Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 2025 22(1): 21-33. OPEN ACCESS

Gastrointestinal symptoms and complications in COVID-19.

Asma Almuhammadi

Biological Sciences Department, Faculty of Science, King Abdulaziz University, Jeddah, **Saudi Arabia**

***Correspondence:** amalmuhammadi@kau.edu.sa **Received: January 07, 2025, Revised: February 11, 2025, Accepted: February 15, 2025 e-Published: February 22, 2025**

COVID-19's common manifestations are fever and respiratory disorders; however, patients may also experience gastrointestinal tract (GI tract) symptoms. Nausea, diarrhoea, and abdominal pain can occur before or after respiratory symptoms. More severe complications, such as acute mesenteric ischemia/thrombosis, have been reported in the late stages of the disease. Although COVID-19 is primarily transmitted through respiratory secretions, evidence showed the presence of SARS-CoV-2 RNA in stool samples. This is likely due to the high expression of host receptor angiotensin converting- enzyme-2 (ACE-2) in both respiratory and gastrointestinal cells. The aim of this review was to examine the prevalence of gastrointestinal symptoms and complications in COVID-19 patients. A thorough systematic search across databases (Google Scholar, PubMed, and Clinical Trials) was conducted from January 1, 2020, to June 30, 2024, using search terms related to the effects of COVID-19 on the GI tract, and an extensive literature review was conducted. Gastrointestinal symptoms are a component of the progression of a COVID-19 infection, and it's crucial to take symptoms like diarrhoea, nausea, vomiting, and abdominal pain seriously. There are several factors that contribute to these symptoms antiviral drugs, and potential harm to the digestive system due to the inflammatory response caused by SARS-CoV-2. The detection of SARS-CoV-2 in faecal samples is vital for clinical practice, particularly for patients with unusual symptoms, and should be conducted as COVID-19 patients are discharged from the hospital to confirm viral clearance. COVID-19 patients with gastrointestinal symptoms often experience delayed diagnosis and treatment, making it necessary to examine stool samples in addition to respiratory samples.

Keywords: COVID-19; Gastrointestinal symptoms; GI Complications; Angiotensin converting enzyme 2 (ACE-2); SARS-CoV-2 RNA; Stool

INTRODUCTION

The World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a pandemic at the beginning of March 2020 (Johnson et al. 2020). An initial pneumonia outbreak in Wuhan, Hubei province, China, with an unknown aetiology, led to the start of this worldwide health emergency (Letchumanan et al. 2020). The Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV) gave the disease's causative virus the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wu et al. 2020). SARS-CoV-2, a single-stranded RNA virus with a positive sense first discovered in bat fields, belongs to the genus Beta coronavirus (Ma et al. 2020 and Muddasir Khan et al. 2021). A coronavirus that leads to severe acute respiratory syndrome (SARS-CoV) and a coronavirus that leads to Middle Eastern respiratory syndrome (MERS-CoV) share 79% of their genomic sequence identity. These commonalities may be the cause of some of the same clinical and epidemiological traits that SARS-CoV-2 and the other two viruses share (Xu et al. 2020).

The global impact of SARSCoV-2 was catastrophic, affecting over 250 million people and causing the deaths of 5,072,046. The virus's rapid spread caused new, more vicious variants of concern [illegible]. While it is known that the virus primarily targets respiratory epithelial cells and spreads through respiratory transmission, the specific target cells and organs of the virus have yet to be definitively identified (Xiao et al. 2020).

Angiotensin-converting enzyme 2 (ACE2) acts like a SARS-CoV-2 functional receptor and is essential to the virus's cellular entry (Wu et al. 2020). It is highlighted in multiple studies that SARS-CoV-2 exploits the ACE2 receptor to enter target cells (Song et al. 2020, Yao et al. 2020, Zhang et al. 2020). ACE2 is expressed in various tissues, including the nasopharynx, oral and nasal mucosa, small intestine, lung, spleen, colon, kidney, liver, and brain. Compared to the respiratory system, the GI tract, mainly the colon, exhibits high levels of ACE2 expression, making the digestive system susceptible to SARS-CoV-2 (Xu et al. 2020). The virus can enter host cells via the interaction between the human ACE2 receptor and the viral spike (S) protein. SARS-CoV-2

(Hoffmann et al. 2020).

As observed in the 2003 SARS and 2012 MERS outbreaks, the common signs of a COVID-19 infection include fever, runny nose, sore throat, cough, and difficulty breathing. However, some individuals may remain asymptomatic despite being infected with the virus.

Further to respiratory symptoms, patients often encounter GI problems; diarrhoea, nausea, vomiting, and stomach aches are the symptoms that were reported (Wu et al. 2020). The GI symptoms may occasionally be the first signs of COVID-19 (Song et al. 2020). SARS-CoV-2 RNA could be found in stool samples (Yao et al. 2020), anal swabs (Zhang et al. 2020), or rectal swabs (Xuet al. 2020) of COVID-19 patients, even after the virus cleared from the respiratory tract (Xiao et al. 2020). These findings indicate the possibility of SARS-CoV-2 faecal-oral transmission. It is important to understand these transmission manners for effective management and prevention of the infection.

The present review addresses the gastrointestinal manifestations of COVID-19. To conduct this review, databases (Google Scholar, PubMed, and Clinical Trials) were searched from January 1, 2020, to June 30, 2023, using search terms related to the effects of COVID-19 on the GI tract. Titles and abstracts were assessed for initial selection, followed by reading the full text. Reference lists of full-text articles were assessed to identify any other relevant studies.

SARS-Cov-2 RNA is found in stool samples of COVID-19 patients.

Regarding the detection of SARS-CoV-2 RNA in stool samples, the first confirmed COVID-19 case in the United States exhibited gastrointestinal symptoms (Wen et al. 2020). Real-time RT-PCR analysis was performed on stool samples, respiratory specimens (nasopharyngeal and oropharyngeal), and serum. SARS-CoV-2 RNA was detected in respiratory specimens (on illness days 4 and 7) and stool (on illness day 7) samples (Wen et al. 2020). The viral RNA was present in patients with and without diarrhoea (Cheung et al. 2020). In research involving patients examined for SARS-CoV-2 via rectal swab or stool PCR, 89% yielded positive analysis, despite 82.6% not displaying gastrointestinal symptoms (Yao et al. 2020). This observation aligns with another study, where 15.3% of COVID-19 cases had SARS-CoV-2 RNA found in stool samples at the time of the disease, irrespective of GI symptoms.

Although viral genetic material is not detectable in oral swabs, it was identified in blood or anal (Zhang et al. 2020). This continual positive detection of SARS-CoV-2 RNA in faeces suggested the release of viral particles from virus-infected cells in the GI tract. For example, in a study involving 73 COVID-19 patients in China, 39 patients (53.42%) exhibited SARS-CoV-2 RNA in stool, and among them, 17 cases (23.29%) still positive for SARS-CoV-2 RNA in stool for a period range from 1 to 12 days, even though respiratory samples tested negative (Xiao et al. 2020). A case study from an asymptomatic child in China reported that the viral RNA was detected for 26 days despite persistently negative respiratory specimens (Tang et al. 2020).

Altogether, these findings indicate that relying solely on conventional testing- utilizing RT-PCR of nasopharyngeal swabs- is not enough to determine the clearance or presence of the viral RNA. Crucially, molecular investigation of Covid patients from Wuhan found the presence of viral RNA in anal swabs and blood, with more anal swab positives than oral swab positives in a later stage of the disease. This suggests the potential transition from initially testing positive in oral samples during early infection to later testing positive in anal swabs (Zhang et al. 2020). The viral RNA is present in faeces, which raises the risk of faecal-oral transmission, particularly in asymptomatic people. Because of this concern, sewage, and wastewater were investigated to seek for the SARS-CoV-2 virus, evaluate the role of faecal-oral transmission in the community, and discover mitigating methods (Randazzo et al. 2020).

Individuals with COVID-19 can have SARS-CoV-2 in their intestines at early or advanced stages of the illness. In contrast, intestinal infections tend to be identified during the later stages for those infected with SARS-CoV and MERS-CoV (Liya et al. 2020). The discrepancy may be due to the cycle threshold (CT) level, where a lower CT level denotes a more enormous viral load, and a CT level below 40 is regarded as positive for SARS-CoV-2 RNA. For SARS-CoV-2 RNA, it has been showed that sputum (31.1), faeces (31.4), and pharyngeal (32.1) swabs had comparable mean CTs, while nasal swabs had the lowest mean CT at 24.3 (Wang et al. 2020).

