Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19

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ABSTRACT

Background The COVID-19 epidemic has affected over 2.6 million people across 210 countries. Recent studies have shown that patients with COVID-19 experience relevant gastrointestinal (GI) symptoms. We aimed to perform a systematic review and meta-analysis on the GI symptoms of COVID-19.

Methods A literature search was conducted via electronic databases, including PubMed, Embase, Scopus, and Google Scholar, from inception until 20 March 2020. Data were extracted from relevant studies. A systematic review of GI symptoms and a meta-analysis comparing symptoms in severe and non-severe patients was performed using RevMan V.5.3.

Results Pooled data from 2477 patients with a reverse transcription-PCR-positive COVID-19 infection across 17 studies were analysed. Our study revealed that diarrhoea (7.8%) followed by nausea and/or vomiting (5.5 %) were the most common GI symptoms. We performed a meta-analysis comparing the odds of having GI symptoms in severe versus non-severe COVID-19-positive patients. 4 studies for nausea and/or vomiting, 5 studies for diarrhoea and 3 studies for abdominal pain were used for the analyses. There was no significant difference in the incidence of diarrhoea (OR=1.32, 95% CI 0.8 to 2.18, Z=1.07, p=0.28, I^2=17%) or nausea and/or vomiting (OR=0.96, 95% CI 0.42 to 2.19, Z=0.10, p=0.92, I^2=55%) between either group. However, there was seven times higher odds of having abdominal pain in patients with severe illness when compared with non-severe patients (OR=7.17, 95% CI 1.95 to 26.34, Z=2.97, p=0.003, I^2=0%).

Conclusion Our study has reiterated that GI symptoms are an important clinical feature of COVID-19. Patients with severe disease are more likely to have abdominal pain as compared with patients with non-severe disease.

INTRODUCTION

At the time of writing this paper, over 2.6 million people across 210 countries have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[1] The impact of the virus has been devastating on a global scale. National healthcare

Summary box

What is already known about this subject?
► Fever, cough, and shortness of breath have been described as the most common symptoms of COVID-19.
► A significant number of patients may present with gastrointestinal (GI) symptoms.

What are the new findings?
► Comparison of GI symptoms between patients with severe disease and patients with non-severe disease.
► Abdominal pain is seen more in patients with severe disease and could be an indicator for disease severity.

How might it impact on clinical practice in the foreseeable future?
► Gives better understanding and insight into the complete spectrum of GI manifestations of COVID-19.
► Helps develop a prognostic tool based on clinical symptoms.

systems have been overwhelmed, resulting in nationwide lockdowns, international travel has come to a complete standstill, and healthcare workers world over have been faced with shortages of personal protective equipment. Since its initial outbreak in Hubei in December 2019, the number of COVID-19-positive patients has risen at an exponential rate.[2–4] As of 24 April 2020, the USA alone has witnessed over 865 000 cases which is a sharp increase from its census of 10 000 merely 4 weeks prior.[5] The transmissibility of the virus, coupled with a large number of asymptomatic cases, has been held as the culprit behind a rapid rise in incidences, with every infected person being able to further infect another 2.2 people.[6]

Numerous studies have attempted to try and describe the virus from both an epidemiological and clinical perspective.[7–10] Although the
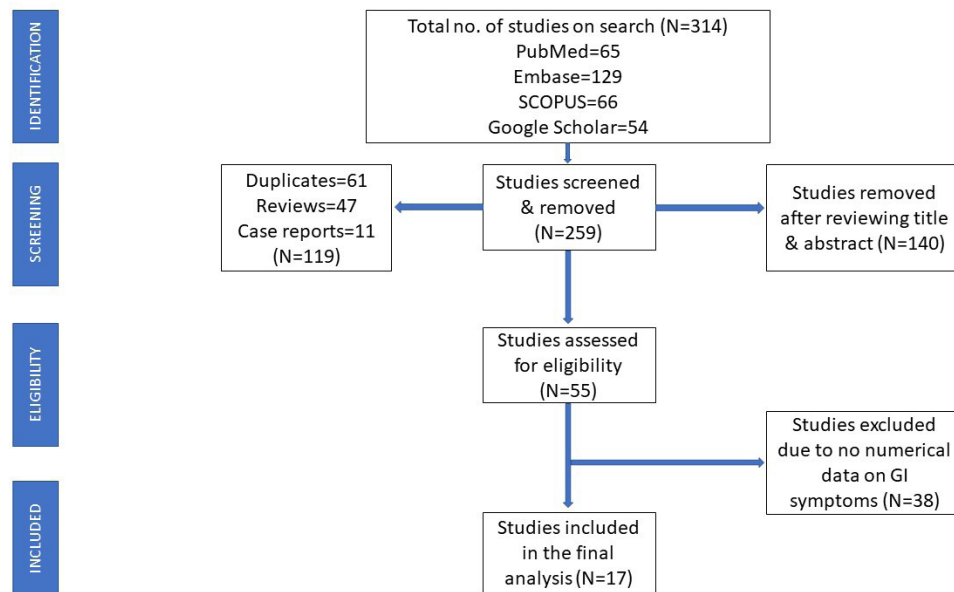
Figure 1 Study flow diagram. GI, gastrointestinal.

