The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently estimated to have infected more than 3 million individuals worldwide and causes the clinical syndrome of coronavirus disease 2019 (COVID-19). Although the primary clinical manifestation is pulmonary disease, increasing data support the involvement of multiple organ systems, including the gastrointestinal (GI) tract and liver, with more than 60% of patients presenting with GI symptoms (anorexia, diarrhea, nausea, and vomiting) and a significant proportion presenting with elevated liver biochemistries.1-4

The SARS-CoV-2 virus is an enveloped, single-stranded virus, and the angiotensin-converting enzyme 2 (ACE2) receptor is thought to be a major receptor for the viral spike protein and critical for infectivity.5,6 The ACE2 protein is found at high levels in the colon, biliary system, and liver,7 and RNA shedding in the GI tract is well described.8 These data suggest that the SARS-CoV-2 may have tropism for the GI tract and liver, and that these may be sites of active viral replication and either direct or indirect tissue injury (Fig. 1).

Liver injury in the setting of COVID-19–related illness poses a unique challenge to the clinician. First, there is often uncertainty whether there is preexisting undiagnosed liver disease. Second, many of the medications used to treat moderate and severe disease have their own profiles of liver toxicity. Finally, in the subset of patients who experience critical illness, multiple factors may influence the trajectory of liver injury. We summarize what is known about liver injury in COVID-19 and provide diagnostic clues to contributing factors to the liver biochemical profile.

**EPIDEMIOLOGY AND CLINICAL ASSOCIATIONS OF LIVER INJURY IN COVID-19**

Several published studies have characterized the frequency and severity of liver biochemistry abnormalities on presentation, and a few have determined whether these abnormalities are associated with increased disease-related morbidity or death, as summarized in
The largest published study to date encompassed 5700 hospitalized patients in New York and examined admission serologies: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were both frequently elevated (58.4% and 39.0% of subjects, respectively), and a separate large cohort found elevations to be more common in severe disease. Two studies suggest that a higher proportion (44%-81%) of patients with underlying liver disease had abnormal liver biochemistries on admission. Elevations have been generally modest on admission, but available data suggest they become more frequently (93% in one series) and more severely deranged during the course of hospitalization.

Furthermore, liver impairment at admission has not been consistently associated with length of hospital stay, but has been found to correlate with time from illness onset to admission and with adverse outcomes. Liver biochemistries do not appear to be associated with GI manifestations in COVID-19.

**TABLE 1. FREQUENCY OF LIVER BIOCHEMISTRY ABNORMALITIES ON ADMISSION AND ASSOCIATION WITH OUTCOMES**

| Laboratory Test | % Patients With Abnormal Value* | Association With Severe Disease† | Association With Death | Comments |
|----------------|-------------------------------|----------------------------------|------------------------|----------|
| AST            | 16%-58%†                     | Yes13,14,16,18                   | Yes21                  | In 1 review of 12 published and unpublished reports, AST was the most frequently elevated biochemistry, and more frequently abnormal in severe disease. In-hospital death is associated with ALT > 40 (OR: 2.87 [1.48-5.57]; P = 0.0018) and PT ≥ 16 |
| ALT            | 13%-39%†                     | Yes13,16,18                     | Yes21,23              | Risk for in-hospital death is associated with ALT > 40 (OR: 2.87 [1.48-5.57]; P = 0.0018) and PT ≥ 16 |
| Alkaline phosphatase Tbilii | 5%,12,10,12,17,18 | Yes13,16 | Yes23 | Murray lung injury score is highly correlated with albumin (r = −0.959, P < 0.001) Increase in GGT in one study was observed despite normal alkaline phosphatase level Elevation of PT on admission significantly associated with risk for death (OR: 4.62 [1.29-16.50]; P = 0.019) |
| Albumin       | 38%-98%†                     | Yes13,16,18                     | Yes23                  | Murray lung injury score is highly correlated with albumin (r = −0.959, P < 0.001) Increase in GGT in one study was observed despite normal alkaline phosphatase level Elevation of PT on admission significantly associated with risk for death (OR: 4.62 [1.29-16.50]; P = 0.019) |
| GGT           | 16%†                          | Yes13                            | Yes23                  | Murray lung injury score is highly correlated with albumin (r = −0.959, P < 0.001) Increase in GGT in one study was observed despite normal alkaline phosphatase level Elevation of PT on admission significantly associated with risk for death (OR: 4.62 [1.29-16.50]; P = 0.019) |
| PT            | 5%-6%†                       | Yes16,18,20,24                  | Yes23                  | Murray lung injury score is highly correlated with albumin (r = −0.959, P < 0.001) Increase in GGT in one study was observed despite normal alkaline phosphatase level Elevation of PT on admission significantly associated with risk for death (OR: 4.62 [1.29-16.50]; P = 0.019) |

