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REVIEW

Outcomes in Patients with Liver Dysfunction Post SARS-CoV-2 Infection: What Should We Measure?

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Aim: Since 2019, the COVID-19 pandemic wreaked havoc all over the world. Early in the course of the pandemic, multiple hepatic manifestations of COVID-19 were noted. We aim to categorize hepatic dysfunction and its outcome in COVID-19 infection.

Methods: This is a review article based on a literature search in PubMed and Medline databases for articles detailing short-term and long-term outcomes of COVID-19 related liver dysfunction.

Results: The most common hepatic manifestation of COVID-19 was aspartate amino transferase (AST) predominant transaminase elevation. Transaminases improve once the COVID-19 infection resolves. In addition, COVID-19 cholangiopathy, autoimmune hepatitis associated COVID-19, and splanchnic venous thrombosis triggered by COVID-19 are other manifestations. Patients with preexisting liver disease, especially those with cirrhosis, have poor prognosis with COVID-19 infections compared to the general population. Elevations in liver tests were associated with severe COVID-19 infections. Patients with chronic liver disease have a higher risk of morbidity and mortality from COVID-19 infection. Among patients with chronic liver disease, decompensated liver cirrhosis, hepatocellular carcinoma and alcohol-associated liver disease were associated with an increased risk of severity and mortality from COVID-19 infection. Interactions between antiviral therapy for COVID-19 and hepatitis B/hepatitis C medications must be considered in patients with chronic viral hepatitis and COVID-19 infection. COVID-19 vaccination-related hepatic dysfunction has been reported.

Conclusion: COVID-19 is here to stay. Hepatic dysfunction in COVID-19 signals severe COVID-19 infections. Patients with chronic liver disease have higher mortality from COVID-19 than general population. It is important to remember the lessons learned throughout the covid pandemic to take care of patients with COVID-19 now and in the future. Further studies are needed to document long-term outcomes in patients with COVID-19 who developed hepatic dysfunction.

Keywords: COVID-19, liver injury, cirrhosis, thrombosis, cholangiopathy

Introduction

The devastating global pandemic of COVID-19 began in Wuhan, China, in 2019. COVID-19 was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus of zoonotic origin.[1] According to World Health Organization (WHO), 753 million cases have been reported, with 6 million reported deaths.[2] The first COVID-19 infection in the United States was diagnosed in Washington on January 20, 2020. In the United States, there have been around 100 million confirmed cases of COVID-19 and 1 million deaths, according to WHO 2023 database.[2]

COVID-19 infection manifestation varies from asymptomatic infection to critical respiratory illness complicated by multisystem involvement.[3] Early in the pandemic, liver dysfunction associated with COVID-19 infection was noted. Elevated liver tests were noted in 14 to 65% of patients admitted to the hospital with COVID-19 infection.[4,5] The most reported hepatic manifestation of COVID-19 infection is elevated liver associated tests, specifically elevated transaminases. COVID-19 also impacted the lives of patients living with chronic liver disease.

Most common manifestation of liver dysfunction from COVID-19 infection is the increased values of liver associated blood work.[3] Most abnormal liver tests are transient and usually resolve as the body recovers from the infection. Liver involvement in COVID-19 generally signifies a severe COVID-19 infection.[4,6]

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We aim to describe the outcomes of COVID-19 liver injury in patients who had de novo liver injury during COVID-19 infection and in patients with preexisting liver disease who developed COVID-19 infection. By describing the liver injuries, we aim to classify the liver injury, describe the evolution of the liver injury, and thereby prognosticate and predict short- and long-term outcomes of liver injury from COVID-19 infection. We also aim to detail the impact that COVID-19 infection had on patients with chronic liver disease and liver transplant patients. We conducted a literature search in PubMed and Medline databases for articles detailing short-term and long-term outcomes of COVID-related liver dysfunction.

Methods

We searched PubMed, Medline, Cochrane, WHO (World Health Organization Database), CDC (Center for Disease Control) database using the search terms coronavirus, severe acute respiratory syndrome coronavirus 2, SARS-CoV, abnormal liver tests, liver injury, cirrhosis, thrombosis, COVID-19 cholangiopathy, long COVID and COVID-19 vaccination for studies published from January 1, 2019, to March 1, 2023. We also manually reviewed the references of relevant articles.

