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DOI:

[10.1177/1756284820934626](https://doi.org/10.1177/1756284820934626)

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Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Iacucci, M, Ghosh, S & Gardner, L (ed.) 2020, 'Involvement of digestive system in Covid-19: manifestations, pathology, management and challenges', *Therapeutic Advances in Gastroenterology*, vol. 13, pp. 1-12.
<https://doi.org/10.1177/1756284820934626>

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Involvement of digestive system in COVID-19: manifestations, pathology, management and challenges

Song Su*, Jun Shen*, Liangru Zhu*, Yun Qiu, Jin-Shen He, Jin-Yu Tan, Marietta Iacucci, Siew C Ng, Subrata Ghosh, Ren Mao  and Jie Liang

Abstract: The pandemic of novel coronavirus disease (COVID-19) has developed as a tremendous threat to global health. Although most COVID-19 patients present with respiratory symptoms, some present with gastrointestinal (GI) symptoms like diarrhoea, loss of appetite, nausea/vomiting and abdominal pain as the major complaints. These features may be attributable to the following facts: (a) COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its receptor angiotensin converting enzyme 2 (ACE2) was found to be highly expressed in GI epithelial cells, providing a prerequisite for SARS-CoV-2 infection; (b) SARS-CoV-2 viral RNA has been found in stool specimens of infected patients, and 20% of patients showed prolonged presence of SARS-CoV-2 RNA in faecal samples after the virus converting to negative in the respiratory system. These findings suggest that SARS-CoV-2 may be able to actively infect and replicate in the GI tract. Moreover, GI infection could be the first manifestation antedating respiratory symptoms; patients suffering only digestive symptoms but no respiratory symptoms as clinical manifestation have also been reported. Thus, the implications of digestive symptoms in patients with COVID-19 is of great importance. In this review, we summarise recent findings on the epidemiology of GI tract involvement, potential mechanisms of faecal-oral transmission, GI and liver manifestation, pathological/histological features in patients with COVID-19 and the diagnosis, management of patients with pre-existing GI and liver diseases as well as precautions for preventing SARS-CoV-2 infection during GI endoscopy procedures.

Keywords: COVID-19, endoscopy, gastrointestinal manifestation, inflammatory bowel disease

Received: 23 April 2020; revised manuscript accepted: 26 May 2020.

Introduction

The rapid outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), initially referred to as the 2019 novel coronavirus (2019-nCoV), has been impacting the entire world since December 2019. As of 22 April 2020, more than 2,471,136 laboratory-confirmed cases and more than 169,006 deaths in over 200 countries had been reported [World Health Organisation (WHO). Novel Coronavirus (2019-nCoV) situation reports: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>]. In this

state-of-the-art review article, we discuss in detail the gastrointestinal (GI) and liver involvement in COVID-19, which may be under-appreciated and pose a diagnostic challenge as well as a public health issue requiring further research.

Literature search

The PubMed, Web of Science and EMBASE databases were comprehensively searched for articles published from 1 December 2019 to 17 April 2020 with the following key words: 'coronavirus disease 2019', 'COVID-19', 'severe acute

Ther Adv Gastroenterol

2020, Vol. 13: 1–12

DOI: 10.1177/
1756284820934626

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respiratory syndrome corona virus 2', 'SARS-CoV-2', '2019 novel coronavirus' or '2019-nCoV'; 'gastroenterology' or 'gastrointestinal' or 'digestive' alone and in combination. Moreover, in light of the fact that considerable numbers of COVID-19 patients were reported in Chinese journals, the following major Chinese medical databases were also systematically searched: CNKI, WANFANG DATA, SinoMed. Two independent researchers (SS and LJ) screened study titles and abstracts and, when necessary, the full-text was further screened. Related articles were defined as COVID-19 literature simultaneously involving information on gastroenterology. Articles published in English and Chinese were both eligible. The reference lists of the included literature were searched manually for additional publications.

