**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 63595

**Manuscript Type:** MINIREVIEWS

**Pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19**

Jin B *et al*. GI symptoms of COVID-19

Byungchang Jin, Rajan Singh, Se Eun Ha, Hannah Zogg, Paul J Park, Seungil Ro

**Byungchang Jin, Rajan Singh, Se Eun Ha, Hannah Zogg, Seungil Ro,** Department of Physiology and Cell Biology, University of Nevada School of Medicine, Reno, NV 89557, United States

**Paul J Park,** Department of Medicine, Renown Health, Reno, NV 89557, United States

**Author contributions:** Jin B, Singh R and Ro S conceived the study; Jin B and Singh R drafted the original manuscript and are joint first authors; Jin B, Singh R, Ha SE, Zogg H and Ro S revised the manuscript and approved the submitted version.

**Corresponding author: Seungil Ro, PhD, Associate Professor,** Department of Physiology and Cell Biology, University of Nevada School of Medicine, Building L-207E, 1664 North Virginia Street, Reno, NV 89557, United States. sro@med.unr.edu

**Received:** January 29, 2021

**Revised:** March 17, 2021

**Accepted:** April 22, 2021

**Published online:**

**Abstract**

Gastrointestinal (GI) symptoms, such as diarrhea, abdominal pain, vomiting, and anorexia, are frequently observed in patients with coronavirus disease 2019 (COVID-19). However, the pathophysiological mechanisms connecting these GI symptoms to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infections remain elusive. Previous studies indicate that the entry of SARS-CoV-2 into intestinal cells leads to downregulation of angiotensin converting enzyme 2 (ACE2) receptors resulting in impaired barrier function. While intestinal ACE2 functions as a chaperone for the amino acid transporter B0AT1, the B0AT1/ACE2 complex within the intestinal epithelium acts as a regulator of gut microbiota composition and function. Alternations to the B0AT1/ACE2 complex lead to microbial dysbiosis through increased local and systemic immune responses. Previous studies have also suggested that altered serotonin metabolism may be the underlying cause of GI disorders involving diarrhea. The findings of elevated plasma serotonin levels and high fecal calprotectin in COVID-19 patients with diarrhea indicate that the viral infection evokes a systemic inflammatory response that specifically involves the GI. Interestingly, the elevated proinflammatory cytokines correlate with elevated serotonin and fecal calprotectin levels further supporting the evidence of GI inflammation, a hallmark of functional GI disorders. Moreover, the finding that rectal swabs of COVID-19 patients remain positive for SARS-CoV-2 even after the nasopharynx clears the virus, suggests that viral replication and shedding from the GI tract may be more robust than that of the respiratory tract, further indicating fecal-oral transmission as another important route of viral spread. This review summarized the evidence for pathophysiological mechanisms (impaired barrier function, gut inflammation, altered serotonin metabolism and gut microbiota dysbiosis) underlying the GI symptoms in patients with COVID-19.

**Key Words:** COVID-19; Gastrointestinal symptoms; Gut microbiota dysbiosis; Impaired barrier function; Serotonin; Angiotensin converting enzyme 2 receptor

Jin B, Singh R, Ha SE, Zogg H, Park PJ, Ro S. Pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19. *World J Gastroenterol* 2021; In press

**Core Tip:** Since the declaration of the pandemic on March 11, 2020 by the World Health Organization, severe acute respiratory syndrome coronavirus 2 infection has quickly become a global health threat. In addition to respiratory symptoms, gastrointestinal (GI) symptoms have been widely observed in coronavirus disease 2019 (COVID-19) patients. Here, we have summarized the GI symptoms seen in COVID-19 patients that have been reported in nineteen studies and recapitulated potential mechanisms that are responsible for the GI symptoms in COVID-19 patients. This biochemical understanding may assist in new therapeutic approaches.

**INTRODUCTION**

Since December 2019, an acute respiratory infection, referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused by the novel coronavirus has rapidly spread worldwide[1-3]. In the United States alone, 198589 deaths (60.3/100000) have been reported due to the coronavirus pandemic from February 13, 2020 to September 19, 2020[4].

Based on next-generation sequencing data from patient samples, SARS-CoV-2 is closely associated with two bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 (88% identity)[5]. The binding of the SARS-CoV-2 spike proteins to the host receptor, angiotensin-converting enzyme 2 (ACE2), is critical for viral invasion[6]. This viral infection may be asymptomatic or cause symptoms, such as fever, cough, headache, and myalgia[7-9]. Interestingly, up to 40% of coronavirus disease 2019 (COVID-19) patients experience gastrointestinal (GI) symptoms, including diarrhea, anorexia, nausea, vomiting, and abdominal pain (Table 1). In order to provide appropriate medical care to COVID-19 patients, it is necessary to explore pathophysiological mechanisms underlying their GI symptoms.

In this review, we summarized the studies that describe the various GI symptoms in COVID-19 patients and highlighted the likely underlying pathophysiological mechanisms. These insights offer potential new therapeutic approaches for containment of the global inflammatory response. Furthermore, we also shed light on the importance of the altered gut microbiota profile in the possible pathogenesis of COVID-19.

**CLINICAL PRESENTATION OF COVID-19 PATIENTS WITH GI SYMPTOMS**

The clinical severity of COVID-19 patients may be stratified into three grades: Placid, ordinary, and grave cases. The incubation period of SARS-CoV-2 ranges from 1-14 d, but is more commonly 3-7 d. The typical clinical presentation of SARS-CoV-2 consists of fever, fatigue, dry cough, and shortness of breath. Other common symptoms involve congestion and rhinorrhea, pharyngalgia, myalgias, and diarrhea. In grave cases, the infection culminates in acute respiratory distress syndrome, which is associated with a high degree of mortality. Although the majority of symptomatic SARS-CoV-2 cases present with pulmonary symptoms, extra-pulmonary symptoms are also common, and several case studies have described the presence of digestive symptoms in the SARS-CoV-2 infection.

We identified and analyzed the GI symptoms of COVID-19 patients reported in nineteen published papers, which included diarrhea, nausea, abdominal pain, vomiting, anorexia, and bleeding (Table 1). Out of the nineteen papers, thirteen were from China, four were from the United States, one was from Singapore, and one was from Europe. Among GI symptoms, diarrhea was the most prevalent, accounting for 2% to 33.7% of all patients. The median duration period of diarrhea in COVID-19 patients was 4 d with a range of 1 d to 9 d[10]. Other frequently reported GI symptoms were anorexia (341/2914, 11.7%), nausea (253/2914, 8.7%), vomiting (131/2914, 4.5%), abdominal pain (90/2914, 3.1%) and bleeding (5/2914, 0.2%). GI symptoms were more frequently reported during hospitalization than at the time of admission[11]. We have also recently reported a strong correlation between diarrhea and the severity of the disease[12]. These data suggest that GI symptoms should be included in the assessment of the disease severity in COVID-19.