most commonly described symptoms in patients appear to be fever (75%–98%) and cough (39%–81%),[7 8 11–13] it appears that a significant number of patients may present with gastrointestinal (GI) symptoms as well.[14 15]

Among the GI symptoms that have been described, diarrhoea appears to be the most common (3%–34%).[12 14–16] Symptoms less reported included nausea (1%–17%),[7–9] vomiting (1%–4%),[7 14] abdominal pain (2%–5%)[8 9 14] and GI bleeding (0%–13%).[10 16] This is of paramount importance as it implies that a patient with COVID-19 may, in fact, masquerade as a presumed gastroenteritis until the respiratory symptoms predominate.

Work on the possible pathophysiology behind the GI symptoms remains ongoing. Studies have hypothesised that the ACE2 receptor, which is used by the virus to infect cells, is also expressed in the mucosa of the GI tract and may play a role in its GI manifestation.[16 17] Viral colonisation of the immune-rich areas of the gut contributes to a systemic inflammatory response.[14] Further, there is growing evidence that the virus present in stool samples can continue to persist in the stool long after the respiratory colonisation resolves to hypothesise a faecal–oral route of transmission.[14 16]

As the evolution of the pandemic continues to be dynamic with new advances being reported on an almost hourly basis, we aimed to perform systematic review of GI symptoms of COVID-19 from its inception until 20 March 2020, and meta-analysis comparing GI symptoms in severe versus non-severe disease. To our knowledge, this is the first study to do so.

METHODS
Search strategy
A comprehensive search of several databases, including PubMed, Embase, Scopus and Google Scholar databases from inception to 20 March 2020, was conducted. An

expert medical librarian using inputs from the authors helped conduct the literature search. Keywords used in the search included a combination of 'COVID-19 or coronavirus or SARS-COV' and 'Gastrointestinal symptoms', and 'Clinical features'. We used the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and a predefined protocol to identify studies reporting GI symptoms of COVID-19. We restricted our search to studies that have been published or accepted in peer-reviewed journals. We restricted our search to studies published in English. Based on preset inclusion and exclusion criteria, three authors (VCSK, SM and AS) independently reviewed the studies and excluded studies that did not address our topic. The selected articles were reviewed to determine whether they contained relevant data. The bibliographic sections were manually searched for similar studies. Any discrepancy in included studies was resolved by a coauthor (PH).

Study selection
We included cohort studies and case series which met our inclusion criteria, which included: (1) reverse transcription-PCR-confirmed COVID-19 cases; (2) age >18 years; (3) description of clinical symptoms; and (4) data on the number of patients with GI symptoms. Studies included satisfied all aspects of the inclusion criteria. We only included studies that were published in English. Our exclusion criteria included: (1) no data on GI symptoms; (2) age <18 years; (3) patients with other SARS-like illnesses; and (4) case reports. Studies that had any one of these were excluded from our final study.

Data extraction and quality assessment
A data extraction sheet was created, and the study characteristics, data on intended outcomes, and patient characteristics were collected. Three of the authors (VCSK, SM, and AS) independently extracted data. Extracted

