

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Overview of COVID-19 and the Liver



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G&H What are the typical presenting symptoms of COVID-19? How may the liver be involved?

DJ Most patients infected with COVID-19 present with respiratory symptoms, particularly dyspnea and hypoxia. Some patients also have gastrointestinal symptoms. At the beginning of the pandemic, the presenting symptoms were mainly respiratory, but as time went on, patients have experienced more extrapulmonary symptoms, such as anorexia, nausea, diarrhea, loss of taste, anosmia, stroke, and cardiovascular disease. In COVID-19, the liver is usually not one of the organs that worries doctors. Doctors only find out that the liver may be affected when patients undergo laboratory testing. Liver involvement is diagnosed mainly by elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). In contrast, alkaline phosphatase (ALP) hardly increases, which is somewhat puzzling. Interestingly, COVID-19 also does not attack or destroy the cells in the cholangial system even though the virus enters liver cells through angiotensin II (ACE2) receptors that are mainly seen in cholangiocytes.

G&H What is the prevalence of hepatic effects in patients with COVID-19?

DJ The prevalence varies depending on when and where the research was performed. Generally, approximately 25% of patients with COVID-19 have AST and ALT elevations, and approximately 20% have increased lactate

dehydrogenase. Bilirubin increases in only approximately 3% of patients, and ALP remains normal in almost all patients. In a study of 5700 patients, 58% had AST elevation and almost 40% had ALT elevation, which are quite significant findings. Another study found that GGT was roughly 3 times higher in approximately 41% of patients.

In addition, hepatic effects differ between patients who are hospitalized with severe COVID-19 and patients who have mild to moderate COVID-19. There is a 9-fold increase in liver enzyme elevation in severe cases compared with milder cases. On average, liver enzymes start increasing when patients are hospitalized for 4 to 17 days. In fact, a study of approximately 1100 patients from China found AST and ALT elevations in roughly 18% and 29%, respectively, of patients with COVID-19 that was not severe, defined as not requiring admission to an intensive care unit (ICU). In contrast, among patients in the ICU with severe COVID-19, 56% had AST elevation and 28% had ALT elevation. At least in this study, the increase in AST was greater than the increase in ALT among patients who were in the ICU.

G&H Has the prevalence of acute liver disease in patients with COVID-19 been changing?

DJ Acute liver disease secondary to COVID-19 may be defined as a liver with normal AST and ALT that suddenly becomes inflamed, leading to elevations in AST and ALT as well as other abnormalities. As previously mentioned, this occurs in patients with severe COVID-19 at times.

Because the number of severe cases is decreasing owing to the increasing number of COVID-19 vaccinations, the prevalence of acute liver disease in patients with COVID-19 is also falling.

G&H What are the main causes of hepatic involvement in COVID-19?

DJ Most important is the severity of the COVID-19 infection. Patients with mild to moderate infection will not have liver involvement unless they have hepatitis A, B, or especially C, which is known to upregulate ACE2 receptors in the liver. It is unclear whether liver injury and underlying liver disease correlate with SARS-CoV-2 tropism to the liver, as there have not been prospective studies on COVID-19 in patients with preexisting chronic liver disease. However, early studies have found an approximately 30-fold increase in ACE2 expression in the liver in patients with cirrhosis secondary to hepatitis C compared with healthy individuals.

The risk of liver damage also increases with hypoxia. Hypoxia can damage the liver just like any other organ, as seen in multi-organ failure. Also, in COVID-19, there is a higher incidence of venous thrombosis leading to stroke, heart attack, deep vein thrombosis, and pulmonary embolism. Similarly, venous thrombosis in the liver can also result in liver damage. In addition, COVID-19 creates inflammation and cytokine storm, which may result in liver damage as well as endothelial dysfunction, leading to stroke and other liver complications.

Finally, the drugs used to treat COVID-19 may cause liver problems. Remdesivir has been approved for COVID-19 in certain cases, and lopinavir, ritonavir, and tocilizumab were used at the beginning of the pandemic, but all of these drugs may cause liver damage. Tocilizumab, which is an interleukin-6 receptor blocker, should be avoided in patients who have an ALT of more than 5 times the upper limit of normal. Baricitinib, which is a Janus kinase (JAK) inhibitor that blocks JAK1 and JAK2 and is currently approved for use in patients with COVID-19, has not been studied in patients with severe hepatic impairment. As such, baricitinib should not be used in patients with severe hepatic impairment if the potential benefit does not outweigh the risks. It is not known if dose adjustment is needed in patients with severe hepatic impairment.