Previously, it was shown that RNA from SARS-CoV-2 was found in fecal samples (four out of eight patients) regardless of the presence of diarrhea[13]. Furthermore, another study demonstrated that SARS-CoV-2 RNA was found in the feces of 22/42 (52.4%) COVID-19 patients with GI symptoms. Among 23 COVID-19 patients without GI symptoms, SARS-CoV-2 RNA was found in the feces of 9 (39.1%) patients[11]. Although the clinical relevance of SARS-CoV-2 RNA in fecal material remains unclear, understanding the biochemical mechanisms behind the SARS-CoV-2 mediated induction of GI symptoms is important to gain further understanding of the pathophysiology of COVID-19. Therefore, we described potential mechanisms, by which GI symptoms might occur in COVID-19 patients and proposed new therapeutic strategies to modulate the global inflammatory response.

**PATHOPHYSIOLOGICAL MECHANISMS FOR GI SYMTOMS IN COVID-19**

***Intestinal ACE2 receptor mediated impaired barrier function***

ACE2 has emerged as a critical regulator of the renin angiotensin system (RAS) by metabolizing angiotensin (Ang) II into the beneficial peptide Ang 1-7[14]. ACE2 has also been identified as the key receptor for SARS-CoV and SARS-CoV-2[15]. Spike protein treatment led to increased Ang II and pulmonary edema, which was mediated by AT1R[16]. Given the similarities between the SARS-CoV and SARS-CoV-2 spike proteins, a similar mechanism of spike-mediated ACE2 down-regulation most likely underlies tissue damage in COVID-19 by skewing the RAS[16].

The pathophysiology of GI symptoms in COVID-19 remains poorly understood. However, evidence points to a role of ACE2 cell-surface receptors and SARS-CoV-2 mediated induced inflammatory processes in the GI tract[17]. A vital structural protein of SARS-CoV-2 is the spike glycoprotein (S). It consists of two functional units, S1 and S2, that bind to the host cell ACE2 receptor by membrane fusion, replicates through replication-transcription complexes, and promotes proliferation by interfering with and suppressing the host’s immune response[18]. SARS-CoV-2 is highly concentrated in air droplets exhaled by infected subjects and inhalation of these particles by a noninfected individual may lead to infection of the recipient’s respiratory tract *via* ACE2 receptors. The respiratory tract is one of the primary sites of viral entry. Interestingly, ACE2 receptors are also highly expressed in the digestive tract making it another potential route of SARS-CoV-2 infection[19]. In the gut, ACE2 has a completely different function independent of RAS. ACE2 stabilizes neutral amino acid transporters, such as B0AT1 and loss of ACE2 compromises intestinal uptake of certain dietary amino acids, such as tryptophan[20]. Because tryptophan plays an important role in immunity, ACE2 knockout mice exhibited altered gut microbiota and developed more severe dextran sulfate sodium–induced colitis compared with wild-type control mice[21]. These studies implicated ACE2 in SARS-CoV-2 infections in the gut.

ACE2 plays a major role in amino acid transport in the intestinal epithelium, a mechanism linked to the production of antimicrobial peptides, which suggests its role in intestinal barrier maintenance and gut microbiota equilibrium[22]. ACE2 controls expression of B0AT1 in the intestine, which is the primary apical membrane transporter in the intestine that permits Na+ coupled uptake of neutral amino acids, such as tryptophan[23]. Notably, B0AT1 substrates, such as tryptophan and glutamine, signal to downregulate lymphoid pro-inflammatory cytokines, maintain the integrity of intestinal tight junctions, activate the release of antimicrobial peptides, and modulate mucosal cell autophagy as defense mechanisms[23]. Altered B0AT1 expression mediated through ACE2 in COVID-19 may be a major contributor to the leaky gut. Thus, it is possible that SARS-CoV-2 mediated disruption of the gut barrier could lead to a systemic elevation of bacterial lipopolysaccharide and peptidoglycan, further worsening GI inflammation. For instance, one study showed that the spike protein of SARS-CoV-2 (S1) interacted with the ACE2 complex and the tryptophan amino acid transporter B0AT1[24]. Furthermore, downregulated intestinal ACE2-B0AT1 cell surface expression led to a series of downstream sequelae to promote a leaky gut as well as gut microbiota dysbiosis[23,24]. Therefore, ACE2 mediated impaired barrier function in combination with microbial dysbiosis may contribute to the cytokine storm seen in patients severely ill with COVID-19 and may also be responsible for their GI symptoms.

***Gut inflammation in COVID-19 patients with diarrhea***

Fecal calprotectin (FC) has evolved as a reliable fecal biomarker allowing detection of intestinal inflammation in inflammatory bowel disease (IBD) and infectious colitis[25]. Previous studies have shown that COVID-19 patients with diarrhea without IBD had high FC compared to patients without diarrhea, indicating that the infection evokes a significant intestinal inflammatory process[25]. Furthermore, FC levels correlated significantly with the pro-inflammatory interleukin - 6 (IL-6) serum concentrations, and a murine study showed that deficiency of ACE2 results in highly increased susceptibility to intestinal inflammation induced by epithelial damage[21]. Collectively, the aforementioned studies highlighted that GI inflammation was overrepresented in patients with COVID-19 that also had functional GI disorders (FGIDs) or post-infection (PI) GI disorders.

***Alterations in serotonin metabolism in COVID-19 patients***

We have reported that plasma serotonin (5-hydroxytrytamine, 5-HT) levels were elevated in COVID-19 patients with diarrhea[12]. 5-HT is a hormone and neurotransmitter that has a monoamine structure. 5-HT synthesis begins with the amino acid L-tryptophan, which is converted to 5-hydroxytryptophan (5-HTP) *via* the rate-limiting enzyme tryptophan hydroxylase (TPH). 5-HTP is then rapidly decarboxylated by aromatic L-amino acid decarboxylase to produce 5-HT[26,27]. 5-HT either circulates in our body or is absorbed by the cells that express serotonin reuptake transporter to act or decompose, resulting in 5-hydroxyindoleacetic acid (5-HIAA)[28]. TPH is an enzyme specifically found in 5-HT producing cells, and there are two different isoforms, TPH1 and TPH2[29,30]. TPH1 dependent 5-HT synthesis occurs in enterochromaffin (EC) cells in GI tract, while TPH2 is involved in 5-HT synthesis in the central nervous system and enteric nervous system[31,32].

Since 95% of total 5-HT is produced by EC cells in GI tract, 5-HT has been widely studied for GI functions, especially in GI motility. Many studies have demonstrated that 5-HT is important for colonic peristaltic reflexes and GI transit[33-35]. Moreover, altered 5-HT levels are closely associated with irritable bowel syndrome (IBS), and it has been shown that platelet-depleted plasma 5-HT levels are increased in IBS patients with diarrhea[36]. Therefore, approaches to target 5-HT signaling have been proposed as a way to alleviate GI dysmotility. A total of seven classes of 5-HT receptors have been identified, and it is well-known that 5-HT1, 5-HT2, 5-HT3, 5-HT4, and 5-HT7 are expressed in the GI tract to influence gut motor function[37]. 5-HT3 antagonists are especially effective in treating IBS with diarrhea[38,39] and 5-HT4 agonists are effective in treating IBS with constipation[40,41].