GI and liver manifestation in COVID-19

GI manifestation

While respiratory tract manifestations such as fever and cough are the most common reported symptoms in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), symptoms in other organs such as the GI tract, including nausea/vomiting and diarrhoea, have also been reported.¹ A study of 138 confirmed patients with COVID-19 showed that the main symptoms of COVID-19 included fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%) and dyspnoea (31.2%), GI symptoms included abdominal pain (3.6%), diarrhoea (10.1%) and vomiting (3.6%). It is worth noting that 14 cases (10.1%) had diarrhoea and nausea first, preceding fever.² Another retrospective analysis of 1099 patients with COVID-19 showed that the main symptoms of COVID-19 were fever (87.9%) and cough (67.7%), whereas diarrhoea (3.7%) and vomiting (5.0%) were less frequent. Among GI symptoms, the incidence of diarrhoea and abdominal pain in patients with severe COVID-19 was higher than that in patients with mild COVID-19.¹ According to the WHO and China collaborative report, the typical symptoms of COVID-19 include fever (87.9%), cough (67.7%), asthenia (38.1%) and dyspnea (18.6%). Unfortunately, although the report includes more than 50,000 COVID-19 infected patients, only diarrhoea as a GI symptom was included in this report (3.7%).³ In a recent systematic review and meta-analysis of 35 studies, comprising 6686 patients on GI manifestations of SARS-CoV-2

infection, the pooled prevalence of all GI symptoms was 15%, with nausea and/or vomiting, diarrhoea and loss of appetite being the three most common.⁴

Currently, loss of appetite was reported, ranging from 1.0% to 79%.⁴ In the study by Lin *et al.*, most COVID-19 patients developed loss of appetite during hospitalization, with a minority of patients having anorexia as initial presentation.⁵ Further they found there was no correlation between antibiotic treatment or antiviral treatment with loss of appetite.⁵ Although anorexia was the most common GI symptom (26.8%) after pooled analysis of prevalence, the mechanism of onset of anorexia in patients with COVID-19 remains unclear. It may be partially explained by gustatory dysfunction, which was found as high as 88.0% in a set of 417 mild-to-moderate COVID-19 patients in Europe. In addition, gustatory dysfunction was also significantly associated with olfactory dysfunction, which was identified with a high prevalence of 85.6% and may further exacerbate loss of appetite.⁶

With regard to the characteristics of diarrhoea, a study collected data from three reports and concluded that the link between diarrhoea and COVID-19 may be underestimated.^{7-9,10} Another study on GI manifestations of COVID-19 in a single center in Wuhan showed that the onset of diarrhoea was 1-8 days after the onset of the COVID-19 (with the median time 3.3 days). The course of disease was 1-14 days, the average duration was (4.1 ± 2.5) days. Bowel movement could be as high as 9 times per day, with the average (3.3 ± 1.6) times per day. In most instances, stool would be watery stool (34.3%). A total of 55% of patients had diarrhoea after taking oseltamivir and/or abidol hydrochloride; 22% of them were judged to be non-drug diarrhoea after ruling out drug-induced diarrhoea. Some of the patients had routine stool test, including stool traits, inflammatory cells like red blood cells as well as white cells, parasite egg and occult blood test, but only 6.9% of them had abnormal results. The abnormal findings included 5.2% positivity of white cells and 1.7% occult blood test positive, with no red blood cells found, which is consistent with the characteristics of virus-infected diarrhoea.¹¹ Virus-infected diarrhoea is also called viral gastroenteritis, and the clinical presentation of patients with symptomatic infections is characterised by non-bloody diarrhoea and vomiting, and can be

accompanied by nausea, abdominal cramps and fever.¹² As for the difference in incidence of diarrhoea across studies, this may relate to variation in definition of symptoms of GI involvement of diarrhoea, and also if diarrhoea was documented on admission, or during the course of hospitalisation, drugs given or concomitant infections (such as *Clostridioides difficile*) may lead to diarrhoea too.

In addition, digestive symptoms appeared to be tied to worse outcomes. Whereas 60% of patients without digestive symptoms recovered and were discharged, in contrast, only 34.3% of the patients with digestive symptoms recovered.¹³ Moreover, another study involving 1141 COVID-19 patients found that 183/1141 (16%) presented with GI symptoms only.¹⁴ Thus, patients with GI symptoms should attract the attention of both patients and doctors.

