not describe the stool characteristics or number of bowel movements. Wang Duan et al.\textsuperscript{10} reported that in the six northern provinces, patients had bowel movements 2–6 times per day, while Wu Huaping in Jiangxi province in China\textsuperscript{21} found that the frequency of diarrhea in affected children was 3–4 times per day.

**Fecal testing for viral nucleic acid**

Fecal nucleic acid testing cannot be ignored. A 35-year-old male patient with COVID-19 was reported for the first time in the US. He was admitted to the hospital with fever and cough as his main complaints. After being admitted to the hospital, the patient developed dysentery and abdominal discomfort. The fecal samples were collected for nucleic acid testing and it was found that the samples were positive for viral nucleic acid.\textsuperscript{31} In January, China reported a case of COVID-19 in a newborn, with gastrointestinal symptoms as the initial manifestation.\textsuperscript{32} Nine reports included in the present study described fecal nucleic acid examination (Table 2), including one from South Korea\textsuperscript{22} and the rest from China. Two were prospective studies\textsuperscript{19,25} and the rest were case studies. In total, 31 people were included in the study (four patients\textsuperscript{25} did not undergo fecal nucleic acid testing; see Table 2 for detailed data). Among the 26 patients confirmed using nucleic acid testing of throat swabs, 24 (92.3\%) were positive for fecal nucleic acid. Of those, 20 (83.3\%) remained fecal nucleic acid-positive after the nucleic acid testing of the respiratory tract specimens was negative. One week after the nucleic acid of respiratory tract specimens became negative, there were still 13 patients (54.4\%) who were fecal nucleic acid-positive; two weeks after the respiratory tract nucleic acid negative, 37.5\% (9/24) of cases were fecal nucleic acid-positive. The longest interval between the respiratory nucleic acid becoming negative and a positive fecal nucleic acid test was more than 19 days. However, in a study of three neonates,\textsuperscript{23} respiratory tract and fecal nucleic acid tests were positive 2 and 4 days after birth, respectively, and the fecal and respiratory tract specimens were negative on the 6th day. An infant with a mild SARS-CoV-2 infection detected only by anal swabs, throat swabs were persistently negative throughout the hospital stay.\textsuperscript{51}

**Publication bias**

The funnel plot Figure 5 shows the presence of possible publication bias. The overall certainty in the body of evidence was low. Our confidence in the pooled estimates of prevalence was reduced because of concerns of risk of bias (selection bias, detection bias and attrition bias), heterogeneity of the tested patient populations (inconsistency), as well as issues of indirectness (the majority of studies included primarily symptomatic hospitalized patients instead of all patients with COVID-19). Additionally, most of the studies were retrospective cohort series and did not specify if consecutive patients were included in the analysis. These factors may have contributed to the heterogeneity of findings across studies. The $I^2$ statistic ranged from 29.1\% to 90.7\%.
Discussion

1. Incidence of gastrointestinal symptoms

In the early stages of the pandemic, there was a shared misconception that children were not easily infected. With the spread of the pandemic, the number of infected children is increasing and there are many severe pediatric cases. It is sometimes difficult to distinguish the gastrointestinal symptoms of pediatric COVID-19 from those caused by another viral illness, side effects caused by drug use, and digestive tract symptoms such as nausea and diarrhea caused by gastrointestinal flora disturbance caused by the fever itself. Some studies have found that 20.4% of children use antibiotics, which cause associated diarrhea, and the younger the patients with lower respiratory tract infection treated with intravenous antibiotics, the more severe their diarrhea is. However, this study found that the total incidence of gastrointestinal symptoms in children with COVID-19 was 21.5%; unfortunately, however, all studies did not describe a control group regarding the incidence of gastrointestinal symptoms between an antibiotic treatment group and non-antibiotic treatment group. In a meta-analysis (mainly adult studies), 60 studies (including 4,243 patients with COVID-19) were analyzed and the incidence of gastrointestinal symptoms was found to be 17.6%. Compared with the incidence rate of clinical manifestations of gastrointestinal tract symptoms in adults, the incidence rate in children is relatively higher, which may be because the intestinal flora of children is infected and can easily cause flora disorder. This study found that the incidence of gastrointestinal symptoms in children in China was higher than that in countries outside China (23.0% and 18.2%), while the incidence of gastrointestinal symptoms in Wuhan was higher than that outside Wuhan China (41.2% and 15.1%). In a systematic review, 43 studies including 10,676 COVID-19 patients (confirmed by laboratory RT[1]PCR testing), the overall analysis The pooled prevalence of diarrhea symptoms across these studies was 7.7% (95% CI 7.2 to 8.2). When analyzing by country (studies from China versus studies from other countries), the pooled prevalence of diarrhea in studies from countries other than China was much higher at 18.3% (95% CI 16.6 to 20.1). This is in comparison to studies from China where the prevalence was much lower: 5.8% (95% CI 5.3 to 6.4)

