



COVID-19 AND THE GASTROINTESTINAL SYSTEM: A SYSTEMATIC REVIEW AND METANALYSIS

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ABSTRACT

Objective: At present, the novel coronavirus disease (COVID-19) is causing a major pandemic. COVID-19 is caused by Severe Acute Respiratory Syndrome-2 (SARS-COV-2). In COVID-19, the patient generally presents with fever, dry cough, and respiratory signs and symptoms. Involvement of other systems has also been reported. Abdominal pain, diarrhea, vomiting, and nausea are the predominant gastrointestinal symptoms, underlined in the literature. In this article, we summarized the important GIT characteristics of the disease. **Methods:** We conducted a literature search using four databases (PubMed, Google Scholar, Web of Science, and Clinicaltrials.gov). Our search strategy included MeSH terms and keywords for COVID-19, SARS-CoV-2, and gastrointestinal system from inception to December 2020. After excluding review articles, duplicates, and non-relevant, we included 60 studies out of 558 articles reporting gastrointestinal (GI) manifestations such as nausea, vomiting, abdominal pain, and diarrhea. Using the 'meta' package (Schwarzer et al.) in the R programming language, version 4.0.2, a compute pooled analysis using the random effect model was performed. **Results:** The overall prevalence of GI signs and symptoms in affected patients with COVID-19, was 27% (95% CI: 21-35) (p<0.05) (I² =94%). GI involvement as an initial presentation was reported in six studies with prevalence of 6% (95% CI: 05-83) (p<0.01) (I² =88%), with diarrhea being 17% (95% CI: 12-19) (p=0.01) (I² =94), anorexia being 34% (95% CI: 22-38) (p<0.01) (I² =96%), abdominal pain being 16% (95% CI: 11-20) (p<0.01) (I² =95%), and nausea/vomiting nearing 17% (95% CI: 13-22) (p<0.01) (I² =88%). Severe COVID-19 with GI symptoms were reported with prevalence of 16% (95%CI: 19-31) (p<0.01) (I² =90%). Hepatic abnormalities in COVID-19 were reported with prevalence of 28% (95% CI: 14-33) (p<0.01) (I² =97%). **Conclusion:** We perceive that COVID-19 may have several gastrointestinal manifestations, and in many cases, GI involvement may precede typical upper respiratory tract symptoms. Holistic knowledge of the spectrum of the COVID-19 GI consequences is crucial to get a hold of the virus spread.

KEYWORDS: COVID-19, SARS-COV-2, Gastrointestinal, Hepatic manifestation.

INTRODUCTION

The novel SARS-CoV-2, also known as coronavirus 2019 (COVID-19), originated in Wuhan, China, in late December of 2019 before rapidly disseminating

throughout the world and being declared a pandemic by WHO in March 2020.^[1] SARS-CoV-2 belongs to the beta-coronavirus genus, which also involves the SARS-CoV and the Middle East Respiratory Syndrome

Coronavirus (MERS-CoV), a single-stranded RNA virus that has a genetically strong resemblance with that of bat coronaviruses.^[2] SARS-CoV-2 is the third coronavirus discovered to cause severe lung disease in humans, like the other two previous coronaviruses, i.e., SARS-CoV and MERS-CoV.^[3]

Most COVID-19 patients generally present with fever and respiratory symptoms.^[4,5] However, some infected patients also have gastrointestinal (GI) manifestations, such as diarrhea, nausea, vomiting, and abdominal pain.^[4] Moreover, in some COVID-19 patients, SARS-CoV-2 RNA was identified in anal/rectal swabs and stool specimens.^[5] Interestingly, in some infected patients, SARS-CoV-2 RNA was detected in feces even after the virus clearance in the respiratory tract. Furthermore, earlier studies^[6] have shown that ACE2 (angiotensin-converting enzyme 2) is responsible for viral adhesion and entry into the host cell. These receptors are expressed in small intestine epithelial cells. Thus, SARS-CoV-2 can actively infect and replicate within the GI tract, which warrants necessary implications for treatment, transmission, and infection control. Hence, reviews and critical evaluations of the rapidly evolving research data on this potentially lethal disease are indispensably necessary.