Previously, we have reported that plasma 5-HT levels are increased in COVID-19 patients and are directly correlated to the severity of COVID-19 symptoms. Moreover, COVID-19 patients with diarrhea had increased plasma 5-HT and a lower ratio of plasma 5-HIAA/5-HT levels compared to healthy subjects or COVID-19 patients without diarrhea[12].These data suggest that 5-HT is not being broken down into 5-HIAA, and 5-HT remains in some COVID-19 patients’ for a longer duration, resulting in GI symptoms such as diarrhea. Thus, regulating the amount of 5-HT might be a therapeutic modality for COVID-19 patients with diarrhea.

***Gut microbiota dysbiosis in COVID-19 patients***

From ancient times, viral infectious diseases have been plaguing mankind through a wide-range of clinical manifestations. Moreover, scientific annals depict the occurrence of life-threatening viral diseases that are enumerated as epidemics and pandemics[42]. Examples include: The flu, polio, Ebola, acquired immune deficiency syndrome and the very recent COVID-19. In the past several months, COVID-19 has reached pandemic status, exposing the world to eminent danger. Previously, two other similar viral infections including the Middle East respiratory syndrome virus and SARS-CoV have been reported[43]. SARS-CoV-2 is an enveloped virus in the *Coronaviridae* family. They harbor single stranded RNA as their genetic material that has positive polarity. Some studies published during the recent pandemic of COVID-19 have provided insight into parameters pertaining to the transmission, susceptibility, clinical presentation and laboratory findings of this potential pathogen[44,45]. Although respiratory droplets and contact are the prime route of transmission for SARS-CoV2, there have been some instances where prolonged exposure to aerosols with elated concentrations of the virus may facilitate transmission. Symptoms and severity of COVID-19 differ from patient to patient[46]. In general, humans of all ages are susceptible. However, individuals with an attenuated immune response including elderly, infants, children below 6 years old, patients with underlying diseases (transplants, cancers, diabetes, asthma, heart ailment, and other peril maladies) are at higher risk.

To inject their genetic material into the host, SARS-CoV-2 pierces the pulmonary epithelial cells of the lower respiratory tract thereby commandeering the host’s cellular machinery[47]. Moreover, this process is enhanced by the spike (S) protein that interacts with ACE2[47,48]. Thus, the importance of the gut and its microbiome cannot be underestimated. The knowledge in gut research has augmented with a plethora of scientific annals that point towards the role of gut microbes in many degenerative and infectious diseases[49]. Gut dysbiosis has been reported in patients with COVID-19 with enrichment of pathogens and depletion of beneficial commensals[17]. An inverse correlation between the abundance of *Faecalibacterium prausnitzii* (*F. prausnitzii*) and disease severity has been observed. *F. prausnitzii* has anti-inflammatory properties, and its depletion has been related to IBS[17]. Another study showed the gut microbiome composition was significantly altered in patients with COVID-19 compared with non-COVID-19 individuals irrespective of whether patients had received medication[50]. Several gut commensals with known immunomodulatory potential such as *F. prausnitzii*, *Eubacterium rectale* and Bifidobacteria were underrepresented in patients and remained hampered in samples collected up to 30 d after disease resolution[17,51]. Moreover, this perturbed composition exhibited stratification with disease severity concordant with elevated concentrations of inflammatory cytokines and blood markers such as C-reactive protein, lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase[17]. The depletion of several bacterial species in the COVID-19 cohort was linked to increased concentrations of tumor necrosis factor-alpha, C-X-C motif chemokine ligand 10, C-C motif chemokine ligand 2 and IL-10. These studies highlighted the need to understand how gut microorganisms are involved in inflammation and COVID-19 pathogenesis[50].

Another study found a signature of active gut viral infection in a subset of patients with COVID-19 even in the absence of GI symptoms, suggesting a ‘quiescent’ GI infection of SARS-CoV-2[52]. The transcriptional activity of viral infection and replication persisted in the gut even after respiratory clearance of SARS-CoV-2. Fecal samples with a signature of high SARS-CoV-2 infectivity harbored a higher abundance of opportunistic pathogens, for instance, *Morganella morganii,* *Collinsella aerofaciens*, *Streptococcus infantis*, and *Collinsella tanakaei* and an enhanced capacity for the biosynthesis of nucleotides and amino acids, along with carbohydrate metabolism, whereas fecal samples with a signature of no SARS-CoV-2 infection had a higher abundance of short-chain fatty acid producing bacteria, for instance, *Bacteroides stercoris*, *Parabacteroides merdae*, *Lachnospiraceae bacterium,* and *Alistipes onderdonkii*[52]. This study provided evidence for active and prolonged ’quiescent’ GI infection even in the absence of GI manifestations and after recovery from respiratory infection of SARS-CoV-2. The gut microbiota of patients with active SARS-CoV-2 GI infection was characterized by enrichment of opportunistic pathogens; loss of salutary bacteria and increased functional capacity for nucleotides, along with increased amino acid biosynthesis and carbohydrate metabolism[52].

In addition, bacterial groups belonging to the genus Bacteroides, known to downregulate the ACE2 expression in the murine colon, inversely correlated with fecal SARS-CoV-2 nucleic acid loads. Similarly, SARS-CoV-2 infection of GI epithelial cells has been associated with: (1) Lamina propria infiltration of plasma cells and lymphocytes, and edema in the stomach, duodenum, and rectum; (2) Increased levels of FC; (3) Higher fecal levels of IL-8 and lower levels of the anti-inflammatory IL-10 when compared with uninfected controls[53]; (4) SARS-CoV-2-specific IgA and limited inflammatory cytokines were also present in the stool of select patients with acute COVID-19; and (5) Gut microbiota dysbiosis. Interestingly, gut microbiota dysbiosis persisted after the resolution of SARS-CoV-2 infection, suggesting that microbiota perturbation may contribute to the persistence of gut dysfunction and symptoms even after the infection has subsided. Indeed, the persistent microbial dysbiosis may contribute to maintaining a chronic state of low-grade GI inflammation, increased intestinal permeability, increased sensory perception, and bile acid malabsorption, which have all been previously associated with symptoms of GI motility disorders.

