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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

REVIEW

Mechanism and potential treatments for gastrointestinal dysfunction in patients with COVID-19

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Abstract

The global coronavirus disease 2019 (COVID-19) has become one of the biggest threats to the world since 2019. The respiratory and gastrointestinal tracts are the main targets for severe acute respiratory syndrome coronavirus 2 infection for they highly express angiotensin-converting enzyme-2 and transmembrane protease serine 2. In patients suffering from COVID-19, gastrointestinal symptoms have ranged from 12% to 61%. Anorexia, nausea and/or vomiting, diarrhea, and abdominal pain are considered to be the main gastrointestinal symptoms of COVID-19. It has been reported that the direct damage of intestinal mucosal epithelial cells, malnutrition, and intestinal flora disorders are involved in COVID-19. However, the underlying mechanisms remain unclear. Thus, in this study, we reviewed and discussed the correlated mechanisms that cause

gastrointestinal symptoms in order to help to develop the treatment strategy and build an appropriate guideline for medical workers.

Key Words: COVID-19; Angiotensin-converting enzyme-2; Transmembrane protease serine 2; Gastrointestinal symptom; Mechanism; Intestinal barrier permeability

Core Tip: Gastrointestinal symptoms in coronavirus disease 2019 patients have ranged from 12% to 61%, which include anorexia, nausea and/or vomiting, diarrhea, abdominal pain, and so on. However, the underlying mechanisms remain unclear. This study reviewed and discussed the correlated mechanisms that cause gastrointestinal symptoms in order to help to develop the treatment strategy and build an appropriate guideline for medical workers.

INTRODUCTION

Since 2019, coronavirus disease 2019 (COVID-19) has become one of the world's most serious threats. In the past, much attention has been given to the respiratory symptoms of patients, but the occurrence of extrapulmonary symptoms has been ignored. The occurrence of gastrointestinal symptoms has ranged from 12% to 61% in patients suffering from COVID-19[1-5], which may result in a longer duration of illness but not increased mortality[2,3]. In a recent meta-analysis from China, the main gastrointestinal symptoms in COVID-19 patients were reported to include anorexia (21%), nausea and/or vomiting (7%), diarrhea (9%), and abdominal pain (3%)[2]. Moreover, gastrointestinal bleeding was rarely observed[6]. A study from the United States reported a higher prevalence of gastrointestinal symptoms (anorexia, 34.8%; diarrhea, 33.7%; and nausea, 26.4%)[4] (Figure 1). Thus, diarrhea, nausea and/or vomiting, abdominal pain, and anorexia are considered to be the main gastrointestinal symptoms.

Currently, after struggling with the Omicron variant, China has found that a large number of COVID-19 patients, especially elderly patients in critical condition, are more likely to suffer from gastrointestinal dysfunction. Over 85% of patients showed symptoms such as intestinal barrier dysfunction, digestive and absorption dysfunction, or gastrointestinal motility dysfunction due to the direct damage the virus caused to the intestinal mucosal epithelial cells. In addition, malnutrition and intestinal flora disorders occurred next. Imaging studies show that COVID-19 patients with gastrointestinal symptoms presented thickening of the bowel wall, sometimes with hyperemia and thickening of the mesentery, and large bowel fluid[7]. However, the underlying mechanisms remain unclear. Thus, in this study, we reviewed and discussed the correlated mechanisms of gastrointestinal symptoms and damage in order to help build an appropriate guideline for medical workers.

PATHOPHYSIOLOGY

The pathophysiology of gastrointestinal damage in COVID-19 is probably multifactorial. The most important factor is due to the direct infection of the virus. High titers of viral RNA from COVID-19 have been isolated from fecal samples[8,9]. Live viral shedding of infectious virions in fecal matter has been reported even after the resolution of symptoms, which may be a potential source of transmission[10]. Angiotensin-converting enzyme-2 (ACE2), as the entry receptor for the causative coronavirus of COVID-19, is expressed in multiple extrapulmonary tissues, including gastrointestinal tissue[11]. A study based on single-cell sequencing also showed that ACE2 and transmembrane protease serine 2 (TMPRS2) are expressed in cholangiocytes, colonocytes, esophageal keratinocytes, gastrointestinal epithelial cells, and so on[12-14]. The expression profile of ACE2 in the digestive system is shown in Figure 2. Histopathological studies also indicated that gastrointestinal tissue is the target organ of COVID-19[15]. This finding indicates that direct viral-induced tissue damage is a plausible mechanism of COVID-19 injury. Here, however, we hold the idea that the expression of ACE2 is related to the virus entering the body, but the expression level of ACE2 does not appear to be directly proportional to the severity of the disease[16].
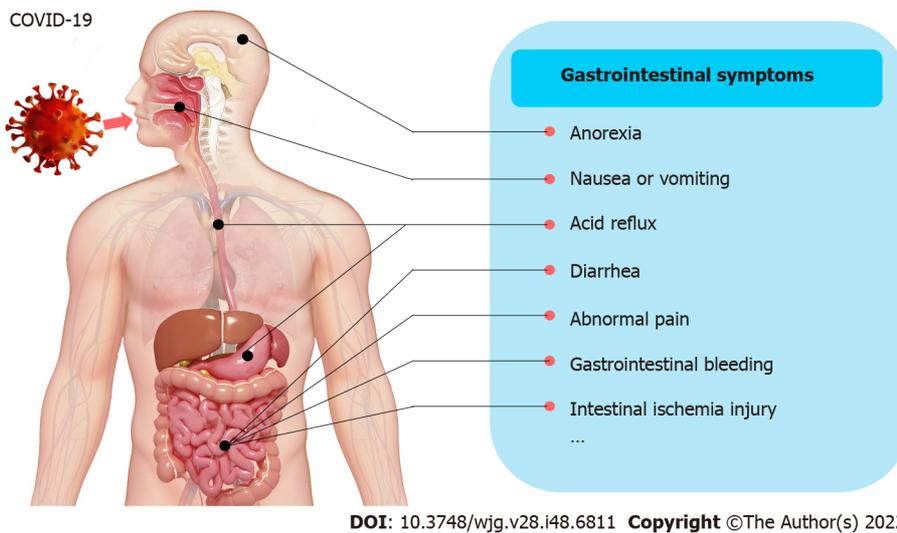
Figure 1 Gastrointestinal symptoms involved in coronavirus disease 2019 infection. COVID-19: Coronavirus disease 2019.

