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Insight into COVID-19 associated liver injury: Mechanisms, evaluation, and clinical implications

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Abstract

COVID-19 has affected millions worldwide, causing significant morbidity and mortality. While predominantly involving the respiratory tract, SARS-CoV-2 has also caused systemic illnesses involving other sites. Liver injury due to COVID-19 has been variably reported in observational studies. It has been postulated that liver damage may be due to direct damage by the SARS-CoV-2 virus or multifactorial secondary to hepatotoxic therapeutic options, as well as cytokine release syndrome and sepsis-induced multiorgan dysfunction. The approach to a COVID-19 patient with liver injury requires a thorough evaluation of the pattern of hepatocellular injury, along with the presence of underlying chronic liver disease and concurrent medications which may cause drug-induced liver injury. While studies have shown uneventful recovery in the majority of mildly affected patients, severe COVID-19 associated liver injury has been associated with higher mortality, prolonged hospitalization, and greater morbidity in survivors. Furthermore, its impact on long-term outcomes remains to be ascertained as recent studies report an association with metabolic-fatty liver disease. This present review provides insight into the subject by describing the postulated mechanism of liver injury, its impact in the presence of pre-existing liver disease, and its short- and long-term clinical implications.

Key Points

1. COVID-19 associated liver injury can have an unpredictable course and variable manifestations
2. The mechanisms of liver injury include direct damage by the virus, liver injury due to hepatotoxic drugs, cytokine release syndrome, and sepsis-induced multiorgan dysfunction.
3. Evaluating a COVID-19 patient with liver injury requires consideration of the pattern of hepatocellular injury, the presence of underlying chronic liver disease, and concurrent medications.
4. Severe COVID-19 associated liver injury is associated with higher mortality, prolonged hospitalization, and greater morbidity in survivors.
5. Long-term clinical implications of COVID-19-associated liver injury include metabolic-associated fatty liver disease, which may have implications for overall health.

Keywords: COVID-19 associated liver injury; cytokine release syndrome; SARS-CoV-2.

Introduction

COVID-19 has affected millions of people worldwide, causing significant morbidity and mortality. As the World Health Organization declares the end of the global health emergency due to COVID-19, the world is still grappling to understand the long-term impact of the disease.[1] SARS-CoV-2 is known to cause multi-organ damage, including injury to the lungs, kidneys, neurological, cardiovascular, and liver, as well as a myriad of hematological abnormalities. Liver injury was amongst the earliest recognized complications of COVID-19.[2,3] The incidence of liver injury has been reported to be between 16% to 29%, and a higher prevalence was observed in hospitalized patients with COVID-19.[4,5] COVID-19-associated liver injury has been defined as any identifiable liver damage that occurs as a direct result of the COVID-19 infection or during the course of the disease or treatment, irrespective of any pre-existing comorbid or liver disease.[6] The presence and extent of liver damage that occurs are primarily measured by taking quantitative measurements of liver enzymes. There are three types of liver injury described in the literature: hepatocellular, cholestatic, and mixed types. An elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times greater than the upper limit of the normal value is indicative of the hepatocellular type of liver injury. Elevations in other liver enzymes, such as alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin that exceed two times the upper normal value, are seen in the cholestatic type. The mixed type is a combination of both hepatocellular and cholestatic ranges.[7] Abnormalities with tests that assess liver function are common, but their overall impact is still under exploration. Furthermore, imaging modalities have also been utilized in identifying COVID-19-associated liver injury. These include ultrasound (US) (the main diagnostic tool for first evaluation), Computed Tomography Scan (CT) (most useful for overall abdominal assessment), and Magnetic Resonance Imaging (MRI) (most helpful in

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better clarifying liver changes in cases where changes on US and CT are indeterminate). Hepatomegaly, steatosis, acute hepatitis, drug-induced liver injury, portal vein thrombosis, and biliary involvement have all been described.[8] Liver injury has also been corroborated from liver biopsy evidence, which has shown moderate microvascular steatosis and mild lobular and portal activity.[9] It is of utmost importance for physicians and researchers to analyze and assess the mechanism of liver injury and its impact on patient outcomes and disease processes. This short review focuses on the pathophysiology of COVID-19-associated liver injury and provides an overview of the management of these patients and the consequences of COVID-19 on people living with pre-existing liver disease, primarily chronic liver disease. Moreover, it elaborates on the short and long-term implications of COVID-19-associated liver injury.