2. Pathogenesis of COVID-19

Regarding the mechanism of infection of the severe acute respiratory syndrome severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is currently believed that the major determinant of SARS-CoV-2 infection is S protein, which binds to membrane receptors on host cells and mediates the fusion of viruses and cell membranes. Angiotensin converting enzyme 2 (ACE2) is a homolog of ACE and one of the important receptors on the cell membrane of host cells. The interaction between the S protein and ACE2 promotes the invasion of host cells by SARS-CoV-2. The structure of the SARS-CoV-2 S protein is highly similar to that of the SARS coronavirus (SARS-CoV) S protein; SARS-CoV-2 S protein binds to ACE2 with higher affinity than the SARS-CoV S protein, indicating that SARS-CoV-2 has stronger invasion ability. ACE2 can control intestinal inflammation and diarrhea, and the interaction between SARS-CoV-2
and ACE2 may lead to diarrhea.\textsuperscript{37-38} ACE2 is highly expressed in the small intestine, especially in the proximal and distal intestinal epithelial cells, so the small intestine is more vulnerable to SARS-CoV-2 infection. Previous investigations may have underestimated the incidence of diarrhea among those infected with SARS-CoV-2. Further research is needed to determine whether diarrhea can provide value for the diagnosis of SARS-CoV-2. Regarding the Middle East Respiratory Syndrome coronavirus (MERS-CoV), which is highly homologous to SARS-CoV-2, it is believed that the intestinal tract is another route of infection and the incidence rate of diarrhea is 20–25\%.

3. Pathological examination

At present, there has been no endoscopic and pathologic study of the digestive tract in pediatric COVID-19. However, a study in adults found that\textsuperscript{42} there is no obvious damage to the mucosal epithelium of the esophagus, stomach, duodenum, and rectum. In the inherent layers of the stomach, duodenum, and rectum, a large number of infiltrating plasma cells and lymphocytes were seen, accompanied by interstitial edema. ACE2, the virus host receptor, is mainly found in the cytoplasm of gastrointestinal epithelial cells and virus nucleocapsid proteins were found in the cytoplasm of duodenal and rectal glandular epithelial cells.

4. Positive rate and significance of fecal nucleic acids

In a recent study\textsuperscript{42} of 73 hospitalized adult patients in China, the feces of 53.42\% of the patients were positive for viral RNA, the duration of fecal positive results ranged from 1 to 12 days, and 23.29\% of the patients were still fecal nucleic acid-positive after being confirmed respiratory nucleic acid-negative. Of the 59 patients with COVID-19 in Hong Kong,\textsuperscript{40} 15 (25.4\%) had gastrointestinal symptoms and nine (15.3\%) had positive stool viral RNA test results. The detection rates of fecal viral RNA were 38.5\% and 8.7\% in people with and without diarrhea, respectively. The analysis of data collected in this study found that the positive rate of fecal nucleic acid in children with COVID-19 was 92.3\% and the rate of fecal nucleic acid-positive children was much higher than that of adults. We do not attach importance to the detection of nucleic acid in children's feces, which is mainly based on the detection of respiratory tract nucleic acid samples. In the early stage of China's epidemic, the discharge standard was reached with two negative respiratory samples (at least 24 h apart) and there are many cases of re-positivity after discharge;\textsuperscript{43} however, it is not known whether it is related to the absence of a stool nucleic acid test at the time of discharge. The positive rate of fecal nucleic acid in COVID-19 patients was 92.3\% (24/26). After the test for nucleic acids in the respiratory tract specimen produced a negative result, 83.3\% (20/24) were fecal nucleic acid-positive; one week after the respiratory tract nucleic acid negative, the fecal nucleic acid positive accounted for 54.4\% (13/24). The longest time between a negative respiratory tract nucleic acid test and positive respiratory tract nucleic acid test exceeded 19 days. Therefore, fecal nucleic acid detection should be used as an indicator of discharge from the hospital.

