Progress in Microbes and Molecular Biology

HH PUBLISHER

Review Article

COVID-19: Gastrointestinal Manifestations and Complications

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Article History

Received: 15 October 2021;

Received in Revised Form: 14 November 2021;

Accepted: 15 November 2021;

Available Online: 22 November 2021

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Abstract: The virus responsible for the COVID-19 pandemic is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the genus Betacoronavirus. This genus also includes the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). The common symptoms of COVID-19 infection are fever and respiratory symptoms, but it can also involve the gastrointestinal tract (GIT), resulting in manifestations such as diarrhea, nausea and/or vomiting and abdominal pain. The emergence of COVID-19 led to public health emphasis on droplet transmission and precautions of contact with respiratory secretions. However, mounting evidence demonstrates detection of SARS-CoV-2 RNA in stool samples of COVID-19 patients. It has also been demonstrated that the host receptor angiotensin-converting-enzyme-2 (ACE-2) is highly expressed not just in respiratory cells but also in gastrointestinal sites involving the glandular cells of gastric, duodenal, and rectal epithelium. This suggests that SARS-CoV-2 can infect the digestive system, serving as another route of transmission. This review aims to study the prevalence of some of the gastrointestinal manifestations following COVID-19 infection and findings of positive SARS-CoV-2 RNA in stool specimens while making parallels to the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) infection. We will also discuss the possible pathophysiology of COVID-19 related gastrointestinal involvement.

Keywords: COVID-19; SARS-CoV-2 RNA; gastrointestinal; angiotensin converting enzyme 2 (ACE-2); stool

1. Introduction

The Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in early March 2020[1-3]. This global pandemic started with an

outbreak of pneumonia of unknown aetiology in Wuhan, Hubei province of China[4-8]. The virus responsible for causing COVID-19 was named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV)[9]. It is a positive sense, single-stranded RNA virus belonging to the genus Betacoronavirus that originated from bats[4, 10]. Interestingly, SARS-CoV-2 has a 79% overlap of genomic sequence identity with the severe acute respiratory syndrome coronavirus (SARS-CoV) and 50% with the Middle East respiratory syndrome coronavirus (MERS-CoV)[11]. At the time this paper went to press, the SARS-CoV-2 had infected over 250,000,000 people and caused 5,072,046 deaths worldwide (as of 10th November 2021)[12]. The virus spread swiftly worldwide, with the emerging of new variants of concern (VOC) with a higher infectivity linked to high fatality rates[13].

The data suggests that SARS-CoV-2 primarily infects respiratory epithelial cells and spreads via respiratory route from human to human, however, the exact viral target cells and organs are yet to be determined[14]. Some of the most common symptoms of COVID-19 infections include fever and respiratory symptoms such as dry cough and dyspnea, which is similar to the severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012. Aside from respiratory symptoms, gastrointestinal symptoms including diarrhea, nausea, vomiting and abdominal pain may also be present[15]. There has been escalating evidence of SARS-CoV-2 RNA being detected in stool specimens[14, 16, 17], and anal[18], or rectal swabs[19], of COVID-19 patients despite the clearance of SARS-CoV-2 in the respiratory cells/upper respiratory tract[14, 18, 20]. Besides that, the angiotensin-converting enzyme-2 (ACE-2) receptor is highly expressed in gastrointestinal epithelial cells, particularly the ileum, duodenum, jejunum, caecum and colon[14, 21]. Taken together, these suggest that SARS-CoV-2 may also demonstrate fecal-oral transmission, in addition to droplet transmission; which has implications on SARS-CoV-2 transmission, infection control and management. The aim of this review is to study the prevalence of some of the gastrointestinal symptoms and the positive detection of SARS-CoV-2 RNA in stool specimens of COVID-19 patients, while making parallels to SARS and MERS infection. We will also discuss some of the possible causes of gastrointestinal involvement following COVID-19.

2. Prevalence of Gastrointestinal Symptoms of COVID-19

The well-established signs and symptoms of COVID-19 patients are fever and respiratory symptoms. However, gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain seem to frequently also be part of the manifestations of the disease. In the United States, the first confirmed COVID-19 case was reported on the 20th January 2020

involving a 35-year-old man who just returned from Wuhan, China. Upon admission, he presented with persistent dry cough and a 2-day history of nausea and vomiting. On the second day of hospitalization, he reported diarrhea and abdominal discomfort[16].