Despite initially moderate symptoms at presentation in the first COVID-19 case in the US, oropharyngeal and nasopharyngeal specimens collected on day 4 of illness exhibited CT values of 21–22 and 18–20, respectively. By the seventh day of the illness, the CT level for nasopharyngeal specimens had grown to 23–24, while the CT levels for stool specimens ranged from 36–38. On days 12 and 11 of the illness, a trend toward diminishing viral levels was seen for oropharyngeal and nasopharyngeal tissues (Holshue et al. 2020). Moreover, a study revealed that SARS-CoV-2 RNA was positive in 48.1% of these samples, 70.3% persistently found in stool samples for an extended duration, spanning up to ≥33 days from illness onset. This contrasted with respiratory samples (Cheung et al. 2020). Therefore, the trend of CT values over the illness course and prolonged shedding of SARS-CoV-2 may reflect the transition from testing positive orally to testing positive anally.

Gastrointestinal symptoms in COVID-19 patients.

Typical manifestations of COVID-19 patients usually involve fever and respiratory problems. Nevertheless, GI

problems like diarrhoea, vomiting, and abdominal pain are commonly observed in those affected by the disease (Holshue et al. 2020). Individuals, whether adults or children, who test positive for COVID-19 can exhibit GI symptoms early in the disease course, emphasizing the importance of recognizing these manifestations. In a meta-analysis involving over 4,000 individuals who tested positive for COVID-19 across 60 researches in six countries [China (n = 53), Singapore (n = 2), South Korea (n=2), United States (n = 1), Vietnam (n = 1), and United Kingdom (n=1)], collective occurrence of GI tract symptoms were calculated to be 17.6% (Cheung et al. 2020). When examining specific GI symptoms, findings from 18 studies indicated the following prevalence rates: diarrhoea (12.5%), nausea/vomiting (10.2%), reduced appetite (26.8%), and abdominal pain (9.2%) (Cheung, Hung et al. 2020). This observation aligns with meta-analysis in adult COVID-19 cases, identifying a gastrointestinal symptom prevalence of 18% (Cheung et al. 2020, Akobeng et al. 2021).

A study conducted in Hubei province, China, involved 204 hospitalized individuals due to confirmed COVID-19. The study found that 103 patients (50.5%) experienced at least one GI symptom, such as vomiting (3.9%), diarrhoea (34%), and abdominal pain (1.9%) [30]. In another study conducted in Hong Kong with 59 confirmed COVID-19 patients, 15 individuals (25.4%) displayed gastrointestinal symptoms, such as diarrhoea (22%), vomiting (1.7%), and abdominal pain (11.9%). It was also observed that 9 patients (15.3%) had detectable viral RNA in stool samples (Cheung et al. 2020). Other research found varying frequencies of diarrhoea (2.0% -10.1%) and nausea and/or vomiting (1.0% -10.1%) (Liu et al. 2020, Sultan et al. 2020).

Children who test positive for COVID-19 may experience GI symptoms, although these symptoms tend to be less severe than those experienced by adults (Mantovani et al. 2021). According to research, around 25% of children who test positive for COVID-19 have at least one GI tract symptom, with diarrhoea being the most prevalent, followed by vomiting and abdominal pain (Akobeng et al. 2021). In 280 children who tested positive for COVID-19, a meta-analysis found that the incidence of GI tract symptoms overall was 22.8%, with diarrhoea, vomiting, and stomach pain having a combined prevalence of 12.4%, 10.3%, and 5.4%, respectively (Akobeng et al. 2021).

On the other hand, another meta-analysis of 2855 children showed a 4% prevalence of diarrhoea and no reported cases of abdominal pain (Mantovani, Rinaldi et al. 2021).

While the precise causes are yet unknown, acts on the gut and central nervous system (CNS) may work in concert to cause nausea and vomiting (Zhou et al. 2020). SARS-CoV-2 can access portal circulation after entering the GI tract and influence the vagus nerve via vascular or lymphatic pathways. Additionally, cytokine storms and the cytopathic effect of SARS-CoV-2 might excite central and peripheral (autonomic nervous system) pathways, resulting in nausea (with or without vomiting). When neuronal circuits are activated, stomach dysrhythmia may develop, which can cause vomiting (Chen et al. 2020). Also, COVID-19 patients commonly utilize antibiotics and antiviral medications, worsening their symptoms (Ye et al. 2021).

Several confounding factors, such as the use of enteral nutrition (tube feeds), antibiotics, antivirals, altered gut flora, hyperinflammatory response, secondary bacterial infections, and use of proton pump inhibitors (PPI), may cause diarrhoea in hospitalized COVID-19 patients (An, Song et al. 2021). It is unknown what exactly causes abdominal pain. Viral sickness during the prodromal can result in momentary stomach cramps and pain. Additionally, nausea with or without vomiting and other GI anorexia symptoms might coexist with abdominal pain. SARS-CoV-2 can cause cytopathic/inflammatory alterations after entering the GI tract, which may result in visceral pain. Due to the peritoneum's involvement, whether this discomfort is somatic or referred is unknown. Patients with COVID-19 have also experienced sporadic complaints of pancreatitis (Aloysius et al. 2020). Additionally, it has been discovered that the pancreatic tissue has significant levels of ACE-2 receptor expression, making it vulnerable to its cytopathic effects. It could result in fatty acid oxidation and pancreatic lipase leakage. Only a few postmortem findings of COVID-19 individuals without clinically apparent acute pancreatitis have persistent pancreatic damage (El-Kurdi et al. 2020). Hyperlipidaemia has been identified in these patients in several research fields (Barlass et al. 2020, McNabb-Baltar et al. 2020). Uncertainty exists regarding the cause of low levels of increased lipase, which could be viral pancreatic inflammation or gastroenteritis (Aloysius et al. 2020, McNabb-Baltar et al. 2020).

Some patients experienced gastrointestinal symptoms, liver damage, pancreatic damage, and acute mesenteric ischemia/thrombosis**.**

Acute mesenteric ischemia or thrombosis.

Nearly half of COVID-19 patients with bowel ischemia displayed macrovascular arterial/venous thrombosis. Retrospective mortality rates were 40% and 38.7%, respectively, for COVID-19 cases with radiologically apparent mesenteric thrombotic occlusion and ischemia in the gastrointestinal tract (Keshavarz et al. 2021). Thromboembolic complications in COVID-19 are a significant concern, given that coagulation dysfunction is a major contributor to the mortality of severe COVID-19 cases. It is essential for clinicians managing individuals with confirmed or suspected SARS-CoV-2 infection to closely monitor potential late complications, as delayed diagnosis could escalate morbidity and mortality risks (Cheung et al. 2020). Severe COVID-19 pneumonia cases that developed ischemic colitis were due to

hypercoagulability, coagulopathy that led to thromboembolic consequences, and the use of vasopressors in critically ill patients with hemodynamic compromise (Paul et al. 2021).

Notably, a man in his twenties who worked as a construction worker experienced left-sided colicky abdomen pain but no severe respiratory symptoms (Thuluva, Zhu et al. 2020). Retrospective cross-sectional research identified bowel-wall changes in CT scans of 31% of COVID-19 ICU patients, including bowel wall thickening and pneumatosis, suggesting late ischemia primarily caused by small-vessel arterial thrombosis (Bhayana, Som et al. 2020). Therefore, prompt assessment of abdominal vessels in COVID-19 cases with abdominal manifestations, mainly those with raised D-dimer levels, is crucial. Low-molecular-weight heparin early thrombosis therapy may substantially impact how well a patient responds to treatment. Researching alternative therapies, such as interleukin (IL)-1 receptor antagonists and anticomplementary medications, is necessary in addition to anticoagulants. Additionally, ongoing studies should result in the development of novel drugs based on a more profound comprehension of pathogenetic pathways (Manolis et al. 2021).

Liver injury.

