Gastrointestinal and Hepatic Manifestations of COVID-19: Evolving Recognition and Need for Increased Understanding in Vulnerable Populations

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Abstract: The novel coronavirus, SARS-CoV-2, has caused a global pandemic with high morbidity and mortality. It was first observed to cause a severe acute respiratory syndrome. However, gastrointestinal and hepatic manifestations have been increasingly recognized.

Gastrointestinal symptoms include diarrhea, epigastric pain, nausea, and vomiting. Diarrhea is the most common GI manifestation of SARS-CoV-2 and can present without or with respiratory symptoms. Patients with GI symptoms have been associated with longer duration of illness and may be associated with more severe illness. Mechanism of diarrhea is thought to be related to direct viral cytotoxicity occurring when the SARS-CoV-3 enters GI cells via the ACE-2 receptor. Inflammatory response and cytokine release likely contributes to symptoms.

SARS-CoV-2 can cause hepatic injury. Studies have shown mild to moderate elevation of liver enzymes. The pattern of liver abnormalities can be hepatocellular, cholestatic or mixed. Patients with severe infection have significantly higher rates of liver injury and worse outcomes. Proposed mechanisms for injury include immune mediated systemic inflammatory response, direct cytotoxicity from viral replication and hypoxia-reperfusion dysfunction.

Recent data suggests that GI and hepatic injury may be under-recognized manifestation of SARS-CoV-2 infection. Patients with diarrhea and liver disease may have a worse prognosis. The rapidly evolving literature continues to reveal a growing body of information which enables updated guidance for management. More investigation is needed which focuses on vulnerable patients, including the elderly, those with underlying illness, as well as, racial and ethnic minorities.

Keywords: COVID-19■SARS-CoV-2■Gastrointestinal symptoms■Diarrhea■Liver■Vulnerable populations

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INTRODUCTION

In December 2019 a novel coronavirus emerged out of Wuhan, China causing a global pandemic with high morbidity and mortality. The virus, SARS-CoV-2, was first observed to cause a severe acute respiratory syndrome, notable for characteristic chest radiography and pneumonia requiring supplemental oxygen support. The coronavirus disease, termed COVID-19, has since spread to 214 countries with 5 million cases as of May 2020. It has been declared a public health emergency of international concern by the World Health Organization (WHO).[1] The virus appears to disproportionately affect men, elderly patients, racial and ethnic minority groups, and those with certain underlying medical conditions, particularly hypertension and diabetes. In the US, African Americans have higher disease burden in part due comorbidities, increased likelihood of living in cramped housing, less equitable access to health care, lower rates of COVID-19 testing, and a higher proportion employed in the service industry.[2,3]

Most common symptoms are fever, cough and fatigue. Other symptoms include sputum production, dyspnea, headache, and anosmia.[4,5] Gastrointestinal (GI) symptoms are increasingly recognized and include diarrhea, epigastric pain, nausea, and vomiting. To improve early diagnosis, treatment, and reduce viral transmission it is important to identify GI symptoms as features of COVID-19. The impact of COVID-19 upon the liver has also been increasingly recognized. It is essential to understand how vulnerable populations are affected by GI and liver manifestations. This paper reviews the impact of COVID-19 on gastrointestinal and hepatic health.

GASTROINTESTINAL SYMPTOMS

The most common digestive symptom is diarrhea, occurring in both mild and severe COVID-19 disease.[6,7] Initial reports from Wuhan suggested a lower percentage of patients with GI symptoms (3%).[8,9] However, mounting evidence reports as many as 30%-50% may have diarrheal symptoms, 1%-29% reported abdominal

pain, and 1%-29% reported nausea and vomiting, and a case report of hemorrhagic enterocolitis.[6,10−13] Meta-analysis of 35 studies with 6686 COVID-19 patients found a pooled prevalence of digestive symptoms to be 15% (10-21; range: 2-57; $I^2 = 96\%$).[14] A larger meta-analysis of 43 studies comprised of 10,676 patients found a pooled prevalence of diarrhea to be 7.7% (95% CI 7.2-8.2); however, when excluding earlier studies from China the prevalence increased to 18.3% (95% CI 16.6-20.1).[15]

