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COVID-19 Gastrointestinal Tract Affection: An Updated Review

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Abstract

Although it was initially believed that the coronavirus disease 2019 (COVID-19) only attacked the respiratory system, reports over time demonstrated that this disease could attack the gastrointestinal tract (GIT) as well. The predominant presenting symptoms in patients infected with COVID-19 were gastrointestinal (GI), resulting in GI pathological changes. While clinicians' concerns are mostly related to respiratory system manifestations, GI symptoms should be monitored and managed appropriately.

This review summarizes the essential information about COVID-19 GIT infection in terms of pathogenesis, major pathological changes, microbiological bases of infection, the possibility of feco-oral transmission, the severity of associated symptoms, the major radiological findings, the impact on GI surgery, the role of therapeutic agents in induction or magnification of GI symptoms, and a pitfall on the nutritional supplementation in COVID-19 patients.

Keywords: Affection, Investigations, Pathogenesis, Presentation, SARS-2

1. Background

The link between the coronavirus disease 2019 (COVID-19) and gastrointestinal (GI) involvement is greatly underestimated, as the bulk of symptoms and signs are respiratory in nature. Most COVID-19 patients representing gastrointestinal tract (GIT) symptoms, such as nausea/vomiting, diarrhea, and abdominal discomfort, have been recently reported by the World Health Organization and China, in partnership (1, 2).

The first case of positive coronavirus RNA in stool was reported in the United States of America (3). Patients with severe COVID-19 infection were reported to have a high rate of GI affection, including symptoms and complications (39%-73.8%) (4).

The present study discusses the pathophysiology, pathological characteristics, the most common clinical picture, possible associated investigations, as well as radiological and surgical associations of GIT COVID-19 patients.

2. Microbiological Characteristics of COVID-19 and the New Mutation

Coronaviruses are the members of the order Nidovirales, the family Coronaviridae, and the subfamily Coronavirinae. The Coronavirinae subfamily contains four well-known species: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus (α-, β-, γ-, and δ-CoV). Seven coronaviruses have been identified in humans: 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus responsible for the Middle East Respiratory Syndrome), SARS-CoV (the beta coronavirus responsible for the Severe Acute Respiratory Syndrome), and SARS-CoV-2(5).

The SARS-CoV-2 shares a genome sequence identity of 79% with SARS-CoV and 50% with MERS-CoV (6). Its genome structure is similar to that of other beta coronaviruses. From 5′ to 3′, the six functional open reading frames (ORFs) are as follows: replicate (ORF1a/ORF1b), spike (S), envelope (E),

membrane (M), and nucleocapsid (N) (N). Additionally, seven putative ORFs encoding accessory proteins are found close to the structural genes (7).

Because SARS-CoV-2 is an RNA virus, it has a higher mutation rate than that of DNA viruses (8). Changes to the surface protein's amino acids can have a major impact on the function of the virus and its interactions with neutralizing antibodies. Despite the recent discovery of SARS-CoV-2, mutations in the Spike (S) protein gene continue to be reported (9). This modification may have resulted in a conformational change in the S protein, increasing its infectivity (10).

A study conducted in the US discovered that the US SARS-CoV-2 has developed into four sub-strains based on the extraction of 7,823 single nucleotide polymorphism profiles from genome isolates. Based on the genotyping results, the top eight missense mutations include 14408C>T-(P323L), 23403A>G-(D614G), 25563G>T-(Q57H), 1059C>T-(T85I), 28144T>C-(L84S), 17858A>G-(Y541C), 17747C>T-(P504L), and 27964C>T-(S24L) (11) Three concurrent mutations, 17747C>T-(P504L), 17858A>G-(Y541C), and 28144T>C, tend to fade out whereas the remaining five mutations can enhance SARS-CoV-2 infectivity.

Several SARS-CoV-2 lineages have evolved after 2019, resulting in the divergence of a large group of SARS-CoV-2 variants known as "variants of concern" (VOCs) (12).

In late 2020, a number of polymorphisms became prominent. The N501Y mutation has been associated with increased S affinity for the cellular angiotensin-converting enzyme 2 (ACE2) receptor in emerging VOCs alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and omicron (B.1.1.529) variants (13).

Several additional mutations have also been discovered along the edges of the furin cleavage site. The H655Y substitution observed in the gamma (P.1) and omicron (B.1.1.529) forms is a case in point. This mutation was linked to alterations in antigenicity by allowing human monoclonal antibodies to escape (13).

3. Pathophysiology of Gastrointestinal Tract Affection by COVID-19

Numerous factors contribute to the etiology of GIT manifestations associated with COVID-19. Due to viral alteration of intestinal permeability and loss of integrity of the gut mucosa, gut microbes can activate innate and adaptive immune cells, which release proinflammatory cytokines into the systemic circulation resulting in systemic inflammation (14).