***Post-COVID-19*** ***functional GI disorders***

Evidence supports the development of FGIDs after a bout of viral, bacterial, or protozoal gastroenteritis or after resolution of an acute flareup of GI inflammatory diseases such as IBD[54]. Individual susceptibility to these so-called PI-FGIDs involves genetic predisposition and the presence of pre-existing psychological disturbances such as anxiety and/or depression[55,56]. PI-FGIDs have also been associated with dysregulation of gut motility, visceral hypersensitivity, microbial dysbiosis, intestinal barrier dysfunction, bile acid malabsorption, and alterations in serotonin metabolism[54,57]. Current data suggest that the resolution of the SARS-CoV-2 infection may lead to persistent GI dysfunction resembling certain aspects of PI-FGIDs[17]. Transient non-specific gut inflammation is the common trigger for long-lasting symptoms of FGIDs, regardless of the initiating event (*i.e.*, viral, parasitic, bacterial, after resolution of IBD flares)[58].

***SARS-CoV-2 in stool: Suggesting fecal-oral transmission***

Evidence of fecal shedding of viral RNA further supports viral replication in the digestive tract and potentially a fecal-oral route of transmission. Studies showed that more than one-half of COVID-19 patients tested positive for fecal SARS-CoV-2 RNA[59]. One study in a group of pediatric patients infected with SARS-CoV-2 had positive rectal swabs for SARS-CoV-2, even after the nasopharynx was cleared of the virus, suggesting that viral shedding from the digestive tract might be more prolonged than that from the respiratory tract[60]. Another study showed that SARS-CoV-2 can infect the enterocytes of bats in an organoid culture system of bat intestinal epithelium[61]. One study indicated that infection by SARS-CoV-2 led to an altered fecal microbiome during hospitalization[62]. The authors showed depletion of opportunistic pathogens and depletion of commensals during SARS-CoV-2 infection. *Coprobacillus*, *Clostridium ramosum*, and *Clostridum mathewayi* were found more commonly in patients with severe COVID-19. In contrast, the presence of *F. prausnitzii* was correlated with milder disease. Gut microbial dysbiosis persisted in the majority of COVID-19 patients in spite of clearance of the virus, suggesting that exposure to SARS-CoV-2 might be associated with more long-lasting deleterious effects to the healthy gut microbiome[23,62]. These studies support the possibility for SARS-CoV-2 fecal-oral route of transmission. Therefore, from both clinical and public health standpoints, it is critical to fully understand all routes of transmission of SARS-CoV-2. If high levels of infectious viruses are present in the intestinal lumen of infected patients, especially in asymptomatic patients, this poses risks during endoscopy and colonoscopy to gastroenterologists, endoscopy personnel and other patients. For the general public, infectious viral particles in the feces shed by infected individuals, if aerosolized, have great implications in confined environments such as cruise ships, hospitals, individual households, and densely populated housing, such as those in regions with poor sanitation[19].

**CONCLUSION**

GI symptoms are overrepresented in patients with COVID-19. A proportion of patients affected by COVID-19 may develop PI-FGIDs based on the following pathophysiological mechanisms: Intestinal barrier dysfunction, chronic low-grade intestinal inflammation, altered serotonin metabolism, and gut microbiota dysbiosis. The question of whether gut inflammation is associated with gut microbiota dysbiosis in patients, which may have a central role in the COVID-19 disease progression warrants further investigation. However, there is mounting evidence that gut microorganisms are linked to GI inflammatory diseases, which highlights the urgent need to understand the specific roles of gut microorganisms that are responsible for the immune dysfunction and systemic inflammation in COVID-19.

The abundance of SARS-CoV-2 viral RNA in stool and the stability of the virus in the environment suggest that fecal contamination may be an important modality for the spread among human hosts. Fecal sources may lead to viral transmission, especially when aerosols are generated. The significance of GI involvement in COVID-19 patients requires attention in clinical practices, such as incorporation of rectal swab testing before discharging patients, as well as the importance of personal protective equipment in the endoscopy setting. These precautions will be imperative in our battle against COVID-19[63].

Considering the critical role of the ACE2 receptor in the pathogenesis of COVID-19 and the potential impact on severity of symptoms in some patients, several therapeutic approaches have been evaluated such as a soluble form of ACE2 (rhACE2), ACE2 blockers, TMPRSS2 inhibitors, and Ang 1-7 receptor agonists. Some of these therapeutic approaches appeared to show promising results and are currently in clinical trials. Another strategy to manage COVID-19 might be to restore the microbiota during the dysbiosis through prebiotic and/or probiotic interventions and dietary nutritional supplementation[64].

This review sheds light on the studies that formulate the pathophysiological mechanisms (impaired barrier function, gut inflammation, altered serotonin metabolism and gut microbiota dysbiosis) underlying GI symptoms in patients with COVID-19 (Figure 1). To the best of our knowledge we are the first to propose altered serotonin metabolism in the pathogenesis of COVID-19 associated with diarrhea. This novel insight of serotonin metabolism might be a key player underpinning GI symptoms and severity in patients with COVID-19 as altered serotonin signaling modulates the majority of pathological mechanisms in patients with FGIDs. Therapeutic modalities regulating serotonin signaling might offer potential treatment options in a subset of COVID-19 patients. Furthermore, we highlighted the important concept of post-SARS-CoV-2-FGIDs, which warrant future studies to dissect persistent GI symptoms after the clearance of SARS-CoV-2 infection. Scientists and clinicians should be aware of this new clinical scenario, and studies will be needed to further characterize and uncover the pathophysiological mechanisms of this phenomenon. Furthermore, studies are warranted to elucidate the following: 1) the cause-and-effect relationship between changes in relative abundance of gut bacteria and COVID-19, 2) the possibility that the microbiota plays a role in illness severity, 3) the relationship between the host’s immune response (T-regulatory response) to SARS-CoV-2 resulting in a high or low cytokine storm.

**REFERENCES**

1 **Hui DS**, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, Drosten C, Zumla A, Petersen E. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020; **91**: 264-266 [PMID: 31953166 DOI: 10.1016/j.ijid.2020.01.009]

2 **Lu H**, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020; **92**: 401-402 [PMID: 31950516 DOI: 10.1002/jmv.25678]

3 **Bogoch II**, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Potential for global spread of a novel coronavirus from China. *J Travel Med* 2020; **27**: taaa011 [PMID: 31985790 DOI: 10.1093/jtm/taaa011]

4 **Bilinski A**, Emanuel EJ. COVID-19 and Excess All-Cause Mortality in the US and 18 Comparison Countries. *JAMA* 2020; **324**: 2100-2102 [PMID: 33044514 DOI: 10.1001/jama.2020.20717]

5 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]

6 **Wan Y**, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol* 2020; **94*: e00127-20*** [PMID: 31996437 DOI: 10.1128/JVI.00127-20]

7 **Dhama K**, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, Chaicumpa W, Bonilla-Aldana DK, Rodriguez-Morales AJ. Coronavirus Disease 2019-COVID-19. *Clin Microbiol Rev* 2020; **33**: e00028-20 [PMID: 32580969 DOI: 10.1128/CMR.00028-20]