Pathophysiology of COVID-19 and Liver Injury

Liver injury was first reported by Zhang et al.[2] from Wuhan. They reported that 43.4% of the cases had mild to moderate elevation of ALT and AST. Since then, liver injury has been observed and reported in several studies, and the degree of liver damage has been associated with a greater risk of progression to severe COVID-19.[3,10] The exact pathophysiology of liver damage in SARS-CoV-2 remains unclear, but proposed mechanisms include direct damage to the liver, drug-induced injury, inflammatory immune response, and hypoperfusion (Fig. 1).[11]

Direct Liver Damage

SARS-CoV-2 targets the angiotensin-converting enzyme 2 (ACE2) receptors, which, besides the lungs, are present in the intestinal endothelium and vascular smooth muscles.[12] ACE2 is also expressed by hepatocytes and cholangiocytes, although expression is higher in bile duct epithelium compared to hepatocytes.[13,14] SARS-CoV-2 can, therefore, cause liver injury either by binding to hepatocytes or by binding to bile duct cells, leading to upregulation of ACE2 in the liver.[14] Tian et al.,[15] however, reported that inclusion bodies of the virus were not found on autopsies of COVID-19 patients.[15] This supports bile duct damage rather than hepatocyte damage as the cause of liver injury. Zhao et al.[16] also reported that liver ductal cultures revealed bile duct injury as the possible cause of liver damage. Liver cirrhosis can lead to increased expression of ACE2 in hepatocytes. This may result in increased invasion of hepatocytes by SARS-CoV-2 and more severe liver injury in patients with chronic liver disease.[13,17]

Cytokine Release Syndrome

COVID-19 leads to multisystem dysfunction as part of the systemic inflammatory response syndrome (SIRS). Many cytokines are released, many of which are produced by the liver, including interleukins, tumor necrosis factors, interferons, and chemokines.[18] IL-6 causes activation of T-cells, B-cell differentiation, and induction of acute phase reactants in the hepatocytes.[19] The acute phase response by the liver is a protective mechanism against the pathogen.[20] The activated T-cells attack the infected cells until they are depleted. The depleted cells, when unable to control the infection, activate secondary inflammatory responses, leading to the production of more inflammatory cytokines.[21] The excessive release of inflammatory cytokines leads to shock, multiorgan dysfunction, and acute respiratory distress syndrome.[22,23]

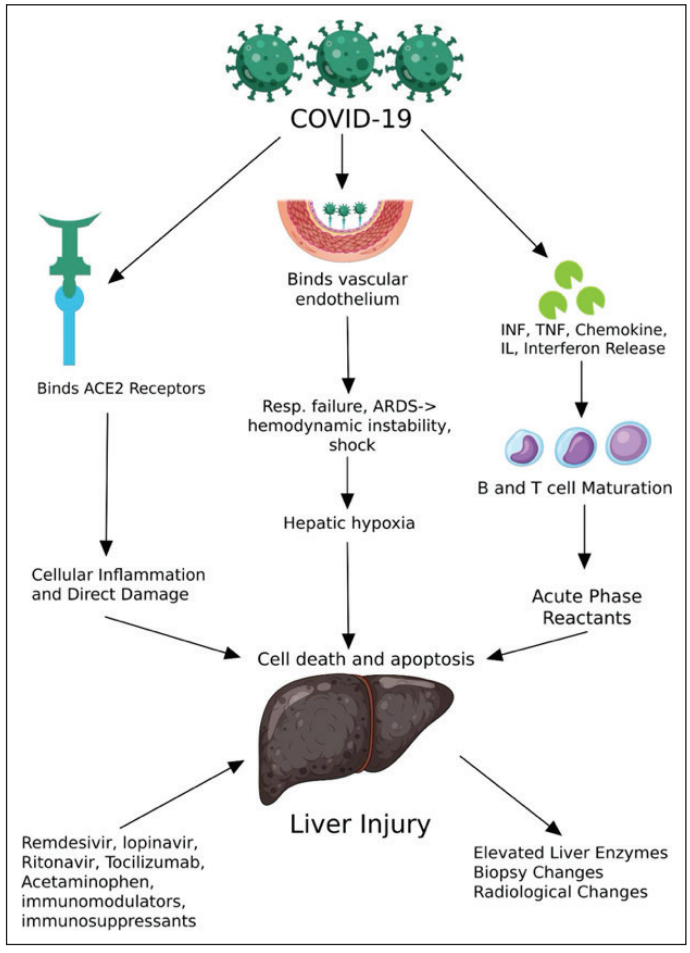

Figure 1. Pathophysiology of COVID-19 associated liver injury.

Hypoxia Reperfusion Syndrome

SARS-CoV-2 binds to several receptors in the vascular endothelium. The subsequent vascular injury leads to respiratory failure and ARDS3. The liver is prone to the effects of hypoxemia due to its complicated vascular supply and high metabolic activity.[24] Hemodynamic instability leads to reduced flow to the liver and periphery, resulting in hypoxemia causing an acute elevation of serum transaminase levels.[25,26] Persistent hypoxia due to respiratory, cardiac failure, or shock causes lipid accumulation in hepatocytes, progressing to cell death and apoptosis.[27] This is followed by mitochondrial damage and release of reactive oxygen species causing further damage, release of proinflammatory markers, and activation of macrophages, neutrophils, and platelets.[27–29] Microcirculatory disturbance leads to coagulopathy and thrombosis. Von Willebrand factor antigen correlates with the severity of vascular endothelial damage, and higher levels are associated with increased mortality.[30]

