

Review Article

Prospective Coronavirus Liver Effects: Available Knowledge

Avishek Mandal*

Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700032, West Bengal, India

Abstract

The global pandemic COVID-19, caused by SARS-CoV-2, affected millions of people. COVID-19 is known for its respiratory symptoms, but new research reveals it may also affect other organ systems, including the liver. This abstract reviews COVID-19 and liver function. The virus enters host cells through liver-expressed angiotensin-converting enzyme 2 (ACE2) receptors. Thus, viral infection and replication may target the liver. Virus-induced inflammation and cytokine production may also harm the liver. ALT and AST elevations are the most prevalent liver abnormalities in COVID-19 patients. Liver function test abnormalities frequently indicate serious illness and poor clinical outcomes. COVID-19 may worsen pre-existing liver diseases such as NAFLD and chronic viral hepatitis. Drug-induced liver damage (DILI) from COVID-19 therapies including antivirals and corticosteroids complicates liver complications care. Recent investigations have also shown that COVID-19 may cause long-term liver damage. In conclusion, COVID-19 infection, immune-mediated damage, and treatment problems may severely compromise liver function. Optimizing patient treatment and discovering targeted medicines requires understanding COVID-19's liver role. To reduce the effects of COVID-19 on liver function, further study is required to understand the mechanisms and long-term effects.

More Information

*Address for correspondence:

Avishek Mandal, Ph.D. Research Scholar,
Department of Pharmaceutical Technology,
Jadavpur University, Kolkata-700032, India,
Email: avishek7477@gmail.com

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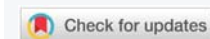
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Keywords: COVID-19; Immunity; Hepatitis; Liver damage



Abbreviations

NAFLD: Non-Alcoholic Fatty Liver Disease; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ICU: Intensive Care Unit; CCU: Coronary Care Unit; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; SIRS: Systemic Inflammatory Response Syndrome; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; EASL: European Association for the Study of the Liver; ESMO: European Society for Medical Oncology; ILCA: International Liver Cancer Association; AASLD: American Association for the Study of Liver Diseases; EASL-ESCMID: European Association for the Study of the Liver-European Society of Clinical Microbiology and Infectious Diseases; NASH: Non-Alcoholic Steatohepatitis; FIB: Fibrosis; ARDS: Acute Respiratory Distress Syndrome; MOF: Multi-Organ Failure; ASCO: American Society of Clinical Oncology; Coronavirus Liver Injury: Coronavirus-Induced Liver Damage

Introduction

The emergence of the coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented an unparalleled global health crisis, impacting a significant number of

individuals across the world [1,2]. COVID-19 was initially acknowledged for its primarily respiratory manifestations, but subsequent observations have demonstrated its capacity to affect various organ systems, including the liver. As the progression of the pandemic continues, there is a growing significance placed on comprehending the impact of COVID-19 on hepatic function in relation to patient management and clinical care [3].

The liver assumes a pivotal role within the human body, participating in a multitude of indispensable functions such as metabolism, detoxification, and regulation of the immune response. It is widely recognized that viral infections can lead to hepatic injury, and SARS-CoV-2 has demonstrated a predilection for targeting cells that express angiotensin-converting enzyme 2 (ACE2) receptors, which are abundantly present in hepatocytes. As a result, the liver may exhibit vulnerability to direct viral invasion, resulting in impaired liver function [4]. The purpose of this introduction is to present a comprehensive summary of the existing knowledge regarding the effects of COVID-19 on liver functionality. In this discourse, we shall examine the prospective mechanisms underlying liver involvement, the documented liver abnormalities observed in individuals afflicted with COVID-19, and the correlation between liver dysfunction and