Besides GI symptoms like diarrhoea, nausea, and vomiting, many COVID-19 patients exhibited liver damage (Wang et al. 2020). COVID-19 can cause liver damage through viral infection, drug-induced damage, cytokine storm inflammation, or pneumonia hypoxia. COVID-19, (Zhang et al. 2020). Most cases presented slightly raised values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) (Liu et al. 2020 and Pan et al. 2020). A study of 56 COVID-19 patients mentioned that 54% had elevated gamma-glutamyl transferase (γGT) (Zhang et al. 2020). (Pan et al. 2020) noted varying degrees of liver insufficiency in 43% of patients with elevated ALT and AST values, and 18% had elevated total bilirubin (TBil). (Sultan et al. 2020) reviewed thirty-four researches, finding abnormal AST in 15.0% of patients, abnormal ALT in 15.0%, and abnormal TBil in 16.7% of patients. In a review of 14 types of research, approximately 24%, 25%, and 13% of cases exhibited elevated ALT, AST, and TBil levels, respectively (Dong, Xiang et al. 2021). Pooled results from 12 studies involving 1878 patients showed that 27.4% had abnormal liver function, with 25.3% having high ALT, 25.4% high AST, and 8.8% high TBil (Wan, Wang et al. 2020). Systemic reviews highlighted that 6.1% and 21.1% of COVID-19 patients had elevated cholestatic liver enzymes, alkaline phosphatase (ALP), and γGT, respectively (Liu et al. 2021). A cohort study found that 23 out of 1099 individuals had hepatitis B that had already been present (Guan et al. 2020).

Different researchers found varying prevalence of hepatic damage in COVID-19, ranging from 15% to 78% (Kunutsor and Laukkanen 2020, Goel, Harmouch et al. 2021, Zarifian et al. 2021, Du et al. 2022). A meta-analysis showed that 4.6% of COVID-19 patients had a mild increase in ALP, 20.6% had a mild increase in ALT, and 22.8% had a mild increase in AST. Additionally, serum bilirubin was mildly reduced in 39.8% of patients (Zarifian et al. 2021). Studies have reported an association between abnormal liver function and disease severity or outcomes, emphasizing that liver injury correlated with a higher risk of admission, intensive care unit (ICU) admission, and/or mortality (Chen et al. 2020, Lin et al. 2020, Zhou et al. 2020). Given this relationship, measuring liver biochemical parameters can aid clinicians in assessing the prognosis of COVID-19 patients (Ye et al. 2021). Research revealed that many discharged COVID-19 cases still had abnormal liver function tests after a 2-month follow-up, especially those with liver illnesses like fatty liver, who were vulnerable to progress to a severe status (Song et al. 2021).

The liver injury mechanism is intricate and includes direct cytotoxicity from active SARS-CoV-2 viral replication, immune-mediated liver destruction caused by a severe inflammatory reaction, vascular alteration from coagulopathy, endothelin from right-sided heart failure, hypoxic alteration from drug-induced liver damage, respiratory loss, and worsening of underlying hepatic illness (Wan et al. 2020). Further research is needed to answer critical questions, such as the specific molecular processes dysregulated by infection and primary factors—hypoxia, direct cytopathic actions, or cytokine storm—in liver injury.

Pancreatic damage.

Research showed that the SARS-CoV-2 virus receptor, ACE2, is present in the pancreas (Fignani et al. 2020 and, Liu et al. 2020). However, studying the scope and specificity of pancreatic damage caused by COVID-19 received little attention (Liu et al. 2020). Fortunately, an increasing number of research have shed light on pancreatic damage in individuals with COVID-19, capturing the attention of researchers and clinicians (Aloysius et al. 2020, Hadi et al. 2020, Kumaran et al. 2020, Suchman et al. 2021). Clinical data has illustrated that pancreatic injury was present in 17% of severe and 1%-2% of non-severe COVID-19 cases (Liu et al. 2020). SARS-CoV-2-induced pancreatic damage could worsen the clinical condition of patients, potentially increasing mortality rates (Akarsu et al. 2022). High ACE2 expression has been found in pancreatic microvasculature's pericytes and insulin-forming β-cells (Fignani et al. 2020). SARS-CoV-2 infection, particularly in diabetic patients, leads, in some cases, to pancreatic injuries or acute pancreatitis. Therefore, it is recommended that COVID-19 cases, particularly those with pre-existing diabetes, monitor their pancreatic enzyme levels (Fignani et al. 2020). Aloysius *et al.*

reported acute pancreatitis associated with SARS-CoV-2 patients, emphasizing the importance of testing serum amylase and lipase enzyme levels in all COVID-19 patients, including those without symptoms (Aloysius et al. 2020). However, other data found no correlation between serum amylase or lipase levels and the severity or mortality of COVID-19. They observed hyperamylasaemia in 33% of patients and elevated lipase in 24.1% of patients with COVID-19 (Bansal et al. 2020). Furthermore, Children with COVID-19 may develop pancreatitis (Suchman et al. 2021). Further research is needed to determine if raised amylase and lipase values are linked to a severe form of this viral infection.

Pathogenesis of COVID-19.

Gastrointestinal symptoms are frequently observed after contracting COVID-19, and this occurrence appears to be linked to various factors. These include the ACE-2 human host receptor [OBJ], the composition of the intestine's microflora, the administration of antibiotics and antiviral drugs [OBJ], and the inflammatory response—directly or indirectly caused by the damage inflicted by SARS-CoV-2 on the GI tract (Wang et al. 2020) (Figure 1).

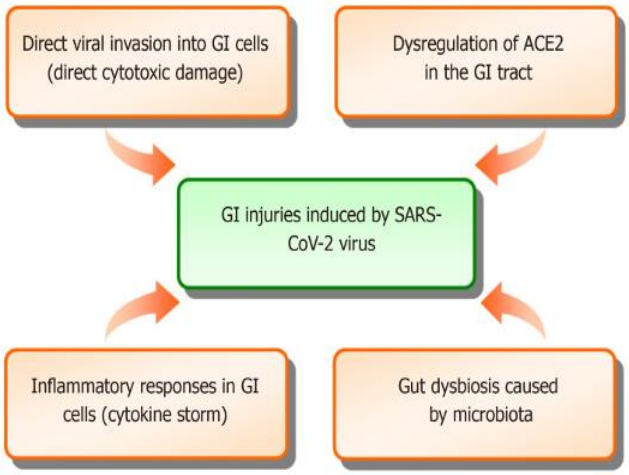

Figure 1: Possibility of a GI tract manifestation following SARS-CoV-2 infection. ACE2: Angiotensin-converting enzyme 2; GI: Gastrointestinal; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Direct invasion into GI tract cells.

First, the spike protein of SARS-CoV-2 combines with the ACE-2 receptor on the surface of host cells to enter host cells (Thye et al. 2021). In Type II, alveolar cells are in the lungs, and goblet cells are in the nasal mucosa (Thye et al. 2021). ACE-2 is excessively expressed in duodenal, gastric, and rectal epithelium glandular cells. Notably, the distribution of ACE-2 varies significantly throughout the GI tract, with infrequent ACE-2 staining in oesophageal mucosa, potentially due to lower expression in squamous epithelial cells compared to glandular epithelial cells (Xiao et al. 2020). Another study identified differentiated small intestine epithelial cells' luminal surfaces as the main location of ACE-2 expression, with lower levels in crypt cells and the colon (Hashimoto et al. 2012). Considering that SARS-CoV-2's infectivity hinges on ACE-2 receptor binding affinity, the abundance of these receptors suggests the potential for virus infection and replication within the GI tract (Wong et al. 2020) (Figure 2).

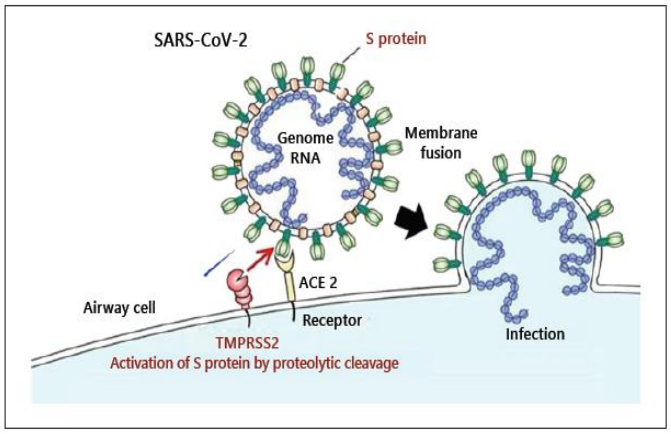

Figure 2: Viral entry dynamics into human cells. The type II transmembrane serine protease (TMPRSS2) attaches to and cleaves the ACE 2 receptor while spiking proteins on the surface of the SARS-CoV-2 bind to ACE 2 receptors on the target cell's surface. Spike protein is consequently activated. C-cleaved ACE 2 and activated spike protein facilitate viral entrance, which causes infection(Hunt, East et al. 2021).