Table 1 Study characteristics

Study	Country	Study type	Total number of patients	Male	Female	Age range (years)	Median age (years)	Severe disease	Non-severe disease	Nausea and/or vomiting	Diarrhoea	Anorexia	Abdominal pain
Huang et al[11]	China	PO	41	30	11	41–50	49.0	13	28	NA	1	NA	NA
Chen et al[2]	China	CS	9	0	9	<30	29.9	NA	NA	NA	1	NA	NA
Chan et al[15]	China	CS	6	3	3	41–50	50.0	NA	NA	NA	2	NA	NA
Chen et al[7]	China	RO	99	67	32	51–60	55.5	NA	NA	1	2	NA	NA
Young et al[26]	Singapore	RO	18	9	9	41–50	47.0	NA	NA	NA	3	NA	NA
Xu et al[12]	China	RO	62	35	27	41–50	41.0	NA	NA	NA	3	NA	NA
COVID-19, Australia: Epidemiology Report 2	Australia	CS	15	9	6	41–50	43.0	NA	NA	1	5	NA	NA
Huang Y et al[31] (Elsevier)	China	RO	34	14	20	51–60	56.2	NA	NA	NA	5	NA	NA
Song et al[23]	China	RO	51	25	26	41–50	49.0	NA	NA	3	5	9	NA
Wu et al[32], Investigative Radiology	China	RO	80	42	38	41–50	44.0	NA	NA	NA	7	NA	NA
Yang et al[10]	China	RO	149	81	68	41–50	45.1	NA	NA	2	11	NA	NA
Wang et al[9]	China	RO	138	75	63	51–60	56.0	36	102	19	14	NA	3
Zhang et al[8]	China	RO	140	71	69	51–60	57.0	58	82	24	18	17	8
Pan et al[14]	China	RO	204	107	97	51–60	52.9	27	66	4	35	81	2
Xiao et al[16]	China	RO	73	41	32	41–50	43.0	NA	NA	NA	26	NA	NA
Guan et al[22]	China	RO	1099	640	459	41–50	47.0	173	926	55	42	NA	NA
Zhou et al[24]	China	RO	191	119	72	51–60	56.0	119	72	7	9	NA	NA
Sum (n)			2477	1406	1071	Weighted average -->	49.077	426	1276	116	194	107	13

CS, case series; NA, not applicable; PO, prospective observational study; RO, retrospective observational study.
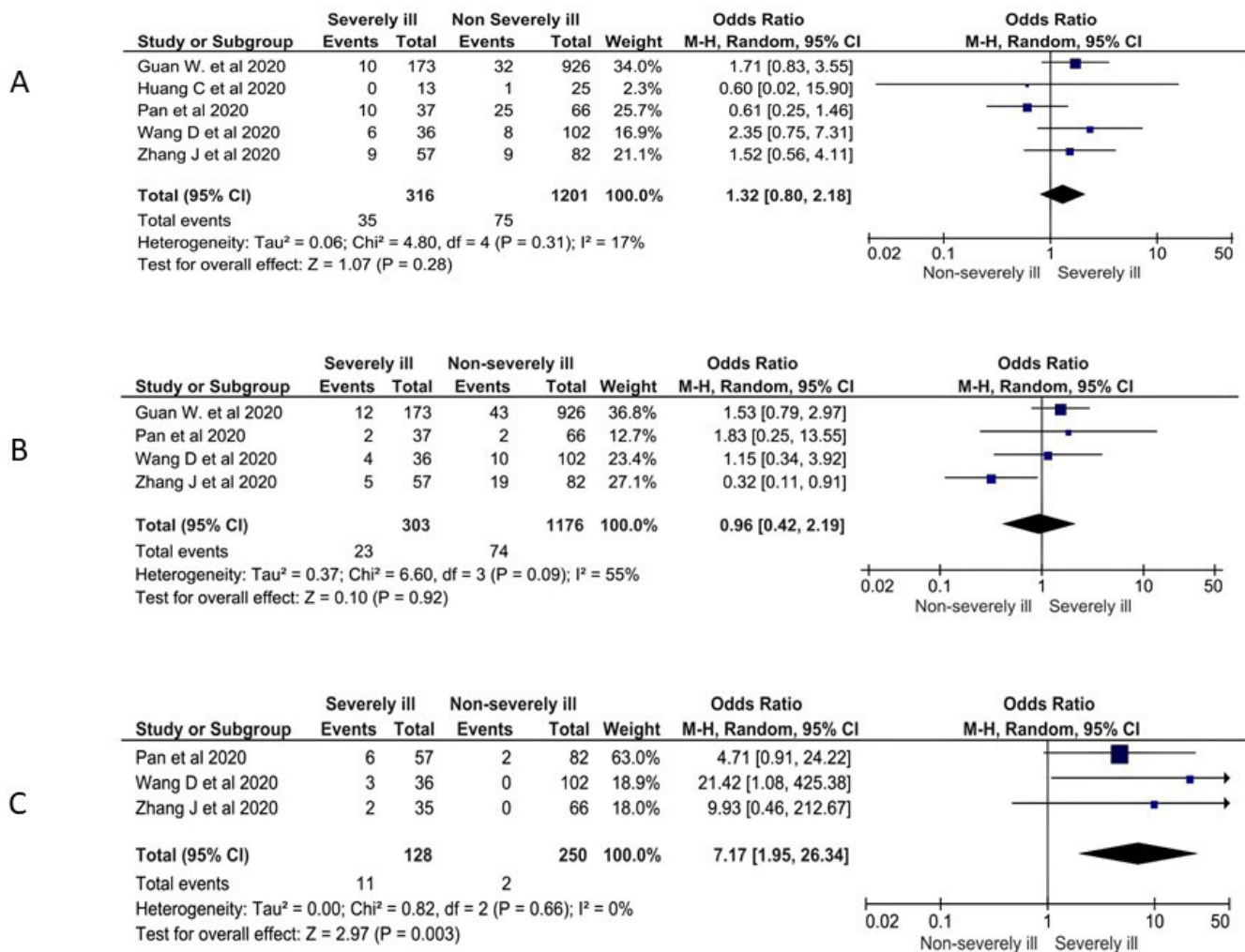
Figure 2 Forest plots comparing patients with severe versus non-severe disease based on symptoms. (A) Diarrhoea, (B) nausea and/or vomiting, (C) abdominal pain.