De novo Liver Injury Related to COVID-19 Infection

COVID-19-Related Direct Parenchymal Liver Injury

Liver injury was expected from COVID-19, given the similarity of the virus to SARS-CoV and the Middle East Respiratory Syndrome virus, both of which caused liver injury.[7] SARS CoV-2 aka COVID-19 enters target cells via the ACE 2 entry receptor.[8] The COVID-19 virus spike protein binds to ACE2 receptors to gain cell entry. Single-cell RNA sequencing analyses in normal healthy livers have shown gene expression for ACE2 in the liver parenchyma, highest in cholangiocytes, followed by sinusoidal endothelial cells and hepatocytes.[9]

Increase in the values of liver tests associated with COVID-19 infection was noted early on in studies from China.[10,11] The exact mechanism of COVID-19 virus infection causing parenchymal liver injury is unknown. Proposed pathogenesis includes a) COVID-19 virus-induced hepatic cytopathy;[9] b) collateral damage from cytokine storm;[12] and c) microthrombi in liver.[13] In addition, COVID-19 infection-mediated endothelial injury was found in multiple vascular beds, including the lungs, kidney, heart, small intestine, and liver.[14] Patients with severe COVID-19 develop systemic hyperinflammation resulting in cytokine storm that can cause parenchymal injury.[12]

The pattern of transaminases appears to differ between hepatotropic viral hepatitis (B and C) and COVID-19. Whereas alanine transaminase (ALT) increases are characteristic of hepatitis B and C infection, aspartate aminotransferase (AST) is the predominant transaminase noted in de novo COVID-19 related liver injury.[3,10,15] Severe hepatitis from COVID-19 is uncommon.[16] Concurrent elevation in bilirubin with synthetic dysfunction has been associated with prolonged from COVID-19 infection and ARDS.[17,18] The mechanism of AST predominance is not clearly understood, and proposed mechanisms include COVID-19 related mitochondrial dysfunction, micro thrombosis in the liver, systemic hypoxia, and cytokine injury.

Increase in transaminase values has been associated with increased morbidity and mortality.[19–22] A study by Lei et al showed that an AST level higher than 40 U/L was associated with a significantly increased risk of all-cause mortality.[19] Transaminases generally tend to resolve with improvement in COVID-19 infection-related illness. American Association for Study of Liver Diseases (AASLD) consensus 2022 recommends regular monitoring of liver tests in patients with COVID-19. Several studies have noted a correlation between disease severity and a rise in liver tests.[20,21] There is no clear association between long covid and transient elevation of liver tests during COVID-19 infection.[23]

DILI from Medications Used to Treat COVID-19 Infection

Multiple medications used to treat COVID-19 infection can cause drug-induced liver injury.[24,25] Culprits for drug-induced liver injury (DILI) in COVID-19 included antivirals, antibiotics, health supplements, and new COVID-19 medications. A recent publication by Teschke et al described 996 cases of DILI in patients infected with COVID-19.[26] This study noted that the use of empirical antiviral drugs was the most common cause of DILI in patients with COVID-19 infection. Hepatocellular drug injury was the most common type of liver injury. Of the current medications that are mainstream in treatment for COVID-19, Paxlovid (nirmatrelvir/ritonavir) is not recommended in patients with severe liver disease (Child-Pugh C).[27] Ritonavir has significant drug interactions with calcineurin inhibitors, Tor inhibitors, and

antiviral medications.[27] Remdesivir also has the potential to cause hepatotoxicity and should be monitored if used. Nevirapine and tocilizumab are other current medications that were implicated in DILI.[28,29]