Moreover, ACE-2 plays a role in modulating intestinal inflammation, raising the possibility that ACE-2 function disruption by SARS-CoV-2 could lead to diarrhoea (Cheung et al. 2020). ACE-2 regulates intestinal amino acid balance, influences antimicrobial peptide expression, and is linked to GI tract microbial ecology (Hashimoto et al. 2012). Inadequate quantities of amino acids cause diarrhoea and intestinal irritation. There has been suspicion that COVID-19 and the gut microbiota may be related due to ACE-2 mutants' lower expression of antimicrobial peptides and changes in gut microbial components (Gao et al. 2020).

Dysregulation of ACE2 in the intestinal epithelium.

The virus binds to ACE2, reducing its levels and affecting intestinal functions (Vaduganathan et al. 2020). The dysregulation of sodium-dependent glucose transporter (SGLT) in intestinal epithelium mediated by ACE2 is potentially linked to increased mortality in COVID-19 cases with diabetes mellitus (Kumar et al. 2020). Additionally, although the direct cytotoxic damage caused by SARS-CoV-2 in the liver is unknown, ACE2's

function in regulating the renin-angiotensin-aldosterone pathway may be essential in developing chronic liver disorders (Galanopoulos et al. 2020). Additionally, ACE2 regulates amino acid transport, particularly tryptophan, to keep the balance of amino acids in the intestine without the assistance of the renin-angiotensin-aldosterone system (Galanopoulos et al. 2020 and Zhong et al. 2020). Consequently, SARS-CoV-2 directly infiltrates the GI tract by binding to ACE2 or CD147, replicating in host cells and influencing pertinent signaling pathways, ultimately leading to gastrointestinal dysfunction.

Inflammatory responses in GI tract cells

SARS-CoV-2 can indirectly or directly damage the GI tract through inflammatory reactions. Infections caused by SARS-CoV-2 can incite an "inflammatory storm," wherein hyperactive cytokines, inflammatory responses, and immune imbalances damage the intestines, potentially leading to diarrhoea (Wu et al. 2020). The growing body of evidence demonstrating SARS-CoV-2 RNA presence in stool samples of COVID-19 cases may indicate that the virus directly harms the intestinal mucosa, triggering digestive symptoms like diarrhoea.

SARS-CoV-2 enters mucous membranes (oral cavity, nose) via the functional receptor ACE-2 (Aziz et al. 2020). Although it can enter the gastric lumen by salivary secretions, it is vulnerable to side effects of the stomach's acidic environment. Virus survival is strongly impacted by a pH of 2 (Ramachandran et al. 2022). Patients with hypochlorhydria are more likely to contract a virus because a more enormous viral load enters the small intestine (Dibner 2021). Varied GI tract tissues have varied concentrations of ACE-2 receptors, with ileal enterocytes having the highest expression (Zhang et al. 2020). SARS-CoV-2 can continue its viral production and multiplication once it enters enterocytes, resulting in a cytopathic effect (as shown by the intracellular staining of the viral nucleocapsid) (Xiao et al. 2020). Through the portal circulation, the virus can travel to other organs from this point. These modifications might lead to the presence of viral RNA in the faeces. It must be determined whether viral RNA in faeces indicates cytopathic changes or is only an incidental finding.

Gut dysbiosis caused by microbiota.

The human gut harbours an extensive and diverse population of gut microbiota. For instance, the colon hosts the highest microbial abundance among gastrointestinal sites, constituting about 33% of the total bacterial cells in the human body (Dibner 2021). The GI tract microbiota performs crucial functions, such as supporting the host's metabolism, safeguarding the host against harmful pathogens by colonizing the habitat, inducing immunoregulatory responses, and orchestrating the development and maturation of the body's immune system (Barlass et al. 2020).

Changes in gut flora can be attributed to factors like disease, concurrent infections, the utilization of antimicrobial agents, and elevated proinflammatory mediators due to viral-induced inflammation (Mitsuyama et al. 2020). Disruptions in the flora of the respiratory tract might affect the GI tract through immune control, and changes in the functions and compositions of the GI tract microbiota may impact the respiratory tract via the typical mucosal immune system. The gut-lung axis effect is the name for this reciprocal phenomenon that likely elucidates the onset of digestive symptoms following COVID-19 infection (Barlass et al. 2020).

Research indicates that COVID-19 infection can alter the gut microbiome, leading to an increase in harmful bacteria and imbalance (Segal et al. 2020, Shinu et al. 2020, Penninger et al. 2021). There are five possible reasons why GI tract flora is altered in COVID-19 cases. First, the viral infection causing increased production of proinflammatory cytokines may change the flora in the gut (Xiao et al. 2020). This is supported by the research indicating that inflammatory markers and cytokines were elevated in SARS-CoV-2 patients (Ramachandran, Gajendran et al. 2022). Second, different antimicrobial drugs (antibiotics, antivirals) can alter the composition of the gut flora, making people more susceptible to GI tract adverse effects (Wei et al. 2020). Thirdly, since COVID-19 individuals frequently present with respiratory symptoms, changes in lung flora may also affect gut flora (Dhar and Mohanty 2020). Growing evidence points to this "gut-lung" axis as a potential contributor to GI tract symptoms in people with respiratory signs (Dhar and Mohanty 2020). The fourth factor is that flora changes can affect the percentage of harmful organisms that cause diseases like *Clostridium difficile* (Sandhu et al. 2020). Fifth, using enteral nourishment, such as tube feedings, can alter the gut flora. Due to a lack of data on whether any of the mechanisms individually or collectively contribute to the start of GI tract symptoms in COVID-19 patients, they are all only theorized.

Tryptophan absorption is linked to neurological irregularities, as it serves as a precursor for synthesizing 5-hydroxytryptophan (5HT) in the brain (Shinu et al. 2020). Tryptophan also regulates antimicrobial peptide values that impact gut microbiota composition, making individuals more susceptible to intestinal inflammation and epithelial malfunction (Mitsuyama et al. 2020). Consequently, this viral infection disrupts the equilibrium of the gut-brain axis via alterations in intestinal microbiota (Shinu et al. 2020). Nevertheless, more research is necessary to determine whether this dysbiosis is specific to SARS-CoV-2 infection or a result of severe illness.

Probiotics are being considered as a new therapy or addition to treatment for severe COVID-19 infections. China's National Health Commission and National Administration of Traditional Chinese Medicine have recommended using probiotics to manage the virus, as stated in their guidance (version 5) (Mak et al. 2020). This recommendation maintains the balance of intestinal

microecology and inhibits secondary bacterial infections. The fact that healthcare professionals and the Chinese government trust this approach highlights gut microbiota's critical role in COVID-19 infections (Gao et al. 2020).

GI tract conditions increasing the risk of COVID-19.

The impact of SARS-CoV-2 on chronic liver diseases is still being investigated. According to Guan et al. (2020) those with pre-existing hepatitis B may experience a severe form of COVID-19, highlighting the importance of further research into the replication of SARS-CoV-2 and its potential to cause persistent liver damage in patients with chronic HBV infection (Guan et al. 2020). Additionally, it is crucial to conduct screenings for SARS-CoV-2 and/or active COVID-19 in potential hepatic donors before transplantation to prevent transmitting the virus to the recipient. Early research indicates that individuals with cancer or liver cirrhosis are more vulnerable to SARS-CoV-2, likely due to compromised immune status (Mao et al. 2020, Zhang et al. 2020).

Lack of information makes it difficult to say whether the processes alone or in combination cause the onset of GI tract symptoms in COVID-19 patients. Patients with pre-existing GI issues like inflammatory bowel disease (IBD), malabsorption syndromes, etc., contracting SARS-CoV-2 are at risk of developing severe GI tract symptoms (Thabane and Marshall 2009, Garg et al. 2020). Although the gut flora of these populations has permanently changed, IBD and inflammatory conditions have higher levels of ACE-2 expression (Garg et al. 2020). Individuals with COVID-19 who experience ongoing diarrhoea have been found to have higher levels of faecal calprotectin, a sign of intestinal inflammation (Effenberger et al. 2020). It is crucial to investigate whether these individuals' symptoms could worsen due to this enhanced expression. Further research is needed to fully understand the effects of SARS-CoV-2-induced liver injury. Information on other chronic liver illnesses, such as non-alcoholic fatty liver disorder, alcohol-related liver disorder, and autoimmune hepatitis, is scant. Investigating the severity and frequency of these patients' consequences, such as secondary infections, hepatic encephalopathy, and liver failure, is also crucial (Galanopoulos et al. 2020).