the severity of the disease. Furthermore, this study aims to investigate the impact of pre-existing liver conditions and the effects of COVID-19 treatments on hepatic well-being. As the epidemic has progressed, most policymakers have attempted to safeguard their people. The highest-risk COVID-19 patients are recommended to "shield," avoiding all social interaction. Understanding how distinct illness characteristics affect COVID-19 susceptibility and clinical outcomes is essential for customizing public health guidance to patient subgroups [5]. Direct antiviral and immune-modifying drugs are being tested in SARS-CoV-2 randomized clinical studies. Clinical priority is identifying patient populations that need early or unique therapy interventions. SARS-CoV-2 vaccine research has also advanced rapidly, with the main contenders reporting encouraging phase III safety and effectiveness results. There will be an unprecedented worldwide demand for vaccine deployment, therefore identifying patients most at risk of COVID-19 outcomes is crucial to prioritizing vaccination programs [6,7]. There has been apprehension regarding the potential association between pre-existing Chronic Liver Disease (CLD) and unfavorable outcomes subsequent to SARS-CoV-2 infection since the commencement of the pandemic. This concern arises from the shared risk factors for severe COVID-19 and CLD, such as advancing age, obesity, and diabetes. Furthermore, it should be noted that advanced liver disease is characterized by immune dysregulation and coagulopathy, factors that may potentially exacerbate the severity of the COVID-19 infection. Chronic Liver Disease (CLD) poses a significant global burden, as evidenced by the substantial number of individuals affected by cirrhosis worldwide. Specifically, over 122 million people are impacted by cirrhosis, with approximately 10 million experiencing decompensated disease [8]. Therefore, it is of utmost importance to comprehend the natural progression of COVID-19 in individuals with Chronic Liver Disease (CLD), encompassing various causes and varying degrees of liver disease severity. This study seeks to educate healthcare professionals and academics on the need for thorough liver monitoring and treatment in COVID-19 patients. It also emphasizes the need for greater study to understand the mechanisms and long-term effects of COVID-19 on liver function to create tailored therapy options and improve patient outcomes.

ALT, AST, and bilirubin levels in COVID-19 patients vary from 14.8 to 53%, according to the newest SARS-CoV-2 investigations. Severe COVID-19 patients also had increased plasma ALT and AST values [9]. Elevated AST and bilirubin levels increase the risk of ICU and CCU admission and death. COVID-19 individuals also show bile duct cell damage and abnormal GGT and ALP values. Most patients' ALT levels normalize following this transitory response. High-ALT patients had increased 30-day mortality and longer hospital stays. In severe instances, albumin decreases with illness severity and death. In severe SARS-CoV-2 patients, low

albumin levels imply inhibited hepatic production. In early SARS and MERS, ALT, AST, and bilirubin rise mildly. In addition, high liver enzymes independently predict a poor SARS prognosis. SARS patients' prognoses are negatively affected by age and pre-existing conditions, however, peak ALT levels did not vary between high and low patients [10,11]. 50% of severe MERS ICU patients had increased aminotransferases. A few research found low albumin predicts MERS severity [12]. SARS liver biopsies showed substantial increases in eosinophilic bodies and balloon-like hepatocytes, suggesting coronavirus may induce hepatocyte necrosis. Protein 7a, a SARS-CoV unique protein, may also necrotic cell lines from numerous organs. SARS-CoV-2-infected livers show mild microvascular steatosis and significant lobular and portal inflammation. MERS patients had significant portal tract infection, lobular lymphocytic inflammation, and hydropic hepatic parenchymal cell degeneration, like SARS and COVID-19 patients [13]. Several pathophysiological explanations may explain coronavirus-induced liver damage.

COVID-19 liver biochemistry

The present study examines the patterns and frequency of liver biochemistry abnormalities observed in individuals diagnosed with COVID-19. The specific impact of COVID-19 on the liver is not yet fully understood; however, it is observed that individuals infected with SARS-CoV-2 commonly experience irregularities in liver biochemistries. These abnormalities are reported in approximately 15% - 65% of COVID-19 patients [14]. The observed variations in these reported frequencies may be attributed to discrepancies in the definition of the upper limit of normal, differences in the laboratory values used to classify liver enzymes, and regional differences in the prevalence and nature of the underlying chronic liver disease. Liver biochemistry abnormalities observed in patients with COVID-19 are typically characterized by slight elevations (1-2 times the upper limit of normal) in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These elevations have been reported in approximately 29% - 39% and 38% - 63% of patients, respectively [15]. Hypoalbuminemia, a general indicator of the severity of illness, has been found to be linked to poorer outcomes in COVID-19 cases. However, severe liver damage, elevated levels of bilirubin in the blood, and impaired liver function are infrequently observed in individuals infected with SARS-CoV-2 [16]. Similar frequencies of abnormalities in liver biochemistries are reported, irrespective of the presence of pre-existing liver disease. COVID-19 may raise liver enzymes for many reasons. Steatosis, moderate lobular and/or portal inflammation, and vascular pathology are non-specific findings in SARS-CoV-2 liver biopsy results [17]. In most instances, aberrant biochemistries are complex, including immune-mediated inflammatory response, drug-induced liver damage, hepatic congestion, extrahepatic transaminase release, and hepatocyte infection. In hospitalized COVID-19