data were reviewed by two authors (PH and MKG) for potential discrepancies, which, if present, were resolved.

The quality of included studies was determined objectively using a scale based on the Newcastle-Ottawa Scale for meta-analysis.[18] The scale consisted of eight questions, each of which was awarded one star, amounting to a maximum possible eight stars per study. We scored the comparability questions based on the outcomes that our study intended to find and not based on comparison outcomes for individual outcomes from the original studies. We considered a total score of >/=7, 3–6, and <2 represented high, fair, and poor-quality studies, respectively. Two authors (SM and VCSK) independently assessed the quality of the studies. The senior author (BS) reviewed the final quality assessment table and resolved discrepancies if there were any.

Outcomes

The primary outcome of the systematic review was to describe the occurrence of GI symptoms in patients tested positive for COVID-19 and to establish the most

common of the symptoms. The secondary outcome was to compare GI symptoms in patients with severe versus non-severe COVID-19 disease. The definition of 'severe' was based on either the National Chinese Health Commission (seventh) edition definition[19] or the American Thoracic Society[20] definition as these had been the criteria used within the analysed studies.

Statistical analysis

Our analysis includes cumulative descriptive statistics expressed as counts (n) and percentages (%) with a comparative analysis for the selected studies and a subgroup analysis for each symptom using TIBCO Spotfire analytics and spreadsheet tools. For comparing GI symptoms in severe versus non-severe cases, a meta-analysis was performed using the RevMan V.5.3 generating forest plots and funnel plots. Publication bias was assessed based on symmetry of the funnel plots. Due to a small sample set (<10 studies), statistical testing using Egger's or Begg's test was deferred. We computed the OR as our effect estimate using the Mantel-Haenszel method

Table 2 Abdominal pain in patients with severe versus non-severe disease

| Study | Severe | | Non-severe | | Total n |
	Abdominal pain	No pain	Abdominal pain	No pain	
Zhang et al[8]	6	51	2	80	139
Wang et al[9]	3	33	0	102	138
Pan et al[14]	2	35	0	66	103
Total, n	11	119	2	248	380

with random effects with a study CI of 95%. We have used MOOSE guidelines and checklist for reporting our meta-analysis for this being an observational epidemiological review.

RESULTS

A total of 314 studies were identified using our search strategy, of which 119 studies were removed after initial screening for duplicates, review articles, and case reports. A further 140 studies were removed after reviewing the title and abstract. A total of 55 articles were assessed for eligibility, and after excluding 38 studies which did not contain numerical data of GI symptoms, 17 studies were included in the final analysis (figure 1). The study characteristics are described in table 1. All 17 studies described the gender and mean age of the patients. The number of patients with diarrhoea was described in all the studies. However, only six studies had data on patients with nausea and/or vomiting, and only three studies had data on patients with anorexia and abdominal pain.

There is a considerable overlap of symptoms with at least nine out of the 17 studies reporting two or more symptoms. With a minimal estimate of 323 patients having at least one GI symptom of the 2477 patients, one in every eight (13%) had at least one GI symptom. In our subgroup analysis, 115 (5.6%) had nausea and/or vomiting of 2071 patients included from eight studies. One hundred and ninety-four patients (7.8%) reported diarrhoea of 2477 from 17 studies. One hundred and seven (27.1%) patients reported anorexia of the 395 included from three studies. Thirteen (2.7%) were noted to have abdominal pain of the 482 patients from three studies.

