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## COVID-19 in gastroenterology and hepatology: Lessons learned and questions to be answered

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### Abstract

#### BACKGROUND

Although coronavirus disease 2019 (COVID-19) presents primarily as a lower respiratory tract infection, increasing data suggests multiorgan, including the gastrointestinal (GI) tract and liver, involvement in patients who are infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

#### AIM

To provide a comprehensive overview of COVID-19 in gastroenterology and hepatology.

#### METHODS

Relevant studies on COVID-19 related to the study aim were undertaken through a literature search to synthesize the extracted data.

#### RESULTS

We found that digestive symptoms and liver injury are not uncommon in patients with COVID-19 and varies in different individuals. The most common GI symptoms reported are diarrhea, nausea, vomiting, and abdominal discomfort. Other atypical GI symptoms, such as loss of smell and taste and GI bleeding, have also been reported along with the evolution of COVID-19. Liver chemistry abnormalities mainly include elevation of aspartate transferase, alanine transferase, and total bilirubin. It is postulated to be related to the binding of severe acute

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respiratory syndrome coronavirus 2 (SARS-CoV-2) virus to the angiotensin converting enzyme-2 receptor located on several different human cells.

## CONCLUSION

Standardized criteria should be established for diagnosis and grading of the severity of GI symptoms in COVID-19 patients. Gastroenterology and hepatology in special populations, such as children and elderly, should be the focus of further research. Future long-term data regarding GI symptoms should not be overlooked.

**Key Words:** COVID-19; SARS-CoV-2; Gastroenterology; Hepatology; Endoscopy; Inflammatory bowel disease

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**Core Tip:** Recent studies suggest multiorgan, including in the gastrointestinal tract and liver, involvement in patients who are infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Digestive symptoms and liver injury are not uncommon in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and symptoms vary between individuals. The most common gastrointestinal symptoms reported are diarrhea, nausea, vomiting, and abdominal discomfort. Liver chemistry abnormalities are also common, including elevation of aspartate transferase, alanine transferase, and total bilirubin. It is postulated to be related to the binding of severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2) to the angiotensin converting enzyme-2 receptor located on several different human cells.

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## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic in the past year, significantly impacting health care systems and global economies. As of January 18, 2021, coronavirus disease 2019 (COVID-19) has caused the death of 2039144 individuals worldwide and infected more than 95464676 people. A typical presentation of COVID-19 includes fever, cough, myalgia, fatigue, and pneumonia and is well recognized[1]. Significant levels of SARS-CoV-2 are detected in the respiratory tract as well as other organs such as the kidneys, liver, heart, brain, and blood. Patients with COVID-19 may present with a broad spectrum of clinical signs and symptoms indicating the involvement of various vital organs[2].

Gastrointestinal (GI) symptoms, such as nausea, vomiting, or diarrhea, and liver injury together with abnormal levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin along with elevations in bilirubin, gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP) can also be present in patients with COVID-19[3,4]. SARS-CoV-2 resembles SARS-CoV-1 and invades the human body by binding to the human angiotensin-converting enzyme-2 (ACE-2) receptor. The receptor is widely expressed in most human cells, and its upregulation may cause tissue injury. The pathophysiological mechanism underlying the SARS-CoV-2-mediated digestive symptoms, including GI symptoms and liver injury, has been thought to be related to the virus' affinity for ACE-2 receptors located in specific enterocytes in the ileum and colon[5].

In this study, we aimed to systematically review the status of COVID-19 research in gastroenterology, liver injury, endoscopy, and inflammatory bowel disease. We also aimed to identify questions that remain to be answered and suggest future research directions in the field of COVID-19 in gastroenterology and hepatology.

**Aim of the review**

The objective of this review was to analyze and summarize COVID-19 research in gastroenterology and hepatology, including endoscopy and inflammatory bowel disease.

