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Review Article

Gastrointestinal, Hepatobiliary, and Pancreatic Manifestations of SARS-CoV-2: What Do We Know and Where Are We Heading

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Abstract

The Severe acute respiratory syndrome virus 2 (SARS-CoV-2) is a novel strain of zoonotic coronavirus first discovered in December 2019 in Wuhan, China. The Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, rapidly evolved into a pandemic throughout the world. COVID-19 is regarded as a respiratory disease primarily; however, numerous reports have shown that gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain, are not uncommon in patients with COVID-19. Moreover, recent studies have shown evidence of damage to digestive organs such as the liver, the pancreas, and the gallbladder by SARS-CoV-2. The virus is primarily transmitted person-to-person through respiratory droplets or close contact. However, recent studies have shown evidence of prolonged shedding of the viral RNA in the feces of infected patients even after the respiratory symptoms have resolved and SARS-CoV-2 is no longer detectable in the nasopharyngeal samples, raising suspicion for the potential fecal-oral spread of the virus. The knowledge base regarding the involvement of the digestive system and symptoms continues to grow over the last few months. We believe future work should focus on developing stool testing to understand possible fecal-oral transmission, and to support the confirmation of recovery which further helps healthcare providers and patients to take appropriate measures to prevent the spread of COVID-19 disease.

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Introduction

The situation around the Coronavirus disease 19 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been rapidly evolving. First discovered in December 2019 in Wuhan, China, the virus has rapidly spread throughout the world, with nearly eight million confirmed cases and over 430,000 related deaths in 187 countries as of June 16. The first confirmed case in the United States was reported on January 20, 2020, and in a mere five months, over 2 million cases have been confirmed in the US, and the number of deaths has exceeded 110,000 [1,2].

SARS-CoV-2 is a positive-sense, single-stranded RNA virus [3]. As the name suggests, it most commonly causes respiratory symptoms such as cough and dyspnea and is thought to be primarily transmitted person-to-person through respiratory droplets or close contact [4]. However, less frequent manifestations, including gastrointestinal (GI) symptoms such as anorexia, nausea, vomiting, abdominal pain, and diarrhea, have been widely reported.The Centers for Disease Control and Prevention (CDC) include nausea, vomiting and diarrhea in the COVID-19 description of symptoms. SARS-CoV-2 enters the lower respiratory tract by binding to the angiotensin-converting enzyme 2 (ACE2) receptors, which are also highly expressed in the gastrointestinal tract, including the gastric, duodenal, and rectal epithelia [5]. Recent studies have also found that TMPRSS2 and TMPRSS4, two related serine proteases that are abundant in the gastrointestinal tract, can enhance virus entry into enterocytes by priming the spike protein [6]. Multiple small studies outside the US have confirmed the presence of the viral RNA in stool samples of infected patients, sometimes even after the viral RNA cleared from the respiratory tract samples [7]. The prolonged viral RNA shedding in feces raises suspicion for active viral replication in the gastrointestinal tract and potential fecal-oral transmission of SARS-CoV-2. Currently, there is no specific treatment designated for COVID-19. Even though there have been promising results in the clinical trials for certain medications and vaccine candidates, symptomatic management remains the mainstay of treatment for COVID-19 [8]. Therefore, understanding the symptomology of COVID-19 and routes of transmission of SARS-CoV-2 infection is critical to reduce the morbidity and mortality of COVID-19.

Gastrointestinal System

GI symptoms have been frequently reported as common symptoms of COVID-19 with a prevalence ranging from 11.3% to 79.1% in different studies [7]. In a meta-analysis study that analyzed findings from 6,686 COVID-19 patients in 35 studies, the pooled prevalence of digestive symptoms was 15% [9]. Overall, the most common gastrointestinal symptoms are nausea and vomiting, diarrhea, loss of appetite, and abdominal pain with a pooled prevalence of 9%, 7%, 21%,

and 3% in the same study. Another meta-analysis of 47 studies with 10,890 patients reported similar results as earlier studies, in which diarrhea, nausea, vomiting, and abdominal pain were present in 7.7%, 7.8%, and 3.6% of patients, respectively [10]. Of note, the majority of studies (70%) in this meta-analysis were from China, and the estimates of gastrointestinal symptoms in studies outside of China are higher when compared to those in studies from China. For example, the pooled prevalence of diarrhea in china vs outside china is 5.8% and 18% respectively. Interestingly, in some cases, the gastrointestinal symptoms either present before the respiratory ones or are the sole symptoms of their disease presentation. In a study that analyzed 1,141 confirmed COVID-19 cases admitted to Zhongnan Hospital of Wuhan University, 183 (16%) presented with isolated gastrointestinal symptoms, and anorexia was the most common initial presentation in this cohort of patients in the study [11].