Drug-Induced Liver Injury

Drugs may be a crucial factor leading to liver injury in COVID-19. This has been supported by autopsy reports showing microvascular steatosis and hepatic inflammation.[31] Many classes of drugs have been used to treat COVID-19 since the beginning of the pandemic; among these, many are known to be hepatotoxic. Drugs used include antipyretics

(e.g., Acetaminophen), antivirals (e.g., Remdesivir, Lopinavir/Ritonavir), antibiotics (e.g., Azithromycin), immunosuppressants and immunomodulators (e.g., corticosteroids, Hydroxychloroquine), Tocilizumab, and herbal medicines. Besides this, many antimicrobial agents such as azoles, used for treating superimposed fungal infections such as COVID-19-associated pulmonary aspergillosis, are also associated with liver enzyme dysfunction. Use of multiple drugs at the same time, possible interaction between drugs for treating COVID-19, medications used to treat other comorbid conditions, and discontinuation of drugs being used by a patient for prior liver disorders may all contribute to liver injury.[24]

There is a substantial variability of transaminitis in patients with COVID-19 infection. Many patients receive multiple combinations of drugs for treatment; thus, it becomes difficult to evaluate the component of liver injury related to a particular drug. The drug-induced liver injury may either be an intrinsic liver injury or an idiosyncratic one, with an unspecified latency period. Thus, most drug-induced liver injuries may remain as a diagnosis of exclusion unless specific testing, including biopsies, are performed. Many host factors including age, gender, pregnancy, malnutrition, obesity, and comorbidities like diabetes, NAFLD have been implicated as factors in idiosyncratic drug-induced liver injury.[32] Among the common medications used in COVID-19 infections are acetaminophen, NSAIDs, antivirals like Remdesivir, Lopinavir/Ritonavir, antibiotics (e.g., Azithromycin), immunosuppressants and immunomodulators (e.g., corticosteroids, Hydroxychloroquine), antibodies (e.g., Tocilizumab), and herbal medicines. The occurrence of DILI with acetaminophen is one of the most common drug adverse events. Mortality rates have been approximated at 0.4% in overdose patients, translating to 300 deaths annually in the United States. Although the majority of patients experience mild adverse reactions, such as hepatitis, cholestasis, or asymptomatic liver enzyme elevation, APAP hepatotoxicity is generally estimated to account for approximately 48% of acute liver failure diagnoses.[33–35] DILI follows a dose-dependent toxicity ranging from 0.02% up to 30%.[36]

Remdesivir

In the initial study reporting the safety of remdesivir for COVID-19 patients, conducted by Grein et al.,[37] the effect of 5 to 10-day courses of remdesivir on the changes in the category of oxygen-support status was investigated in a small cohort of 53 patients. The most common adverse event in this study was increased hepatic enzymes, with an incidence of 23%. A similar pattern was replicated in the study on 402 patients, evaluating the optimum time course for intravenous remdesivir, conducted by Goldman et al.[38] In that study, ALT and AST elevation (7% and 6%, respectively) was reported as the most common liver adverse effects.[38] Furthermore, in the placebo-controlled double-blinded clinical trial on a total sample of 255 patients, conducted by Wang et al.,[39] grade 1–2 increased AST was detected as an adverse liver effect (12% in the placebo group, 7% in the remdesivir group), and grade 1–2 increased ALT led to drug discontinuation (1%).[39]

Lopinavir/Ritonavir

The other drug combination used for the treatment of COVID-19 infections was lopinavir/ritonavir. A significant number of studies have reported the association of lopinavir/ritonavir use in COVID-19 patients with adverse liver effects. In a study by Sun et al.[40] on a sample of 217 patients, 63% of total adverse drug reactions (ADRs) were associated with the use of lopinavir/ritonavir. Liver ADRs were the second most common ADRs, with a prevalence of 18%. However, the percentage of liver ADRs due to lopinavir/ritonavir was not reported by the same study.[40] Later, Fan et al.[41] reported that among the 148 patients, 45 patients had normal baseline liver functions, of which 48% developed an abnormality in the liver after admission to the hospital. They highlighted that among the patients with abnormal liver functions, a higher proportion had used lopinavir/ritonavir (57.8%) compared to the patients with normal liver function tests (31.3%).

Hydroxychloroquine

Hydroxychloroquine has remained in use for rheumatological disorders and is implicated in the treatment of malaria. Short-term use is associated with very limited adverse effects pertaining to liver injuries. However, it is implicated that when used in combination with other medications like ritonavir, the adverse effects may increase.