patients, serum AST levels positively correlate with ALT but not with indicators of muscle breakdown (creatinine kinase) or systemic inflammation (CRP, ferritin). Although COVID-19-associated rhabdomyolysis is uncommon, study data suggest direct hepatic damage causes increased liver enzymes [18]. Finally, AST often exceeds ALT during COVID-19, which is unusual for a classic hepatocellular pattern of liver injury outside of alcohol-related liver disease, certain drug-induced liver injuries (like lamotrigine), ischemic hepatitis, and cirrhosis. COVID-19-related mitochondrial dysfunction³³, SARS-CoV-2-induced hepatic steatosis, and micro thrombotic disease-induced hepatic perfusion³¹ may cause AST-predominant aminotransferase increase. Hepatic vascular thrombosis was 29% in a COVID-19 comprehensive review and meta-analysis of biopsy and autopsy data. Systemic hypoxia in COVID-19 may also contribute, and AST increases have been described with various viral pneumonias, including influenza A H1N1, where levels rose with decreasing peripheral oxygen saturations [19]. Ischemic hepatitis, cardiomyopathy-related hepatic congestion, and transaminase release from skeletal and cardiac muscle breakdown may also cause aberrant liver biochemistries in COVID-19. COVID-19 may cause liver biochemistries to rise due to arterial and venous thromboses [20]. Finally, drug-induced liver damage may increase liver enzymes and was more prevalent early in the pandemic owing to experimental therapies. No research has yet mapped the pattern of liver function tests in pandemic investigations. Lopinavir, ritonavir, tocilizumab, and remdesivir are COVID-19 drugs linked to liver damage. Remdesivir hepatotoxicity is debated. Although randomized COVID-19 studies show equal liver enzyme increases across treatment and control groups, WHO safety reports database screening shows a statistically significant odds ratio for liver damage with remdesivir [21,22]. Fortunately, the SOLIDARITY study showed no benefit of remdesivir in hospitalized COVID-19 patients, making these factors less practically important [23].

COVID-19 increased liver enzymes prognosis. Elevated liver enzymes in SARS-CoV-2 individuals may be prognostic. Serum liver enzyme increases have been linked to shock, ICU hospitalization, and mechanical ventilation. If severe illness patients underwent thorough laboratory testing to identify liver impairment, these studies might be biased. Elevated liver enzyme levels, especially AST and ALT levels greater than five times the upper limit of normal, are associated with an increased risk of death, according to some studies [24]. Elevated liver enzyme levels may be prognostic in severe disease owing to a stronger host response and intensive treatments [25].

Immune-mediated injury

Coronaviruses stimulate the immune system to fight the virus. The liver contains many immune cells and is vital to immunological function. Immune cell-released

cytokines attack pathogens and safeguard liver functioning in the hepatic acute-phase response. CD4+ and CD8+ T cell differentiation maintains the balance between anti-coronavirus immunological responses and immune tolerance. 80% of SARS-CoV-2-infected liver immune cells are CD8+ T cells, which may survive in inflamed tissue [26,27]. Decreased CD4+ T cell infiltration may lower B cell activation, SARS-CoV-2-specific neutralizing antibody, and proinflammatory cytokines such IL-1, IL-6, and TNF- α , affecting liver clearance. CD4+ T cells are more sensitive to MERS-CoV and SARS-CoV infections than CD8+ cells [28]. In severe coronavirus infection, hepatocytes enlarge and steatosis, hepatic sinus cells proliferate, Kupffer cells hyperplasia, and immune cells infiltrate [29]. Cytokines cause ischemia, hypoxia, hepatocyte damage, and necrosis. Early coronavirus infection has been linked to abnormal blood cytokines and chemokines such as TNF, IL-6, and IL-18 [30]. SARS patients with hepatic failure had greater blood levels of IL-1, IL-6, and IL-10 than those with normal hepatic function, linking hepatic damage to SARS cytokine storms [31]. The severity of SARS-CoV-2 infection was linked to higher blood IL-2-receptor and IL-6 levels. SARS-CoV-2 patients also have increased Th1 and Th2 cytokines, including TNF- α , IFN- γ , IL-6, IL-8, IL-4, and IL-10. In the acute phase of MERS-CoV infection, serum IFN- γ , TNF- α , IL-15, and IL-17 levels rose substantially [32-34]. These findings imply that coronavirus-induced SIRS and cytokine storms may cause liver damage. Pro-inflammatory cytokine activity and liver damage are little studied.

