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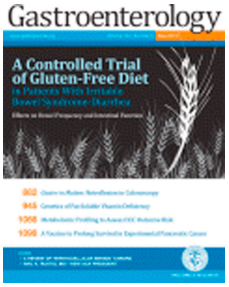

Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis

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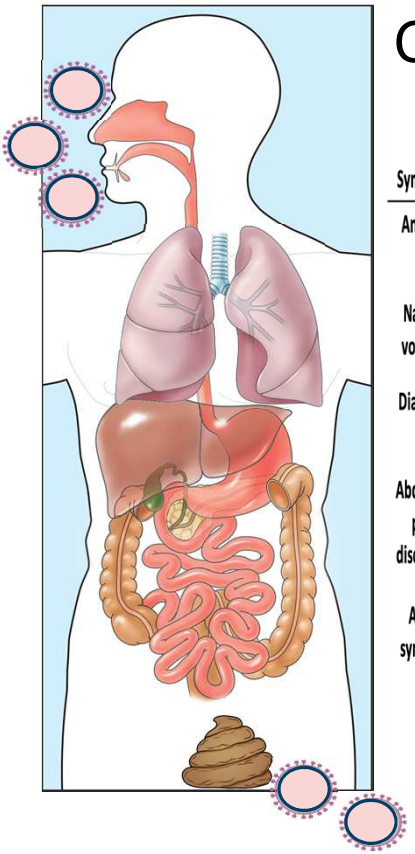
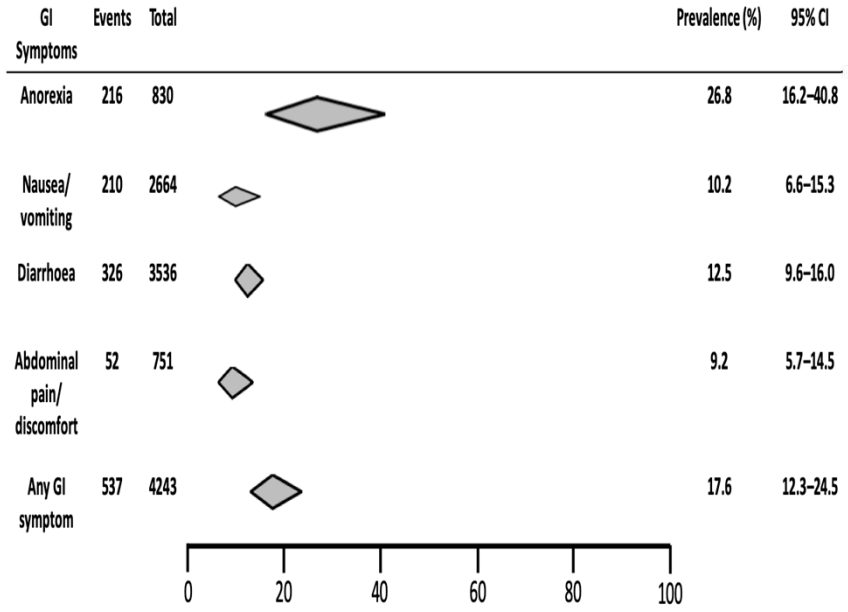
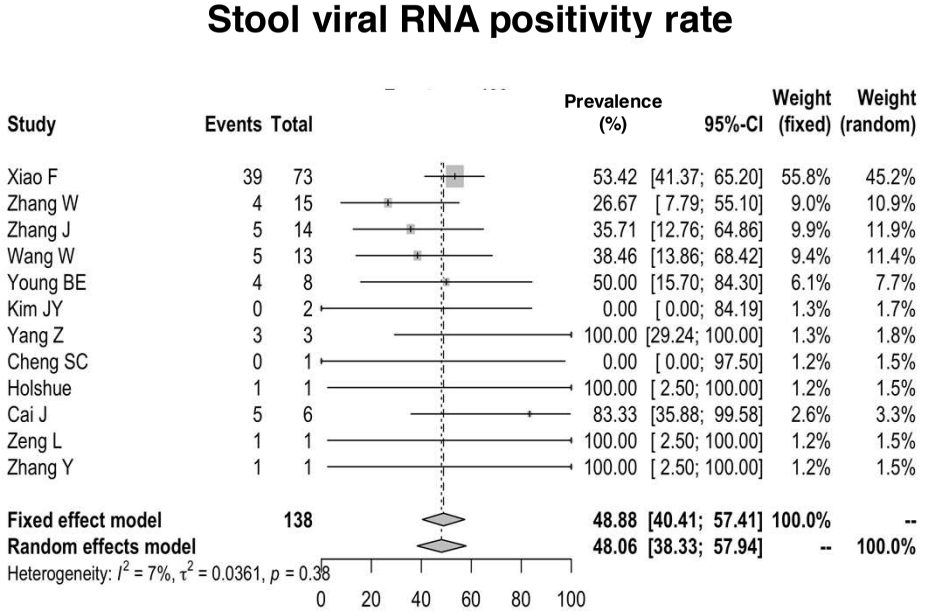


Gastrointestinal Symptoms & stool viral RNA positivity rate in COVID-19





Gastroenterology

Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis

Short title: GI manifestations of COVID-19

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ABSTRACT

Background & Aims: Infection with SARS-CoV-2 causes COVID-19, which has been characterized by fever, respiratory, and gastrointestinal symptoms as well as shedding of virus RNA into feces. We performed a systematic review and meta-analysis of published gastrointestinal symptoms and detection of virus in stool, and also summarized data from a cohort of patients with COVID-19 in Hong Kong.

Methods: We collected data from the cohort of patients with COVID-19 in Hong Kong (n=59; diagnosis from February 2 through Feb 29, 2020), and searched PubMed, Embase, Cochrane and three Chinese databases through March 11, 2020 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We analyzed pooled data on the prevalence of overall and individual gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, and abdominal pain or discomfort) using a random effects model.

Results: Among the 59 patients with COVID-19 in Hong Kong, 15 patients (25.4%) had gastrointestinal symptoms and 9 patients (15.3%) had stool that tested positive for virus RNA. Stool viral RNA was detected in 38.5% and 8.7% among those with and without diarrhea, respectively (P=.02). The median fecal viral load was 5.1 $\log_{10}$cpm in patients with diarrhea vs 3.9 $\log_{10}$cpm in patients without diarrhea (P=.06). In a meta-analysis of 60 studies, comprising 4243 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6% (95% CI, 12.3%–24.5%); 11.8% of patients with non-severe COVID-19 had gastrointestinal symptoms (95% CI, 4.1%–29.1%) and 17.1% of patients with severe COVID-19 had gastrointestinal symptoms (95% CI, 6.9%–36.7%). In the meta-analysis, the pooled prevalence of stool samples that were positive for virus RNA was 48.1% (95% CI, 38.3%–

57.9%); of these samples, 70.3% of those collected after loss of virus from respiratory specimens tested positive for the virus (95% CI, 49.6%–85.1%).

Conclusions: In an analysis of data from the Hong Kong cohort of patients with COVID-19 and a meta-analysis of findings from publications, we found that 17.6% of patients with COVID-19 had gastrointestinal symptoms. Virus RNA was detected in stool samples from 48.1% patients—even in stool collected after respiratory samples tested negative. Healthcare workers should therefore exercise caution in collecting fecal samples or performing endoscopic procedures in patients with COVID-19—even during patient recovery.

KEY WORDS: PRISMA, SARS, viral persistence, fecal to oral transmission

INTRODUCTION

In December 2019, a cluster of unidentified form of viral pneumonia cases was first reported in Wuhan, China, which swiftly spread to the rest of China and then the rest of the world within a very short period. The virus was subsequently identified to be a novel coronavirus (CoV) that belongs to the beta-coronavirus lineage B with more than 80% resemblance to the previously reported SARS-CoV in 2003. Up until 16 March of 2020, more than 150,000 cases were reported from more than 150 countries or regions across the globe, with more than 81,000 cases in China, 21,000 cases in Italy, 12,000 cases in Iran and 8,100 cases from Korea. Although the number of new cases seem to be declining in China, the numbers of cases are rising in an exponential manner in Europe, North America and Middle East countries. The death toll has already reached more than 5,700 globally with more than 3,000 from the Hubei Province of China, where Wuhan city is located. In response to the emerging threat posed by this virus, the World Health Organization (WHO) has declared a Public Health Emergency of International Concern on 30 January 2020, and further labelled it as a pandemic on 11 March 2020.

The disease was named as COVID-19, which was an abbreviation for coronavirus disease 2019, by the WHO and the virus was termed as the SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV). The SARS-CoV-2 is a positive-sense single-stranded RNA virus and has strong genetic similarity to bat coronaviruses but the intermediate reservoir has yet to be identified.[1] Together with the other two previously identified coronaviruses SARS-CoV and MERS-CoV that cause Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome (MERS), this is the third coronavirus identified to cause severe viral pneumonia in humans (**Table 1**). Similar to the other two

coronaviruses, the SARS-CoV2 has very high infectivity as no one has immunity, resulting in an ongoing global health crisis.