In a recent report detailing from January 16, 2020 to February 8, 2020, China CDC reported 2,135 pediatric COVID-19 patients (including confirmed and suspected cases), 94 of whom were asymptomatic (4.4\%).\textsuperscript{44}
However, a recent study in New York\textsuperscript{45} reported that 29 (87.9\%) of 33 pregnant women who tested positive for SARS-CoV-2 on admission did not have symptoms of COVID-19 at the time of treatment. A Boston research team\textsuperscript{46} found that 1/6 of the 147 homeless people with COVID-19 had symptoms (fever, cough, shortness of breath, etc.), but 5/6 of the patients did not have any symptoms. The results of the two studies are similar. This is very worrying data, because it shows that there are more asymptomatic patients than symptomatic ones, so controlling asymptomatic patients is the key to controlling the pandemic. However, it remains unknown whether children in whom the symptoms have resolved, with respiratory tract specimens negative and stool samples positive for viral nucleic acids, are asymptomatic infectious sources. Therefore, it is necessary to recommend that after recovery and discharge, pediatric patients be isolated at home for more than 2 weeks.

5. Prognosis

In terms of prognosis, in the United States,\textsuperscript{47} a retrospective comparative study was carried out in patients over 18 years old. The experimental group included 278 patients with fever and cough with COVID-19, and the control group included 238 patients with fever and cough due to a common respiratory tract infection. The incidence of gastrointestinal symptoms in the two groups was 34.8\% and 26.4\%, respectively (P = 0.04).\textsuperscript{47} In the 278 patients with COVID-19, the course of gastrointestinal symptoms was longer, but the mortality rate and rate of severe disease were lower than in those without gastrointestinal symptoms. At present, there is no prognostic study of children with COVID-19.

6. Prevention and treatment

At present, there is no specific drug for COVID-19. Plasma therapy for convalescent patients is considered for those with severe disease;\textsuperscript{48} however, this treatment is controversial. For children with diarrhea, abdominal pain, nausea, vomiting, and other gastrointestinal symptoms, accompanied by low fever, attention should be paid to their epidemiological history and screening of suspected patients. Nucleic acid examination should be performed using throat swabs and anal tests. In daily life, the risk of transmission can be reduced through good hygiene practices, such as washing hands frequently, and closing the toilet lid when flushing.\textsuperscript{49}

7. Study limitations

The number of studies included in the meta-analysis was relatively small, with a relatively large proportion of case reports. Most studies did not report on the duration of the GI symptoms preceding the presentation. The number of patients included was relatively small and the description of the gastrointestinal tract of children in the included study was not sufficiently detailed. Therefore, it is necessary to conduct a large-scale double-blind randomized controlled study and include more research factors, such as stool frequency, stool characteristics, rate of patients with gastrointestinal symptoms and positive fecal nucleic acid test results, length of hospitalization of fecal nucleic acid-positive patients,
severity of illness, and interrelation between respiratory tract sample nucleic acid and stool nucleic acid findings.

8. Conclusions

Gastrointestinal symptoms in pediatric COVID-19 are relatively common. Attention should be paid to the detection of fecal nucleic acids in children. Especially in high-risk epidemic areas, all children with digestive tract symptoms as the first diagnosis were tested for fecal nucleic acid. Fecal nucleic acid-negative status should be considered as one of the discharge standards.