Diarrhea can be the presenting symptoms and may be the only symptom, although rare.[7,11,14,16] Studies have observed it to last 1-14 days with an average of 4-5 days duration.[6,7] Frequency of diarrhea is reported to average 3-4 times per day, defined as loose or watery stools[6,11]; most cases were self-limiting.[7]

Patients with GI symptoms with or without respiratory symptoms appear to have a different clinical course than those with only respiratory symptoms. Multiple studies found patients with GI symptoms to present later than those without digestive symptoms,[6,11,12,14] possibly due to less recognition of non-respiratory symptoms. However, GI symptoms have been associated with longer duration of illness, measured by days from symptom onset to viral clearance from PCR of naso-pharyngeal swab.[6,11,12] Many studies have linked GI symptoms to more severe disease,[7,11,17] including a meta-analysis of 6686 patients across 35 studies (odds ratio [OR] 1·60 [95% CI 1·09-2·36]; p = 0·0020; $I^2 = 44\%$). Few studies found no association with disease severity.[10,16] Still, even in mild disease, GI symptoms often coexist with fever.[6] To date, there have been no reports of differences in GI symptoms between sex.[7,12] Pediatric and adult populations also appear to have similar rates of GI symptoms.[14] Disparities among racial and ethnic groups are generally unknown.

MECHANISM OF ACTION

SARS-CoV-2 enters cells via the ACE-2 receptor. The spike (S) protein on the virus has the capacity to bind human ACE-2 with high affinity and fuse into host cells. The ACE-2 receptor is highly expressed on type II alveolar cells in the lung, and is also highly expressed on esophageal, gastric, and intestinal epithelial cells as well as salivary glands and cholangiocytes.[7,18] It is likely that intestinal inflammation and diarrhea occur as a result of virus damages to ACE-2 receptors along the gastrointestinal tract.[19] Viral nucleocapsid protein has also been detected in the cytoplasm of gastric, duodenal and rectal glandular epithelial cells, suggesting direct viral attack. Additionally, COVID-19 is associated with elevated levels of pro-inflammatory cytokines and chemokines, and the immune response may also contribute to organ damage.[20,21]

FECAL/ORAL TRANSMISSION

Growing evidence supports SARS-CoV-2 can be transmitted person to person through saliva and feces, in addition to droplet and airborne spread. Viral RNA has been observed in saliva and stool samples, and those with digestive symptoms are more likely to be fecal virus positive.[6,18,22] A study by Cheung et al. reported up to 50% of patients may test positive for stool viral RNA. Viral RNA in stool can stay positive for longer periods of time compared to respiratory samples.[17] At this time, it is unclear whether this is live virus or RNA fragments. The extent of fecal shedding is also largely unknown. Evidence is limited by lack of systematic stool collection. Interestingly, those with digestive symptoms have been shown to have statistically longer viral clearance.[6]

Given potential for fecal oral spread, handwashing and contact precautions (gowns, gloves, booties/shoe coverings) are essential to disease prevention in addition to masks for airborne and droplet transmission of aerosolized saliva. For gastroenterologists this has implications on practices. Endoscopy poses risk of fecal-oral transmission as does fecal transplants.[23,24] Screening for COVID-19 will be imperative prior to procedures to prevent spread.

LIVER DISEASE AND HEPATOXICITY

In addition to diarrhea, COVID-19 can cause liver damage. Studies have shown mild to moderate elevation of aminotransferase, bilirubin, and gamma-glutamyl transferase (GGT). Typically liver tests are 1-2 times upper limit normal (ULN) but have been observed to increase up to 3× ULN.[8,9,24-26] Aspartate aminotransferase (AST) and GGT are more likely to be elevated, compared to Alanine aminotransferase (ALT) and bilirubin. The pattern of liver injury can be hepatocyte, cholestatic or mixed type. Meta-analysis of 12 studies of 1267 patients found abnormal liver studies in 19% of patients (9-32; range 1-53; $I^2 = 96\%$).[14] In another meta-analysis AST was increased in 15% across 16 studies of 2514 patients and ALT was increased in 15% of 2711 patients across 17 studies (95% CI 13.6-16.5; 95% CI 13.6-16.4, respectively).[15] Patients with abnormal liver tests were more likely to be older, male, have higher BMI and have underlying liver disease.[25]