**MATERIALS AND METHODS**

Studies were identified through searches in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, the China VIP database, and the China Wanfang database. Moreover, unpublished studies in bioRxiv and medRxiv were also searched to exclude publication bias. Studies and reviews were limited to English or Chinese reports concerning gastroenterology and hepatology in COVID-19 infected patients. The following keywords were used for searching with specific modifications according to the different databases: ('coronavirus disease 2019' OR 'COVID-19' OR 'SARS-CoV-2' OR 'novel coronavirus pneumonia' OR 'novel coronavirus') AND ('gastroenterology' OR 'gastrointestinal tract (GIT)' OR 'stomach' OR 'intestinal tract' OR 'intestine' OR 'GI') AND ('endoscopy' OR 'endoscopic') AND 'inflammatory bowel disease' OR ('hepatology' OR 'liver' OR 'hepatic').

Our research team includes members practicing in the United States and China who are fluent in English and Chinese. Relevant information was independently searched and extracted, and disagreement was settled through discussion to maintain validity and reliability. The references of the retrieved articles were manually screened to identify other relevant publications.

**RESULTS****COVID-19 in gastroenterology**

A considerable number of studies from China have described the laboratory characteristics of patients confirmed to have SARS-CoV-2 infection. GI symptoms, such as diarrhea, vomiting, and nausea, were present in a small percentage of patients with COVID-19[4,6-9] (shown in Table 1). Mao *et al*[10] analyzed 6686 patients with COVID-19 from 35 studies, and the pooled prevalence of diarrhea was 9%, nausea or vomiting 7%, loss of appetite 21%, and abdominal pain 3%. It is worth noting that in a single center case series of 138 hospitalized COVID-19 patients, intensive care unit (ICU) patients exhibited more abdominal pain than non-ICU patients[11]. Subsequently, studies from China[12], Singapore[13], and Japan[14] have reported GI symptoms as the initial symptoms of COVID-19. Luo *et al*[15] analyzed the laboratory characteristics of those patients who presented only with GI symptoms without fever or respiratory manifestations (about 16%). They showed that the most common GI symptom was a loss of appetite followed by nausea and vomiting rather than the commonly noted onset GI symptom diarrhea. Thus, it will be important for healthcare providers to pay attention to digestive symptoms to avoid potentially severe consequences to the patients and their contacts. Moreover, patients with digestive symptoms frequently had longer times from symptom onset to hospital admission, longer coagulation times, and higher liver enzyme levels than patients without digestive symptoms[16].

The prevalence of GI symptoms in patients with COVID-19 was higher in Western populations than in China[17-20]. Chen *et al*[18] performed a prospective, single center, case-control study that showed a higher incidence of GI symptoms in COVID-19-positive patients. Moreover, symptoms of anorexia and diarrhea combined with a loss of smell and taste are 99% specific for COVID-19 infection. Several factors could be responsible for the heterogeneity in GI symptom prevalence observed in different studies, including documentation of GI symptoms at the time of hospitalization, early recognition and diagnosis of suspected patients, and earlier treatment in outpatient or inpatient settings.

Other atypical manifestations include changes in or loss of smell[21], taste[22], or GI bleeding[23]. A six-months follow-up cohort study reported that loss of smell might persist for six months after onset[21]. A well-known complication related to viral illness, altered taste sensation, was present in almost half of the patients (49.8%) with COVID-19[22]. Chen *et al*[24] described a critically ill COVID-19 patient in whom acute respiratory distress syndrome progressed rapidly but who ultimately died from massive GI bleeding even after improvement of the respiratory status. In this patient, the repeat real-time reverse transcriptase PCR SARS-CoV-2 test was positive in stool