On the other hand, other less common, but potentially severe gastrointestinal symptoms such as upper or lower gastrointestinal tract bleeding should not be overlooked. The prevalence of gastrointestinal bleeding in COVID-19 patients is unclear; reports from a few studies in China range from 4% to 13.7%, but the sample sizes were small [12]. The manifestations of upper gastrointestinal bleeding include hematemesis and melena, as reported in a case series of six patients [13]. Of note, gastrointestinal bleeding in COVID-19 can present in the absence of respiratory symptoms. A case of hematochezia as the initial presentation of COVID-19 was reported, and the interval between the onset of hematochezia and respiratory symptoms, in this case, was as long as nine days [14].

The understanding of the mechanisms of gastrointestinal bleeding in COVID-19 cases is incomplete. In most reported cases, endoscopy or colonoscopy was not performed for fear of transmission of SARS-CoV-2. The American Society of Gastrointestinal Endoscopy (AGSE) regards invasive GI procedures in the digestive tract as high-risk in their guideline issued in March 2020 because of the potential fecal-oral transmission of SARS-CoV-2, and later published updated guidance for resuming GI endoscopy in late April [15,16]. One hypothesis potencially explaining the propensity for gastrointestinal bleeding in COVID-19 patients is the presence of underlying ulcers in the upper digestive tract, as the 1-year prevalence of peptic ulcer disease is estimated to be 0.12%-1.50% in the general population [17]. However, COVID-19 related coagulopathy could also play a role in severe cases [18].

Hepatobiliary System

Abnormalities of liver enzymes have also been widely observed in COVID-19 cases, indicating liver injury in such cases. The pooled prevalence was 15% for both alanine aminotransferase (ALT) and aspartate aminotransferase (ALT) abnormalities [10]. Most liver injuries were mild and transient, but severe liver damage was not uncommon. There are various mechanisms of liver injuries in COVID-19, which include direct hepatocellular damage by SARS-CoV-2, pre-existing liver diseases, immune-mediated inflammation, and possible drug toxicity [19]. Whether patients with pre-existing liver disease are at higher risk for contracting COVID-19 is poorly defined at present [20]. Further research is also needed to determine if liver injury is associated with worse outcomes in COVID-19 patients, or in turn, if COVID-19 could result in worse liver outcomes in patients with underlying liver disease. The current recommendations for the management of liver disease in COVID-19 patients are summarized in (Table 1).

Liver Disease	Recommendations for COVID+ Patients
Compensated cirrhosis [21-24]	• Antiviral treatment for chronic hepatitis B and C is not immediately required unless hepatitis B flare or receiving immunotherapy • Vaccinate against Streptococcus pneumonia and influenza • Avoid endoscopy unless GI bleeding, bacterial cholangitis, or other life-threatening condition • Delay HCC screening until the pandemic passes • Screen for varices based on thrombocyte count or Baveno VI criteria • Avoid acetaminophen or NSAIDs
Decompensated cirrhosis [22,23,25]	• Vaccinate against Streptococcus pneumonia and influenza • Provide care via telemedicine/telephone • Limit transplants to poor short-term prognosis • Closely follow SBP and encephalopathy prophylaxis • Test for SARS-CoV-2 in acute decompensation • Lopinavir/ritonavir contraindicated • Avoid acetaminophen or NSAIDs
Liver Transplant [22,23,26,27]	• Test donors/recipients on the transplant list for SARS-CoV-2 • Consider CT chest in pre-transplant workup • Continue immunosuppression without reducing the dose unless medication-induced lymphopenia or bacterial/fungal superinfection present • Close monitoring, dose adjustment or avoiding co-administration of immunosuppressants and COVID-19 specific therapy as appropriate • Lopinavir/ritonavir contraindicated with m-TOR inhibitors • Monitor calcineurin inhibitors closely • Consider liver biopsy if concern for acute rejection • Avoid acetaminophen or NSAIDs
Autoimmune Liver Disease [22]	• Continue immunosuppression without reducing the dose (C) • Vaccinate against Streptococcus pneumonia and influenza • Avoid acetaminophen or NSAIDs
Hepatocellular Carcinoma [22,23]	• Postpone locoregional therapies and temporarily withdraw immune-checkpoint inhibitor therapy • Individualize dosing/continuation of kinase inhibitors in tumor board meetings • Avoid acetaminophen or NSAIDs

Table 1: Current recommendations for the management of liver diseases in COVID-19 patients.