8 **Vabret N**, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, Levantovsky R, Malle L, Moreira A, Park MD, Pia L, Risson E, Saffern M, Salomé B, Esai Selvan M, Spindler MP, Tan J, van der Heide V, Gregory JK, Alexandropoulos K, Bhardwaj N, Brown BD, Greenbaum B, Gümüş ZH, Homann D, Horowitz A, Kamphorst AO, Curotto de Lafaille MA, Mehandru S, Merad M, Samstein RM; Sinai Immunology Review Project. Immunology of COVID-19: Current State of the Science. *Immunity* 2020; **52**: 910-941 [PMID: 32505227 DOI: 10.1016/j.immuni.2020.05.002]

9 **Machhi J**, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, Blomberg WR, Meigs DD, Hasan M, Patel M, Kline P, Chang RC, Chang L, Gendelman HE, Kevadiya BD. The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections. *J Neuroimmune Pharmacol* 2020; **15**: 359-386 [PMID: 32696264 DOI: 10.1007/s11481-020-09944-5]

10 **Jin X**, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, Hao SR, Jia HY, Cai H, Zhang XL, Yu GD, Xu KJ, Wang XY, Gu JQ, Zhang SY, Ye CY, Jin CL, Lu YF, Yu X, Yu XP, Huang JR, Xu KL, Ni Q, Yu CB, Zhu B, Li YT, Liu J, Zhao H, Zhang X, Yu L, Guo YZ, Su JW, Tao JJ, Lang GJ, Wu XX, Wu WR, Qv TT, Xiang DR, Yi P, Shi D, Chen Y, Ren Y, Qiu YQ, Li LJ, Sheng J, Yang Y. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020; **69**: 1002-1009 [PMID: 32213556 DOI: 10.1136/gutjnl-2020-320926]

11 **Lin L**, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020; **69**: 997-1001 [PMID: 32241899 DOI: 10.1136/gutjnl-2020-321013]

12 **Ha S**, Jin B, Clemmensen B, Park P, Mahboob S, Gladwill V, Lovely FM, Gottfried-Blackmore A, Habtezion A, Verma S, Ro S. Serotonin is elevated in COVID-19-associated diarrhoea. *Gut* 2021 epub ahead of print [PMID: 33402416 DOI: 10.1136/gutjnl-2020-323542]

13 **Young BE**, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA* 2020; **323**: 1488-1494 [PMID: 32125362 DOI: 10.1001/jama.2020.3204]

14 **Gheblawi M**, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res* 2020; **126**: 1456-1474 [PMID: 32264791 DOI: 10.1161/CIRCRESAHA.120.317015]

15 **Zhang H**, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med* 2020; **46**: 586-590 [PMID: 32125455 DOI: 10.1007/s00134-020-05985-9]

16 **Ni W**, Yang X, Yang D, Bao J, Li R, Xiao Y, Hou C, Wang H, Liu J, Yang D, Xu Y, Cao Z, Gao Z. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care* 2020; **24**: 422 [PMID: 32660650 DOI: 10.1186/s13054-020-03120-0]

17 **Schmulson M**, Ghoshal UC, Barbara G. Managing the Inevitable Surge of Post-COVID-19 Functional Gastrointestinal Disorders. *Am J Gastroenterol* 2021; **116**: 4-7 [PMID: 33273261 DOI: 10.14309/ajg.0000000000001062]

18 **Xu X**, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020; **63**: 457-460 [PMID: 32009228 DOI: 10.1007/s11427-020-1637-5]

19 **Ding S**, Liang TJ. Is SARS-CoV-2 Also an Enteric Pathogen With Potential Fecal-Oral Transmission? A COVID-19 Virological and Clinical Review. *Gastroenterology* 2020; **159**: 53-61 [PMID: 32353371 DOI: 10.1053/j.gastro.2020.04.052]

20 **Camargo SMR**, Vuille-Dit-Bille RN, Meier CF, Verrey F. ACE2 and gut amino acid transport. *Clin Sci (Lond)* 2020; **134**: 2823-2833 [PMID: 33140827 DOI: 10.1042/CS20200477]

21 **Hashimoto T**, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 Links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487**: 477-481 [PMID: 22837003 DOI: 10.1038/nature11228]

22 **Perlot T**, Penninger JM. ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes Infect* 2013; **15**: 866-873 [PMID: 23962453 DOI: 10.1016/j.micinf.2013.08.003]

23 **Penninger JM**, Grant MB, Sung JJY. The Role of Angiotensin Converting Enzyme 2 in Modulating Gut Microbiota, Intestinal Inflammation, and Coronavirus Infection. *Gastroenterology* 2021; **160**: 39-46 [PMID: 33130103 DOI: 10.1053/j.gastro.2020.07.067]

24 **Yan R**, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 2020; **367**: 1444-1448 [PMID: 32132184 DOI: 10.1126/science.abb2762]

25 **Effenberger M**, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, Hilbe R, Seiwald S, Scholl-Buergi S, Fritsche G, Bellmann-Weiler R, Weiss G, Müller T, Adolph TE, Tilg H. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; **69**: 1543-1544 [PMID: 32312790 DOI: 10.1136/gutjnl-2020-321388]

26 **Boadle-Biber MC**. Regulation of serotonin synthesis. *Prog Biophys Mol Biol* 1993; **60**: 1-15 [PMID: 8480026 DOI: 10.1016/0079-6107(93)90009-9]

27 **Höglund E**, Øverli Ø, Winberg S. Tryptophan Metabolic Pathways and Brain Serotonergic Activity: A Comparative Review. *Front Endocrinol (Lausanne)* 2019; **10**: 158 [PMID: 31024440 DOI: 10.3389/fendo.2019.00158]

28 **Bian X**, Patel B, Dai X, Galligan JJ, Swain G. High mucosal serotonin availability in neonatal guinea pig ileum is associated with low serotonin transporter expression. *Gastroenterology* 2007; **132**: 2438-2447 [PMID: 17570217 DOI: 10.1053/j.gastro.2007.03.103]

29 **Côté F**, Thévenot E, Fligny C, Fromes Y, Darmon M, Ripoche MA, Bayard E, Hanoun N, Saurini F, Lechat P, Dandolo L, Hamon M, Mallet J, Vodjdani G. Disruption of the nonneuronal tph1 gene demonstrates the importance of peripheral serotonin in cardiac function. *Proc Natl Acad Sci U S A* 2003; **100**: 13525-13530 [PMID: 14597720 DOI: 10.1073/pnas.2233056100]

30 **Walther DJ**, Peter JU, Bashammakh S, Hörtnagl H, Voits M, Fink H, Bader M. Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* 2003; **299**: 76 [PMID: 12511643 DOI: 10.1126/science.1078197]

31 **Bellono NW**, Bayrer JR, Leitch DB, Castro J, Zhang C, O'Donnell TA, Brierley SM, Ingraham HA, Julius D. Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory Neural Pathways. *Cell* 2017; **170**: 185-198.e16 [PMID: 28648659 DOI: 10.1016/j.cell.2017.05.034]