The exact pathophysiological mechanisms underlying the associated COVID-19 disorder are unknown. There is a mechanism that serves multiple purposes as follows: SARS-CoV-2 extreme acute respiratory syndrome attaches to ACE2 and enters the lung, resulting in the production of angiotensin II (ANG II) and a decrease in angiotensin levels. The ANG II facilitates cytokine release and increases receptor cells of type 9 gut-homing chemokine receptor C-C chemokine receptor type 9 (CCR9) CD4 T cells when combined with the angiotensin type-1 receptor. C-C Motif Chemokine Ligand 25 promotes the recruitment of CCR9 CD4 T cells in the small intestine, referred to as the gut-lung axis. The altered flora then promotes Th17 cell polarization, and the Interleukin 17A (IL-17A) recruits neutrophils. Bacteria and cytokines infiltrate the bloodstream and affect lung inflammation (15). Kopel et al. discovered that the viral host receptor ACE2 was predominantly expressed in the cytoplasm of gastric epithelial and the alveolar epithelial cells. The esophagus and glandular epithelia both express ACE2 (16).

The interaction of SARS-CoV-2 with ACE2 reduces the number of receptors available in the GIT. It also reduces tryptophan intake and eventually destroys the intestinal flora's stable equilibrium, one of the main causes of GI symptoms, including diarrhea (17). If the intestinal flora is compromised and the intestinal mucosa is weakened, a virus may use this mechanism to initiate infection (18).

The incidence of liver affection in COVID-19 patients ranged from 39.6% to 42.4%, with the most common manifestations being elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, as well as hypoalbuminemia (19).

The pathogenesis of liver affection reported in COVID-19-infected patients is unknown; however, numerous hypotheses have been advanced to account for it. Among these theories is that the virus can directly injure hepatocytes, similar to how the SARS virus was discovered in low titer hepatocytes. However, SARS-CoV-2 has not been detected in hepatocytes yet (20).

Another theory is that cytokine storm, a type of immune-mediated inflammation, plays a role while immune dysfunction, including lymphopenia, may play a role (21).

Additionally, drug-induced liver injury is possible, particularly in critically ill patients receiving multiple medications. The medications frequently prescribed to treat COVID-19 are hydroxychloroquine sulfate or chloroquine phosphate, ritonavir/lopinavir, oseltamivir, and ribavirin, which are metabolized in the liver and can cause hepatotoxicity.

Finally, hypoxia caused by pneumonia and hypotension may play a role in liver injuries caused by COVID-19 (22).

4. Pathological Features of Gastrointestinal Tract Affected Organs

Table 1 summarizes pathological changes observed in various parts of the GIT in COVID-19 patients (1).

Table 1. Summary of pathological changes in different gastrointestinal tract parts

Gastrointestinal Tract Part	Main pathological changes	Reference
Esophagus	- Occasional lymphocytic infiltration in esophageal squamous epithelium without significant damage to the mucosa	(25)
Stomach	- Abundant lymphocytic and plasma cells infiltration with interstitial edema in the lamina propria without apparent mucosal epithelial damage	(25)
Duodenum	- Numerous lymphocytic and plasma cells infiltration in addition to interstitial edema in the lamina propria without apparent mucosal epitheli necrosis	(25)
Rectum	- The mucosa showed no significant necrosis, but many lymphocytes and plasma cells infiltrated the lamina propria with interstitial edema.	(25)
Liver	- The liver tissue showed moderate micro vesicular steatosis and mild lobular activity.	(25)

The first autopsy for SARS-CoV-2 was performed on an 85-year-old man. This macroscopic examination revealed small intestine stenosis and segmental dilatation (23). Necrosis, degeneration, and varying degrees of mucosal shedding were also observed (24). Pathological examinations of patients revealed lymphocytic infiltration of the Squamous epithelium of the esophagus. There was extensive lymphocytic and plasma cell infiltration with interstitial edema in the stomach, duodenum, and rectum lamina propria without apparent mucosal epithelial injury (25). Bhayana et al. reported the presence of four cases of ischemic enteritis. Two of them had complete necrosis while the remaining two had a diffuse ischemic injury with multifocal, marked submucosal edema and empty spaces consistent with pneumatosis. There were few fibrin thrombi in submucosal arterioles beneath the necrotic mucosa (26). Remmelink et al. described one case of ischemic enteritis that occurred during the autopsies of 17 COVID-19 patients.

Pathological examinations of the liver from 22 post-mortem biopsies revealed sinusoidal congestion and red blood cell extravasation into the Disse space in all cases. Only a few cases revealed necrosis and infiltration of hepatocytes. Additionally, in cases without comorbidity, macrovascular and microvacuolar steatosis were observed (27). Tian et al. found mild sinusoidal dilatation, mild lobular lymphocytic infiltration, and patchy hepatic necrosis in the periportal and centrilobular areas of four post-mortem COVID-19 patients using liver core biopsy (28).