Based on existing observation, the case fatality rate of COVID-19 is lower than SARS and MERS and is estimated to be about 1-2%, but is much higher in older patients. In addition to age, a high Sequential Organ Failure Assessment (SOFA) score and D-dimer level >1ug/L on admission are associated with poor prognosis.[2] Apart from respiratory symptoms, gastrointestinal manifestations are common in patients with SARS, MERS and the latest COVID-19. We previously reported the high prevalence of enteric symptoms in patients with SARS and demonstrated acute viral replication in the small intestinal mucosa of SARS patients.[3] It is estimated that 16–73% of patients had diarrhea during the course of SARS illness. Fecal shedding of SARS-CoV RNA was found in 86-100% of patients during day 6-14 of illnesses and could persist for >30 days of illness.[4, 5] It was subsequently found that SARS-CoV bind to the angiotensin-converting enzyme 2 (ACE2) receptors of the intestinal and respiratory tracts, which is the entry point for the virus to the epithelial cells.[6] Similarly, up to a quarter of patients with MERS also reported gastrointestinal symptoms such as diarrhea or abdominal pain.[7] Again, MERS-CoV could be detected in 15% of stool samples, and could persist for up to 24 days after diagnosis.[8] It was shown that the human intestinal tract including primary intestinal epithelial cells, small intestine explants, and intestinal organoids are highly susceptible to MERS-CoV.[9]

Enteric manifestations of SAR-CoV2 not only pose important diagnostic challenge to clinicians when facing patients with mild COVID-19 symptoms on initial presentation, but also signify potential fecal transmission of this virus. With increasing number of reported cases of COVID-19, there is a pressing need to systemically summarize the enteric

manifestations of COVID-19 and the temporal pattern of fecal shedding of the SARS-CoV-2 virus, particularly to gastroenterologists and endoscopists who may not be familiar with this disease.

This study aimed to summarize the existing data on gastrointestinal manifestations of COVID-19 and the temporal pattern of fecal shedding of SARS-CoV2 based on published data as well as the data from our recent cohort of COVID-19 patients in Hong Kong.

METHODS

COVID-19 cohort from Hong Kong

We included a cohort of 59 patients with virologically confirmed COVID-19 diagnosed between 2nd and 29th February 2020 in Hong Kong. The prevalence of gastrointestinal symptoms (including nausea/vomiting, diarrhea and abdominal pain/discomfort) and viral load in stool collected on admission was reported.

Studies selection

Three databases including Pubmed, Embase, and Cochrane Library were searched following the PRISMA guideline[10] from 1 Dec 2019 until 11 March 2020. Keywords were 2019-nCoV-2, coronavirus, COVID-19, SARS-CoV-2, or novel coronavirus. The search details are listed in **Supplementary file**. Additional related articles were retrieved from three Chinese electronic databases (CQVIP, Wanfang Data, and Chinese National Knowledge Infrastructure [CNKI]). Potential studies were retrieved after title/abstract screening by the investigator (KSC). All articles were imported to Endnote X9.2 (Thompson and Reuters, Philadelphia, Pennsylvania), and duplicates were removed.

Selection criteria

Two authors (KSC, IFH) determined the eligibility of studies independently, and dissonance was resolved by the third author (WKL). The inclusion criteria included (1) study population: COVID-19 patients (including adult or pediatric patients and pregnant women); (2) study design: case reports/case series, prospective/retrospective cohort study, case-control study, and randomized controlled trials. There was no language restriction. The exclusion criteria were (1) patients without virological proof of SARS-CoV2 infection; (2) asymptomatic

patients infected with SARS-CoV2; (3) studies that did not report gastrointestinal symptoms; and (4) review articles, meta-analyses, editorials, and other forms (e.g. commentary).

If all gastrointestinal symptoms were not reported and the number of events of any individual gastrointestinal symptom was less than one, it was regarded as "not available" and excluded from the meta-analysis of all gastrointestinal symptoms. However, this study was still included in the meta-analysis of individual gastrointestinal symptom if the proportion of patients with that symptom was reported. Two additional studies[11, 12] which did not report on gastrointesitnal symptoms but provided data on stool viral RNA was included in the meta-analysis of stool viral RNA only.

Data extraction

For eligible articles, we recorded items including first authors, site of study, inclusion/exclusion criteria, sample size, age, sex, disease severity, any gastrointestinal symptoms (anorexia, nausea/vomiting, diarrhea, or abdominal pain), other symptoms (fever, cough, expectoration and dyspnea). Severe disease was defined according to the American Thoracic Society and Infectious Disease Society of America guidelines for community-acquired pneumonia,[13] need of intensive care unit (ICU) admission, and death.

Data analysis

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median (interquartile range [IQR]) or mean (± standard deviation [SD]). The prevalence of gastrointestinal symptoms was expressed as proportion and 95% confidence interval (95% CI) using the random effects model, and was presented as Forest plot. We used Cochran Q test to

detect heterogeneity among studies, with a p-value <0.10 indicating significant heterogeneity. We calculate 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.[14]

Subgroup analysis was performed according to whether studies were from China or other countries, in or outside of the Hubei province, the disease severity, and patient group (adults, pediatric patients and pregnant women).

RESULTS

COVID-19 cohort in Hong Kong

A total of 59 patients with confirmed COVID-19 in Hong Kong were recruited. The median age was 58.5 years (IQR: 43.5–68.0; range: 22–96) with 27 (45.8%) men. Fever was present in 56 (94.9%), cough in 22 (37.3%), dyspnea in 4 (6.8%) patients. Thirty-six (61.0%) patients did not have respiratory symptoms of cough or dyspnea on presentation. Among 15 (25.4%) patients who had gastrointestinal symptoms (vomiting: 1 [1.7%], diarrhea: 13 [22.0%], and abdominal pain/discomfort:7 [11.9%]), all had fever but 8 (53.5%) did not have cough or dyspnea.

On presentation, stool viral RNA was positive in 9 (15.3%) patients, and the median viral load was 4.7 (range: 3.4–7.6) $\log_{10}$ copies per mL (cpm). The proportion of patients with detectable stool viral RNA was higher among those with diarrhea than those without diarrhea (38.5% vs 8.7%; p=0.019). There was also a trend for higher stool viral load in patients with diarrhea (median: 5.1 [IQR: 4.8–5.6] vs 3.9 [IQR: 3.5–4.4] $\log_{10}$cpm; p=0.06). Of the 44 patients without gastrointestinal symptoms, 4 (9.1%) had positive stool viral RNA.

Study characteristics of meta-analysis

Figure 1 depicts the study selection process. Of the 2,034 studies identified, 69 were included in the meta-analysis (60 studies with data on all gastrointestinal symptoms and 11 on stool viral load).

The characteristics of the included studies are shown in **Table 2** including the hospital admission period, places in which the patients were recruited, sample size, age, sex, disease severity, non-gastrointestinal symptoms (fever and respiratory symptoms) on presentation,

and gastrointestinal symptoms (anorexia, nausea/vomiting, diarrhea and abdominal pain/discomfort). The median age of patients was 45.1 years (IQR: 41.0–54.8), and 57.3% were male. Among studies that reported disease severity, severe disease accounted for 1.3–62.3%.

Meta-analysis of gastrointestinal symptoms

For the meta-analysis of all gastrointestinal symptoms (60 studies), there was a total of 4,243 COVID-19 patients. Fifty-three (88.3%) studies were from China and 7 (11.7%) were from other countries (South Korea: 2, Singapore: 2, Vietnam: 1, United States of America: 1, and United Kingdom: 1). Of the 53 studies from China, 27 (50.9%) were from Hubei Province where Wuhan is located. One study by Guan et al[15] used the data reported to the National Health Commission of China from 552 hospitals across the country. The pooled prevalence of all gastrointestinal symptoms was 17.6% (95% CI: 12.3–24.5) (**Figure 2**), with significant heterogeneity noted among studies ($p<0.001$; $I^2=91.5\%$).

For individual gastrointestinal symptoms, there were 18 studies reporting prevalence of anorexia, 32 on nausea/vomiting, 58 on diarrhea, and 12 on abdominal pain. The pooled prevalence of anorexia was 26.8% (95% CI: 16.2–40.8) (**eFigure 1**), nausea/vomiting was 10.2% (95% CI: 6.6–15.3) (**eFigure 2**), diarrhea was 12.5% (95% CI: 9.6–16.0) (**eFigure 3**), and abdominal pain/discomfort was 9.2% (95% CI: 5.7–14.5) (**eFigure 4**). **Figure 3** shows the summary estimates for the prevalence of individual and all gastrointestinal symptoms. Significant heterogeneity among studies was seen for anorexia, nausea/vomiting, and diarrhea ($p<0.001$; $I^2=74.6–85.2\%$), while the heterogeneity was less for abdominal pain/discomfort ($p=0.008$; $I^2=57.0\%$).

Subgroup analysis

Geographic variations and gastrointestinal symptoms

The pooled prevalence of all gastrointestinal symptoms was 16.1% (95% CI: 10.9–23.0) and 33.4% (95% CI: 15.2–58.3) in studies from China and other countries, respectively (**Figure 2**). There was no significant subgroup difference between the studies based on country origin (p=0.09). However, there was significant heterogeneity among the studies conducted in China (p=<0.001; I^2=92.4%) but not among the studies from other countries (p=0.174; I^2=33.2%).