Patients with severe COVID have been shown to have significantly higher rates of liver injury (OR (2.20 [1.60-3.02]; p < 0.00001; $I^2 = 36\%$).[14] Furthermore, the extent

of lab abnormality is associated with severity of disease and worse outcomes. Studies have observed significant differences in AST, ALT, bilirubin, and GGT values between those with severe and non-severe disease.[9,25] In a study of 1099 patients in China, 18.2% with non-severe disease had abnormal liver tests compared to 39.4% with severe disease.[8] Of note, underlying liver disease was uncommon and only observed in 2.3% of the study population. A smaller study reported 25% of non-severe cases had abnormal AST compared to 62% of intensive care (ICU) patients.[9] Few reports have documented liver failure, often associated with multiorgan failure.[25] Given liver dysfunction, it has been recommended baseline liver tests are collected at hospital admission.

The cause of liver injury is likely multifactorial. Proposed mechanisms of liver injury include immune mediated from systemic inflammatory response, direct cytoxicity from viral replication, and hypoxia-reperfusion dysfunction from shock. Additionally, hepatoxicity from medical therapy used to treat COVID-19, including antivirals (lopinavir/ritonavir, remdesivir, uminefovir), chloroquine, tocilizumab, Chinese traditional medicine, and acetaminophen may further contribute to liver dysfunction.[27,28] In a study by Cai et al. the use of lopinavir/ritonavir was shown to increase odds of livery injury by 4-fold.[25] It is also hypothesized that SARS-CoV-2 and some of the trial drugs may lead to reactivation of pre-existing liver disease, particularly hepatitis B virus, prompting consideration for serologic testing of high risk patients.[28]

Special populations

Inflammatory bowel disease (IBD). Current evidence suggests patients with inflammatory bowel disease (IBD) do not have increased risk of COVID-19. It is unclear why IBD patients are not more susceptible to COVID-19, and theories include improved hygiene and disease prevention measures.[29] As of May 2020, the SECURE- IBD registry has reported 1170 cases COVID-19 in IBD patients.[30] Of these patients, 32% required hospitalization and 6% required ICU care, with a 4% mortality. Bezzio et al. found age over 65 significantly associated with COVID-19 pneumonia but IBD treatment was not associated with COVID-19.[31]

Guidelines recommend patients should continue their medication regimen.[29,32,33] Several immunotherapies, including steroids, thiopurines, JAK1/3 inhibitors and tumor necrosis factor (TNF) inhibitors, used to treat IBD are associated with increased risk for infection. Given limited evidence, the risks of discontinuation are not believed to outweigh benefits. Alternatively, is hypothesized that immunosuppressants may actually help prevent cytokine storm seen in COVID-19 pneumonia.[32] The cytokine profile

in severe COVID-19 resembles inflammation in IBD with hyper activation of T cells and massive production of IL 2, IL6, TNF, and interferon gamma (IFNG). Cytokines upregulate ACE-2, and there is evidence that IBD patients may actually have greater ACE expression. TNF inhibitors, commonly used in IBD, have potential therapeutic effects in COVID as TNF is thought to augment ACE-2 expression. ICU patients have been shown to have higher TNF levels, further suggesting a correlation.[29]

