Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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CLINICAL—ALIMENTARY TRACT

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

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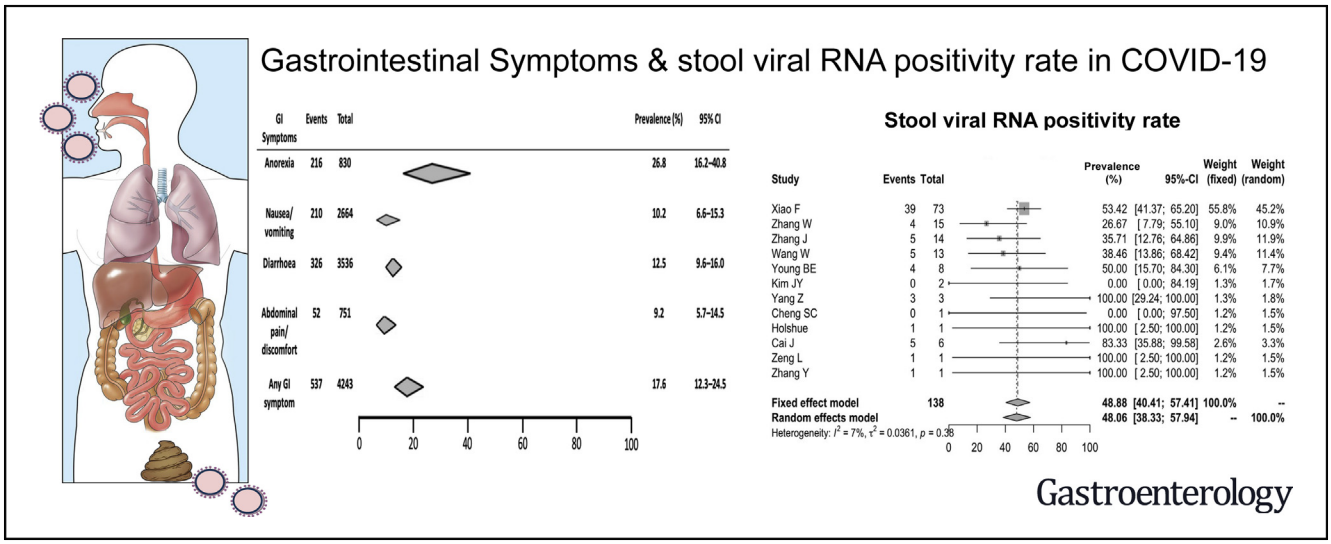

See Covering the Cover synopsis on page 4.

BACKGROUND & AIMS: Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (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 February 29, 2020),and searched PubMed, Embase, Cochrane, and 3 Chinese databases through March 11, 2020, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We analyzed pooled data on the prevalence of overall and individual gastrointestinal symptoms (loss of appetite, 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 $\log_{10}$ copies per milliliter in patients with diarrhea vs 3.9 $\log_{10}$ copies per milliliter 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% confidence interval [CI], 12.3–24.5); 11.8% of patients with nonsevere 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 had negative test results. Health care workers should therefore exercise caution in collecting fecal samples or performing endoscopic procedures in patients with COVID-19, even during patient recovery.

Keywords: Fecal-to-Oral Transmission; PRISMA; SARS; Viral Persistence.

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.

In December 2019, a cluster of an unidentified form of viral pneumonia cases was first reported in Wuhan, China, and 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 severe acute respiratory syndrome (SARS) CoV in 2003. Through March 16, 2020, more than 150,000 cases had been 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 8100 cases in Korea. Although the number of new cases seems to be declining in China, the numbers of cases are rising in an exponential manner in Europe, North America, and the Middle East. The death toll has already reached more than 5700 globally, with more than 3000 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) declared a Public Health Emergency of International Concern on January 30, 2020 and further labeled it as a pandemic on March 11, 2020.

The disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization, and the virus was termed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. 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 2 previously identified coronaviruses, SARS-CoV and Middle East respiratory syndrome (MERS) CoV, which cause SARS and MERS, this is the third coronavirus identified to cause severe viral pneumonia in humans (Table 1). Similar to the other 2 coronaviruses, SARS-CoV-2 has very high infectivity because no one has immunity, resulting in an ongoing global health crisis.

Based on existing observations, the case fatality rate of COVID-19 is lower than that of SARS and MERS; it is estimated to be about 1%–2% but is much higher in older patients. In addition to age, a high Sequential Organ Failure Assessment score and D-dimer level >1 μg/L on admission are associated with poor prognosis.[5] 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 patients with SARS.[6] 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 days 6–14 of illness and could persist for >30 days of illness.[7,8] It was subsequently found that SARS-CoV binds to angiotensin-converting enzyme 2 (ACE2) receptors of the intestinal and respiratory tracts, which is the entry point for the virus to the epithelial cells.[9] Similarly, up to a quarter of patients with MERS also reported gastrointestinal symptoms such as diarrhea or abdominal pain.[10] Again, MERS-CoV could be detected in 15% of stool samples and could persist for up to 24 days after diagnosis.[11] It was shown that the human intestinal tract, including primary intestinal epithelial cells, small intestine explants, and intestinal organoids, is highly susceptible to MERS-CoV.[12]

Enteric manifestations of SAR-CoV-2 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 the increasing number of reported cases of

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Abbreviations used in this paper: **ACE2, angiotensin-converting enzyme 2; CI, confidence interval; CoV, coronavirus; cpm, copies per milliliter; IQR, interquartile range; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.**

Most current article

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

Characteristics	SARS	MERS	COVID-19
Genus	*Betacoronavirus* B lineage	*Betacoronavirus* C lineage	*Betacoronavirus* B lineage
Virus	SARS-CoV	MERS-CoV	SAR-CoV-2
Presumed reservoir host	Asian civet cat (*Paguma larvata*)	Dromedary camel	Bat (?)
First reported	November 2002 in China	2012 in Saudi Arabia	December 2019 in China
Incubation period, *d*	Median: 4–5 Maximum: 14	Median: 5–7 Range: 2–14	Mean: 6.4 Range (2.5th–97.5th percentile)[2]: 2.1–11.1
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 (Choi et al[3]) (range: 2–5)	Average: 3.3 (Liu et al[4]) Median: 2.8
Countries and regions affected	29	27	>110
Number of cases	8096	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 (eg, DM, malignancy, chronic lung/kidney/liver/heart disease)	Age High SOFA score High D-dimer levels
Stool RT-PCR positive rate, %	Days 6–14 from illness onset: 86–100 Days 21–23: 43	15 Up to 24 days	52.7 Up to ≥33 days

DM, diabetes mellitus; SOFA, Sequential Organ Failure Assessment; RT-PCR, reverse transcription polymerase chain reaction.

