Digestive system infection by SARS-CoV-2: Entry mechanism, clinical symptoms and expression of major receptors (Review)

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Abstract. Besides causing severe acute respiratory syndrome (SARS), SARS-coronavirus 2 (SARS-CoV-2) also harms the digestive system. Given the appearance of numerous cases of SARS-CoV-2, it has been demonstrated that SARS-CoV-2 is able to harm target organs such as the gastrointestinal tract, liver and pancreas, and either worsen the condition of patients with basic digestive illnesses or make their prognosis poor. According to several previously published studies, angiotensin-converting enzyme II (ACE2) and transmembrane serine protease II (TMPRSS2) are expressed either singly or in combination in the digestive system and in other regions of the human body. In order to change the viral conformation, create a fusion hole and release viral RNA into the host cell for replication and transcription, SARS-CoV-2 is capable of binding to these two proteins through the spike protein on its surface. As a result, the body experiences an immune reaction and an inflammatory reaction, which may lead to nausea, diarrhea, abdominal pain and even gastrointestinal bleeding, elevated levels of liver enzymes, acute liver injury, pancreatitis and other serious lesions. In order to provide possible strategies for the clinical diagnosis and treatment of digestive system diseases during the COVID-19 pandemic, the molecular structure of SARS-CoV-2 and the mechanism via which SARS-CoV-2 enters the human body through ACE2 and TMPRSS2 were discussed in the present review, and the clinical manifestations of SARS-CoV-2 infection in the digestive system were also summarized. Finally, the expression characteristics of ACE2 and TMPRSS2 in the main target organs of the digestive system were described.

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Contents

1. Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is the pathogen responsible for causing SARS-CoV-2 pneumonia [coronavirus disease 2019 (COVID-19)]. The initial clinical symptoms of viral infection are frequently atypical and include mild coughing and headaches (1,2). The increase in SARS-CoV-2 infection cases has also led to the emergence of a number of characteristic stomach symptoms. According to a multicenter retrospective study by Rizvi *et al* (3), 3,229 (18.5%) of the 17,462 hospitalized patients exhibited various gastrointestinal manifestations. During follow-up, these manifestations included gastrointestinal bleeding, pancreatitis and conditions arising from the manifestations, such as malnutrition. Although the exact mechanism of SARS-CoV-2 infection in the gastrointestinal tract remains unknown, it is generally accepted that the expression of angiotensin-converting enzyme II (ACE2) and transmembrane serine protease II (TMPRSS2) in the stomach, liver, pancreas, duodenum and colon is essential for infection to occur (4). Through the tethering of the virus to both these proteins via its spike (S) protein, the virus is able to enter the digestive tract.

ACE2 is a vital part of the renin-angiotensin-aldosterone system, being produced from the conversion of ACE (5). ACE2 acts as a key effector peptide that causes vasodilation (5). TMPRSS2 is a type II transmembrane protein that

acts as a serine protease (6,7). The principal mediators of viral S protein binding are these two proteins. Several factors, such as age, sex, obesity, smoking, *Helicobacter pylori* (*H. pylori*) infection and tumors, have been indicated to be capable of promoting the upregulation of the genes encoding ACE2 and TMPRSS2 in the digestive system, making it easier for SARS-CoV-2 to enter the body (5,7). For instance, two recent studies revealed that stomach and colorectal adenocarcinomas have high levels of ACE2 and TMPRSS2 expression (8,9). In addition, Viveiros *et al* (10) reported that older male mice expressed higher levels of ACE2 compared with younger mice. Furthermore, Da Eira *et al* (11) observed that obese mice have comparatively higher levels of ACE2 and TMPRSS2 expression.

Taken together, the findings of previous studies have established that the entry of SARS-CoV-2 into the digestive tract, which causes diarrhea, nausea, vomiting and lack of appetite, depends on ACE2 and TMPRSS2. In addition, SARS-CoV-2 is able to influence the severity, prognosis and outcome of conditions such as liver damage and severe pancreatitis. It also has a direct or indirect association with a number of common digestive ailments. Through introducing the microstructure of SARS-CoV-2 and detailing the process via which SARS-CoV-2 enters the human body through ACE2 and TMPRSS2, the present review summarizes the effects of SARS-CoV-2 infection on the digestive system and the expression characteristics of ACE2 and TMPRSS2 in major target organs. Several potential strategies for the diagnosis, identification and treatment of digestive system diseases during the COVID-19 pandemic are also described.

2. Structural features and molecular mechanism of SARS-CoV-2 entry into cells

Classification and microstructure of SARS-CoV-2. At present, coronavirus has been divided into four major subclades, namely the α-, β-, γ- and δ-coronaviruses. SARS-CoV-2 belongs to the β-coronavirus group and mainly arises in humans and mammals. It belongs to the same branch of coronaviruses as SARS-CoV, SARS, human coronavirus (HCoV)-OC43, HCoV-HKU1 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) (6,12,13). SARS-CoV-2 and SARS-like coronavirus share 88% homology, whereas SARS-CoV-2 and SARS-CoV share 79% homology, and SARS-CoV-2 and MERS-CoV share a relatively low homology of 50%. However, a computational analysis of the crystal structure of SARS-CoV-2 revealed that its manner of attachment to host ACE2 was comparable with that of the SARS-CoV and HCoV-NL63 viruses (13).

The viral particles of SARS-CoV-2 are single-stranded positive RNA envelope particles, having a spherical shape and a size between 100 and 160 nm. Its genome, 29,903 bp in length, has been demonstrated to have a highly conserved structure (12,14,15). The genome includes three regions. The open reading frames (ORFs) ORF1a and ORF1b comprise the first two-thirds of the genome, whereas the final third of the genome encodes structural proteins, including the S protein, envelope (E) protein, membrane (M) protein and nucleocapsid (N) protein (Fig. 1) (12).

