

**Sara El Ouali, MD**

Department of Gastroenterology, Hepatology & Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic

**Carlos Romero-Marrero, MD**

Department of Gastroenterology, Hepatology & Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic

**Miguel Regueiro, MD**

Department of Gastroenterology, Hepatology & Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic

# Hepatic manifestations of COVID-19

Posted August 20, 2020

## ■ ABSTRACT

Patients with COVID-19 commonly have elevated liver enzyme levels, which is associated with adverse outcomes during hospitalization including increased risk of ICU admission, intubation, and mortality. When assessing these patients, it is important to consider causes of liver injury unrelated to COVID-19. Therapies for COVID-19 may increase liver enzyme levels but are not contraindicated in patients with baseline abnormal liver tests. Liver enzymes should be regularly monitored in all hospitalized patients with COVID-19. Patients with preexisting liver disease such as cirrhosis and those who have received a liver transplant may be at an increased risk of severe COVID-19 outcomes.

## ■ PREVALENCE AND PATTERN OF LIVER INJURY

Physician burnout has serious consequences to the individual physician, to patients, and to healthcare institutions. Research has shown the prevalence of burnout to be more than 40%, with highest rates in frontline healthcare providers such as emergency medicine, primary care, and critical care.<sup>1</sup> COVID-19 presents new stressors for healthcare providers, and recent events involving self-harm by physicians have brought increased attention to the emotional impacts of caring for these critically ill patients.<sup>2</sup>

## ■ NEW STRESSORS IN COVID-19

Elevated liver enzyme levels can be found in 14% to 76% of patients with coronavirus disease 2019 (COVID-19).<sup>1,2</sup> In a recent meta-analysis of 107 studies consisting of 20,874 COVID-19–positive patients, the pooled incidence of elevated liver enzymes on presentation was 23.1%.<sup>3</sup>

The pattern of liver injury is more commonly

hepatocellular<sup>1</sup> and is mild and transient in most patients.<sup>4,6</sup> In a retrospective study of 2,273 patients with COVID-19, 45% had mild liver injury, which was defined as a levels of alanine aminotransferase (ALT) above the upper limit of normal (ULN) and below 2 times ULN.<sup>6</sup> Liver injury was moderate (ALT between 2-5 times ULN) in 21% of cases and severe (above 5 times ULN) in 6.4% of cases.<sup>6</sup> Severe acute hepatitis associated with COVID-19 is rare, but has been described.<sup>7</sup>

In a large retrospective study out of New York City, levels of aspartate aminotransferase (AST) were frequently higher than levels of ALT, suggesting that AST may be a useful indicator of COVID-19 infection.<sup>8</sup> A cholestatic pattern of injury, however, is rarely associated with COVID-19.<sup>6,9</sup> Other abnormalities in liver enzymes include elevations in gamma-glutamyl transferase (GGT), which, in one study, occurred in 13.6% of patients with COVID-19.<sup>10</sup>

## ■ APPROACH TO ELEVATED LIVER ENZYMES

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters host cells by binding to angiotensin-converting enzyme-2 (ACE2), which is present in hepatocytes.<sup>1</sup> Although a direct viral cytopathic effect is possible, limited histopathologic data have not identified SARS-CoV-2 in liver tissue.<sup>5</sup>

When evaluating COVID-19 patients with elevated liver enzymes, other etiologies should be considered including COVID-19 unrelated causes such as hepatitis A, B, and C. Ischemia,<sup>1</sup> cardiac and muscle injury,<sup>11</sup> and cytokine release syndrome can be associated with COVID-19 and transaminase elevations.<sup>3</sup> In addition, other hepatic manifestations of COVID-19 have been reported. Acute portal vein thrombosis in a patient with abdominal pain, fever, jaundice, and elevated levels of transaminases has been reported and likely represents a prothrombotic state associated with the systemic inflammatory response to the virus.<sup>12</sup> Furthermore, drug-induced liver injury (DILI) can be seen in up to 25.4% of patients with COVID-

The statements and opinions expressed in COVID-19 Curbside Consults are based on experience and the available literature as of the date posted. While we try to regularly update this content, any offered recommendations cannot be substituted for the clinical judgment of clinicians caring for individual patients.

doi:10.3949/ccjm.87a.ccc061

19.<sup>3</sup> Remdesivir is associated with increased liver enzymes in about 15.2% of patients.<sup>3</sup>