32 **Israelyan N**, Del Colle A, Li Z, Park Y, Xing A, Jacobsen JPR, Luna RA, Jensen DD, Madra M, Saurman V, Rahim R, Latorre R, Law K, Carson W, Bunnett NW, Caron MG, Margolis KG. Effects of Serotonin and Slow-Release 5-Hydroxytryptophan on Gastrointestinal Motility in a Mouse Model of Depression. *Gastroenterology* 2019; **157**: 507-521.e4 [PMID: 31071306 DOI: 10.1053/j.gastro.2019.04.022]

33 **Li Z**, Chalazonitis A, Huang YY, Mann JJ, Margolis KG, Yang QM, Kim DO, Côté F, Mallet J, Gershon MD. Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons. *J Neurosci* 2011; **31**: 8998-9009 [PMID: 21677183 DOI: 10.1523/JNEUROSCI.6684-10.2011]

34 **Heredia DJ**, Gershon MD, Koh SD, Corrigan RD, Okamoto T, Smith TK. Important role of mucosal serotonin in colonic propulsion and peristaltic reflexes: *in vitro* analyses in mice lacking tryptophan hydroxylase 1. *J Physiol* 2013; **591**: 5939-5957 [PMID: 24127620 DOI: 10.1113/jphysiol.2013.256230]

35 **Heredia DJ**, Dickson EJ, Bayguinov PO, Hennig GW, Smith TK. Localized release of serotonin (5-hydroxytryptamine) by a fecal pellet regulates migrating motor complexes in murine colon. *Gastroenterology* 2009; **136**: 1328-1338 [PMID: 19138686 DOI: 10.1053/j.gastro.2008.12.010]

36 **Atkinson W**, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2006; **130**: 34-43 [PMID: 16401466 DOI: 10.1053/j.gastro.2005.09.031]

37 **De Ponti F**. Pharmacology of serotonin: what a clinician should know. *Gut* 2004; **53**: 1520-1535 [PMID: 15361507 DOI: 10.1136/gut.2003.035568]

38 **Gershon MD**, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology* 2007; **132**: 397-414 [PMID: 17241888 DOI: 10.1053/j.gastro.2006.11.002]

39 **Fayyaz M**, Lackner JM. Serotonin receptor modulators in the treatment of irritable bowel syndrome. *Ther Clin Risk Manag* 2008; **4**: 41-48 [PMID: 18728719 DOI: 10.2147/tcrm.s140]

40 **Sullivan KL**, Staffetti JF, Hauser RA, Dunne PB, Zesiewicz TA. Tegaserod (Zelnorm) for the treatment of constipation in Parkinson's disease. *Mov Disord* 2006; **21**: 115-116 [PMID: 16142776 DOI: 10.1002/mds.20666]

41 **Di Palma JA**, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. *Am J Gastroenterol* 2007; **102**: 1964-1971 [PMID: 17573794 DOI: 10.1111/j.1572-0241.2007.01365.x]

42 **Bloom DE**, Cadarette D. Infectious Disease Threats in the Twenty-First Century: Strengthening the Global Response. *Front Immunol* 2019; **10**: 549 [PMID: 30984169 DOI: 10.3389/fimmu.2019.00549]

43 **Elfiky AA**. SARS-CoV-2 Spike-Heat Shock Protein A5 (GRP78) Recognition may be Related to the Immersed Human Coronaviruses. *Front Pharmacol* 2020; **11**: 577467 [PMID: 33362542 DOI: 10.3389/fphar.2020.577467]

44 **Kakodkar P**, Kaka N, Baig MN. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus* 2020; **12**: e7560 [PMID: 32269893 DOI: 10.7759/cureus.7560]

45 **Voto C**, Berkner P, Brenner C. Overview of the Pathogenesis and Treatment of SARS-CoV-2 for Clinicians: A Comprehensive Literature Review. *Cureus* 2020; **12**: e10357 [PMID: 33062480 DOI: 10.7759/cureus.10357]

46 **Shah SJ**, Barish PN, Prasad PA, Kistler A, Neff N, Kamm J, Li LM, Chiu CY, Babik JM, Fang MC, Abe-Jones Y, Alipanah N, Alvarez FN, Botvinnik OB, Castaneda G; CZB CLIAhub Consortium, Dadasovich RM, Davis J, Deng X, DeRisi JL, Detweiler AM, Federman S, Haliburton J, Hao S, Kerkhoff AD, Kumar GR, Malcolm KB, Mann SA, Martinez S, Mary RK, Mick E, Mwakibete L, Najafi N, Peluso MJ, Phelps M, Pisco AO, Ratnasiri K, Rubio LA, Sellas A, Sherwood KD, Sheu J, Spottiswoode N, Tan M, Yu G, Kangelaris KN, Langelier C. Clinical features, diagnostics, and outcomes of patients presenting with acute respiratory illness: A retrospective cohort study of patients with and without COVID-19. *EClinicalMedicine* 2020; **27**: 100518 [PMID: 32864588 DOI: 10.1016/j.eclinm.2020.100518]

47 **Xu J**, Xu X, Jiang L, Dua K, Hansbro PM, Liu G. SARS-CoV-2 induces transcriptional signatures in human lung epithelial cells that promote lung fibrosis. *Respir Res* 2020; **21**: 182 [PMID: 32664949 DOI: 10.1186/s12931-020-01445-6]

48 **Carvalho T**. Extrapulmonary SARS-CoV-2 manifestations. *Nat Med* 2020; **26**: 1806 [PMID: 33288941 DOI: 10.1038/s41591-020-01162-z]

49 **Villapol S**. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. *Transl Res* 2020; **226**: 57-69 [PMID: 32827705 DOI: 10.1016/j.trsl.2020.08.004]

50 **Yeoh YK**, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, Chung AC, Cheung CP, Tso EY, Fung KS, Chan V, Ling L, Joynt G, Hui DS, Chow KM, Ng SSS, Li TC, Ng RW, Yip TC, Wong GL, Chan FK, Wong CK, Chan PK, Ng SC. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021; **70**: 698-706 [PMID: 33431578 DOI: 10.1136/gutjnl-2020-323020]

51 **Lordan C**, Thapa D, Ross RP, Cotter PD. Potential for enriching next-generation health-promoting gut bacteria through prebiotics and other dietary components. *Gut Microbes* 2020; **11**: 1-20 [PMID: 31116628 DOI: 10.1080/19490976.2019.1613124]

52 **Zuo T**, Liu Q, Zhang F, Lui GC, Tso EY, Yeoh YK, Chen Z, Boon SS, Chan FK, Chan PK, Ng SC. Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. *Gut* 2021; **70**: 276-284 [PMID: 32690600 DOI: 10.1136/gutjnl-2020-322294]