The S protein, one of the four abovementioned structural proteins, is essential for viral entrance into the host cells. The S protein is a homotrimeric class I membrane protein (6,16). Located on the surface of the virus particles, the protein forms a crown (17) and, indeed, SARS-CoV-2 acquired its name for this reason (Fig. 1B). There are 22 N-linked glycosylation sites on each monomer of the highly glycosylated protein (66 in total) (18). The S protein contains an N-terminal signal peptide, the S1 subunit (responsible for receptor binding) and the S2 subunit (responsible for membrane fusion), with a total length of 1,273 amino acid residues (18). Receptor binding is performed by the S1 (N-terminal) subunit, whereas membrane fusion is accomplished by the S2 (C-terminal) subunit (16). The N-terminal domain, receptor-binding domain (RBD) and C-terminal domain 1 (CTD1) and CTD2 are other divisions of the S1 subunit. Regarding the S2 subunit, this comprises a central helix, junction region, heptapeptide repeat sequence 1 (HR1) and HR2, fusion peptide (FP), FP proximal region, transmembrane fragment and cytoplasmic tail (18). According to recent studies, RBD and FP are the structures specifically linked to viral invasion.

Molecular mechanism through which SARS-CoV-2 enters the human body. The RBD, a protein mainly composed of four cysteine residues that form disulfide bonds and seven β-fragments, is able to bind to ACE2 (17,19). Viruses may enter host cells in two different ways (Fig. 2A). In the first scenario, if the host cell only expresses ACE2 but does not express TMPRSS2 (or if the expression of TMPRSS2 is insufficient), the viral S protein may bind to ACE2 to change the conformation of the S1 subunit, thereby exposing the S2 subunit; subsequently, via the process of reticulin-mediated endocytosis, the entire viral molecule enters the cell and after the S2 subunit is dissociated by cathepsins, channels are opened for the release of viral RNA (6). Alternatively, if the host cell co-expresses ACE2 and TMPRSS2, viral RNA enters the cell through membrane fusion. First, ACE2 combines with RBD, resulting in a change in the conformation of the S protein (Fig. 2B). At this stage, the furin protease, a proprotein conversion enzyme that is able to activate the S protein, recognizes and cleaves the polybase insertion (also termed 'PRRAR') site in S1/S2, and S1/S2 subunit dissociation occurs (20,21). After S1 is separated from S2, the conformation of the S2 subunit undergoes a change, thereby exposing the S2' cleavage site, which is recognized and cleaved by TMPRSS2 (or cathepsin B/L), and then the exposed fusion peptide is inserted into the target cell membrane (12,22). Subsequently, HR1 and HR2 of the S2 subunit form a stable six-helix bundle fusion core that binds the viral and cellular membranes together to form a fusion pore to release the RNA (Fig. 2C and D) (15).

Previous studies have also indicated that mutant strains may enhance their ability to bind to ACE2 due to their own mutations, and for other reasons. For instance, the B.1.1.7, B.1.351, P.1 and B.1.617.2 mutant variants of SARS-CoV-2 have a high affinity for ACE2 and these mutant strains express multiple mutations of the S protein. These mutations may change the structure of the protein, resulting in greater infectivity (23-26). Storti *et al* (27) discovered that the B.1.1.7 strain is able to internalize faster and this accelerated internalization may be directly associated with the N501Y mutation of the S protein, which enhances the binding of RBD to ACE2. When the RBD gene is mutated, it may lead to an increase in the