Liver injury

The incidence of liver injury in patients with COVID-19 was reported as 39.6% to 43.4%, manifested mainly by the elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, as well as hypoalbuminemia. A few patients had a slight increase in total bilirubin (TBIL) level.^{8,15} In a study by Wang *et al.*, 132 COVID-19 patients with liver injury were identified, of whom 72 were male (54.5%) and 60 were female (45.5%). The median age (range) was 62 years (26–88 years). Most of these patients showed mild liver injury, with elevated levels of ALT and/ or AST ranging from 40 to 80 U/l at the time of admission. Only a minority of patients had higher levels of TBIL (13/132), direct bilirubin (DBIL) (18/132) and indirect bilirubin (IBIL) (8/132). Notably, around one-fourth had albumin levels <35 g/l (lower than the normal reference value). In addition, 12 patients were found to have a history of chronic hepatitis B and 2 patients had a history of chronic hepatitis C, but viral nucleic acid test showed no active hepatitis B and C.¹⁵ In a large cohort study by Guan *et al.*, 23 out of 1099 cases were identified with preexisting hepatitis B infection.¹

Liver abnormalities of COVID-19 patients may be due to liver cell dysfunction like the preexisting viral hepatitis described above or other causes such as drug toxicity and systemic inflammation. The receptor of SARS-CoV-2, angiotensin converting enzyme 2 (ACE2), has been found to be

highly expressed both in GI epithelial cells and liver, suggesting a direct damage potential of SARS-CoV-2 on livers.¹⁶ Almost the entire GI tract, including stomach, duodenum, small intestine and rectal epithelial cells were found to have viral nucleocapsid protein of SARS-CoV-2 and ACE2 protein expression. Especially in the proximal and distal enterocytes, ACE2 receptors are remarkably highly expressed.^{10,17} However, currently, there is no data describing the impact of preexisting viral hepatitis on COVID-19. Also, the mutual effect between COVID-19 and viral hepatitis deserves more attention and further investigation. On the other hand, a variety of drugs have been used in the treatment of COVID-19, including antipyretic and analgesic drugs to relieve fever symptoms, antiviral drugs such as abidol, oseltamivir, remdesivir and lopinavir, as well as glucocorticoids, antibiotics, proprietary Chinese medicine and traditional Chinese medicine prescriptions. All of these might increase the risk of drug-induced liver injury.^{18–20} Additionally, a report from Singapore found that three out of five patients treated with lopinavir-ritonavir developed abnormal liver function.²¹ Moreover, systemic inflammatory response syndrome (SIRS) caused by pneumonia may also aggravate liver injury. According to the results of pathological anatomy of the first case of COVID-19, the liver tissue of patients with COVID-19 showed mild active inflammatory lesions in the hepatic lobular portal area, which may lead to liver injury.²²

Potential faecal–oral transmission and mechanism

SARS-CoV-2 RNA was first detected in a stool specimen from the first reported COVID-19 case in the United States (US).²³ In another subsequent Chinese cohort with 73 SARS-CoV-2-infected hospitalised patients, viral RNA was detected in the stools of 53.42% (39/73) of patients. Viral RNA was still positive in 17 patients (23.29%), even after levels had become undetectable in the respiratory tract.¹⁷ Meanwhile, SARS-CoV-2 has also been detected in stool samples from patients without GI symptoms.²⁴

Though controversial, evidence is accumulating to support the notion that SARS-CoV-2 viral particles are viable in environmental conditions that could facilitate faecal–oral transmission. A recent study showed the possibility of extended duration of faecal viral shedding for up to 5 weeks after the



Figure 1. The intestine with normal color, alternating segmental dilatation and stenosis in an 85-year-old man with COVID-19 autopsy.

patients' respiratory specimens tested negative for SARS-CoV-2 RNA.²⁵ A paediatric study also confirmed that majority of children continued to have positive viral rectal swabs after nasopharyngeal swabs were negative.²⁶ These data suggest that the virus could remain viable in the environment for days, with the potential risk of faecal-oral transmission. Similarly, another coronavirus, SARS-CoV, which induced the global pandemic of severe acute respiratory syndrome (SARS) in 2003, was also detected in the stool from SARS patients. In contrast, SARS-CoV was negative in urine and stool from recovery patients or healthy controls.²⁷ However, viral detection in the stool does not necessarily equate to virus infectivity, and direct evidence of faecal transmission of COVID-19 has yet to be identified.²⁸

Pathology/histology findings of GI and liver involvement in COVID-19

The main target organ of COVID-19 is lung. The pathological features of COVID-19 are similar to those seen in Middle Eastern respiratory syndrome (MERS) coronavirus infection and SARS.^{8,22} Histological examination showed diffuse alveolar damage with cellular fibromyxoid exudates. Desquamation of pneumocytes and hyaline membrane formation were found in lung tissue, indicating acute respiratory distress syndrome (ARDS). Interstitial mononuclear inflammatory infiltration was seen in lungs.

