

Systematic review

Gastrointestinal manifestations of COVID-19 in children: a systematic review and meta-analysis

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ABSTRACT

Objectives To summarise the published evidence on the gastrointestinal manifestations of COVID-19 in children and to determine the prevalence of gastrointestinal symptoms.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, CINAHL and the WHO's database of publications on novel coronavirus. We included English language studies that had described original demographic and clinical characteristics of children diagnosed with COVID-19 and reported on the presence or absence of gastrointestinal symptoms. Meta-analysis was conducted using the random-effects model. The pooled prevalence of gastrointestinal symptoms was expressed as proportion and 95% CI.

Results The search identified 269 citations. Thirteen studies (nine case series and four case reports) comprising data for 284 patients were included. Overall, we rated four studies as having a low risk of bias, eight studies as moderate and one study as high risk of bias. In a meta-analysis of nine studies, comprising 280 patients, the pooled prevalence of all gastrointestinal symptoms was 22.8% (95% CI 13.1% to 35.2%; $I^2=54%$). Diarrhoea was the most commonly reported gastrointestinal symptom followed by vomiting and abdominal pain.

Conclusions Nearly a quarter of children with COVID-19 have gastrointestinal symptoms. It is important for clinicians to be aware of the gastrointestinal manifestation of COVID-19.

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BACKGROUND

COVID-19 is a highly contagious disease that was first reported in Wuhan, Hubei Province, China in December 2019. Within weeks of the emergence of the disease, it had spread to several countries and the WHO declared the outbreak as

Significance of this study

What is already known on this topic

- ▶ COVID-19 has been declared as a pandemic by the WHO.
- ▶ The main features of COVID-19 are respiratory and include cough, sore throat, dyspnoea and pneumonia.

What this study adds

- ▶ Gastrointestinal symptoms are common in children with COVID-19.
- ▶ Nearly a quarter of children with COVID-19 have gastrointestinal symptoms.
- ▶ The most common gastrointestinal symptom is diarrhoea followed by vomiting and abdominal pain.

a Public Health Emergency of International Concern in January 2020 and as a pandemic in March 2020.¹ According to the dashboard of the Center for Systems Science and Engineering at Johns Hopkins University, Baltimore, USA,² the disease has been reported in 187 countries, affected over 3 million people worldwide and caused over 230 000 deaths as at 30 April 2020.

COVID-19 is caused by SARS-CoV-2, previously known as the 2019 novel coronavirus (2019-nCoV). SARS-CoV-2 is a novel member of coronaviruses which are a large class of highly diverse, enveloped, positive-sense, single-stranded RNA viruses.³ Most reported cases of the disease are adults, but the disease also affects children, including neonates.⁴ The first reported paediatric case of COVID-19 was probably a 10-year-old boy from Shenzhen, China, who was diagnosed with the condition in January 2020.⁵

There have been a number of studies describing the clinical features of COVID-19 since the disease was first

reported in December 2019. While the disease typically presents as acute respiratory disease and pneumonia, it has been reported to impact other systems including the gastrointestinal tract. Indeed, the recognition that the gastrointestinal tract may be a source of transmission of SARS-CoV-2 has led to many endoscopy units having had to postpone a large proportion of endoscopic procedures. A number of reports on patients with COVID-19 mention gastrointestinal symptoms such as diarrhoea, nausea, vomiting and abdominal pain.⁶ Despite these, the gastrointestinal manifestations of the disease are not widely recognised by clinicians. As COVID-19 continues to spread throughout the world, it is essential for its gastrointestinal manifestations to be understood as they have the potential of distracting the clinician from making a diagnosis of COVID-19, especially in situations when the gastrointestinal symptoms precede the typical respiratory symptoms. The aim of this systematic review and meta-analysis is to describe the gastrointestinal manifestations of COVID-19 in children and to determine the prevalence of such symptoms.

METHODS

Search strategy and study selection

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses⁷ and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (<https://www.crd.york.ac.uk/prospero/>). Considering the date of the earliest confirmed reports of COVID-19, we searched PubMed, Embase and CINAHL from 1 December 2019 to 1 April 2020. The WHO database of publications on novel coronavirus was also searched for potentially relevant publications.⁸ We also searched reference lists of retrieved articles to identify additional citations that may have been missed through the electronic searches. Eligible studies were published in English language articles that have described original demographic and clinical characteristics of children diagnosed with COVID-19 and reported the presence or absence of gastrointestinal symptoms. Eligible studies included case reports, case series, cohort studies and retrospective studies. Review articles and opinion articles not reporting original data were excluded.