Coronaviruses and HBV/HCV hepatitis

2 billion individuals are afflicted with HBV and 350 million with HCV, a chronic illness that is widespread. In one research, 3.6 and 0.6% of COVID-19 patients had hepatitis B and C, respectively [34-37]. HBsAg positive was 6.5% in 324 Shanghai COVID-19 patients in a liver biochemical parameters investigation [38]. Thus, coronavirus infection affects HBV and HCV. SARS-CoV coinfection enhanced hepatitis virus proliferation, increasing the risk of liver damage and severe hepatitis in HBV/HCV-infected SARS patients. Despite SARS-CoV coinfection, chronic hepatitis B and HBsAg-negative individuals had similar unfavorable clinical outcomes [37-40]. Acute hepatitis and decompensated liver cirrhosis increase SARS mortality. 23/1099 Wuhan SARS-CoV-2 patients were HBV-positive, 2.4% of mild cases and 0.6% of severe cases [41,42]. COVID-19 patients exhibited a higher death rate (32.9%) than HBV-negative patients (15.3%). Some studies reported COVID-19 patients with HBV infection took longer to eliminate the virus (21 days, 95%) than those without HBV (14 days, 95%) [42-44]. These findings suggest that coronavirus infection and viral hepatitis interact, therefore understanding the mechanism would help optimize COVID-19 therapy.

Effect of coronaviruses on liver cancers

Coronaviruses, like other viruses, burden the immune

system and liver. In people with pre-existing liver problems, severe COVID-19 (produced by the SARS-CoV-2 virus) may induce liver harm. The liver filters pollutants and metabolizes drugs, thus viral infection or other conditions might impair its function. Any viral infection might worsen liver cancer. COVID-19 may worsen liver damage in liver cancer patients, which might affect treatment results. Due to immunological suppression, liver cancer patients may be more prone to severe COVID-19. Liver cancer patients must take steps to avoid COVID-19. Liver cancer patients should have particular COVID-19 therapies to avoid serious consequences [45-48]. In patient-saturated hospitals, a lack of clinical and medical resources has hindered proper radiological assessment, pathological diagnosis, and liver cancer therapy. SARS-CoV-2-infected liver cancer patients are monitored, examined, and treated according to EASL, ESMO, and ILCA guidelines. The Society of Surgical Oncology recommends surgery for all aggressive liver, pancreatic, and gall bladder malignancies [49]. Neoadjuvant chemotherapy may postpone surgery for people who require systemic chemotherapy. All but high-risk individuals now postpone esophageal varices and liver cancer screening. After weighing the pros and cons, AASLD advises delaying liver cancer monitoring for two months in COVID-19 patients. Semiannual monitoring may enhance early detection and patient survival compared to annual surveillance, according to retrospective investigations. Thus, postponing screening for over a year may cause liver cancer to grow, missing the ideal opportunity for surgery and perhaps liver failure or death.

Effect of coronaviruses on liver transplantation

Immunosuppressive drugs prevent organ rejection in liver transplant patients. They may be more susceptible to severe consequences from viral infections, notably COVID-19-causing coronaviruses like SARS-CoV-2. COVID-19's effects on liver transplant patients depend on infection severity and health. The chance of serious illness may rise. Due to their compromised immune systems, transplant recipients, notably liver transplant recipients, may have worse COVID-19 symptoms and consequences. Liver function concerns: COVID-19 may induce liver harm in certain individuals, which is especially problematic for liver transplant recipients with reduced liver function. Interaction with immunosuppressive medications: COVID-19 and other viral infections may interact with immunosuppressive treatments used after transplantation, reducing their effectiveness or requiring dose or prescription changes. After-transplant care: The pandemic may have hampered healthcare services and transplant follow-up treatment, which transplant patients need to monitor organ function and drug administration. Liver transplant patients should wash their hands, wear masks in crowds, and keep their distance to avoid infection. Transplant patients should also acquire COVID-19 vaccinations to lower the risk of severe sickness and hospitalization. For COVID-19 symptoms or other health

