

World Journal of *Clinical Cases*

World J Clin Cases 2021 July 6; 9(19): 4881-5351



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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJCC as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing, Production Department Director: Yun-Xiaoqian Wu, Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

July 6, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Gastroenterology and liver disease during COVID-19 and in anticipation of post-COVID-19 era: Current practice and future directions

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Author contributions: Zafeiridis T, Papamichalis P and Oikonomou KG designed the review; Papamichalis P and Oikonomou KG analyzed and interpreted the data and wrote the final version of the manuscript; Zafeiridis T, Xanthoudaki M, Papapostolou E, Valsamaki A, Bouliaris K and Skoura AL collected the data and drafted the manuscript; Papamichalis M, Karvouniaris M, Vlachostergios PJ and Komnos A critically reviewed the paper; Oikonomou KG and Vlachostergios PJ performed English editing.

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a major threat to global public health. The virus causes the clinical syndrome known as coronavirus disease 2019 (COVID-19), in which multiple organs can get affected. Apart from manifestations of the respiratory system, which predominate, its clinical presentation is frequently accompanied by symptoms of the gastrointestinal (GI) tract and liver abnormalities. The correlation of symptoms and abnormalities with disease severity is discussed, leading to ambiguous results from international literature. Moreover, the disease infects patients with co-existing liver and GI disorders affecting both their health status and the availability of healthcare services provided to them. The risk of transmission of

Conflict-of-interest statement: The authors have no conflict of interest to declare.

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Manuscript source: Invited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 23, 2021

Peer-review started: February 23, 2021

First decision: March 28, 2021

Revised: April 10, 2021

Accepted: May 25, 2021

Article in press: May 25, 2021

Published online: July 6, 2021

P-Reviewer: Cichoż-Lach H

S-Editor: Gao CC

L-Editor: A

P-Editor: Xing YX



the disease during aerosol-generating procedures has changed the diagnostic approach and follow-up algorithms for liver and GI diseases. For the safety of both doctors and patients, telemedicine and distant evaluation have become everyday practice, whereas several routines and emergency visits at outpatient and emergency departments have been postponed or delayed. Vaccination against SARS-CoV-2 is underway, providing hope to humanity and the expectation that the post-COVID-19 era is near. This review aims to update knowledge about the manifestations of COVID-19 related to liver and GI diseases and the effect of the pandemic on the diagnostic and therapeutic procedures for these diseases with a special focus on how current practices have changed and what changes will possibly remain in the future.

Key Words: COVID-19; SARS-CoV-2; Liver disease; Gastroenterology practice; Endoscopy

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Core Tip: Coronavirus disease 2019 (COVID-19) pandemic has affected every aspect of current medical practice. Patients with gastro-intestinal and liver diseases are not only prone to develop serious complications from COVID-19 but also to have their disease incorrectly or not timely diagnosed and not properly followed up. In this review, we summarize the impact of the pandemic on the course of the disease and the treatment of these patients. In addition, we discuss the changes in everyday practice that were adapted in our effort to protect patients and healthcare workers, with a focus on emerging tools such as telemedicine.

Citation: Oikonomou KG, Papamichalis P, Zafeiridis T, Xanthoudaki M, Papapostolou E, Valsamaki A, Bouliaris K, Papamichalis M, Karvouniaris M, Vlachostergios PJ, Skoura AL, Komnos A. Gastroenterology and liver disease during COVID-19 and in anticipation of post-COVID-19 era: Current practice and future directions. *World J Clin Cases* 2021; 9(19): 4918-4938

URL: <https://www.wjgnet.com/2307-8960/full/v9/i19/4918.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i19.4918>

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which emerged in December 2019 in China. The virus belongs to the family of the Coronaviruses, which are single-stranded RNA viruses[1,2]. SARS-CoV-2 has spread worldwide, causing a pandemic and affecting a significant number of patients. It has become a major public health problem, with several burdened health systems worldwide changing practices and struggling to overcome the consequences of the morbidity and mortality associated with the disease [3].

COVID-19 presents primarily with respiratory manifestations ranging from mild upper respiratory symptoms to fulminant respiratory failure. Recently, increasing data support the involvement of multiple organ systems, such as the gastro-intestinal (GI) tract and the liver. Although data for SARS-CoV-2 are still limited, conclusions can be extrapolated from data from previous epidemics related to coronaviruses, including the SARS-CoV outbreak of 2002-2003[4,5].

The pathophysiology of GI manifestations of COVID-19 mainly involves direct interstitial inflammation with infiltration of epithelial cells and lamina propria of the GI tract by neutrophils, macrophages, and T cells. The entry of the virus into the GI cells is mediated by the interaction between an envelope-anchored viral spike protein and a host receptor consisting of angiotensin-converting enzyme 2 receptor (ACE2), expressed in the liver, upper esophagus, lung alveolar type 2 cells, kidneys, brain, and absorptive enterocytes from ileum and colon. The process requires priming by cellular serine proteases (transmembrane serine protease 2, TMPRSS2) that are highly co-expressed with ACE2 in enterocytes, and in the esophagus and lungs[6]. The inflam-

matory response in the gut, clinically manifested as diarrhea, is evidenced through elevated fecal calprotectin and associated with systemic interleukin-6 (IL-6) response [7]. Other receptors, which may facilitate viral entry into cells are sialic acid, CD147, and neuropilin-1, whereas the human leukocyte antigen system may present viral peptides and activate cross-protective T-cell mediated immunity[8-11].

The present review aims to describe the most common clinical and laboratory GI and liver manifestations of COVID-19, summarize how common clinical operations and procedures have changed in the setting of the pandemic, and shed a light on future perspectives for the management of GI and liver diseases.