Long-lasting COVID-19 and the GI tract.

Long-lasting COVID-19 syndrome, also known as post-COVID syndrome, is more than just fatigue and shortness of breath. Symptoms such as headaches, brain fog, and ringing in the ears have been reported, and recently, more patients have complained of gastrointestinal symptoms. Among 147 patients with no previous gastrointestinal problems, 16% reported new gastrointestinal symptoms about 100 days after COVID-19 infection. The most common symptoms included abdominal pain: 7.5%, Constipation: 6.8%, and diarrhoea and vomiting: 4.1% (Blackett et al. 2022). In another review of post-acute COVID-19 symptoms, diarrhoea ranked among the top 10 complaints, affecting about 6% of individuals. Persistent symptoms include vomiting, nausea, reduced appetite, and abdominal pain (Aiyegbusi et al. 2021).

Similarly, researchers found that long-term COVID-19 patients had conditions known as *gut-brain interaction disorders*. Symptoms include heartburn, difficulty swallowing, irritable bowel syndrome, constipation, diarrhoea, bloating, and incontinence (Ebrahim et al. 2022). These enduring manifestations might be attributed to the continued replication of the virus in the GI tract, given the prolonged presence of SARS-CoV-2 in faecal samples even after respiratory tests turn negative (Xiao et al. 2020and Xu et al. 2020). COVID-19 also disrupts the gut microbiome, although its implications for long-term symptoms need further investigation (Donati et al. 2020). Twenty-eight publications, comprising case reports and case series, were chosen for a comprehensive review of qualitative information concerning gastrointestinal issues linked to COVID-19 (Silva-Neto et al. 2021). The research findings covered a range of complications such as haemorrhagic, thrombotic, ischemic, perforation issues, acute pancreatitis, and pneumatosis intestinalis (Barrett et al. 2020, Gadiparth et al. 2020, Hadi et al. 2020, Karki et al. 2020, Kumaran et al. 2020, Liu et al. 2020, Martin et al. 2020, Meini et al. 2020, Melazzini et al. 2020, Nahas et al. 2020, Rodriguez et al. 2020, Schepis, et al. 2020, Wang, Zheng et al. 2020, Mauro, De Grazia et al. 2021).

In a prospective, multi-centre study, Marasco et al. examined the prevalence of gut symptoms and post-COVID-19 disorders of gut-brain interaction after hospitalization to evaluate the effect of COVID-19 on the GI tract. The study involved 614 patients with COVID-19 and 269 control participants without COVID-19 diagnoses. Researchers assessed patients at the time of hospital admission and following hospitalization at 1, 6, and 12 months. Compared with the control group, COVID-19 patients showed a higher prevalence of GI symptoms (59.3% vs 39.7%). Patients with COVID-19 also showed higher rates of irritable bowel syndrome (IBS) according to Rome IV criteria: 0.5% versus 3.2%) (Marasco, Cremon et al. 2022). The pathophysiology of post-COVID-19 IBS is incompletely understood and most likely caused by several factors. Enterocyte invasion by the COVID-19 virus leads to a series of inflammatory responses, leading to intestinal dysbiosis. Also, the high risk of post-COVID-19 diabetes can lead to GI dysmotility. Altered visceral hypersensitivity and autonomic dysfunction also play an important role in post-COVID-19 GI dysfunction, which can lead to a variety of symptoms.

potential contributor to GI tract bleeding is coagulopathy, a common condition in COVID-19 patients due to the hypercoagulable state linked to the disease's pathophysiology. Consequently, the treatment approach involves administering preventive anticoagulation, potentially heightening the risk of GI tract bleeding associated with the disease. Indications of typical

thromboembolic occurrences in COVID-19 may arise from the viral infiltration into endothelial cells. This infiltration triggers an immune response and lymphocytic infiltration, culminating in conditions like leukocytoclastic vasculitis and heightened growth of small blood vessels with thickening and narrowing. These vascular changes could potentially cause organ damage.

CONCLUSION.

COVID-19 patients with gastrointestinal symptoms often experience delayed diagnosis and treatment, making it necessary to examine stool samples in addition to respiratory samples. Public education programs on the gastrointestinal symptoms of COVID-19 are crucial for early detection and intervention. Future research should focus on ACE2 and abnormal immune responses and the relationship between COVID-19 and chronic gastrointestinal disorder.

Supplementary materials

The supplementary material / supporting for this article can be found online and downloaded at: https://www.isisn.org/article/

Author contributions

Conceptualization, A.A. writing original manuscript, review and editing the final format. The author has read and agreed to the published version of the manuscript.

Funding statement

Not applicable

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The author declares no conflict of interest.

REFERENCES

Aiyegbusi, O. L., S. E. Hughes, G. Turner, S. C. Rivera, C. McMullan, J. S. Chandan, S. Haroon, G. Price, E. H. Davies and K. Niranthara kumar (2021). "Symptoms, complications and management of long COVID: a review." Journal of the Royal Society of Medicine 114(9): 428-442.

Akarsu, C., M. Karabulut, H. Aydin, N. A. Sahbaz, A. C. Dural, D. Yegul, K. D. Peker, S. Ferahman, S. Bulut and T. Dönmez (2022). "Association between acute pancreatitis and COVID-19: could pancreatitis be the missing piece of the puzzle about increased mortality rates?" Journal of Investigative Surgery 35(1): 119-125.

Akobeng, A. K., C. Grafton-Clarke, I. Abdelgadir, E. Twum-Barimah and M. Gordon (2021). "Gastrointestinal manifestations of COVID-19 in children: a systematic review and meta-analysis." Frontline gastroenterology 12(4): 332-337.

Aloysius, M. M., A. Thatti, A. Gupta, N. Sharma, P. Bansal and H. Goyal (2020). "COVID-19 presenting as acute pancreatitis." Pancreatology 20(5): 1026-1027.

An, Y.-W., S. Song, W.-X. Li, Y.-X. Chen, X.-P. Hu, J. Zhao, Z.-W. Li, G.-Y. Jiang, C. Wang and J.-C. Wang (2021). "Liver function recovery of COVID-19 patients after discharge, a follow-up study." International journal of medical sciences 18(1): 176.

Aziz, M., A. Perisetti, W. M. Lee-Smith, M. Gajendran, P. Bansal and H. Goyal (2020). "Taste changes (dysgeusia) in COVID-19: a systematic review and meta-analysis." Gastroenterology 159(3): 1132.

Bansal, P., S. L. Margekar, V. Suman, R. Sud, S. Meena, A. K. Sharma, S. Y. Islam, A. Gurtoo, A. Agrawal and G. S. Pangtey (2020). "Pancreatic injury in COVID-19 patients." J. Assoc. Physicians India 68: 58-60.

Barlass, U., B. Wiliams, K. Dhana, D. Adnan, S. R. Khan, M. Mahdavinia and F. Bishehsari (2020). "Marked elevation of lipase in COVID-19 disease: a cohort study." Clinical and translational gastroenterology 11(7).

Barrett, L. F., K. B. Lo, S. R. Stanek and J. W. Walter (2020). "Self-limited gastrointestinal bleeding in

COVID-19." Clinics and Research in Hepatology and Gastroenterology 44(4): e77-e80.

Bhayana, R., A. Som, M. D. Li, D. E. Carey, M. A. Anderson, M. A. Blake, O. Catalano, M. S. Gee, P. F. Hahn and M. Harisinghani (2020). "Abdominal imaging findings in COVID-19: preliminary observations." Radiology 297(1): E207-E215.

Blackett, J. W., J. Li, D. Jodorkovsky and D. E. Freedberg (2022). "Prevalence and risk factors for gastrointestinal symptoms after recovery from COVID-19." Neurogastroenterol Motil 34(3): e14251.

Chen, T., D. Wu, H. Chen, W. Yan, D. Yang, G. Chen, K. Ma, D. Xu, H. Yu and H. Wang (2020). "Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study." bmj 368.