COVID-19 Cholangiopathy

Post-covid cholangiopathy is a rare but severe complication of COVID-19 infection.[30] This has been described in patients with severe and prolonged cases of infection from COVID-19.[31] The exact mechanism of covid cholangiopathy is unknown. Patients who required mechanical ventilation were at the highest risk of developing cholangiopathy. Cholangiocytes have ACE2 receptors, which are the host receptors for COVID-19 may lead to direct injury from the COVID-19 virus.[32] Cholangiopathy developing from shock associated with sepsis is another possible etiology.[33,34] Yanny et al identified 30 cases of cholangiopathy related to COVID-19 infection.[30] In this study, 23.3% died, 27.2% underwent transplant evaluation, and 16% were transplanted. Durazo et al described another case of covid cholangiopathy requiring a liver transplant.[35] The natural history of patients who developed cholangiopathy but did not require liver transplantation is largely unknown due to limited follow-up. The results of a small case series suggested improved clinical outcomes in patients with post-covid cholangiopathy who received antiplatelet therapy.[36]

De novo Autoimmune Hepatitis (AIH) Triggered by COVID-19

There are case reports of AIH triggered by COVID-19 infection.[35,37,38] There have been case reports of infection triggering AIH, for example – EBV (Epstein Barr virus) infection triggering AIH in the literature.[39] COVID-19 infection is known to cause immune dysregulation. There are case reports of autoimmune hepatitis triggered by COVID-19 in adult and pediatric literature.[35,37,38,40] Episodes of AIH typically manifest a few weeks after patients recover from COVID-19 infection. Patients typically respond to immunosuppression.

De novo Thrombosis of the Splanchnic Venous System in COVID-19

COVID-19 infection can cause dysfunction of the coagulation cascade. Thromboembolic events during COVID-19 infection are associated with higher mortality.[41] Splanchnic vein thrombosis related to COVID-19 infection is reported in literature including Budd Chiari, Portal vein thrombosis, splenic vein thrombosis, and mesenteric vein thrombosis.[42–53] El-Hady et al did a systematic review that described 33 cases of splanchnic vein thrombosis in COVID-19 cases worldwide.[54] Patients who developed extensive clots in the splanchnic system had a higher mortality risk. The long-term prognosis of patients who develop splanchnic vein thrombosis is unknown. In addition, Saab et al described a case of thrombosis involving IVC, bilateral renal veins and right hepatic vein in a patient with history of primary biliary cholangitis (PBC) who developed COVID-19 infection.[55] Patient underwent successful thrombectomy with no complication. Early identification and treatment are crucial in these patients.

Others

In addition, sepsis resulting from COVID-19 by itself can cause liver injury.[56] Hypoxic/ischemic hepatitis and sepsis-induced cholestasis result in liver injury in sepsis.[57] Other proposed mechanisms of de novo liver injury from COVID-19 include myositis and cardiac injury.[58]

COVID-19 Infection in Patients with Preexisting Liver Disease

COVID-19 and Chronic Liver Disease (CLD)

It is well established that patients with chronic liver disease who contract COVID-19 infection have a worse prognosis than the general population.[59] Singh et al conducted a multicenter study involving 2780 patients with COVID-19 infection across 34 centers in the United States.[60] Of the 2780 patients, 250 had preexisting liver disease. Patients with liver disease had a higher incidence of co-morbidities like Diabetes Mellitus and Hypertension. Fatty liver is the most common cause of liver disease (42%). Patients in the liver disease group had a higher mortality risk and hospital admission. In subgroup analysis, patients with cirrhosis had a higher relative mortality risk than patients in the non-liver disease group.

Kim et al conducted a retrospective multicenter study across 21 US States, enrolling 867 patients with CLD and COVID-19 infections to follow the natural history of COVID-19 infection in patients with chronic liver disease.[61] In this

study, alcohol-related liver disease, decompensated liver disease, and HCC were found to be liver-specific predictors of all-cause mortality. Increasing age, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, smoking history, and Hispanic ethnicity were identified as additional independent predictors for all-cause mortality in this cohort. In patients with cirrhosis, hepatic decompensation and HCC were associated with an increase in all-cause mortality. In patients with non-cirrhotic CLD, alcohol-related liver disease was associated with higher all-cause mortality. About 7.7% of cirrhotic patients developed new decompensation of liver cirrhosis with COVID-19 infection.

Data from 2 international covid registries, COVID-Hep.net and COVIDcirrhosis.org, were analyzed by Moon et al.[62] The data set included 103 patients with cirrhosis and 49 patients with non-cirrhotic CLD from 21 countries spanning four continents. The most common etiology of liver disease was fatty liver disease. Among patients with cirrhosis, Child–Pugh class B and C and Model for End-Stage Liver Disease (MELD) score higher than 14 were predictors of mortality. Hepatic decompensation was reported in 36.9% of patients with compensated cirrhosis.