LIVER DISEASE AND COVID-19

Liver involvement in COVID-19 disease

Although under investigation, patients with pre-existing chronic liver diseases may be more susceptible to COVID-19. Certain recent data revealed that patients with underlying liver disease and COVID-19 may be at an increased risk for worse outcomes[12,13]. In a study that included 250 patients with chronic liver disease out of a total of 2780 patients, those with chronic liver disease had higher rates of mortality [12]. In addition, recent studies have shown that patients with chronic liver diseases and specifically, cirrhosis have higher mortality rates ($P < 0.001$)[4,12,13]. In contrast, it is still unknown whether SARS-CoV-2 infection exacerbates cholestasis in patients with underlying cholestatic liver diseases.

The extent of liver participation in COVID-19 is not well defined yet. It is speculated that SARS-CoV-2 can enter the hepatocytes and cholangiocytes through ACE2[14]. Medications such as anti-virals (*e.g.*, lopinavir-ritonavir), acetaminophen/paracetamol, steroids, and antibiotics used for bacterial superinfections affect liver function as well. Biological drugs such as tocilizumab and baricitinib might also cause hepatitis B reactivation, deteriorating liver function. Moreover, the cytokine storm and hypotension, as well as the liver congestion due to positive pressure ventilation, particularly in critically ill patients, could cause liver impairment. In the intensive care unit (ICU) setting, a study reported elevated aspartate aminotransferase (AST) activity in 62% of patients in the ICU and 25% in non-ICU patients[15].

Histologically, findings are non-specific and include microvesicular steatosis, lobular and portal inflammation, focal hepatocyte necrosis, and lymphocytic infiltration to a certain extent, and sinusoidal dilatation. The above-mentioned findings represent immune-mediated liver injury rather than the direct effect of the virus[4,16].

Elevated liver function tests (LFTs) may be one of the laboratory manifestations of COVID-19. In 16% to 53% of patients, elevated alanine aminotransferase (ALT) and AST activities were found[17,18]. AST activity is often more elevated than the ALT activity; this finding can be related to disease severity[19]. A recent study on 1099 patients reported significantly elevated ALT and AST activities in patients with severe disease (28% and 39%, respectively) in comparison with patients without the severe disease (20% and 18%, respectively)[20]. In addition, an association between lower albumin levels and severe COVID-19 has been reported[21,22]. AST and ALT activities are frequently more elevated than bilirubin level or alkaline phosphatase activity[21, 23]. A study reported elevated total bilirubin level and AST and ALT activities in 10%, 21%, and 22% of patients, respectively[20].

It is recommended to test for COVID-19 in all hospitalized patients with elevated LFTs, irrespective of the presence or absence of respiratory symptoms. Preliminary data have shown that up to 25% of patients with liver abnormalities may not have any respiratory symptoms at the time of diagnosis[13]. In patients with already diagnosed chronic liver diseases, the COVID-19 test should be performed when there is a change in clinical condition and symptoms such as jaundice, abdominal pain, or hepatic encephalopathy[13].

In patients with COVID-19 and elevated LFTs, it should not be assumed that liver dysfunction is only related to COVID-19. A careful history, review of the medication list, and complete physical examination should be performed. Viral hepatitis serologies should be checked, whereas imaging should be reserved for cases of suspected biliary obstruction or acute vascular events[24]. The presence of elevated LFTs is not an absolute contraindication for the administration of COVID-19-specific treatments such as remdesivir. Patients with LFTs that are five times higher than the upper normal limit may be excluded. In addition, close monitoring of LFTs is required if the medication is administered[18].

EVALUATION AND MANAGEMENT OF COVID-19 PATIENTS WITH CHRONIC LIVER DISEASES: SPECIAL CONSIDERATIONS, CURRENT MANAGEMENT, AND FUTURE PERSPECTIVES

Autoimmune liver diseases

Patients with autoimmune hepatitis (AH) are on immunosuppressive treatment to prevent disease relapses. The major concerns in this patient population are a potentially unfavorable course of COVID-19 in the setting of immunity impairment and the risk for disease relapse if immunosuppression is stopped[3,25]. Routine discontinuation of immunosuppressants is not recommended because the immunosuppressive effect of certain medications could take weeks to disappear, and generally, the course of disease appears to be similar as in the general population[25]. Overall, a case-by-case evaluation and individualized approach are recommended[3,25]. Factors that should be considered are disease severity, comorbidities, and regimens used, also in light of the potential benefit of steroids in patients with COVID-19 who require supplemental oxygen and additionally the presence of lymphopenia or concomitant bacterial or fungal infection[3,26]. In patients with mild COVID-19 disease, immunosuppression is not usually adjusted. In patients who require hospitalization or develop acute respiratory failure, a careful review of the patient's history is recommended, and a reduction of 25% to 50% of the dose of the baseline regimen is usually implemented. Patient's symptoms and LFTs are monitored and recorded daily in hospitalized patients and once every one or two weeks in non-hospitalized patients. In the case of viral-induced lymphopenia, the white blood cell count and differential are also monitored[25]. In the setting of disease flares, escalation of immunosuppression is indicated to prevent further liver damage. Similarly, in patients with a new diagnosis of AH, immunosuppressive therapy can be initiated[27,28]. In addition, particular emphasis should be given on vaccination for influenza and *Streptococcus pneumoniae* infection in the immunosuppressed host[3]. In patients with primary biliary cholangitis and primary sclerosing cholangitis (PSC) who receive ursodiol, the medication should be continued without changes in dosing[3].

Non-alcoholic steatohepatitis

Patients with non-alcoholic steatohepatitis (NASH) are at high risk for severe COVID-19 disease due to its predisposing conditions such as diabetes mellitus (DM) and obesity. Several recent studies showed that patients with a history of NASH were at a higher risk for disease progression, liver function abnormalities, and prolonged viral shedding. It is estimated that patients with NASH are infectious for approximately 5 d or longer. This is probably related to increased proinflammatory cytokines produced by adipose and Kupffer cells[29,30]. Patients with NASH and COVID-19 treatment for underlying medical conditions, such as DM and hypertension, should be optimized and patients should be counseled on preventive measures and practices.