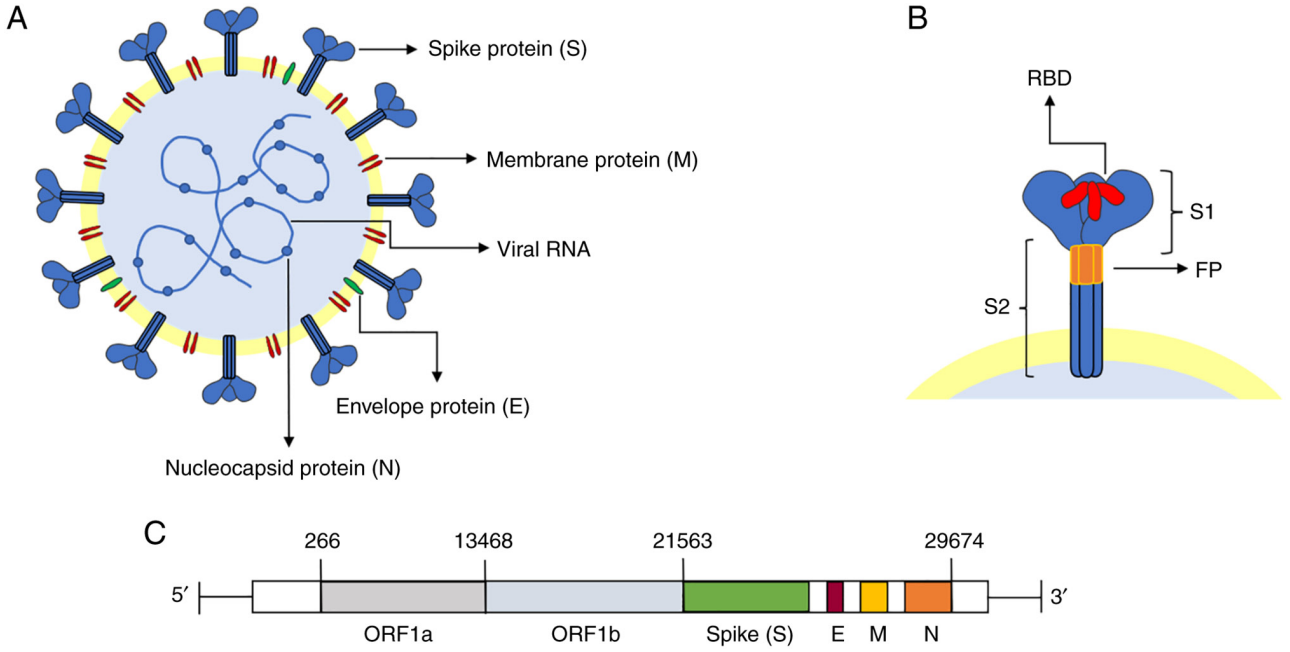

Figure 1. Molecular structure of SARS-CoV-2. (A) SARS-CoV-2 viral particles are single-stranded positive RNA spherical envelope viruses. The viral membrane is composed of the spike protein, membrane protein, envelope protein, nucleocapsid protein and genetic material (RNA). (B) The two subunits that make up each monomer of the spike protein, S1 and S2, are arranged in a trimer shape. The RBD subunit in the S1 subunit is in charge of receptor binding. The S2 subunit's FP structure is responsible for attachment to the target cell membrane. (C) The genome's length is 29,903 base pairs and it comprises open reading frames ORF1a and ORF1b, as well as the structural S, E, M and N proteins. SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; FP, fusion peptide; ORF, open reading frame; S, spike protein; M, membrane protein; E, envelope protein; N, nucleocapsid protein; RBD, receptor-binding domain.

infection rate of SARS-CoV-2 (28). For instance, the D164G mutation was indicated to change the structure of the S protein, thereby increasing the affinity between RBD and ACE2 (29). Although limited studies have been published on the infection of the digestive system by mutant strains of SARS-CoV-2, the potential threat cannot be denied.

3. Clinical manifestations of SARS-CoV-2 infection and gastrointestinal expression of ACE2 and TMPRSS2

Clinical features of SARS-CoV-2 that damage the digestive system

SARS-CoV-2 causes atypical gastrointestinal symptoms, including bleeding. Since SARS-CoV-2 swept across the globe, a sizable number of digestive symptoms or disorders have been linked to viruses, primarily the most widespread and fundamental of digestive symptoms. SARS-CoV-2 has been positively identified in stool tests of numerous patients with COVID-19, which may provide evidence of the replication and presence of the virus in the digestive tract (30). In another SARS-CoV-2 RNA sample test, 44 (29%) of 153 stool samples were found to be positive for SARS-CoV-2 (31). Certain patients with COVID-19 have tested positive for the virus in their stool, even after throat swab tests were negative (32,33). In addition, SARS-CoV-2 RNA was found in the stool of 53% of hospitalized patients with COVID-19, and biopsies of the stomach, duodenum and rectum tested positive for the viral nucleocapsid, suggesting that the virus may infect the digestive tract (34). Xiao *et al* (35) performed a gastrointestinal endoscopy on a patient with COVID-19 and found that the esophageal mucosa was damaged; a subsequent histological examination revealed the presence of a large number of plasma cells and lymphocyte infiltration in the lamina propria of the stomach, duodenum and rectum. In addition, viral nucleocapsid proteins were detected in the cytoplasm of these sites. The prevalence of gastrointestinal symptoms in individuals with COVID-19 ranges from 12 to 61%, and gastrointestinal symptoms were manifested in the digestive tract more frequently in patients with a longer disease course (36). The signs and symptoms include diarrhea, nausea and vomiting. Diarrhea is the most typical symptom (37). Retrospective case studies have indicated that diarrhea, nausea, vomiting and anorexia are the most typical digestive symptoms in patients with COVID-19 (38-40). In addition, evidence suggests that nausea frequently starts at an early stage in patients infected with SARS-CoV-2, indicating that the gastrointestinal tract may be infected by the virus. Nausea was associated with the first case of COVID-19 in both China and the USA (41). In excess of 12,000 patients with COVID-19 were included in the analysis of 41 studies by Andrews *et al* (42), and the findings revealed a median incidence of nausea and diarrhea of 10.5 and 11%, respectively. Therefore, patients with SARS-CoV-2 infection should be vigilant of symptoms of both nausea and diarrhea with similar care. Epidemiological data have also indicated that nausea should be taken into consideration as a potential early symptom of SARS-CoV-2 (41). The most frequent abdomen computed tomography findings for imaging viral invasion of the digestive tract in patients with COVID-19 were found to be colonic thickening and edema, gastritis and small intestine gas buildup (43).

Several SARS-CoV-2-positive individuals have also experienced gastrointestinal hemorrhage. Carvalho *et al* (44)