Schaller et al. examined 10 SARS-CoV-2-positive patients post-mortem. The primary histological features of fibrosis and periportal lymphoplasmacytic infiltration of the liver were fibrosis and periportal lymphoplasmacytic infiltration (29). Elsoukkary et al. described the post-mortem findings in nine cases of steatosis and six cases of mild portal lymphocytic infiltration in the liver (30). Lymphocytic infiltration is extensive in the esophageal squamous epithelium. Additionally, lymphocytic and plasma cell infiltration with interstitial edema was observed in the duodenum and rectum lamina propria without apparent mucosal epithelial damage (25).

5. COVID-19-related Symptoms and Signs and a Possible Explanation for the Difference in COVID-19 between Children and Adults

Anorexia, nausea, vomiting, abdominal pain, and diarrhea have been reported as GI symptoms (31). Patients with GI symptoms have a delayed diagnosis and hospital admission (9.0 vs. 7.3 days), as well as a higher incidence of acute renal insufficiency (9.3% vs. 3.1%) (32, 33). Notably, the presence of GI symptoms was associated with disease severity and its prevalence in critically ill patients (31).

Lin et al. previously investigated 95 SARS-CoV-2 cases and found that 58 (61.1%) developed GI symptoms, with diarrhea being the most prevalent symptom (24.2%). Other GI symptoms included anorexia (17.9%), nausea (17.9%), vomiting (4.2%), and elevated liver enzymes (32.6%). Additionally, endoscopy was performed on six SARS-CoV-2 positive cases; one severe case had esophageal ulcers, as well as erosions, and two severe cases had specimens from the esophagus, stomach, duodenum, and rectum positive for SARS-CoV-2 RNA (34).

Numerous GI complications have been reported in critically ill COVID-19 patients, including mesenteric ischemia, GI bleeding, pancreatitis, acute acalculous cholecystitis, Ogilvie syndrome, and severe ileus. This may be explained by the high expression of ACE2 receptors along the gut epithelial lining (35).

Pancreatic injury has also been reported in patients infected with COVID-19, more frequently in severe critical cases (36). Gubatan et al. discovered a 7.8% prevalence of COVID-19 infection in patients who had previously experienced pancreatitis, compared to a 2.8% prevalence in the general population (37). Acute pancreatitis can be precipitated by various factors, including the virus's direct cytotoxic effect, a cytokine storm resulting in multi-organ failure, and medications, such as corticosteroids and NSAIDs, which are frequently used to treat COVID-19 infection (38).

Numerous types of research have established that the liver is one of the most affected organs by COVID-19 infection, second only to the lung (39). Numerous

studies have indicated that the proportion of infected patients with abnormal serum transaminases levels ranged between 14.8% and 53.1%. A slight increase was observed in the serum level of bilirubin (40) (41). Additionally, Zhang et al. (42) reported an increase in gamma-glutamyl transferase and alkaline phosphatase.

In comparison with elderly patients, pediatric patients with COVID-19 typically have milder symptoms (43). Pediatrics may have a lower level of ACE2 expression (44). Aging results in a shift in the distribution of T cell subsets from naive to core memory, effector, and effector memory T cells, as well as a loss of co-stimulatory molecules, such as CD27 and CD28, which increase susceptibility to infection (45).

Physical intercourse can also affect ACE2 expression since the ACE2 gene is located on the X chromosome (46). Men have higher ACE2 levels than women (47). This may contribute to disparities in prevalence and mortality rates between men and women in the adult and pediatric populations (48).

6. COVID-19 Gastrointestinal Tract-Infection-Related Investigations

Table 2 summarizes laboratory tests that may be used to diagnose and monitor SARS-CoV-2 GIT manifestations while Table 3 summarizes the major blood laboratory findings.

SARS-CoV-2 RNA shedding in the stool occurs in 54% of patients. It has a significant advantage over nasopharyngeal swabs in that it appears earlier in stool, persists longer, and is concomitant with the decrease of inflammation peak (14). There is growing evidence of persistent viral shedding in infected people's stool seven days after pharyngeal swab negativity. Such evidence raises concerns about feco-oral transmission and the safety of patient discharge following nasopharyngeal swab