Among studies from China, the prevalence of all gastrointestinal symptoms in the single study of 1,099 patients from 552 hospitals by Guan et al[15] was 5.0% (95% CI: 3.9–6.5). (**Figure 2**). For studies from Hubei Province, the pooled prevalence of all gastrointestinal symptoms was 16.2% (95% CI: 9.3–26.7), whereas those from outside of Hubei Province was 18.6% (95% CI: 12.2–27.2). There was a significant subgroup difference between the studies from and outside of Hubei Province (p<0.001), and there was also significant heterogeneity among the studies (p=<0.001; I^2=93.5% and I^2=76.8%).

Disease severity and gastrointestinal symptoms

There were 11 studies that compared the prevalence of all gastrointestinal symptoms according to the severity of COVID-19 (number of patients with severe and non-severe disease was 451 and 1,731, respectively) (**eTable 1**). The pooled prevalence of all gastrointestinal symptoms was 17.1% (95% CI: 6.9–36.7) and 11.8% (95% CI: 4.1–29.1) in patients with severe and non-severe disease, respectively (**Figure 4**). There was significant heterogeneity among the studies (p<0.001; I^2=90.9% and I^2=97.7%).

Adult, pediatric patients and pregnant women

There were 53 studies on adults, 4 on pediatric patients, and 3 on pregnant women. The corresponding pooled prevalence of all gastrointestinal symptoms in adults, pediatric patients, and pregnant women was 16.7% (95% CI: 11.4–23.9), 24.8% (95% CI: 9.6–50.4), and 20.0% (95% CI: 4.3–58.2). There was no significant subgroup difference (p=0.717).

Detection of viral RNA in stool

None of the studies tested stool viral RNA on the day of hospitalization except our current study. There were 12 studies which tested for viral RNA in stool; the study by Wang et al[16] reported stool viral RNA positivity rate according to number of stool specimens (44/153 [28.8%]) rather than number of patients, but reported the stool viral RNA results among 13 patients who tested positive for respiratory specimens. 68 of 138 patients (pooled prevalence: 48.1%, 95% CI: 38.3–57.9) tested positive for both respiratory and stool specimens ("R+S+") after hospitalization (**eFigure 5**). In nine studies with serial viral RNA test results of "R+S+" patients, 87 of 124 patients (pooed prevalence: 70.3%, 95% CI: 49.6–85.1) had persistent positive stool viral RNA despite negative respiratory samples ("R-S+") (**eFigure 6**). Ling et al[12] reported that the stool viral clearance was longer in patients with steroid use compared to those without steroid use (20 vs 11 days; p<0.001).

Figure 5 shows the timeline of the symptoms and viral test results (nasopharyngeal/throat swab, sputum and stool samples) in 38 patients with available details. Based on the available data, none of the studies reported patients presenting with diarrhea on presentation (except for the study by Young et al[75] which did not report the association between stool viral RNA and diarrhea). Persistence of viral RNA in stool was longer than respiratory specimens ("R-S+") in 13 including seven pediatric patients. Viral RNA was detected as early as day 3 of

illness onset in these patients, and remained positive in a 78-year-old patient for ≥33 days from illness onset.

DISCUSSION

In this meta-analysis of 4,243 COVID-19 patients from six countries, the pooled prevalence of all gastrointestinal symptoms (including anorexia, nausea/vomiting, diarrhea or abdominal pain) was 17.6%. Anorexia was the most common gastrointestinal symptom (26.8%), followed by diarrhea (12.5%), nausea/vomiting (10.2%) and abdominal pain/discomfort (9.2%). In the Hong Kong cohort, viral RNA was detected in the stool of 15.3% of patients on presentation, including patients without any gastrointestinal symptoms. Moreover, patients with diarrhea on presentation had higher stool RNA positivity and viral load than those without diarrhea. We also noted that 48.1% of patients had detectable stool viral RNA during the course of illnesses. More importantly, prolonged shedding of viral RNA in stool rather than respiratory samples was observed in 70.3% of patients, which could be up to ≥33 days from illness onset.

Although diarrhea is one of the common gastrointestinal manifestations, the presence of constipation could not rule out COVID-19, as a case report of four patients reported that constipation was noted in two.[17] Despite the inclusion of >60 reports, the actual prevalence of any gastrointestinal symptoms could be underestimated as many earlier studies did not report other gastrointestinal symptoms except for diarrhea[18-23]. Moreover, majority of studies only reported gastrointestinal symptoms on the day of admission but not throughout the disease course. The issue is further complicated by the difference in the criteria on diagnosing diarrhea in various hospitals.[24]

With more than 80% resemblance to SARS-CoV, infection of the gastrointestinal tract by SARS-CoV-2 is not unexpected, which is proposed to be mediated via the ACE2 cell receptors. ACE2 receptors are highly expressed in the small intestine, especially in proximal

and distal enterocytes,[6, 24] and the binding affinity of ACE2 receptors determines infectivity. As ACE2 modulates intestinal inflammation,[25] SARS-CoV-2 may cause disruption of the ACE2 function and result in diarrhea. A recent study demonstrated the intracellular staining of viral nucleocapsid protein and ACE2 protein expression in the human gastric, duodenal and rectal epithelial cells, further suggesting that the ACE2 receptors could act as the entry point of the SARS-CoV-2 virus in the intestinal tract.[23]

Gastrointestinal manifestations were also commonly reported during the SARS and MERS outbreaks. In the previous SARS outbreak in Hong Kong, 16% patients reported diarrhea.[5] Similarly, up to a quarter of patients with MERS also reported gastrointestinal symptoms such as diarrhea or abdominal pain.[7] In our COVID-19 cohort in Hong Kong, 22% of patients reported diarrhea, which was slightly higher than our previous SARS cohort. However, many of these patients were from a large outbreak during dinner gathering in the Lunar New Year, who might contract the virus through both fecal-oral and respiratory routes, thus partly explaining the higher frequency of gastrointestinal manifestations. Previous studies during SARS demonstrated that viral load in the stool was strongly associated with presence of diarrhea.[26] In our COVID-19 cohort, patients with diarrhea also had higher prevalence of detectable stool viral RNA on presentation. Importantly, gastrointestinal manifestations may be the only initial symptoms in some COVID-19 patients. In the study by An et al,[27] nine patients reported only gastrointestinal symptoms (predominantly anorexia [66.7%]) in the absence of fever or respiratory symptoms on presentation.

Subgroup analysis showed that the pooled prevalence of all gastrointestinal symptoms was lower in studies from China than other countries (16.1% vs 33.4%). While any true difference between countries remains to be investigated, this observation could be due to the smaller

number of patients in studies from outside of China. Also, it is noteworthy that many of these early reports from outside of China included visitors from China. As China was the first country affected by the COVID-19 outbreak with a large number of patients, the gastrointestinal manifestations may be overlooked in the beginning of the outbreak, particularly Wuhan city, leading to under-reporting of gastrointestinal symptoms in earlier studies.

Our meta-analysis showed that the prevalence of severe disease was more common in patients who had gastrointestinal symptoms than those who did not (17.1% vs 11.8%). Wang et al reported that abdominal pain was more frequent in patients who required ICU care than those who did not.[28] Healthcare professionals should be aware of the potential prognostic implications in patients with gastrointestinal symptoms, whom may require more close monitoring.

In our COVID-19 cohort in Hong Kong, we found that 15.3% of patients tested positive for stool viral RNA on the day of admission. As for the meta-analysis, we found that 48.1% of patients had stool samples ever tested positive for viral RNA during the illness. Due to the lack of systematic stool collection protocol in currently published studies, the full extent of the stool positive rate remains to be characterized, particularly the peak timing and extent of fecal shedding. It is however alarming to note that 70.3% of patients had stool viral RNA remaining positive despite negative respiratory specimens. Although it is uncertain at this moment whether these are live virus particles or just RNA fragments released from the intestinal cells, this finding could raise a serious concern on the isolation policy for the COVID-19 patients, particularly during the recovery phase. During the SARS outbreak in 2003, it was reported that the sewage system of the Amoy Gardens in Hong Kong served as

the major source of infection from patients excreting coronavirus RNA.[4] The sewage concentrates of two hospitals receiving SARS patients in Beijing were also found to have SARS-CoV RNA detected at that time.[29] Intuitively, proper handling of the excreta of COVID-19 patients should still be strongly enforced despite repeatedly negative results in respiratory specimens.

Another interesting feature of COVID-19 is the recurrent infection in some patients, i.e. recurrent symptoms after apparent recovery with positive respiratory specimens for viral RNA again after initial clearance. It remains to be determined whether the persistence of viral RNA in stool may be used as surrogate monitor for the recurrent infection in some patients.

There are several strengths of our study. This is the first meta-analysis that summarized the rapidly emerging and sometimes confusing literature on COVID-19 on the prevalence of the overall and individual gastrointestinal manifestations. The comprehensive inclusion of >60 studies allows a more precise estimation of the prevalence of gastrointestinal symptoms. Subgroup analysis found that the presence of gastrointestinal symptoms was associated with a more severe disease course, highlighting the importance of a more detailed inquiry into gastrointestinal symptoms for both diagnostic and prognostic purposes. The alarmingly high prevalence of viral shedding in stool, particularly after viral RNA negativity in respiratory specimens, prompts further research into the viral shedding dynamics in different systems, as well as the potential transmission risk via fecal-oral route, which carries significant infection control and public health implications. A few limitations of this study should be noted. As mentioned, gastrointestinal symptoms may be under-reported in some studies, which may lead to a lower pooled prevalence rate. Second, studies of large sample size on ethnic groups

other than Chinese are currently lacking, precluding a more precise estimate of the prevalence of gastrointestinal manifestations in other ethnic groups.