Few studies investigated the impact of preexisting HBV and HCV without cirrhosis in COVID-19. The study sample was small, and the results were not congruent. However, there is a risk of reactivation of HBV with immunosuppressive medications like tocilizumab, baricitinib, and high-dose steroids that are used to COVID-19.[63] Attention must be paid to HBV serology before starting patients on strong immunosuppressant medication.[64,65] Drug interaction between antivirals for hepatitis B virus (HBV) and COVID-19 should also be kept in mind while initiating treatment for COVID-19. American Association for the Study of Liver Disease (AASLD) 2022 guideline recommendation is not to stop HBV treatment during COVID-19 infection. In COVID-19 infected hepatitis B surface antigen (HBsAg) positive patients who are not on anti-HBV therapy, prophylaxis with tenofovir disoproxil (TDF), tenofovir alafenamide (TAF), and entecavir (ETV) are recommended for prolonged corticosteroid use or immunosuppressant drug usage, to decrease the risk of reactivation and the possibility of liver failure.[66]

Special Population

COVID-19 and Preexisting Autoimmune Hepatitis (AIH)

Efe et al performed a multicenter study of patients with AIH who developed COVID-19 infection.[67] This was a multicenter study with 119 patients involved.[67] According to this study, ongoing immunosuppression was not associated with an increased risk of severe COVID-19, and maintenance of immunosuppression was associated with a lower risk for new-onset liver injury. Among patients with AIH, cirrhosis patients had a higher risk for severe COVID-19 outcomes (43.8% versus 3.9%). Overall mortality was also significantly higher in patients with cirrhosis than those without (31.3% versus 1.3%). Their study also noted 4 cases of AIH relapse with non-severe COVID-19 infection. AASLD (2022 consensus) recommends initiating/continuing treatment for AIH as clinically warranted.

COVID-19 and Preexisting Vascular Liver Disease

Vascular liver disease (VLD) includes Porto sinusoidal vascular disease, chronic non-cirrhotic splanchnic vein thrombosis, and Budd-Chiari syndrome.[68] A multicenter study from the REHEVASC network (including tertiary centers from Spain and France) investigated the effect of COVID-19 infection on patients who have preexisting vascular liver disease.[68] In this study, out of nine hundred and sixty-eight patients with VLD, one hundred and thirty-eight patients contracted COVID-19 infection. The study noted that patients with VLD had higher hospital admission, ICU admission, and mortality rates than the general population.

COVID-19 Vaccination and Liver Effects

There have been several case series describing abnormal liver tests related to COVID-19 vaccination. Roy et al 2022 published a descriptive analysis of post-COVID-19 vaccination liver anomaly reports.[69] Immune-mediated liver injury from the COVID-19 vaccination was noted to be transient in this study and responds to steroids without any true causality. The result of a literature review from around the globe from December 2019 to November 2022 revealed 32 cases of autoimmune-like syndrome after receiving the COVID-19 vaccine.[70] In this review, 31 patients responded to immunosuppression. One patient deteriorated due to unknown reasons and passed away. Overall, patients in this review seemed to respond to treatment.

At the time of the study, about 4 million people globally received at least one dose of COVID-19 vaccine. Hence, the few case reports may or may not represent a true vaccine-triggered autoimmune syndrome. If true, AIH triggered by

Covid vaccine is extremely rare and seems to have a good prognosis with immunosuppression. Clinicians should inquire about history of COVID-19 vaccine exposure while evaluating a patient with new liver test anomaly.

VALDIG (Vascular liver disease group) initiative from Europe identified 26 new cases of hepatobiliary venous thrombosis from 6 countries after vaccination.[52] Of those, 27% had underlying coagulation disorder on work up.81% of patients had portal vein thrombosis, and 7% had Budd-Chiari. Again, given the vast number of people vaccinated globally, and the different kinds of vaccines used, it is difficult to establish any true causation.