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Tables

Table 1 gastrointestinal manifestations of COVID-19 patients
| Author                   | Date                      | Region                  | Research type                  | Total patients | Number of gastrointestinal symptoms (%) | Age of patients average/median (range) | Frequency of diarrhe a | Disease severity of patients with GI symptoms | Patient s with GI symptoms but no respiratory symptoms |
|-------------------------|----------------------------|-------------------------|--------------------------------|----------------|-----------------------------------------|----------------------------------------|------------------------|-----------------------------------------------|---------------------------------------------------|
| US CDC[8]               | February -2 April          | US                      | Retrospective case series      | 291            | Nausea and vomiting 31(11 %)            | < 18 y                                 | NA                     | NA                                            | NA                                                |
|                         |                            |                         |                                |                | Abdominal pain                                 |                                        |                        | Diarrhea 37(13 %)                                         |                                                   |
| Xiao Xiaolu, et al. [9] | 28 January -26 February    | Wuhan Children's Hospital | Retrospective case series      | 171            | Diarrhea 15(8.8 %)                        | 1 d -16 y (average 6 y 7 mo)            | NA                     | NA                                            | NA                                                |
|                         |                            |                         |                                |                | Vomiting 11(6.4 %)                           |                                        |                        |                                               |                                                   |
| Wang Duan, et al. [10]  | 25 January -27 February    | Six Provinces in Northern China | Retrospective case series      | 31             | Diarrhea 3(10%)                           | 6 mo to 17 y (average 7 y 1 mo)         | 2-6 times /d,         | Mild                                          | NA                                                |
|                         |                            |                         |                                |                | Vomiting 2(6.4 %)                           |                                        |                        |                                               |                                                   |
| Liu W[11]               | January                   | Wuhan Children's       | Retrospective                  | 6              | 4 vomited                                 | 1-7 y (average 6 y 7 mo)                | NA                     | One person                                    | NA                                                |
|                         |                            | Hospital                |                                |                |                                        |                                        |                        |                                               |                                                   |
| Name     | Animal | Location                                           | Case Series Type           | No. of Cases | Main Symptoms | Age | Condition | Location |
|----------|--------|---------------------------------------------------|----------------------------|--------------|---------------|-----|-----------|----------|
| Xia W[12]| -15Jan | Hospital                                          | Retrospective case series  | 20           | Diarrhea 3    | 1d-14y7mo | NA        | NA       |
|          | -8Feb  | Maternal and Child Health Hospital                |                            |              | Vomiting 2    | (10%)     |           |          |
|          | uary    |                                                   |                            |              |               |           |           |          |
| Qiu H[13]| 17Jan   | Hubei Maternal and Child Health Hospital          | Retrospective case series  | 36           | Vomiting and diarrhea 2 | 0-16y (average 7y1mo) | NA | Ordinary | NA       |
|          | uary    |                                                   |                            |              |               |           |           |          |
| Shen Q[14]| 8Jan | Zhejiang, China                                   | Retrospective case series  | 9            | Diarrhea 2    | 1-12y     | NA        | Ordinary | NA       |
|          | uary    |                                                   |                            |              |               |           |           |          |
| Han YN[15]| 31Jan | Zhejiang, China                                   | Retrospective case series  | 7            | Diarrhea or vomiting 4 | 2mo-16y (average 1y3mo) | NA | Ordinary | NA       |
|          | uary    |                                                   |                            |              |               |           |           |          |
| Cai Jiehao[16]| 19Jan | Shanghai, China                                  | Case reports              | 1            | Nausea with poor appetite | 7y     | NA        | NA       |
|          | uary    |                                                   |                            |              |               |           |           |          |
| Lin L[17]| 17Jan   | The Fifth Affiliated Hospital of Guangdong Sun Yat-sen | Retrospective case series  | 5            | Gastrointestinal Symptoms 1 | <15y   | NA        | NA       |
|          | uary    |                                                   |                            |              |               |           |           |          |
| Study | Dates | Location | Study Type | Number | Symptoms | Age | Severe Cases | Notes |
|-------|-------|----------|------------|--------|----------|-----|--------------|-------|
| Sun D, [18] | 24 January - 24 February | Wuhan Children's Hospital | Retrospective case series | All 8 were ICU patients | Nausea and vomiting 4 (50%), Diarrhoea 3 constipation 1, accompanied by diarrhe a vomiting 2 | 2mo-15y | NA | At the time of publication, 1 child was still hospitalized | NA |
| Xu, Y. [19] | 22 January - 20 February | Guangzhou Medical Center for Women and Children | Randomized clinical trial | 10 | Diarrhoea 3 (30%) | 2m-15y | NA | Ordinary | No |
| Tagarro A [20] | 2 March - 16 March | Spain | Retrospective case series | 41 | Gastroenteritis or vomiting 2 (5%) | 1y (average 0.35y - 8.5y) | NA | NA | NA |
| Wu Huaping [21] | 21 January - 29 February | Jiangxi, China | Retrospective case series | 23 | 2 cases of diarrhe a (8.6%) | 5.7y (average 3mo-17y8mo) | 3-4 times/day | NA | NA |
| Sun Chan [28] | 24 January | Henan Province | Case-series | 4 | Nausea, vomiting | Age (8±5) | NA | No severe cases | NA |
### Table 2 Fecal Nucleic Acid Test of Patients with COVID-19