Multinucleated syncytial cells were identified in the intra-alveolar spaces, showing viral cytopathic-like changes. Intranuclear or intracytoplasmic viral inclusions were not identified.²² The injury of other tissues and organs affected by SARS-CoV-2 are still in the process of becoming further understood. Histological involvement of the digestive system was observed in a limited number of cases of puncture and autopsy.^{22,29}

GI endoscopy and biopsy findings

Previously, in the only case who underwent endoscopy because of upper GI bleeding from the cohort of 73 patients, no abnormalities were observed in the stomach, duodenum, colon and rectum, with the exception of mucosa damage in the oesophagus at endoscopy. Histology showed numerous infiltrating plasma cells and lymphocytes as well as interstitial oedema in the lamina propria of the stomach, duodenum and rectum.¹⁷ A recent cohort of 95 COVID-19 patients reported an additional 6 cases who underwent endoscopy examination, and identified SARS-CoV-2 RNA in the oesophagus, stomach, duodenum and rectum from two severe COVID-19 patients, whereas only one case out of four non-severe cases were found to have SARS-CoV-2 in the duodenum.⁵

Autopsy

Gross appearance showed increased liver volume and enlarged gallbladder. The colour of the stomach mucosa was dark red; a small number of bleeding points could be seen. The colour of the intestine was normal, with segmental dilatation and stenosis alternating in an 85-year-old man with COVID-19 autopsy (Figure 1). Whether this finding is secondary to COVID-19 or a pre-existent GI comorbidity such as ischemia remains unknown. No abnormality was found in the spleen.³⁰

Liver biopsy

Histological findings of liver from four post-mortem biopsies showed mild sinusoidal dilatation, mild lobular lymphocytic infiltration and patchy hepatic necrosis in the periportal and centrilobular areas. In general, there was no significant lymphocytic infiltration of the portal tracts and no obvious fatty changes (Figure 2).³¹ Another study of one biopsy specimen from a patient who died

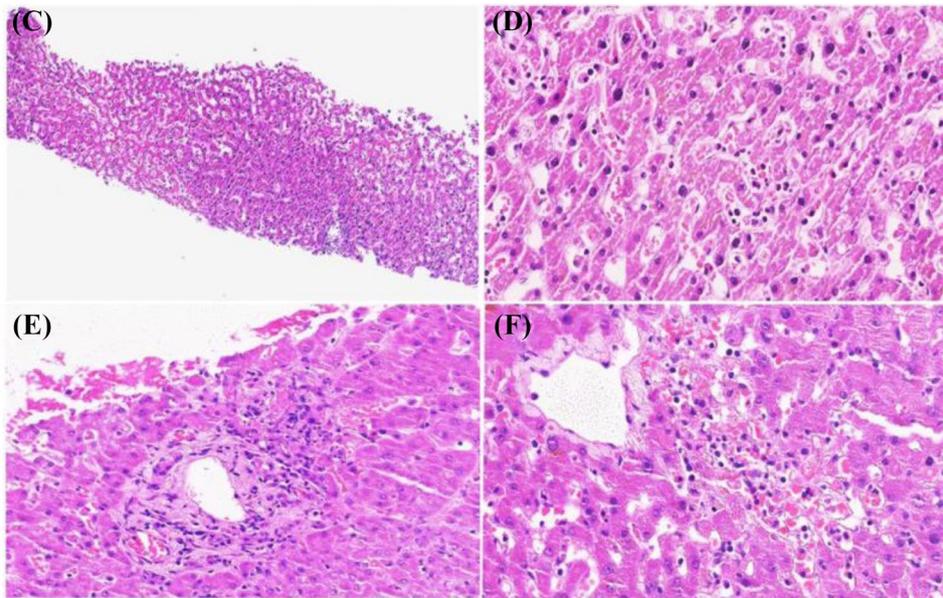


Figure 2. (C) Mild sinusoidal dilatation with increased lymphocytic infiltration. (D) Higher power view showing sinusoidal lymphocytes. (E) Focal hepatic necrosis in periportal zone. (F) Focal centrilobular hepatic necrosis. (Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.).

from COVID-19 showed moderate microvesicular steatosis, and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury.²²

Therefore, the histological features of GI and liver involvement in COVID-19 are in general quite non-specific but there is also a paucity of data from large cohorts of patients, which is understandable.