In clinical practice, respiratory symptoms are prioritized by both patients and healthcare workers for testing and pre-emptive isolation precautions, following the worldwide effort to halt the virus spread and mitigate its effects on the global population.^[3] The objective of this review and meta-analysis is to determine whether isolated GI symptoms warrant testing for COVID-19 and whether GI symptoms, alone or in combination with respiratory symptoms, are associated with severe disease or mortality.

MATERIAL AND METHODS

Search strategy and study design

We conducted a literature search using four databases (PubMed, Web of Science, Google Scholar, and Clinicaltrials.gov). Our search strategy included MeSH terms and keywords for COVID-19, SARS-CoV-2, and gastrointestinal system from inception to December 2020. After excluding review articles, duplicates, and non-relevant, we included 60 studies out of 558 articles reporting gastrointestinal (GI) manifestations such as nausea, vomiting, abdominal pain, and diarrhea as per PRISMA guidelines (Figure 1). We included any literature that reported the presence or absence of GI manifestations in a sample of more than five COVID-19 positive patients, including diarrhea, nausea, vomiting, anorexia, abdominal pain, or hepatic injury, with or without the presence of respiratory viral manifestations. Three authors independently reviewed each article for inclusion and extracted data.

Study characteristics and Quantitative analysis

Our search identified 558 unique articles, of which 60 met the inclusion criteria (Table1). These comprised 10796 COVID-19 positive patients from different countries. Most studies focused on adult patients and the hospital setting. Many studies centered on specific hospitalized subpopulations, such as medical staff, healthcare workers, family clusters, orthopedic, pregnant, or critically ill patients. All defined COVID-19 cases exclusively by positivity on an upper respiratory swab polymerase chain reaction (PCR).

We performed a random-effects meta-analysis. Our study's primary outcome was the proportion of COVID-19 infected patients who experienced isolated gastrointestinal symptoms, as well as a combination of both GI and respiratory symptoms. We calculated pooled ratios of patients who experienced GI manifestations for COVID-19 positive patients with elevated alanine transaminase (ALT) or aspartate transaminase (AST) and weighted according to the number of patients in each study with enzyme level measurements. In the secondary analysis, we measured the odds ratio (OR) of severe COVID-19 versus non-severe COVID-19 based on the presence of any GI symptom. Using the 'meta' package (Schwarzer et al.) in the R programming language, version 4.0.2, a compute pooled analysis using the random effect model was performed.