In a meta-analysis consisting of 4,243 COVID-19 positive patients (60 studies) from 6 countries (China *n*=53, South Korea and Singapore *n*=2, Vietnam, United States and United Kingdom *n*=1) the pooled prevalence of gastrointestinal symptoms was 17.6%[22]. For individual gastrointestinal symptoms, 18 studies reported the prevalence as follows: lack of appetite (26.8%), diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal pain (9.2%)[22]. A cross sectional multicenter study involving 204 hospitalized COVID-19 positive patients in China's Hubei province found 103 (50.5%) patients had ≥ 1 digestive symptoms, including diarrhea (34%), vomiting (3.9%), abdominal pain (1.9%)[23]. Furthermore, in a Hong Kong cohort with 59 COVID-19 positive patients, 15 (25.4%) patients presented gastrointestinal symptoms of diarrhea (22%), abdominal pain (11.9%), vomiting (1.7%), and 9 (15.3%) had positive viral RNA in stool specimens[22]. A few other cohorts also reported frequencies of diarrhea ranging 2.0–10.1% and nausea and/or vomiting ranging 1.0–10.1%[10, 24-32].

Similar to adults, children also displayed gastrointestinal symptoms following positive COVID-19 assays. However, in terms of COVID-19 severity, children and/or adolescents were found to have less severe COVID-19 infection, with milder symptoms and possibly better prognosis than adults[33, 34]. In a meta-analysis of 280 COVID-19 positive children, the pooled prevalence of gastrointestinal symptom was 22.8%. The pooled prevalence of diarrhea, vomiting and abdominal pain was respectively 12.4%, 10.3%, and 5.4% respectively[35]. On the other hand, another meta-analysis consisting of 2855 children showed 4% had diarrhea and none had abdominal pain[33]. The variability in rates in different studies could be a result of variability in clinical presentation and study size. Hence, more clinical data is needed.

Similar to COVID-19, SARS and MERS outbreaks also demonstrated gastrointestinal (GI) manifestations during the course of the disease. A retrospective study in Hong Kong involving 138 SARS patients revealed diarrhea to be the most common GI symptom with an average (±SD) duration of diarrhea of 3.7±2.7 days. Out of 138 patients, 28 (20.3%) had diarrhea at presentation while 53 (38.4%) had diarrhea at the first 3 weeks of illness[36]. Using reverse transcriptase-polymerase chain reaction (RT-PCR), it was also demonstrated that the stool specimens from SARS patients had a 16% detection rate of severe acute respiratory syndrome coronavirus (SARS-CoV) RNA, comparable to the detection rate in nasopharyngeal aspirates[36]. MERS also presented with gastrointestinal symptom — in a study of 47 MERS infected patients in Saudi Arabia, diarrhea (26%), vomiting (21%) and

abdominal pain (17%) were present at presentation[37]. A retrospective observational study from Korea with 186 MERS patients also showed gastrointestinal symptoms of diarrhea (19.4%), nausea and vomiting (14%) and abdominal pain (8.1%)[38].

It is clear that COVID-19 has a similar gastrointestinal presentation as that seen in SARS and MERS. COVID-19 positive patients whether children or adults can present with gastrointestinal symptoms early in the course and it should not be taken lightly. For instance, a study found nearly a quarter of COVID-19 positive children have at least one gastrointestinal symptom with diarrhea being the most common symptom followed by vomiting and abdominal pain[35]. This finding was quite consistent with a meta-analysis in adult COVID-19 patients that found the prevalence of gastrointestinal symptoms to be 18%[22, 35]. Nonetheless, there could be variation in the rate of prevalence among different studies due to variability in study size and clinical presentation.

3. Detection of SARS-Cov-2 RNA in Stool Specimens of COVID-19 Patients

In relation to SARS-CoV-2 RNA detection in stool specimens, US's first COVID-19 positive patient presented with gastrointestinal symptoms and his stool sample together with respiratory specimens (nasopharyngeal and oropharyngeal) and serum were sent for real time RT-PCR testing in which both stool (illness day 7) and respiratory specimens (illness day 4 and day 7) detected SARS-CoV-2 RNA[16]. It is also important to note that there is also positive live SARS-CoV-2 detection in stool samples of patients without diarrhea[17]. A study showed among children tested for SARS-CoV-2 by stool PCR or rectal swab, 89% had positive results even though 82.6% of them had no gastrointestinal symptoms[19]. This finding is consistent with a Hong Kong cohort where 15.3% of COVID-19 patients have SARS-CoV-2 RNA detected in their stool specimen on presentation regardless of whether or not they have gastrointestinal symptoms, and when compared to those without diarrhea, those with diarrhea have higher stool RNA positivity and viral load[22]. This suggests, with or without gastrointestinal symptoms, SARS-CoV-2 could be present in stool samples.