We performed meta-analyses comparing the odds of having GI symptoms in severe versus non-severe patients. Four studies for nausea and/vomiting, five studies for diarrhoea, and three studies for abdominal pain were used for the analyses. There was no significant difference in the incidence of diarrhoea (OR=1.32, 95% CI 0.8 to 2.18, Z=1.07, p=0.28, I^2=17%) as indicated in figure 2A or nausea and/vomiting (OR=0.96, 95% CI 0.42 to 2.19, Z=0.10, p=0.92, I^2=55%) as mentioned in figure 2B in severe versus non-severe patients. However, when evaluating abdominal pain, it was revealed that severely affected patients were over 7.17 times likely to possess

abdominal pain when compared with non-severe patients (OR=7.17, 95% CI 1.95 to 26.34, Z=2.97, p=0.003, I^2=0%), as displayed in figure 2C. Abdominal pain, diarrhoea and nausea and/or vomiting in patients with severe versus non-severe disease are shown in tables 2–4, respectively.

Study quality and bias assessment

A total of five studies were included in the meta-analysis. Four of these had a Newcastle-Ottawa Scale score of 7 or greater, signifying high quality. The remaining study was evaluated to be of fair quality with a score of 5. Overall, studies included in the meta-analysis were of moderate to high quality (table 5).

There seemed to be no significant heterogeneity for the studies included in the analysis of diarrhoea (I^2=17%) and abdominal pain (I^2=0%), but the studies included in the analysis of nausea and/or vomiting exhibited moderate heterogeneity (I^2=55%).

There seemed to be evidence for publication bias based on the funnel plots (figure 3).

DISCUSSION

From its inception in December 2019 until the date of this manuscript, the COVID-19 pandemic has rapidly spread across the world with over 2.6 million cases being reported across different continents.[1] Although much is already known of its commonly presenting symptoms such as fever (75%–98%) and cough (39%–81%),[7 8 11–13] our review seeks to present an interesting association of GI symptoms with COVID-19 as depicted in figure 4.

In their study of 204 patients, Pan et al reported GI symptoms as a part of the initial presentation in about 50% of the patients while Zhang et al reported GI symptoms in 39.6% of their sample of 140 patients.[8 14] In the former study, they had additionally reported six cases that solely presented with GI symptoms devoid of respiratory complaints. In line with these studies, our analysis revealed that a minimal estimate of 323 patients had at least one GI symptom of the 2477 patients. One in every eight patients (13%) had at least one GI symptom.

We attempted to break our primary and secondary outcomes down as per the commonly reported GI symptoms in COVID-19-positive patients.

Abdominal pain

Three studies, including 380 patients, were analysed in our meta-analysis.[8 9 14] Our findings suggested that patients with severe COVID-19 infection were almost seven times more likely to have abdominal pain as compared with their non-severe disease counterparts. Based on these results, abdominal pain could potentially serve as an indicator of severity in patients with COVID-19 infection to aid from triaging to deciding the aggressiveness of management.

In the systematic review, this was a sparsely reported complaint. A combined total of 13 out of 482 patients (2.7%) reported abdominal pain. Pan et al reported abdominal pain in 2 (1.9%) of the 103 patients, Zhang

Table 3 Diarrhoea in patients with severe versus non-severe disease

| Study | Severe | | Non-severe | | Total |
	Diarrhoea	No diarrhoea	Diarrhoea	No diarrhoea	n
Huang et al[11]	0	13	1	24	38
Zhang et al[8]	9	48	9	73	139
Wang et al[9]	6	30	8	94	138
Pan et al[14]	10	27	25	41	103
Guan et al[22]	10	163	32	894	1099
Total, n	35	281	75	1126	1517

et al in 8 (5.8%) patients, and Wang et al in 3 (2.2%) patients.[8 9 14]

Diarrhoea

In our meta-analysis, five studies met the inclusion criteria to measure the incidence of diarrhoea in patients with non-severe and severe COVID-19 infection. In our analysis of 1517 patients, we found that patients were more likely to have diarrhoea in the severe COVID-19 group when compared with its non-severe disease counterpart. This result was however not statistically significant, suggesting the need for more studies on the same to establish a true association.