Table 2. Gastrointestinal tract-related investigations finding

Investigation name	Main finding	Reference
SARS-CoV-2 RNA shedding in stool	- SARS-CoV-2 RNA shedding in stool appears in 54% of patients. - It has a major advantage over nasopharyngeal swab as it appears earlier in stool and remains for an extended period as it may reach COVID-19 second phase. It is concomitant with the decrease of inflammation peak.	(14)
Fecal calprotectin	-Fecal calprotectin in COVID-19 patients indicates the urgency for mechanical ventilation. -It can distinguish between mild and severe SARS-CoV-2 induced colitis. -In addition, fecal calprotectin showed a significant positive correlation with IL-6, TNF-β, SAA, and IL-17A ($P<0.05$).	(51) (52) (88)
Serum calprotectin	-Serum calprotectin levels could predict COVID-19 severity, suggesting that neutrophils have a big role in maintaining inflammation and respiratory compromise in COVID-19.	(88)
Expression of ACE2 receptors	-The ACE2 receptors alteration in response to viral entry can lead to an imbalance in the intestinal microbiota and inflammation. -RAS-ACE2 system imbalance increases the chance for severe outcomes in COVID-19 patients due to exacerbation of inflammation. -Single-cell RNA sequencing is the technique used for its demonstration.	(89) (90)
Transmembrane protease serine-type 2	-TMPRSS2 is responsible for cleaving the spike of major SARS-CoV-2 antigens, thus facilitating its entry. -It is a potential therapeutic target for coronavirus infections.	(91)
Blood proteomic risk score (blood PRS)	-Its increase in the score can predict the severity of COVID-19, especially in old patients.	(92)
Vitamin A, D, C, and E, in addition to Zn	-Low levels of vitamin A, D, C, and E, in addition to trace element Zn, are associated with low immunity and an increased risk of COVID-19	(14)

ACE2: angiotensin-converting enzyme 2
TMPRSS2: Transmembrane protease serine-type 2
SARS-Cov-2: Coronavirus responsible for the severe acute respiratory syndrome
IL17A: Interleukin-17A

Table 3. Blood-related investigations finding

Investigation name	Main finding	Reference
CBC	Lymphopenia Leucocytosis or leukopenia	(93)
CRP	Increased even in early stage	(93)
IL6	Very high increase in cytokine storm on the sixth day of symptoms	(94)
Ferritin	Increased indicating inflammation	(94)
LDH	Increased with organ failure	(93)
D-dimer	Increased in correlation with vascular coagulopathy	(95)
Procalcitonin	Increase in case of accompanying sepsis	(94)

CBC: Complete Blood Count
CRP: C-Reactive Protein
IL6: Interleukin-6
LDH: Lactate Dehydrogenase

negativity. Additionally, viral RNA has been detected in the vicinity of patients' toilet seats, doorknobs, and bathroom tabs, even in the absence of diarrhea (1).

Thrombotic complications associated with COVID-19 may be a factor in the etiology of ischemia-induced colitis (49). Increased fecal calprotectin levels suggest that neutrophils migrate to the GI mucosa during intestinal inflammation, including that caused by systemic inflammation. The fecal calprotectin test is frequently used to differentiate between inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis) and irritable bowel syndrome (50).

Calprotectin was found to be capable of discriminating between mild and severe forms of the disease and predicting the need for mechanical ventilation and mortality in SARS-CoV-2 induced colitis (51) (52). Additionally, serum calprotectin levels were found to be strongly associated with the current COVID infection and severity prediction, implying that neutrophils are active agents of inflammation and respiratory compromise in COVID-19 (53). Fecal calprotectin correlated positively with Interleukin-6 (IL-6), TNF-, SAA, and IL-17A (P 0.05) (54).

The ACE2 receptors are expressed ubiquitously throughout the body cells, including the GIT and the respiratory system (55). As it is a major route of SARS-CoV-2 infection, its alteration in response to viral infection can result in an imbalance of the intestinal microbiota and inflammation. Due to the exacerbation of inflammation, this RAS-ACE2 system imbalance increases the risk of severe outcomes in COVID-19 patients. The technique used is single-cell RNA sequencing (14).

The encoded protein is TMPRSS2, which contains a type II transmembrane domain, a receptor class A domain, a cysteine-rich scavenger receptor domain, and a protease domain. It is a type II transmembrane serine protease that cleaves the coronavirus S protein, facilitating viral cell entry and proteolytic cleavage of the viral E; therefore, it may be a target for viral therapy.

Proteomics is the study of the entire set of proteins that an organism or system produces or modifies. Proteomic analysis increased the number of identified proteins by addressing all aspects of protein identification (composition, structure, and activity). It plays a significant role in functional genomics. It also improved patients' chances of receiving an accurate diagnosis, a favorable prognosis, and tailored therapy for various diseases, including cancer, transplantation rejection, and infectious disease. Proteomic technologies included surface-enhanced laser desorption ionization-time of flight–mass spectrometry (SELDI-TOF-MS), chromatography on protein chip arrays, and mass spectrometry, which enables the identification of multiple expressed biomarkers (proteomes) (56).

7. Impact of COVID-19 on Gastrointestinal Tract Surgery

Patients should be carefully selected for emergency surgery during the COVID-19 outbreak (57). COVID-19 positive cases may contaminate the operating theatre, exposing other patients and health care providers to infection. The indication of an emergency must be managed swiftly and effectively, with extreme caution taken to minimize operation time and exposure to medical personnel (57).