**Table 1 Clinical studies concerning the gastrointestinal symptoms in patients with coronavirus disease 2019**

Ref.	n	Countries	Research type	Gastrointestinal symptoms				
				Diarrhea	Loss of appetite	Nausea	Vomiting	Abdominal discomfort
Chen <i>et al</i> [6]	99	China	Retrospective, single center study	2%	-	1%	1%	-
Huang <i>et al</i> [7]	41	China	Retrospective study	3%	-	-	-	-
Shi <i>et al</i> [8]	81	China	Retrospective, descriptive study	4%	-	-	5%	-
Xu <i>et al</i> [9]	62	China	Retrospective case series	8%	-	-	-	-
Wang <i>et al</i> [11]	Total (138), ICU (36), non-ICU (102)	China	Retrospective, single center case series	ICU: 16.7%, non-ICU: 7.8%	-	ICU: 11.1%, non-ICU: 9.8%	ICU: 8.3%, non-ICU: 2.0%	ICU: 8.3%, non-ICU: 0%
Luo <i>et al</i> [15]	Total (1141), GI symptoms only (183)	China	Retrospective study	37%	98%	73%	65%	25%
Pan <i>et al</i> [16]	Experimental group (with digestive symptom): 103, control (without digestive symptom): 101	China	Descriptive, cross-sectional, multicenter study	Experimental group: 34%, control: -	Experimental group: 78.6%, control: -	-	Experimental group: 3.9%, control: -	Experimental group: 1.9%, control: -
Cholankeril <i>et al</i> [17]	116	United States	Retrospective study	10.3%	25.3%	10.3%	10.3%	8.8%
Hajifathalian <i>et al</i> [19]	1059	United States	Retrospective study	22%	-	16%	9%	7%
Chen <i>et al</i> [18]	COVID-19 negative (239), COVID-19 positive (101)	United States	Prospective, single center, case-control study	Negative: 30%, positive: 50%	Negative: 26%, positive: 53%	Negative: 26%, positive: 30%	Negative: 12%, positive: 14%	Negative: 19%, positive: 20%
Young <i>et al</i> [13]	18	Singapore	Descriptive case series	17%	-	-	-	-

COVID-19: Coronavirus disease 2019; GI: Gastrointestinal; ICU: Intensive care unit.

rather than respiratory specimens, indicating direct and continuous viral invasion of the GI tract.

Patients with COVID-19 are subjected to pharmacological interventions, which may contribute to the GI symptoms seen in patients infected by SARS-CoV-2[13]. Thus, it is challenging to clarify the exact reason for GI symptoms if documentation of these symptoms is missing at the time of hospitalization. Further study of the patients' detailed medical and medication histories is needed to clarify this issue.

There are many reasons why COVID-19 causes digestive symptoms: (1) Cytopathic effects: The ACE-2 receptor, a cellular receptor widely expressed throughout the GI tract, might play a critical role in the life cycle and pathogenesis of SARS-CoV-2[25]; (2) Inflammatory response: SARS-CoV-2 may indirectly (inflammatory factors) or directly (viremia) damage the digestive system[16,26]; (3) Altered gut microbiota: many factors such as increased proinflammatory cytokines, antimicrobial medications, altered lung flora, and the use of enteral nutrition might alter the gut flora, which plays a significant role in maintaining GI homeostasis[20]; and (4) Drug administration: GI symptoms are common adverse drug reactions that may aggravate pre-existing conditions or infections and may further explain why patients with COVID-19 often have digestive symptoms.

### COVID-19 in hepatology

Various studies have suggested that SARS-CoV-2 also affects the liver[5]. Typical coronavirus particles with their spikes were found in the cytoplasm of hepatocytes from liver tissue biopsies of deceased COVID-19 patients[27]. The SARS-CoV-2 virus may adversely affect liver function by inducing mitochondrial swelling, endoplasmic

reticulum dilation, and cell membrane dysfunction.

Recent clinical studies of COVID-19 indicate that hepatic injury presents with elevated transaminases (ALT, AST) and bilirubin (BIL), prolonged prothrombin time (PT), and hypoproteinemia, which may predict poor outcome[28]. The severity of COVID-19 infection in patients also correlated with ALT and ALP liver functional tests [27]. It was shown in a retrospective single center study that approximately 43% of patients had differing degrees of abnormal liver function with some patients having suffered severe damage[6]. Moreover, patients with severe COVID-19 appear to have higher rates of liver dysfunction[3,29]. Similarly, increased ALT, lactate dehydrogenase (LDH), and prolonged PT were found in those who died from SARS-CoV-2 infection[30]. However, in another retrospective, single center study, only prolonged PT and elevated LDH were found in hospitalized patients with the novel coronavirus-infected pneumonia[11]. Xu *et al*[9] compared the laboratory results of patients and found that patients who had symptoms for longer than 10 d post-onset had higher LDH levels than those with shorter symptom duration. Because only one of the patients described was admitted to an ICU, further data on critically ill patients are required.