Tocilizumab

Interleukin-6 (IL-6) blockers, including tocilizumab and sarilumab, were approved in June 2021 for the treatment of patients with moderate to severe COVID-19. There has been a noticeable difference in the peak onset times of adverse reactions between the two drugs. Some studies have reported TCZ-related DILI accounted for 67.01% in the first four days after receiving TCZ therapies, and SAR-associated DILI accounted for 83.13% in the first six days after receiving SAR therapies. Furthermore, it is also associated with reactivation of Hepatitis B, as has been described in patients with rheumatological disorders being treated with tocilizumab along with DMARDs.[42,43]

Impact of COVID-19 on Patients with Pre-existing Liver Disorders

The impact of COVID-19 on liver function in patients with preexisting liver disease depends on the underlying etiology and severity of the underlying liver pathology. The disease presentation of COVID-19 is highly variable; thus, many confounding factors can be attributed to increased morbidity and mortality. Multiple studies evaluated the outcomes of COVID-19 with liver pathology and found variable and conflicting results. As compared to individuals without CLD, the patients with CLD and cirrhosis may have more severe disease and a greater COVID-19-associated mortality rate. According to a systematic review, the likelihood of COVID-19-associated severe diseases and death was 2.44 times greater in patients with CLD compared to those without underlying liver diseases.[44,45] COVID-19 can be stratified into the following groups when considering underlying liver disease.

Chronic Viral Hepatitis and COVID-19

Chronic viral hepatitis in the absence of chronic liver disease does not seem to affect morbidity and mortality among patients with COVID-19. However, studies have shown that COVID-19 patients with Hepatitis B (HBV) co-infection tend to have a poorer prognosis, with a 2.2-fold increased severity of COVID-19 and an in-hospital mortality rate of 6.0%. Similarly, chronic hepatitis C (HCV) patients with COVID-19 are more prone to hospitalization but not at a higher risk of death.[46] The results of a comprehensive meta-analysis by Hariyanto et al.[47] have also shown an association of viral hepatitis with severe COVID-19. COVID-19 can reactivate or cause a sudden increase in HBV DNA

levels in the blood, hepatitis failure, and flare of acute hepatitis in patients with chronic HBV. Risk factors for HBV reactivation in patients with COVID-19 are immunosuppressive therapy, including steroids, advanced age, male sex, lymphopenia, and significant comorbidities (including chronic renal disease, hypertension, diabetes, and hypercholesterolemia).[48,49] The presence of chronic HCV infection, history of HCV infection, and acute liver injury are strong predictors of hospital mortality in patients with COVID-19. The mechanisms may be connected to baseline cytokine-mediated pro-inflammation and endothelial dysfunction, as well as extrahepatic effects of HCV that promote ACE-2/TMPRSS mechanisms of SARS-CoV-2 viral entry.[50]

Another study found that age greater than 60 years, male gender, elevated ALT and procalcitonin levels, and high HCV viral load were all individually associated with liver damage. Additionally, ALT levels in men, an elevated HCV viral load, and a higher age above 60 were all independent risk factors for all-cause mortality.[51]

It is recommended to initiate or continue anti-HBV therapy in all patients with COVID-19 with concomitant or chronic HBV infections. Based on data on reactivation of HBV with immunosuppressive therapy, studies have suggested starting antiviral prophylaxis in patients with HBV infection and receiving corticosteroids or other immunosuppressive therapy while closely monitoring HBV virological indicators and signs of liver injury.[48,52] Antiviral therapy for HCV direct-acting antiviral (DAA) should be continued to maximize the sustained virological response rate, with close monitoring for any adverse events, because the majority of COVID-19 regimens do not have significant drug-drug interactions with agents used to treat HCV.[53] Interferon therapy for both HBV and HCV should be stopped in patients with severe COVID-19, as it is one of the potent cytokines and can contribute to SARS-CoV-2-induced cytokine release syndrome.[54]

Patients with viral hepatitis encountered difficulties during the pandemic as medical resources were diverted to the COVID-19 issue. Access to standard medical care for identifying early-stage hepatitis was restricted, and follow-up visits of patients with CLD were decreased because of concerns about exposure to COVID-19 infection from HCW and healthcare facilities. Essential testing available in large centers, like ultrasonography and nucleic acid tests, was hampered by travel restrictions, and treatment interruptions were brought on by antiviral shortages due to travel restrictions and limited flight options. Infant hepatitis B vaccination rates were also similarly affected by lockdowns. Telemedicine has evolved as a valuable patient-healthcare link on a worldwide scale, but its usefulness is limited in LMIC.[55–57] Health authorities must take steps to preserve the continuity of vital programs like HCV, HBV, and TB in order to reduce the impact of future pandemic-related interruptions, especially in low-resource nations. To minimize disruptions and sustain important health services during any potential future crises, strong contingency plans, strengthened healthcare infrastructure, and flexible service delivery methods are crucial.