Studies were identified with the following search terms: (coronavirus OR COVID-19 OR COVID 19 OR SARS-CoV-2 OR 2019-nCoV) AND (children OR child* OR pediatric OR paediatrics) AND (symptom OR symptoms OR characteristics OR characteristic* OR data OR features OR clinical). We included both medical subject headings and free text terms. The search strategy of the PubMed search is shown in online supplementary appendix 1S. Two independent reviewers evaluated the titles and abstracts of papers to identify relevant studies. Articles identified were independently assessed by two reviewers using predefined

eligibility criteria. Any disagreements between authors regarding study inclusion were resolved through discussion among the reviewers.

Risk of bias

All the studies that met our inclusion criteria were case series and case reports. We used the checklist developed by Murad *et al*⁹ to assess risk of bias. This tool was specifically developed to assess risk of bias in case series and case reports and had previously been used in published systematic reviews.¹⁰ The checklist was adapted from the Newcastle-Ottawa tool¹¹ by the removal of items that relate to comparability and adjustment (which are not relevant to non-comparative studies) and retained items that focused on selection, representativeness of cases and ascertainment of outcomes and exposure. This resulted in five criteria in the form of questions with a binary response (yes/no), whether the item was suggestive of bias or not. We considered the quality of the report good (low risk of bias) when all five criteria were fulfilled, moderate when four were fulfilled and poor (high risk of bias) when three or fewer were fulfilled.

Severity of COVID-19

We classified the severity of COVID-19 as asymptomatic, mild, moderate or severe based on the degree of respiratory symptoms.¹² Asymptomatic cases had no respiratory symptoms. Mild cases had fever, cough, upper respiratory tract symptoms but without pneumonia or intensive care unit (ICU) admission. Moderate cases had mild symptoms together with pneumonia. Severe cases had moderate symptoms in addition to ICU admission, acute respiratory distress syndrome or organ failure.

Data extraction

Data were extracted independently by two reviewers into a Microsoft Excel spreadsheet using a predefined checklist. Extracted data included the following: study design, year of publication, country, author name(s), number of patients, patient demographics, gastrointestinal symptoms and/or signs, other clinical symptoms and timing of gastrointestinal symptoms in relation to respiratory symptoms. Any differences were discussed and resolved by consensus.

Data analysis

Initial statistical analyses were descriptive. Meta-analysis was conducted using the random-effects model. The pooled prevalence of gastrointestinal symptoms was expressed as proportion and 95% CI and was presented in a forest plot. We calculated I^2 statistic to measure the proportion of total variation in study estimates attributed to heterogeneity. I^2 values of <25%, 25%–75% and >75% indicate low, moderate and high heterogeneity, respectively.¹³ Meta-analysis was performed using Comprehensive Meta-Analysis