Cheung, K. S., I. F. N. Hung, P. P. Y. Chan, K. C. Lung, E. Tso, R. Liu, Y. Y. Ng, M. Y. Chu, T. W. H. Chung, A. R. Tam, C. C. Y. Yip, K. H. Leung, A. Y. Fung, R. R. Zhang, Y. Lin, H. M. Cheng, A. J. X. Zhang, K. K. W. To, K. H. Chan, ... and W. K. Leung (2020). "Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis." Gastroenterology 159(1): 81-95.

Cheung, S., J. C. Quiwa, A. Pillai, C. Onwu, Z. J. Tharayil and R. Gupta (2020). "Superior mesenteric artery thrombosis and acute intestinal ischemia as a consequence of COVID-19 infection." The American journal of case reports 21: e925753-925751.

Dhar, D. and A. Mohanty (2020). "Gut microbiota and Covid-19-possible link and implications." Virus research 285: 198018.

Dibner, J. (2021). "Fecal-oral transmission of COVID-19: Could hypochlorhydria play a role?" Journal of Medical Virology 93(1): 166.

Donati Zeppa, S., D. Agostini, G. Piccoli, V. Stocchi and P. Sestili (2020). "Gut Microbiota Status in COVID-19: An Unrecognized Player?" Front Cell Infect Microbiol 10: 576551.

Dong, Z.-y., B.-J. Xiang, M. Jiang, M.-j. Sun and C. Dai (2021). "The prevalence of gastrointestinal symptoms, abnormal liver function, digestive system disease and liver disease in COVID-19 infection: a systematic review and meta-analysis." Journal of clinical gastroenterology 55(1): 67.

Du, M., S. Yang, M. Liu and J. Liu (2022). "COVID-19 and liver dysfunction: Epidemiology, association and potential mechanisms." Clin Res Hepatol Gastroenterol 46(2): 101793.

Ebrahim Nakhli, R., A. Shanker, I. Sarosiek, J. Boschman, K. Espino, S. Sigaroodi, I. Al Bayati, S. Elhanafi, A. Sadeghi, J. Sarosiek, M. J. Zuckerman, A. Rezaie, R. W. McCallum, M. J. Schmulson, A. Bashashati and M. Bashashati (2022). "Gastrointestinal symptoms and the severity of COVID-19: Disorders of gut-brain interaction are an outcome." Neurogastroenterol Motil 34(9): e14368.

Effenberger, M., F. Grabherr, L. Mayr, J. Schwaerzler, M. Nairz, M. Seifert, R. Hilbe, S. Seiwald, S. Scholl-Buergi and G. Fritsche (2020). "Faecal calprotectin indicates intestinal inflammation in COVID-19." Gut 69(8): 1543-1544.

El-Kurdi, B., B. Khatua, C. Rood, C. Snozek, R. Cartin-Ceba, V. P. Singh, S. Kostenko, S. Trivedi, C. Folmes and K. M. Dykhouse (2020). "Mortality from coronavirus disease 2019 increases with unsaturated fat and may be reduced by early calcium and albumin supplementation." Gastroenterology 159(3): 1015-1018. e1014.

Fignani, D., G. Licata, N. Brusco, L. Nigi, G. E. Grieco, L. Marselli, L. Overbergh, C. Gysemans, M. L. Colli and P. Marchetti (2020). "SARS-CoV-2 receptor angiotensin I-converting enzyme type 2 (ACE2) is expressed in human pancreatic β-cells and in the human pancreas microvasculature." Frontiers in endocrinology 11: 876.

Gadiparthi, C., A. Perisetti, H. Sayana, B. Tharian, S. Inamdar and A. Korman (2020). "Gastrointestinal bleeding in patients with severe SARS-CoV-2." The American journal of gastroenterology.

Galanopoulos, M., A. Doukatas and M. Gazouli (2020). "Origin and genomic characteristics of SARS-CoV-2 and its interaction with angiotensin converting enzyme type 2 receptors, focusing on the gastrointestinal tract." World journal of gastroenterology 26(41): 6335.

Galanopoulos, M., F. Gkeros, A. Doukatas, G. Karianakis, C. Pontas, N. Tsoukalas, N. Viazis, C. Liatsos and G. J. Mantzaris (2020). "COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract." World J Gastroenterol 26(31): 4579-4588.

Gao, Q. Y., Y. X. Chen and J. Y. Fang (2020). "2019 Novel coronavirus infection and gastrointestinal tract." Journal of digestive diseases 21(3): 125.

Garg, M., S. G. Royce, C. Tikellis, C. Shallue, D. Batu, E. Velkoska, L. M. Burrell, S. K. Patel, L. Beswick and A. Jackson (2020). "Imbalance of the renin–angiotensin system may contribute to inflammation and fibrosis in IBD: a novel therapeutic target?" Gut 69(5): 841-851.

Goel, H., F. Harmouch, K. Garg, P. Saraiya, T. Daly, A. Kumar and J. T. Hippen (2021). "The liver in COVID-19: prevalence, patterns, predictors, and impact on outcomes of liver test abnormalities." Eur J Gastroenterol Hepatol 33(1S Suppl 1): e274-e281.

Guan, W. J., Z. Y. Ni, Y. Hu, W. H. Liang, C. Q. Ou, J. X. He, L. Liu, H. Shan, C. L. Lei, D. S. C. Hui, B. Du, L. J. Li, G. Zeng, K. Y. Yuen, R. C. Chen, C. L. Tang, T. Wang, P. Y. Chen, J. Xiang, ... and N. S. Zhong (2020). "Clinical Characteristics of Coronavirus Disease 2019 in China." N Engl J Med 382(18):

1708-1720.

Hadi, A., M. Werge, K. T. Kristiansen, U. G. Pedersen, J. G. Karstensen, S. Novovic and L. L. Gluud (2020). "Coronavirus disease-19 (COVID-19) associated with severe acute pancreatitis: case report on three family members." Pancreatology 20(4): 665-667.

Hashimoto, T., T. Perlot, A. Rehman, J. Trichereau, H. Ishiguro, M. Paolino, V. Sigl, T. Hanada, R. Hanada and S. Lipinski (2012). "ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation." Nature 487(7408): 477-481.

Hoffmann, M., H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N. H. Wu, A. Nitsche, M. A. Müller, C. Drosten and S. Pöhlmann (2020). "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor." Cell 181(2): 271-280.e278.

Holshue, M. L., C. DeBolt, S. Lindquist, K. H. Lofy, J. Wiesman, H. Bruce, C. Spitters, K. Ericson, S. Wilkerson and A. Tural (2020). "First case of 2019 novel coronavirus in the United States." New England journal of medicine 382(10): 929-936.

Hunt, R. H., J. E. East, A. Lanas, P. Malfertheiner, J. Satsangi, C. Scarpignato and G. J. Webb (2021). "COVID-19 and Gastrointestinal Disease: Implications for the Gastroenterologist." Dig Dis 39(2): 119-139.

Johnson, D., S. E. C. Ren, H. D. Johnson and V. Letchumanan (2020). "COVID-19: Are Malaysians embracing or suffering the new normality?" Progress In Microbes & Molecular Biology 3(1).

Karki, S., S. B. Rawal, S. Malla, J. Rayamajhi and B. B. Thapa (2020). "A case report on spontaneous hemoperitoneum in COVID-19 patient." International Journal of Surgery Case Reports 75: 211-213.

Keshavarz, P., F. Rafiee, H. Kavandi, S. Goudarzi, F. Heidari and A. Gholamrezanezhad (2021). "Ischemic gastrointestinal complications of COVID-19: a systematic review on imaging presentation." Clinical imaging 73: 86-95.

Kumar, A., M. A. Faiq, V. Pareek, K. Raza, R. K. Narayan, P. Prasoon, P. Kumar, M. Kulandhasamy, C. Kumari and K. Kant (2020). "Relevance of SARS-CoV-2 related factors ACE2 and TMPRSS2 expressions in gastrointestinal tissue with pathogenesis of digestive symptoms, diabetes-associated mortality, and disease recurrence in COVID-19 patients." Medical Hypotheses 144: 110271.

Kumaran, N. K., B. K. Karmakar and O. M. Taylor (2020). "Coronavirus disease-19 (COVID-19) associated with acute necrotising pancreatitis (ANP)." BMJ Case Reports CP 13(9): e237903.