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-CoV-2 based on published data as well as the data from our recent cohort of COVID-19 patients in Hong Kong.

Methods

Coronavirus Disease 2019 Cohort From Hong Kong

We included a cohort of 59 patients with virologically confirmed COVID-19 diagnosed between February 2 and 29, 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.

Study Selection

Three databases, PubMed, Embase, and Cochrane Library, were searched following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13] from December 1, 2019, through March 11, 2020. Keywords were *2019-nCoV-2*, *coronavirus*, *COVID-19*, *SARS-CoV-2*, or *novel coronavirus*. The search details are listed in the Supplementary Material. Additional related articles were retrieved from 3 Chinese electronic databases (Chongqing VIP [CQVIP], Wanfang Data, and Chinese National Knowledge Infrastructure). Potential studies were retrieved after title/abstract screening by 1 investigator (KSC). All articles were imported to Endnote X9.2 (Thompson and Reuters, Philadelphia, PA), and duplicates were removed.

Selection Criteria

Two authors (KSC and IFH) determined the eligibility of studies independently, and dissonance was resolved by a third author (WKL). The inclusion criteria included (1) study population: patients with COVID-19 (including adult or pediatric patients and pregnant women); (2) study design: case reports/case series, prospective/retrospective cohort studies, case-control studies, and randomized controlled trials. There was no language restriction. The exclusion criteria were (1) patients without virologic proof of SARS-CoV-2 infection; (2) asymptomatic patients infected with SARS-CoV-2; (3) studies that did not report gastrointestinal symptoms; and (4) review articles, meta-analyses, editorials, and other forms (eg, commentaries).

If all gastrointestinal symptoms were not reported and the number of events of any individual gastrointestinal symptom was less than 1, this was considered not available and was excluded from the meta-analysis of all gastrointestinal symptoms. However, the 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[14,15] that did not report on gastrointestinal 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), and 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,[16] need for intensive care unit admission, and death.

Data Analysis

All statistical analyses were performed using R, version 3.2.3, statistical software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as median (interquartile range [IQR]) or mean ± standard deviation. The prevalence of gastrointestinal symptoms is expressed as proportion and 95% confidence interval (CI) using the random effects model and is presented as a forest plot. We used the Cochran Q test to detect heterogeneity among studies, with a P value of <.10 indicating significant heterogeneity. We calculated the 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.[17]

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

Results

Corona Virus Disease 2019 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 years) 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 test results were positive in 9 (15.3%) patients, and the median viral load was 4.7 $\log_{10}$ copies per milliliter (cpm) (range, 3.4–7.6 $\log_{10}$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%; $P = .019$). 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 2034 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, nongastrointestinal 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 4243 patients with COVID-19. Fifty-three (88.3%) studies were from China, and 7 (11.7%) were from other countries (South Korea, n = 2; Singapore, n = 2; Vietnam, n = 1; United States, n = 1; and United Kingdom, n = 1). Of the 53 studies from China, 27 (50.9%) were from Hubei Province where Wuhan is located. One study by Guan et al[18] 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 ($P < .001$; $I^2 = 91.5\%$).

For individual gastrointestinal symptoms, there were 18 studies reporting on the prevalence of loss of appetite, 32 on nausea/vomiting, 58 on diarrhea, and 12 on abdominal pain. The pooled prevalence of loss of appetite was 26.8% (95% CI, 16.2–40.8) (Supplementary Figure 1), of nausea/vomiting was 10.2% (95% CI, 6.6–15.3) (Supplementary Figure 2), of diarrhea was 12.5% (95% CI, 9.6–16.0) (Supplementary Figure 3), and of abdominal pain/discomfort was 9.2% (95% CI, 5.7–14.5) (Supplementary Figure 4). Figure 3 shows the summary estimates for the prevalence of individual and all gastrointestinal symptoms. Significant heterogeneity among studies was seen for loss of appetite, nausea/vomiting, and diarrhea ($P < .001$; $I^2 = 74.6\%$–85.2%), whereas the heterogeneity was less for abdominal pain/discomfort ($P = .008$; $I^2 = 57.0\%$).

Subgroup Analysis

Geographic Variations and Gastrointestinal Symptoms. The pooled prevalences of all gastrointestinal symptoms were 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 ($P = .09$). However, there was significant heterogeneity among the studies conducted in China ($P < .001$; $I^2 = 92.4\%$) but not among the studies from other countries ($P = .174$; $I^2 = 33.2\%$).