CONCLUSION

In this study, we found that gastrointestinal symptoms were present in 17.6% of patients diagnosed with COVID-19. Moreover, viral shedding in stool was detected in 48.1% of patients, and could persist for up to ≥33 days from illness onset even after viral RNA negativity in respiratory specimens.

FIGURE LEGEND

Figure 1. Study selection flow diagram

If all gastrointestinal symptoms were not reported and the number of events of any individual GI symptoms was less than one, it was regarded as "not available" and was excluded from the meta-analysis of all gastrointestinal symptoms. However, this study was still included in the meta-analysis of individual gastrointestinal symptom if the proportion of patients with that symptom was reported.

Figure 2. Pooled prevalence of all gastrointestinal symptoms in COVID-19 patients (all studies and according to geographical variation – China versus outside of China)

Abbreviations: COVID-19, coronavirus disease 2019

Figure 3. Summary estimates of the prevalence of individual and all gastrointestinal symptoms in COVID-19 patients

Abbreviations: COVID-19, coronavirus disease 2019

Figure 4. Pooled prevalence of all gastrointestinal symptoms according to the severity of COVID-19

Abbreviations: COVID-19, coronavirus disease 2019

Figure 5. Timeline of the symptomatology and viral test results (respiratory and stool specimens) of 38 COVID-19 patients.

Filled circle represents a positive result whereas empty circle represents a negative result. Gastrointestinal symptoms are color coded as shown (abdominal pain/discomfort, orange; vomiting, yellow; diarrhea, green).

The details of 13 "R-S+" patients are shown in case number: 2, 5, 8, 10, 11, 14, 15, 18, 24, 26, 27, 28 and 29.

Abbreviations: COVID-19, coronavirus disease 2019; D, Day of symptom onset; "R-S+", respiratory specimen negative for viral RNA but stool specimen still positive for viral RNA

* Nasopharyngeal/oropharyngeal and stool samples were tested for viral RNA within 4–48 hours and 3–13 days after illness onset respectively in the study by Cai J et al; the authors did not state the exact day from illness onset on which the respiratory and stool samples were tested for individual patients; in addition, all patients were tested negative for two consecutive respiratory specimens, but the exact day on which the second consecutive respiratory specimens tested negative for viral RNA was not stated

sample size of Young BE et al was 18 (3 had diarrhea on presentation); the authors did not state which particular patient who tested for stool viral RNA (n=8) had diarrhea

^ The number of days (D) represents the days from the symptom onset (fever, cough, dyspnea, sore throat, nasal congestion, rhinorrhea, sneezing, anorexia) was not reported in the study by Zhang J et al; hence, the 1st day on which respiratory specimens were tested was regard as Day 1 in this graph

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Table 1. Comparison between SARS, MERS and COVID-19

	SARS	MERS	COVID-19
Genus	*Betacoronavirus* B Lineage	*Betacoronavirus* C Lineage	*Betacoronavirus* B Lineage
Virus	SARS-CoV	MERS-CoV	SAR-CoV2
Presumed reservoir host	Asian civet cat (*Paguma larvata*)	Dromedary Camel	? Bat
First reported	Nov 2002 in China	2012 in Saudi Arabia	Dec 2019 in China
Incubation period	Median 4-5 days (maximum 14 days)	Median 5-7days (range 2-14 days)	Mean 6.4 days Range: 2.1 – 11.1 days (2.5^{th} – 97.5^{th} percentile)[30]
Mode of transmission	Human to human Hospital (direct mucous membrane contact with respiratory droplets and/or through exposure to fomites)	Human to human Hospital Zoonotic	Human to human Hospital
Reproductive number (R0)	2-4	3.9[31] (range: 2-5)	Average: 3.3[32] Median: 2.8
Countries and regions affected	29	27	>110
No of cases	8,096	2494	>140,000*
Mechanical ventilation rate		50-89%	
Case fatality ratio	9.6%	34.4%	2.4%*
Risk factors for severe disease		Age >65 years Comorbidities (e.g. DM, malignancy, chronic lung/kidney/liver/heat disease)	Age High SOFA score High D-dimer levels
Stool RT-PCR positive rate	Day 6-14 from illness onset: 86-100% Day 21-23: 43%	15% Up to 24 days	52.7% Up to ≥33 days

Abbreviations: SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; SOFA, Sequential Organ Failure Assessment; RT-PCR, reverse transcription polymerase chain reaction

Table 2. Characteristics of the studies included for meta-analysis

Study	Study Date	Place of study	No.	Age (mean or median [± 1 SD or IQR]; range)	Male (%)	Severe Disease* (n, %)	Fever (n, %)	Respiratory symptoms (n, %)	All GI symptoms# (n, %)	Anorexia (n, %)	Nausea/ vomiting (n, %)	Diarrhea (n, %)	Abdominal pain/ discomfort (n, %)
China													
Guan W[15]	11 Dec –29 Jan	552 hospitals in China	1099	Median: 47y (35–58)	637/1096 (58.1%)	173 (15.7%)	975/1099 (88.7%)	C: 745 (67.8%) E: 370 (33.7%) D: 205 (18.7%)	≥55 (5.0%)	n.a.	55 (5.0%)	42 (3.8%)	n.a.
Cheng J[21]	Up to 19 Feb	Henan	1079	Mean: 46y (range: 3m–94y)	573 (53.2%)	72 (5.7%)	553/605 (91.4%)	C: 110/605 (18.2%) E: 19/605 (3.1%)	21/605 (3.5%)	n.a.	n.a.	n.a.	n.a.
F Fang D[33]	27 Jan–14 Feb	Hubei	305	Median: 57y	146 (47.9%)	46 (15.1%)	163/201 (81.1%)	C: 79/201 (39.3%)	159/201 (79.1%)	101/201 (50.2%)	N: 59/201(29.4%) V: 32/201(15.9%)	66/295 (22.4%)	12/201 (6.0%)
Zhou F [2]	29Dec–31 Jan	Hubei	191	Median: 56y (46–67)	119 (62.3%)	119 (62.3%)	180 (94.2%)	C: 151 (79.1%) E: 44 (23.0%)	≥9 (4.7%)	n.a.	7 (3.7%)	9 (4.7%)	n.a.
Yang W[34]	17 Jan–10 Feb	Zhejiang	149	Mean: 45.1y (±13.4)	81 (54.4%)	2 (1.3%)	114 (76.5%)	C: 87 (58.4%) E: 48 (32.2%) D: 2 (1.3%)	≥11 (7.4%)	n.a.	2 (1.3%)	11 (7.4%)	n.a.
Zhang JJ[35]	16 Jan–3 Feb	Hubei	140	Median: 57y (25–87)	71 (50.7%)	58 (41.4%)	110/120 (91.7%)	C: 90/120 (75.0%) D: 44/120 (36.7%)	55/139 (39.6%)	17/139 (12.2%)	N: 24/139 (17.3%) V: 7/139 (5.0%)	18/139 (12.9%)	8/139 (12.9%)
Wang D[28]	1– 28 Jan	Hubei	138	Median: 56y (42–68)	75 (54.3%)	ICU: 36 (26.1%)	136 (98.6%)	C: 82 (59.4%) E: 37 (26.8%) D: 43 (31.2%)	≥14 (10.1%)	55 (9.9%)	N: 14 (10.1%) V: 5 (3.6%)	14 (10.1%)	3 (2.2%)
Liu K[22]	30 Dec–24 Jan	Hubei	137	Median: 57y (range: 20–83)	61 (44.5%)	34 (24.8%)	112 (81.8%)	C: 66 (48.2%) E:6 (4.4%) D: 26 (19.0%)	11 (8.0%)	n.a.	n.a.	11 (8.0%)	n.a.
Peng YD[36]	20 Jan–15 Feb	Hubei	112	Median: 67y (55–67)	53 (47.3%)	ICU: 16 (14.3%)	101 (90.2%)	C: 76 (67.9%) D: 13 (11.6%)	15 (13.4%)	n.a.	n.a.	15 (13.4%)	n.a.
Zhao W[37]	n.a.	Hunan	101	Mean: 44.4y (range: 17–75)	56 (55.4%)	14 (13.9%)	79 (78.2%)	C: 63 (62.4%) D: 1(1.0%)	≥3 (3.0%)	n.a.	2 (2.0%)	3 (3.0%)	n.a.
Chen N[38]	1–20 Jan	Hubei	99	Mean: 55.5y (±13.1; range: 21–82)	67 (67.7%)	17 (17.2%)	82 (82.8%)	C: 81 (81.8%) D: 31 (31.3%)	≥2 (2.0%)	1 (1.0%)	2 (2.0%)	n.a.	n.a.
Xu X[39]	23 Jan–4 Feb	Guangdong	90	Median: 50y (range: 18–86)	39 (43.3%)	n.a.	70 (77.8%)	C: 57 (63.3%) E: 11 (12.2%)	≥5 (5.6%)	n.a.	N: 5 (5.6%) V: 2 (2.2%)	5 (5.6%)	n.a.
Li K[40]	Jan – Feb	Chongqing	83	Mean: 45 (± 12.3)	44 (53.0%)	25 (30.1%)	7 2 (86.7%)	C: 65 (78.3%) E: 15 (18.1%) D: 9 (10.8%)	7 (8.4%)	n.a.	n.a.	7 (8.4%)	
Shi H[41]	20 Dec – 23 Jan	Hubei	81	Mean: 49.5y (±11.0)	42 (51.9%)	n.a.	59 (72.8%)	C: 48 (59.2%) E: 15 (18.5%) D: 34 (42.0%)	≥4 (4.9%)	1 (1.2%)	Vomiting: 4 (4.9%)	3 (3.7%)	n.a.
Wu J[42]	22 Jan–14 Feb	Jiangsu	80	Mean: 46.1y (±15.4)	39 (48.8%)	3 (3.8%)	63 (78.8%)	C: 51 (63.8%) D: 30 (37.5%)	≥1 (1.3%)	n.a.	1 (1.3%)	1 (1.3%)	n.a.
Wu J[43]	Jan–Feb	Chongqing	80	Mean: 44y (±11)	42 (52.5%)	n.a.	61 (76.3%)	C: 58 (72.5%) E: 11 (13.8%) D: 7 (8.8%)	7 (8.8%)	n.a.	n.a.	7 (8.8%)	
Fang X[44]	22 Jan–18 Feb	Anhui	79	Mean: 45.1 (±16.6)	45 (60.0%)	24 (30.4%)	67 (84.8%)	C: 45 (57.0%) E: 10 (12.7%) D: 9 (11.4%)	≥5 (6.3%)	5 (6.3%)	n.a.	4 (5.1%)	n.a.
Xiao F[23]	1–14 Feb	Guangdong	73	43y (range: 10m–78y)	41 (56.2%)	ICU: 4 (5.5%)	n.a.	53 (72.6%)	26 (35.6%)	n.a.	n.a.	26 (35.6%)	n.a.