Gallbladder

To date, no gallbladder or bile involvement has been histopathologally confirmed in COVID-19 patients. However, a COVID-19 case complicated by acute cholecystitis requiring percutaneous cholecystostomy was reported in a patient with advanced heart failure with Left Ventricular Assistant Device (LVAD) [28]. In another recently published article, three patients admitted to the hospital for management of COVID-19 developed acalculous cholecystitis during recovery required laparoscopic cholecystectomy, which confirmed gangrenous gallbladder [29]. In both reports, the extent of gallbladder involvement secondary to COVID-19 is not known as no pathology reports are available and neither the tissue nor the bile was sent for testing for SARS-CoV-2 RNA. As gallbladder diseases are highly prevalent, particularly in western populations, the management of patients who develop symptomatic gallbladder disease during the current pandemic has also gained attention. A brief outline of the management of such cases has been published by the American College of Surgeons with goals of limiting exposure of both patients and healthcare providers to SARS-CoV-2 [30]. Further studies are needed to investigate whether the viral RNA is present in the gallbladder wall or bile as well as the effects of SARS-CoV-2 on gallbladder function.

Pancreas

The ACE2 receptor is highly expressed in pancreatic cells as well, which suggests that SARS-CoV-2 could theoretically cause damage to the pancreas [31]. In a study of 52 COVID-19 cases, pancreatic injury defined by elevations of amylase or lipase was found in 17% of patients [32]. Clinical symptoms of severe pancreatitis, however, was not present in any of the cases in the study. Meanwhile, severe acute pancreatitis was reported in two patients with COVID-19 who were admitted to the intensive care unit at the Copenhagen University Hospital Hvidovre, Denmark. In both cases, there were no other apparent causes of acute pancreatitis [33]. Similar to liver injuries mentioned above, possible mechanisms of pancreatic damage caused by SARS-CoV-2 include direct viral infection, immune-mediated injuries, and adverse reactions caused by certain medications such as antipyretics [32,34].

COVID-19 in Patients with Inflammatory Bowel Disease (IBD)

As gastrointestinal symptoms are common in COVID-19 cases, patients with underlying gastrointestinal conditions should be closely screened. First, their baseline gastrointestinal symptoms could mask symptoms related to COVID-19, leading to a possible delay in the diagnosis. Second, patients with chronic medical conditions are at a higher risk of developing severe illness from COVID-19, especially considering the fact that long-term immunosuppressant medications are used as treatments for some of the conditions such as inflammatory bowel syndrome (IBD). The CDC recognizes that people with prolonged use of corticosteroids and other immune weakening medications are at higher risk for severe illness from COVID-19 [35].

As of May 26, a total of 1302 cases of IBD patients with confirmed COVID-19 were reported on Surveillance Epidemiology of Coronavirus under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) international registry [36]. In 396 (30%) of the cases, the patients were hospitalized, of which 72, or 6.2% of the total cases required ICU-level care. Ventilators were utilized in 57 (4.9%) of the cases, and 44 (3.7%) patients eventually died of COVID-19. This is comparable to the overall illness severity and case fatality of COVID-19 in all patients, with an estimated 5% of the cases requiring ventilator use and an overall case fatality of 2.3%. There have been studies that support such an impression that IBD patients do not seem to be more susceptible to COVID-19, nor are they more likely to develop severe illness from COVID-19 overall [37-39]. There are no significant differences between male and female COVID-19 patients with IBD regarding the incidence or severity of COVID-19; however, age seems to play an important role in predicting the outcomes in such patients, similar to what was observed in the general population [36]. Compared to younger patients, the risk for developing severe illness (defined here as cases requiring ICU-level care or ventilator use, and cases resulting in deaths) greatly increases in older patients age 60 and above (Table 2). Comorbidities also have a significant effect on the outcomes of COVID-19 patients with IBD. In patients with more than three comorbidities, as high as 36% were reported to develop severe illness; in contrast, in patients with no other underlying condition, the risk is only 3%.The use of corticosteroids is controversial in the treatment of COVID-19. A few studies have reported a delay in viral clearance with the use of corticosteroids [40-42]. However, a more recent study conducted in the United Kingdom, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, reported that dexamethasone could reduce death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [43]. Data from SECURE-IBD suggest that in patients that use oral or parenteral steroids, 22% developed severe COVID-19, a much higher rate compared with other immunosuppressants and biologics (Table 2). The American Gastroenterological Association has released a guideline for the management of IBD during the pandemic which suggests that 1) patients who are not infected by SARS-CoV-2 should continue the treatment for IBD; 2) patients who are infected but asymptomatic should hold thiopurines, methotrexate, and tofacitinib, and delay the dosing of biological therapies for two weeks of monitoring for COVID-19 symptoms; 3) patients with COVID-19 symptoms should hold thiopurines, methotrexate, tofacitinib, and biological therapies which can be restarted after complete symptom resolution. In addition, amino-salicylates, topical rectal therapy, dietary management, and antibiotics are considered safe in all patients, while systemic corticosteroids should be avoided and discontinued quickly if possible [44].