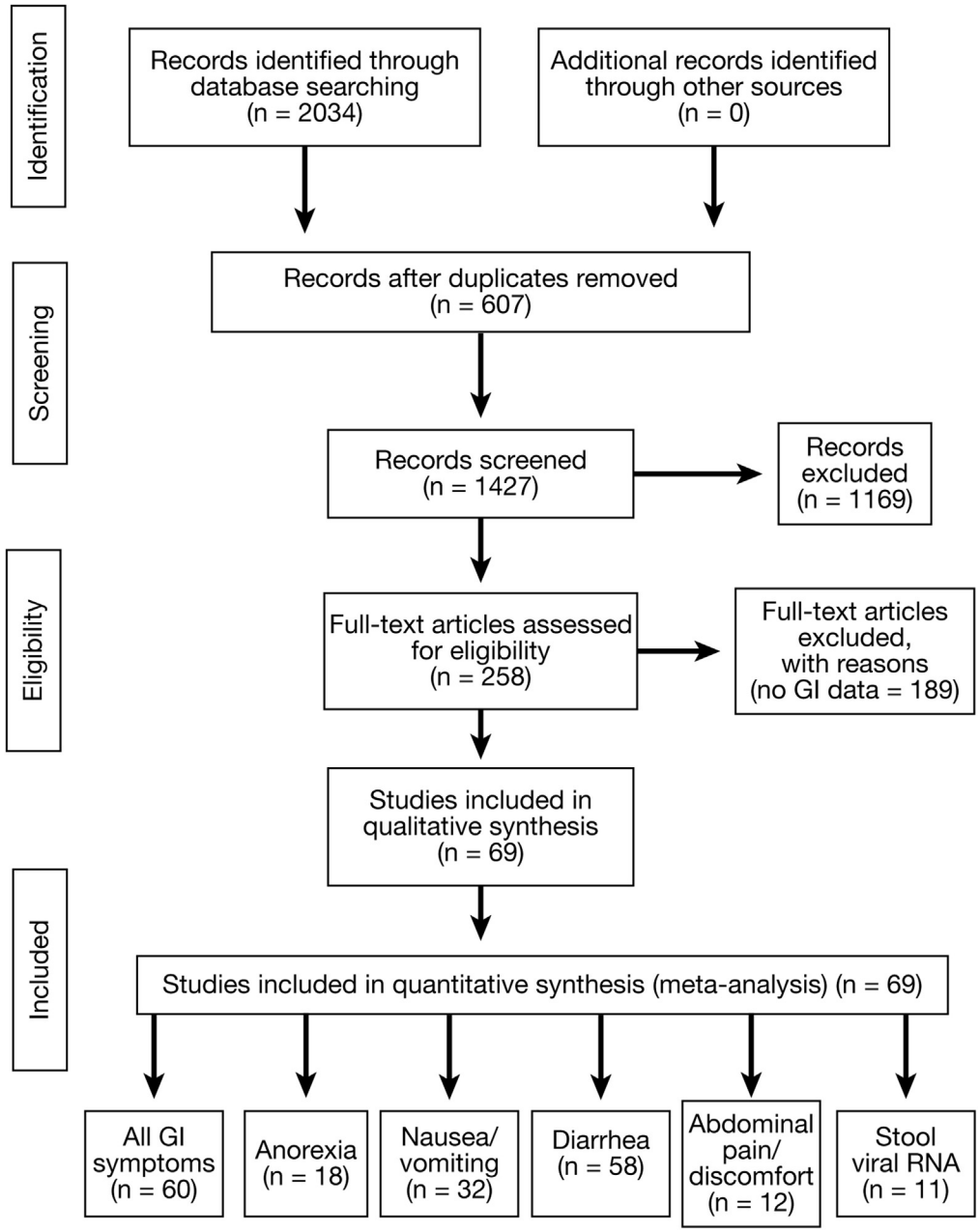

Figure 1. Study selection flow diagram. If all gastrointestinal symptoms were not reported and the number of events of any individual gastrointestinal symptom was >1, it was regarded as not available and was excluded from the meta-analysis of all gastrointestinal symptoms. However, the study was still included in the meta-analysis of individual gastrointestinal symptom if the proportion of patients with that symptom was reported.

Among studies from China, the prevalence of all gastrointestinal symptoms in the single study of 1099 patients from 552 hospitals by Guan et al[18] 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 for those from outside Hubei Province, it was 18.6% (95% CI, 12.2–27.2). There was a significant subgroup difference between the studies from and outside of Hubei Province ($P < .001$), and there was also significant heterogeneity among the studies ($P < .001$; $I^2 = 93.5\%$ and $I^2 = 76.8\%$, respectively).

Disease Severity and Gastrointestinal Symptoms. There were 11 studies that compared the prevalence of all gastrointestinal symptoms according to the severity of COVID-19 (the numbers of patients with severe and nonsevere disease were 451 and 1731, respectively) (Supplementary Table 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 nonsevere disease, respectively (Figure 4). There was significant heterogeneity among the studies ($P < .001$; $I^2 = 90.9\%$ 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 prevalences of all gastrointestinal symptoms in adults, pediatric patients, and pregnant women were 16.7% (95% CI, 11.4–23.9), 24.8% (95% CI, 9.6–50.4), and 20.0% (95% CI,

Table 2. Characteristics of the Studies Included for Meta-analysis:

Study	Study date	Study location	No.	Age, *y* (unless otherwise noted)	Male, n/total (%) or n (%)	Severe disease,[a] n (%)	Fever, n/total (%) or n (%)	Respiratory symptoms, n/total (%) or n (%)	All GI symptoms,[b] n (%)	Anorexia, n/ total (%) or n (%)	Nausea/ vomiting, n/ total (%) or n (%)	Diarrhea, n/ total (%) or n (%)	Abdominal pain/ discomfort, n/total (%) or n (%)
China													
Guan et al[18]	December 11, 2019–29 January 2020	552 hospitals in China	1099	Median: 47 IQR 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)	NA	55 (5.0)	42 (3.8)	NA
Cheng et al[19]	Up to February 19	Henan	1079	Mean: 46 Range: 3 mo–94 y	573 (53.2)	72 (5.7)	553/605 (91.4)	C: 110/605 (18.2) E: 19/605 (3.1)	21/605 (3.5)	NA	NA	NA	NA
Fang et al[20]	January 27–February 14, 2020	Hubei	305	Median: 57	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 et al[5]	December 29, 2020–January 31, 2020	Hubei	191	Median: 56 IQR: 46–67	119 (62.3)	119 (62.3)	180 (94.2)	C: 151 (79.1) E: 44 (23.0)	≥9 (4.7)	NA	7 (3.7)	9 (4.7)	NA
Yang et al[21]	January 17–February 10, 2020	Zhejiang	149	Mean ± SD: 45.1 ± 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)	NA	2 (1.3)	11 (7.4)	NA
Zhang et al[22]	January 16–February 3, 2020	Hubei	140	Median: 57 IQR: 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 et al[23]	January 1–28, 2020	Hubei	138	Median: 56 IQR: 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 et al[24]	December 30, 2019–January 24, 2020	Hubei	137	Median: 57 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)	NA	NA	11 (8.0)	NA
Peng et al[25]	January 20, 2020–February 15, 2020	Hubei	112	Median: 67 IQR: 55–67	53 (47.3)	ICU: 16 (14.3)	101 (90.2)	C: 76 (67.9) D: 13 (11.6)	15 (13.4)	NA	NA	15 (13.4)	NA
Zhao et al[26]	NA	Hunan	101	Mean: 44.4 Range: 17–75	56 (55.4)	14 (13.9)	79 (78.2)	C: 63 (62.4) D: 1(1.0)	≥3 (3.0)	NA	2 (2.0)	3 (3.0)	NA
Chen et al[27]	January 1–20, 2020	Hubei	99	Mean ± SD: 55.5 ± 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)	NA	NA
Xu et al[28]	January 23–February 4, 2020	Guangdong	90	Median: 50 Range: 18–86	39 (43.3)	NA	70 (77.8)	C: 57 (63.3) E: 11 (12.2)	≥5 (5.6)	NA	N: 5 (5.6) V: 2 (2.2)	5 (5.6)	NA
Li et al[29]	January–February 2020	Chongqing	83	Mean ± SD: 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)	NA	NA	7 (8.4)	
Shi et al[30]	December 20, 2019–January 23, 2020	Hubei	81	Mean ± SD: 49.5 ± 11.0	42 (51.9)	NA	59 (72.8)	C: 48 (59.2) E: 15 (18.5) D: 34 (42.0)	≥4 (4.9)	1 (1.2)	V: 4 (4.9)	3 (3.7)	NA
Wu et al[31]	January 22–February 14, 2020	Jiangsu	80	Mean ± SD: 46.1 ± 15.4	39 (48.8)	3 (3.8)	63 (78.8)	C: 51 (63.8) D: 30 (37.5)	≥1 (1.3)	NA	1 (1.3)	1 (1.3)	NA
Wu et al[32]	January–February 2020	Chongqing	80	Mean ± SD: 44 ± 11	42 (52.5)	NA	61 (76.3)	C: 58 (72.5) E: 11 (13.8) D: 7 (8.8)	7 (8.8)	NA	NA	7 (8.8)	
Fang et al[33]	January 22–February 18, 2020	Anhui	79	Mean ± SD: 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)	NA	4 (5.1)	NA
Xiao et al[34]	February 1–14, 2020	Guangdong	73	43 Range: 10 mo–78 y	41 (56.2)	ICU: 4 (5.5)	NA	53 (72.6)	26 (35.6)	NA	NA	26 (35.6)	NA
Xu et al[35]	January 10–26, 2020	Zhejiang	62	Median: 41 IQR: 32–52	35 (56.5)	ICU: 1 (1.6)	48 (77.4)	C: 50 (80.6) E: 35 (56.5)	3 (4.8)	NA	NA	3 (4.8)	NA
Zhou et al[36]	January 16–30, 2020	Hubei	62	Mean ± SD: 52.8 ± 12.2 Range: 30–70	39 (62.9)	NA	54	C: 28 D: 15	9 (14.)	NA	NA	9 (14.)	

Table 2. Continued

Study	Study date	Study location	No.	Age, *y* (unless otherwise noted)	Male, n/total (%) or n (%)	Severe disease,[a] n (%)	Fever, n/total (%) or n (%)	Respiratory symptoms, n/total (%) or n (%)	All GI symptoms,[b] n (%)	Anorexia, n/total (%) or n (%)	Nausea/vomiting, n/total (%) or n (%)	Diarrhea, n/total (%) or n (%)	Abdominal pain/discomfort, n/total (%) or n (%)
Yang et al[37]	December 24, 2019–January 26, 2020	Hubei	52	Mean ± SD: 59.7 ± 13.3	35 (67.3)	ICU: 52 (100)	51 (98.1)	C: 40 (46.9) D: 33 (63.5)	2 (3.8)	NA	2 (3.8)	NA	NA
Xu et al[38]	January–February 2020	Beijing and Hebei	50	Mean ± SD: 43.9 ± 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)	NA	NA	NA	NA
Xiong et al[39]	January 11–February 5, 2020	Hubei	42	Mean ± SD: 49.5 ± 14.1 Range: 26–75	25 (59.5)	NA	36 (85.7)	C: 27 (64.3) D: 8 (19.0)	10 (23.8)	NA	NA	10 (23.8)	NA
Huang et al[40]	December 16, 2019–January 2, 2020	Hubei	41	Median: 49 IQR: 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)	NA	NA	1/38 (2.6)	NA
Wu et al[41]	January 19–25, 2020	Tianjin	40	Mean: 45 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)	NA	3 (7.5)	6 (15.0)	3 (7.5)
Huang et al[42]	December 21, 2019–January 8, 2020	Hubei	34	Mean ± SD: 56.2 ± 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)	NA	NA	5 (14.7)	NA
Li et al[43]	January–February 2020	Hubei	31	Mean ± SD: 54 ± 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)	NA
Liu et al[44]	January 11–February 3, 2020	Hubei	30	Mean ± SD: 35 ± 8 Range: 21–59	10 (33.3)	4 (13.3)	23 (76.7)	C: 25 (83.3) D: 14 (46.7)	9 (30)	NA	N/V/D: 9 (30.0)		NA
Pan et al[45]	January 12–February 6, 2020	Hubei	21	Mean ± SD: 40 ± 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)	NA	NA	NA
Zou et al[46]	January 7–26, 2020	Guangdong	18	Median: 59 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 et al[47]	January 21–February 5, 2020	Henan	18	Median: 39 IQR: 29–55	10 (55.6)	ICU: 2 (11.1)	17 (94.4)	C:10 (55.6) D: 4 (22.2)	3 (16.7)	NA	1 (5.6)	3 (16.7)	NA
Zhang et al[48]	January 27–February 10, 2020	Zhejiang	14	Median: 41 IQR: 18–87	7 (50.0)	NA	13 (92.9)	C: 10 (71.4)	NA	NA	0	0	NA
Chang et al[49]	January 16–29, 2020	Beijing	13	Median: 34 IQR: 34–78	10 (76.9)	0	12 (92.3)	C: 6 (46.2) E: 2 (15.4)	1 (7.7)	NA	NA	1 (7.7.)	NA
Liu et al[50]	Up to January 21, 2020	Shenzen	12	Range: 10–72	8 (66.7)	6 (50.0)	10 (83.3)	C: 11 (91.7)	≥3 (25.0)	NA	2 (16.7)	2 (16.7)	NA
Huang et al[51]	January 21–February 1, 2020	Jiangsu	11	NA	4 (36.4)	NA	9 (90.0)	C: 8 (80.0)	1 (10.0)	NA	NA	1 (10.0)	NA
Shen et al[52]	February 2020	Liaoning	10	Range: 33–85	6 (60)	2 (20.0)	9 (90)	C: 9 (90)	4 (40.0)	NA	NA	4 (40.0)	NA
Zhang et al[53]	January 18–February 3, 2020	Beijing	9	Median: 36 Range: 15–49	5 (55.6)	NA	8 (88.9)	C: 5 (55.6) E: 1 (11.1)	1 (11.1)	NA	NA	1 (11.1)	NA
An et al[54]	January 17–24, 2020	Hubei	9	Median: 35.8 IQR: 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 et al[55]	February 3, 2020	Henan	8	Range: 4–53	4 (50.0)	0	5 (62.5)	C: 3 (37.5)	1 (12.5)	NA	NA	1 (12.5)	NA
Chan et al[56]	January 10, 2020	Shenzhen	6	Range: 36–66y	3 (50)	0	5 (83.3)	C: 4 (66.7) E: 1 (16.7)	2 (33.3)	NA	NA	2 (33.3)	NA
Ren et al[57]	December 18–29, 2020	Hubei	5	Range: 41–65	3 (60.0)	4 (80.0)	5 (100)	C: 5 (100) E: 1 (20.0) D: 4 (80.0)	NA	NA	NA	0	NA
Wang et al[58]	January 21–24, 2020	Shanghai	4	Range: 19–63	3 (75.0)	0	4 (100)	C: 3 (75.0)	NA	NA	NA	0	NA
Yu et al[59]	January 20–23, 2020	Shanghai	4	Range: 65–88	2 (50.0)	1 (25.0)	4 (100)	C: 1 (25.0)	1 (25.0)	1 (25.0)	NA	NA	NA
Yang et al[60]	January 23–25, 2020	Guandong	3	Range: 25–62	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 et al[61]	NA	Taiwan	2	Range: 73–74	0	0	2 (100)	C: 1 (50.0)	2 (100)	2 (100)	NA	0	0