Diarrhoea appeared to be the most common GI complaint in our review on patients with COVID-19, with its incidence ranging from 3% to 34%. One hundred and ninety-four out of 2477 patients (7.8%) reported diarrhoea from all 19 studies combined. Pan et al and Xiao et al recorded it to be present in 34% and 35% out of the study samples of 105 and 73 patients, respectively.[14 16] These studies may suggest that COVID-19 can masquerade as viral gastroenteritis leading to possible delayed and missed diagnosis.

In their case series of five patients who travelled from Wuhan, Chan et al found two patients to have had diarrhoea with fever as the sole presentation, prior to the onset of respiratory complaints. Diarrhoea can thus serve as an early manifestation of certain COVID-19 infections which may be implemented as a sign of early quarantine.[15]

It is also imperative that secondary causes of diarrhoea be ruled out, such as medications in patients with COVID-19 like hydroxychloroquine, lopinavir/ritonavir, which may serve as confounders. Hu et al found two out

of their 24 'asymptomatic' patients developing diarrhoea in the setting of being recently started on lopinavir/ritonavir and darunavir/cobicistat.[21]

Nausea and/or vomiting

In our meta-analysis, four studies were included in the analysis of 1497 patients focusing on nausea and/or vomiting as a symptom.[8 9 14 22] It was seen that patients with severe disease were more likely to report nausea than their non-severe disease counterparts; however, this finding was not statistically significant.

In our subgroup analysis, 115 (5.6%) had nausea and/or vomiting of the 2071 patients included from eight studies. The incidence ranged from 1% to 17% in all the included studies. These symptoms, along with a lack of appetite (107/395 (27.1%) from three studies), seem to be a non-specific finding. However, given the right clinical setting, this may expedite COVID-19 diagnoses.

Pathophysiology and possibility of feco-oral spread

The virus is a positive-sense non-segmented single-stranded beta coronavirus.[22 23] The proposed mechanism of entry for the virus lies in its ability to attach to the ACE2, an extracellular membrane receptor expressed on epithelial cells.[24 25] A study conducted by Xiao et al revealed that the viral nucleocapsid protein was heavily expressed in the areas of the GI tract that possessed strong ACE2 expression such as the stomach, duodenum, and rectum and was noticeably lower in areas devoid of the receptor such as the oesophagus. This also coincides with the degree of expression of the ACE2 receptor in the aforementioned segments of the GI tract.[16 17] The viral colonisation of the gut via the gut expressed ACE2 receptors will result in continued viral shedding in the stool in the form of diarrhoea, long after resolution of the initial respiratory infection.[16] Recent data also suggest that viral detection in the stool occurs independent of the presence of diarrhoea and can be as common as 50% of patients.[26]

The clinical implications of this are profound, as it brings to light a possible faecal mode of transmission, as has been postulated by recent studies.[16] One may infer that the presence of GI symptoms, in addition to the commonly reported symptoms of cough and fever, should be monitored as a sign of an actively infectious state.

Table 4 Nausea and/or vomiting in patients with severe versus non-severe disease

| Study | Severe | | Non-severe | | Total |
	Nausea	No nausea	Nausea	No nausea	n
Zhang et al[8]	5	52	19	63	139
Wang et al[9]	4	32	10	92	138
Pan et al[14]	2	35	2	64	103
Guan et al[22]	12	161	43	883	1099
Total, n	23	280	74	1102	1479

Table 5 Quality assessment for studies

Newcastle–Ottawa Quality Assessment Scale for cohort studies[18]

| Study | Type of study | Selection | | | | Comparability | Outcome | | | Total score (out of 8 stars) |
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure/risk factor, that is, severe versus non-severe	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Huang et al[11]	Prospective cohort	*	*	*	0 (No)	*	*	*	*	7 stars
Zhang et al[8]	Retrospective cohort study	*	*	*	0 (No)	*	*	Follow-up period not mentioned	Unable to assess	5 stars
Wang et al[9]	Retrospective cohort study	*	*	*	* (Yes)	*	*	*	*	8 stars
Pan et al[14]	Descriptive cross-sectional study with a prospective cohort component	*	*	*	* (Yes)	*	*	*	*	8 stars
Guan et al[22]	Retrospective cohort study	*	*	*	* (Yes)	*	*	*	*	8 stars