Possibility of Fecal-oral Transmission

Although ACE2, the receptor used by SARS-CoV-2 to enter cells, is abundant in the gastrointestinal tract, including the glandular cells of gastric, duodenal, and rectal epithelia, whether the virus can be spread via fecal-oral route is still under investigation [5]. Multiple studies have observed persistent positive results for SARS-CoV-2 virus RNA in stool samples of COVID-19 patients [45]. A systematic review by Cheung et al. found that even after respiratory specimens turn negative for the virus, 70.3% of the stool samples remain positive for viral RNA [46]. The prolonged viral RNA shedding in feces raises suspicion for active viral replication in the gastrointestinal tract and potential fecal-oral transmission of SARS-CoV-2. However, to date, all attempts to isolate infectious virus from the stool specimens have been unsuccessful, even when there is high stool viral RNA load. So far, there is still no direct evidence for fecal-oral transmission of SARS-CoV-2, and further research with larger cohorts of patients is needed to investigate this matter.

Characteristics	Total	ICU	Ventilator	Death	ICU/Ventilator/Death
Overall	1170	72 (6.2%)	57 (4.9%)	44 (3.7%)	100 (8.5%)
Age (years)					
0-19	49	0 (0%)	0 (0%)	0 (0%)	0 (0%)
20-39	452	9 (1.9%)	4 (0.8%)	2 (0.4%)	9 (1.9%)
40-49	221	10 (4.5%)	7 (3.2%)	2 (0.9%)	11 (5.0%)
50-59	195	16 (8.2%)	14 (7.2%)	5 (2.6%)	18 (9.2%)
60-69	138	26 (18.8%)	22 (15.9%)	14 (10.1%)	33 (23.9%)
70-79	65	9 (13.8%)	6 (9.2%)	8(12.3%)	14 21.5%)
80 and above	45	1 (2.2%)	4 (8.9%)	12 (26.7%)	14 (31.1%)
Gender					
Male	604	39 (6.5%)	30 (5.0%)	31(5.1%)	56 (9.3%)
Female	548	33 (6.0%)	27 (4.9%)	13 (2.4%)	44 (8.0%)
Comorbidities					
0	728	17 (2.3%)	12 (1.6%)	5 (0.7%)	21 (2.9%)
1	273	23 (8.4%)	15 (5.5%)	14 (5.1%)	30 (11.0%)
2	96	15 (15.6%)	16 (16.7%)	10 (10.4%)	22 (22.9%)
3 and above	73	17 (23.3%)	14 (19.2%)	15 (20.5%)	27 (37.0%)
Medications for IBD treatment					
Anti-TNF without 6MP/AZA/MTX	337	7 (2.1%)	3 (0.9%)	3 (0.9%)	8 (2.4%)
Sulfasalazine/mesalamine	334	33 (9.9%)	32 (9.6%)	22 (6.6%)	51 (15.3%)
Anti-TNF+6MP/AZA/MTX	117	10 (8.5%)	5 (4.3%)	3 (2.6%)	12 (10.3%)
Anti-integrin	115	6 (5.2%)	7 (6.1%)	4 (3.5%)	9 (7.8%)
6MP/azathioprine monotherapy	113	10 (8.8%)	8 (7.1%)	3 (2.7%)	12 (10.6%)
IL 12/23 inhibitor	112	3 (2.7%)	2 (1.8%)	1 (0.9%)	3 (2.7%)
Oral/parenteral steroids	98	18 (18.4%)	14 (14.3%)	11 (11.2%)	23 (23.5%)
Other IBD medications	104	9 (8.7)	5 (4.8)	5 (4.8)	10 (9.6)

Table 2: Outcomes in COVID-19 patients with IBD.