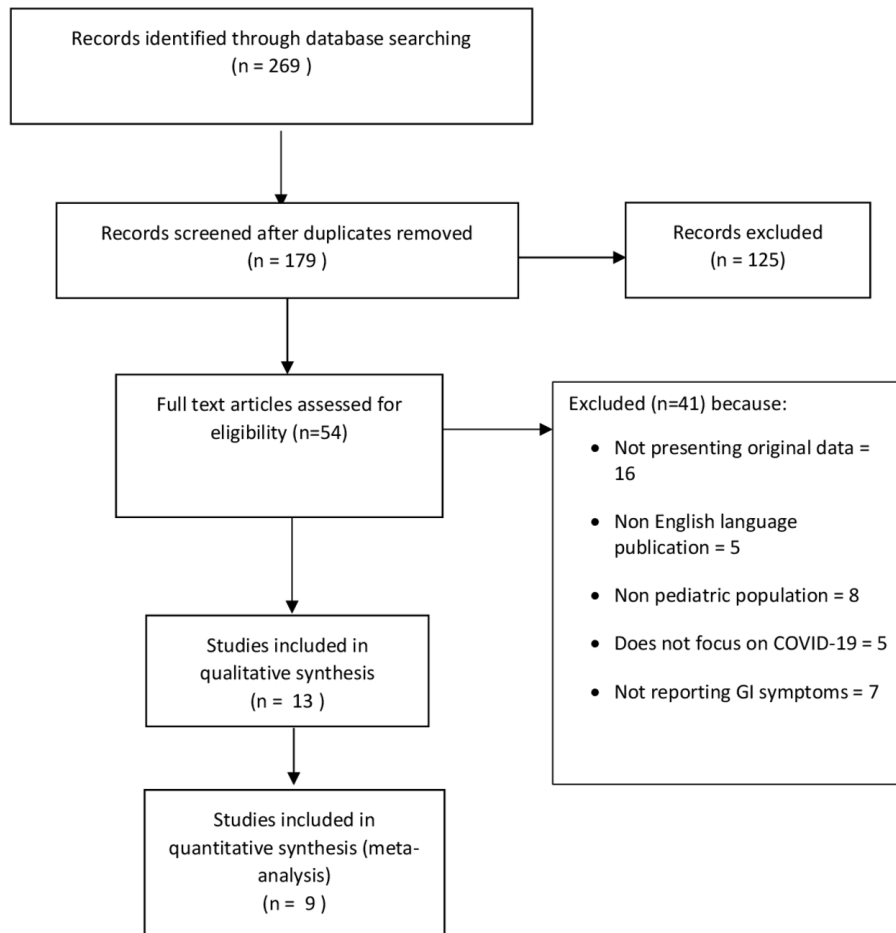


Figure 1 Flow diagram of the study selection process. GI, gastrointestinal.

Statistical Software (V.3). We planned to perform subgroup analyses based on country of publication and severity of COVID-19.

RESULTS

Overview of the included studies

The search strategy identified a total of 269 citations, of which 54 met the criteria for full-text review. A flow-chart detailing the studies' selection process is shown in [figure 1](#). Following full-text review, we included 13 papers comprising data for 284 patients.^{14–26} The characteristics of the included studies are provided in [table 1](#). Two of the included studies were from Singapore¹⁷ and Korea,²¹ and the other 11 studies were from China. All the included studies had been published between 9 February 2020 and 29 March 2020. Nine of the included papers were case series,^{14 16 18 20 22–26} and the other four were case reports.^{15 17 19 21} The nine case series,^{14 16 18 20 22–26} involving 280 patients, had adequate data to allow estimates of prevalence and these were included in a meta-analysis. The risk of bias assessment in the studies is summarised in online supplementary table 1S. Overall, we rated four studies^{14 15 19 22} as having a low risk of bias, eight

studies^{16–18 20 21 23 25 26} as moderate and one study²⁴ as high risk of bias.

Diagnosis of COVID-19

All the included studies reported patients admitted to hospital with COVID-19. In 12 of the included studies,^{14–23 25 26} the diagnosis of COVID-19 was established by reverse transcription polymerase chain (RT-PCR) and in one study,²⁴ by the nucleic acid test. The severity of COVID-19 varied from asymptomatic cases to severe cases ([table 1](#)). Reported non-gastrointestinal symptoms/features included fever, cough, dyspnoea, blocked nose, sore throat and rhinorrhoea.

Gastrointestinal symptoms of COVID-19

A variety of gastrointestinal symptoms were reported in children with COVID-19. Reported gastrointestinal symptoms included diarrhoea, vomiting and abdominal pain. One study¹⁸ reported that the gastrointestinal symptoms developed after the onset of respiratory symptoms but the other studies did not specify the timing of gastrointestinal symptoms in relation to respiratory symptoms.

Table 1 Characteristics of included studies

Study and country	Sample size	Study type	Mean age	Age range	Severity of Covid-19	Method of diagnosis
Ji <i>et al</i> and China ¹⁶	2 (0 female)	Case series	12 years	9–15 years	Mild (n=2)	RT-PCR
Liu <i>et al</i> and China ¹⁸	5 (1 female)	Case series	5.9 years	7 months to 13 years	Asymptomatic (n=1), mild (n=1), moderate (n=3)	RT-PCR
Lu <i>et al</i> and China ²⁰	171 (67 female)	Case series	6.7	1 day to 15 years	Asymptomatic (n=27), mild (n=33), moderate (n=108), severe (n=3)	RT-PCR
Qiu <i>et al</i> and China ²²	36 (13 female)	Case series	8.3	1–16	Mild (n=17), moderate (n=19)	RT-PCR
Sun <i>et al</i> and China ²³	8 (2 female)	Case series	Not stated	2 months to 15 years	Severe (n=8)	RT-PCR
Xia <i>et al</i> and China ²⁴	20 (7 female)	Case series	2.1 years	1 day to 14.7 years	Moderate (n=20)	Nucleic acid test
Zhang <i>et al</i> and China ²⁵	3 (0 female)	Case series	7.7 years	6–9 years	Mild (n=1), moderate (n=2)	RT-PCR
Zheng <i>et al</i> and China ²⁶	25 (11 female)	Case series	3 years (median)	3 months to 14 years	Mild (n=8), moderate (n=15), severe (n=2)	RT-PCR
Cui <i>et al</i> and China ¹⁵	1 (1 female)	Case report	55 days	N/A	Moderate (n=1)	RT-PCR
Kam <i>et al</i> and Singapore ¹⁷	1 (0 female)	Case report	6 months	N/A	Mild (n=1)	RT-PCR
Liu <i>et al</i> and China ¹⁹	1 (0 female)	Case report	10 years	N/A	Mild (n=1)	RT-PCR
Park <i>et al</i> and Korea ²¹	1 (1 female)	Case report	10 years	N/A	Moderate (n=1)	RT-PCR
Cai <i>et al</i> and China ¹⁴	10 (6 female)	Case series	6 years	3–131 months	Mild (n=6), moderate (n=4)	RT-PCR