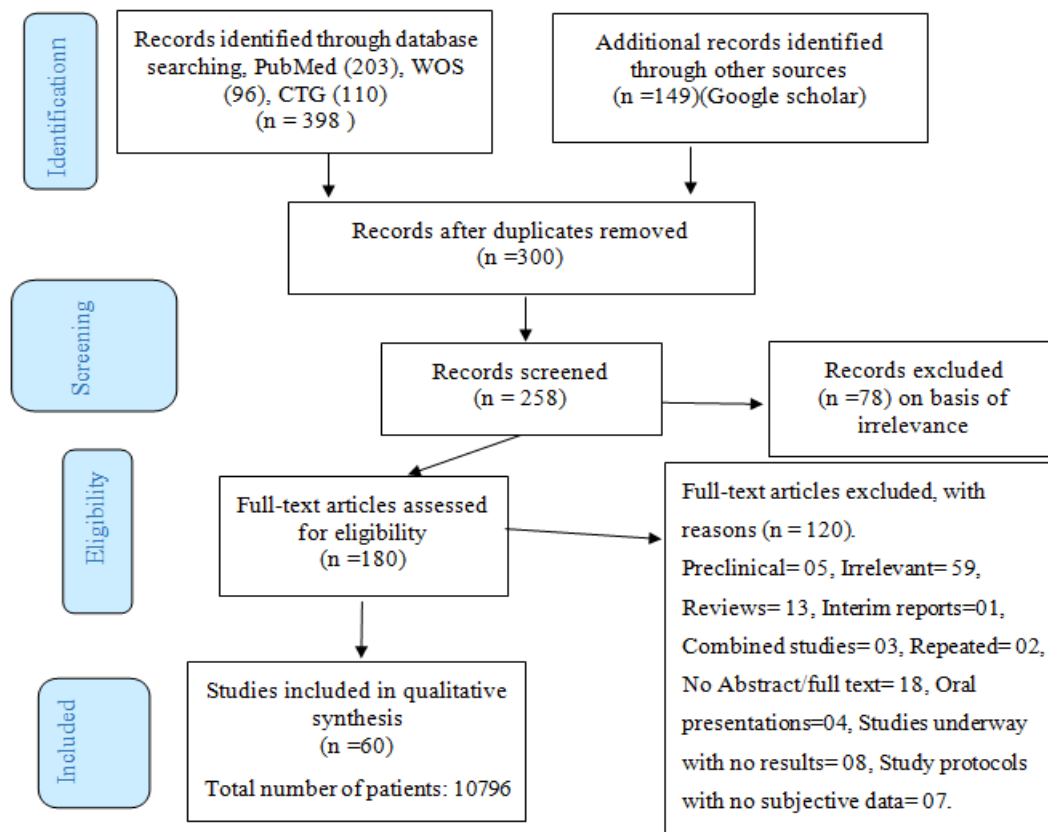


Table 1: Studies included in our study. ^[1-60]

Author	Location	Number of COVID Patients	Any GI symptom	GI First Symptom	Diarrhea	Anorexia	Elevated LFTs	Severe COVID
Cai X	China	5	4	4	2	2	3	2
Chang	China	13	1	N/A	1	N/A	N/A	0
Chen G	China	21	4	N/A	4	N/A	6	11
Chen J	China	12	4	0	4	N/A	0	0
Chen J	China	249	N/A	N/A	8	8	N/A	N/A
Chen M	China	11	5	N/A	2	N/A	N/A	N/A
Chen N	China	99	N/A	N/A	2	N/A	N/A	N/A
Chen Q	China	9	2	N/A	2	N/A	N/A	4
Chen Q	China	145	N/A	N/A	39	62	N/A	43
Chen T	China	274	N/A	N/A	77	66	84	274
Chen Y	China	42	8	N/A	7	N/A	N/A	11
Cholankeril	USA	116	37	0	12	22	26	N/A
Dai	China	234	N/A	N/A	9	N/A	N/A	15
Diao	China	6	1	N/A	1	N/A	N/A	0
Effenberger	Austria	40	N/A	N/A	22	N/A	N/A	N/A
Garazzino	Italy	168	N/A	N/A	22	N/A	N/A	N/A
Guan	China	1099	N/A	N/A	42	N/A	158	173
Hajifathalian	USA	1059	350	N/A	234	240	657	N/A
Han C	China	206	117	13	67	102	N/A	0
Han R	China	108	15	N/A	15	N/A	N/A	N/A
Han YN	China	32	6	N/A	N/A	N/A	10	4
He	China	204	N/A	N/A	19	12	N/A	69
Hossain	USA	119	60	N/A	N/A	N/A	N/A	29
Huang C	China	38	1	N/A	1	N/A	15	13
Huang L	China	7	1	1	1	N/A	N/A	N/A
Huang LE	China	8	7	0	6	3	0	0
Huang Y	China	34	5	N/A	5	N/A	15	N/A