Kunutsor, S. K. and J. A. Laukkanen (2020). "Hepatic manifestations and complications of COVID-19: A systematic review and meta-analysis." J Infect 81(3): e72-e74.

Letchumanan, V., N.-S. Ab Mutalib, B.-H. Goh and L.-H. Lee (2020). "Novel coronavirus 2019-nCoV: Could this virus become a possible global pandemic." Progress In Microbes & Molecular Biology 3(1).

Lin, L., X. Jiang, Z. Zhang, S. Huang, Z. Zhang, Z. Fang, Z. Gu, L. Gao, H. Shi and L. Mai (2020). "Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection." Gut 69(6): 997-1001.

Liu, C., Z.-C. Jiang, C.-X. Shao, H.-G. Zhang, H.-M. Yue, Z.-H. Chen, B. Ma, W. Liu, H. Huang and J. Yang (2020). "Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study." Zhonghua Gan Zang Bing Za Zhi: 107-111.

Liu, F., X. Long, B. Zhang, W. Zhang, X. Chen and Z. Zhang (2020). "ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection." Clinical Gastroenterology and Hepatology 18(9): 2128-2130. e2122.

Liu, R., L. Zhao, X. Cheng, H. Han, C. Li, D. Li, A. Liu, G. Gao, F. Zhou and F. Liu (2021). "Clinical characteristics of COVID-19 patients with hepatitis B virus infection—a retrospective study." Liver International 41(4): 720-730.

Liya, G., W. Yuguang, L. Jian, Y. Huaiping, H. Xue, H. Jianwei, M. Jiaju, L. Youran, M. Chen and J. Yiqing (2020). "Studies on viral pneumonia related to novel coronavirus SARS-CoV-2, SARS-CoV, and MERS-CoV: a literature review." Apmis 128(6): 423-432.

Ma, C., Y. Cong and H. Zhang (2020). "COVID-19 and the Digestive System." Am J Gastroenterol 115(7): 1003-1006.

Mak, J. W., F. K. Chan and S. C. Ng (2020). "Probiotics and COVID-19: one size does not fit all." The lancet Gastroenterology & hepatology 5(7): 644-645.

Manolis, A. S., T. A. Manolis, A. A. Manolis, D. Papatheou and H. Melita (2021). "COVID-19 infection: viral macro-and micro-vascular coagulopathy and thromboembolism/prophylactic and therapeutic management." Journal of cardiovascular pharmacology and therapeutics 26(1): 12-24.

Mantovani, A., E. Rinaldi, C. Zusi, G. Beatrice, M. D. Saccomani and A. Dalbeni (2021). "Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis." Pediatric research 89(4): 733-737.

Mao, R., J. Liang, J. Shen, S. Ghosh, L. R. Zhu, H. Yang, K. C. Wu and M. H. Chen (2020). "Implications of COVID-19 for patients with pre-existing digestive diseases." Lancet Gastroenterol Hepatol 5(5): 425-427.

Marasco, G., C. Cremon, M. R. Barbaro, G. Cacciari, F. Falangone, A. Kagramanova, D. Bordin, V. Drug, E. Miftode, P. Fusaroli, S. Y. Mohamed, C. Ricci, M. Bellini, M. M. Rahman, L. Melcarne, J. Santos, B. Lobo, S. Bor, S. Yapali, ... and G. Barbara (2022). "Post COVID-19 irritable bowel syndrome." Gut.

Martin, T. A., D. W. Wan, K. Hajifathalian, S. Tewani, S. L. Shah, A. Mehta, A. Kaplan, G. Ghosh, A. J. Choi and T. I. Krisko (2020). "Gastrointestinal bleeding in patients with coronavirus disease 2019: a matched case-control study." The American journal of gastroenterology.

Mauro, A., F. De Grazia, M. V. Lenti, R. Penagini, R. Frego, S. Ardizzone, E. Savarino, F. Radaelli, M. Bosani and S. Orlando (2021). "Upper gastrointestinal bleeding in COVID-19 inpatients: Incidence and management in a multicenter experience from Northern Italy." Clinics and Research in Hepatology and Gastroenterology 45(3): 101521.

McNabb-Baltar, J., D. X. Jin, A. S. Grover, W. D. Redd, J. C. Zhou, K. E. Hathorn, T. R. McCarty, A. N. Bazarbashi, L. Shen and W. W. Chan (2020). "Lipase elevation in patients with COVID-19." The American journal of gastroenterology.

Meini, S., C. Zini, M. T. Passaleva, A. Frullini, F. Fusco, R. Carpi and F. Piani (2020). "Pneumatosis intestinalis in COVID-19." BMJ Open Gastroenterology 7(1): e000434.

Melazzini, F., M. V. Lenti, A. Mauro, F. De Grazia and A. Di Sabatino (2020). "Peptic ulcer disease as a common cause of bleeding in patients with coronavirus disease 2019." The American journal of gastroenterology.

Mitsuyama, K., K. Tsuruta, H. Takedatsu, S. Yoshioka, M. Morita, M. Niwa and S. Matsumoto (2020). "Clinical features and pathogenic mechanisms of gastrointestinal injury in COVID-19." Journal of Clinical Medicine 9(11): 3630.

Muddasir Khan , S. H. S., Fawad Khalid , Ihteshamul Haq ,, S. S. K. Abdullah , Ibrar Ahmad , Sabih Ullah , Muhammad Salman, M. Munir Malik , Zeeshan Nasar , Muhammad Salman and Sohail and A. Jan. (2021). "Highly-sensitive and rapid detection of COVID-19 in wastewater: a comprehensive review based on graphene field effect transistor biosensor." Bioscience Research 18(SI-1): 01-09.

Nahas, s. c., j. d. d. meira-júnior, l. f. sobrado, m. sorbello, v. segatelli, e. abdala, u. ribeiro-júnior and i. cecconello (2020). "Perfuração Intestinal Causada Pelo Covid-19." ABCD. Arquivos Brasileiros de Cirurgia Digestiva (São Paulo) 33.

Pan, L., M. Mu, P. Yang, Y. Sun, R. Wang, J. Yan, P. Li, B. Hu, J. Wang and C. Hu (2020). "Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study." The American journal of gastroenterology 115.

Paul, T., A. R. Joy, H. A. R. S. Alsoub and J. V. Parambil (2021). "Case report: ischemic colitis in severe COVID-19 pneumonia: an unforeseen gastrointestinal complication." The American Journal of Tropical Medicine and Hygiene 104(1): 63.

Penninger, J. M., M. B. Grant and J. J. Sung (2021). "The role of angiotensin converting enzyme 2 in modulating gut microbiota, intestinal inflammation, and coronavirus infection." Gastroenterology 160(1): 39-46.

Ramachandran, P., M. Gajendran, A. Perisetti, K. O. Elkholy, A. Chakraborti, G. Lippi and H. Goyal (2022). "Red blood cell distribution width in hospitalized COVID-19 patients." Frontiers in Medicine 8: 582403.

Ramachandran, P., A. Perisetti, M. Gajendran, F. Jean-Louis, P. Bansal, A. K. Dwivedi and H. Goyal (2022). "Pre-hospitalization proton pump inhibitor use and clinical outcomes in COVID-19." European Journal of Gastroenterology & Hepatology 34(2): 137-141.

Randazzo, W., P. Truchado, E. Cuevas-Ferrando, P. Simón, A. Allende and G. Sánchez (2020). "SARS-CoV-2 RNA in wastewater anticipated COVID-19 occurrence in a low prevalence area." Water research 181: 115942.

Rodriguez-Nakamura, R. M., M. Gonzalez-Calatayud and A. R. M. Martinez (2020). "Acute mesenteric thrombosis in two patients with COVID-19. Two cases report and literature review." International Journal of Surgery Case Reports 76: 409-414.

Sandhu, A., G. Tillotson, J. Polistico, H. Salimnia, M. Cranis, J. Moshos, L. Cullen, L. Jabbo, L. Diebel and T. Chopra (2020). "Clostridioides difficile in COVID-19 patients, Detroit, Michigan, USA, March–April 2020." Emerging Infectious Diseases 26(9): 2272.

Schepis, T., A. Larghi, A. Papa, L. Miele, F. Panzuto, L. De Biase, B. Annibale, P. Cattani and G. L. Rapaccini (2020). "SARS-CoV2 RNA detection in a pancreatic pseudocyst sample." Pancreatology 20(5): 1011-1012.

