# COVID-19 and Liver Disease

## *Synthesis of the Current Literature*

In December 2019, a novel coronavirus was identified as the cause of severe pneumonia, respiratory failure and mortality in Wuhan China (1). The virus was found to have 82% genetic homology with SARS-CoV, a virus identified in 2002 as the cause of Severe Acute Respiratory Syndrome and 50% homology with MERS-CoV identified in 2012 as the cause of Middle Eastern Respiratory Syndrome. In February 2020, WHO named the virus SARS-CoV-2 and the related disease Coronavirus Disease 2019 (COVID-19).[1] Epidemiologic studies revealed SARS- CoV-2 readily transmitted through exposures to respiratory droplets of infected persons (2,3). SARS-CoV-2 spread rapidly in China and progressively and quickly to other countries globally. On March 11, 2020, WHO declared COVID-19 a pandemic. As of March 28, 2020, a total of 571,678 confirmed COVID-19 cases and 26,494 deaths have been reported worldwide (4). In the absence of a vaccine or licensed therapies, countries are implementing public health measures to prevent transmission and marshalling clinical care capacity for those with severe COVID-19 disease.

The emergence of SARS-CoV-2 as a major pathogen raises the question of the interrelationship between this infection and liver disease (13,14). Reports from China identified older age, immunocompromised states, and underlying health conditions as risks for severe COVID-19 disease (2,3,5-11). Chronic liver disease (CLD) is considered an underlying disease placing COVID patients at risk (4). In case series published to date, only a small proportion (3-11%) of COVID-19 patients had CLD at diagnosis (4, 8,10). A recent CDC study found persons with underlying health conditions were more likely to be hospitalized (27-%-30%) and to require intensive care (13%-14%) than others with COVD-19, (7%–8%) and (2%), respectively. Diabetes mellitus (11%), chronic lung disease (9%), and cardiovascular disease (9%) were the most frequently reported conditions. CLD was reported for less than 1% of the study population. Additional case series can add experience to the management of COVID-19 patients with CLD.

Liver injury is relatively common during the course of COVID disease. Available data suggest ~15% - 45% of patients with COVID-19 have some evidence of liver injury during the course of disease. Alanine aminotransferase (ALT) levels are typically mildly elevated and often accompanied by elevations of enzymes on other liver function tests (LFTs) including alkaline phosphatase, aspartate aminotransferase (AST), and lactate dehydrogenase. Some studies find increases in LFTs (ALT, AST) correlate with severity of disease requiring longer hospitalizations and intensive care (5, 8, 10). A study of the clinical course of deceased COVID-19 patients found elevations in ALT and AST associated with shorter survival after hospitalization; however, liver failure was not listed as a cause of death for any patient (9). A study of 52 COVID-19 patients requiring intensive care found 15 (29%) with liver dysfunction; there was no difference in hepatitis impairment among survivors versus non-survivors (11).

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019

In the United States, the first patient reported with COVID-19 had progressive increases in ALT exceeding four times the upper limit of normal (ULN) by the 9th hospital day. However, by that time, the patient's clinical course was improving and was soon discharged (12). Evidence regarding SARS-CoV-2/ HBV and SARS-CoV-2/HCV coinfections is needed.

The observations in previous years regarding liver impairment among persons with SARS is instructive (12-16). Elevations in LFTs are common (22%-56%). Increases in ALT tend to be modest with a median ALT levels on admission and during hospitalization of 0.55 and 1.53 times the ULN, respectively (15). For most patients, LFT elevations are transient; in one study of SARS patients with abnormal ALT, ~70% had normal values by hospital discharge. Large increases (>5 X ULN) in ALT are associated with poor outcomes from SARS. However, in this series, HBV co-infection was not associated with high peak ALT level, ICU admission, or mortality. Another study of SARS patients revealed chronic HBV infection as a significant risk for acute respiratory distress and intensive care; however liver damage was not greater for these severely ill patients (17).

The liver damage observed among patients with COVID-19 is probably related to several factors. Viral infection of liver cells could play a role. SARS-CoV has been isolated from liver tissue although not in large quantities; isolation of SARS- CoV-2 has yet to be reported. For cell entry, both SARS-CoV and SARS-CoV-2 bind to the receptor angiotensin converting enzyme 2 (ACE2); ACE2 is found on hepatocytes and in greater quantities cholangiocytes providing a site for direct viral binding and impairment of hepatitis function (18). Interestingly, cholestatic liver disease is not a common feature of COVID-19 disease (13). Other etiologies can have a role. Certain medications cause hepatotoxicity. One study found the elevation in LFTs in COVID-19 patients significantly associated with administration of lopinavir/ritonavir (5). Postmortem biopsies of patients with COVID-19 show findings- moderate microvascular steatosis, mild lobular and portal activity- indicative of injuries from either SARS-CoV-2 infection or medications (7,19). Clinical trials can look for hepatotoxicity among promising therapeutic agents for COVID-19 (20). Liver damage can also result from immune mediated inflammation. (9,10). This is observed for other viral infections. Elevation in ALT can be accompanied by increases in LDH and creatinine kinase suggesting extra-hepatic origins of these enzyme elevations.

In summary, SARS-CoV-2 infection is the cause of an ongoing and growing pandemic. The understanding of the relationship between this infection, COVID-19 disease and liver disease continues to evolve. The cause of liver injury among patients with COVID-19 appears multifactorial. The liver injury is often mild with but can be severe for patients with advanced COVID-19 disease. There is scant evidence regarding SARS-CoV-2 infection among persons with current HBV or HCV infection. Based on current evidence, persons with viral hepatitis and chronic liver disease should continue to be regarded as populations at increased risk for co-morbid complications during the course of COVID-19 disease.

CGHE will update this resource as data become available. CGHE encourages partners to submit reports for inclusion in the series.

# Resources


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