Acute appendicitis is the most frequently encountered surgical emergency. Appendicitis often presents late or even perforated during the acute pandemic period. There has been an increase in severe cases, which has increased associated morbidity and mortality (58).

COVID-19 has been reported in children, particularly those with prominent atypical GI symptoms, such as acute appendicitis, mesenteric adenitis, and flank tenderness. These uncommon and atypical manifestations may conceal an abdominal infection (59).

In numerous studies, hypercoagulability has been linked to an increased risk of venous and arterial thromboembolism (60). There have been reports of abdominal visceral infarctions, including renal, splenic, and small bowel infarctions (60).

Early, accurate, and appropriate management of acute abdominal conditions, including appropriate antimicrobial therapy, may result in the cessation or containment of the abdominal infection. This will assist the surgeon in determining whether non-operative management or surgery is the best course of action (61).

According to the World Society of Emergency Surgery guidelines, non-operative management may be a viable option for uncomplicated intra-abdominal infection (localized to the organ without involving the peritoneum). This concept reduces viral exposure, environmental contamination, and length of stay in the hospital. Surgical treatment is required if a patient presents with persistent abdominal pain (that does not respond to non-operative management), fever, or signs of shock (61). Procedures and operations should be performed if delaying them would likely prolong the hospital stay, increase the likelihood of subsequent hospital admission, or result in patient harm (62).

The use of laparoscopic surgery carries a theoretical risk of occupational exposure and infection for the operating room personnel (61). Exposure to infection may occur during intubation and extubation, smoke and air evacuation via a valve on a trocar, tissue extraction during tissue removal, desufflation of abdominal pressure after surgery, or as a result of the operating room's positive air pressure, which pushes aerosols out (63).

Additionally, CO2 leakage should be minimized to

the greatest extent possible by replacing leaking ports, narrowing leaking skin incisions, as well as utilizing balloon trocars and air evacuation systems (64).

Patients with cancer are more susceptible to infection due to the immunosuppressive state caused by cancer, chemotherapy, and surgery. Furthermore, cancer patients were found to have a higher risk of severe events (65).

The oncological consequences of postponing surgery can be weighed against the increased mortality risk associated with a severe respiratory infection caused by COVID-19 (66).

8. Gastrointestinal Tract Radiological Finding with COVID-19 Infection

COVID-19 is well known to cause significant pulmonary radiological findings. However, the radiological manifestations of COVID-19 GIT are frequently encountered in routine practice (42).

COVID-19 patients frequently develop various imaging-detectable GIT manifestations, including hepatitis, biliary stasis, portal vein thrombosis, bowel wall thickening due to micro or macrovascular arterial and venous thrombosis, mesenteric congestion/inflammation, pneumatosis, as well as pneumoperitoneum (26).

Numerous cases of enterocolitis and bowel ischemia have been reported in adult COVID-19 patients, as well as hemorrhagic and necrotizing enterocolitis in infants infected with COVID-19 (26). Abdominal imaging frequently reveals solid-organ infarcts in patients with COVID-19 affecting the kidney, spleen, and liver, as well as the pancreatic inflammatory process (67).

Ultrasound, duplex, and multi-slice computed tomography (CT) scans, CT angiography, and magnetic resonance imaging (MRI) all play critical roles in the diagnosis of the aforementioned GIT imaging findings (68).

During the current global pandemic crisis, ultrasound is the primary imaging modality for patients with GIT symptoms. It can detect liver disease (steatosis of the liver), gallbladder disease (stones and sludge), and biliary stasis. The presence of stones and sludge within the distended gallbladder and intrahepatic biliary ductal dilatation without a calcular or neoplastic cause indicates biliary stasis in 54% of patients with COVID-19, compared to 10%-20% in the normal population (26) (Figure 1).

Doppler imaging is critical for detecting portal venous thrombosis, mesenteric macrovascular arterial occlusion, and venous thrombosis, indicated by the absence of flow on both colored and pulsed Doppler indices (68).

Additionally, solid organ infarctions manifest as wedge-shaped hypoattenuating areas within the organ parenchyma and intraluminal filling defects caused by thrombosis in mesenteric vessels (68) (Figure 2).

Furthermore, solid organ infarctions manifest as wedge-shaped hypoattenuating areas within the organ parenchyma and an intraluminal filling defect caused by thrombosis within the feeding vessels (68). (Figure3).