Viral hepatitis

A study conducted early on the COVID-19 epidemic in China, where the prevalence of chronic hepatitis B virus (HBV) is high, found no evidence that underlying chronic HBV infection increased the adverse outcomes in individuals with COVID-19[20]. It is uncertain whether, in patients with viral hepatitis, COVID-19 infection alters the course of the disease and the outcomes[15]. Patients with chronic hepatitis B infection may experience disease reactivations, particularly in the setting of treatment with steroids or immunosuppressive agents, such as tocilizumab. In such cases, prophylaxis may be indicated[31]. The need for prophylaxis administration to prevent the reactivation of chronic HBV infection in patients receiving corticosteroids as COVID-19 treatment is based on the guidelines of the American Gastroenterological Association (AGA) for risk assessment and stratification according to the serologic status of the patient. For patients who are considered low risk for reactivation, routine use of prophylaxis is not indicated. In patients who are considered moderate or high risk for HBV reactivation, anti-viral prophylaxis is recommended, and it should be continued for six months after discontinuation of steroids. The AGA recommends the use of anti-viral regimens with a higher barrier to resistance, such as entecavir[32]. There is limited experience regarding the use of tocilizumab and prophylaxis from HBV reactivation, mainly from patients with rheumatoid arthritis. Therapy with tocilizumab is considered relatively safe in resolved HBV infection, while hepatitis B surface antigen-positive patients present a higher risk for reactivation[33]. Recent guidelines propose the same strategies for tocilizumab with anti-tumor necrosis factor

agents for preventing HBV reactivation, as they are considered to present similar risk [34]. This approach of anti-viral prophylaxis, preferably with entecavir, is recommended for patients receiving tocilizumab with moderate or high risk for HBV reactivation[32].

Patients with viral hepatitises do not appear to be at an increased risk for severe COVID-19, and those who are already on anti-virals should continue taking their medications as prescribed. Prescriptions should be sent to patients with refills of longer duration[3].

Hepatocellular carcinoma

In patients with hepatocellular carcinoma (HCC), care should be maintained by using telemedicine services. In the case of HCC patients with COVID-19, early admission is preferable[3]. Screening delay or delay of surgical intervention and locoregional treatments is usually safe; however, it may lead to the diagnosis of HCC at a later stage in about 25% of patients[35]. Care should be continued according to the guidelines regarding continuing systemic treatments and evaluation for liver transplants and by following all the measures for preventing transmission[3].

One of the potential challenges during the pandemic may be the lack of surgical rooms and ICU beds. For early-stage HCC, to avoid interval progression, surgery for patients with smaller disease load should be prioritized, and alternative treatment options, such as radiofrequency and microwave ablation, should be considered[36]. For intermediate stage HCC, centers should identify patients that would benefit from transarterial chemoembolization (TACE). In case TACE services cannot be provided, systemic treatments or regular imaging surveillance should be implemented[37]. For patients with advanced stage HCC, patients on oral treatment with tyrosine kinase inhibitors may be followed up by telemedicine or longer intervals of follow-up visits, if applicable[36].

During the course of a pandemic, special efforts should be made to contain the viral spread in healthcare facilities and the community and to maintain close patient follow-up. This is particularly valid in patients with chronic liver diseases who require close and frequent monitoring. Telehealth and video visits are one option to consider, whereas the involvement of a multidisciplinary team is vital in preserving patient's health and well-being. In the outpatient setting, triage and infection prevention protocols should be maintained in each setting, and proper social distancing measures and deferral of non-urgent visits are recommended. Routine laboratory tests should be performed in non-COVID-19 facilities[3,38]. In case of an emergency or when a visit cannot be performed virtually, screening of all patients for COVID-19 symptoms and testing should be implemented, while the use of a facemask and hand hygiene is essential. Patients who test positive for COVID-19 should be isolated in separate rooms for further evaluation and work-up. Endoscopic procedures such as esophago-gastroduodenoscopy and endoscopic retrograde cholangiopancreatography (ERCP) should be performed after careful and individualized risk assessment for urgent indications and evaluation of local capabilities, because these procedures may accelerate COVID-19 spread[3]. The same factors apply to patients with liver biopsy. Certain indications for performing a liver biopsy are the presence of significant elevation of LFTs or in suspicious liver nodules. Liver biopsy should be deferred in patients who are clinically stable with stable laboratory values[3].

In the inpatient setting, a close collaboration of the primary care team with the liver specialist and frequent consultations for visits and procedures should be performed [38]. In addition, patients with liver disease should be hospitalized in non-COVID-19 wards when non-infected. Patients with liver disease who get infected with SARS-CoV-2 should be admitted to COVID-19 wards sooner rather than later when they have underlying comorbidities and additional risk factors for severe disease[23]. Paracetamol/acetaminophen overdose should be avoided. Moreover, non-steroidal anti-inflammatory medications (NSAIDs) should be avoided in patients with cirrhosis, portal hypertension, and a high probability of GI bleeding.

The above-mentioned strategies can reduce the spread of COVID-19 and prevent its transmission. A potential long course of the pandemic may also lead to financial challenges, thereby jeopardizing the insurance coverage for patients and affecting the compensation of healthcare systems. Potential delays in diagnosis, treatment, and procedures add to additional burdens. Vaccination strategies followed worldwide represent the beginning of a new era for the elimination of COVID-19; however, a long way remains ahead until the effects of the massive vaccination and herd immunity are apparent on the population.