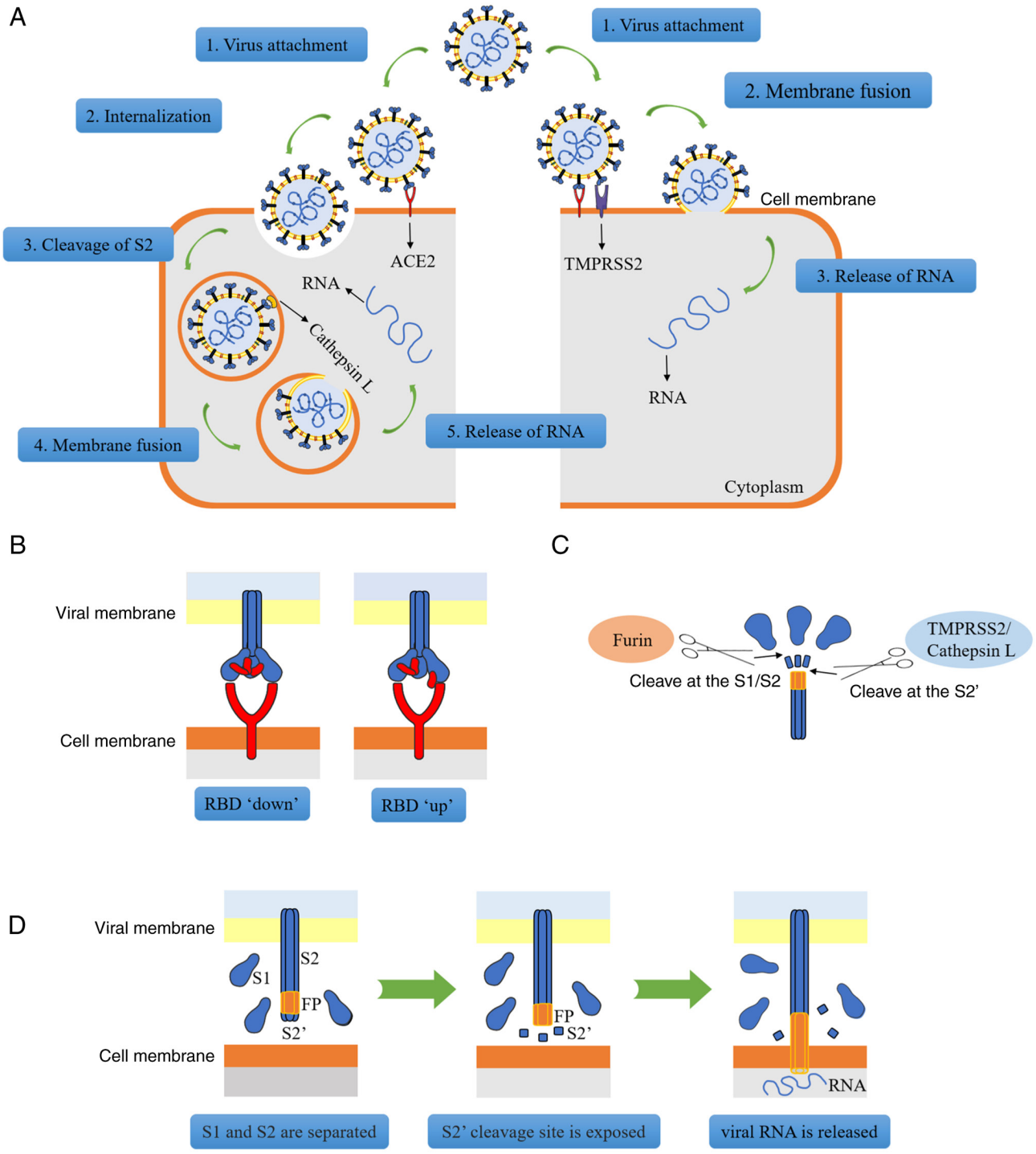

Figure 2. Mode of SARS-CoV-2 infection of target cells. (A) On the left, when TMPRSS2 is not fully expressed in the cells, the viral spike protein interacts with ACE2, changing the structure of the S1 subunit. At this point, the S1 and S2 subunits are broken down by furin protease, which allows reticular protein to facilitate endocytosis. Cathepsin disintegrates the S2' subunit, exposing its FP sequence, which then causes FP to release viral RNA in the cells. On the right, the stimulatory protein associated with ACE2, the furin protease, lyses the S1-S2 site and exposes the S2' site. TMPRSS2 lyses the S2' site, the exposed FP is inserted into the cell membrane, membrane fusion occurs on the cell surface and viral RNA is released. (B) The spike protein binds to ACE2 via the RBD. When the RBD is not associated with ACE2, it is in a 'downward' position; however, when the RBD is bound to ACE2, its conformation changes and it is then in an 'upward' position. (C) RNA must be released from spinous proteins by a two-step cleavage process. Furin protease cleaves at the S1/S2 subunit site; TMPRSS2 or cathepsin cleave at the S2' site. (D) The process via which FP attaches to the cell membrane. After S1 and S2 are separated, the S2' cleavage site is exposed. In order to create a fusion hole (membrane fusion), FP is exposed and is then inserted into the cell membrane. As the S2' cleavage site is segmented, viral RNA is released from the fusion hole. SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; TMPRSS2, transmembrane serine protease II; ACE2, angiotensin-converting enzyme II; RBD, receptor-binding domain; FP, fusion peptide; S, spike protein.

reported on a 71-year-old female patient with hemorrhagic colitis brought to the hospital on account of SARS-CoV-2 infection; endoscopic investigation identified a patchy localized erythema without any ulcer in the gut. The lamina propria had modest enlargement and edema, as observed by H&E staining of the colon and rectal biopsy. In addition, the particular

case of a 77-year-old male patient with upper gastrointestinal hemorrhage was reported by Li *et al* (45). Lymphocyte infiltration and the presence of SARS-CoV-2 RNA in the samples taken from this patient provided conclusive evidence that the upper gastrointestinal bleeding in this case was caused by esophageal SARS-CoV-2 infection. A total of 95 patients with COVID-19 were studied by Lin *et al* (38), six of whom received endoscopies due to gastrointestinal symptoms. A severely ill patient also experienced esophageal hemorrhage, erosion and ulceration. In addition, SARS-CoV-2 RNA was found in the rectum, duodenum, stomach and esophagus of two seriously ill patients.

In the event of an epidemic breakout, symptoms that may be encountered in clinical practice include nausea, diarrhea and stomach pain. It is fitting to contemplate the connection between these manifestations and SARS-CoV-2, if other possible causes that may account for the gastrointestinal symptoms have been ruled out. For hospitalized patients, it is also important to look out for SARS-CoV-2 infection to prevent the virus's impact on the onset and prognosis of digestive illnesses.

Effects of SARS-CoV-2 on the digestive system may be prolonged. Hospitalization of patients with COVID-19 with SARS-CoV-2 gastrointestinal infections led to a prolongation of the symptoms in 104 patients in China, according to a retrospective cohort research study (46). Hu *et al* (47) tested for the virus in 289 patients with COVID-19 and 21 (7.3%) of these patients were readmitted after discharge due to re-detection of SARS-CoV-2. In the positive retest, the percentage of the readmitted patients for whom the virus was detected by anal swab was 71.4% (15/21). The subsequent phylogenetic analysis of the patients' full-length SARS-CoV-2 genome revealed that the virus detected in the retest had evolved from the parental virus involved in the initial infection. Therefore, the virus was indicated to participate in the primary, rather than the secondary infection. Hu *et al* (47) also determined that the presence of SARS-CoV-2 may remain undetected and that the virus may be replicated at low levels, mainly in the gastrointestinal tract, for a long time; furthermore, periodic shedding of the virus may lead to a resurgence of the virus, as mainly found in the anal swab samples. In patients with acute diarrhea, Noviello *et al* (48) discovered that moderate gastrointestinal symptoms persisted for ~5 months after SARS-CoV-2 infection. In addition, these researchers considered that acute SARS-CoV-2 infection may also have an impact on the brain-gut axis, resulting in symptoms such as headaches, backaches, irregular sleep patterns, low mood and anxiety (48).