Table 2. Continued

Study	Study date	Study location	No.	Age, *y* (unless otherwise noted)	Male, n/total (%) or n (%)	Severe disease,[a] n (%)	Fever, n/total (%) or n (%)	Respiratory symptoms, n/total (%) or n (%)	All GI symptoms,[b] n (%)	Anorexia, n/total (%) or n (%)	Nausea/vomiting, n/total (%) or n (%)	Diarrhea, n/total (%) or n (%)	Abdominal pain/discomfort, n/total (%) or n (%)
Cheng et al[62]	January 20, 2020	Taiwan	1	55	0	0	1 (100)	C: 1 (100) D: 1 (100)	1 (100)	NA	NA	NA	1 (100)
Li et al[63]	January 24, 2020	Sichuan	1	33	1 (100)	0	1 (100)	0	1 (100)	1 (100)	NA	NA	NA
Han et al[64]	January 21, 2020	Gansu	1	47	1 (100)	1 (100)	1 (100)	C: 1 (100)	1 (100)	NA	N: 1 (100)	NA	NA
Song et al[65]	January 29, 2020	Shandong	1	22	1 (100)	0	1 (100)	0	1 (100)	NA	NA	1 (100)	NA
Zhang et al[66]	January 18, 2020	Hubei	1	57	1 (100)	0	1 (100)	C: 1 (100) D: 1 (100)	1 (100)	NA	NA	1 (100)	NA
Wu et al[67]	February 8, 2020	Hubei	1	48	1 (100)	0	1 (100)	C: 1 (100)	NA	NA	0	NA	NA
Lin et al[68]	January 25, 2020	Gansu	1	61	1 (100)	0	0	D: 1 (100)	NA	NA	NA	0	NA
Outside of China													
Kong et al[69]	Up to February 14, 2020	South Korea	28	Mean: 42.6 IQR: 20–73	15 (53.6)	NA	9 (32.1)	Cough: 5 (17.9)	2/18 (11.1)	NA	NA	2/18 (11.1) (days 3 and 4)	NA
Young et al[70]	January 23–February 3, 2020	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)	NA	NA	3 (16.7)	NA
Kim et al[71]	January 10–19, 2020	South Korea	2	Range: 35–55	1 (50)	1 (50.0)	2 (100)	2 (100)	2 (50.0)	0	0	2 (100)	0
Lillie et al[72]	January 30–3,1 2020	United Kingdom	2	Range: 23–50	1 (50.0)	0	2 (100)	C: 2 (100)	1 (50.0)	NA	NA	NA	NA
Phan et al[73]	January 22, 2020	Vietnam	2	Range: 27–65	2 (100)	0	2 (100)	C: 1 (100)	1 (50.0)	NA	1 (50.0)	1 (50.0)	NA
Yan et al[74]	February 9–13 2020	Singapore	2	Both 57	1 (50.0)	NA	2 (100)	C: 2 (100) D: 1 (50.0)	1 (50.0)	NA	NA	1 (50.0)	NA
Holshue et al[75]	January 20, 2020	United States	1	35	1 (100)	1 (100)	1 (100)	C: 1 (100)	1 (100)	NA	1 (100)	1 (100)	1 (100)
Pediatric patients													
Wang et al[76]	January 25–February 21, 2020	6 provinces (northern China)	31	Median: 7.1 Range: 6 mo–17 y	15 (48.4)	0	20 (64.5)	C: 14 (45.2) E: 6 (19.4)	5 (16.1)	NA	2 (6.5) (1 as first presenting symptom)	3 (9.7) (all as first presenting symptom)	NA
Xia et al[77]	January 23– February 8, 2020	Hubei	20	Median: 2.1 Range: 1 d–14.6 y	13 (65.0)	NA	12 (60.0)	C: 13 (65.0)	≥3 (15.0)	NA	2 (10.0)	3 (15.0)	NA
Cai et al[78]	January 19, 2020–February 3, 2020	Shanghai, Hainan, Anhui, and Shandong	10	Mean: 74 mo Range: 3–131 mo	4 (40.0)	0	8 (80.0)	C: 6 (60.0)	NA	NA	NA	0	NA
Chen et al[79]	January 27, 2020	Hubei	1	13 mo	1 (100)	1 (100)	1 (100)	0	1 (100)	1 (100)	1 (100)	1 (100)	NA
Zeng et al[80]	February 5, 2020	Hubei	1	17 d	1 (100)	0	0	0	1 (100)	1 (100)	1 (100)	1 (100)	NA
Zhang et al[81]	January 26, 2020	Hainan	1	3 mo	0	0	1 (100)	0	NA	0	0	0	NA
Pregnant women													
Chen et al[82]	January 20–31, 2020	Hubei	9	Range: 26–40	0	NA	7 (77.8)	C: 4 (44.4) D: 1 (11.1)	1 (11.1)	NA	NA	1 (11.1)	NA
Zhu et al[83]	January 20–February 5, 2020	Hubei	9	Range: 25–35	0	NA	8 (88.9)	C: 4 (44.4)	1 (11.1)	NA	NA	1 (11.1)	NA
Chen et al[84]	January 21–February 4, 2020	Hubei	3	Range: 23–34	0	0	1 (33.3)	D: 1 (33.3)	NA	NA	NA	0	NA
Liu et al[85]	February 5, 2020	Shandong	1	38	0	0	0	0	1 (100)	1 (100)	N: 1 (100)	1 (100)	0