*Indicates one star.
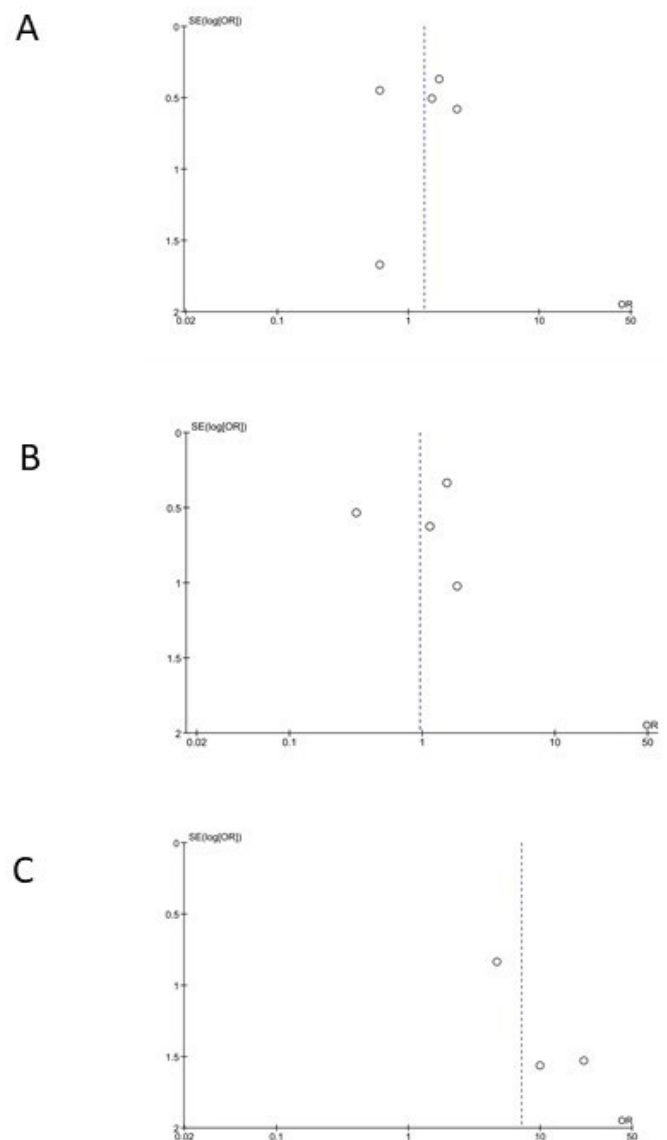
Figure 3 Funnel plots showing publication bias. (A) Abdominal pain, (B) diarrhoea, (C) nausea and/or vomiting.

Another mechanism of injury involving the GI tract would include the possibility of a systemic inflammatory response to the gut, secondary to viraemia which may lead to an alteration of the gut microbiota. This, in turn, may affect the lung microbiota via the 'gut-lung axis' increasing the risk of developing acute respiratory distress syndrome.[14 27 28]