53 **Britton GJ**, Chen-Liaw A, Cossarini F, Livanos AE, Spindler MP, Plitt T, Eggers J, Mogno I, Gonzalez-Reiche A, Siu S, Tankelevich M, Grinspan L, Dixon RE, Jha D, Martinez-Delgado G, Amanat F, Hoagland DA, tenOever B, Dubinsky MC, Merad M, van Bakel H, Krammer F, Bongers G, Mehandru S, Faith JJ. SARS-CoV-2-specific IgA and limited inflammatory cytokines are present in the stool of select patients with acute COVID-19. 2020 Preprint. Available from: medRxiv [PMID: 32909002 DOI: 10.1101/2020.09.03.20183947]

54 **Barbara G**, Grover M, Bercik P, Corsetti M, Ghoshal UC, Ohman L, Rajilić-Stojanović M. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. *Gastroenterology* 2019; **156**: 46-58.e7 [PMID: 30009817 DOI: 10.1053/j.gastro.2018.07.011]

55 **Barbara G**, Cremon C, Stanghellini V. Inflammatory bowel disease and irritable bowel syndrome: similarities and differences. *Curr Opin Gastroenterol* 2014; **30**: 352-358 [PMID: 24811054 DOI: 10.1097/MOG.0000000000000070]

56 **Marshall JK**, Thabane M, Borgaonkar MR, James C. Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. *Clin Gastroenterol Hepatol* 2007; **5**: 457-460 [PMID: 17289440 DOI: 10.1016/j.cgh.2006.11.025]

57 **Ghoshal UC**, Rahman MM. Post-infection irritable bowel syndrome in the tropical and subtropical regions: Vibrio cholerae is a new cause of this well-known condition. *Indian J Gastroenterol* 2019; **38**: 87-94 [PMID: 31073702 DOI: 10.1007/s12664-019-00959-2]

58 **Barbara G**, Feinle-Bisset C, Ghoshal UC, Quigley EM, Santos J, Vanner S, Vergnolle N, Zoetendal EG. The Intestinal Microenvironment and Functional Gastrointestinal Disorders. *Gastroenterology* 2016; **150**: 1305-1318 [PMID: 27144620 DOI: 10.1053/j.gastro.2016.02.028]

59 **Gupta S**, Parker J, Smits S, Underwood J, Dolwani S. Persistent viral shedding of SARS-CoV-2 in faeces - a rapid review. *Colorectal Dis* 2020; **22**: 611-620 [PMID: 32418307 DOI: 10.1111/codi.15138]

60 **Donà D**, Minotti C, Costenaro P, Da Dalt L, Giaquinto C. Fecal-Oral Transmission of SARS-CoV-2 In Children: is it Time to Change Our Approach? *Pediatr Infect Dis J* 2020; **39**: e133-e134 [PMID: 32304466 DOI: 10.1097/INF.0000000000002704]

61 **Zhou J**, Li C, Liu X, Chiu MC, Zhao X, Wang D, Wei Y, Lee A, Zhang AJ, Chu H, Cai JP, Yip CC, Chan IH, Wong KK, Tsang OT, Chan KH, Chan JF, To KK, Chen H, Yuen KY. Infection of bat and human intestinal organoids by SARS-CoV-2. *Nat Med* 2020; **26**: 1077-1083 [PMID: 32405028 DOI: 10.1038/s41591-020-0912-6]

62 **Zuo T**, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology* 2020; **159**: 944-955.e8 [PMID: 32442562 DOI: 10.1053/j.gastro.2020.05.048]

63 **Goh KL**, Chuah KH. COVID-19 and the digestive system: More than just a "flu". *JGH Open* 2020; **4**: 318-319 [PMID: 32514430 DOI: 10.1002/jgh3.12364]

64 **Viana SD**, Nunes S, Reis F. ACE2 imbalance as a key player for the poor outcomes in COVID-19 patients with age-related comorbidities - Role of gut microbiota dysbiosis. *Ageing Res Rev* 2020; **62**: 101123 [PMID: 32683039 DOI: 10.1016/j.arr.2020.101123]

65 **Zhang JJ**, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730-1741 [PMID: 32077115 DOI: 10.1111/all.14238]

66 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

67 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

68 **Chen Q**, Quan B, Li X, Gao G, Zheng W, Zhang J, Zhang Z, Liu C, Li L, Wang C, Zhang G, Li J, Dai Y, Yang J, Han W. A report of clinical diagnosis and treatment of nine cases of coronavirus disease 2019. *J Med Virol* 2020; **92**: 683-687 [PMID: 32162699 DOI: 10.1002/jmv.25755]

69 **Chang**, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, Sharma L. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* 2020; **323**: 1092-1093 [PMID: 32031568 DOI: 10.1001/jama.2020.1623]

70 **Liu K**, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, Li GC, Liu HG. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020; **133**: 1025-1031 [PMID: 32044814 DOI: 10.1097/CM9.0000000000000744]

71 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]

72 **Wang Z**, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis* 2020; **71**: 769-777 [PMID: 32176772 DOI: 10.1093/cid/ciaa272]

73 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

74 **Spiteri G**, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, Bella A, Sognamiglio P, Sierra Moros MJ, Riutort AN, Demina YV, Mahieu R, Broas M, Bengnér M, Buda S, Schilling J, Filleul L, Lepoutre A, Saura C, Mailles A, Levy-Bruhl D, Coignard B, Bernard-Stoecklin S, Behillil S, van der Werf S, Valette M, Lina B, Riccardo F, Nicastri E, Casas I, Larrauri A, Salom Castell M, Pozo F, Maksyutov RA, Martin C, Van Ranst M, Bossuyt N, Siira L, Sane J, Tegmark-Wisell K, Palmérus M, Broberg EK, Beauté J, Jorgensen P, Bundle N, Pereyaslov D, Adlhoch C, Pukkila J, Pebody R, Olsen S, Ciancio BC. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. *Euro Surveill* 2020; **25** [PMID: 32156327 DOI: 10.2807/1560-7917.ES.2020.25.9.2000178]

75 **Han C**, Duan C, Zhang S, Spiegel B, Shi H, Wang W, Zhang L, Lin R, Liu J, Ding Z, Hou X. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. *Am J Gastroenterol* 2020; **115**: 916-923 [PMID: 32301761 DOI: 10.14309/ajg.0000000000000664]

76 **Nobel YR**, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczyk ME, Freedberg DE. Gastrointestinal Symptoms and Coronavirus Disease 2019: A Case-Control Study From the United States. *Gastroenterology* 2020; **159**: 373-375.e2 [PMID: 32294477 DOI: 10.1053/j.gastro.2020.04.017]

77 **Zhou Z**, Zhao N, Shu Y, Han S, Chen B, Shu X. Effect of Gastrointestinal Symptoms in Patients With COVID-19. *Gastroenterology* 2020; **158**: 2294-2297 [PMID: 32199880 DOI: 10.1053/j.gastro.2020.03.020]

78 **Cholankeril G**, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer SP, Kim D, Hsing A, Ahmed A. High Prevalence of Concurrent Gastrointestinal Manifestations in Patients With Severe Acute Respiratory Syndrome Coronavirus 2: Early Experience From California. *Gastroenterology* 2020; **159**: 775-777 [PMID: 32283101 DOI: 10.1053/j.gastro.2020.04.008]