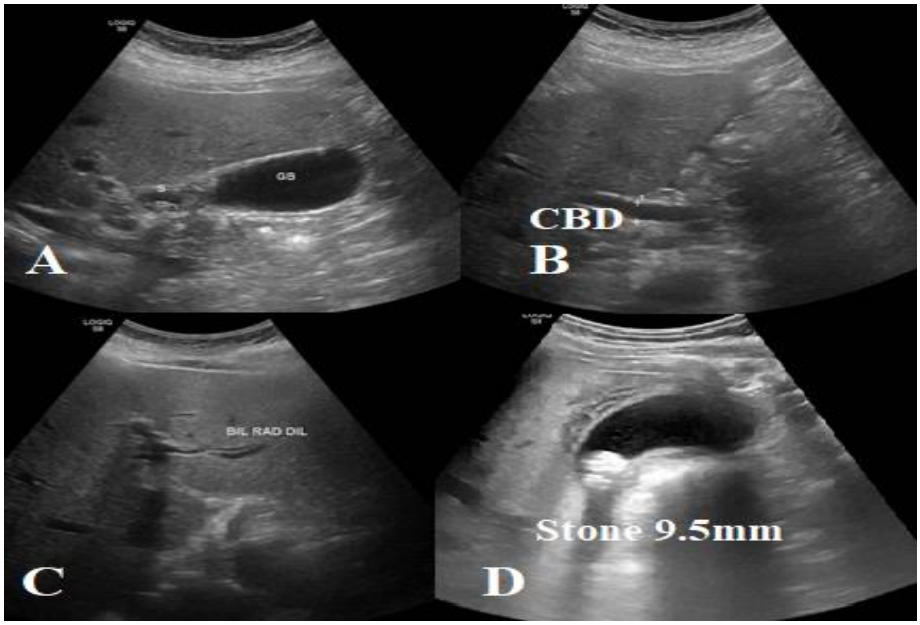

Figure 1. Abdominal US images (A-C) of a 55-year-old COVID-19 male patient with an elevated liver enzyme level show distended gall bladder with thickened wall and 6mm echogenic stone (S) at its neck and dilated 9mm common bile duct, mild intrahepatic biliary radicles dilatation, as well as cholestasis and biliary stasis. (Image D): another 65-year-old COVID-19 female patient showing thick edematous walled distended gall bladder and pericholecystic edema with 9.5mm echogenic stone lodged at its neck.

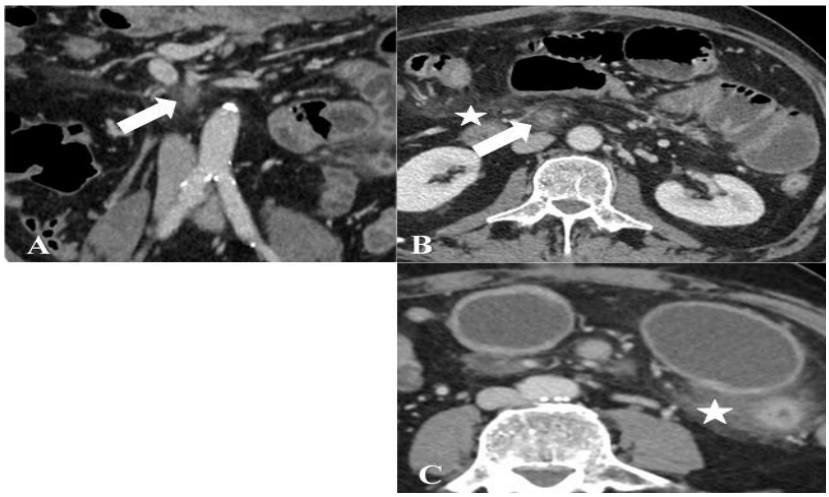

Figure 2. Bowel ischemia as a complication of COVID-19 in a 60-year-old man (A-C) coronal (A) and axial (B, C) intravenous contrast material–enhanced CT images of the abdomen and pelvis show intraluminal filling defect of thrombosis involving the superior mesenteric shortly after its origin, its jejunal branches (arrow) with small bowel dilatation with special stranding of the related fat panes, as well as mesenteric root (star).

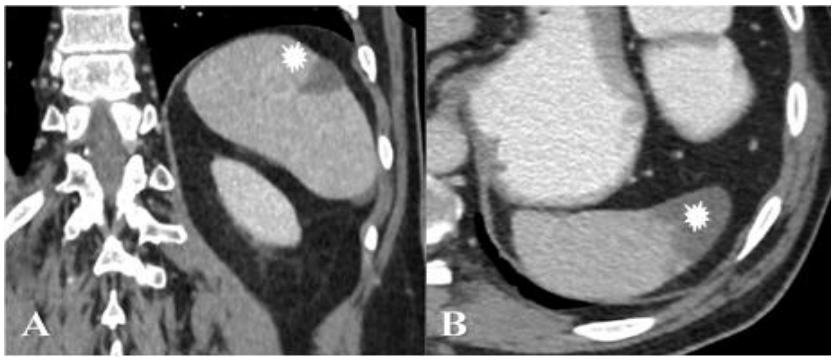

Figure 3. Splenic infarct in a 55-year-old COVID-19 female Coronal and axial contrast-enhanced CT image of the abdomen (A, B) shows a wedge-shaped area of hypodensity reaching splenic capsule at the mid-splenic pole (asterisk).