In addition, responses following ACE2 activation are closely related to gastrointestinal side effects. ACE2 is also a key enzyme in the renin-angiotensin system (RAS)[17]. RAS dysregulation may exacerbate ion imbalance and inflammation, potentially affecting cellular metabolic status, microbial composition, and cell viability, leading to progressive bowel function and diarrhea[18]. Histopathological evidence also shows diffuse endothelial inflammation and mesenteric ischemia in the submucosal vessels of the small intestine in patients with COVID-19[19]. Furthermore, infiltrating plasma cells, lymphocytes, and interstitial edema have been found in the lamina propria of COVID-19 patients' stomachs, duodenums and rectums. Virus-induced cytokine storms, as well as inflammatory responses, may also contribute to enhanced permeability of the mucosal barrier, damaged enteric nervous system, altered intestinal flora[20], and gut-brain axis communication disorders and then form a vicious circle (Figure 3). The syndrome-correlated underlying mechanism is discussed in the following sections.

METHODOLOGY

A literature review was conducted using a keyword search in PubMed from 2019 to 2022. Keyword search items included "COVID-19", "severe acute respiratory syndrome coronavirus 2", "gastrointestinal disorders", "nausea", "vomiting", "diarrhea", "ACE2", "abdominal pain", "anorexia", and "combinations thereof". The inclusion criteria included articles with randomized or blinded studies, case-control studies, descriptive research, and studies with objective outcomes. Exclusion criteria included articles of primary opinion papers with no reference to available data and industry-sponsored publications.

GASTROINTESTINAL SYMPTOMS AND THE UNDERLYING MECHANISMS

Nausea and/or vomiting

Nausea and/or vomiting is an early alerting symptom of a challenge (toxic food and chemicals, bacterial toxin, and virus) to the upper digestive tract, which can also be the early presenting symptom in COVID-19 patients[21]. The reported incidences of vomiting and nausea were 1.0%-12.5% and 1.0%-27.5%, respectively[4,22]. Some of the patients may eject aerosolized, virally contaminated vomit, which also occurs in patients infected with norovirus[23]. Importantly, nausea and vomiting can be the early presenting symptoms of COVID-19[21].

The virus enters the digestive tract with the air during swallowing and binds to ACE2 receptors, which are highly expressed in the airways and digestive tract. COVID-19 could increase the release of neuroactive agents from enteroendocrine cells and inflammatory mediations, which act by stimulating/sensitizing abdominal vagal afferent terminals and/or act on the area postrema in the dorsal medulla where the blood-brain and blood-cerebrospinal fluid barriers are relatively permeable [21]. The consequences of vagal afferent and area postrema activation induce nausea and vomiting by the projection of information to higher brain regions (nausea and anorexia) and vomiting by motor pathways in the ventral brainstem and spinal cord[21]. Some researchers also indicated that the
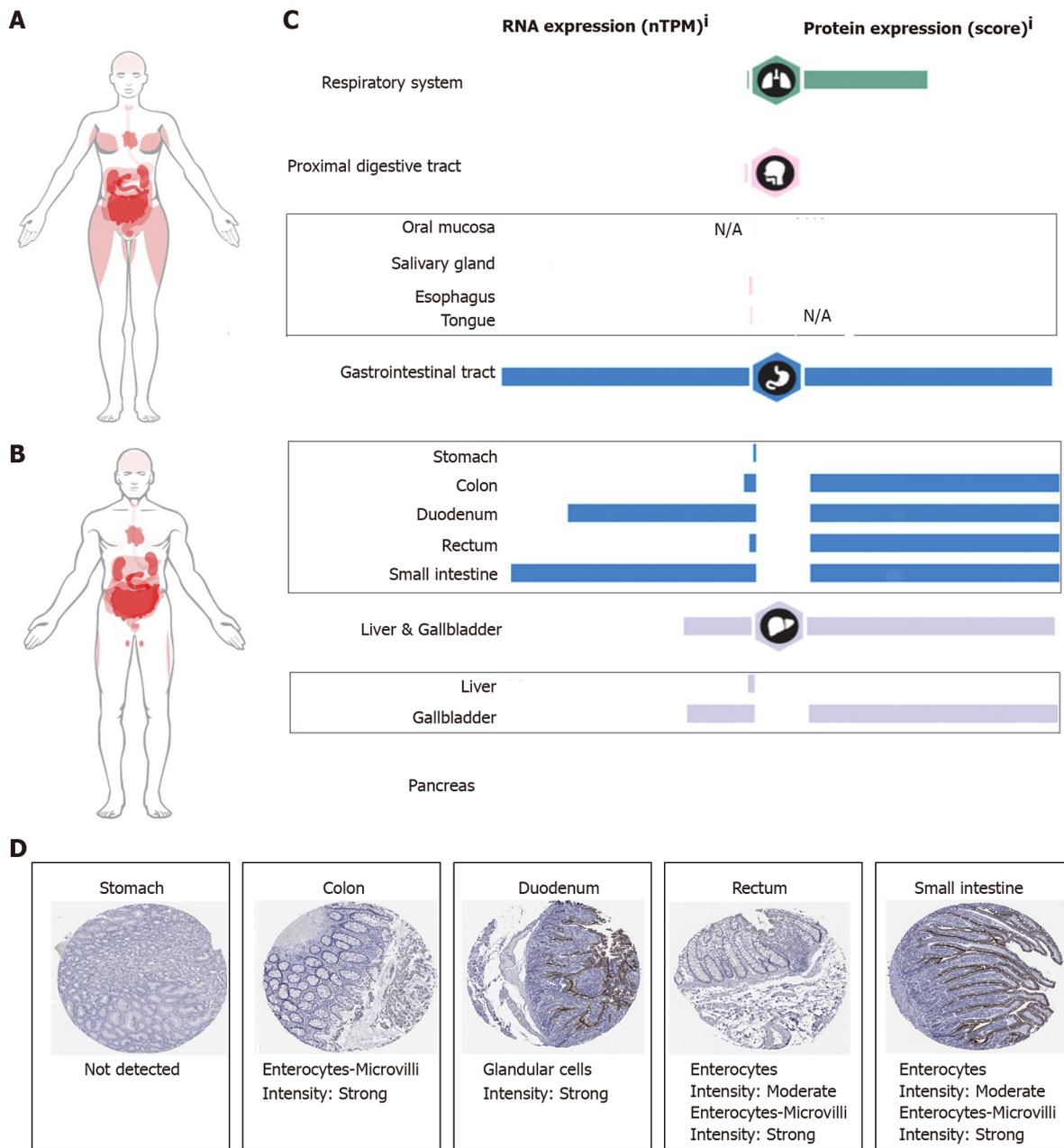
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Figure 2 Angiotensin-converting enzyme 2 expression in human gastrointestinal tissues. A: Angiotensin-converting enzyme 2 (ACE) expression in females; B: ACE expression in males, darker colors indicate higher expression levels; C: ACE2 mRNA and protein expression in the respiratory system and digestive system; D: ACE2 positive cell types in the stomach, colon, duodenum, rectum, and small intestine. These data are summarized from the human protein atlas https://www.proteinatlas.org/. N/A: Not applicable.