With the current evidence of prolonged shedding of viral RNA in the feces, the possibility of fecal-oral spread of SARS-CoV-2 must be taken into consideration by healthcare professionals caring for COVID-19 patients. There has been evidence of droplet nuclei and bioaerosols produced with toilet flushing [47], which further raises concern, especially in the healthcare settings, for possible contamination with viral particles from feces of COVID-19 patients. Notably, in a few undeveloped countries, shared restrooms and bathrooms are used in the hospital, which could lead to an even higher risk for potential transmission via the fecal-oral route. Appropriate measures of personal protection, isolation, and disinfection should be utilized to minimize the risk for further spread of the virus.

Conclusion

The COVID-19 pandemic, as a global health crisis, has posed complex challenges to the medical and public health systems worldwide. The understanding of the disease, as well as the causative virus, continues to evolve, but much is still unknown. Although SARS-CoV-2 has been classified as a respiratory pathogen, gastrointestinal symptoms are not uncommon presentations. Progress has been made in the research of pharmaceutical treatment of COVID-19. Remdesivir, a nucleoside analog, was found to shorten the recover time from 15 days to 11 days in hospitalized adult patients [48]. Another large clinical trial showed that Dexamethasone could reduce death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [43]. However, optimized symptomatic management remains the key in the battle against the disease. Gastrointestinal manifestations of COVID-19 should not be overlooked, and in patients with such symptoms, maintaining adequate nutrition and hydration is crucial. Further research is necessary to determine the effect of SARS-CoV-2 infection on the liver, pancreas, and gallbladder. Although most current studies point out that patients with IBD, in general, are not at a higher risk for contracting SARS-CoV-2 or developing severe illness from COVID-19, current evidence does indicate that the use of corticosteroids in patients with IBD is associated with adverse outcomes [49]. It is generally recommended that treatment for IBD should be continued in such patients if the disease is stable, but the corticosteroid use should proceed with caution and close monitoring.

Current evidence suggests that SARS-CoV-2 is primarily transmitted person-to-person through respiratory droplets or close contact, but our understanding of the transmission is still incomplete. Although currently there is no definitive evidence that the virus can be transmitted via the fecal-oral route, the possibility should certainly not be overlooked as multiple studies have shown evidence of persistent high viral RNA load in the stool samples. While further research is needed to investigate the possibility of fecal-oral transmission, measures for additional precautions are presently warranted.