| Author                        | Date           | Location            | Study Design       | Case Number | Main Symptoms | Other Symptoms          |
|-------------------------------|----------------|---------------------|--------------------|-------------|----------------|-------------------------|
| Xing Y[29]                    | 17 January - 23 February 2020 | Qingdao, China      | Retrospective case series | 3           | Gastrointestinal manifestations (33.3%) | NA | NA | NA | NA |
| Xiong Jingxian [30]           | 2 February - 15 February 2020 | Chongqing, China    | Retrospective case series | 6           | Diarrhea (16.7%) | 8 months - 13 years | NA | Mild | NA |
| Garazzino S[50]               | as at 10 April 2020 | Italian             | Retrospective case series | 168         | Diarrhea 22% | Vomiting 9% (44%) | NA | NA | NA |
| Author          | Date         | Regions     | Research type | Total patients | Number of fecal nucleic acid positive results | Age | Clinic picture | CT and chest radiography | The respiratory tract PCR test was negative while the stool test was positive. | Time Differences between negative PCR test in stool and negative PCR test in respiratory specimens (d) |
|-----------------|--------------|-------------|---------------|----------------|-----------------------------------------------|-----|----------------|--------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Park JY[22]     | 18February  | South Korea | Case reports  | 1              | 1                                             | 10 y| Low fever, a little phlegm | CT findings were mild pneumonia.                                               |                                                                                                 | 0                                                                                               | >1                                                                                             |
| Cui Y[23]       | 28January   | Guizhou, China | Case reports  | 1              | 1                                             | 55 d| Runny nose, dry cough     | Flake shadows and frosted glass opacity                                        |                                                                                                 | 0                                                                                               | +18                                                                                           |
| Zhan Yuehua[24] | 26January   | Haikou, China | Case reports  | 1              | 1                                             | 3mo | Fever, no gastrointestinal symptoms | There seem to be a few patchy shadows in the right lower lung field             |                                                                                                 | 0                                                                                               | +1                                                                                           |
| Author(s) | Date Range | Location | Study Type | Participants | Duration | Symptoms | Findings |
|-----------|------------|----------|------------|--------------|----------|----------|----------|
| Xu, Y[19] | 22 January - 20 February | Guangzhou, China | Randomized clinical trial | 10 | 2 mo - 15y | Fever, cough and diarrhea | Isolated or multiple spotted vitreous opacities occurred in 5 patients |
| Zengling Kong[26] | 5 February | Wuhan Children's Hospital | Case reports | 1 | 17 ds | Sneezing, spitting milk | Small strip-shaped blur can be seen in CT double lung fields |
| Cai J[25] | 19 January - 3 February | Shanghai, China | Prospective study | 10 | 3-131 mo, average 74 mo | Respiratory tract infection symptoms, no digestive tract symptoms | Of the 10 patients with chest radiograph, 4 had unilateral patchy infiltration |

All patients were discharged on Feb. 19.
yin were discharged from hospital on the date of publication.

| Author | Date       | Location | Case Reports | One-day newborn | Diagnosis | Radiology | Days Alive | Days Dead |
|--------|------------|----------|--------------|-----------------|-----------|-----------|------------|-----------|
| Zeng L[27] | January-February | Wuhan Children's Hospital | 3 | 3 | One-day newborn | All had fever and pneumonia | Chest films all showed pneumonia | 0 | 0 |
| Xing Y[29] | 17 January-23 February | Qingdao, China | Case reports | 3 | 3 | Mild fever | NA | NA | +8 |
| Li J[51] | Feb 25, Sichuan, China | Case reports | 1 | 1 | 8-month-8-day | Fever and cough | Chest CT results had no abnormal | 1 | NA |

Figures
Figure 1

PRISMA flow diagram of included studies
### Figure 2

Pooled estimate of the prevalence of gastrointestinal symptoms in patients with COVID-19
Figure 3

Forest plot of the gastrointestinal Symptoms prevalence between China and Outside China
Figure 4

Forest plot of gastrointestinal Symptoms Prevalence in Wuhan and Outside Wuhan, China and Outside China
Figure 5

Funnel plot for studies on the prevalence of Gastrointestinal symptoms.