Even if viral nucleotides cannot be detected in oral swabs, they can be found in anal swabs or blood[18]. Furthermore, there is a rising number of studies that have detected SARS-CoV-2 RNA in stool samples. Worryingly, the constant positive detection of SARS-CoV-2 RNA from feces, indicates virions are secreted from the virus-infected gastrointestinal cells. For instance, in a China study consisting of 73 COVID-19 patients, 39 (53.42%) patients were found to have SARS-CoV-2 RNA in stool, whereas 17 (23.29%) patients remained positive for SARS-CoV-2 RNA in stool with a duration of positive stool ranging from 1–12 days despite negative results in respiratory samples[14]. A study from China also showed an asymptomatic 10 year old child who had persistently positive stool samples for 26 days even

though respiratory specimens were persistently negative[39]. Taken together, these indicate that the conventional testing using RT-PCR of nasopharyngeal swabs alone may not be an accurate diagnostic test to detect the presence or clearance of SARS-CoV-2 RNA.

Importantly, a study based on patients from Wuhan also found that there could be a possible shift from oral positive during early infection to anal swab positive during late infection[18]. SARS-CoV-2 can be detected in the intestine of COVID-19 infected patients at early or late stages, whereas SARS-CoV and MERS-CoV infected individuals, intestinal infections were detected at later stages[18, 40-42]. This may be related to the cycle threshold (CT) value. A lower CT value corresponds to a higher viral load and CT value <40 indicates positive SARS-CoV-2 RNA. Wang *et al* showed there is a similar mean cycle threshold between feces (31.4), sputum (31.1) and pharyngeal (32.1) swabs of SARS-CoV-2 RNA, while nasal swab had the lowest mean cycle threshold of 24.3[17]. In the US's first COVID-19 case, despite initial mild symptoms at presentation, the nasopharyngeal and oropharyngeal specimens obtained on illness day 4 showed CT values of 18-20 and 21-22 respectively. On illness day 7, the CT value of nasopharyngeal specimens increased to 23-24 while stool specimens showed greater CT value of 36–38. But, on illness day 11 and 12, there is a trend of decreasing viral levels observed for nasopharyngeal and oropharyngeal specimens[16]. Furthermore, a study found that in 70.3% of patients, prolonged shedding of SARS-CoV-2 RNA was detected in stool rather than respiratory samples, which could be up to ≥33 days from illness onset[22]. Similarly, in a SARS patient, even postmortem examination (a few days after death of patients) of biopsy specimens of the small intestine yielded viable SARS-CoV when all other organ tissues collected during autopsy had no viable virus recovered. In addition, non-viable SARS-CoV can be detected in stool specimens by PCR for up to 73 days from symptom onset[36]. Thus, it seems like that the shift from oral positive to anal positive can be seen via the trend in CT value throughout the course of illness and the prolonged shedding of SARS-CoV-2.

4. Implications of COVID-19 on the Liver

COVID-19 infection may have an effect on liver enzymes and other indices of hepatic function. One study hypothesized that liver tissue injury is caused by the upregulation of ACE-2 expression in liver tissue as a result of compensatory proliferation of hepatocytes derived from bile duct epithelial cells[43]. Various studies have reported various rates of prevalence of liver injury in COVID-19, ranging between 15% and 78%[44]. In a single-center study consisting of 148 COVID-19 positive patients, 55 (37.2%) patients had abnormal liver function upon hospital admission and this cohort were hospitalized longer[45]. Besides that, in the first reported case in the US, the patient had raised levels of creatine kinase and changes

in hepatic function measures whereby on day 5 of hospitalization, levels of alkaline phosphatase (ALP)(68 U per liter), alanine aminotransferase (ALT)(105 U per liter), aspartate aminotransferase (AST)(77 U per liter), and lactate dehydrogenase (LDH)(465 U per liter) were all raised[16]. Another meta-analysis also showed a mild increase in ALP, ALT and AST in 4.6%, 20.6%, and 22.8% COVID-19 patients and a mild reduction in serum bilirubin (39.8%)[44].

The implications of COVID-19 on the liver seems to follow a pattern as seen in MERS, as the concentrations of ALT, AST and LDH were elevated in five (11%), seven (15%) and 23 (49%) MERS patients, respectively[37]. Nonetheless, findings linking liver injury with COVID-19 is still debatable. It is unsure why there are dissimilarities among different studies. For instance, Pan et al and Wu et al found COVID-19 patients had no significant liver injury[23, 46], however 2 other studies stated otherwise[47, 48]. There is also study on the pathological analysis of liver tissue from a deceased COVID-19 patient that showed no viral inclusion in the liver[49, 50]. Hence, more studies must be conducted to fully understand the association of COVID-19 and hepatic function abnormalities.