COVID-19 and Liver Transplant Patients

The results of Spanish study noted an increased risk of acquiring COVID-19 infection but a lower mortality rate than the general population among post-liver transplant patients.[71] In this study, patients on mycophenolate had more severe COVID-19 infection. Liver graft dysfunction has been mentioned with COVID-19 infection.

However, Khazaaleh 2023 et al noted increased mortality in patients with COVID-19.[72] A review of 18 studies, including 1522 COVID-19 infected LT recipients, showed a similar risk of morbidity and mortality as compared to the general population.[73] Rabiee et al noted that change in immunosuppression during Covid infection was not associated with liver injury (mostly dose reduction of mycophenolate and calcineurin inhibitors).[74] Alanine transaminase (ALT) elevation was higher in post-transplant patients with Covid compared to the general population. In a multicenter European study, COVID-19 with a history of cancer was associated with an overall increase in morbidity AASLD recommends decreasing or holding antimetabolites if patients develop COVID-19.[27,75] AASLD recommends against decreasing or holding calcineurin inhibitors. AASLD recommends against adjusting or holding immunosuppressive medications in anticipation of COVID-19 infection or vaccination.[27]

Conclusion

Patients can develop abnormal liver tests associated with COVID-19 infection through a variety of mechanisms (Box 1). The liver test anomaly pattern is usually AST-predominant transaminitis. Hepatic involvement during covid infection

Box 1 Mechanism of COVID-Related Liver Injury

1. Direct COVID mediated hepatic cell injury[9]
2. Immune mediated hepatocyte injury[12]
3. Sepsis[56]
4. Drug induced liver injury[26]
5. Microthrombi in liver[13]
6. Hepatic congestion[36]
7. COVID Cholangiopathy[30]
8. Ischemic Hepatitis[57]
9. Systemic Hypoxia[57]
10. Thrombosis of splanchnic system[54]
11. Cytokine storm related liver injury[12]
12. Myositis[58]
13. Cardiac injury[58]
14. De novo autoimmune hepatitis[35]

indicates a severe infection. The abnormal liver test usually resolves once the infection resolves. Patients who developed severe hepatitis from covid, covid-related cholangiopathy, autoimmune hepatitis, and splanchnic venous thrombus formation all need careful continued follow-up in the liver clinic after discharge. Some of these patients could go on to develop significant hepatic dysfunction and might warrant liver transplant evaluation. Caution should be exercised while using antivirals and be mindful of potential drug-to-drug interactions.

Patients with preexisting chronic liver disease have a higher risk of COVID-19 disease severity if infected. Hence, patients with chronic liver disease, especially those with end-stage liver disease, should avoid exposure to the COVID-19 virus if possible. Most cases of hepatic dysfunction are reported from 2020 prior to vaccination. Clustering of hepatic manifestations from COVID-19 in the early pandemic phase could be linked to changes in the virulence of the covid virus variants and from the protective effect of covid vaccination.[60,76,77] Vaccination has significantly reduced morbidity and mortality related to COVID-19 infection. AASLD 2022 guidance strongly recommends vaccination against covid, especially in patients with chronic liver disease and cirrhosis. In fact, Kulkarni et al showed better prognosis for patients vaccinated against COVID-19 who developed cholestasis in comparison to unvaccinated patients.[78] COVID-19 continues to be relevant globally. Even if the infection transitions from the pandemic to the endemic stage, it still results in morbidity and mortality. Globally, nearly 2.8 million new cases and over 1000 deaths were reported in the last 28 days (27 March to 23 April 2023).[79] Per CDC data, in May 2023, 77,000 people developed covid weekly in the United States, and 1000 people died from covid weekly from COVID-19 related illnesses in the United States.[80]

Improvement in the severity of COVID-19 from vaccination and change in virus strain are reassuring. However, the natural history of COVID-19 pandemic is still evolving. COVID-19 is here to stay in the pandemic/endemic stage. Hence, we still need to be cautious. The knowledge base created during the pandemic will continue to help us manage patients who develop COVID-19. However, we need further studies to expand the scientific data pool regarding the long-term outcomes for patients who developed covid-related liver injury. Long covid seems to be sparing the liver, despite having other gastrointestinal system involvement.[81]

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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