interaction between transient receptor potential (TRP) channels and food intake might be associated with anorexia due to COVID-19[24,25]. Some TRP channels are broadly expressed in the gastrointestinal tract and play important roles in noxious irritants[26]. TRPV1 expression in esophageal sensory neurons, stomach-labeled vagal nodose neurons and colon-labeled afferent neurons has been well described[27-29]. A TRPV1 agonist, capsaicin, can evoke nausea[30]. Moreover, TRPV1 and TRPA1 are co-expressed in the esophagus, stomach, intestine, and colon[31-33]. TRPV1 can participate in appetite regulation by affecting hormones and gastrointestinal vagal afferent nerves[25]. *In vitro* activation of TRPA1 by allyl isothiocyanates can increase serotonin release, leading to the stimulation of vomiting [34]. These results suggest that TRP channel activation is involved in COVID-19-induced nausea and vomiting. However, whether inhibiting TRP channels can alleviate the gastrointestinal symptoms caused by COVID-19 needs further investigation. The underlying mechanisms are summarized in Figure 4.
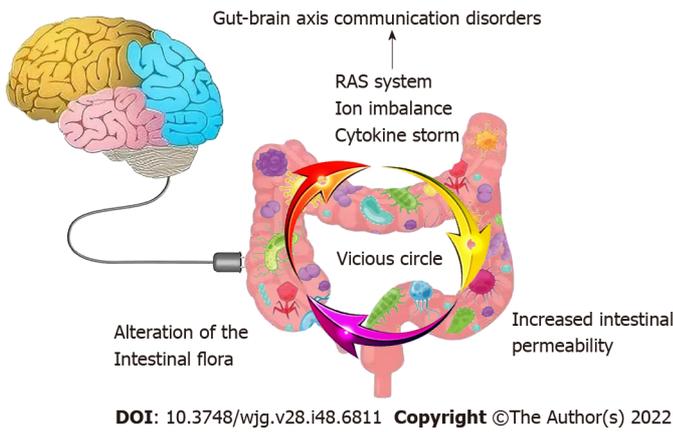
Figure 3 Main mechanisms involved in coronavirus disease 2019-induced gastrointestinal syndromes. Gut infection of coronavirus disease 2019 (COVID-19) results in cytokine storm, increased intestinal permeability and alteration of the intestinal flora, and forming a vicious circle, extending the recovery time. Moreover, COVID-19 binding to gastrointestinal angiotensin-converting enzyme 2 also leads to ion imbalance and activation of renin-angiotensin system. Abnormal enteric neurotransmitters may further lead to gut-brain axis communication disorders. RAS: Renin-angiotensin system.
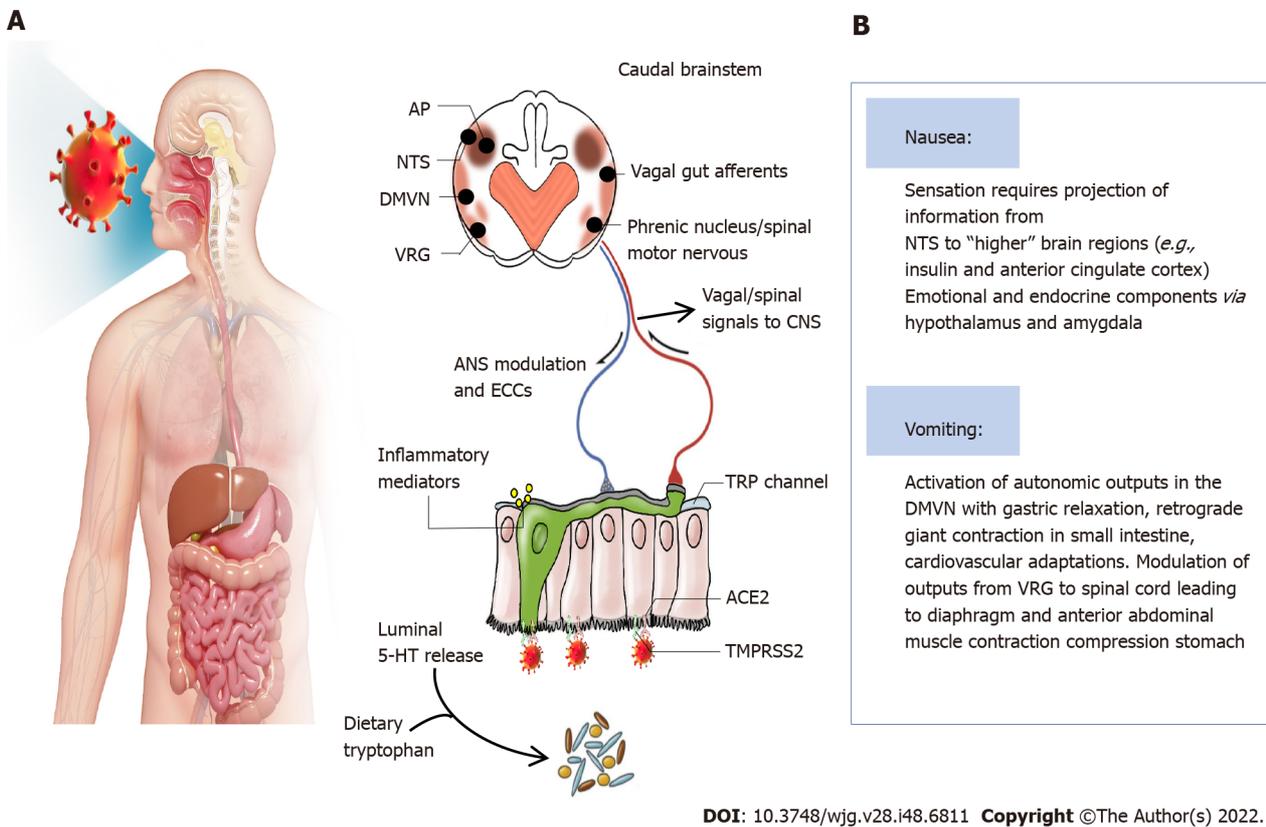
Figure 4 Potential mechanisms for coronavirus disease 2019-induced nausea and vomiting. A: The virus enters the body through the airways and digestive tract during swallowing and the potential mechanisms for coronavirus disease 2019 to induce nausea and vomiting (based on the evidence discussed in the text). The virus interacts with digestive tract epithelium leading to the release of neuroactive agents from enteroendocrine cells and inflammatory mediations, and these can act by stimulating or sensitizing abdominal vagal afferent terminals; B: The consequences of vagal afferent and area postrema activation induce nausea and vomiting by projection of information to nausea and anorexia-related regions, and vomiting by motor pathways in the ventral brainstem and spinal cord. 5-HT: 5-hydroxytryptamine; ACE2: Angiotensin-converting enzyme-2; AP: Area postrema; DMVN: Dorsal motor vagal nucleus; NTS: Nucleus tractus solitarius; TMPRSS2: Transmembrane protease serine 2; VRG: Ventral respiratory group of neurons; TRP: Transient receptor potential; ANS: Autonomic nervous system; ECCs: Enteroendocrine cells.