concerns, contact the transplant care team immediately. Based on your health and circumstances, they may provide advice. Immunosuppressive drugs may control inflammatory activity against SARS-CoV-2 infection, but liver transplant patients should evaluate the risks. Early therapy may help avoid serious pneumonia in liver transplant patients [50,51]. Liver disease patients should undergo antiviral medication immediately. Remdesivir, chloroquine/hydroxychloroquine with or without azithromycin, lopinavir/ritonavir, and tocilizumab are EASL-ESCMID-recommended COVID-19 treatments following liver transplantation. To prevent transmission, coronavirus-infected organ donors and recipients must be screened [52].

Coronaviruses and the risk of alcoholic and non-alcoholic liver disease

SARS-CoV-2, which induces COVID-19, may affect alcoholic and non-alcoholic liver disease. Chronic alcohol abuse causes alcoholic liver disease (ALD). Coronaviruses and ALD Increased risk: Due to their reduced liver function and weaker immune systems, people with ALD, particularly extensive liver impairment, are at increased risk of catastrophic COVID-19 outcomes. Alcohol and COVID-19 severity: Heavy alcohol intake may weaken the immunological system, making COVID-19 more likely. Alcohol also worsens COVID-19 respiratory symptoms. Treatment issues alcohol may affect medicine metabolism and effectiveness, affecting COVID-19 therapy in ALD patients. NAFLD and NASH NAFLD causes liver fat storage [53,54], whereas NASH causes inflammation and liver cell destruction. COVID-19 and NAFLD/NASH interact as follows. COVID-19 may worsen liver disease in those with pre-existing NAFLD/NASH. Metabolic comorbidities: Obesity, diabetes, and metabolic syndrome risk NAFLD/NASH and COVID-19. When these comorbidities overlap, severe consequences may rise. NAFLD, a chronic dysmetabolic illness, is the most prevalent liver disease in the world, affecting 30% of Westerners. NAFLD is linked to risk factors, metabolic syndromes, and other disorders [55]. NAFLD comorbidity enhances SARS-CoV-2 infection severity. Male sex, age >60, higher BMI, and NAFLD were linked with COVID-19 advancement in 202 individuals. This research found that NAFLD independently increases COVID-19 development (OR 6.4; 95% CI 1.5 – 31.2). NAFLD increases the likelihood of impaired liver function and viral clearance. In another study, moderate or high Fibrosis 4 (FIB-4) scores substantially and independently enhance the likelihood of severe COVID-19 development. NAFLD patients are at risk due to metabolic dysfunction and hepatic disease [56-58].

A brief overview of how a virus can affect various organ systems in the body

The effects of viruses on various organ systems vary depending on the virus, the person's health, and other circumstances. Some viruses target specific organs, while others are more widespread. Medical studies and therapies

also improve our knowledge of how viruses influence organ systems. System of the Respiratory System Many viruses, including influenza and the SARS-CoV-2 virus that causes COVID-19, attack the respiratory system first. They infect cells in the airways and lungs, causing coughing, shortness of breath, pneumonia, and acute respiratory distress syndrome (ARDS) in severe instances [59]. In the cardiovascular system, myocarditis (inflammation of the heart muscle) and heart failure are both possible outcomes of viral infections. This may cause discomfort in the chest, heart palpitations, and even heart failure. Nausea, vomiting, diarrhea, and stomach discomfort are all indications of a viral infection of the digestive system. Inflammation and damage to the liver are two possible outcomes of infection with the hepatitis virus. A variety of neurological symptoms may be brought on by a viral infection of the nervous system. In the case of herpes simplex virus, encephalitis may result in high body temperature, haziness, convulsions, and even coma. Viruses that infect the immune system cause a response from the body, which may sometimes be too strong. Symptoms including fever, tiredness, and muscular pains might result from systemic inflammation brought on by this.