Diagnosis of COVID-19 in patients with GI diseases and relevant risk factors

The updated diagnosis criteria of COVID-19 recommended by National Health Commission of the People's Republic of China is summarised in Appendix 1. Patients with comorbidities such as diabetes, cardiovascular diseases and cancer in general are more susceptible to infection and have worse prognosis.^{1,32} However, whether patients with underlying GI and liver conditions are more likely to be infected with SARS-CoV-2 remains unknown.

Regarding patients with inflammatory bowel disease (IBD), a baseline increased risk of

SARS-CoV-2 infection or development of COVID-19 has not been identified.^{33,34} However, IBD patients under the following scenarios deserve more attention³⁵:

- (1) Patients with IBD on immunosuppressive agents;
- (2) Patients with active IBD with malnutrition;
- (3) Elderly patients with IBD;
- (4) Patients with IBD frequently visiting medical clinic;
- (5) Patients with IBD with underlying health conditions, such as hypertension and diabetes;
- (6) Patients with IBD who are pregnant.

Management of patients with pre-existing GI and liver diseases

Liver disease (hepatitis B infection, non-alcoholic fatty liver disease and alcohol-related liver disease)

In a large cohort study of 1099 COVID-19 patients, 261 (23.7%) reported having at least one comorbidity. As to pre-existing GI and liver diseases, hepatitis B was found in 23 (2.1%) patients and a higher prevalence in severe cases was found compared with non-severe cases (2.4%

versus 0.6%).¹ Although increasing evidence suggests that severe COVID-19 cases are more likely to suffer liver injury than mild cases, data about other underlying chronic liver conditions, such as non-alcoholic fatty liver disease, alcohol-related liver disease and autoimmune hepatitis, and their impact on prognosis of COVID-19 needs to be further evaluated.

GI cancers

In another nationwide cohort study of 1590 COVID-19 patients, 18 (1%) cases were identified having a history of cancer, of which 3 had history of colorectal cancer (1 colonic tubular adenocarcinoma, 1 rectal carcinoma and 1 colorectal carcinoma). Further, a higher risk of developing severe types of COVID-19 was found in patients with pre-existing cancer or a cancer history. To manage these patients, several recommendations have been given, such as an intentional postponement of adjuvant chemotherapy or elective surgery on a patient-by-patient basis, stronger personal protection provisions, and more intensive surveillance or treatment.³⁶

Inflammatory bowel disease

In mainland China, the outbreak of COVID-19 is currently close to extinction. Fortunately, no IBD patient is reported to be infected with SARS-CoV-2 in the IBD network. The Chinese IBD Elite Union incorporating the seven largest IBD referral centres and the three largest tertiary IBD centres in Wuhan city, which covers over >20,000 IBD patients, report no SARS-CoV-2 infection to 22 April 2020. The Chinese IBD Society officially issued guidelines for managing IBD patients in early February 2020.³⁷ Worldwide, however, the International Organisation for Study of IBD (IOIBD) has been collecting data on IBD patients who developed COVID-19, and 704 patients have been identified globally to 22 April 2020 (<https://covidibd.org/current-data/>). In a recent large cohort study involving 525 IBD cases from 33 countries, corticosteroids, but not tumour necrosis factor (TNF) antagonists, are associated with severe COVID-19. In addition, increasing age and comorbidities are also risk factors for adverse COVID-19 outcomes.³⁸ Current practical recommendations by Chinese IBD Society highlights that IBD patients taking biologics or/and immunosuppressants are not at increased risk of contracting COVID-19. The IOIBD and

Crohn's and Colitis UK (CCUK) also confirm the opinion that biologics and immunosuppressants are generally safe.^{39,40} It is essential to weigh the risk of COVID-19 and the risk of an IBD flare. Guidelines issued by the Chinese IBD Society suggests that it is better for that IBD patient to stay on their existing medications, while choosing alternative biologics, and immunosuppressants should be fully discussed with own doctors. Thus, avoidance of contact with the high-risk public is a more rigorous and optimised option for IBD patients.