C, cough; D, dyspnea; E, expectoration; GI, gastrointestinal; ICU, intensive care unit; N, nausea; NA, not available; SD, standard deviation; V, vomiting.
[a]*Severe disease* was defined based on the American Thoracic Society and Infectious Disease Society of America guidelines for community-acquired pneumonia, need of ICU admission, and death.
[b]If all gastrointestinal symptoms were not reported and the number of events of any individual gastrointestinal symptom was less than 1, 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 symptoms if the proportion of patients with that symptom was reported.

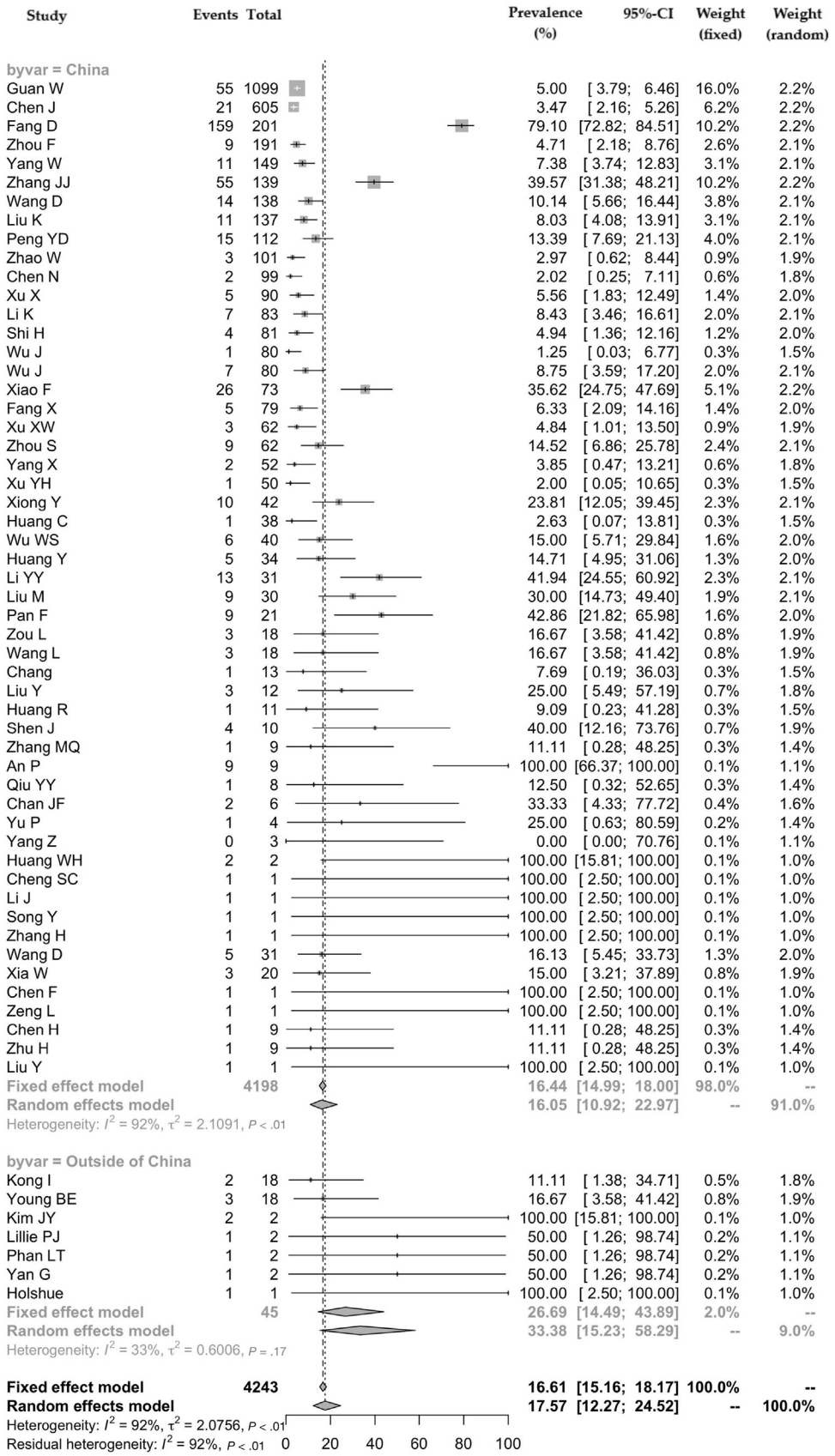

Figure 2. Pooled prevalence of all gastrointestinal symptoms in patients with COVID-19 (all studies and according to geographical variation—China vs outside of China).