Furthermore, patients with underlying gastrointestinal problems may potentially be impacted by SARS-CoV-2. In a retrospective analysis of surgical resection specimens from patients with gastrointestinal cancer, the specimens were tested for SARSCoV-2 to determine whether the patients had COVID-19. The results indicated that among 52 patients with gastrointestinal cancer, the mortality rate of patients with early or asymptomatic COVID-19 following surgery was 16.7%, which was much higher compared with that of patients without COVID-19 (49). In addition, the presence of certain underlying conditions, such as inflammatory bowel disease (IBD), was indicated to boost the expression of ACE2, with the result that the patients may have been more susceptible to SARS-CoV-2 (50). There is evidence that patients with IBD express ACE2 and TMPRSS2 more frequently in the colorectum compared with non-IBD patients (51,52). The study by Tao *et al* (53) revealed that patients with COVID-19 with IBD were more likely to experience symptoms of diarrhea and abdominal pain, and have elevated levels of biomarkers compared with patients without IBD. Due to viral infection, colitis is easily induced via direct damage caused to the intestinal epithelial cells. As a result, patients with IBD may be more vulnerable to intestinal damage caused by COVID-19 (54). Viganò *et al* (55) surveyed 709 patients with IBD, 53 of whom were also infected with COVID-19. They found that the probability of diarrhea was 49%, significantly higher than the probability for patients with IBD alone (42.2%). Furthermore, active IBD has been indicated to be significantly associated with COVID-19. Derikx *et al* (56) also found that ~38.6% of patients with IBD who were infected with COVID-19 had diarrhea symptoms. IBD patients with COVID-19 are also more likely to develop digestive diseases than those infected with COVID-19 or IBD alone, suggesting that COVID-19 may be associated either with the aggravation of IBD symptoms or with the promotion of its transition to the active phase.

The gastrointestinal tract may become infected with SARS-CoV-2 on a recurring, periodic and persistent basis. Patients with COVID-19 must continue to be monitored in order to assess whether the virus is still active after their gastrointestinal symptoms have improved. In addition, as far as possible, SARS-CoV-2 infection should always be avoided by those with fundamental digestive problems, in order to prevent the condition from getting worse or changing the prognosis.

SARS-CoV-2 with TMPRSS2 and ACE2 expression in the gastrointestinal tract

Connection between ACE2, SARS-CoV-2 and the stomach. Both healthy individuals and SARS-CoV-2-infected patients have digestive organs that express ACE2 and TMPRSS2. ACE2 is expressed in stomach tissues, according to recent investigations (57,58). According to Lee *et al* (59), who performed single-cell RNA sequencing (scRNA-seq) analyses of various parts of the gastrointestinal tract, the expression ratios of ACE2 in the upper digestive tract (esophagus, stomach and duodenum) and the lower digestive tract (ileum and colorectum) were 1.04% (1,084/104,174 cells) and 14.06% (4,754/33,808 cells), respectively. In the gastrointestinal tract, the co-expression of ACE2 and TMPRSS2 was found to be the highest in the small intestine and colorectum. More than 20% of intestinal epithelial cells and ~5% of colon cells were found to co-express ACE2 and TMPRSS2 (59). According to An *et al* (60), the main cells of the stomach manufacture pepsinogen and express ACE2 at a higher level in gastric tissue than in parietal cells, which may help to explain why patients with SARS-CoV-2 who have anorexia display this clinical characteristic. Due to the fact that ACE2 is still expressed in the gastric mucosa, further investigations have discovered that *H. pylori* infection and intestinal metaplasia may render subjects vulnerable to SARS-CoV-2 (61). Finally, Sun *et al* (62) developed a human ACE2 (hACE2)-expressing mouse model and demonstrated that hACE2 mice are sensitive to SARS-CoV-2 infection.

Characteristics of SARS-CoV-2 intestinal infection and expression of ACE2 and TMPRSS2 in intestinal cells. Numerous studies have confirmed that the intestinal tract is one of the susceptible sites for SARS-CoV-2. SARS-CoV-2-infected gastrointestinal tracts were indicated to shed a large number of infectious viruses, according to an African green monkey viral infection experiment. Furthermore, infectious viruses were repeatedly isolated over time from mucosal swabs, including from the rectum (63). Using monkey experiments, Jiao *et al* (64) also indicated that SARS-COV-2 infection led to an inhibition of gastrointestinal goblet cell proliferation, with the induction of apoptosis. Goblet cells secrete mucins, which prevent the entry of pathogens into the cells; a lack of mucins renders hosts more susceptible to pathogens. Therefore, SARS-CoV-2 infection has been shown to result in an inhibition of the proliferation of goblet cells and a decrease in the levels of mucins, which induces apoptosis, leading to the destruction of the intestinal barrier and further infection of multiple tissues (64).