Diarrhea

Diarrhea is a frequent presenting symptom in patients suffering from COVID-19. In the clinical case analysis, the incidence of diarrhea is between 2% and 50%[35]. It may precede or trail respiratory symptoms. Although the specific mechanisms involved in COVID-19-related diarrhea are not entirely known, we hold the idea that the targeting of intestinal ACE2 by the virus, virus infection-induced

cytokine storms, increased intestinal barrier permeability, and even changes in microbiome are all considered to be the main causes of gastrointestinal symptoms. Moreover, hepatic and pancreatic injuries may also cause diarrhea. Antibiotic-induced iatrogenic diarrhea caused by the activation of *Clostridium spp.* should also be taken into consideration.

The direct effect of binding ACE2: ACE2 mRNA appears to increase with age and to display higher levels in patients taking ACE inhibitors. This may be one of the causes of gastrointestinal symptoms such as diarrhea being more common in elderly patients or those with hypertension. ACE2 controls the production of antimicrobial peptides and participates in the uptake of dietary amino acids[36], which promote the homeostasis of the gut flora. Additionally, ACE2 expression is positively correlated with the severity of colitis, suggesting that virus activity may lead to changes in the way certain enzymes function, making people more susceptible to developing diarrhea and intestinal inflammation[37].

Altered serotonin metabolism: Altered serotonin metabolism has been found in COVID-19 patients [38]. Serotonin, known as the mood neurotransmitter, is important in certain bodily processes, such as sleep, libido, and body temperature. Studies have reported that enterohemorrhagic *Escherichia coli* O157 can significantly reduce the expression of a group of genes that cause infection after exposure to serotonin[39,40]. In addition, a study in mice showed that increased serotonin levels in the gastrointestinal tract could reduce the ability of murine *Citrobacter* to infect the host and cause disease. Intervention with fluoxetine, a selective serotonin reuptake inhibitor, produced similar results[40]. Activation of intestinal serotonin receptors may also lead to diarrhea by modulating the enteric nervous system and intestinal motility[41,42]. The authors believe that COVID-19-related diarrhea is correlated with increased serotonin levels and that elevated serotonin levels may be a protective regulatory mechanism that accelerates the excretion of enteroviruses.