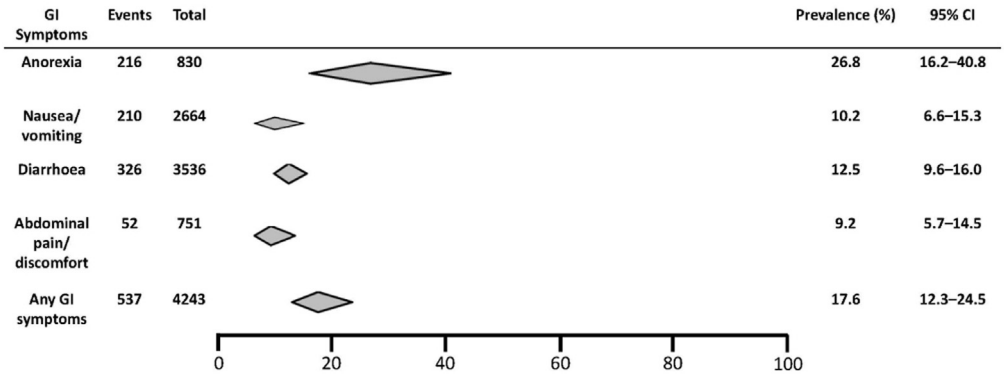

Figure 3. Summary estimates of the prevalence of individual and all gastrointestinal symptoms in patients with COVID-19. GI, gastrointestinal.

4.3–58.2). There was no significant subgroup difference ($P = .717$).

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 that tested for viral RNA in stool; the study by Wang et al[86] 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. Of 138 patients, 68 (pooled prevalence, 48.1%; 95% CI, 38.3–57.9) tested positive for both respiratory and stool specimens (R^+S^+) after hospitalization (Supplementary Figure 5). In 9 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^+) (Supplementary Figure 6). Ling et al[15] reported that the stool viral clearance was longer in patients with steroid

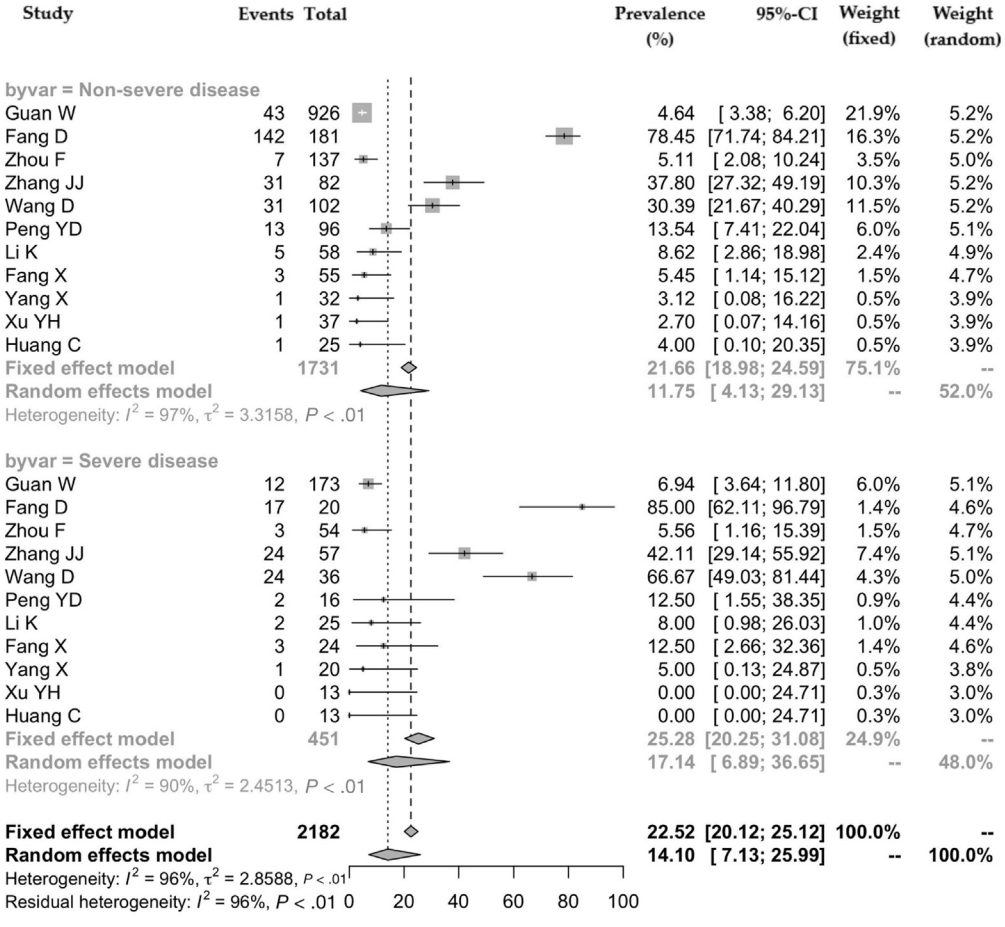

Figure 4. Pooled prevalence of all gastrointestinal symptoms according to the severity of COVID-19.