Regarding the human gut, Livanos *et al* (65) observed strong expression of ACE2 on the brush border of the small intestine in both uninfected and SARS-CoV-2-infected patients. In addition, using immunofluorescence and electron microscopic experiments, these researchers detected viral nucleocapsid proteins in the small intestinal epithelial cells of 11 out of 12 COVID-19 patients (mainly goblet cells), suggesting that these cells were infected with the virus. In addition, Lee *et al* (59) found that ACE2 and TMPRSS2 are mainly co-expressed in the intestinal epithelial cells of the lower digestive tract, with the highest co-expression rates occurring in progenitor and stem-like epithelial cells, particularly in the small intestine, suggesting a potential mechanism for the gastrointestinal manifestations of acute COVID-19 infection. As far as the large intestine is concerned, studies have confirmed that ACE2 is mainly expressed on the membrane and in the cytoplasm of goblet cells, and the expression of ACE2 on the basal side of the colonic epithelium was found to be lower than that on the luminal side. Since colonic basal cells are able to regenerate and differentiate into mature functional glandular epithelial cells, the damaged colonic epithelial cells will be repaired after the SARS-CoV-2 virus is cleared, which may provide the explanation for the self-limiting diarrhea found in patients with COVID-19 (60). Qi *et al* (66) analyzed scRNA-seq data from the digestive system and found that ACE2 and TMPRSS2 are highly expressed in goblet cells throughout the intestine (both small intestine and large intestine), thereby identifying the intestine as a high-risk organ.

A large number of previously published studies (60,65) have otherwise demonstrated that ACE2 and TMPRSS2 are fully expressed in numerous intestinal regions, particularly in goblet cells. The severity of a viral infection in the intestine may be directly correlated with the expression of these two proteases. Consequently, close attention should be paid to the areas where these proteases are highly expressed while a clinical diagnosis is being made.

4. SARS-CoV-2 and the liver

General characteristics of liver damage with SARS-CoV-2. According to the study by Wang *et al* (67), 303 (46.1%) of 657 patients with COVID-19 experienced liver injury, with the frequency of severe and critical cases being greater [148/257 (57.6%)] compared with that of moderate cases [155/400 (38.8%)]. Males [192/303 (63.4%)] were also found to be substantially more likely to experience liver damage [111/303 (36.6%)] as compared to females. Zhang *et al* (68) discovered that male patients were more likely to experience liver injury than female patients in a multivariate analysis of 218 patients performed at Wuhan Central Hospital. This increased likelihood of liver injury in male patients may have been due to the liver-protecting effects of increased estrogen levels in women. High levels of D-dimer and neutrophils are additional risk factors for liver damage in individuals with COVID-19, in addition to their sex. The prognosis may be poor for individuals who have underlying liver illness, such as alcoholic liver disease or cirrhosis, if they contract SARS-CoV-2 (69). Yang *et al* (70) noted in *in vivo* studies that the livers of hamsters infected with SARS-CoV-2 displayed structural abnormalities and had large vacuoles. The expression of the viral protein was compatible with the placement of large vacuoles in hepatocytes, as revealed by immunohistochemical nucleoprotein staining, indicating viral replication in the liver. A previous study also revealed that patients with COVID-19 who had liver injury had a high viral load during the early stages of infection, suggesting that the virus may harm the liver directly (71). When SARS-CoV-2 infects cells, a huge number of inflammatory mediator and chemokine molecules are released, which leads to the aggregation of neutrophils. In addition, their secretions, containing cytokines and chemokines, encourage immune cell aggregation and the immune response (72). According to another previously published study, the inflammatory cytokine storm that SARS-CoV-2 generates raises patients' levels of interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-17, interferon, interferon-γ-induced protein 10 and monocyte and results in damage to the liver (73).

The prognosis is typically poor once a patient is infected with SARS-CoV-2, whether or not there is an underlying liver condition. The liver is more susceptible to injury in males due to their levels of estrogen being lower than those in females. Therefore, when male patients are infected with SARS-CoV-2, more focus should be placed on liver protection.

SARS-CoV-2 infection is able to cause liver damage that may result in increased liver enzyme levels. In a large tertiary care health system in Detroit (USA), out of 1,935 patients who were hospitalized with COVID-19, 1,031 (53.2%) of them had mildly elevated levels of liver enzymes and 396 (20.5%) had liver damage (74). According to a meta-analysis study performed by Wijarnpreecha *et al* (75), a quarter of all patients with COVID-19 had increased levels of liver enzymes and the extents of the increases were associated with the severity of the condition. Previous studies have also demonstrated that liver damage, which manifests as high levels of the enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase and total bilirubin, was observed in numerous patients with COVID-19, particularly in those who were critically ill. Typically, the levels peak in 8-9 days, whereas in patients only moderately affected by COVID-19, the increase in these indicators was barely perceptible (41,76,77). According to a retrospective study by