Changes in fecal calprotectin: Increased levels of fecal calprotectin expression have also been detected in COVID-19 patients[43,44]. Fecal calprotectin is a reliable fecal marker for the detection of inflammatory bowel disease and infectious colitis[45]. The calprotectin value in stool is elevated in patients with acute or bloody diarrhea[46]. Calprotectin is a calcium-containing protein derived from neutrophils and macrophages that serves as a marker of inflammatory cell activation[47]. Therefore, diarrhea and increased fecal calprotectin levels could be related to the immune activation and inflammatory responses caused by COVID-19.

Cytokine storms and their induced inflammatory cascade: Cytokine release syndrome caused by a dysregulated immune response is also one of the important factors causing multiple organ dysfunction, especially diarrhea, in patients with COVID-19. Severe COVID-19 manifests as acute respiratory distress syndrome (ARDS) with elevated plasma proinflammatory cytokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α), C-X-C motif chemokine ligand 10, macrophage inflammatory protein 1 α, and chemokine (C-C motif) ligand 2, with low levels of interferon type I (IFN-I) in the early stage and elevated levels of IFN-I during the advanced stage of COVID-19[48]. Changes in these proinflammatory cytokines can also be found in clinical and experimental colitis[49,50], accompanied by increased intestinal permeability *via* activation of the inflammatory-related cascade. High levels of circulating cytokines and mediators of the toxic response, including IL-6, TNF-α, nitric oxide, and activity modulation of the calcium channel, have been described[51]. Toll-like receptors (TLRs) are important sensors that interact with COVID-19. Previous studies indicated that COVID-19 interacts with TLRs in the host cell membrane and increases gene 88 of the primary response to myeloid differentiation (MyD88), following active nuclear transcription factor-κB (NF-κB), promoting an inflammatory cascade [52], which in turn aggravates the inflammatory response and increases intestinal permeability. Additionally, severe COVID-19 individuals have been found to have significant levels of indicators for tight junction permeability as well as the translocation of bacterial and fungal products into the blood [53,54]. Thus, virus infection-induced cytokine storms and their induced inflammatory response may be other factors that cause diarrhea.

Increased intestinal barrier permeability and microbiome change: Accumulating evidence shows that the intestinal microbiome is broadly altered in COVID-19 patients, which may be followed by increased intestinal permeability. The incidence of sepsis and ARDS, two high-mortality risks in COVID-19, may be minimized by the intestinal microbiota[55]. 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[56], which can also be considered a marker of inflammation and disease severity[57]. Changes in ACE2 by COVID-19 can impair intestinal uptake of certain dietary amino acids, such as tryptophan, which is involved in enteritis[58-60]. ACE2 knockout mice also exhibit microbiome dysbiosis[61-63]. Through shotgun sequencing of total DNA extracted from stool, researchers found that the gut microbial ecological network was markedly weakened and became sparse, which combined with a decrease in gut microbiome diversity[64], could reflect the disease's severity[65]. The infection causes intestinal microbiome disturbance and reduction, which may activate immune cells and provoke the release of inflammatory cytokines that increase systemic inflammation [66,67]. In addition, probiotics may help enhance the host immune system, improve the gut microbiome

and gut barrier function, and reduce COVID-19-related diarrhea[68].

More significantly, B0AT1 substrates such as tryptophan and glutamine operate as signals to reduce lymphoid proinflammatory cytokines, activate antimicrobial release peptides, and control mucosal autophagy as a defensive mechanism[69]. Downregulated intestinal ACE2-B0AT1 on the cellular surface leads to a series of downstream sequelae to promote leaky gut and dysbiosis of gut flora[69]. Gut microbiomes also play important roles in gut inflammatory regulation. Butyric acid from gut flora was reported to inhibit cytokine storms[27]. This indicates the disrupted composition of intestinal microbiota and impaired gut permeability, followed by the creation of a destructive cycle. In summary, we propose the important role of intestinal microbiota in preventing and decreasing COVID-19 complications. The underlying mechanism involved in COVID-19-correlated diarrhea is summarized in Figure 5.

Abdominal pain

Abdominal pain is uncommon and extremely rare in patients with COVID-19. Clinical data indicate that abdominal pain is more common in intensive care unit (ICU) patients than in non-ICU patients[41]. The aggregative presence rate of RNA from COVID-19 in stool samples from COVID-19 patients was 54% [2]. In previous clinical research based on COVID-19 patients who underwent emergency abdominal surgery due to different conditions, the peritoneal samples from 5 patients were sufficient for reverse transcription polymerase chain reaction analysis, and no intraperitoneal viral RNA was observed in these 5 patients[70]. Although the number of cases is rare, we can speculate that abdominal pain is linked to gastrointestinal but not intraperitoneal viral infection. The possible mechanisms are summarized as follows.