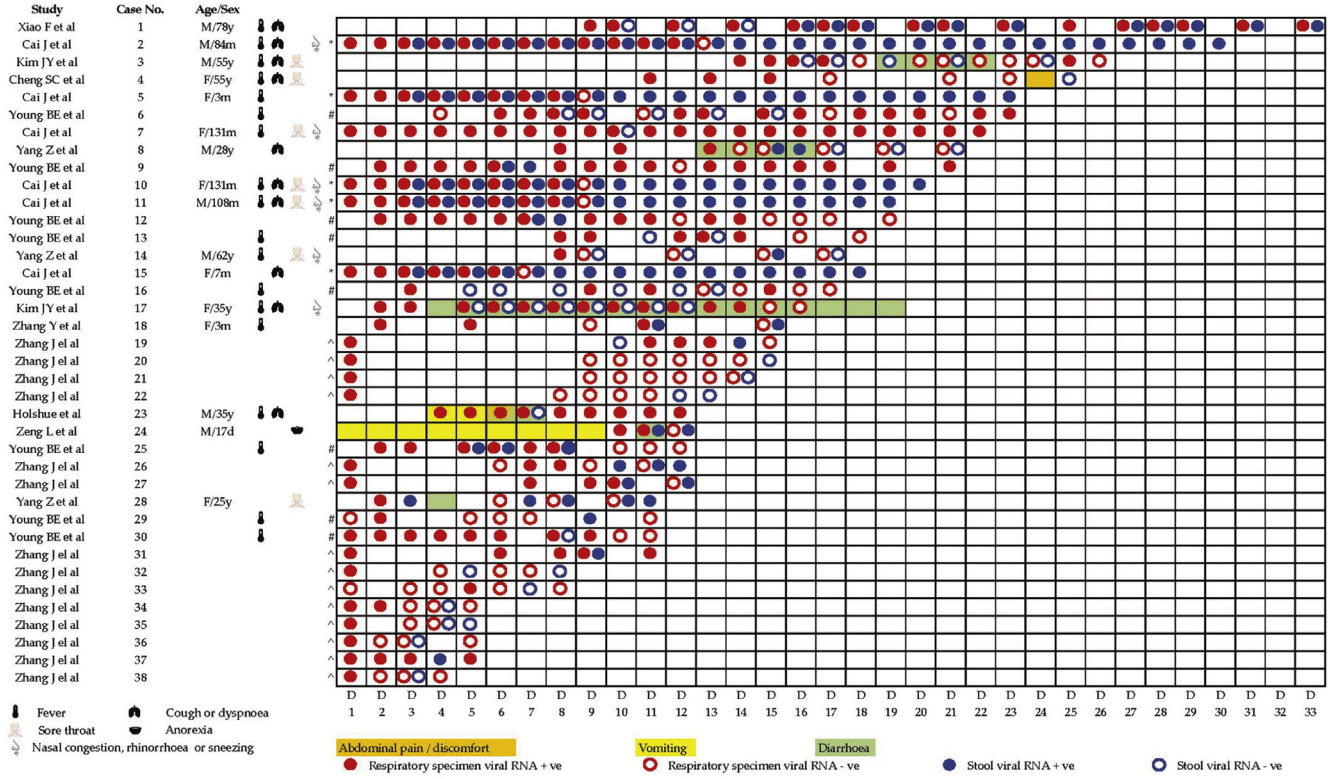

Figure 5. Timeline of the symptomatology and viral test results (respiratory and stool specimens) of 38 patients with COVID-19. A filled circle represents a positive result, and an empty circle represents a negative result. Gastrointestinal symptoms are color coded as shown (abdominal pain/discomfort, orange; vomiting, yellow; diarrhea, green). The details of 13 R^-S^+ patients are shown in case numbers 2, 5, 8, 10, 11, 14, 15, 18, 24, 26, 27, 28, and 29. 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 et al[78]; 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 tested negative for 2 consecutive respiratory specimens, but the exact day on which the second consecutive respiratory specimen tested negative for viral RNA was not stated. The sample size of Young et al[70] 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 symptom onset (fever, cough, dyspnea, sore throat, nasal congestion, rhinorrhea, sneezing, loss of appetite) and was not reported in the study by Zhang J et al[48]; hence, the first day on which respiratory specimens were tested was regarded as day 1 in this graph.

use compared to those without steroid use (20 vs 11 days; $P < .001$).

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,[70] 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 7 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 4243 patients with COVID-19 from 6 countries, the pooled prevalence of all gastrointestinal symptoms (including loss of appetite, nausea/vomiting, diarrhea, or abdominal pain) was 17.6%. Loss of appetite 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 4 patients reported that constipation was noted in 2.[58] Despite the inclusion of >60 reports, the actual prevalence of any gastrointestinal symptoms could be underestimated because many earlier studies did not report other gastrointestinal symptoms except for diarrhea.[19,24,34,35,40,42] Moreover, the majority of

studies reported gastrointestinal symptoms only on the day of admission but not throughout the disease course. The issue is further complicated by differences in the criteria for diagnosing diarrhea in various hospitals.[87]

With more than 80% resemblance to SARS-CoV, infection of the gastrointestinal tract by SARS-CoV-2 is not unexpected and 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,[9,87] and the binding affinity of ACE2 receptors determines infectivity. Because ACE2 modulates intestinal inflammation,[88] SARS-CoV-2 may cause disruption of ACE2 function and result in diarrhea. A recent study showed 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.[34]

Gastrointestinal manifestations were also commonly reported during the SARS and MERS outbreaks. In the previous SARS outbreak in Hong Kong, 16% of patients reported diarrhea.[8] Similarly, up to a quarter of patients with MERS also reported gastrointestinal symptoms such as diarrhea or abdominal pain.[10] 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 contracted the virus in a large outbreak during a dinner gathering in the Lunary New Year, probably via both fecal-oral and respiratory routes, thus partly explaining the higher frequency of gastrointestinal manifestations. Previous studies during SARS showed that viral load in the stool was strongly associated with presence of diarrhea.[89] 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 patients with COVID-19. In the study by An et al,[54] 9 patients reported only gastrointestinal symptoms (predominantly loss of appetite [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%). Although 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. Because China was the first country affected by the COVID-19 outbreak with a large number of patients, the gastrointestinal manifestations may have been overlooked in the beginning of the outbreak, particularly Wuhan city, leading to underreporting 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.[23] Health care professionals should be aware of the potential prognostic implications in patients with gastrointestinal symptoms, who may require closer 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. Because of the lack of systematic stool collection protocol in currently published studies, the full extent of the stool positivity 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 about the isolation policy for patients with COVID-19, 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.[7] The sewage concentrates of 2 hospitals receiving patients with SARS in Beijing were also found to have SARS-CoV RNA detected at that time.[90] Intuitively, proper handling of the excreta of patients with COVID-19 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, that is, 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 a surrogate monitor for recurrent infection in some patients.

There are several strengths of our study. To our knowledge, this is the first meta-analysis to summarize 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 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 the 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 underreported in some studies, which may lead to a lower pooled prevalence rate. Second, studies with large sample sizes of 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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.03.065.

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Conflicts of interest
The authors disclose no conflicts.