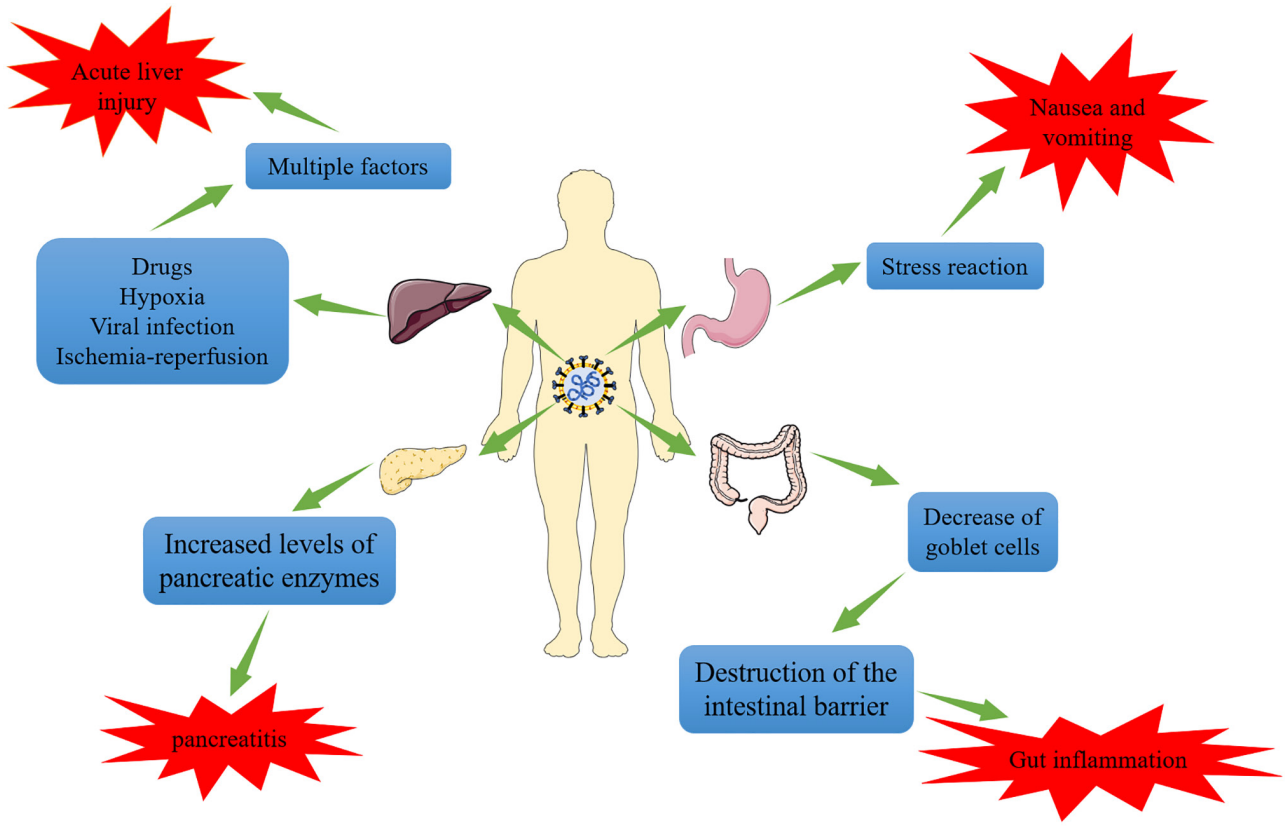

Figure 3. SARS-CoV-2 affects different organs of the digestive system.

Gomi *et al* (78) that included 216 subjects, patients with mild and moderate COVID-19 infection were more likely to have impaired liver function. In addition, it is possible to distinguish COVID-19 from other illnesses using elevated ALT and AST without alkaline phosphatase or γ-glutamyl transpeptidase. These studies, in addition to others, have found that it is the activation of hepatic infiltrating lymphocytes, which results in the rise of hepatic cytokine levels, that causes the indirect liver harm resulting from SARS-CoV-2 infection.

Types and multiple factors of liver injury induced by SARS-CoV-2. There is evidence that liver injury in patients with COVID-19 is not only caused by SARS-CoV-2, but also that SARS-CoV-2 infection is associated with drug-induced liver injury, secondary liver injury caused by hypoxia, viral liver injury and liver ischemia-reperfusion injury (Fig. 3) (73,79,80). Studies have indicated that SARS-CoV-2 may infect endothelial cells and cause diffuse dermatitis. Subsequently, microvascular dysfunction may lead to hypercoagulable states, tissue edema and organ ischemia (81,82). In addition, a pathological examination of one case of mortality resulting from COVID-19 revealed moderate microvascular steatosis and mild active inflammation of the hepatic lobule-portal vein region in the liver, which indicated that the liver injury of COVID-19 is frequently secondary damage caused by hypoxia (83). *In vitro* experiments also suggested that the expression and activity of ACE2 increased markedly in hepatocytes and cholangiocytes under hypoxic conditions (84). A retrospective analysis of 551 patients with COVID-19 in New York (USA) examined liver function during the time that they were hospitalized, and this analysis revealed that SARS-CoV-2 and other factors may have contributed to liver injury (85). According to the study by Chew *et al* (86), anomalies in liver tests linked with COVID-19 were predominantly found to be secondary to ischemia or drug-induced liver injury. As localized necrosis and liver neutrophil and Kupffer cell growth were observed in the autopsies of individuals who had died from COVID-19, Vishwajeet *et al* (87) concluded that SARS-CoV-2 and other factors probably contribute to liver damage in patients with COVID-19. Del Nonno *et al* (77) discovered from liver biopsies from three patients with coronavirus pneumonia and the autopsies of three individuals infected with SARS-CoV-2 that in an increase in the amount of iron in the liver. It is hypothesized that SARS-CoV-2 may elevate serum ferritin levels and cause damage to the liver. Multifactorial liver injury, however, has increased the difficulty of treating liver injury during the SARS-CoV-2 pandemic.

5. SARS-CoV-2-infected pancreatic symptoms and expression of associated proteins

Acute pancreatitis may be caused by SARS-CoV-2. Acute pancreatitis, and even abrupt onset diabetes with ketoacidosis, are common in adult patients with COVID-19, and numerous case reports over the course of the last two years have demonstrated that SARS-CoV-2 appears to be able to affect pancreatic (exocrine and endocrine) cells (88-90). Elevated lipase or amylase levels, or other potential explanations, may be eliminated when patients with COVID-19 experience abdominal pain and do not also have any underlying digestive

illnesses. In a case study involving three family members, the mother and daughter both experienced severe acute pancreatitis (thereby eliminating other potential causes of pancreatitis) and had increased levels of pancreatic lipase (91). In a different cohort study, 83 patients hospitalized with COVID-19 also exhibited increased lipase levels (>3 times the upper limit of normal), which were regarded as a separate indicator of severe illness (92). According to a retrospective cohort analysis, out of 48,012 hospitalized patients, 11,883 (24.75%) tested positive for SARS-CoV-2 at admission and 189 (point prevalence, 0.39%) met the diagnostic criteria for pancreatitis. Of these 189 individuals, 32 (17%) tested positive for SARS-CoV-2. The point prevalence of pancreatitis among COVID-19 hospitalized patients was found to be 0.27% (93). Children have also been reported to have acute pancreatitis. According to a case report by Samies *et al* (94), three children who were hospitalized for severe pancreatitis also tested positive for SARS-CoV-2 in blood tests. Although pancreatitis is not a direct result of SARS-CoV-2 infection, there appears to be an association between pancreatitis and the COVID-19 diagnostic timeframe. In addition, subjects who already have pancreatitis may be affected by SARS-CoV-2. In a multicenter investigation, Pandanaboyana *et al* (95) discovered that, among 1,777 individuals with acute pancreatitis, the incidences of severe pancreatitis, morbidity and death were significantly higher when SARS-CoV-2 infection was present.