Jin	China	651	74	N/A	56	N/A	N/A	64
Kim	Korea	28	N/A	N/A	14	N/A	6	6
Klopfenstein	France	114	55	N/A	55	N/A	N/A	4
Lechien	Europe	1420	N/A	N/A	473	649	N/A	0
Lei P	China	14	3	N/A	3	N/A	4	N/A
Lei Z	China	20	N/A	N/A	5	N/A	N/A	N/A
Li	China	658	N/A	N/A	18	N/A	39	N/A
Li	China	83	7	N/A	N/A	N/A	N/A	25
Lian	China	465	N/A	N/A	36	N/A	99	49
Lin	China	95	11	N/A	5	5	1	20
Liu F	China	10	3	N/A	0	N/A	N/A	5
Liu J	China	40	N/A	N/A	3	N/A	N/A	13
Liu J-Y	Taiwan	321	26	N/A	23	N/A	N/A	N/A
Liu K	China	137	11	N/A	11	N/A	N/A	N/A
Liu W	China	6	4	N/A	N/A	N/A	4	1
Liu Y	China	12	3	N/A	2	N/A	3	5
Liu Z	China	72	N/A	N/A	2	N/A	15	8
Lo	Macau	10	N/A	N/A	8	N/A	1	4
Luo	China	183	N/A	N/A	68	180	N/A	N/A
Mao	China	214	N/A	N/A	41	N/A	N/A	88
Mi	China	10	1	N/A	0	N/A	4	7
Mo	China	155	N/A	N/A	7	N/A	N/A	37
Nicoletti	Italy	42	13	N/A	2	N/A	8	N/A
Nobel	USA	278	97	N/A	56	N/A	N/A	N/A
Palaiodimos	New York	200	N/A	N/A	66	N/A	N/A	N/A
Pan	China	204	103	6	35	81	N/A	N/A
Pung	Singapore	17	N/A	N/A	4	N/A	N/A	2
Qian GQ	China	91	N/A	N/A	21	23	N/A	9
Redd	USA	318	195	N/A	107	110	N/A	N/A
Saeed	Norway	9	9	9	1	N/A	N/A	0
Shao	China	136	N/A	N/A	27	N/A	N/A	5
Shen	China	9	2	2	2	N/A	2	0
Shi S	China	416	16	N/A	16	N/A	N/A	N/A

RESULTS

The most frequent symptom recorded in the studies was diarrhea (54 studies), abdominal pain (40 studies), nausea/vomiting (30 studies), anorexia (15 studies). The overall prevalence of any GI sign and symptom in affected patients with COVID-19 was 27% (95% CI: 21-35) ($p < 0.05$), and consequent heterogeneity (I^2) was 94%. Diarrhea, nausea, abdominal pain, and vomiting were included in the definition of GI symptoms. Anorexia was not included in the description of GI symptoms. GI features as an initial presentation were reported in six studies with a prevalence of 6% (95% CI: 05-83) ($p < 0.01$), with consequent heterogeneity being 88%. Out of 576 patients, 35 patients reported GI symptoms as an initial presentation of COVID-19. GI symptoms lasted for a median duration of 4.5 (± 1.9) days, based on three studies, but patients presented later in their natural disease course (median duration of 13.2 [± 5.4] days after onset of first symptoms).

Regarding specific symptoms, diarrhea was reported in 1771 patients out of 10556 patients with a prevalence of 17% (95% CI: 12-19) ($p = 0.01$) with consequent heterogeneity being 94%. Diarrhea was defined as usually more than three loose stools per day, but few

studies quantified the severity of any GI symptoms. Anorexia was reported in 1565 patients out of 4577 patients with a prevalence of 34% (95% CI: 22-38) ($p < 0.01$), with consequent heterogeneity equal to 96%. Abdominal pain was reported in 1291 patients out of 8070 patients with a prevalence of 16% (95% CI: 11-20) ($p < 0.01$) with consequent heterogeneity of 95%. Nausea or vomiting was reported in 573 patients out of 3372 patients with a prevalence of 17% (95% CI: 13-22) ($p < 0.01$) and a consequent heterogeneity of 88%. Out of 60 studies, 30 studies reported severe cases of COVID-19. A severe case of COVID-19 includes those patients that require hospitalization, fever more than 101 °F, and symptomatic for the last ten days. Severe cases were reported in 1000 patients out of 6114 patients with a prevalence of 16% (95% CI: 19-31) ($p < 0.01$), with consequent heterogeneity of 90%. Twenty-one studies reported abnormalities in liver function in COVID-19 patients. A total of 1160/4119 patients reported hepatic enzyme abnormality with a prevalence of 28% (95% CI: 14-33) ($p < 0.01$) and a consequent heterogeneity of 97%.