Alcohol-Associated Liver Disease and COVID-19

Due to several reasons, alcohol consumption increased during the COVID-19 pandemic, leading to higher rates of alcoholic hepatitis. Data has suggested that greater mortality and morbidity were seen among these patients, with a greater incidence of acute-on-chronic liver failure and acute-on-chronic hepatitis. One postulated mechanism of injury is related to ferritin excess in patients with alcoholic hepatitis and COVID-19 infection, leading to greater free radical damage to the liver.[58–60]

The high risk of severe COVID-19 in patients with alcohol use disorder (AUD) or alcohol-induced hepatitis is secondary to the presence of underlying comorbid illnesses, suppressed immunity, concomitant smoking in many cases with underlying respiratory diseases, social isolation leading to psychological stress and increased consumption of alcohol, and use of steroids or other immunosuppressive therapy for treatment of SARS-CoV-2 infection.[61]

The medications used for treatment of alcohol use disorder (AUD) are naltrexone, nalmefene, disulfiram, acamprosate, sodium oxybate (SO), and baclofen.[62] Patients receiving treatment for AUD or antipsychotics should be closely monitored for drug-drug interactions as well as potential adverse reactions while receiving treatment for COVID-19.

Management of AUD or alcohol-related hepatitis has faced numerous difficulties during the COVID-19 pandemic due to limited access to routine medical visits, which makes it difficult to monitor diseases and implement prompt interventions. Furthermore, forced social isolation causes psychological anguish, which could lead to increased drinking or relapse. A crucial option that enables remote patient monitoring, consultation, and action is telemedicine. The psychological effects of isolation can also be addressed through online support groups and teletherapy.[54]

Metabolic Dysfunction-associated Fatty Liver Disease (MAFLD) and Severity of COVID-19

Limited data exists regarding patients with metabolically associated liver disease, also called non-alcoholic fatty liver disease, and COVID-19. The damage to hepatocytes seems to have a similar mechanism of injury as described with alcoholic hepatitis and COVID-19. In a retrospective study by Ji D. et al.,[63] consecutive patients with COVID-19 and MAFLD were studied, and liver injury was observed in 50% on admission and 75% during hospitalization. Moreover, 33% of patients had persistent abnormal liver function from admission to the last follow-up. Patients with progressive disease were older, had higher BMI, and a higher percentage of comorbidity along with MAFLD63. Studies have reported an increased risk of severe COVID-19 in patients with a high body mass index, a combination of metabolic risk factors with increased risks related to diabetes mellitus, hypertension, and coronary heart disease, and MAFLD patients with increased noninvasive liver fibrosis scores (FIB-4 score).[64,65] MAFLD patients had a longer viral shedding time, a higher likelihood of liver damage, and a higher probability of the disease progressing to severe COVID-19.[66]

There is a high risk of respiratory complications related to COVID-19 in patients with MAFLD. There is little data on the effectiveness and safety of COVID-19 therapies for MAFLD patients. The choice of medication for these patients is based on variables such as the severity of the illness, the ALT level, and probable interactions, and medication discontinuation may be required if ALT levels are six times above average. For the treatment of MAFLD in COVID-19 cases, more research is required.[67] It is recommended that MAFLD patients receive lifestyle counseling with an emphasis on reducing risk factors (such as obesity) that indicate a poor prognosis for COVID-19.

Autoimmune Liver Disease and COVID-19

AILDs, which include overlapping syndromes, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and primary biliary cholangitis (PBC), are a diverse collection of inflammatory disorders of the liver attributed to an autoimmune response. Patients with AILDs are not at increased risk of acquiring COVID-19 infection as compared to the general population.[68]

Autoimmune hepatitis (AIH) is a chronic inflammatory disease affecting the liver, which is treated either with steroids alone or in combination with azathioprine. Other immunosuppressive agents may be required in some cases.[69,70] Prolonged use of immunosuppression can lead to an increased risk of acquiring infections; however, results of a multicenter survey in Europe suggest that AIH is not associated with an increased risk of acquiring COVID-1968. Furthermore, according to data compiled from three large-scale international reporting registries—European Association for the Study of the Liver supported COVID-Hep registry, the European Reference Network on Hepatological Diseases (ERN RARE-LIVER), and the American Association for the Study of Liver Diseases supported SECURE-cirrhosis registry—patients with AIH did not exhibit an elevated risk of adverse outcomes, such as hospitalization, intensive care unit stay, and mortality in comparison to other causes of CLD and without any liver diseases.[71] Efe et al.[72] analyzed the factors associated with severe COVID-19 outcomes in patients with AIH. They reported 37% new-onset liver injury, and the use of antivirals was associated with liver injury. The rates of severe COVID-19 and mortality were similar in both AIH and non-AIH CLD patients. In another study, a comparison of COVID-19 patients with AIH to those without liver disease showed a higher risk of hospitalization but a similar risk of all other outcomes, including mortality.[71] In both studies, cirrhosis was an independent predictor of severe COVID-19.