SARS-CoV-2 may induce acute pancreatitis, or is a risk factor for acute pancreatitis, impacting its severity and prognosis, even though the connection between acute pancreatitis and SARS-CoV-2 infection is still being investigated.

Correlation between SARS-CoV-2, ACE2, TMPRSS2 and pancreatic infection

Pancreatic cell expression of SARS-CoV-2-associated proteins. It has been reported that ACE2 is expressed in pancreatic exocrine and endocrine tissues (96). Co-expression of ACE2 and TMPRSS2 in pancreatic duct and acinar cells has been demonstrated in numerous studies to be essential for effective viral entry into cells. Pancreatic damage is induced by viral attachment to ACE2 (59,97,98). In a previous study, researchers examined the expression of TMPRSS2 in 30 normal human tissues and discovered that the target organs of SARS-CoV-2 infection, namely the stomach, pancreas, lung, small intestine and salivary glands, had the highest levels of TMPRSS2 expression (99). This protease is considered to be the primary serine protease required for SARS-CoV-2 infection, since studies have revealed that TMPRSS2 is expressed at a relatively higher level in duct and acinar cells compared with β-cells (100). Previous studies also indicated that TMPRSS2 is primarily expressed in duct cells, although ACE2 and TMPRSS2 are only infrequently co-expressed in pancreatic duct and endocrine cells. ACE2 is primarily expressed in islets and exocrine tissue capillaries, including pericytes and a subset of duct cells (59,101). An *et al* (60) used immunohistochemistry staining to identify the expression levels of the ACE2 protein in the colon, stomach, liver and pancreas. This group discovered that islet cells were stained with ACE2 more strongly than acinar cells. In addition, it has also been previously demonstrated that SARS-CoV-2 is able to enter islet cells and infect them, resulting in diabetes, which may be attributed to the selective expression of the cell-surface receptors neuropilin-1 (NRP1) and transferrin receptor (TFRC) in cells (22). According to this study, the enhancement in the levels of NRP1 and TFRC may be a potential mechanism for the SARS-CoV-2 tropism of cells.

SARS-CoV-2-induced pancreatic injury-associated protein phenotypes. In the islets of six of 11 patients with COVID-19, Steenblock *et al* (102) employed RNA *in situ* hybridization to identify the RNA of the virus SARS-CoV-2. Another study (103) identified that SARS-CoV-2 may penetrate and infect induced pluripotent stem cell-derived pancreatic cells, including endocrine and exocrine cell types. This resulted in morphological abnormalities and impaired expression of critical markers, which corresponds to inflammatory features. In addition, the postmortem pancreas examination of a patient who died from SARS-CoV-2-19 revealed SARS-CoV-2-19 infection of the pancreatic tissue. Therefore, taken together, these findings suggest that pancreatic cells may be directly infected by SARS-CoV-2. Drug-induced pancreatic injury cannot be ruled out; however, certain patients with digestive issues who are treated in hospitals also have a history of medicine use (96). According to data from one study, ACE2 is not expressed in pancreatic acinar cells, but only in islets and duct cells (60). 83.6% (56/67) of the biopsy islet tissues were found to be labeled positively for ACE2, whereas 15.3% (20/131) of the biopsy pancreatic acinar cells were mildly stained for ACE2 (60). In addition, capillary endothelial cells on 98.5% (129/131) of the acinar cells stained positive for ACE2. It is possible that SARS-CoV-2 may spread through the duct system cells in pancreatic tissue, eventually causing islet destruction and aberrant blood glucose levels. Therefore, this phenotype would result from the unique expression of SARS-CoV-2 in the pancreas following infection. Consequently, SARS-CoV-2 infection, and the ensuing damage, may increase due to the elevated expression level of ACE2 in the pancreas (60). According to other studies, SARS-CoV-2 infection and pancreatic cell inflammation may activate pancreatic stellate cells and cause fibrosis, as seen in infected non-human primate and human pancreas (97). As a result, ACE2 expression is essential for pancreatic SARS-CoV-2 infection.

6. Conclusions

Investigations are ongoing to determine how SARS-CoV-2 infects the gastrointestinal tract. It is known that the SARS-CoV-2 S protein binds to ACE2 of the host cell, cleaves the S protein with the help of proteases such as TMPRSS2 and then forms fusion pores to release RNA into the cytoplasm. The virus is multiplied in infected cells, which sets off an inflammatory reaction. It is not possible to rule out the possibility of SARS-CoV-2 infection when diagnosing digestive illnesses in the setting of the outbreak. The risk of SARS-CoV-2 cannot be denied, regardless of whether it directly affects the target organ, causing severe pancreatitis, gastrointestinal hemorrhage or liver damage, or whether it indirectly aggravates these conditions. Secondly, it is important to take into account both drug and viral harm to target organs while treating digestive system disorders, and to minimize the combined effects of medications. It is possible to investigate how to lessen the injury

caused by SARS-CoV-2 to the digestive system by moderately decreasing the expression of ACE2 and TMPRSS2, or by creating medications that block the viral S protein. If there are further entry points into the digestive system, this will require extensive testing. Finally, the damage that SARS-CoV-2 causes to the digestive system should always be a concern.

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Availability of data and materials

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Authors' contributions

LZhe and LZha drafted the manuscript and contributed equally. YZ participated in the literature search and analysis of the data to be included in the review. JA and HJ were involved in the design of the study and assisted in the preparation of the figures and tables. GW and BT edited and revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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