Several vaccines for SARS-CoV-2 have been developed, and some of them have received regulatory approvals[39]. Little is known about the efficacy of those vaccines in specific subpopulations, such as in patients with chronic liver diseases. The percentage of patients with chronic liver diseases, who were included in the Pfizer and Moderna vaccine trials is limited. In addition, immunosuppressed patients were not studied, and as a result, accurate conclusions cannot be made for patients with autoimmune liver diseases on immunosuppressants[39]. Innate immune deficits related to underlying cirrhosis may also affect immune responses in patients who receive vaccines against SARS-CoV-2[39]. Nevertheless, patients with advanced liver disease should be informed and educated about the benefits of the vaccination against SARS-CoV-2. Further studies are required to investigate the potential side effects of the vaccines on LFTs and the exact rates of reduction in COVID-19 cases in liver patients after vaccination.

Another field that requires further investigation is the effect of SARS-CoV-2 variants on clinical presentation and disease severity on the general population and specifically on patients with chronic liver diseases. At present, there is ongoing research and existing data are still limited. In addition, further studies are required to clarify the exact mechanisms of liver involvement in COVID-19 and the effects of new treatments on the liver, not only for the general population but also on subpopulations such as geriatric and pediatric patients.

GASTROENTEROLOGY PERSPECTIVES OF COVID-19

Considerations regarding upper GI tract: Prevalence and clinical significance of symptoms

Apart from the respiratory presentations, gastroenterological symptoms are common for patients with COVID-19. Loss of appetite, a usual GI symptom, is the result of the inflammatory process induced by the virus or the side effect of medications. Abdominal pain has been recognized as a clinical predictor of more severe disease based on its possible association with increased viral replication in the gut and high viral load[40].

Another subset of systematic symptoms, dizziness, and fatigue, is explained based on the gut-brain axis. Metabolic disorders caused by the virus and changes in the intestinal microbiota increase the absorption of harmful metabolites, which affect the central nervous system[41].

Gut dysbiosis induced by alterations in the gut microbiota, caused either by drugs for COVID-19 or by the virus itself with the mediation of lung-derived effector CD4⁺ T cells that reach the small intestine through the gut-lung axis, is another basic mechanism for GI manifestations and their pathophysiology[42,43]. Gut microbiomes produce interferon-gamma and other cytokines, which may play a key role in the development of cytokine release syndrome, characterized by profound hyper inflammation and exacerbation of disease severity in COVID-19 patients[44-46]. The gut-lung axis is bidirectional; gut dysbiosis has possible implications in respiratory manifestations of diseases such as COVID-19, giving promises for future therapeutic interventions to restore gut microbiota such as fecal microbiota transplantation[47].

A collection of published articles on the most common gastroenterological symptoms, such as diarrhea, nausea or vomiting, loss of appetite, and abdominal pain, is presented in Tables 1 and 2. A great degree of diversity characterizes not only the prevalence of the symptoms but also their correlation with disease severity and clinical course. The prevalence ranges from 4.9% to 74%, whereas five studies had positive, 8 had negative, and 14 reported no correlation with the clinical severity markers and outcomes. The possible explanations for this heterogeneity could be based on the design of the studies. Many of them are obtained from one hospital or center; the risk of selection bias for most of them is expressed by the authors themselves. All of them are retrospective, except for one, which is prospective/case-controlled[48]. Some studies included only hospitalized patients, others non-hospitalized, and others both hospitalized and non-hospitalized patients. Consequently, the prevalence of symptoms is influenced by other factors. Diarrhea due to antibiotics, anti-virals, other drugs, or *Clostridium difficile* is a good example of how hospitalization increases the prevalence[49]. The result is that no secure conclusion can be drawn on how GI symptoms relate to disease severity; well-designed multi-center studies are required. However, several studies report a proportion of patients that presents with only GI and without respiratory symptoms and agree that patients with GI symptoms have delayed diagnosis and hospital admission, which may influence the outcome and

Table 1 Gastro-intestinal symptoms (frequency < 30%) and correlation with the clinical course of coronavirus disease 2019

Ref.	No. of patients	Frequency of GI symptoms, n (%)	Diarrhea, n (%)	Nausea or vomiting, n (%)	Loss of appetite, n (%)	Abdominal pain, n (%)	Correlation with worse or better clinical course	Comments/limitations
Jin <i>et al</i> [119]	651	74 (11.4)	53 (8.1)	21 (3.2)	No	No	Yes, worse	Not prospective or cohort study
Papa <i>et al</i> [120]	34	3 (8.8)	1 (2.9)	1 (2.9)	No	1 (2.9)	Yes, better	Limited number of patients, possible underestimation of GI-symptoms and digestive comorbidities
Zheng <i>et al</i> [121]	1320	192 (14.6)	107 (8.1)	57 (4.3)	62 (4.7)	11 (0.8)	Yes, worse	Single-center, small sample, mild and common type patients
Ai <i>et al</i> [122]	142	7 (4.9)	6 (4.2)	6 (4.2)	7 (4.9)	6 (4.2)	No	The lowest prevalence
Zhang <i>et al</i> [123]	788	88 (11.2)	NA	NA	No	No	Yes, worse	Laboratory results not included in ordinal logistic regression model
Zhou <i>et al</i> [41]	254	66 (26)	46 (18.1)	36 (14.2)	No	3 (1.2)	No	Most cases were clinically confirmed patients, difficulty in assessing clinical outcomes
Lei <i>et al</i> [124]	115	32 (27.8)	14 (12.2)	9 (7.83)	9 (7.83)	No	No	Single-center, selection bias, patients with mild manifestations excluded, aged patients, follow-up data not provided
Remes-Troche <i>et al</i> [125]	112	23 (20.5)	20 (17.8)	8 (7.1)	No	11 (9.8)	No	Possible selection bias
Ramachandran <i>et al</i> [126]	150	31 (20.6)	22 (14.7)	16 (10.7)	No	3 (2)	No	Possible selection bias, No test for the presence of SARS-CoV-2 RNA
Aghemo <i>et al</i> [127]	292	69/245 (28.2)	69/255 (27.1)	11/274 (4.0)	No	No	Yes, better	Patients admitted in critical conditions were excluded
Ferm <i>et al</i> [128]	892	219 (24.6)	177 (19.8)	239 (26.8)	105 (11.8)	70 (7.8)	No	Collection of data limited by recall bias of both patients and health care professionals
Luo <i>et al</i> [51]	1141	183 (16)	68 (6)	134 (11.7)	180 (15.8)	45 (3.8)	No	Hospitalized patients, only gastro-intestinal (no respiratory) symptoms

GI: Gastro-intestinal; NA: Not available; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

disease spread due to the fecal-oral transmission[50-52].