Precautions for preventing SARS-CoV-2 infection during GI endoscopy procedures

Healthcare workers are especially at increased risk of exposure to COVID-19 according to previous data in China and Italy.^{41,42} Although COVID-19 is spread primarily through respiratory droplets from talking, coughing, sneezing and close contact with symptomatic individuals, all endoscopies should be considered aerosol-generating procedures and can lead to subsequent airborne transmission. Upper endoscopy can cause coughing, gagging and retching, whereas passing flatus and pathogen-containing liquid stools can occur during colonoscopy.^{43,44} It is of course very important when looking after confirmed COVID-19 patients and to adhere to hospital protocols, including properly wearing personal protective equipment (PPE), but of concern are unknown infected persons such as asymptomatic carriers or patients with mild symptoms undergoing endoscopic procedures.⁹ Thus, assessment and screening for signs of infections, travel history, contact with potentially infected patients must be protocol-driven in high-throughput clinical areas such as endoscopy suites. Of note, the classification of high-risk regions is going not to be a uniform concept even in the same months of March to April.^{45,46} The inconstant evolution of high-risk regions and countries has shifted from Asia to Europe and America in the last 4 weeks.

Currently, non-essential endoscopic procedures are recommended to be cancelled and only emergency endoscopies are permitted.^{28,47} However, deferring endoscopic procedures in IBD patients may harbour potential risks such as increasing the risk of high-grade dysplasia and colorectal cancer diagnosis, failing to assess the efficacy of treatment especially agents such as biologics, Janus

kinase (JAK) inhibitors, or azathioprine, missed detection of early post-operative recurrence and missing monitoring colonoscopies in clinical trials. In the study by Iacucci *et al.*, the following four scenarios were deemed urgent and recommended to necessitate endoscopy: to establish new diagnosis of moderate-to-severe IBD, to assess severe acute flare-up of ulcerative colitis, to diagnose sub-acute obstruction in patients with IBD, and in cases of worsening cholangitis and jaundice in patients with IBD and primary sclerosing cholangitis (PSC).⁴⁴ Of course, GI bleeding is generally a urgent situation and standard criteria should be used to decide on endoscopic intervention.

As to PPE needed during endoscopy, the American Gastroenterological Association (AGA) Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic suggest N95 (or N99 or PAPR) masks instead of surgical masks as part of appropriate PPE in health care workers performing upper or lower GI procedures, regardless of COVID-19 status. As for confirmed or suspected COVID-19 patients, the AGA guideline recommends against only using surgical masks as part of adequate PPE.⁴³ Several recommendations for GI endoscopy during the pandemic of COVID-19 are summarised in Appendix 2.^{28,35,43,44,48}

Management of GI symptoms and abnormal liver function tests in patients with COVID-19

At present, there is no specific drug for COVID-19, and there is little literature on the treatment of GI symptoms. Certain drugs used in the early phase to treat COVID-19, including Lopinavir-Ritonavir, were associated with liver dysfunction. A recent randomised trial of Lopinavir-Ritonavir in hospitalised adults with severe COVID-19 showed benefit beyond standard care.⁴⁹ COVID-19 patients with diarrhoea were mostly treated with montmorillonite powder or probiotics. Berberine and some other traditional Chinese medicine have been suggested in China for diagnosis and treatment of general COVID-19, but this might need further clinical trials.⁵⁰ Broad spectrum antibiotics are best avoided for the treatment of COVID-19, as these might cause antibiotic-associated diarrhoea. In the study of 1099 patients with COVID-19, 57.5% received intravenous antibiotics, which was significantly lower than

during SARS, whereas only 3.7% of these patients had diarrhoea.^{51–53} Generally, the diarrhoea improved rapidly. Most of the patients who had severe and stubborn diarrhoea had received antivirals such as oseltamivir and abidol.⁵⁴ Intestinal microbiota play an important role in maintaining human health. The metabolites of intestinal flora can also be useful for the treatment of virus by the interferon pathway. Therefore, it is recommended to use probiotics to maintain the intestinal microecological balance and prevent bacterial secondary infection in the COVID-19 diagnosis and treatment plan,⁵³ though further evidence is necessary.