Xu XW[20]	10–26 Jan	Zhejiang	62	Median: 41y (32–52)	35 (56.5%)	ICU: 1 (1.6%)	48 (77.4%)	C: 50 (80.6%) E: 35 (56.5%)	3 (4.8%)	n.a.	n.a.	3 (4.8%)	n.a.
Zhou S[45]	16–30 Jan	Hubei	62	Mean: 52.8y (±12.2; range: 30–70)	39 (62.9%)	n.a.	54	C: 28 D: 15	9 (14.%)	n.a.	n.a.	9 (14.%)	
Yang X[46]	24 Dec –26 Jan	Hubei	52	Mean: 59.7y (±13.3)	35 (67.3%)	ICU: 52 (100%)	51 (98.1%)	C: 40 (46.9%) D: 33 (63.5%)	2 (3.8%)	n.a.	2 (3.8%)	n.a.	n.a.
Xu YH[47]	Jan–Feb	Beijing & Hebei	50	Mean: 43.9y (±16.8; range: 3–85)	29 (58.0%)	13 (26%)	43 (86.0%)	C:20 (40.0%) E: 7 (14.0%) D: 4 (8.0%)	1 (2.0%)	n.a.	n.a.	n.a.	n.a.
Xiong Y[48]	11 Jan–5 Feb	Hubei	42	Mean: 49.5y (±14.1; range: 26–75)	25 (59.5%)	n.a.	36 (85.7%)	C: 27 (64.3%) D: 8 (19.0%)	10 (23.8%)	n.a.	n.a.	10 (23.8%)	n.a.
Huang C[18]	16 Dec –2 Jan	Hubei	41	Median: 49y (41–58)	30 (73.2%)	ICU: 13 (31.7%)	40 (97.5%)	C: 31 (75.6%) E: 11/39 (28.2%) D: 22/40 (55.0%)	1/38 (2.6%)	n.a.	n.a.	1/38 (2.6%)	n.a.
Wu WS[49]	19–25 Jan	Tianjin	40	Mean: 45y (range: 10–76)	13 (32.5%)	17 (42.5%)	38 (95.0%)	C: 14 (35.0%) E: 3 (7.5%) D: 2 (5.0%)	≥6 (15.0%)	n.a.	3 (7.5%)	6 (15.0%)	3 (7.5%)
Huang Y[19]	21 Dec –8 Jan	Hubei	34	Mean: 56.2y (±17.1; range: 26–88)	14 (41.2%)	8 (23.5%)	32 (94.1%)	C: 17 (50.0%) E: 8 (23.5%) D: 5 (14.7%)	5 (14.7%)	n.a.	n.a.	5 (14.7%)	n.a.
Li YY[50]	Jan–Feb	Hubei	31	Mean: 54y (±13)	18 (58.1%)	11 (35.5%)	25 (80.6%)	C: 25 (80.6%) E: 16 (51.6%) D: 10 (32.3%)	≥13 (41.9%)	13 (41.9%)	5 (16.1%)	3 (9.7%)	n.a.
Liu M[51]	11 Jan–3 Feb	Hubei	30	Mean: 35y (±8; range: 21–59	10 (33.3%)	4 (13.3%)	23 (76.7%)	C: 25 (83.3%) D: 14 (46.7%)	9 (30%)	n.a.	N/V/D: 9 (30.0%)		n.a.
Pan F[52]	12 Jan–6 Feb	Hubei	21	Mean: 40y (±9; range: 25–63	6 (28.6%)	0	18 (85.7%)	C: 12 (57.1%) E: 6 (28.6%)	9 (42.9%)	9 (42.9%)	n.a.	n.a.	n.a.
Zou L[53]	7–26 Jan	Guangdong	18	Median: 59y (range: 26–76)	9 (50.0%)	ICU: 3 (16.7%)	10 (55.6%)	C: 10 (55.6%) D: 3 (16.7%)	3 (16.7%)	1 (5.6%)	N: 1 (5.6%)	1 (5.6%)	0
Wang L[54]	21 Jan – 5 Feb	Henan	18	Median: 39y (29–55)	10 (55.6%)	ICU: 2 (11.1%)	17 (94.4%)	C:10 (55.6%) D: 4 (22.2%)	3 (16.7%)	n.a.	1 (5.6%)	3 (16.7%)	n.a.
Zhang J[55]	27 Jan–10 Feb	Zhejiang	14	Median: 41y (18–87)	7 (50.0%)	n.a.	13 (92.9%)	C: 10 (71.4%)	n.a.	n.a.	0	0	n.a.
Chang[56]	16–29 Jan	Beijing	13	Median: 34y (34–78)	10 (76.9%)	0	12 (92.3%)	C: 6 (46.2%) E: 2 (15.4%)	1 (7.7%)	n.a.	n.a.	1 (7.7.%)	n.a.
Liu Y[57]	Up to 21 Jan	Shenzen	12	Range: 10–72y	8 (66.7%)	6 (50.0%)	10 (83.3%)	C: 11 (91.7%)	≥3 (25.0%)	n.a.	2 (16.7%)	2 (16.7%)	n.a.
Huang R[58]	21 Jan–1 Feb	Jiangsu	11	n.a.	4 (36.4%)	n.a.	9 (90.0%)	C: 8 (80.0%)	1 (10.0%)	n.a.	n.a.	1 (10.0%)	n.a.
Shen J[59]	Feb	Liaoning	10	Range: 33–85y	6 (60%)	2 (20.0%)	9 (90%)	C: 9 (90%)	4 (40.0%)	n.a.	n.a.	4 (40.0%)	n.a.
Zhang MQ[60]	18 Jan–3 Feb	Beijing	9	Median: 36y (range: 15–49)	5 (55.6%)	n.a.	8 (88.9%)	C: 5 (55.6%) E: 1 (11.1%)	1 (11.1%)	n.a.	n.a.	1 (11.1%)	n.a.
An P[27]	17 – 24 Jan	Hubei	9	Median: 35.8y (28–45)	4 (44.4%)	0	After admission :5 (55.6%)	After admission: 5 (55.6%)	9 (100%)	6 (66.7%)	1 (11.1%)	1 (11.1%)	0
Qiu YY[61]	3 Feb	Henan	8	Range: 4–53y	4 (50.0)%	0	5 (62.5)	C: 3 (37.5%)	1 (12.5%)	n.a.	n.a.	1 (12.5%)	n.a.
Chan	10 Jan	Shenzhen	6	Range: 36–66y	3	0	5 (83.3%)	C: 4 (66.7%)	2 (33.3%)	n.a.	n.a.	2 (33.3%)	n.a.