5. Possible Reasons for Gastrointestinal Symptoms Following COVID-19

There are several reasons gastrointestinal symptoms manifest quite frequently following COVID-19 infection, and they seem to be associated with the human host receptor ACE-2[23], the intestinal microflora[23], the use of antibiotics and antiviral medicines[51, 52], and the direct or indirect inflammatory response as SARS-CoV-2 damages the digestive system[53] (**Figure 1**).

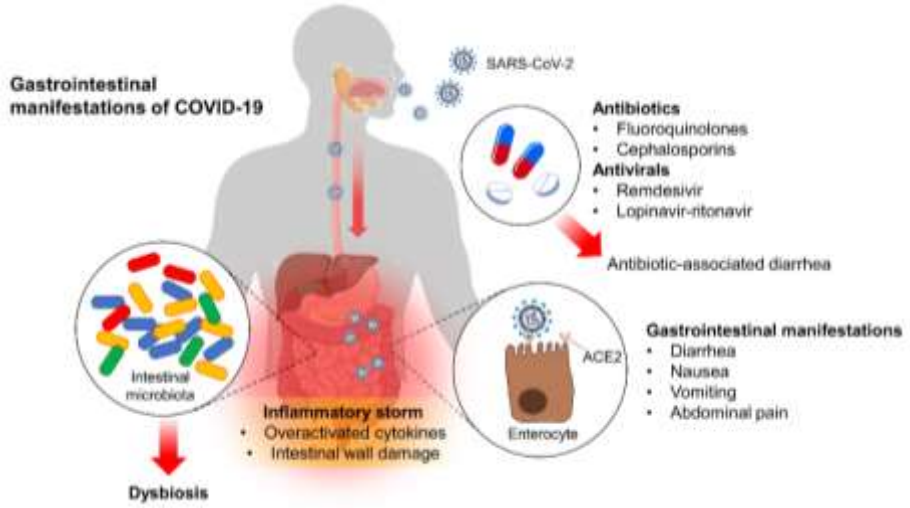

Figure 1. The possible explanation for gastrointestinal manifestations following SARS-CoV-2 infection.

Firstly, SARS-CoV-2 entry into host cells is mediated by the binding of viral surface spike protein to the host receptor ACE-2[54, 55]. ACE-2 is expressed in Type II alveolar cells

in the lungs and goblet cells in the nasal mucosa[54, 56]. However, ACE-2 is also abundantly present in the glandular cells of gastric, duodenal, and rectal epithelium. There is marked variation throughout the GI tract as ACE-2 staining is seldom found in esophageal mucosa, probably because ACE-2 is less expressed in squamous epithelial cells (esophageal epithelium) than glandular epithelial cells[14]. Another study showed ACE-2 is expressed primarily on the luminal surface of differentiated small intestinal epithelial cells, while crypt cells and the colon have lower expressions[57]. Given that the infectivity of SARS-CoV-2 is determined by the binding affinity of ACE-2 receptors[22], the high levels of these receptors indicate that the virus could possibly infect and replicate within the gastrointestinal tract[10]. Furthermore, intestinal inflammation is modulated by ACE-2[57], so it may be possible that the disruption of ACE-2 function by the SARS-CoV-2 results in diarrhea[22]. ACE-2 also has a RAS independent function, it regulates the intestinal amino acid homeostasis, is involved in the expression of antimicrobial peptides and is associated with the gut microbial ecology[57]. Amino acid malnutrition can result in intestinal inflammation and diarrhea; ACE-2 mutants demonstrated reduced expression of antimicrobial peptides and an altered gut microbial composition. This leads to the speculation of an association between COVID-19 and the gut microbiota[57, 58].

Secondly, the intestinal microbiota. The human intestine houses a diverse and huge amount of gut microbiota. For instance, comparing sites in the gastrointestinal system, the colon has the most microbes, consisting of 33% of total bacteria cells in the human body[59]. The gut microbiota plays vital roles including supporting the host's metabolism, defending the host against harmful pathogens through habitat colonization and immunoregulatory responses, and regulating the development and maturation of the body's immune system[23, 59-64]. Reasons for changes in gut flora include the disease itself, concomitant infections, the use of antimicrobials, and an increase in proinflammatory mediators as a result of viral-induced inflammation[52]. Alterations to the composition and function of the gastrointestinal tract microbiota may affect the respiratory tract through the common mucosal immune system, and respiratory tract flora disorders also influence the digestive tract via immune regulation. This is the gut-lung axis effect[23, 65, 66], which possibly explains why digestive symptoms occur following COVID-19 infection. Hence, probiotics may be a new treatment option or an adjuvant treatment. In the treatment of severe COVID-19 infections, probiotics is recommended by the guidance (version 5) established by the China's National Health Commission and National Administration of Traditional Chinese Medicine, to maintain the balance of intestinal microecology and the prevention of secondary bacterial infection, indicating that first-line medical staffs and the Chinese government trust the importance of the role of gut microbiota in COVID-19 infection[58, 67].