Immune and inflammatory regulation: The most common cause of pain is the inflammation-induced release of many cytokines and chemokines. Cytokine storms are a potentially fatal immune disease characterized by high levels of activation of immune cells and excessive production of a large number of inflammatory cytokines and chemical mediators, and they have been reported to be associated with the exacerbation of a number of infectious diseases, including severe acute respiratory syndrome[71] and Middle East respiratory syndrome. They are also considered to be the main cause of disease severity and death in patients with COVID-19[72,73]. T cells play an important role in antiviral immunity. A rise in T cell activation and differentiation was found in early COVID-19-infected patients, resulting in immune rebalancing between IFN and NF-κB activity and restoration of cell homeostasis. Two major intracellular transduction antigen-activating signals, the phosphatidylinositol pathway and the MAP kinase-related pathway, are activated. However, the number of T cells is significantly decreased with increasing infective time in COVID-19 patients, accompanied by an increase in the T cell exhaustion marker programmed death 1[74]. The T cell count is negatively correlated with serum cytokine levels in patients with COVID-19[74]. Despite the lack of direct evidence for a relationship between T cell status and abdominal pain in COVID-19 patients, we hypothesized that abdominal pain is related to T cells. Moreover, COVID-19 can rapidly activate pathogenic Th1 cells to secrete proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor and IL-6. Increased cytokines, chemokines, and other compounds can simultaneously cause a secondary pain response by activating pain-sensing neurons[75]. The COVID-19 cytokine storm is characterized by high expression of IL-6 and TNF-α[76]. Elevated IL-6 levels also increase mortality. Therefore, we hypothesized that the abdominal pain of COVID-19 patients may be associated with the high expression of IL-6 and TNF-α.

Eosinophils are circulating and tissue-resident white blood cells that have a powerful proinflammatory effect in many diseases. Recently, eosinophils have been shown to have a variety of other functions, including immunomodulatory and antiviral activity. Peripheral eosinophilia is hypothesized to play a protective role in COVID-19 patients[77]. In the United States, a review of administrative data compared the hospitalization rates, ventilator dependence, and death of patients with and without eosinophilic gastrointestinal disorders from an extensive central medical system. The results indicated that eosinophilic gastrointestinal disorder might provide a protective immune response[78]. The mechanism may be related to the upregulation of IL-13 in eosinophilic gastrointestinal disorder and the decreased expression of ACE2 and TMPRS2 on epithelial cells of eosinophilic gastrointestinal disorder patients. In addition, eosinophil-derived neurotoxins may exert direct antiviral effects[79]. Moreover, eosinophilia-related disorders such as eosinophilic gastroenteritis[80] and eosinophilic esophagitis[81] are often accompanied by symptoms of abdominal pain and vomiting, suggesting that abdominal pain in patients with COVID-19 may also be caused by increased eosinophils.

Regulation of the enteric and central nervous systems: Intestinal pain perception can be coregulated by the central and enteric nervous systems. A balance between neuronal excitatory and inhibitory signaling pathways maintains the physiological pain threshold in the intestine. Altered neurotransmitter levels may be closely linked to abdominal pain. A variety of receptors and their endogenous ligands are involved in pain signaling, including receptors responsible for nociceptive sensations [*e.g.,* 5-hydroxytryptamine (5-HT) receptors, TRP channels, IL receptors] and antinociceptive sensations (*e.g.,* opioid and cannabinoid receptors). In COVID-19 patients, intestinal inflammatory infiltration increases intestinal mucosal permeability, and the direct effect of viruses can aggravate dysbiosis and cause changes in tryptophan metabolism. Studies have shown that tryptophan is a precursor of 5-HT. 5-HT plays an