They are also useful for assessing the pancreatic inflammatory process, which manifests as diffuse pancreatic swelling, peripancreatic fat stranding, and fluid collection, as well as exacerbated complications, such as acute necrotizing pancreatitis (68).

9. COVID-19 Medications Treatment and its Related Gastrointestinal Tract Side Effects

Several commonly used medications for treating COVID-19 can have GI adverse effects, aggravating associated GIT symptoms. Antiviral, anthelminthic, and antimalarial medications are included in this group (69). The most frequently reported GI symptoms associated with COVID-19 drug therapy are summarized in Table 4.

Diarrhea is one of the most distinctive symptoms associated with the use of antibacterial and antiviral medications in treating SARS-CoV-2 (15) (70). When broad-spectrum antibiotics are used, the risk of Clostridioides difficile infection increases, resulting in nosocomial diarrhea (71).

Numerous antiviral medications, including oseltamivir, remdesivir, arbidol, lopinavir, and ritonavir, are used to alleviate the symptoms of COVID-19 patients (72).

A phase III randomized open-label trial with remdesivir was conducted on hospitalized SARS-CoV-2 patients. The study documented adverse GIT events in study patients. The GIT symptoms associated with it include abdominal pain, constipation, nausea, vomiting, and diarrhea (73). Arbidol (Umifenovir) is another antiviral medication that is used in the treatment of COVID-19. Numerous observational studies and clinical trials identified mild diarrhea and nausea as arbidol-related adverse events (74).

Chloroquine phosphate is another antiviral and anti-inflammatory medication that has been associated with diarrhea in patients with COVID-19-associated pneumonia (15, 75).

Colchicine is a beneficial medicine that has been shown to reduce the severity of COVID-19 by

Table 4. Commonly used COVID-19 medications and their possible related-gastrointestinal tract side effects

Medication name	Indication in COVID-19 treatment	Its gastrointestinal tract -related side effects	Reference
Oseltamivir, Remdesivir, arbidol, lopinavir, and ritonavir	antiviral drugs	-Hepatitis -Abdominal pain -Constipation -Nausea, vomiting, and diarrhea	(72-74, 79, 96-98)
Chloroquine phosphate	antiviral and anti-inflammatory drug	-Diarrhea -Hepatitis -Pancreatitis	(15, 75, 99, 100)
Colchicine	Inhibits microtubule polymerization, which is required for the entry and replication of SARS-CoV-2	-Nausea, vomiting, and diarrhea -Gastrointestinal toxicity of colchicine is dose-dependent	(76, 77, 101)
Ivermectin	Semisynthetic antiparasite that causes loss of the viral material of SARS-CoV-2	-Gastrointestinal symptoms	(78, 102)
Anakinra and canakinumab	Interleukin-1 inhibitors	-Nausea, vomiting, and diarrhea -gastroenteritis	(103)
Tocilizumab, Siltuximab, and Sarilumab	interleukin-6 antagonists stopping the cytokine release syndrome	-Vomiting -Increased risk of gastrointestinal perforation	(104-106)
Azithromycin	Antibiotic	-Hepatitis	(99, 100)

SARS-Cov-2: Coronavirus responsible for the severe acute respiratory syndrome

inhibiting microtubule polymerization, which is required for SARS-CoV-2 entry and replication (76). Colchicine users experience GI adverse events, such as nausea, vomiting, and diarrhea, in more than 20% of cases. The GI toxicity of Colchicine is dose-dependent and can be reduced by decreasing the dose (77)

The GI symptoms are the most frequently reported adverse reactions to ivermectin, a semisynthetic antiparasitic that inhibits the virus's nuclear transport within 48 h after a single dose (78).

Hepatitis and hepatotoxicity have been observed following the administration of several medications for COVID-19. Remdesivir, chloroquine, and lopinavir-ritonavir are just a few antiviral medications linked to hepatitis and hepatotoxicity, as indicated by elevated ALT and AST levels. Hepatotoxicity has also been observed in COVID-19 patients who present with jaundice, an enlarged liver, and other digestive system symptoms, such as abdominal pain, diarrhea, nausea, and vomiting (79).

The intestinal flora synthesizes a variety of substances, including immune factors, vitamins, fatty acids, and bile acids, through a variety of mechanisms of fermentation, hydrolysis, and decomposition of various types of food, as well as its involvement in the regulation of various immune system functions, which is significantly disrupted when this flora is destroyed by various types of infection, including viruses (80).