DISCUSSION

This meta-analysis represents the most extensive study of gastrointestinal manifestations of COVID-19 to date,

with more than 10,000 patients from 60 articles. The COVID-19, because of its high infectivity, is currently causing a major pandemic and constitutes a global health crisis. Consequently, in the short six-month period (January to June) since December 2019, we have been experienced an explosion of publications concerning COVID-19 cohorts of patients. COVID-19 patients commonly develop fever and respiratory illness. However, some patients also report GI symptoms. This meta-analysis pooled current individual data concerning the digestive system's involvement in COVID-19 and showed that a percentage of the COVID-19 patients manifest GI symptoms. Thus, the pooled prevalence rate for all symptoms is 27% (95% CI: 21-35) ($p < 0.05$), diarrhea with prevalence of 17% (95% CI: 12-19) ($p = 0.01$) ($I^2 = 94$), anorexia with prevalence of 34% (95% CI: 22-38) ($p < 0.01$) ($I^2 = 96\%$), abdominal pain with prevalence of 16% (95% CI: 11-20) ($p < 0.01$) ($I^2 = 95\%$), and nausea/vomiting with prevalence of 17% (95% CI: 13-22) ($p < 0.01$) ($I^2 = 88\%$). We found hepatic abnormality to be even more prevalent than GI symptoms, with 28% of patients having elevated transaminases. Presentation with GI symptoms without any typical respiratory symptoms or fever is uncommon but remains clinically pertinent for a pandemic of this extent, occurring in 1.5% of patients.

Our primary analysis demonstrated that 1% (95% CI: 0–6%) of COVID-19 patients presented with isolated GI symptoms, lower than reported up to 2% in previous studies. For example, an earlier study by Mao *et al.* reported that 10% of the patients infected with COVID-19 presented with only GI signs and symptoms, and a corresponding cohort study from a single hospital in China by Han *et al.* described isolated GI symptoms in 23% of SARS-CoV-2 patients.^[3,42] However, a study by Han *et al.* was not able to evaluate a true prevalence of gut symptoms among all COVID-19 patients. Furthermore, our data-analysis identifies and comprises several studies with zero prevalence of isolated GI symptoms that were not involved in the Mao review. Even if the inclusive prevalence of isolated GI symptoms is comparatively low, 1% represents hundreds of COVID-19 cases daily in the US alone, with both clinical and public health implications, and requires urgent evaluation.^[43,44]

During the endemic of SARS-CoV disease in 2003, among other symptoms, almost 20% of the patients manifested GI symptoms.^[60,61] GI symptoms were also reported in MERS-CoV disease^[62], with cohorts underlying symptoms in 11.5-32% of the infected patients. Interestingly, there is evidence showing that coronaviruses express a tropism to the GI tract, which might explain the frequent occurrence of GI symptoms in coronavirus infections. SARS-CoV RNA has also been detected in stool specimens of infected patients, with active viral replications seen by electron microscopy on biopsy or autopsy specimens of intestines.^[61] Similarly, it has been reported that MERS-CoV often resulted in GI

infection, with human epithelial cells of the GI tract is highly susceptible to MERS-CoV.^[64] Since the genome sequence of SARS-CoV-2 has approximately 80% identity with SARS-CoV, GI infection by SARS-CoV-2 is not surprising. Interestingly, this meta-analysis revealed that the prevalence of GI symptoms was noted higher in patients with severe disease than those with less severe infection. This finding might have potential prognostic implications, as COVID-19 patients who manifest GI symptoms may necessitate closer monitoring.