Intriguingly, the rate of chronic liver disease was higher in patients with COVID-19-related GI symptoms than those without GI symptoms. The LDH level was found to be an independent risk factor for critical COVID-19 in patients with GI symptoms[4]. Shi *et al*[8] found that abnormal AST levels were more common in patients after symptom onset than before the onset of symptoms. Despite the above evidence, serum indices of liver function including ALT, AST, BIL, GGT, and LDH in COVID-19 patients were not significantly different from patients with community-acquired pneumonia, which indicates that the liver might not be the main target organ of SARS-CoV-2 infection[28]. The essential information on the clinical research included in this review is listed in Table 2.

Several underlying mechanisms have been proposed to explain hepatic injury during COVID-19 infections. First, hypoxia and cardiac failure in critically ill patients predispose the patient to hypoxic hepatitis and can partly explain hepatic injury during COVID-19 infections[31]. Second, treatments using positive end-expiratory pressure in COVID-19 infections may cause hepatic congestion by increasing the right atrial pressure and hindering venous return[32]. Third, examination of postmortem liver tissue biopsies from COVID-19 patients indicated that the virus was able to replicate in hepatocytes, which may damage liver function through mitochondrial swelling, endoplasmic reticulum dilation, and cell membrane dysfunction[33]. Fourth, ACE-2 receptors expressed in the liver can interact with SARS-CoV-2 and induce direct cytopathic effects[34]. Furthermore, a hyperinflammatory reaction to COVID-19 may aggravate liver injury and alternations in the gut vascular barrier and microbiota may also contribute to liver dysfunction. Lastly, drug-induced toxicity from, for example, antiviral or anti-malaria medications, antibiotics, and steroids should also be considered.

### **GI endoscopy in COVID-19**

Upper GI endoscopy is an aerosol-generating procedure, and its use has, therefore, been restricted during the pandemic. A web-based survey performed in France demonstrated that the COVID-19 pandemic led to a significant reduction in the number of GI endoscopies performed, which may lead to a delay in the management of patients with GI cancers[35]. Data from the National Endoscopy Database indicate that total endoscopic activity fell rapidly to 5% of normal levels during the peak phase of the COVID-19 epidemic in the United Kingdom[36]. International digestive endoscopy societies have recommended high-level protection measures during procedures in patients with COVID-19 or in regions with high COVID-19 incidence [37]. However, different countries have different COVID-19 incidences and capacities for performing semi-urgent endoscopy, resulting in different guidelines from leading organizations in different countries. In general, all organizations agree that cases should be individually assessed and reviewed pre-endoscopy. Elective nonurgent cases should be deferred depending on risk assessment, whereas for emergent cases, endoscopy should be performed in a negative pressure room[38]. PCR testing should also be performed before endoscopy to protect staff and prevent mass nosocomial infection.

To ensure a safe environment for patients and to prevent infection in the endoscopy units, endoscopy staff have instituted significant changes. Cennamo *et al*[39] reported a practical model of a GI endoscopy unit during the COVID-19 emergency, involving a reorganization of the environment using a risk-based color-coding redesign of current spaces such as the waiting room, recovery room, and endoscopy suites, implemen-

**Table 2 Clinical studies concerning the serum index of liver function in patients infected by severe acute respiratory syndrome coronavirus**