Certain viruses have the ability to induce skin rashes, exemplified by the chickenpox virus which manifests as pruritic blisters. The Human Papillomavirus (HPV), among other viruses, has the potential to induce the formation of warts. The reproductive system may be affected by some viruses, such as the Human Immunodeficiency Virus (HIV), which has the potential to compromise the immune system and have negative effects on reproductive health. In the context of persons who are pregnant, it is possible for viruses to provide a potential risk to the growing baby [60]. The musculoskeletal system may be affected by viral infections, leading to symptoms such as muscle pains, joint pain, and inflammation, which bear a resemblance to those seen in cases of influenza [25].

Management and treatment of COVID-19 patients with liver involvement

This could include things to think about for doctors, follow-up plans, and treatment plans. COVID-19 people with liver involvement need to be treated and managed in a way that takes into account both the virus and how it might affect liver function.

Patient assessment and monitoring

- A comprehensive evaluation of liver function may be conducted by analyzing many indicators, including liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin levels. Additionally, coagulation measures including international normalized ratio (INR) and prothrombin time (PT) can be examined, along with markers of liver synthetic

function such as albumin. Monitor liver function regularly, especially in patients with pre-existing liver conditions or those receiving medications that could impact liver function.

- It is advisable to closely monitor clinical manifestations indicative of liver damage, including jaundice, right upper quadrant discomfort, or alterations in mental state. Drug Selection and Monitoring:
- Drugs that have the potential to damage liver function should be used with caution, particularly in individuals who already have liver disease. For instance, several antiviral drugs used to treat COVID-19 may have an impact on liver enzymes. Regularly monitor liver function in patients receiving medications known to impact the liver.
- Adjust drug dosages based on liver function if necessary.

Treatment strategies

- Consider the possible effects on liver function while concentrating on treating the underlying COVID-19 infection.
- Apply supportive treatment, such as preserving fluid and electrolyte balance, treating fever, and making sure the patient is getting enough oxygen.
- Think about antiviral medications new coming, but keep a careful eye on your liver enzymes while using them.
- Use corticosteroids sparingly since they may affect liver function, particularly in individuals with pre-existing liver problems.

Follow-up protocols

- Plan for post-discharge monitoring of all patients, but notably those whose livers were severely compromised by their illness.
- Schedule regular check-ups to assess liver function and overall health.
- Address chronic liver damage symptoms immediately.

Nutritional support

- Patients diagnosed with COVID-19 should be given proper nutritional assistance, particularly those whose livers have been affected, since starvation may make liver function worse.
- It may be helpful to consult with a qualified dietitian when developing specific dietary goals.



Collaboration with specialists

- In cases of severe liver involvement or decompensated liver disease, collaborate with hepatologists and other specialists.
- Consult an expert when managing complex cases or patients with preexisting liver diseases.

Patient education

- Inform patients of the potential effects of COVID-19 on liver function and the significance of adhering to treatment plans.
- Encourage patients to report any new symptoms or symptoms that are becoming worse as soon as possible.

Preventive measures

- Encourage eligible individuals to get COVID-19 vaccinations to avoid serious diseases, especially liver involvement.
- Encourage basic precautions like washing one's hands, wearing a mask, and staying isolated from others.

Managing COVID-19 patients with liver involvement is a dynamic process requiring individualized care. Medical recommendations and guidelines may evolve as new research emerges. Therefore, healthcare professionals should remain abreast of the most recent scientific evidence and adjust their strategies accordingly. Consultation with medical specialists and hepatologists can provide useful insights for managing complex cases.

Discussion

The developing COVID-19 epidemic threatens global health. Previous coronavirus and influenza pandemics have shown that systemic and partial inflammatory responses can cause severe respiratory syndromes and complications like abnormal liver function, cardiac insufficiency, and renal failure. Coronavirus infection severely affects the liver, the body's main metabolic organ. However, pre-existing liver disorders affect coronavirus infection severity and motility. SARS-CoV, MERS-CoV, and SARS-CoV-2 may induce acute respiratory inflammation in humans due to their genetic similarities. SARS-CoV and SARS-CoV-2 connect to host cells through the ACE2 receptor, whereas MERS-CoV attaches to DPP4 [61,62]. However, they all had reduced albumin and elevated ALT, AST, liver enzymes, and bilirubin. COVID-19 individuals had elevated GGT and ALP, indicating liver bile duct cell damage [63,64]. As liver biopsies from certain COVID-19 patients showed microvesicular steatosis rather than viral inclusions, bile duct cell damage may also cause liver harm. The three coronaviruses cause microvascular steatosis and mild lobular and portal inflammation. According