G&H Does preexisting chronic liver disease predispose patients to becoming infected with COVID-19 or having poor outcomes?

DJ Cirrhosis in particular leads to poor outcomes. For example, patients with COVID-19 who have Child-Pugh

class C cirrhosis have an 80% chance of dying if they are admitted to the ICU and a 90% chance of dying if they are intubated. On the other hand, patients with Child-Pugh class B cirrhosis have a 60% chance of dying if admitted to the ICU and a 75% chance of dying if they are intubated. Thus, there is a direct correlation between liver damage and death in patients who have COVID-19 and severe liver disease.

I do not think that other chronic liver diseases such as nonalcoholic fatty liver disease or autoimmune hepatitis are associated with poor outcomes or have a direct correlation with mortality in patients with COVID-19. Nonalcoholic fatty liver disease may be associated with increased ACE2 receptors on fatty tissue, which may increase infections, but it does not raise the risk of acquiring COVID-19. The condition of the liver is more important than the reason for the liver damage.

It should be noted that the immunosuppressants used in conditions such as autoimmune hepatitis may negatively affect outcomes. On the other hand, prednisone may protect patients from the cytokine storm started by COVID-19. More research is needed on the current use of prednisone and its effect on mortality and morbidity in patients with COVID-19.

G&H What are the outcomes of patients undergoing liver transplantation?

DJ Patients who need a liver transplant have Child-Pugh class C cirrhosis and a high Model for End-Stage Liver Disease score and, as such, have a bad prognosis. If they are hospitalized, admitted to the ICU, and require a ventilator, their chance of death is very high. However, liver transplant recipients have a good prognosis because they have a new transplanted liver, although they are still on immunosuppression. The disease course of COVID-19 in patients with preexisting chronic liver disease has been well described in large cohorts; patients with cirrhosis have high rates of death, whereas pharmacologically immunosuppressed liver transplant recipients seem to have comparatively better outcomes.

G&H How should patients with hepatic involvement of COVID-19 be treated?

DJ No special adjustments are needed except for avoiding the use of any drugs that affect the liver. Although remdesivir is approved by the US Food and Drug Administration, studies have shown that it is effective against COVID-19 only in a small subset of patients. When a patient presents with liver dysfunction, it is important not to worsen it by using agents or doses that are hepatotoxic; thus, proper selection of medications should be made,

and doses must be adjusted accordingly. Most of the time when a patient is in the ICU with COVID-19 and has liver dysfunction, he or she will recover from COVID-19 with good ICU care, and recovery of the liver will follow.

G&H What are the key unresolved issues in this area?

DJ One key unresolved issue is the role of ACE2 receptors in the liver. It is not known if those receptors enable COVID-19 to replicate in the liver. Researchers have looked at single-cell RNA in autopsy specimens of the liver. Although viral replication has been shown in the liver, it is not known how much the liver contributes to the disease itself by viral replication. Also unresolved are the effects of drugs on the liver during COVID-19, as well as the role of the microbiome. It is thought that there is a direct correlation between the microbiome and the rest of the body, including the liver. However, the effect of the microbiome on COVID-19 and the liver is unclear, and vice versa. Prospective studies are also needed on how liver transplant recipients respond to COVID-19, as well as on why patients who have cirrhosis and COVID-19 have such a high mortality when intubated. It is unclear whether this risk of mortality is due to organs shutting down or if it is a specific liver issue when patients are on ventilators. I am not sure whether any research has been performed on the effect of hepatitis B on COVID-19 because COVID-19 is generally a self-limiting disease. Studies have shown reactivation of hepatitis B virus infection following treatment with tocilizumab and corticosteroids, emphasizing the need for caution when using these agents to treat patients with COVID-19 and hepatitis B. Hepatitis B screening and prophylaxis should be

considered in patients with elevated transaminase levels and in high prevalence populations. COVID-19 is not a chronic condition except in post-COVID-19 syndrome, in which patients have multiple long-term symptoms such as backache, cough, lack of energy, and brain fog. Research is needed to determine if patients with chronic liver disease have a different natural history when they have post-COVID-19 syndrome.

Disclosures

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Suggested Reading

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