In exploring the remarkable heterogeneity inherent in analyzing large numbers of studies, geography and data publication date developed a significant association with the reported prevalence of GI manifestations. The prevalence of diarrhea, abdominal pain, and nausea/vomiting in publications written after 1st April were almost twice that of papers before 1st April. A similar trend was seen in Europe or North American publications compared to those conducted in Asia. This might be because earlier COVID cases and related publications began in Asia. Having said that, the effect of country versus publication date is challenging to unscramble. As COVID-19 was first demonstrated as a respiratory illness, a comprehensive collection of signs and symptoms in literature occurred to a lesser extent earlier in the COVID-19 pandemic. Guan *et al.* underlined 3.8% of infected patients had diarrhea and 5% nausea or vomiting. However, study investigators and reviewers said disease course records were incomplete due to overwhelmed medical infrastructure and clinically rather than research-driven data collection.^[47] Cholankeril *et al.* reported a higher prevalence of diarrhea (12%) and nausea or vomiting (12%). However, the authors and investigators acknowledged testing criteria had not included extra-pulmonary symptoms at the time of review.^[48] In contrast, Hajifathalian *et al.* clearly defined GI symptoms and systematically evaluated the infected patients for extra-pulmonary manifestations. They reported an even higher incidence of diarrhea among infected patients (22%).^[29]

The mechanism of GI and hepatic involvement in SARS-CoV-2 infection could be explained by the presence of ACE2 cell receptors. Indeed, previous studies concerning SARS-CoV have revealed that both viral glycoproteins, encoding and expressing the spike (S), can bind to cellular receptor ACE2, thus entering human cells.^[65] Besides, it has been shown that the receptor-binding domain on COVID-19 could bind to human ACE2 with high affinity.^[66,67] While ACE2 is expressed in abundance in the lung alveolar cells, the receptor is also highly expressed in the GI tract, especially in the small and large intestines.^[68] These data provide valuable perception into the receptor-mediated entry into the enteric cells and offer a basis for its possible transmission route through the feces. The direct impact of this analysis data refers to the infectivity of the COVID-19. Towards this notion, a recent study revealed

that COVID-19 could remain viable in aerosols for hours and could be stable on plastic and stainless steel for at least 72 hours.^[45] While more studies are required in this field, viral excretion in feces and its environmental stability would result in a favorable spread of COVID-19 among human hosts, as stated during the SARS epidemics in Hong Kong.^[69] The GI involvement of COVID-19 may warrant the need to consider suitable hospital policies, such as adopting rectal swab COVID-19 testing before a patient's discharge. Undoubtedly, this study's results are important and should be taken seriously into account in our fight against COVID-19.

Our meta-analysis has notable limitations. As a review of many observational studies, there is a great degree of heterogeneity, which is only partially described by subgroup analyses. The majority of included studies in our study are from China and were conducted in hospitalized settings. So generalizability to other regions and less critically ill patients is one limitation. Lastly, no reviews had a low bias risk. This rating was usually due to the absence of COVID-19 hostile comparison groups, suboptimal depth of GI symptoms, and lack of proper follow-up of COVID-19 patients. Recent articles have drawn attention to the flawed methodology and systematic approach of many early COVID-19 studies, driven by overwhelmed healthcare organizations needing rapid information dissemination with high-quality peer review.^[55,56] These limitations are notwithstanding. Our review is one of the largest to-date of the peer-reviewed data and literature, including a separate subgroup analysis of literature published since early 2020, to provide the most updated estimates of the prevalence of GI manifestations of COVID-19 infection.

CONCLUSION

We perceive that COVID-19 may have several gastrointestinal manifestations, and in many cases, GI involvement may precede typical upper respiratory tract symptoms. Our study highlights the need for high-quality data from the recent studies, including patients from the community settings, and further explores the underlying mortality causes. The most prevalent GI manifestations which we met are diarrhea and nausea/vomiting. Therefore, an extraordinary catalog of suspicion for such patients will be essential to prevent or, at least, minimize contact to health care providers and other high-risk patients. There is the advocacy of comprehensive testing for COVID-19, including patients presenting with isolated GI symptoms or unexplained LFTs elevations—especially when testing resources are abundant. The significant role of digestive manifestations in COVID-19 is precise, but many knowledge gaps regarding their pathophysiology and prognostic value persist. Further research should continue through well-designed prospective studies for more detailed data.

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