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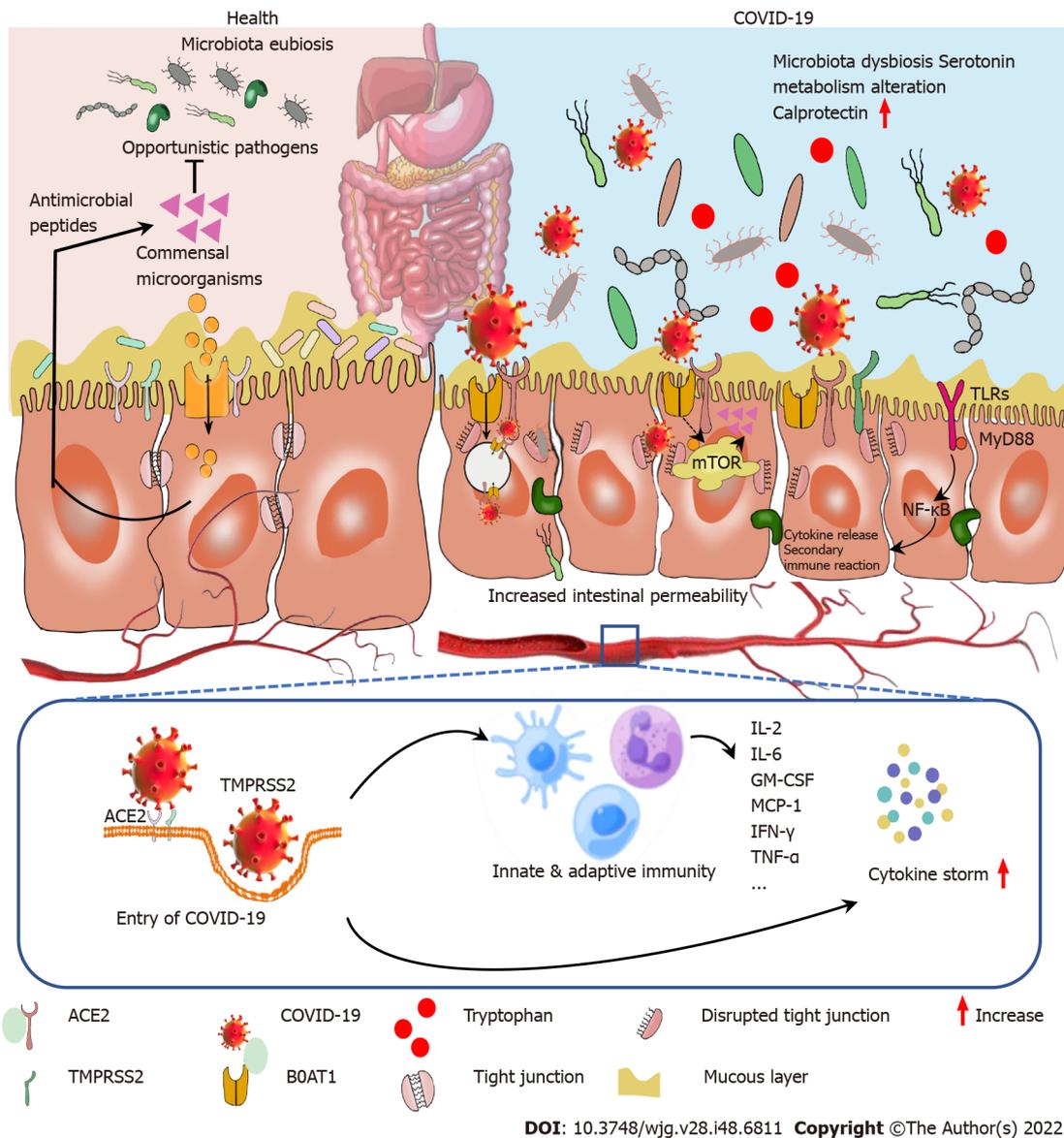
Figure 5 Potential mechanism of cytokine storm and secondary pathogen infection resulting in diarrhea in patients with coronavirus disease 2019. After coronavirus disease 2019 (COVID-19) virus entry into the body, innate and adaptive immunity have been activated, followed by a cytokine storm. Gut microbiota is also disrupted by COVID-19 infection which potentially triggers cytokine storm and secondary pathogen infections. B0AT known as an angiotensin-converting enzyme-2 chaperone, mediates neutral amino acid uptake by luminal epithelial cells. B0AT substrates (tryptophan and glutamine) activate antimicrobial peptide release and promote tight junction formation, inhibit cytokine release and promote mucosal cell autophagy *via* mechanistic target of rapamycin signaling pathway. COVID-19 infection blocked this pathway, promoting opportunistic pathogen invasion, cytokine storm, activating toll-like receptors/nuclear factor-κB pathway and aggravated COVID-19. COVID-19: Coronavirus disease 2019; ACE2: Angiotensin-converting enzyme-2; TMPRSS2: Transmembrane protease serine 2; IL: Interleukin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; MCP-1: Monocyte chemoattractant protein-1; IFN-γ: Interferon-γ; TNF: Tumor necrosis factor; mTOR: Mechanistic target of rapamycin; TLRs: Toll-like receptors; NF-κB: Nuclear factor-κB.

important role in gastrointestinal, nervous, and liver diseases. 5-HT acts on 5-HT receptors to initiate peristaltic and secretory reflexes in the viscera[82,83]. Research also indicated that 5-HT might be the key to exacerbating inflammatory bowel disease symptoms, including diarrhea and abdominal pain [84]. Intraperitoneal injection of 5-HT can significantly increase the expression of IL-1β and IL-6 and the activity of myeloperoxidase by activating $5-HT_3$ and $5-HT_4$ receptors in the colonic mucosa of mice with colitis and block the signal of pain relief[85]. Further studies have reported that elevated 5-HT can increase the expression of IL-6 and IL-8 and the production of monocyte chemoattractant protein-1, thereby leading to the initial event of intestinal inflammation[86]. However, the plasma 5-HT level is increased in hospitalized patients with COVID-19. The change in 5-HT in patients with COVID-19 may be an important cause of abdominal pain[87]. Therefore, we speculate that the abdominal pain in COVID-19 may be related to 5-HT. Moreover, regulating the level of 5-HT may be a therapeutic modality for the treatment of patients with abdominal pain due to COVID-19.

Ion channel: Pain signals are detected in response to harmful stimuli and release nerve impulses that encode pain. Many of these nociceptive neurons are equipped with a large number of specific ion channels that act as nociceptors. Stretching, inflammation, ischemia, pH, bacterial products, immune mediators, and neurotransmitters have all been implicated in visceral pain[88]. Studies have reported multiple electrolyte abnormalities in patients with COVID-19 infection[89]. COVID-19 infection is associated with decreased serum concentrations of sodium, potassium, magnesium, and calcium. Thus, we speculate that ion channels may play important roles in COVID-19-induced abdominal pain. As TRP channels are widely expressed in COVID-19-infected tissues, TRP channels and TRPML2 are also involved in the fusion of viral envelopes with endolysosomal membranes[90,91]. Thus, TRP channels may be valuable targets for disrupting the COVID-19 life cycle. A report indicated that TRP channels were involved in abdominal pain caused by COVID-19. TRPV1 and TRPA1 induce inflammation, increase sensory or vagal secretions, and cause pain[92]. It has also been suggested that afferent neuronal TRPV1 desensitization (*via* RTX) can reduce pain-related complications in COVID-19 patients [93]. Because TRP channels are widely expressed in the gastrointestinal tract, we speculate that the abdominal pain caused by COVID-19 is related to TRP channel activation.

Anorexia

Social pressure: Anorexia nervosa is an eating disorder characterized by restrictive eating and an intense fear of gaining weight. A study in 2020 evaluated the early effects of COVID-19 on patients with eating disorders and reported an increase in anxiety and alarming eating behaviors during the pandemic. This report shows that 69% of individuals had anorexia nervosa and experienced worries about their dietary schedules, while subjects with bulimia nervosa or binge eating disorders reported more episodes of binging[94]. This may be due to new living conditions, social distancing, self-isolation, changes in food access, daily habits, and so on; in addition, more difficult access to health care practitioners is also an essential factor leading to an increased incidence of anorexia[95].