Segal, J. P., J. W. Mak, B. H. Mullish, J. L. Alexander, S. C. Ng and J. R. Marchesi (2020). "The gut microbiome: an under-recognized contributor to the COVID-19 pandemic?" Therapeutic Advances in Gastroenterology 13: 1756284820974914.

Shinu, P., M. A. Morsy, P. K. Deb, A. B. Nair, M. Goyal, J. Shah and S. Kotta (2020). "SARS CoV-2 organotropism associated pathogenic relationship of gut-brain axis and illness." Frontiers in Molecular Biosciences 7: 606779.

Silva-Neto, W. D. B., C. Quirese, E. G. H. D. Moura, F. F. Coelho and P. Herman (2021). "A Queda Da Pressão Portal Após Desvascularização Esofagogástrica E Esplenectomia Influencia A Variação Do Calibre Das Varizes E As Taxas De Ressangramento Na Esquistossomose No Seguimento Em Longo Prazo?" ABCD. Arquivos Brasileiros de Cirurgia Digestiva (São Paulo) 34.

Song, Y., P. Liu, X. L. Shi, Y. L. Chu, J. Zhang, J. Xia, X. Z. Gao, T. Qu and M. Y. Wang (2020). "SARS-CoV-2 induced diarrhoea as onset symptom in patient

with COVID-19." Gut 69(6): 1143-1144.

Suchman, K., K. L. Raphael, Y. Liu, D. Wee, A. J. Trindade and N. C.-R. Consortium (2021). "Acute pancreatitis in children hospitalized with COVID-19." Pancreatology 21(1): 31-33.

Sultan, S., J. K. Lim, O. Altayar, P. Davitkov, J. D. Feuerstein, S. M. Siddique, Y. Falck-Ytter and H. B. El-Serag (2020). "AGA rapid recommendations for gastrointestinal procedures during the COVID-19 pandemic." Gastroenterology 159(2): 739-758. e734.

Tang, A., Z. D. Tong, H. L. Wang, Y. X. Dai, K. F. Li, J. N. Liu, W. J. Wu, C. Yuan, M. L. Yu, P. Li and J. B. Yan (2020). "Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China." Emerg Infect Dis 26(6): 1337-1339.

Thabane, M. and J. K. Marshall (2009). "Post-infectious irritable bowel syndrome." World journal of gastroenterology: WJG 15(29): 3591.

Thuluva, S. K., H. Zhu, M. M. Tan, S. Gupta, K. Y. Yeong, S. T. C. Wah, L. Lin and E. S. Yap (2020). "A 29-year-old male construction worker from India who presented with left-sided abdominal pain due to isolated superior mesenteric vein thrombosis associated with SARS-CoV-2 infection." The American Journal of Case Reports 21: e926785-926781.

Thye, A. Y.-K., J. W.-F. Law, P. Pusparajah, V. Letchumanan, K.-G. Chan and L.-H. Lee (2021). "Emerging SARS-CoV-2 variants of concern (VOCs): an impending global crisis." Biomedicines 9(10): 1303.

Vaduganathan, M., O. Vardeny, T. Michel, J. J. McMurray, M. A. Pfeffer and S. D. Solomon (2020). "Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19." New England Journal of Medicine 382(17): 1653-1659.

Wan, J., X. Wang, S. Su, Y. Zhang, Y. Jin, Y. Shi, K. Wu and J. Liang (2020). "Digestive symptoms and liver injury in patients with coronavirus disease 2019 (COVID-19): A systematic review with meta-analysis." JGH Open 4(6): 1047-1058.

Wang, F., S. Zheng, C. Zheng and X. Sun (2020). "Attaching clinical significance to COVID-19-associated diarrhea." Life Sciences 260: 118312.

Wang, M., W. Yan, W. Qi, D. Wu, L. Zhu, W. Li, X. Wang, K. Ma, M. Ni and D. Xu (2020). "Clinical characteristics and risk factors of liver injury in COVID-19: a retrospective cohort study from Wuhan, China." Hepatology international 14: 723-732.

Wang, W., Y. Xu, R. Gao, R. Lu, K. Han, G. Wu and W. Tan (2020). "Detection of SARS-CoV-2 in Different Types of Clinical Specimens." Jama 323(18): 1843-1844.

Wei, X.-S., X. Wang, Y.-R. Niu, L.-L. Ye, W.-B. Peng, Z.-H. Wang, W.-B. Yang, B.-H. Yang, J.-C. Zhang and W.-L. Ma (2020). "Diarrhea is associated with prolonged symptoms and viral carriage in corona virus disease 2019." Clinical Gastroenterology and Hepatology 18(8): 1753-1759. e1752.

Wen, Q., J. Yang and T. Luo (2020). "First Case of Covid-19 in the United States." N Engl J Med 382(21): e53.

Wong, S. H., R. N. Lui and J. J. Sung (2020). "Covid-19 and the digestive system." Journal of gastroenterology and hepatology 35(5): 744-748.

Wu, J., J. Liu, X. Zhao, C. Liu, W. Wang, D. Wang, W. Xu, C. Zhang, J. Yu and B. Jiang (2020). "Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu Province: a multicenter descriptive study." Clinical infectious diseases 71(15): 706-712.

Wu, Y., W. Ho, Y. Huang, D. Y. Jin, S. Li, S. L. Liu, X. Liu, J. Qiu, Y. Sang, Q. Wang, K. Y. Yuen and Z. M. Zheng (2020). "SARS-CoV-2 is an appropriate name for the new coronavirus." Lancet 395(10228): 949-950.

Xiao, F., M. Tang, X. Zheng, Y. Liu, X. Li and H. Shan (2020). "Evidence for Gastrointestinal Infection of SARS-CoV-2." Gastroenterology 158(6): 1831-1833.e1833.

Xu, Y., X. Li, B. Zhu, H. Liang, C. Fang, Y. Gong, Q. Guo, X. Sun, D. Zhao and J. Shen (2020). "Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding." Nature medicine 26(4): 502-505.

Xu, Z., L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu and L. Zhu (2020). "Pathological findings of COVID-19 associated with acute respiratory distress syndrome." The Lancet respiratory medicine 8(4): 420-422.

Yao, N., S. Wang, J. Lian, Y. Sun, G. Zhang, W. Kang and W. Kang (2020). "Clinical characteristics and influencing factors of patients with novel coronavirus pneumonia combined with liver injury in Shaanxi region." Zhonghua Gan Zang Bing Za Zhi: 234-239.

Yao, N., S. N. Wang, J. Q. Lian, Y. T. Sun, G. F. Zhang, W. Z. Kang and W. Kang (2020). "[Clinical characteristics and influencing factors of patients with novel coronavirus pneumonia combined with liver injury in Shaanxi region]." Zhonghua Gan Zang Bing Za Zhi 28(3): 234-239.

Ye, L., B. Chen, Y. Wang, Y. Yang, J. Zeng, G. Deng, Y. Deng and F. Zeng (2021). "Prognostic value of liver biochemical parameters for COVID-19 mortality." Annals of hepatology 21: 100279.

Zarifian, A., M. Zamiri Bidary, S. Arekhi, M. Rafiee, H. Gholamalizadeh, A. Amiriani, M. S. Ghaderi, M. Khadem-Rezaiyan, M. Amini and A. Ganji (2021). "Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis." Journal of Medical Virology 93(1): 336-350.

Zhang, C., L. Shi and F. S. Wang (2020). "Liver injury in

COVID-19: management and challenges." Lancet Gastroenterol Hepatol 5(5): 428-430.

Zhang, H., Z. Kang, H. Gong, D. Xu, J. Wang, Z. Li, Z. Li, X. Cui, J. Xiao and J. Zhan (2020). "Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process." Gut 69(6): 1010-1018.

Zhang, W., R. H. Du, B. Li, X. S. Zheng, X. L. Yang, B. Hu, Y. Y. Wang, G. F. Xiao, B. Yan, Z. L. Shi and P. Zhou (2020). "Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes." Emerg Microbes Infect 9(1): 386-389.

Zhong, P., J. Xu, D. Yang, Y. Shen, L. Wang, Y. Feng, C. Du, Y. Song, C. Wu and X. Hu (2020). "COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms." Signal transduction and targeted therapy 5(1): 256.

Zhou, F., T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song and X. Gu (2020). "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." The lancet 395(10229): 1054-1062.