RT, reverse transcription.

Prevalence of gastrointestinal symptoms in COVID-19

The prevalence of gastrointestinal symptoms in the individual primary studies ranged from 0% to 88%. In a meta-analysis of nine studies comprising 280 children, the pooled prevalence of gastrointestinal symptoms was 22.8% (95% CI 12.7% to 37.6%) with a moderate degree of heterogeneity ($I^2=59%$) (figure 2). The pooled prevalence of diarrhoea (figure 3), vomiting (figure 4) and abdominal pain (figure 5) was,

respectively, 12.4% (95% CI 7.8% to 19.2%), 10.3% (95% CI 4.9% to 20.3%) and 5.4% (95% CI 2.2% to 12.7%). The I^2 statistic for these respective symptoms was 19.6%, 45% and 19.9%.

Subgroup analysis

We planned to perform subgroup analyses based on country of publication and severity of COVID-19 but there was not enough data available in the included studies.

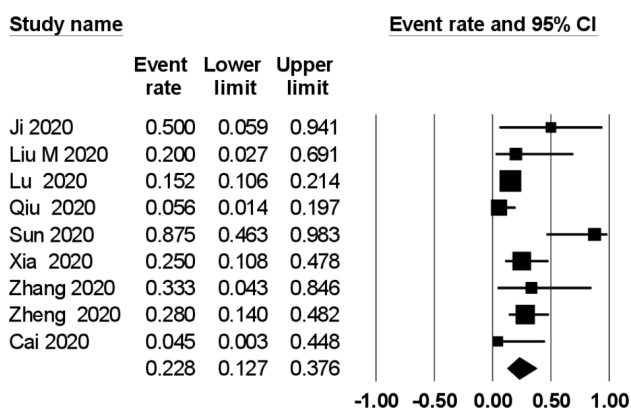


Figure 2 Prevalence of gastrointestinal symptoms in children with COVID-19.

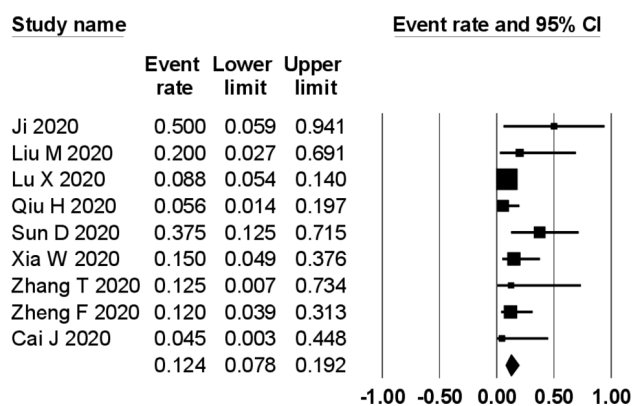


Figure 3 Prevalence of diarrhoea in children with COVID-19.

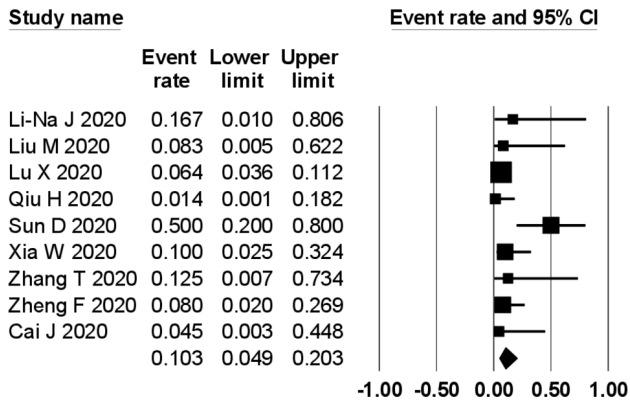


Figure 4 Prevalence of vomiting in children with COVID-19.