Ref.	n	Countries	Research type	Liver chemistry abnormalities			
				Abnormal AST, ALT, LDH	Bilirubin, ALP	Decreased albumin	Prolonged PT
Chen <i>et al</i> [6]	99	China	Retrospective, single center study	AST: 35%, ALT: 28%, LDH: 76%	BIL: 18%	98%	5%
Liu <i>et al</i> [29]	Nonsevere (28), severe (4)	China	Retrospective, multicenter study	Nonsevere: AST: 3.6%, ALT: 21%; Severe: AST: 25.0%, ALT: 75.0%	ND	ND	ND
Guan <i>et al</i> [3]	Nonsevere (926), severe (173)	China	Retrospective	Nonsevere: AST: 18.2%, ALT: 19.8%, LDH: 37.2%; Severe: AST: 39.4%, ALT: 28.1%, LDH: 58.1%	Nonsevere: BIL: 9.9%; Severe: BIL: 13.3%	ND	ND
Zhou <i>et al</i> [30]	Nonsurvivor (54), survivor (137)	China	Retrospective, multicenter cohort study	Nonsurvivor: ALT: 48%, LDH: 98%; survivor: ALT: 24%, LDH: 54%	ND	ND	Nonsurvivor: 13%; Survivor: 3%
Wang <i>et al</i> [11]	138	China	Retrospective, single center study	LDH: 39.9%	ND	ND	58.0%
Xu <i>et al</i> [9]	62	China	Retrospective	AST: 16%, LDH: 27%	ND	ND	ND
Wu <i>et al</i> [49]	80	China	Retrospective, multicenter study	AST: 3.75%, ALT: 3.75%, LDH: 21.25%	BIL: 1.25%	2.50%	ND
Shi <i>et al</i> [8]	81	China	Retrospective, descriptive study	AST: 53%	ND	ND	ND

ALP: Alkaline phosphatase; ALT: Alanine transferase; AST: Aspartate transferase; BIL: Bilirubin; LDH: Lactate dehydrogenase; ND: Not mentioned; PT: Prothrombin time.

tation of new areas including checkpoints, areas for changing personal protective equipment, and droplet areas, and the creation of separate access routes and processes according to the new color-coded design and dedicated areas. Until now, endoscopy units have been largely untouched by infectious disease concerns. COVID-19 is likely to change the traditional endoscopy model to protect patients, colleagues, and staff from COVID-19 and to help conquer future pandemics[40].

Patient factors, procedural factors, infection prevention, and control strategies should be considered. Patients may be unwilling to attend hospitals during the pandemic, or patients may be in a designated 'shielded' category. The training of staff for new appropriate triage, screening, and infection prevention procedures is required. Prevention and control strategies will severely curtail the capacity of staff who will need time to adjust to the new procedures[36]. These factors make it challenging to implement endoscopies even in patients without COVID-19. Thus, innovative noninvasive endoscopy methods, like magnetically assisted capsule endoscopy during the COVID-19 pandemic, need further exploration[41].

### **Inflammatory bowel disease and COVID-19**

During the pandemic, particular concern has been raised in populations with the highest risk, such as the elderly and patients with preexisting medical conditions, with a specific focus on inflammatory bowel disease (IBD)[42], a gastroenterological disease caused by immune dysregulation. Upregulated expression of ACE-2 in the inflamed mucosa as well as a soluble form of ACE-2 circulating in the blood of IBD patients has been found[43,44]. However, no evidence suggests that COVID-19 occurs more frequently in IBD than in the general population[43]. Low rates of IBD/SARS-CoV-2 association have been reported in Italy[45] where about 0.25% (15/6000) of patients with IBD tested positive for COVID-19[46]. Rodríguez-Lago *et al*[47] reported 40 cases of IBD with confirmed positive tests for SARS-CoV-2 in Spain. According to the Spanish database, the rate of IBD/SARS-CoV-2 is 0.63% (12/1912)[44]. In the United States, the prevalence of IBD among COVID-19 patients was found to be 1.2%, and an age greater than 66-years-old was a strong independent predictor[48]. Similarly, low rates have also been reported in pediatric IBD patients in Europe, China, Canada, Israel, and South Korea[42].

As previously mentioned, many patients with COVID-19 will develop GI complaints. Several questions remain to be answered: Do IBD patients have more GI symptoms and are they more severe? How should IBD patients with known or suspected COVID-19 be treated? How should IBD be managed during the COVID-19 pandemic?