Strengths and limitations

To the best of our knowledge, this is one of first GI-specific meta-analysis and largest systematic review that has been conducted regarding COVID-19 comparing severe and non-severe disease. The total analysed sample size was over 2477 patients, allowing for adequate evaluation of the various clinical symptoms. The systematic review also allowed for inferences such as the possibility of a feco-oral transmission of the disease and the possibility of a delay in diagnosis due to GI symptoms being the sole initial presenting complaint of the disease.
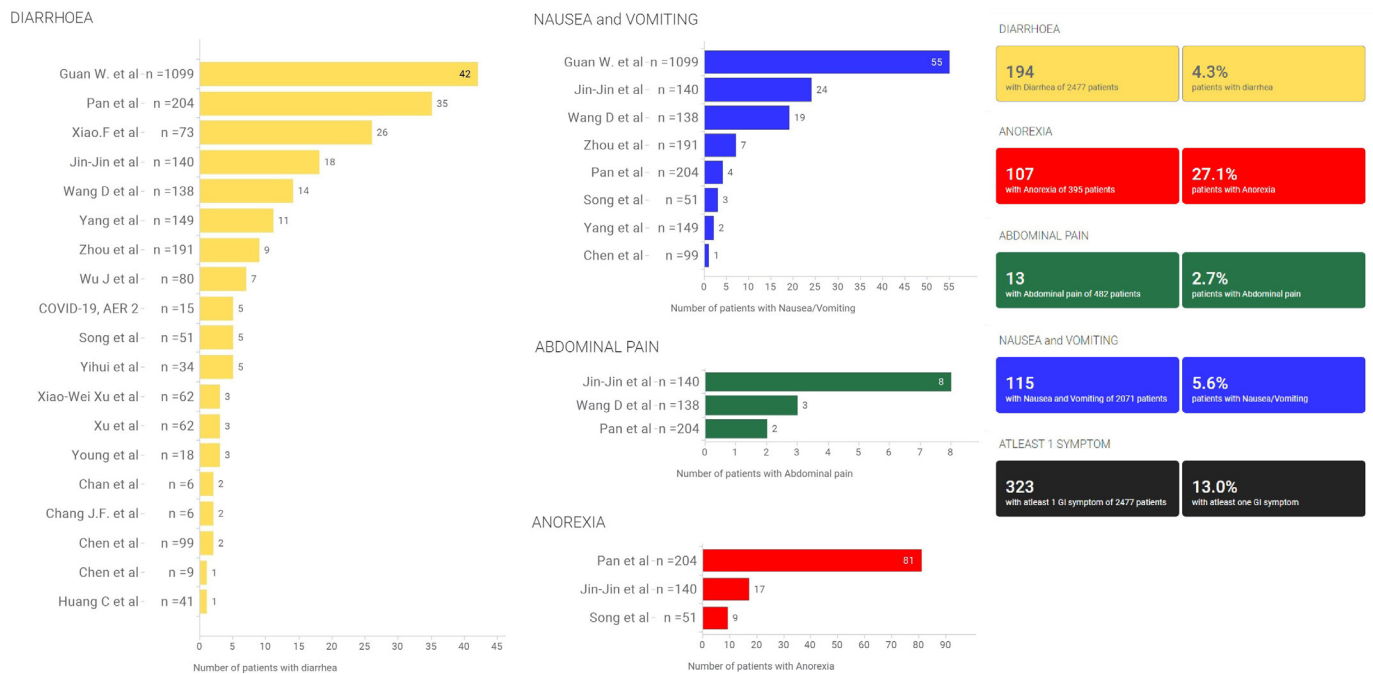
Figure 4 Percentage of patients with gastrointestinal symptoms. AER, Australian epidemiological report.

The analysis was not without its own set of limitations. First, the patient samples were geographically isolated to the east and southeast Asian regions, particularly China. Data from elsewhere are lacking. Second, there exists no standardisation on the definition of 'severity' as different studies have implemented different severity grading scales for the same.[19 20] Third, in accordance with other studies, the patient data are limited to those who were hospitalised, creating a selection bias. Fourth, patients had been treated with hydroxychloroquine, lopinavir, and ritonavir, which may have confounded results by virtue of their GI side effects. Fifth, Chinese databases were not included in this study. Lastly, the studies included in the review and analysis were retrospective in nature, introducing a possible bias.[29]

Despite the limitations, the paper seeks to provide valuable insight into the GI manifestations of the COVID-19. It provides evidence that the GI manifestations of the disease sometimes precede the respiratory symptoms, thereby delaying diagnosis. Our findings also reveal that GI symptoms are more common in the severe forms of the disease. This is in concert with some of the data that have been published.[14] While one may argue that this may be due to the fact that patients with severe disease may possess severe forms of all aspects of the clinical spectrum, it may serve as an important prognostic marker for the overall progression of the disease. Further complicating the matter is the fact that patients with no typical respiratory complaints may delay their presentation to the hospital, thereby delaying the overall diagnosis.

Scope for future research

As data for COVID-19 continue to grow, so does our understanding of its pathophysiology, mechanism of spread, and clinical features. Future studies exploring

a possible feco-oral route of infection via animal models may provide conclusive evidence for the same. At present, very little is known about drugs such as remdesivir, which are undergoing clinical trials.[30] It is likely that such medications may present with their own possible GI side effects. The studies that have been published at present are largely retrospective in nature, and we anticipate that there will be more prospective studies in the near future. Given that most of the current data are from the inpatient setting, there is a need for studies exploring the disease in the outpatient scenario.

CONCLUSIONS

GI symptoms are an important clinical finding in patients with COVID-19. Symptoms analysed in this study include diarrhoea, abdominal pain, nausea, and vomiting. Diarrhoea occurs in about 7.8%, and nausea and/or vomiting occurs in 5.5% of the patients infected. Our meta-analysis using the data from pooled studies indicates that patients with severe disease are seven times more likely to have abdominal pain when compared with patients with non-severe disease leading to a thought that it might be an indicator of severity.

original draft: supporting). BS (Methodology: supporting; Supervision: lead; Writing–review and editing: equal).

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