DISCUSSION

As at 30 April 2020, COVID-19 has been reported in 187 countries, affected over 3 million people worldwide and caused about 230 000 deaths.² The primary manifestations of COVID-19 are mainly respiratory with features such as fever, cough, sore throat, dyspnoea and pneumonia.²⁷ However, a number of studies make mention of gastrointestinal symptoms.⁶ The first confirmed patient with COVID-19 in the USA reported a 2-day history of nausea and vomiting in addition to a dry cough on admission, and also started to pass loose stools from Day 2 of admission.²⁸

To our knowledge, this is the first systematic review and meta-analysis that has reported the gastrointestinal manifestations of COVID-19 in children and estimated the pooled prevalence of such symptoms. The results of our pooled analyses show that gastrointestinal symptoms are common in children with COVID-19 with nearly a quarter of patients exhibiting at least one gastrointestinal symptom. The most common gastrointestinal symptom was diarrhoea, followed by vomiting and then abdominal pain. The results of our study are generally consistent with a recent meta-analysis in adult patients with COVID-19 which found the prevalence of gastrointestinal symptoms to be about 18%.²⁹ Perhaps it is not surprising that gastrointestinal symptoms are common in patients with COVID-19. A number of

studies have suggested a possible faecal–oral transmission.^{6 30} Xiao *et al* showed that SARS-CoV-2 RNA can be found in stool samples of patients with COVID-19 and that the positive stool test may persist for up to 12 days and remain positive even after respiratory samples have tested negative.³¹ While gastrointestinal symptoms in patients with COVID-19 do not lead to mortality, they nonetheless, contribute to the overall picture of the disease. Unfortunately, there was a paucity of information in the primary studies regarding how the presence of gastrointestinal symptoms impact on the overall course of patients’ disease.

Our study has a number of strengths. A comprehensive literature search was performed to identify eligible studies. Two review authors independently assessed studies for inclusion, extracted data and rated study quality. By including data from all available reports, the overall sample size was increased thereby improving the statistical power of our meta-analysis. Although this is a comprehensive review, there are also limitations. The primary studies were either case series or case reports and the limitations of these study designs must be borne in mind. All the included studies were from China, Singapore and Korea so the prevalence of gastrointestinal symptoms in other geographic regions may or may not be similar. The included studies primarily aimed to describe children with COVID-19 and as respiratory symptoms are the most serious symptoms, it is possible that some gastrointestinal symptoms might have been under-reported. Similarly, we excluded studies which did not report the presence or absence of gastrointestinal symptoms, and non-reporting was not assumed to equate to not present.

In conclusion, our review found that gastrointestinal symptoms are common in children with COVID-19 with nearly a quarter of patients developing such symptoms. Diarrhoea, vomiting and abdominal pain were the main gastrointestinal symptoms. It is important for clinicians to be aware of the gastrointestinal manifestation of COVID-19.

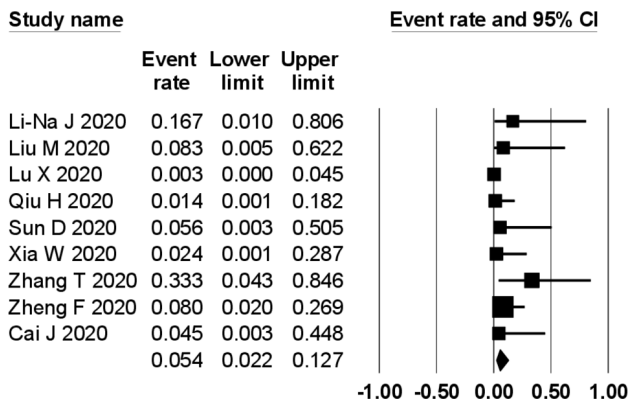


Figure 5 Prevalence of abdominal pain in children with COVID-19.

Contributors AA had the idea for the review. CG-C, IA and MG selected studies for inclusion and abstracted data. AKA wrote the first draft. MG, CG-C, IA, ET-B and AKA interpreted data and critically revised the paper for important intellectual content. All authors approved the final version.

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