Patients with AIH are on immunosuppressive therapy for prolonged periods, and several studies have shown no association between immunosuppressive therapy and the severity of COVID-19. However, a subsequent study showed an increased risk of COVID-19 severity in those patients who were on steroids and azathioprine as compared to those who were not on treatment.[71,73] Tacrolimus and mycophenolate mofetil (MMF) were associated with similar outcomes.[74] The effect of tacrolimus and MMF on COVID-19 outcomes, however, requires further validation on larger cohorts, as although there are several studies. [75–77] that support the association of these drugs with COVID-19 severity, there are others which show no impact of these drugs on COVID outcomes.[78,79]

Vaccination against SARS-CoV-2 is an important preventive measure for COVID-19. Effective vaccination has reduced the need for hospitalizations and mortality due to COVID-19 in the general population throughout the World.[80] Similar outcomes have been reported in patients with chronic liver disease (CLD).[81–83] Patients on immunosuppressive therapy and those with CLD have a low antibody response to SARS-CoV-2 vaccination, and this has also been seen in AIH. An early third booster is recommended for these patients to maintain the antibody levels in the body.[84–86] Efe et al.[87] in their study on AIH patients with COVID-19 reported a significantly reduced risk for hospitalization, supplemental oxygen, and mortality in those who had received the SARS-CoV-2 vaccination.

Autoimmune Liver Disease and COVID-19

Among other adverse effects post SARS-CoV-2 vaccine, autoimmune hepatitis-like liver injury has also been reported.[88,89] A large case series of 87 patients describes 84% hepatocellular type injury, with 57% having features of immune-mediated hepatitis. Approximately half the cases received steroids. All showed complete resolution except one patient, and no relapse was reported on follow-up.[90] Although the current recommendation is against changing immunosuppressive treatment in patients with AIH, the available data to date supports the continuation of low-dose steroid therapy to keep the disease in remission.[91]

Cirrhosis and COVID-19

Decompensated cirrhosis is among the independent predictors of mortality in patients with COVID-19. Attributable factors include worsening sepsis and immune dysregulation, along with complications of cirrhosis. Data from two international reporting registries (SECURE-cirrhosis USA and COVID-Hep.net coordinated by the University of Oxford and the European Association for the Study of the Liver) showed poorer outcomes. Hepatic decompensation during COVID-19 was strongly associated with a subsequent risk of death: 63.2% of those with new decompensation died compared to 26.2% of those without new decompensation. Notably, 24.3% of those with new hepatic decompensation had no respiratory symptoms of COVID-19 at the time of diagnosis. Hence, decompensated liver disease is a significant risk factor for mortality in patients with COVID-19.[92]

A multicenter study concluded that patients with cirrhosis and COVID-19 had similar mortality compared with patients with cirrhosis alone, albeit higher than those with only COVID-19.[93] In another study, deaths occurred in 12.2% of patients with chronic liver disease (CLD) without cirrhosis, 24% of patients with Child-Turcotte-Pugh Class A (CTP-A) cirrhosis, 43% with CTP-B cirrhosis, and 63% with CTP-C cirrhosis. The cause of death in patients with cirrhosis was reported to be due to COVID-19 lung disease in 78.7%, cardiac-related in 4.3%, and liver-related in 12.2%.[94] However, studies have been conflicting, and the pooled results have shown that CLD has played a minor role in influencing patient progression toward the severe form of the disease.[95]

Cirrhosis is common, and its course is characterized by life-limiting complications such as variceal hemorrhage, ascites, hepatic encephalopathy, and hepatocellular carcinoma (HCC) that require active surveillance. Cirrhosis has a negative impact on COVID-19; thus, management and treatment should be more rigorous in terms of medication, monitoring, and follow-up. The pandemic has severely affected the management of patients with CLD and cirrhosis, both with and without COVID-19. The delay has resulted in rapid progression of hepatic diseases, variceal bleed, increased incidence of hepatocellular carcinoma (HCC), delay in procedures including liver transplant, and overall mortality.[96]

There should be provision of holistic, personalized, and continuous care plans for patients with cirrhosis and CLD to avoid such complications in future crisis situations. There are new recommendations suggested by experts, i.e., changing HCC surveillance from 3 months to 12 months, telemedicine, prioritizing care to high-risk patients, availability of medicine, and simpler surveillance techniques in the community; the effectiveness of these is yet unknown.[97,98] More clinical data is required to determine the effect of these recommendations on patient outcomes and to ensure they are appropriate given the ongoing healthcare issues.

Approach to a COVID-19 Patient with Liver Injury

Hepatic involvement in COVID-19 can range from asymptomatic status to severe disease. Males are substantially more likely than females to get liver damage. The liver injury is predominantly found in patients with severe and critical COVID-19 and those with prior comorbid illnesses like hypertension, diabetes mellitus, cardiovascular diseases, and malignancies.[99] Studies have identified several risk factors for hepatic impairment in COVID-19 patients, including old age, obesity, severe and critical COVID-19, male gender, existing liver diseases, high C-Reactive Protein, lymphopenia, and low AST/ALT ratio.[7,100]