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## DISCUSSION

To date, the laboratory characteristics of patients with COVID-19 have been extensively studied. According to the available evidence, a subset of patients might initially present atypical symptoms, such as GI symptoms including diarrhea, vomiting, nausea, loss of appetite, abdominal discomfort, loss of smell and taste, and GI bleeding. Hepatic injury presenting together with elevated ALT, AST, BIL, GGT, LDH, prolonged PT, and hypoproteinemia has also been documented in COVID-19 patients. It is worth noting that upper GI endoscopy has been restricted during the pandemic, and innovative methods are urgently needed. Furthermore, there is no evidence to suggest that COVID-19 occurs more frequently in patients with IBD. However, the mechanism by which SARS-CoV-2 influences digestive symptoms and hepatic injury is still unclear. Several underlying mechanisms have been proposed, and it is possible that the binding of the SARS-CoV-2 virus to the ACE-2 receptor, which is widely expressed on different human cells, might be the crucial reason.

There are various unanswered questions suggesting directions for future research. These are: (1) standardized criteria for the diagnosis and grading of the severity of GI symptoms are missing in current original studies related to COVID-19; (2) there are a lack of data comparing the presence or absence of GI symptoms in laboratory-confirmed positive and negative COVID-19 patients and the association between severity of GI symptoms and COVID-19; (3) more evidence is needed to verify whether GI symptoms can be used in early testing, diagnosis, and prognosis of COVID-19 severity and mortality; (4) there is an urgent need for the standardization of stool testing, disease severity, a strict definition of GI symptoms, and the evaluation of potential confounders; (5) more attention should be paid to gastroenterology and hepatology in specific populations, such as children or elderly; (6) evidence of persistent liver injury after SARS-CoV-2 infection needs further investigation; (7) changes in liver function in COVID-19 patients with primary liver diseases should be investigated; (8) information on the dynamic process of liver function after close COVID-19 contact, symptom onset, treatment, cure, and recurrence is absent; (9) the serum indices of liver function in COVID-19 patients should be compared with those of other viral infections, especially SARS-CoV-1; and (10) there are limited pathological studies of COVID-19 patients, indicating that more attention should be paid to pathological examinations or postmortem studies of the liver.

This narrative review retrieved relevant studies to provide an objective analysis of COVID-19 infection in relation to gastroenterology and hepatology. Our review has several limitations: First, it was challenging to set general inclusion and exclusion criteria for studies. Second, the quality and grade of the included studies and quantitative analyses were not assessed. Third, the included investigations and reviews were limited to English or Chinese, which might lead to information bias. Lastly, it is difficult to distinguish whether the manifestations were caused by COVID-19 itself or related to the treatment regimen, which might increase the bias of our study.

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## CONCLUSION

In conclusion, digestive symptoms and liver injury are common in patients with COVID-19, and their incidence and severity vary between individuals. The reviewed studies provide new insights into our understanding of the prevalence, etiology, and potential mechanisms of COVID-19 effects in gastroenterology and hepatology. Further studies are needed to improve our knowledge as more information becomes available as this pandemic unfolds.

## ARTICLE HIGHLIGHTS

### Research background

Recent studies suggest multiorgan, including in the gastrointestinal tract and liver, involvement in patients infected by coronavirus disease-2019 (COVID-19).

### Research motivation

We hope to raise the unsolved problems of COVID-19 in the field of gastroenterology and hepatology and point out the directions for future research.

### Research objectives

The purpose of this paper is to analyze and summarize the critical issues of COVID-19 in the field of gastroenterology and hepatology.

### Research methods

We completed this paper by searching many relevant studies and then sorting and analyzing the data.

### Research results

Gastrointestinal symptoms and liver damage due to COVID-19 infection can vary depending on the patient.

### Research conclusions

Digestive symptoms and liver damage are not uncommon in COVID-19 patients and vary from person to person. But with the development of the disease, further research and exploration are still needed.

### Research perspectives

Based on the monitoring of patients infected with COVID-19, gastrointestinal symptoms and liver injury characteristics were summarized.

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