Fecal-oral transmission has been investigated by international literature. Several studies have reported 50% fecal detection of SARS-CoV-2 RNA with cases remaining positive for 33 d after negative respiratory samples and cases reaching viral shedding in feces for nearly 5 wk[53-56]. In another study, SARS-CoV-2 could be detected in the esophagus, stomach, duodenum, and rectum of two severely diseased patients with COVID-19[57]. These findings imply possible invasion of the virus into the ACE2-expressing enterocytes, suggesting that the GI tract serves as a replication site and a route of infection other than the respiratory system[54]. Furthermore, the staining of viral nucleocapsid protein in gastric, duodenal, and rectal epithelia strongly supports this hypothesis[53]. Thus, surfaces potentially contaminated by feces and endoscopes should be strongly disinfected, and a negative rectal swab test should possibly be adopted before discharge, especially for those patients with GI symptoms[58,59]. In contrast, other studies suggested that the detection of viral RNA in feces and respiratory secretions of patients could be prolonged but is not directly associated with the infectiousness of the virus as the viability of the virus diminishes over time[60].

Table 2 Gastro-intestinal symptoms (frequency > 30%) and correlation with the clinical course of coronavirus disease 2019

Ref.	No. of patients	Frequency of GI symptoms, n (%)	Diarrhea, n (%)	Nausea or vomiting, n (%)	Loss of appetite, n (%)	Ab-dominal pain, n (%)	Correlation with worse or better clinical course	Comments/limitations
An <i>et al</i> [50]	205	79 (38.5)	20 (9.8)	18 (8.8)	59 (28.8)	4 (2.0)	Yes, worse for patients with classic, better for patients with only GI symptoms	Possible selection bias, stool testing for virus needed further investigation
Zhang <i>et al</i> [129]	505	164 (32.5)	62 (12.3)	40 (7.2)	93 (18.4)	17 (3.3)	Yes, worse	Possible selection bias, not prognostic index scores obtained
Pan <i>et al</i> [52]	204	103 (50.5)	35 (17.2)	4 (2)	81 (39.7)	2 (1)	No	Small sample, not test for SARS-CoV-2 RNA in the stool
Sierpiński <i>et al</i> [130]	1942	1041 (53.6)	470 (24.2)	No	913 (47)	No	No	Nonhospitalized patients
Lin <i>et al</i> [57]	95	58 (61.1)	23 (24.2)	21 (22.1)	17 (17.9)	2 (2.1)	No	49.5% cases exhibited GI symptoms during hospitalization
Cao <i>et al</i> [131]	157	63 (40.1)	25 (15.9)	21 (13.4)	47 (30)	No	No	Lack of data of reverse transcriptase polymerase chain reaction on COVID- GI specimens
Nobel <i>et al</i> [132]	278	97 (35)	56 (20.1)	63 (22.6)	No	No	Yes, better	Short follow-up time
Kaafarani <i>et al</i> [133]	141	64 (45)	42 (29.8)	31 (22.0)	No	21 (14.9)	Yes, worse	Critically ill patients
Renelus <i>et al</i> [134]	734	231 (31.5)	149 (20.3)	171 (23.3)	No	68 (9.3)	Yes, better	Possible selection bias, only hospitalized patients
Moura <i>et al</i> [135]	400	133 (33.3)	69 (17.3)	85 (21.3)	46 (11.5)	24 (6.00)	No	Possible selection bias, only hospitalized patients
Redd <i>et al</i> [136]	318	195 (61.3)	107 (33.7)	133 (41.8)	110 (34.8)	46 (14.5)	No	Lack of validated symptom instruments, exclusion of ambulatory patients
Zhan <i>et al</i> [137]	405	248 (61.2)	112 (27.7)	76 (18.8)	170 (42)	41 (10.1)	Yes, worse	Only hospitalized patients
Cholankeril <i>et al</i> [138]	207	70 (33.8)	32 (15.5)	32 (15.5)	No	14 (7.1)	Yes, worse	Initial experience treating COVID-19, short study duration, unable to further assess hospitalization outcomes
Chen <i>et al</i> [48]	101	75 (74)	51 (50)	44 (43.6)	54 (53)	26 (26)	No	Prospective case-control study, mostly with outpatients, with mild to moderate symptoms

GI: Gastro-intestinal; NA: Not available; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

CURRENT GASTROENTEROLOGY PRACTICE AND TRANSITION TO POST COVID-19 ERA

Healthcare workers at endoscopy units and outpatient gastroenterology departments are at high risk of COVID-19 transmission through the inhalation of airborne droplets, conjunctival contact, and potential fecal-oral transmission[53]. Upper GI endoscopy, especially when certain circumstances occur (such as open suction of the upper respiratory tract), is an aerosol-generating procedure with increased occupational hazards for doctors and nurses. ERCP is another high-risk procedure, whereas lower GI endoscopy has a lower risk for transmission[61].