Neuromodulation: Researchers have reported that neuroendocrine pathways are disrupted by miscommunication between brain-gut-adipose tissue in patients suffering from COVID-19[96]. Studies have shown that dopamine neurons in the ventral tegmental area of the midbrain and serotonin neurons in the dorsal raphe nucleus are involved in the regulation of motivational behaviors, including feeding[22, 97], and increased serotonin levels have been observed in COVID-19 patients[38]. However, there is no direct evidence of whether it is related to anorexia nervosa. Changes in the microbiota-gut-brain axis from COVID-19 as well as gender differences may also be responsible for anorexia nervosa[98]. Moreover, changes in brain serotonin and tryptophan concentrations have been reported to be critical mechanisms in the regulation of eating behavior both in mice and humans[99]. Coincidentally, post-COVID-19 infection was also accompanied by changes in serotonin and tryptophan levels. We speculate that COVID-19-induced anorexia is at least partly correlated with increased serotonin and tryptophan levels. In addition, COVID-19 infection of nonneuronal cells can lead to anosmia and related odor perception impairment[100], which may be associated with the development and aggravation of anorexia[101,102].

Acid reflux

In a retrospective study of poor prognosis of gastrointestinal symptoms in patients with COVID-19, 12 (n = 1077, 1.1%) patients developed acid reflux[103], and the incidence of acid reflux was relatively low compared with other gastrointestinal symptoms. Generally, the main causes of gastric acid reflux include: (1) Relaxation of the lower esophageal sphincter; (2) Gastric and duodenal dysfunction leading to obstruction of gastric emptying; and (3) Esophageal mucosal barrier damage. In a clinical study, the prevalence of acid reflux was associated with poorer clinical outcomes in COVID-19, and the mechanism was related to damage to the upper esophageal sphincter[104]. We believe that increased serotonin levels and mucosal barrier damage caused by cytokine storms may also be risk factors for acid reflux. Antacid therapy is generally used, but some studies have noted that the use of proton pump inhibitors may increase the risk of achlorhydria-related intestinal infections in patients with COVID-19 [105], while histamine H_2 receptor antagonists do not increase this risk. Some studies have suggested that high-dose famotidine may be clinically beneficial to COVID-19 patients[106]. Therefore, the clinical use of histamine receptor antagonists may be more beneficial; however, due to low incidence and insufficient samples, there has been no systematic clinical evaluation of COVID-19 patients accompanied by acid reflux.

Gastrointestinal bleeding

A case-control study noted that the main causes of gastrointestinal bleeding in COVID-19 patients were peptic and rectal ulcers. Among the many potential predictors of upper gastrointestinal bleeding, a history of upper gastrointestinal bleeding was the only significant risk factor[107,108]. Gastrointestinal bleeding may be the direct impact of COVID-19 on gastrointestinal mucosa integrity. However, in a case of a COVID-19 patient who showed vomiting coffee crumbs and esophageal mucosal injury by esophagogastroscopy and duodenoscopy, there was no mucosal injury[107]. This may exist in other

mechanisms that have not been elucidated. Compared with patients in the initial presentation, most bleeding occurred during hospitalization. The results suggested that bleeding may be one of the treatment-related or secondary factors related to critical illness.

Intestinal ischemia injury

It has been reported in the literature that exposure to COVID-19 may lead to an increased risk of ischemia associated with extremity venous thrombosis, pulmonary embolism, and mesenteric ischemia [109,110]. The overall mortality in COVID-19 patients with gastrointestinal ischemia and imaging-diagnosed mesenteric ischemia was 38.7% and 40%, respectively[111]. Mesenteric ischemia can be a fatal clinical emergency with high mortality[112]. Existing studies also have shown that the incidence of intestinal obstruction and intestinal ischemia is positively correlated with elevated aminotransferase levels[113].

Other gastrointestinal symptoms

Abdominal distension and loss of taste also have been indicated in the previous investigation[114], however, the specific underlying mechanism needs to be further explored. Another important issue we should be concerned about is that some adverse gastrointestinal events in COVID-19 patients are related to medication[115]. An observation line cohort study among patients with moderate severity of COVID-19 pointed out that patients receiving hydroxychloroquine or chloroquine treatment may occur serious gastrointestinal adverse practices (diarrhea, nausea, abdominal pain, *etc*.) which is an important reason make the patients are forced to withdrawal[115].

CONCLUSION

Patients suffering from COVID-19 are often accompanied by various types of gastrointestinal symptoms. Gastrointestinal symptoms may be accompanied by or precede respiratory symptoms. This suggests that gastrointestinal symptoms may indicate the possibility of a new COVID-19 infection in the context of this unmanageable pandemic trend. During COVID-19 infection, the main mechanisms of gastrointestinal symptoms include the interaction between virus and gastrointestinal ACE2, inflammatory factor storm, intestinal mucosal barrier damage, and composition and metabolites of intestinal flora change. A vicious cycle is formed between the above factors in COVID-19 patients, which prolongs the recovery time. This also suggests that focusing on gut symptoms and alterations in gut microbes or their metabolites may be a beneficial option for coping with COVID-19. Adjunctive treatment with probiotics may help break this vicious cycle and help the patients recover. However, this review has some limitations. The assumptions in this review are mostly based on clinical observations. To clearly elucidate the mechanism of gastrointestinal symptoms caused by COVID-19 and find appropriate treatments still needs a lot of basic research.

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