79 **Redd WD**, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, Shen L, Chan WW. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. *Gastroenterology* 2020; **159**: 765-767.e2 [PMID: 32333911 DOI: 10.1053/j.gastro.2020.04.045]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 29, 2021

**First decision:** March 6, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

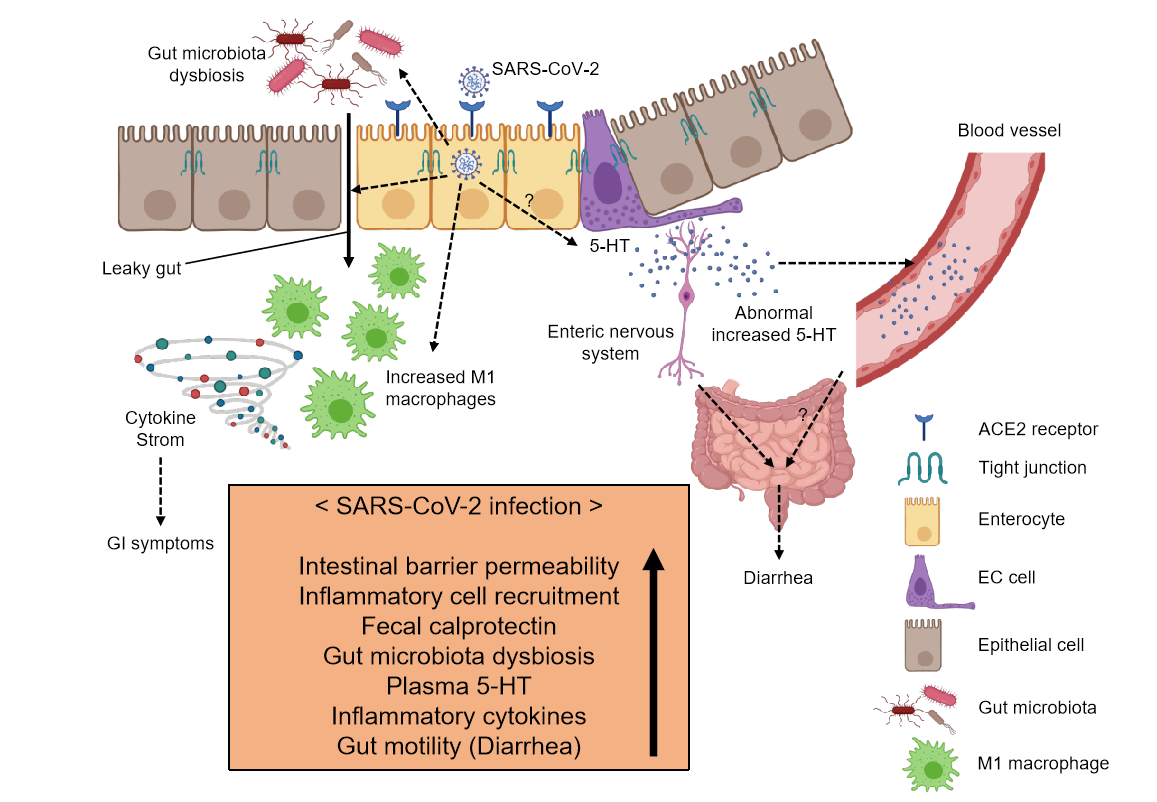
Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Luo A **S-Editor:** Liu M **L-Editor: P-Editor:**

**Figure Legends**

****

**Figure 1 A simplified diagram of the potential pathological mechanisms for gastrointestinal symptoms associated with severe acute respiratory syndrome coronavirus 2 infection.** The figure was created with BioRender.com. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; 5-HT: 5-hydroxytrytamine; EC: Enterochromaffin; ACE2: Angiotensin converting enzyme 2.

**Table 1 Clinical presentation of gastrointestinal symptoms among coronavirus disease 2019 patients, *n* (%)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of patients** | **Diarrhea** | **Anorexia** | **Nausea** | | **Vomiting** | **Abdominal pain** | **GI**  **Bleeding** |
| Ha *et al*[12] | 80 | 10 (12.5) | - | 6 (7.5) | | 2 (2.5) | 7 (8.8) | 1 (1.3) |
| Jin *et al*[10] | 651 | 53 (8.1) | - | 10 (1.5) | | 11 (1.7) | - | - |
| Lin *et al*[11] | 95 | 23 (24.2) | 17 (17.9) | 17 (17.9) | | 4 (4.2) | 2 (2.1)1 | 2 (2.1)2 |
| Zhang *et al*[65] | 139 | 18 (12.9) | 17 (12.2) | 24 (17.3) | | 7 (5) | 8 (5.8) | - |
| Wang *et al*[66] | 138 | 14 (10.1) | 55 (39.9) | 14 (10.1) | | 5 (3.6) | 3 (2.2) | - |
| Chen *et al*[67] | 99 | 2(2) | - | 1 (1)c |  | | - | - |
| Chen *et al*[68*]* | 9 | 2 (22.2) | - | - | | - | - | - |
| Young *et al*[13] | 18 | 3 (16.7) | - | - | | - | - | - |
| Chang *et al*[69] | 13 | 1 (7.7) | - | - | | - | - | - |
| Liu *et al*[70] | 137 | 11 (8) | - | - | | - | - | - |
| Pan *et al*[71] | 204 | 35 (17.2) | 81 (39.7) | - | | 4 (2) | 2 (1) | - |
| Wang *et al*[72] | 69 | 10 (14.5) | 7 (10.1) | - | | 3 (4.3) | - | - |
| Yang *et al*[73] | 52 | - | - | - | | 2 (3.8) | - | - |
| Spiteri *et al*[74] | 38 | 1 (2.6) | - | 1 (2.6) | | - | - | - |
| Han *et al*[75] | 206 | 67 (32.5) | 32 (15.5) | - | | 24 (11.7) | 9 (4.4) | - |
| Nobel et al[76] | 278 | 56 (20.1) | - | 63 (22.7)3 |  | | - | - |
| Zhou *et al*[77] | 254 | 46 (18.1) | - | 21 (8.3) | | 15 (5.9) | 3 (1.2) | - |
| Cholankeril *et al*[78] | 116 | 12 (10.3) | 22 (25.3) | 12 (10.3) | | 5 (4.3) | 10 (8.8) | - |
| Redd *et al*[79] | 318 | 107 (33.7) | 110 (34.8) | 84 (26.4) | | 49 (15.4) | 46 (14.5) | 2 (0.63) |
| Total | 2914 | 471 (16.2) | 341 (11.7) | 253 (8.7) | | 131 (4.5) | 90 (3.1) | 5 (0.2) |

1Epigastric discomfort; 2Upper gastrointestinal hemorrhage; 3Nausea and vomiting. GI: Gastrointestinal.