Thirdly, the use of antibiotics and antiviral drugs could result in gastrointestinal symptoms in some COVID-19 patients. Patients suspected with secondary bacterial infection are commonly treated with antibiotics in which some antibiotics (fluoroquinolones and cephalosporins) can cause antibiotic-associated diarrhea. Furthermore, antimicrobial use can have serious effects on the gut microbiota, antibody production, and immune system which could prolong the clearance of SARS-CoV-2 from the gut[52]. In patients being treated with antiviral drugs such as remdesivir, chloroquine phosphate, hydroxychloroquine, and lopinavir-ritonavir, the medications themselves can also cause diarrhea[51, 52].

Fourthly, SARS-CoV-2 can cause direct or indirect damage to the digestive system via the inflammatory response[9]. SARS-CoV-2 infection could cause an "inflammatory storm", in which overactivated cytokines, inflammatory storms, and immune dysregulation causes inflammatory damage to the intestine resulting in diarrhea[9, 68]. With mounting evidence showing the presence of SARS-CoV-2 RNA in stool specimens of COVID-19 patients, it might suggest SARS-CoV-2 directly damages the intestinal mucosa, causing digestive symptoms such as diarrhea.

6. Conclusions

Gastrointestinal manifestations seem to be part of the course of COVID-19 infection and presentation with symptoms including — but not limited to — diarrhea, nausea and/ or vomiting and abdominal pain, should definitely not be taken lightly. Some of the possible causes of gastrointestinal manifestations seems to be associated with direct viral invasion utilizing the ACE-2 receptor[23], alterations in the intestinal microflora[23], the use of antibiotics and antiviral medicines[51, 52], and the direct or indirect inflammatory response as SARS-CoV-2 damaging the digestive system[9]. As COVID-19 severity increases, the digestive symptoms are more distinct. Clinicians should be alert to patients presenting with gastrointestinal symptoms due to the important implications as this cohort of patients have much longer duration from symptom onset to admission resulting in late diagnosis and treatment, compared to patients without digestive symptoms. It is possible that the increased viral load and replication in the gastrointestinal tract (GIT) results in more severe disease and the delay in reporting by patients with extrapulmonary symptoms but without the typical respiratory symptoms led to a later and less curable stage[23]. This is consistent with a meta-analysis that showed a higher prevalence of gastrointestinal symptoms in those with severe COVID-19 than non-severe COVID-19 (17.1% vs 11.8%)[22]. Importantly, with the detection of SARS-CoV-2 in specimens from other sites other than the nasopharyngeal site, it is likely that SARS-CoV-2 can be transmitted in ways other than respiratory droplets. It is also likely that the virus can infect and replicate in other sites, in this case, the gastrointestinal tract of the human host. This suggests possible tissue tropism of SARS-CoV-2 in the intestinal cells and a possible fecal-oral transmission.

With these findings, there will be implications on the disease transmission, viral detection, infection control and management. Hence, changes must be made to efficiently combat the worsening of SARS-CoV-2. Clinicians and health care workers should be more cautious if patients present with initial gastrointestinal symptoms and take precautionary measures including droplet and fomite precautions, proper handling of COVID-19 patients' excreta, and have barrier precautions when performing colonoscopy[36]. Furthermore, testing of stool specimens for SARS-CoV-2 RNA should be made in addition to respiratory specimens. Efforts should also be made to alert all people on the gastrointestinal manifestations of COVID-19 so there can be early detection, diagnosis, isolation, and intervention, and reduce SARS-CoV-2 transmission within the family and in the community.

Author Contributions: AY-KT performed the literature search, critical data analysis as well as manuscript writing. PP, LT-HT, JW-FL, VL, and L-HL provided review, editing, and proofreading for the manuscript. VL and L-HL conceptualize the project.

Funding: The SEED Funding funded this work from Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, (Vote Number: MBRS/JCSMHS/02/2020) awarded to VL.

Acknowledgments: Professor Dr. Shajahan Yasin, Professor, and Head of School, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia.

Conflicts of Interest: The authors declare no conflict of interest.

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