*Above normal limits, as designated by study authors.
†Abnormal laboratory value at any point in disease course. Severe disease is a composite definition composed of author designation of “severe disease,” disease progression, lung injury, and intensive care unit level care. Abbreviation: Tbilii, Total Bilirubin

**PATTERNS OF LIVER INJURY**

Aminotransferase elevation is the most common abnormality in patients presenting with COVID-19 (Table 1).
Published reports suggest that AST is more frequently elevated than ALT. Elevated alkaline phosphatase is rare, and an increase in bilirubin has less commonly been observed. However, interestingly, one report found elevated gamma-glutamyl transferase (GGT) levels in nearly 50% of subjects. The trajectory of liver biochemistry changes during hospitalization for COVID-19 infection is marked by elevation in aminotransferases, with rare severe liver injury, and liver test abnormalities are more frequent in patients with more severe COVID-19.

This pattern of liver injury is unlike that commonly observed in other forms of viral hepatitis, such as hepatitis B and C, but at least one report describes a similar pattern during influenza A/H1N1 influenza infection. In the prior severe acute respiratory syndrome (SARS) outbreak of 2003, a similar pattern of liver injury was observed. The pattern of abnormal liver biochemistries characterized by an AST level greater than ALT, with accompanying GGT elevation, is also commonly encountered in both alcoholic liver disease and ischemic or congestive liver injury. Thus, the liver injury observed in COVID-19 may reflect a direct viral effect, but other potential contributors must be considered, both at the time of initial presentation and during disease progression and management.

**POTENTIAL CAUSES OF LIVER INJURY IN COVID-19**

Hepatic injury from SARS-CoV2 infection is observed from the time of initial contact with the medical system, suggesting that the primary insult is unrelated to medical management but rather due to either direct effect of the virus or a consequence of the systemic disease. However, the trajectory of liver injury is likely influenced by multiple additional factors (Fig. 2).

There may be a direct viral cytopathic effect, given the known presence of the ACE2 receptor in the liver. In SARS infection, viral RNA was detected in liver tissue. Further, recently published data suggest that mitochondrial proteins may directly interact with the virus, providing a potential mechanistic explanation for the AST-dominant injury profile. Alternatively, the robust inflammatory response seen in COVID-19 may play a central role. The immune response to SARS-CoV-2 is characterized by very high levels of IL-6, which has been implicated in both the inflammatory and the repair responses in liver disease.

Cardiomyopathy is a well-described consequence of COVID-19, occurring in 33% of individuals in one US series. Thus, it is possible that cardiac dysfunction and
hepatic congestion contribute to hepatic injury in severe COVID-19 infection. Congestive hepatopathy may occur as a consequence of an acute cardiomyopathy, and it is commonly associated with elevations in aminotransferases and GGT.\textsuperscript{36,37} Severe ischemic hepatitis is a condition characterized by severe AST-predominant hepatitis\textsuperscript{38} and may be observed in critically ill patients with COVID-19. The infrequently observed alkaline phosphatase elevation occurs late in COVID-19 disease progression and could reflect the cholestasis of sepsis, critical illness,\textsuperscript{39} or medication effect.

An increasing number of drugs are being investigated and empirically used in hospitalized patients with COVID-19. Many of these medications have a distinct risk, time course, and pattern of liver injury, as summarized in Table 2.\textsuperscript{41} Remdesivir (a nucleoside analog inhibitor of viral RNA polymerase, recently approved for use under a US Food and Drug Administration [FDA] Emergency Use Authorization) is experiencing growing use in COVID-19 trials and was associated with a 23% increase in liver enzymes in one small published report.\textsuperscript{40}

**CONCLUSIONS**

There is a high prevalence of abnormal liver biochemistries on presentation in patients with COVID-19. In light of the risk for additional injury due to the complications and management of moderate-to-severe disease, it is important to monitor hepatic enzymes during the course of disease.\textsuperscript{42} If biochemistries worsen during disease progression, consideration must be given to possible contributors, including cardiac dysfunction, cytokine storm, ischemia, sepsis, and medication effect.

**CORRESPONDENCE**

Esperance A. K. Schaefer, M.D., M.P.H., Liver Center and GI Division, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114. E-mail: eschaefer@partners.org

**REFERENCES**

1) Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929-936.

2) Redd WD, Zhou JC, Hathorn KE, et al. Prevalence and characteristics of gastrointestinal symptoms in patients with SARS-CoV-2 infection in the United States: a multicenter cohort study. Gastroenterology. Available at: https://doi.org/10.1053/j.gastro.2020.04.045

3) Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-1069.

4) Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:7766-7773.

5) Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol 2013;11:836-848.

6) Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. Available at: https://doi.org/10.1002/jmv.25783

---

**TABLE 2. DRUGS COMMONLY USED IN COVID-19 AND HEPATOTOXICITY PROFILE**

| Drug                        | Liver Toxicity Score | Pattern of Injury                        | Time Frame of Injury          | Comments                                                                                       |
|-----------------------------|----------------------|------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------|
| Acetaminophen               | A                    | Hepatocellular                           | Protracted therapy (>4 g daily): 3-7 days | Injury due to overdose is often associated with jaundice, confusion, renal insufficiency, and hepatic failure, at 48-96 hours |
|                            |                      |                                          | Single overdose: 24-72 hours  |                                                                                                 |
| Azithromycin                | A                    | Cholestatic > hepatocellular             | Cholestatic: 1-3 weeks Hepatocellular: 1-3 days 6 months to several years | Associated with fatigue, jaundice, abdominal pain, and pruritus                                 |
| Statins                     | A/B                  | Hepatocellular > cholestatic             |                               |                                                                                                 |
| Hydroxychloroquine          | C                    | Very rare                                | NR*                          | Case report level data                                                                          |
| Lopinavir/ritonavir          | D                    | Hepatocellular/cholestatic/mixed         | 1-8 weeks                     | May exacerbate underlying chronic viral hepatitis                                               |
| Remdesivir                  | NA**                 | Hepatocellular                           | 5-25 days                     | ALT elevation observed in the majority of healthy patients; FDA recommends hepatic function testing prior to initiating, and then daily while on therapy; stop drug if ALT > 5 times the upper limit of normal\textsuperscript{41} |

\*Not reported.  
\**Not applicable.  

Data are adapted from LiverTox (livertox.nih.gov).\textsuperscript{43}
7) Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8.

8) Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020;158:1831-1833.e3.

9) Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. Available at: https://doi.org/10.1001/jama.2020.6775

10) Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-1720.

11) Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. Clin Gastroenterol Hepatol. Available at: https://doi.org/10.1016/j.cgh.2020.04.00

12) Cai Q, Huang D, Yu H, et al. Characteristics of liver tests in COVID-19 patients. J Hepatol 2020. https://doi.org/10.1016/j.jhep.2020.04.006

13) Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy. Available at: https://doi.org/10.1111/all.14309

14) Bloom P, et al. Liver biochemistries in patients with COVID-19. Hepatology 2020. https://doi.org/10.1002/hep.31326

15) Qi X, Liu C, Jiang Z, et al. Multicenter analysis of clinical characteristics and outcome of COVID-19 patients with liver injury. J Hepatol. Available at: https://doi.org/10.1016/j.jhep.2020.04.010

16) Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

17) Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.

18) Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620-2629.

19) Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606.

20) Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020;133:1032-1038.

21) Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). Available at: https://doi.org/10.1097/CMI.0000000000000824

22) Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998-1004.

23) Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.

24) Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-374.

25) Seretis C, Lagoudianakis E, Salemis N, et al. Liver biochemistry during the course of influenza A/H1N1 infection. Gastroenterology Res 2013;6:103-105.

26) Papic N, Pangercic A, Vargovic M, et al. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. Influenza Other Respir Viruses 2012;6:e2-e5.

27) Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1977-1985.

28) Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342:1266-1271.

29) Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020;158:1518-1519.

30) Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004;203:622-630.

31) Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004;39:302-310.

32) Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. Available at: https://doi.org/10.1038/s41586-020-2286-9

33) Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. Available at: https://doi.org/10.1016/j.cell.2020.04.026

34) Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014;6:a016295.

35) Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323:1612-1614.

36) Weisberg IS, Jacobson IM. Cardiovascular diseases and the liver. Clin Liver Dis 2011;15:1-20.

37) van Deursen VM, Damman K, Hillege HL, et al. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail 2010;16:84-90.

38) Tapper EB, Sengupta N, Bonder A. The incidence and outcomes of ischemic hepatitis: a systematic review with meta-analysis. Am J Med 2015;128:1314-1321.

39) Fuchs M, Sanyal AJ. Sepsis and cholestasis. Clin Liver Dis 2008;12:151-172, ix.

40) Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. Available at: https://doi.org/10.1056/NEJMoa2007016

41) US Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of Remdesivir
(GS-5734™). Available at: https://www.fda.gov/media/137566/download. Published May 1, 2020.

42) American Association for the Study of Liver Diseases. Clinical Insights for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic. https://www.aasld.org/sites/default/files/2020-04/

AASLD-COVID19-ClinicalInsights-April162020-FINAL.pdf. Published April 7, 2020.

43) LiverTox. Clinical and Research Information on Drug-Induced Liver Injury. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012.