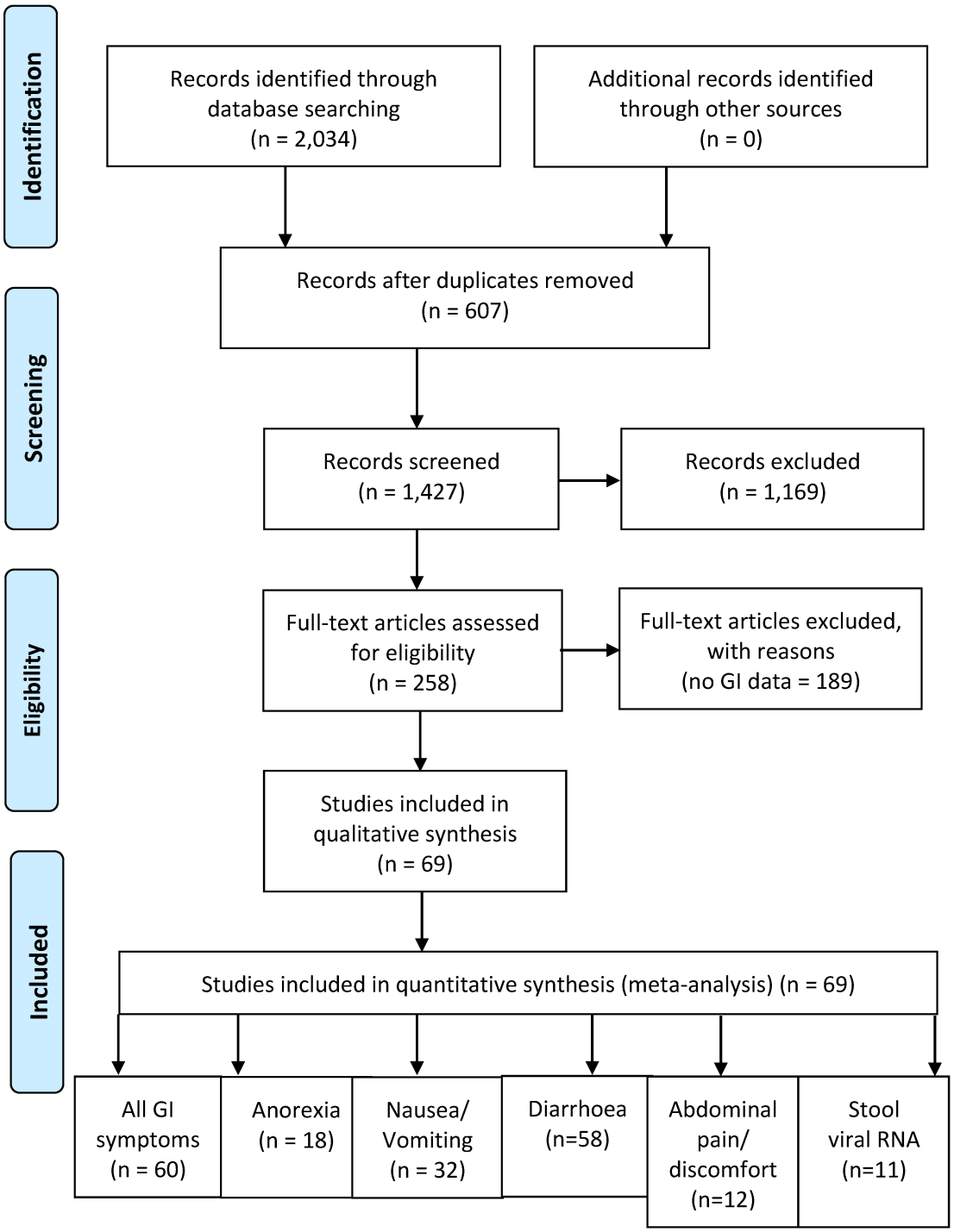
JF[62]					(50%)			E: 1 (16.7%)					
Ren LL[63]	18–29 Dec	Hubei	5	Range: 41–65y	3 (60.0%)	4 (80.0%)	5 (100%)	C: 5 (100%) E: 1 (20.0%) D: 4 (80.0%)	n.a.	n.a.	n.a.	0	n.s.
Wang Z[17]	21–24 Jan	Shanghai	4	Range: 19–63y	3 (75.0%)	0	4 (100%)	C: 3 (75.0%)	n.a.	n.a.	n.a.	0	n.a.
Yu P[64]	20–23 Jan	Shanghai	4	Range: 65–88y	2 (50.0%)	1 (25.0%)	4 (100%)	C: 1 (25.0%)	1 (25.0%)	1 (25.0%)	n.a.	n.a.	n.a.
Yang Z[65]	23–25 Jan	Guandong	3	Range: 25–62y	2 (66.7%)	0	2 (66.7%)	C: 2 (66.7%) E: 1 (33.3%)	2 (66.7%)	0	0	2 (66.7%)	0
Huang WH[66]	n.a.	Taiwan	2	Range: 73–74y	0	0	2 (100%)	C: 1 (50.0%)	2 (100%)	2 (100%)	n.a.	0	0
Cheng SC[67]	20 Jan	Taiwan	1	55y	0	0	1 (100%)	C: 1 (100%) D: 1 (100%)	1 (100%)	n.a.	n.a.	n.a.	1 (100%)
Li J[68]	24 Jan	Sichuan	1	33y	1 (100%)	0	1 (100%)	0	1 (100%)	1 (100%)	n.a.	n.a.	n.a.
Han W[69]	21 Jan	Gansu	1	47y	1 (100%)	1 (100%)	1 (100%)	C: 1 (100%)	1 (100%)	n.a.	N: 1 (100%)	n.a.	n.a.
Song Y[70]	29 Jan	Shandong	1	22y	1 (100%)	0	1 (100%)	0	1 (100%)	n.a.	n.a.	1 (100%)	n.a.
Zhang H[71]	18 Jan	Hubei	1	57y	1 (100%)	0	1 (100%)	C: 1 (100%) D: 1 (100%)	1 (100%)	n.a.	n.a.	1 (100%)	n.a.
Wu T[72]	8 Feb	Hubei	1	48y	1 (100%)	0	1 (100)%)	C: 1 (100%)	n.a.	n.a.	0	n.a.	n.a.
Lin C[73]	25 Jan	Gansu	1	61y	1 (100%)	0	0	D: 1 (100%)	n.a.	n.a.	n.a.	0	n.a.
Outside of China													
Kong I[74]	Up to 14 Feb	South Korea	28	Mean: 42.6y (20–73)	15 (53.6%)	n.a.	9 (32.1%)	Cough: 5 (17.9%)	2/18 (11.1%)	n.a.	n.a.	2/18 (11.1%) (day 3 & 4)	n.a.
Young BE[75]	23 Jan–3 Feb	Singapore	18	Median: 41 (range: 31–73)	9 (50.0%)	3 (16.7%)	13 (72.2%)	C 15 (83.3%) D: 2 (94.4%)	3 (16.7%)	n.a.	n.a.	3 (16.7%)	n.a.
Kim JY[76]	10–19 Jan	South Korea	2	Range: 35–55y	1 (50%)	1 (50.0%)	2 (100%)	2 (100%)	2 (50.0%)	0	0	2 (100%)	0
Lillie PJ[77]	30–31 Jan	UK	2	Range: 23–50y	1 (50.0%)	0	2 (100%)	C: 2 (100%)	1 (50.0%)	n.a.	n.a.	n.a.	n.a.
Phan LT[78]	22 Jan	Vietnam	2	Range: 27–65y	2 (100%)	0	2 (100%)	C: 1 (100%)	1 (50.0%)	n.a.	1 (50.0%)	1 (50.0%)	n.a.
Yan G[79]	9–13 Feb	Singapore	2	Both 57y	1 (50.0%)	n.a.	2 (100%)	C: 2 (100%) D: 1 (50.0%)	1 (50.0%)	n.a.	n.a.	1 (50.0%)	n.a.
Holshue[80]	20 Jan	USA	1	35y	1 (100%)	1 (100%)	1 (100%)	C: 1 (100%)	1 (100%)	n.a.	1 (100%)	1 (100%)	1 (100%)
Pediatric patients													
Wang D[81]	25 Jan–21 Feb	6 provinces (northern China)	31	Median: 7.1y (range: 6m–17y)	15 (48.4%)	0	20 (64.5%)	C: 14 (45.2%) E: 6 (19.4%)	5 (16.1%)	n.a.	2 (6.5%) (1 as 1st presenting symptom)	3 (9.7%) (all as 1st presenting symptom)	n.a.
Xia W[82]	23 Jan–8 Feb	Hubei	20	Median: 2.1y (range: 1d–14.6y)	13 (65.0%)	n.a.	12 (60.0%)	C: 13 (65.0%)	≥3 (15.0%)	n.a.	2 (10.0%)	3 (15.0%)	n.a.
Cai J[83]	19 Jan–3 Feb	Shanghai, Hainan, Anhui & Shandong	10	Mean: 74m (range: 3–131)	4 (40.0%)	0	8 (80.0%)	C: 6 (60.0%)	n.a.	n.a.	n.a.	0	n.a.
Chen F[84]	27 Jan	Hubei	1	13m	1 (100%)	1 (100%)	1 (100%)	0	1 (100%)	1 (100%)	1 (100%)	1 (100%)	n.a.
Zeng	5 Feb	Hubei	1	17d	1 (100%)	0	0	0	1 (100%)	1 (100%)	1 (100%)	1 (100%)	n.a.