A significant proportion of patients with COVID-19 have abnormal liver biochemical tests at the time of presentation to a healthcare facility.[101] Furthermore, patients with normal liver functions can also develop hepatic injury during their stay in the hospital with the progression of the disease course41. Although uncommon, a few cases of fulminant hepatic failure with COVID-19 have also been reported in the literature.[102–104] The biochemical indicators of liver injury are elevated total bilirubin (TB), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), increased prothrombin time (PT) including INR, and reduced levels of serum albumin in patients with COVID-19.[105] The abnormal liver function is found to be associated with critical disease, stay in high dependency units, ICU admission, need for ventilator support, prolonged hospital stay, and death.[41] Among three forms of liver impairments i.e., hepatocellular injury, cholestasis, and hepatocellular dysfunction, patients with hepatocellular dysfunction or mixed type have an increased likelihood of developing a serious illness.[106] Hence, monitoring of liver function tests is warranted for patients with severe or critical COVID-19 from the time of admission.

Management

Most COVID-19 individuals experience minor, transient liver damage which returns to normal without treatment.[24] Supportive treatment is required for the management of hepatic function impairment in patients with COVID-19. Detailed history and examination are required to identify any pre-existing liver diseases, prior medication, or hepatotoxic agent use. Careful monitoring of liver function tests is recommended, especially in the presence of risk factors for hepatotoxicity and previous liver diseases. In patients with severe COVID-19 and pre-existing liver pathology, medical management should not include more than two drugs that have the potential for drug-induced liver injury or drug-drug interactions. Close monitoring of the dosage and drug interactions, along with regular measurement of liver enzymes, is advisable, with a prompt dose adjustment or drug discontinuation as required. Anti-inflammatory liver protection and hepatoprotective drug treatment should also be initiated as required.[107] Abnormal liver functions can persist longer than clinical recovery from acute illness, which necessitates long-term monitoring of liver function tests in patients with severe COVID-19.[24]

HCV and HBV patients should continue taking antiviral medications as discontinuation in the setting of a COVID-19 infection is not recommended in the guidelines issued by the AASLD (American Association for the Study of Liver Diseases) unless there is a pattern of worsening liver enzymes, in which case drug removal can be considered. In patients not on antiviral therapy and with a history of HBV, HbsAg testing can be conducted to rule out flares.[108] In patients with liver cirrhosis, due to the high likelihood of severe complications and death, patients should continue receiving appropriate treatment.[97] Patients with comorbid conditions related to metabolic associated fatty liver disease (MAFLD) such as diabetes, dyslipidemia, and obesity should be evaluated for liver injury as a result of MAFLD in the setting of elevated liver enzymes.[24]

Changing Trends in Management

The management of COVID-19 has evolved considerably over the years with the addition of newer antivirals and use of monoclonal antibodies, as opposed to early in the pandemic when no approved drugs existed for this disease.[109] Furthermore, owing to vaccination, the disease manifests with relatively less severity, leading to lesser requirements for salvage treatment with IL-6 antagonist Tocilizumab. This has a favorable outlook for liver injury arising due to the use of Tocilizumab, as well as liver injury as a result of the disease itself. While one of the antivirals, Remdesivir, has been associated with drug-induced liver injury, the impact has rarely been significant enough to require discontinuation of treatment.

Biopsy Findings in COVID-19 Associated Liver Injury

Post-mortem analysis has shown that there are two possible common pathways that cause the histological changes typified in COVID-associated liver injury: a post-infectious immune response and immune dysregulation.[110]

Post-Infectious Immune Response

After viral infection, there may be an exaggerated immune response, characterized by acute hepatitis and prominent bile duct injury, which can lead to significant damage to the liver.[111] The histological evidence of this would be mild to severe hepatic congestion, focal confluent necrosis, hepatocyte necrosis, and lobular necroinflammation, underscoring the severity of immune-mediated liver injury.[112,113]

Immune Dysregulation and Susceptibility to Subsequent Infections

Another intriguing hypothesis is that the immune dysregulation that occurs during the primary SARS-CoV-2 infection can prime the liver to react abnormally to other pathogens, such as adenoviruses. The liver expresses ACE-2 receptors, which are active binding sites for SARS-CoV-2 in the lungs and may play a role in the binding occurring in the liver as well. This binding occurs potentially more frequently and avidly on cholangiocytes rather than hepatocytes.[114] The histological manifestation of this is present in sinusoidal dilation in zone 3, patchy hepatic necrosis, and the presence of cirrhosis.[115] The presence of cirrhosis may also suggest that there is further exacerbation or reactivation of underlying chronic liver diseases. Furthermore, a constellation of drug-induced liver injury and ischemic liver injury due to hypoxic and shock-like states may also explain the injury occurring to non-cholangiocytic cell types which have a far lower concentration of ACE-2 receptors.[12]

Common Histological Findings

Biopsy findings in patients diagnosed with COVID-19-associated liver injury frequently exhibit the following patterns:

Hepatic Congestion: Ranging from mild to severe, it may occur as a result of severe respiratory disease, which causes right ventricular failure leading to elevated venous pressure within the liver and its vascular system.[113]