Chao *et al.* reported that liver injury in mild cases of COVID-19 was often transient and can recover without any special treatment. When it comes to severe liver injury, liver protective drugs were usually given to such patients, but unfortunately the specific medications for liver protection were not described in that study.⁵⁵

Practice changes during pandemic and post-pandemic period

Generally, according to the experience of Chinese gastroenterologists who volunteered to be dispatched to Hubei province from other parts of China and worked in the forefront, steps were taken to minimise the risk of nosocomial SARS-CoV-2 infection, and telemedicine has been applied widely in the care of non-COVID-19 patients including virtual clinics and nurse-led care support based on interactive social care apps such as WeChat. In most scenarios, the online consultations are free to patients to encourage patients to accept new models of clinical service. These strategies have greatly facilitated care delivery to patients with chronic GI diseases or patients with comorbidities or complications in the GI tract and liver nationwide.²⁸

With regard to IBD patients, an IOIBD international meeting suggested the following practice changes were appropriate⁵⁶:

- (1) patients taking prednisone therapy (≥ 20 mg/day) should reduce the dose or discontinue therapy (taper as appropriate) to prevent SARSCoV-2 infection;
- (2) patients taking prednisone therapy (≥ 20 mg/day) should stop therapy (taper as appropriate) if they test positive for SARS-CoV-2;

Additionally, in scenarios (1) and (2), IBD patients under steroid treatment should be monitored for adrenal crisis, and stress dose steroids should be considered for severe COVID-19 patients who are critically ill.

- (3) Patients taking azathioprine/6-MP/ methotrexate/ tofacitinib should stop therapy if they test positive for SARS-CoV-2;
- (4) Patients taking anti-TNF therapy/ustekinumab should stop therapy if they develop COVID-19, whereas it is uncertain if patients test positive for SARS-CoV-2 but do not have COVID-19;
- (5) Patients taking combination therapy with an anti-TNF and thiopurine/methotrexate should stop the thiopurine/methotrexate if they test positive for SARS-CoV-2;
- (6) Patients taking clinical trial drugs should stop therapy if they test positive for SARS-CoV-2;
- (7) In an IBD patient who tests positive for SARS-CoV-2 and whose IBD medications have been stopped because of this, IBD medications can be restarted after 14 days (provided they have not developed COVID-19);
- (8) In an IBD patient who develops COVID-19 and whose IBD medications have been stopped, IBD meds can be restarted after COVID-19 symptoms resolve or two nasopharyngeal PCR tests are negative.

Lessons learnt

1. GI involvement is common in COVID-19, with digestive symptoms in some patients as the chief complaint or only manifestation; digestive symptoms may be correlated with worse clinical outcomes compared with patients without digestive symptoms.
2. In several cases, GI manifestation could be the first symptoms antedating respiratory symptoms, carrying a potential for delayed diagnosis and increased disease transmission risk; in rare scenarios, digestive symptoms could be the only complaint with absence of any respiratory manifestation, harbouring a risk of misdiagnosis or missed diagnosis.
3. The possibility of faecal–oral transmission of SARS-CoV-2 has important implications and requires further research. Strict precautions must be observed when performing GI endoscopy and when handling the stools of patients infected with coronavirus. The importance of frequent and proper

hand hygiene should be emphasised. Whether rectal swab testing before discharging COVID-19 patients with GI involvement should be incorporated needs to be further evaluated.