The severity and pattern of liver test abnormalities have not yet been well described.<sup>13</sup> Although a hepatocellular pattern appears to be more common,<sup>3</sup> hyperbilirubinemia has also been described.<sup>14</sup> Liver enzyme elevations are predominantly mild to moderate in severity and infrequently lead to treatment discontinuation.<sup>13-15</sup> Lopinavir/ritonavir, hydroxychloroquine (less commonly), azithromycin, and tocilizumab have also been associated with abnormal AST and ALT levels in this setting.<sup>3,8</sup> Although it is important to note that abnormal liver biochemistries are not a contraindication to using COVID-19 therapies, liver enzymes should be monitored regularly in all hospitalized COVID-19 patients.<sup>1</sup> A summary of recommendations for the evaluation of patients with abnormal liver enzymes and COVID-19 can be found in Table 1.

<b>TABLE 1</b> <b>Approach to elevated liver enzymes in patients with COVID-19</b>
<b>Elevated liver enzyme levels: general principles</b> <ul style="list-style-type: none"><li>• Consider etiologies unrelated to COVID-19, including Hepatitis A, B, and C</li><li>• Avoid imaging of the liver unless it is likely to change management, as in the case of suspected venous thrombosis or biliary obstruction</li><li>• Therapies for COVID-19 (including remdesivir or hydroxychloroquine) may increase liver enzymes but are not contra-indicated in patients with baseline abnormal liver tests</li><li>• Regularly monitor liver enzymes in patients hospitalized with COVID-19</li></ul>
<b>Elevated liver enzyme levels in liver transplant recipients or auto-immune hepatitis</b> <ul style="list-style-type: none"><li>• Acute cellular rejection or disease flare should not be assumed without biopsy confirmation</li></ul>
<b>Elevated liver enzyme levels in children</b> <ul style="list-style-type: none"><li>• Because abnormal liver enzymes are uncommon in children with COVID-19, underlying liver disease or infection should be ruled out</li></ul>
Based on information from Fix, et al. <sup>1</sup>

■ **PROGNOSTIC IMPLICATIONS OF LIVER INJURY**

Liver injury appears to be more common in patients with severe COVID-19<sup>3,16</sup> and is associated with negative outcomes. In a large retrospective study of 1,059 COVID-19 patients, liver injury at presentation was an independent predictor of the composite outcome of death or intensive care unit (ICU) admissions.<sup>17</sup> In fact, in this study, liver injury was the second most informative predictor of poor outcomes among patients with severe hypoxia.<sup>17</sup>

In another study, severe liver injury was associated with elevated levels of inflammatory markers and a more severe disease course, including higher rates of intubation, ICU admission, and mortality.<sup>6</sup> Furthermore, an Italian retrospective study of 515 SARS-CoV-2 positive patients found that abnormal baseline liver enzyme levels were associated with an increased risk of ICU admission.<sup>10</sup> Finally, a recently published meta-analysis of 107 studies found that patients with elevated liver enzyme levels had an increased risk of severe disease and mortality.<sup>3</sup>

Specific patterns of liver enzymes have also been shown to be negative prognostic markers. Hypoalbuminemia on admission to the hospital appears to be a marker of severe disease.<sup>6,18</sup> In addition, peak ALT was found to be associated with death or discharge to hospice in a large US cohort study,<sup>6</sup> while an elevated baseline AST level has been associated with ICU admission, intubation, and death in another study.<sup>8</sup> Finally, alkaline phosphatase peak values have also been shown to correlate with the risk of death.<sup>10</sup>

■ **COVID-19 IN PATIENTS WITH UNDERLYING LIVER DISEASE**

**Chronic liver disease**

It is still unclear if patients with underlying liver disease are at higher risk of negative outcomes with COVID-19.<sup>1</sup> Using a large US database, a study of 2,780 COVID-19-positive patients found that those with preexisting liver disease were at increased risk for mortality compared with patients without underlying liver disease. Patients with cirrhosis were at particularly increased risk (risk ratio [RR], 4.6; 95% confidence interval [CI], 2.6–8.3).<sup>19</sup>