Ischemic Changes: The presence of focal confluent necrosis and hepatocyte necrosis suggests the possibility of a low oxygen state within the liver.[113] This may result from shock, a shock-like state, or chronically low oxygen saturation due to a decrease in lung functionality.[115]

Steatosis: A very common finding on biopsies is the presence of increased fat and glycogen accumulation within the liver.[116] This may be present in a pan-lobular pattern and suggests an additional mechanism of liver injury.[112] This may also manifest as microvascular and macrovascular steatosis.[117]

Despite this wide range of abnormalities that may occur in the liver and cause injury that warrants further investigation, the routine usage of biopsies in cases of liver injury associated with COVID-19 infections is not recommended.[117]

Implications of COVID-19 Associated Liver Injury

Short-Term Impact on Patient Outcomes

COVID-19-associated liver injury may be mild to severe. The prevalence of mild transaminitis has been reported between 15% to 50% with ALT/AST ratio reversal, and in the majority of cases, it is self-limiting.[118] In most patients, the ALT and AST values peak after day 6 to up to 2 weeks of illness.[119] However, studies have also reported severe liver injury with incidences reported to be higher than or equal to 70% in those patients who died of the disease.[120,121] Hence, COVID-19-associated liver injury is a marker of severity of disease or a predictor for progression of disease, whether it is a consequence of direct hepatotoxicity of SARS-CoV-2 virus or a manifestation of multi-organ dysfunction. Moreover, the risk of death may be directly proportional to the degree of transaminitis.[119] In patients hospitalized with COVID-19, a moderate rise in liver function tests (LFTs) during admission was linked to a poor short-term outcome. Among patients with pre-existing liver disease, the presence of cirrhosis was reported to be an independent predictor of higher 30-day mortality.[122] Furthermore, the presence of liver injury in hospitalized COVID-19 patients results in a prolonged length of hospital stay.[123–125]

Long-Term Impact on Patient Outcomes

The majority of cases of COVID-19-associated liver injury are acute, with a transient rise in biomarkers that self-resolve over a short period of time. Even in the case of acute-on-chronic liver injury, the rise in hepatic biomarkers is non-permanent, with the patient returning to their pre-COVID baseline soon after.

Although COVID-19 is a self-limited viral infection, its effects can be felt for weeks and even months after resolution. The major manifestation of this is in the form of long-COVID, a constellation of signs and symptoms that affects multiple organ systems and presents after the resolution of the initial acute infection, presenting from 14 to 110 days post-infection with an estimated incidence rate of 80%.[126] The major symptoms are fatigue, breathlessness, arthralgia, and chest pain; however, there is multi-system involvement, including but not limited to respiratory, cardiovascular, neurologic, renal, mental health, and hepatic.[127,128]

A study examining long-term outcomes of liver function derangements in COVID-19 found that approximately 28% of patients have persistent abnormalities at one year of follow-up.[129] In contrast, another study from China reports persistent abnormalities in transaminase levels in 13%, with the majority recovering uneventfully at 12-month follow-up.[130]

After the end of the acute phase, there is still an underlying risk of an increased level of hepatic biomarkers that do not return to their pre-infection baseline.[131] In a study conducted on low-risk individuals with post-COVID-19 syndrome, it was found that 28% had mild injury and increased fat accumulation in the liver, which was associated with a need for hospitalization.[132] Another study looking at patients who had persisting symptoms found that there was increased liver stiffness and steatosis, suggesting that there is an increased buildup of fats and fibrotic/necrotic tissue within the liver.[133]

Furthermore, there is also evidence of damage to the bile ducts, leading to post-COVID cholangiopathy. This results from ischemic changes, microthrombosis, direct liver injury, drug-induced and autoimmune factors. Management with ursodeoxycholic acid and cholestyramine offered no significant clinical benefit.[134]

Moreover, a study exploring liver fibrosis after COVID-19 using a liver fibrosis index found a 5% incidence of liver fibrosis in the post-COVID-19 group when they followed the cohort for 3–6 months.[135] Post-acute COVID syndrome (PACS) is now a well-recognized clinical entity and is associated with several systemic manifestations including metabolic-associated fatty liver disease (MAFLD). A recent study has described an increased prevalence of this condition amongst post-COVID-19 patients. The long-term consequences of MAFLD as a post-COVID-19 condition remain to be ascertained and may potentially have an impact on cardiovascular health outcomes.[136]

Based on the understanding that long-term complications of COVID-19 on the liver are widely reported, the most potent method to ensure that further damage via fibrosis does not take place is to ensure that patients who have suffered liver injury in the acute setting, or are at risk of developing long-COVID related liver injury, be screened to ensure that there is a decrease in hepatic biomarkers.

Conclusion

In conclusion, COVID-19-associated liver injury can occur through multiple mechanisms, and recognition and prompt management are crucial due to its significant impact on mortality and long-term morbidity. Further research and understanding of COVID-19-associated liver injury are needed to improve patient outcomes and develop effective management strategies.

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