Three periods characterized by changes in endoscopy and GI practice and highly influenced by the evolution of the pandemic include the following: (1) During the first wave of the pandemic, all non-emergency, non-essential endoscopy was completely stopped for a short time because exacerbation of the pandemic and dangers from its spread surpassed dangers from not performing elective procedures[58,62,63]; (2) At the end of the first wave and in anticipation of the second one, as risks from

postponing endoscopy procedures, such as bowel cancer screening, became evident and pandemic epidemiology changed toward less prevalence, recommencement of endoscopy was recommended[64-67]. Implementation of these recommendations resulted in a 40 to 50% recovery of previous endoscopic activities[68]; and (3) As the third wave of the pandemic is upon us with new, possibly more transmissible strains, increasing the pressure on healthcare services, new, recently updated guidelines recommend rapid implementation of vaccination of all endoscopy staff and prioritization of vaccination for selected patients before an endoscopic procedure. In addition, all protective measures mentioned in previous recommendations are adhered to even after the vaccination is completed[69,70].

Current guidelines encourage complete endoscopic GI activity in areas without evidence of community transmission. Prioritization of procedures by clinical or oncological indication is recommended for areas with limited endoscopic capacity or a high prevalence of SARS-CoV-2 infection[66,69,71]. Patients with GI emergencies or with alarming symptoms and at high risk for cancer, based on previous examination results, should be given priority. The evaluation of patients with symptoms of non-urgent GI pathology and patients at lower risk for cancer should be temporarily postponed. Telephone screening and triage of referrals for endoscopy units and outpatient clinics are significant in differentiating each patient's status. Emergency or high-priority procedures include acute upper GI bleeding with risk stratification for those who will need endotherapy; removal of upper GI foreign bodies; obstruction of GI lesions requiring stenting/therapy; ERCP for urgent procedures; urgent inpatient percutaneous endoscopic gastrostomy, and nasojejunal tube insertion for nutrition support; endoscopic vacuum therapy for perforations; ongoing lower GI bleeding; endoscopic treatment of high-grade dysplasia or early intramucosal cancer in the esophagus, stomach, or large colonic polyps at high risk of submucosal invasion; malignant stricture stenting; upper GI fistula/Leakage; dysphagia or dyspepsia with the presence of alarming symptoms; colonoscopy for melena after negative upper GI endoscopy; severe anemia; tissue acquisition required for initiating systemic therapy/surgery; colonoscopy within organized positive fecal occult blood test (FOBT)/fecal immunochemical test (FIT) colorectal cancer (CRC) screening program; radiologic evidence of mass, lymph node endoscopic ultrasound (EUS) sampling; gall stone-related pancreatitis; pancreatic mass/stricture; biliary stricture dilation; pancreaticobiliary stent replacement; and necrosectomy. These procedures cannot be differentiated and should be continued with proper precautions. In contrast, non-urgent or low-priority procedures such as all symptomatic routine referrals, FIT and bowel screening colonoscopy, bowel scope flexible sigmoidoscopy, surveillance and disease assessment for inflammatory bowel disease (IBD), polyp follow-up, Barrett's esophagus, outpatient rigid sigmoidoscopy, low-risk follow-up, and repeat scopes, elective therapeutic procedures, bariatric endoscopy, routine small bowel endoscopy, EUS and ERCP for non-urgent procedures and endoscopy for clinical research should be differentiated and rescheduled according to the changes in COVID-19 epidemiology, availability of GI services, and changes in patients' status. However, procedures of moderate priority should be discussed case-by-case, such as the 2-wk wait referrals, EUS for cancer staging/treatment planning, planned endoscopic mucosal resection/endoscopic submucosal dissection for high-risk lesions, new suspected acute colitis, small bowel endoscopy for therapy, variceal banding in high-risk cases (recent bleeding), endoscopic treatment of esophageal or gastric low-grade dysplasia, duodenal polyps, ampullectomies, iron-deficiency anemia, pancreatic cysts, non-emergency biliary strictures, achalasia, and positive FOBT/FIT outside of an organized regional/national screening program[66,71].

The measures proposed by international societies should be followed to ensure the continued safety of GI procedures. These include stratification of patients for the risk of COVID-19 before any examination using questionnaire and/or body temperature, limited clinical examination, use of personal protective equipment (PPE) during procedures with confirmed or highly suspected patients, treating patients with unknown status or doubtful cases or emergency cases in which time delay is unacceptable as confirmed COVID-19 patients and performing real-time reverse transcription-polymerase chain reaction (RT-PCR) whenever possible for the above-mentioned scenarios. Daily screening and regular PCR testing of endoscopy center staff for COVID-19 exposure, reducing the number of healthcare personnel and people accompanying patients to those absolutely necessary, and social distancing measures for all, patients and staff were proposed as feasible choices. Strategies to minimize the time of procedures and thus the time of exposure and maximize the quality of procedural technique such as recruitment of medical and nurse staff with experience were also suggested[72]. Other measures include the use of masks and rooms with

negative pressure or proper air circulation; hand hygiene; special disinfection procedures for rooms and equipment; time delay of examinations; discrimination of units according to the COVID-19 status of patients that they can safely handle with proper and adequate PPE supply; a separate flow of patients to different units according to their possibility of SARS-CoV-2 carriage, the results of pre-procedure tests, and the nature of the procedure to be performed. RT-PCR is still considered the method of choice for pre-procedure testing. It is both safe and effective and has not been replaced by other methods (antibody/point of care antigen testing immunoassays)[64,66,73,74].