4. For patients with chronic GI diseases such as IBD, the way of providing quality of care needs to be improved and changed (such as transition to online virtual clinical visits). To hold or stop immunosuppressive medications including biologics is not advised for IBD patients or others such as those with autoimmune hepatitis with IBD, as the risk of disease flare far outweighs the chance of infection with SARS-CoV-2.
5. It is essential to triage and assess risk of patients with suspected or confirmed COVID-19 before endoscopy; deferred elective endoscopies and strategic performance of urgent endoscopies should be considered to minimise concomitant exposure. Healthcare workers should practice standard infection control and N95 (or N99 or PAPR) masks instead of surgical masks as part of appropriate PPE recommended during GI endoscopic procedure.
6. The comorbidity spectrum of digestive conditions and its impact on treatment and outcome of COVID-19 needs to be investigated urgently. Some registry studies such as SECURE-IBD are ongoing inside and outside China.
7. All the recommendations given in this article should be carefully adapted on the basis of local policy and available health-care resources.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Appendix 1

Diagnosis and treatment of COVID-19 – Recommendations from National Health Commission of the People's Republic of China (<http://www.nhc.gov.cn/zyygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>.)

Suspected cases

Combined with the following comprehensive analysis of epidemiological history and clinical

manifestations. One item in the epidemiological history, and combined with any two in the clinical manifestations would be suspected cases. Or if no clear epidemiological history, but has all three clinical manifestations.

1. Epidemiological history
 - (1) Travel or residence history of the area with COVID-19 case report within 14 days before the onset of the disease;
 - (2) Contact history with the COVID-19 virus infected persons (those with positive nucleic acid test) within 14 days before the onset of the disease;
 - (3) Clustering onset of COVID-19 (2 or more cases of fever and/ or respiratory symptoms within 2 weeks in small areas such as home, office, school, class, etc.).
2. Clinical manifestations
 - (1) Fever and/or respiratory symptoms;
 - (2) Pneumonia imaging features of COVID-19 [chest computed tomography (CT) or magnetic resonance imaging (MRI)];
 - (3) Leukocyte normal or decreased, while lymphocyte count normal or decreased in the early stage of the onset of the disease.

Confirmed cases

The suspected case has one of the following pathogenic or serological evidences at the same time.

- (1) Positive for COVID-19 nucleic acid detection by RT-PCR;
- (2) Highly homologous to the COVID-19 gene by gene sequencing;
- (3) Positive for COVID-19 specific IgM antibodies and IgG antibodies. Specific COVID-19 IgG antibody change from negative to possible or four times higher in the recovery phase than that in acute phase.

Appendix 2. Recommendations for GI endoscopy during the epidemic of COVID-19.^{28,35,43,44,48}

• **Postpone elective endoscopy conditionally**

• **Emergency endoscopy**

- (1) Epidemiological investigation
- (2) Assessment and screening for signs of infection
- (3) Screening COVID-19 (CBC, IgM/IgG, nucleic acid test and chest CT) if condition allows

• **Confirmed COVID-19 patients**

- (1) Endoscopy should be performed in a specific room with protective conditions and room disinfection
- (2) Negative pressure operating room is highly recommended

• **Precautions for healthcare workers in endoscopy centre**

- (1) Level 3 protection for operators and healthcare workers if sharing a room with the patient
- (2) Staffs should exclude COVID-19, quarantine 2 weeks if suspected exposure
- (3) Check body temperature; wear mask (N95 protective mask), wash hands, wear isolation gown and work shoes when entering the endoscopy center
- (4) Endoscopy operators, including doctors and assistants, should wear mask (N95 or PPE-3 or GB 19083 protective mask), protective clothing, isolation gown, protective shelter, goggles, double layer gloves and shoe covers
- (5) The mask should be replaced in time if it is contaminated, wet or over 4 h
- (6) Positive pressure respirator is recommended to use when perform endotracheal intubation or sputum aspiration in addition to above protections
- (7) Staff should pay attention to mutual protection during work and working interval to avoid cross infection
- (8) Those who contact suspected patients during work and fail to meet the protection requirements should be isolated immediately.

• **Protection requirements for endoscopy centre**

- (1) Endoscopic room and equipment should be sterilised after each patient's procedure
- (2) Although the efficacy of air disinfection is suspicious in endoscopic centres, it is still recommended to use medical dynamic air disinfection equipment to carry out air disinfection continuously if ventilation is not possible
- (3) The final disinfection shall be carried out in accordance with 'Technical Code for Disinfection of Medical Institutions' and 'Management Standard of Hospital Air Purification' presented by CDC

CBC, complete blood count; CDC, Centers for Disease Control and Prevention; CT, computed tomography; GI, gastrointestinal; PPE, personal protective equipment.