References

1. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, et al. (2020) First Case of 2019 Novel Coronavirus in the United States. The New England Journal of Medicine 382: 929-936.
2. https://coronavirus.jhu.edu/map.html.
3. Satija N, Lal SK (2007) The molecular biology of SARS coronavirus. Annals of the New York Academy of Sciences 1102: 26-38.
4. Chan JF, Yuan S, Kok KH, Wang KK, Chu H, et al. (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet 395: 514-523.
5. Xiao F, Tang M, Zheng X, Liu Y, Li X, et al. (2020) Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 158: 1831-1833. e1833.
6. Zang R, Castro MFG, McCune BT, Zeng Q, Rothlauf PW, et al. (2020) TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Science Immunology 5: eabc3582.
7. Patel KP, Patel PA, Vunnam RR, Hewlett AT, Jain R, et al. (2020) Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. Journal of Clinical Virology 128: 104386.
8. Jing R, Vunnam RR, Yang Y, Karevoll A, Vunnam SR (2020) Current Status of Treatment Options, Clinical Trials, and Vaccine Development for SARS-CoV-2 Infection. Journal of Pure and Applied Microbiology.
9. Mao R, Qiu Y, He JS, Tan JY, Li XH, et al. (2020) Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: A systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology.
10. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, et al. (2020) AGA Institute Rapid Review of the GI and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology.
11. Luo S, Zhang X, Xu H (2020) Don't Overlook Digestive Symptoms in Patients With 2019 Novel Coronavirus Disease (COVID-19). Clin Gastroenterol Hepatol 18: 1636-1637.
12. Tian Y, Rong L, Nian W, He Y (2020) Review article: Gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther 51: 843-851.
13. Cavaliere K, Levine C, Wander P, Sejpal DV, Trindade AJ (2020) Management of upper GI bleeding in patients with COVID-19 pneumonia. Gastrointest Endosc.
14. Guotao L, Xingpeng Z, Zhihui D, Huirui W (2020) SARS-CoV-2 infection presenting with hematochezia. Med Mal Infect 50: 293-296.
15. https://www.asge.org/docs/default-source/default-document-library/press-release_impact-of-covid-19-on-endoscopy.pdf
16. https://www.asge.org/docs/default-source/default-document-library/asge-guidance-for-reopeningl_4-28-2020.pdf
17. Sung JJ, Kuipers EJ, Serag HB (2009) Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther 29: 938-946.
18. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, et al. (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. Journal of Thrombosis and Haemostasis 18:1023-1026.
19. Li J, Fan JG (2020) Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. Journal of Clinical and Translational Hepatology 8: 13-17.
20. Pawlotsky JM (2020) COVID-19 and the liver-related deaths to come. Nature Reviews Gastroenterology & Hepatology.
21. Fix OK, Hameed B, Fontana RJ, Kwok RM, Mcguire BM, et al. (2020) Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. Hepatology.
22. Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, et al. (2020) Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Reports: Innovation in Hepatology 2: 100113.
23. Yapali S (2020) What hepatologists need to know about COVID-19? Hepatology Forum.
24. Maurice JB, Brodkin E, Arnold F, Navaratnam A, Paine H, et al. (2016) Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. Journal of Hepatology 65: 899-905.
25. Casado JL, Del Palacio M, Moya J, Rodriguez JM, Moreno A, et al. (2011) Safety and pharmacokinetics of lopinavir in HIV/HCV coinfected patients with advanced liver disease. HIV Clinical Trials 12: 235-243.
26. https://www.covid19-druginteractions.org/
27. Alqahtani SA, Schattenberg JM (2020) Liver injury in COVID-19: The current evidence. United European Gastroenterology Journal 8: 509-519.
28. Singh R, Domenico C, Rao SD, Urgo K, Prenner SB, et al. (2020) Novel Coronavirus Disease 2019 in a Patient on Durable Left Ventricular Assist Device Support. Journal of Cardiac Failure 26: 438-439.
29. Asti E, Lovece A, Bonavina L (2020) Gangrenous cholecystitis during hospitalization for SARS-CoV2 infection. Updates in Surgery 2020:1-3.
30. https://www.facs.org/-/media/files/covid19/symptomatic_gallbladder_recommendations.ashx.
31. Liu F, Long X, Zhang B, Zhang W, Chen X, et al. (2020) ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol.
32. Wang F, Wang H, Fan J, Zhang Y, Wang H, et al. (2020) Pancreatic injury patterns in patients with COVID-19 pneumonia. Gastroenterology.
33. Hadi A, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, et al. (2020) Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family members. Pancreatology.
34. Hussain A, Bhowmik B, do Vale Moreira NC (2020) COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract 162: 108142.
35. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.
36. https://covidibd.org/current-data/
37. Al Ani AH, Prentice RE, Rentsch CA, Johnson D, Ardalan J, et al. (2020) Review article: Prevention, diagnosis and management of COVID-19 in the IBD patient. Aliment Pharmacol Ther 52: 54-72.
38. Higgins PDR, Ng S, Danese S, Rao K (2020) The Risk of SARS-CoV-2 in Immunosuppressed IBD Patients. Crohns Colitis 2: otaa026.
39. Taxonera C, Sagastagoitia I, Alba C, Mañas N, Olivares D, et al. (2020) 2019 Novel Coronavirus Disease (COVID-19) in patients with Inflammatory Bowel Diseases. Aliment Pharmacol Ther.
40. Tang C, Wang Y, Lv H, Guan Z, Gu J (2020) Caution against corticosteroid-based COVID-19 treatment. Lancet 395: 1759-1760.
41. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB (2020) Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 323: 1824-1836.

42. Russell CD, Millar JE, Baillie JK (2020) Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 395: 473-475.

43. https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf.

44. Rubin DT, Feuerstein JD, Wang AY, Cohen RD (2020) AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary. Gastroenterology.

45. Patel KP, Patel PA, Vunnam SR, Jain R, Vunnam RR (2020) Patients with COVID-19: Are current isolation guidelines effective enough? Public health 183: 38-39.

46. Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, et al. (2020) Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. Gastroenterology.

47. Liu Y, Ning Z, Chen Y, Guo M, Liu Y, et al. (2020) Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature.

48. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, et al. (2020) Remdesivir for the Treatment of Covid-19 - Preliminary Report. The New England Journal of medicine.

49. Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Lewis JD, et al. (2020) Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an International Registry. Gastroenterology.

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