The need for social distancing and the high risk for complications from COVID-19 that many patients with GI disorders present have changed the method of outpatient evaluation of these patients. Telemedicine with virtual visits, telephone or video consultation, and nurse-led care support offer inexpensive, quality, and safe healthcare services by minimizing the risk for COVID-19 and other infectious diseases[58,75-77]. Patients and physicians have reported a great degree of satisfaction from telemedicine services[78]. It has already been successfully used to follow-up patients with GI disorders and IBD, and some chronic liver conditions, and its role has been strengthened during the COVID-19 pandemic. Nevertheless, telemedicine is not a panacea and is not suitable in situations where physical examination is crucial or when alarming GI symptoms (involuntarily loss of weight, the inability of oral intake, jaundice) are present. It requires access to and knowledge of technology, which may be difficult for many patients, especially the elderly[77,79]. Patient's informed consent, secure use of medical data, and adherence to ethics – local and international laws – are extremely significant. The legal framework regarding telemedicine applications and services requires further clarifications. Thus, telemedicine is expected to have a long-lasting impact on GI practice in the post-COVID-19 era, with the adoption of many elements and after clarification of certain details regarding its limits and the procedures related to its use.

Another element from COVID-19 pandemic and GI practice that will exist in the post-COVID-19 era is the enhanced use of non-invasive or less-invasive diagnostic procedures such as FIT, fecal calprotectin assessment, video capsule, and radiological imaging[80]. These present minimal danger for airborne or fecal-oral transmission of COVID-19 or other diseases. Safety, cost-effectiveness, and comparison of this approach to the traditional endoscopic methods are subjects of ongoing research[81].

IBD AND COVID-19

Patients with IBD are at an increased risk for developing infectious complications. Although their disease is not considered immunosuppressive, they receive immunosuppressive or immunomodifying therapies, making them vulnerable to opportunistic infections[82-84]. Nevertheless, lower or similar incidence, similar severity of disease, and similar mortality from COVID-19 with the general population have been reported for IBD patients[85-88]. The possible explanations for these findings are the protection of these patients from COVID-19 due to compliance with recommendations for social distancing, distal follow-up, and avoidance of unnecessary exposure, and the suppressive effect of the immunosuppressive therapies that these patients receive against cytokine storm[89]. Cytokine storm is very harmful to the host's immune system; it is an overreaction with excessive release of cytokines during COVID-19. The cost from the enhanced replication of COVID-19 promoted by immunodeficiency caused by immunosuppressant drugs is outweighed by the gain from the deterioration of the cytokine storm that these drugs induce in these patients. High rates of diarrhea as a COVID-19 symptom may mislead to the diagnosis of IBD exacerbation and result to incorrect steroid use[90,91].

Especially during the first wave of the pandemic where the preparation of healthcare systems was inadequate with enhanced fear of the use of medical services, patients' initial diagnosis and follow-up were affected[92]. For instance, there were reports for the delay at the infusion of biologic or other treatments in IBD patients[87, 93].

Performance of endoscopic procedures in IBD patients is considered necessary and not postponed only in urgent situations such as acute GI bleeding, confirmation of new IBD diagnosis especially in moderate-to-severe cases in which biologic therapies are used instead of high-dose corticosteroids, an acute flare-up of ulcerative colitis, bowel obstruction in IBD patients, and cholangitis in PSC patients[94]. Other indications are considered case-by-case. Telemedicine and distal evaluation play a

crucial role in the safe management of these patients.

The up-regulation of ACE2 in the intestinal epithelial cells of IBD patients provides an interesting insight into the virulence and the subsequent intestinal inflammation by COVID-19 in IBD patients. Interestingly, IBD therapies were not associated with altered mucosal ACE2 expression, possibly explaining why patients with IBD are not at greater risk for more serious COVID-19 disease[95].

The immunogenicity of IBD patients to COVID-19 mRNA vaccines is unknown. Furthermore, IBD dysregulation of immune response along with the immunosuppressive effect of IBD therapies raises questions about the effectiveness of vaccines [96]. However, vaccination of IBD patients is strongly recommended given their safety profile and the risks from COVID-19 complications.

Recommendations from international associations on IBD patients' management during COVID-19 are outlined in the article by Sultan *et al*[97]. In patients with stable disease who are COVID-19 negative, the continuation of most categories of drugs (mesalazine, immunosuppressants, biologics, Janus Kinase-inhibitors); possible careful de-escalation of combination immunosuppressive therapy; and avoidance or reduction or cessation of steroids while postponing the use of new immunosuppressive drugs and biologics with individual risk assessment, especially in high-risk endemic areas, are suggested. In contrast, if an IBD patient tests positive for COVID-19, certain biologic or immunosuppressive therapies should be temporarily discontinued, and steroids should be tapered until the patient recovers. Lately, steroids have been a subject of debate because recent studies have shown potential benefits from their use in patients with COVID-19 and need of supplemental oxygen. In addition exacerbation of IBD after steroid withdrawal poses an additional danger. Steroids remain the mainstream element of effective therapy in IBD emergencies such as acute severe ulcerative colitis[26,98].

HOW GASTROENTEROLOGICAL CANCER IS AFFECTED BY COVID-19 PANDEMIC

Another concern that has arisen during the COVID-19 era is the delay in extremely important aspects of clinical practice such as cancer care. A very direct sequela of the pandemic is the postponement of screening programs for GI cancers, especially for CRC. Endoscopy, a crucial part of the screening process, has been affected to varied and substantial degrees worldwide[99]. Despite significant efforts for recommencing endoscopy practice, delayed and advanced-stage diagnosis of esophageal, colorectal, or gastric cancer in GI patients is an emerging concern[100-103]. Consequently, cancer-related mortality is expected to increase in the future[104]. The same fears arise for all GI cancers, although their screening perspectives are not equal to those of CRC. In addition, access of patients to their chemotherapy centers and therapies and secure management of their follow-up are concerns, especially because they represent an extremely vulnerable population to COVID-19 complications. Their vulnerability is attributed either to increased ACE2 expression found in tissues from gastric and colon tumors, which may serve as an entry and proliferation site for the virus, posing these patients to increased risk for more severe SARS-CoV-2 infection or the frailty that these patients present due to their immunosuppression and comorbidity status[105, 106]. Resources of healthcare systems and availability of healthcare personnel are prioritized for COVID-19 and the pandemic has not left considerable space for procedures whose postponement can significantly affect the outcome and quality of life of patients with cancer. All these concerns require the implementation of measures that can provide optimal care to patients with GI or other cancer until vaccination is performed with successful outcomes in containing limiting COVID-19 spread and recovering healthcare systems and societies from the COVID-19 burden. International societies have started recommending the management of patients with GI cancers during COVID-19[107,108].