Chronic liver disease/cirrhosis. Chronic liver disease and cirrhosis may be related to increased morbidity and mortality from COVID-19. As of May 24, 2020, the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE)- Cirrhosis registry reported 629 cases and 139 deaths in COVID-19 patients with chronic liver disease from 28 countries.[33] Of a reported 491 cases, 209 had cirrhosis, 197 had non-cirrhosis chronic liver disease and 85 had liver transplants. Ninety percent of registry cases where hospitalized, and death was documented in over a third of cirrhotic patients, compared to 7% of non-cirrhotic chronic liver disease patients, suggesting worse outcomes for cirrhotic patients. Multicenter analysis of 2780 COVID-19 patients in the United States compared clinical outcomes in those with underlying liver disease (n = 250, 9%) to those without.[34] Most common liver disease was Nonalcoholic steatohepatitis (42%). Liver disease patients were found to be older age and have higher rates of diabetes and hypertension, making them significantly more likely to require hospitalization. While majority of all studied patients had COVID-19 related liver injury with elevations in AST, ALT, GGT, alkaline phosphatase, and total bilirubin from baseline and hospitalization rate was similar after adjusting for co-morbidities, those with underlying liver disease had significantly higher mortality even when adjusting for co-morbidities (RR 3.0, 95% CI 1.5-6.0, p-value 0.001). Cirrhotic patients had even higher risk of mortality compared to non-liver disease patients (RR 4.6, 95% CI 2.6-8.3, p-value <0.001). However, present data is inconsistent. Pooled analysis of 6 studies by Lippi et al. found no association between chronic liver disease with either increased odds of severe COVID-19 (PR 0.96 95% CI 0.36-2.52) p = 0.86) or of mortality from COVID-19 (OR 2.33 CI 0.77-7.04) p = 0.230).[35] Further investigation is needed and special attention should be given to this potentially high risk population to improve outcomes.

Liver transplant. There is question whether liver transplant patients are more susceptible to COVID-19 due to their immunocompromised status. As of May 2020, the SECURE Registry has reported COVID-19 in

85 transplant patients; 17 of which died.[33] In April 2020, the Lancet analyzed data from the SECURE registry. At that time the population consisted of 39 patients (30 survivors and 9 deaths). There were no significant different in age, comorbidity, time from transplant, or immunosuppression regimen between those who survived and those who died.[36] Bhoori et al. investigated outcomes of patients of a Lombardy, Italy transplant center in March 2020.[37] They observed 6 cases of COVID-19 in their population of 150 transplant patients. There were three COVID-19 deaths of the 111 long term liver transplant survivors and zero death in their cohort of 44 recent transplant patients. All three were male, over 65, with metabolic disease, known risk factors for worse COVID-19 outcomes. Notably, these patients had uneventful transplant courses with tapered immunosuppression regimens. These cases suggest post-transplant metabolic complications from medications might contribute more to morbidity and mortality than immunosuppression for developing severe disease. In Madrid, Spain Fernandez- Ruiz et al. analyzed solid organ transplant patients.[38] In March 2020, 18 patients had been diagnosed with COVID-19, 6 of which had received a liver transplant. Majority (15) presented with fever, 5 presented with GI symptoms, and 5 with respiratory failure. Mortality was observed in 5/18 (27.8%), and of survivors 4/13 had severe respiratory failure. The study was limited by small sample size, did not take into account individual characteristics of study population, and subject to inclusion bias; nevertheless, this preliminary data suggests transplant patients could have higher case fatality and may have atypical presentations. Further investigation is needed to better understand the relationship between transplant and COVID-19 to better treat these patients.

DISCUSSION AND IMPLICATIONS

COVID-19 has a major impact on gastrointestinal and hepatic health. Patients with diarrhea and liver injury appear to have a different clinical course and may have a worse prognosis. Recent data is suggesting this is more widespread than previously thought. Thus, it is important patients and providers are familiar with these clinical features to improve early diagnosis, treatment, and reduce viral transmission. This review analyzes the rapidly evolving literature between January and May 2020. Little is still known, and the growing body of evidence is helping to give updated guidance. Further research is still need to better understand prevalence, pathology, transmission, and treatment. In particular, more investigation focusing on vulnerable patients — those with underlying GI illness

(chronic liver disease, cirrhosis, liver transplant, and IBD) as well as racial and ethnic minorities, elderly patients, men, and those with comorbid illness is needed.

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