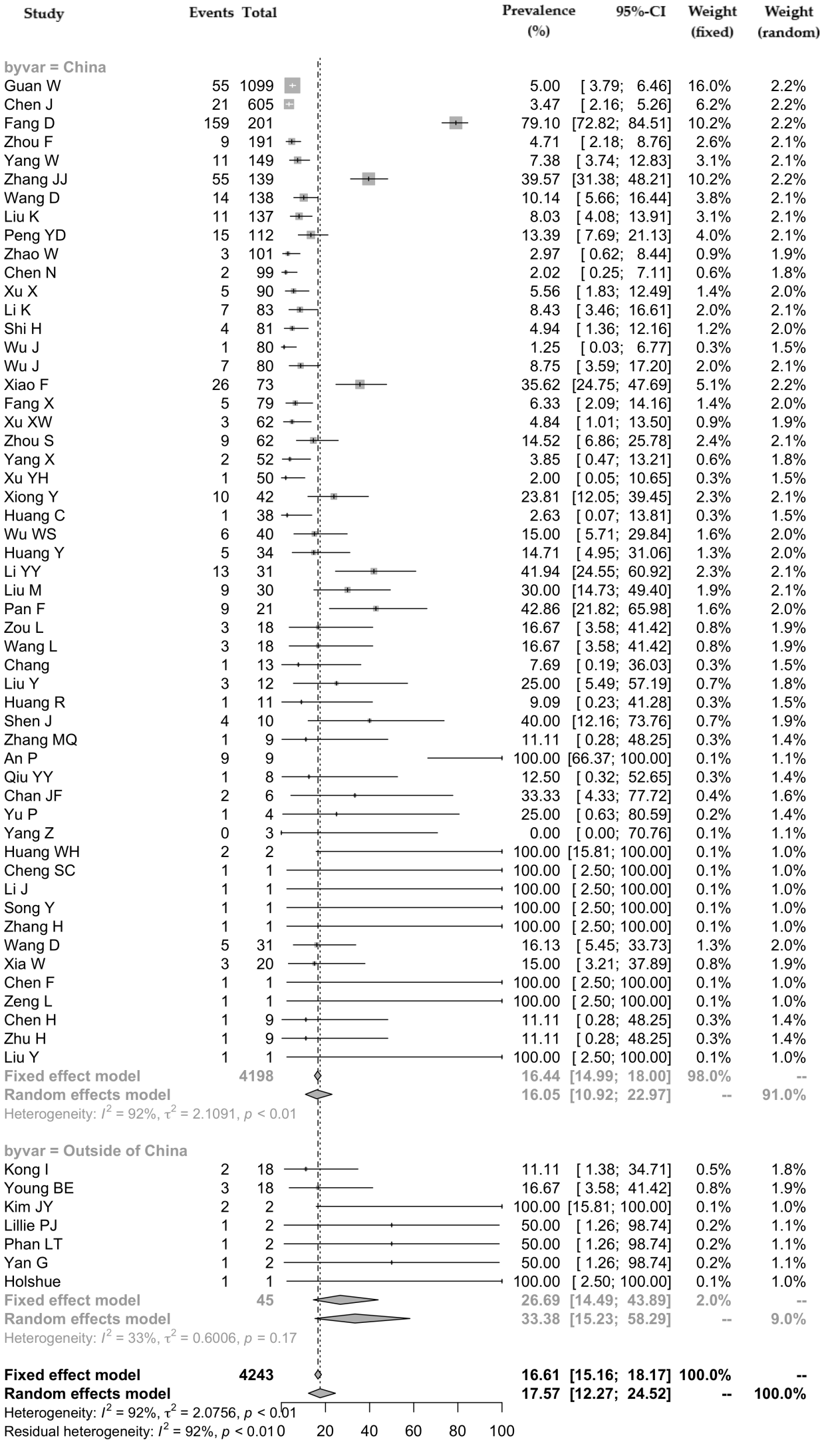
L[85]													
Zhang Yl[86]	26 Jan	Hainan	1	3m	0	0	1 (100%)	0	n.a.	0	0	0	n.a.
Pregnant women													
Chen H[87]	20 – 31 Jan	Hubei	9	Range: 26–40y	0	n.a.	7 (77.8%)	C: 4 (44.4%) D: 1 (11.1%)	1 (11.1%)	n.a.	n.a.	1 (11.1%)	n.a.
Zhu H[88]	20 Jan–Feb 5	Hubei	9	Range: 25–35y	0	n.a.	8 (88.9%)	C: 4 (44.4%)	1 (11.1%)	n.a.	n.a.	1 (11.1%)	n.a.
Chen S[89]	21 Jan–4 Feb	Hubei	3	Range: 23–34y	0	0	1 (33.3%)	D: 1 (33.3%)	n.a.	n.a.	n.a.	0	n.a.
Liu Y[90]	5 Feb	Shandong	1	38y	0	0	0	0	1 (100%)	1 (100%)	N: 1 (100%)	1 (100%)	0

* Severe disease was defined as the American Thoracic Society and Infectious Disease Society of America guidelines for community-acquired pneumonia, need of ICU admission, and death.

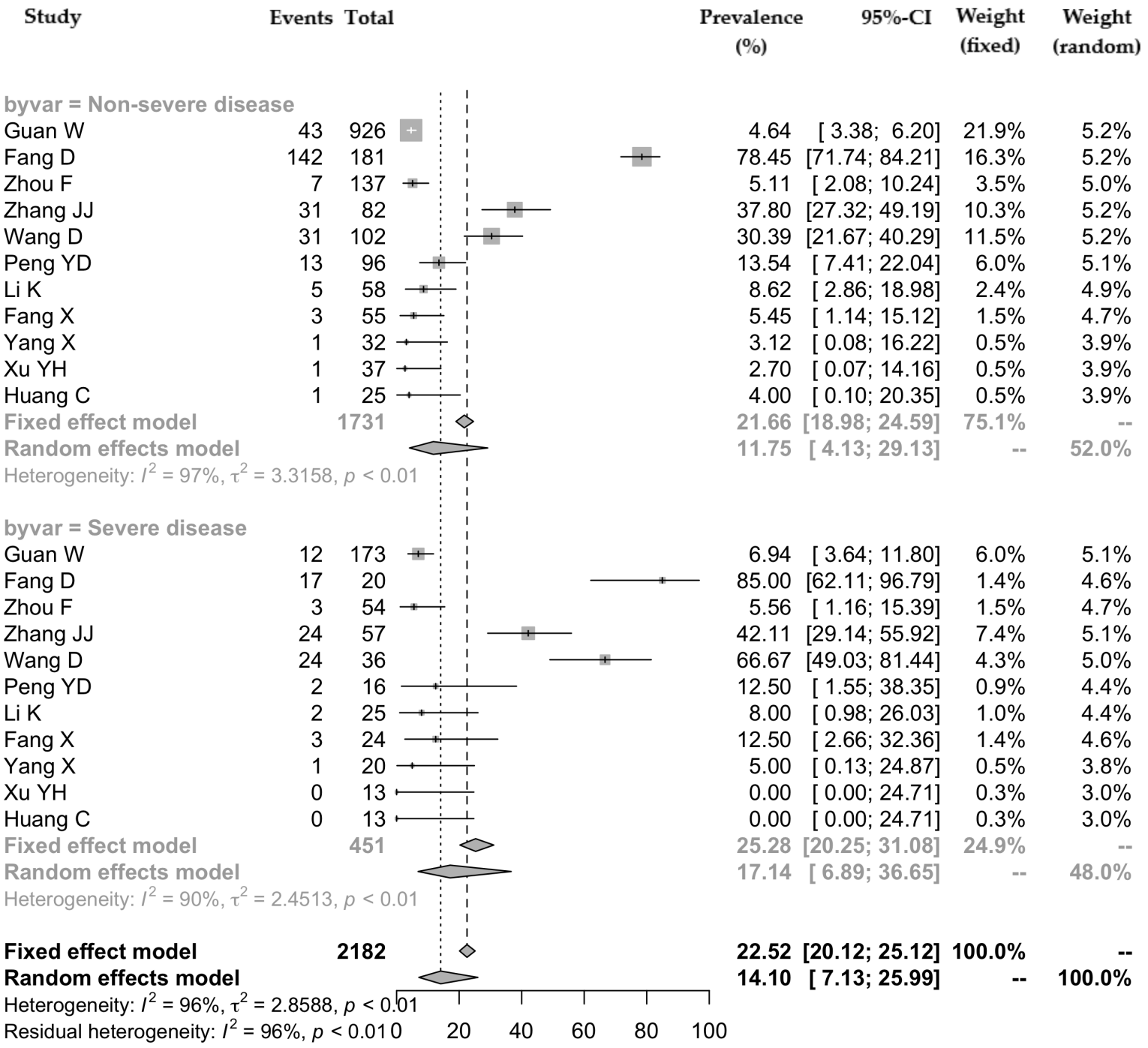
If all gastrointestinal symptoms were not reported and the number of events of any individual GI symptoms was less than one, it was regarded as "not available" and was excluded from the meta-analysis of all gastrointestinal symptoms. However, this study was still included in the meta-analysis of individual gastrointestinal symptom if the proportion of patients with that symptom was reported.