High-priority CRC patients are susceptible to developing potential complications, such as an acute abdomen, bowel obstruction, chemotherapy toxicities, febrile neutropenia. It is speculated that the timely intervention for those patients can significantly impact the disease progression and survival. Medium-priority patients are those with no symptoms and a new diagnosis of the disease with or without prior surgery, who are evaluated for chemotherapy initiation and treatment planning. Established patients who develop new problems or symptoms should be encouraged to use telemedicine services for non-life-threatening problems. Low-priority patients are those who seek a second physician opinion, those who require restaging in

metastatic disease without undergoing surgery with curative intent, and those who require restaging in third-or fourth-line regimens. Patients who are on maintenance treatment and who require follow-up visits should be encouraged to use telemedicine services as well. In healthcare settings, patients should be triaged for fever and other symptoms relevant to COVID-19 infection. Furthermore, preventative measures such as social distancing should be followed. Patients with suspected COVID-19 infection should be evaluated in dedicated examination areas and all the transmission precautions should be followed. Imaging in patients with suspected bowel obstruction, active bleeding, GI perforation, or postsurgical complications and those with suspected pathologic fractures should be highly prioritized. Similarly, radiologically confirmed bowel obstruction, peritonitis, massive GI bleed, anastomotic leak, and spinal fractures with potential spinal cord compression should be managed surgically on a high-priority basis[107].

Similar principles apply to the management of patients with gastro-esophageal cancer.

Patients with a new diagnosis of the disease, those who are potentially unstable and undergo perioperative treatment, and patients diagnosed with metastatic disease, should be medically evaluated with proper interventions on a high-priority basis. Post-operative or post-chemotherapy patients without complications or those who receive oral maintenance regimens are of medium priority, whereas telemedicine services should be used for patients in palliative care treatment and those without acute medical needs. Low-risk patients are those without acute issues and those who are followed up for survivorship visits.

Patients with acute symptoms, those who require initial staging or pre-operative evaluation, and patients with suspected disease progression should be evaluated with appropriate imaging as high-priority cases. Patients with life-threatening conditions such as perforation, active bleeding, or post-operative complications are considered high-priority patients for surgical interventions and endoscopic procedures. Patients on pre-operative chemotherapy are of high priority, whereas decisions should be individualized according to the clinical benefit for those on post-operative chemotherapy[108].

PANCREAS AND COVID-19

The extrapulmonary manifestations of COVID-19 infection include involvement of the pancreas[109]. The potential mechanisms of pancreatic damage are variable. Direct injury can occur through the ACE2 receptors, whereas systemic inflammation and immune dysregulation also play a significant role[110,111]. Medication-induced pancreatic injury is often related to corticosteroids or NSAIDs. COVID-19 investigational treatments such as tocilizumab can cause acute pancreatitis through hypertriglyceridemia[112]. It is speculated that pancreatic injury is more prominent in patients with severe disease as compared to mild cases of COVID-19[113]. Abnormal laboratory values indicative of possible pancreatic involvement have been reported in 8.5% to 17.3% of cases[113]. The associated symptoms are nausea, vomiting, abdominal pain, and diarrhea[114,115]. In addition, there are several reports of acute pancreatitis in the setting of COVID-19 infection[116,117].

A balance should be maintained between patient care and prevention of transmission in patients with pancreatic cancer. For stable patients, telemedicine services should be used. Diagnostic and therapeutic procedures such as ERCP, EUS, or regular imaging studies should be reserved for patients with symptoms. Given the poor prognosis in pancreatic malignancies, surgery for a potentially curable disease should be prioritized based on local epidemiologic burden and facility resources. The decision to proceed with chemotherapy should be made by a multidisciplinary team approach and should be tailored based on the disease stage, individual patient characteristics, the risk for disease progression, and potential risk for COVID-19 transmission [109]. Several organizations have developed tools and recommendations for the management of pancreatic cancer during the pandemic[118].

CONCLUSION

Patients with GI and liver disorders have presented with several challenges in everyday clinical practice, even in the pre-COVID-19 era. COVID-19 is an additional burden to these patients and their healthcare practitioners. The pandemic's cost in

human lives is high and the consequences will be evident for many years after the pandemic declines. The pandemic has taught many lessons to the medical society. In our effort to protect ourselves and protect and treat our patients properly, we have learned to accumulate knowledge with speed and perform our best under pressing and extreme conditions. This is evident by several aspects of recent medical research and practice regarding protection from and treatment of COVID-19 and has led to the rapid adoption of new and constantly changing recommendations from international societies. Accordingly, the vaccines for COVID-19 were prepared with speed, effectiveness, and safety, and the struggle for the desired herd immunity is underway. Apart from international recommendations, the need for individualization of medicine has become more evident during the pandemic. Every GI or liver disorder is unique for the patient that has it. Although recommendations can assist and provide directions, every patient has to be considered with his/her special requirements. Finally, we anticipate that in the future, approaches such as telemedicine and minimally invasive diagnostic or therapeutic procedures will have a more significant role in patient management. Despite our fears and disappointments from what we have seen during the pandemic, the passage to the post-COVID-19 era appears hopeful.

ACKNOWLEDGEMENTS

This paper is dedicated to the memory of Zafeiridis T (1974-2021), whose early and unexpected death left a tremendous scientific and emotional gap in our lives.

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