In addition, metabolic-associated fatty liver disease (MAFLD, previously termed non-alcoholic fatty liver disease) appears to be associated with an increased risk of severe disease.<sup>1,20</sup> In a study of 202 COVID-19-positive patients, those with MAFLD had an increased risk of severe disease and a longer

viral shedding time.<sup>9</sup> However, MAFLD is frequently associated with other comorbidities such as diabetes or cardiovascular disease, which are also established risk factors for severe COVID-19 and could contribute to worse outcomes among these patients.<sup>21</sup>

Contrary to previous findings, a recent meta-analysis showed that patients with chronic liver disease were not at higher risk of severe COVID-19.<sup>3</sup> In this study, chronic liver disease was defined as cirrhosis of any cause, autoimmune hepatitis, chronic hepatitis B and C, and MAFLD.<sup>3</sup> Although this was the largest systematic review published on this topic to date, the high heterogeneity among the included studies may limit the generalizability of the findings.

### Liver transplantation

While early data from Italy did not show worse outcomes among liver transplant recipients<sup>22,23</sup> more recent US data have found these patients to be at increased risk of severe COVID-19 disease,<sup>24</sup> with a mortality rate of 29% among hospitalized patients.<sup>25</sup> Of note, hepatitis associated with COVID-19 has been described in a living donor liver recipient on postoperative day 6. The donor was subsequently found to be SARS-CoV-2 positive.<sup>26</sup>

### CONCLUSION

In summary, elevated levels of liver enzymes are often seen in patients with COVID-19 and are associated with more severe outcomes, including increased risk of ICU admission, intubation, and mortality. Other causes of liver injury should be considered when evaluating patients with COVID-19. Although COVID-19 therapies may be associated with abnormal liver tests, they may still be used in patients with elevated liver enzyme levels with close monitoring.

Emerging data suggest that patients with preexisting liver disease such as cirrhosis and those who have received a liver transplant may have an increased risk of severe COVID-19 outcomes. The American Association for the Study of Liver Diseases has released expert consensus statements to help guide management of patients with liver disease in the context of the COVID-19 pandemic.<sup>1</sup> Selected recommendations for patients with severe liver disease are summarized in Table 2. Further research is needed to better characterize the disease course and outcomes among COVID-19 patients with chronic liver disease.

**TABLE 2**  
**Recommendations for outpatient management of patients with decompensated cirrhosis, for liver transplant evaluations, and on a transplant waiting list during the COVID-19 pandemic**

#### Clinic visits and consultations

- Continue to prioritize in-person transplant evaluations for patients with hepatocellular carcinoma or severe disease and high MELD scores, who are likely to benefit from immediate liver transplant listing
  - Consider telemedicine or virtual alternatives for less urgent patients
  - Consider developing online education programs and avoid group sessions for patient education
- Consider using a “COVID-19-free” path through the hospital for transplantation candidates

#### Laboratory testing and imaging

- Obtain labs and imaging only if clinically necessary and do not update labs or imaging simply to update MELD score
- Obtain SARS-CoV-2 testing for patients with new onset hepatic decompensation

#### Medications

- Ensure refills are available for essential medications
- Prescribe 90-day supplies instead of 30-day supplies

#### SARS-CoV-2 positive patients

- Have a low threshold for hospitalizing patients on the transplant waiting list who develop COVID-19

#### General recommendations

- Advise patients to avoid in-person community support group meetings and provide virtual alternatives
- Advise patients to avoid travel during the pandemic

MELD = model for end-stage liver disease

Based on information from Fix, et al.<sup>1</sup>

### REFERENCES

1. Fix OK, Hameed B, Fontana RJ, et al. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; 72(1):287–304. doi:10.1002/hep.31281
2. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; 73(3):566–574. doi:10.1016/j.jhep.2020.04.006
3. Kulkarni AV, Kumar P, Tevethia HV, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020; 10.1111/apt.15916. doi:10.1111/apt.15916
4. Hao SR, Zhang SY, Lian JS, et al. Liver Enzyme Elevation in Coronavirus Disease 2019: A Multicenter, Retrospective, Cross-Sectional Study. *Am J Gastroenterol* 2020; 115(7):1075–1083. doi:10.14309/ajg.0000000000000717

5. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World J Gastroenterol* 2020; 26(19):2323–2332. doi:10.3748/wjg.v26.i19.2323
6. Phipps MM, Barraza LH, LaSota ED, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large US Cohort. *Hepatology* 2020; 10.1002/hep.31404. doi:10.1002/hep.31404
7. Wander P, Epstein M, Bernstein D. COVID-19 Presenting as Acute Hepatitis. *Am J Gastroenterol* 2020; 115(6):941–942. doi:10.14309/ajg.0000000000000660
8. Fenn S, Fisher C, Pakala T, et al. Analysis of Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY. *Clin Gastroenterol Hepatol* 2020; S1542-3565(20)30756-4. doi:10.1016/j.cgh.2020.05.049
9. Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; 73(2):451–453. doi:10.1016/j.jhep.2020.03.044
10. Ponziani FR, Del Zompo F, Nesci A, et al. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2 positive patients. *Aliment Pharmacol Ther* 2020; 10.1111/apt.15996. doi:10.1111/apt.15996
11. Xu Y, Gu J. Cardiac and Muscle Injury Might Partially Contribute to Elevated Aminotransferases in COVID-19 Patients. *Clin Gastroenterol Hepatol* 2020; S1542-3565(20)30539-5. doi:10.1016/j.cgh.2020.04.042
12. La Mura V, Artoni A, Martinelli I, et al. Acute Portal Vein Thrombosis in SARS-CoV-2 Infection: A Case Report. *Am J Gastroenterol* 2020; 115(7):1140–1142. doi:10.14309/ajg.0000000000000711
13. Sultan S, Altayar O, Siddique SM, et al. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. *Gastroenterology* 2020; 159(1):320–334.e27. doi:10.1053/j.gastro.2020.05.001
14. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395(10236):1569–1578. doi:10.1016/S0140-6736(20)31022-9
15. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med* 2020; NEJMoa2015301. doi:10.1056/NEJMoa2015301
16. Zhang H, Liao YS, Gong J, Liu J, Xia X, Zhang H. Clinical characteristics of coronavirus disease (COVID-19) patients with gastrointestinal symptoms: A report of 164 cases. *Dig Liver Dis*. 2020; S1590-8658(20)30189-4. doi:10.1016/j.dld.2020.04.034
17. Hajifathalian K, Krisko T, Mehta A, et al. Gastrointestinal and Hepatic Manifestations of 2019 Novel Coronavirus Disease in a Large Cohort of Infected Patients From New York: Clinical Implications. *Gastroenterology* 2020;S0016-5085(20)30602-8. doi:10.1053/j.gastro.2020.05.010
18. 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(10229):1054–1062. doi:10.1016/S0140-6736(20)30566-3
19. Singh S, Khan A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. *Gastroenterology* 2020;S0016-5085(20)30585-0. doi:10.1053/j.gastro.2020.04.064
20. Zhou YJ, Zheng KI, Wang XB, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. *J Hepatol* 2020; 73(3):719–721. doi:10.1016/j.jhep.2020.04.027
21. Ponziani FR, Gasbarrini A, Pompili M. NAFLD or comorbidities, that is the question. *J Hepatol* 2020; 73(3):723. doi:10.1016/j.jhep.2020.04.026
22. Donato MF, Invernizzi F, Lampertico P, Rossi G. Health Status of Patients Who Underwent Liver Transplantation During the Coronavirus Outbreak at a Large Center in Milan, Italy. *Clin Gastroenterol Hepatol* 2020; 18(9):2131–2133.e1. doi:10.1016/j.cgh.2020.04.041
23. D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; 26(6):832–834. doi:10.1002/lt.25756
24. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant* 2020; 20(7):1800–1808. doi:10.1111/ajt.15941
25. Lee BT, Perumalswami PV, Im GY, Florman S, Schiano TD. COVID-19 in Liver Transplant Recipients: An Initial Experience from the U.S. Epicenter. *Gastroenterology* 2020;S0016-5085(20)34703-X. doi:10.1053/j.gastro.2020.05.050
26. Lagana SM, De Michele S, Lee MJ, et al. COVID-19 Associated Hepatitis Complicating Recent Living Donor Liver Transplantation. *Arch Pathol Lab Med* 2020;10.5858/arpa.2020-0186-SA. doi:10.5858/arpa.2020-0186-SA

**Correspondence:** Sara El Ouali, MD, Department of Gastroenterology, Hepatology & Nutrition, A30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; ELOUALS2@ccf.org