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation; IQR: interquartile range; GI, gastrointestinal; C, cough; E, expectoration; D, dyspnea; n.a., not available; N: nausea; V: vomiting; ICU, intensive care unit; UK, United Kingdom; USA, United States of America


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2,034)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 607)
Records screened (n = 1,427)
Records excluded (n = 1,169)
Full-text articles assessed for eligibility (n = 258)
Full-text articles excluded, with reasons (no GI data = 189)
Studies included in qualitative synthesis (n = 69)
Studies included in quantitative synthesis (meta-analysis) (n = 69)
All GI symptoms (n = 60)
Anorexia (n = 18)
Nausea/ Vomiting (n = 32)
Diarrhoea (n=58)
Abdominal pain/ discomfort (n=12)
Stool viral RNA (n=11)


Study
Events Total
Prevalence (%)
95%-CI
Weight (fixed)
Weight (random)
byvar = China
Guan W 55 1099 5.00 [3.79; 6.46] 16.0% 2.2%
Chen J 21 605 3.47 [2.16; 5.26] 6.2% 2.2%
Fang D 159 201 79.10 [72.82; 84.51] 10.2% 2.2%
Zhou F 9 191 4.71 [2.18; 8.76] 2.6% 2.1%
Yang W 11 149 7.38 [3.74; 12.83] 3.1% 2.1%
Zhang JJ 55 139 39.57 [31.38; 48.21] 10.2% 2.2%
Wang D 14 138 10.14 [5.66; 16.44] 3.8% 2.1%
Liu K 11 137 8.03 [4.08; 13.91] 3.1% 2.1%
Peng YD 15 112 13.39 [7.69; 21.13] 4.0% 2.1%
Zhao W 3 101 2.97 [0.62; 8.44] 0.9% 1.9%
Chen N 2 99 2.02 [0.25; 7.11] 0.6% 1.8%
Xu X 5 90 5.56 [1.83; 12.49] 1.4% 2.0%
Li K 7 83 8.43 [3.46; 16.61] 2.0% 2.1%
Shi H 4 81 4.94 [1.36; 12.16] 1.2% 2.0%
Wu J 1 80 1.25 [0.03; 6.77] 0.3% 1.5%
Wu J 7 80 8.75 [3.59; 17.20] 2.0% 2.1%
Xiao F 26 73 35.62 [24.75; 47.69] 5.1% 2.2%
Fang X 5 79 6.33 [2.09; 14.16] 1.4% 2.0%
Xu XW 3 62 4.84 [1.01; 13.50] 0.9% 1.9%
Zhou S 9 62 14.52 [6.86; 25.78] 2.4% 2.1%
Yang X 2 52 3.85 [0.47; 13.21] 0.6% 1.8%
Xu YH 1 50 2.00 [0.05; 10.65] 0.3% 1.5%
Xiong Y 10 42 23.81 [12.05; 39.45] 2.3% 2.1%
Huang C 1 38 2.63 [0.07; 13.81] 0.3% 1.5%
Wu WS 6 40 15.00 [5.71; 29.84] 1.6% 2.0%
Huang Y 5 34 14.71 [4.95; 31.06] 1.3% 2.0%
Li YY 13 31 41.94 [24.55; 60.92] 2.3% 2.1%
Liu M 9 30 30.00 [14.73; 49.40] 1.9% 2.1%
Pan F 9 21 42.86 [21.82; 65.98] 1.6% 2.0%
Zou L 3 18 16.67 [3.58; 41.42] 0.8% 1.9%
Wang L 3 18 16.67 [3.58; 41.42] 0.8% 1.9%
Chang 1 13 7.69 [0.19; 36.03] 0.3% 1.5%
Liu Y 3 12 25.00 [5.49; 57.19] 0.7% 1.8%
Huang R 1 11 9.09 [0.23; 41.28] 0.3% 1.5%
Shen J 4 10 40.00 [12.16; 73.76] 0.7% 1.9%
Zhang MQ 1 9 11.11 [0.28; 48.25] 0.3% 1.4%
An P 9 9 100.00 [66.37; 100.00] 0.1% 1.1%
Qiu YY 1 8 12.50 [0.32; 52.65] 0.3% 1.4%
Chan JF 2 6 33.33 [4.33; 77.72] 0.4% 1.6%
Yu P 1 4 25.00 [0.63; 80.59] 0.2% 1.4%
Yang Z 0 3 0.00 [0.00; 70.76] 0.1% 1.1%
Huang WH 2 2 100.00 [15.81; 100.00] 0.1% 1.0%
Cheng SC 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Li J 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Song Y 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Zhang H 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Wang D 5 31 16.13 [5.45; 33.73] 1.3% 2.0%
Xia W 3 20 15.00 [3.21; 37.89] 0.8% 1.9%
Chen F 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Zeng L 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Chen H 1 9 11.11 [0.28; 48.25] 0.3% 1.4%
Zhu H 1 9 11.11 [0.28; 48.25] 0.3% 1.4%
Liu Y 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Fixed effect model 4198 16.44 [14.99; 18.00] 98.0% --
Random effects model 16.05 [10.92; 22.97] -- 91.0%
Heterogeneity: I^2 = 92%, τ^2 = 2.1091, p < 0.01
byvar = Outside of China
Kong I 2 18 11.11 [1.38; 34.71] 0.5% 1.8%
Young BE 3 18 16.67 [3.58; 41.42] 0.8% 1.9%
Kim JY 2 2 100.00 [15.81; 100.00] 0.1% 1.0%
Lillie PJ 1 2 50.00 [1.26; 98.74] 0.2% 1.1%
Phan LT 1 2 50.00 [1.26; 98.74] 0.2% 1.1%
Yan G 1 2 50.00 [1.26; 98.74] 0.2% 1.1%
Holshue 1 1 100.00 [2.50; 100.00] 0.1% 1.0%
Fixed effect model 45 26.69 [14.49; 43.89] 2.0% --
Random effects model 33.38 [15.23; 58.29] -- 9.0%
Heterogeneity: I^2 = 33%, τ^2 = 0.6006, p = 0.17
Fixed effect model 4243 16.61 [15.16; 18.17] 100.0% --
Random effects model 17.57 [12.27; 24.52] -- 100.0%
Heterogeneity: I^2 = 92%, τ^2 = 2.0756, p < 0.01
Residual heterogeneity: I^2 = 92%, p < 0.01
0
20
40
60
80
100

GI Symptoms	Events	Total	Prevalence (%)	95% CI
Anorexia	216	830	26.8	16.2–40.8
Nausea/ vomiting	210	2664	10.2	6.6–15.3
Diarrhoea	326	3536	12.5	9.6–16.0
Abdominal pain/ discomfort	52	751	9.2	5.7–14.5
Any GI symptom	537	4243	17.6	12.3–24.5




Study
Case No.
Age/Sex
Xiao F et al 1 M/78y
Cai J et al 2 M/84m
Kim JY et al 3 M/55y
Cheng SC et al 4 F/55y
Cai J et al 5 F/3m
Young BE et al 6
Cai J et al 7 F/131m
Yang Z et al 8 M/28y
Young BE et al 9
Cai J et al 10 F/131m
Cai J et al 11 M/108m
Young BE et al 12
Young BE et al 13
Yang Z et al 14 M/62y
Cai J et al 15 F/7m
Young BE et al 16
Kim JY et al 17 F/35y
Zhang Y et al 18 F/3m
Zhang J el al 19
Zhang J el al 20
Zhang J el al 21
Zhang J el al 22
Holshue et al 23 M/35y
Zeng L et al 24 M/17d
Young BE et al 25
Zhang J el al 26
Zhang J el al 27
Yang Z et al 28 F/25y
Young BE et al 29
Young BE et al 30
Zhang J el al 31
Zhang J el al 32
Zhang J el al 33
Zhang J el al 34
Zhang J el al 35
Zhang J el al 36
Zhang J el al 37
Zhang J el al 38
D 1 D 2 D 3 D 4 D 5 D 6 D 7 D 8 D 9 D 10 D 11 D 12 D 13 D 14 D 15 D 16 D 17 D 18 D 19 D 20 D 21 D 22 D 23 D 24 D 25 D 26 D 27 D 28 D 29 D 30 D 31 D 32 D 33
Fever
Cough or dyspnoea
Sore throat
Anorexia
Nasal congestion, rhinorrhoea or sneezing
Abdominal pain / discomfort
Vomiting
Diarrhoea
Respiratory specimen viral RNA + ve
Respiratory specimen viral RNA - ve
Stool viral RNA + ve
Stool viral RNA - ve

What you need to know:

BACKGROUND AND CONTEXT: Infection with SARS-Co-2 virus, which causes COVID-19, results in respiratory as well as gastrointestinal symptoms; virus RNA has been detected in fecal samples.

NEW FINDINGS: A meta-analysis of publications found that gastrointestinal symptoms have been reported in 17.6% of patients with COVID-19. Stool samples from 48.1% of patients tested positive for virus RNA; stool samples from 70.3% of these patients tested positive for virus RNA even after respiratory specimens tested negative.

LIMITATIONS: This study analyzed mostly data from reported cases from China; systematic data collection was lacking for most studies.

IMPACT: Gastrointestinal symptoms occur in almost 18% of patients with COVID-19. Virus RNA can be detected in fecal samples—even those collected after respiratory samples test negative.

Lay Summary: Many patients with COVID-19 develop gastrointestinal symptoms. The virus can be detected in stool, so patients and caregivers should take care to avoid fecal–oral transmission of the virus.