The administration of bifidobacteria and lactic acid bacteria can stimulate the human body to produce antiviral antibodies, increasing the rapid removal of viruses. Additionally, probiotics are recommended as a treatment for rotavirus-associated diarrhea (81).

Ceccarelli et al. recently recommended using probiotics in the treatment of antibacterial and antiviral drug-induced diarrhea in patients with COVID-19 (82).

Although additional clinical studies are required, berberine and other traditional Chinese medicines have been used to treat COVID-19 in China (83). Montmorillonite powder, in addition to probiotics, can be used to treat diarrhea in COVID-19 patients (84).

10. Nutritional Supplement in COVID-19

Numerous supplements have been studied for their ability to alleviate the severe symptoms of CVID-19. Additional research is required before any option can be used as a potentially beneficial supplement.

A nutritional supplement with potential human benefit was tested *in vivo* against lung infection and a cell line expressing COVID-19 inflammatory biomarkers. The broader category of supplements that many people recommend to one another is not well-researched, yet they are widely recommended based on personal experience. Alcohol and tobacco or marijuana use have been shown to impair the immunity of healthy individuals. Many canned foods contain lead and mercury, and unmonitored foods may act as an immunotoxin. Excessive exposure to colloidal silver purchased over the counter resulted in decreased inflammatory mediators (85).

The therapeutic arsenal that has been shown to reduce COVID-19 mortality may result from virus-induced "cytokine storm syndrome" (86). Most COVID-19 protocols include supplements and vitamins that act as anti-inflammatory agents. The variety of nutrients that can help modulate

inflammation and the oxidative stress associated with it helps maintain healthy immune function. Several amino acids, antioxidant vitamins and minerals, long-chain n-3 fatty acids, as well as nucleotides, are included in this group (87). Extensive survival analysis was performed on patients who did not exhibit severe symptoms and were discharged from the hospital to determine which nutrients were the most beneficial.

11. Conclusion

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta coronavirus with antigenic similarity to other mammalian coronaviruses known to show GIT manifestations. About 17.6% of COVID-19 patients reported having GIT symptoms, and 48.1% have viral shedding in stool, which raises concern about its feco-oral transmission. As an RNA virus, SARS-CoV-2 continuous mutations are being reported, among which D614G mutation is the most commonly occurring one.

The GIT and liver disease should be considered in COVID-19 patients. The underlying association pathways between COVID-19 and diseases in the digestive system remain unreliable and still receiving updates. SARS-CoV-2 can penetrate GIT cells directly via an ACE2 receptor, impacting the normal GIT and the liver. There are other different pathways of its penetration, such as the cytokine activation cascade. However, more intensive care is needed in patients with underlying liver disease.

Viral fecal shedding and its detection is diagnostic for GIT involvement and highlights a potential source of feco-oral transmission. Where SARS-CoV-2 RNA shedding in stool, serum and fecal calprotectin, as well as blood proteomic risk score (blood PRS), may aid in the follow-up. SARS-CoV-2 RNA has a major advantage over nasopharyngeal swabs. It appears earlier in stool and remains for an extended period as it may reach COVID-19 second phase and is concomitant with the decrease of the inflammatory peak. Additionally, the estimation of ACE2 and TMRPSS2 receptors with the serum assay of vitamins and trace elements may allow targeted therapy for these patients.

Gall bladder stasis, bowel wall abnormalities, solid organ infarction, mesenteric vascular occlusion, and pancreatitis are possible GIT radiological findings in COVID-19 cases. Both clinicians and radiologists should be familiar with these imaging findings and know the optimal imaging modality for highlighting the disease.

Attention should be directed toward some COVID-19 symptoms and signs that may wrongly be diagnosed as surgical cases, such as appendicitis and abdominal pain. As the risk of transmission during laparoscopy is not established, it is recommended to use closed smoke and CO2 evacuation system to minimize aerosolization of particles. However, there is no reason to abandon laparoscopic surgery in favor of open surgery.

Certain medications used in Covid-19 treatment, such as antibiotics, antivirals, and interleukin inhibitors, may cause GI side effects. These side effects should be monitored and managed appropriately during the COVID-19 treatment. Probiotics and bifidobacterium may be useful in the treatment of COVID-19-associated diarrhea, based on their GIT pathophysiology.

The GI symptoms associated with COVID-19 may be critical for pathogenesis-targeted therapy and the follow-up of COVID-19 patients. The authors hope that additional future research on this subject will concentrate on GIT affection and recommend more effective preventative measures, medical therapies, and therapeutic strategies. Additional data and research are required, particularly for difficult cases, such as IBD and cancer, to characterize the COVID-19 GIT imaging finding.

Increased awareness among healthcare workers is necessary to develop a high index of suspicion for unusual SARS-CoV infection presentations to facilitate early diagnosis and management.

Footnotes

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