to prior investigations, severe coronavirus infections had much greater liver damage rates than moderate ones [65,66]. Thus, these three coronaviruses may induce liver damage with comparable symptoms, and liver injury increases infection severity. Coronaviruses damage hepatocytes and alter hepatic function, although the mechanism is unknown. Pathophysiological hypotheses abound. SARS-CoV-2's main direct liver consequence is ACE2-mediated hepatocyte destruction. Hepatocyte ACE2 upregulation aids SARS-CoV-2 invasion and liver pathogenicity. SARS-CoV and SARS-CoV-2 patients may benefit from hrsACE2, given ACE2's function in coronavirus infection. Coronavirus infection boosts immunity [67]. Immune cells produce many cytokines (IL-6, IL8, IFN-g, and TNF-a) into the blood during coronavirus infection, causing tissue inflammation and potentially ARDS, SIRS, and MOF. Due to their anti-inflammatory properties, interferon-a and corticosteroids are often utilized for coronavirus immunotherapy. Immunotherapy requires continuous cytokine monitoring since immunological malfunction has devastating effects [68,69]. Hypoxia may increase reactive oxygen species, which can cause liver damage by releasing pro-inflammatory chemicals. Thus, monitoring hypercoagulable conditions such as thrombocytopenia and elevated D-dimer and ALP levels can help avoid thrombosis, ischemia, and hypoxia [70-75]. All of these variables may harm the liver during coronavirus infection. Since liver damage is caused by various variables, laboratory investigations, clinical monitoring, and follow-up visits should focus on pathogenic pathways. Coronavirus infection depends on the patient's health and pre-existing conditions. Hepatitis B, C, liver cirrhosis, liver cancer, and immunosuppressive medicines following liver transplantation usually cause immunocompromised states. SARS-CoV-2 has more infected people and clinical trials than SARS-CoV or MERS-CoV, hence the association between pre-existing liver illness and COVID-19 is stronger [75-78]. HBV infection delays SARS-CoV-2 clearance, increasing severity and death. COVID-19-induced liver damage may raise Child-Pugh scores in cirrhotics. Systemic immunocompromised persons develop COVID-19 problems early and more severely. COVID-19 strongly impacts liver disease therapy [79]. Discontinuing high-dose corticosteroids during SARS-CoV-2 infection may reactivate HBV in hepatitis B/C patients. In HBV and HCV patients, lopinavir and ritonavir enhance liver damage risk. Endoscopy and vascular radiography are limited to situations like internal bleeding to reduce viral spread. ASCO, ESMO, ILCA, EASL, and AASLD have provided liver disease treatment guidelines for SARS-CoV-2 infection, but more optimized treatments are needed to reduce disease deterioration and complications [80-82]. Remdesivir, lopinavir, and ritonavir raise the risk of liver damage, which is dose-dependent. IFNs may cause hepatocyte destruction, autoimmune hepatitis, and serious consequences such as ARDS and SIRS. Baricitinib, a JAK inhibitor, increases thrombosis and liver damage. Tocilizumab may reactivate



HBV in SARS-CoV-2 coinfection, delaying viral hepatitis and COVID-19 recovery. ACE inhibitors and particularly ACE2 may reduce coronavirus invasion and adhesion to host cells in the lung, liver, gastrointestinal system, and kidney, preventing organ damage [83-85]. Coronavirus vaccinations will help reduce outbreaks, but various aspects must be examined to avoid an activated innate inflammatory response, autoimmune illness, and vaccine-induced liver harm. RNA or DNA-based vaccinations have the most promise, however owing to species differences between humans and lab animals, their positive and negative effects are seldom discovered [86-88]. Thus, vaccine production requires extensive animal and clinical testing before being licensed for public use, which is difficult for society and scientists. But it is crucial to ensure that individuals with autoimmunity are consistently provided with the advantage that high-efficacy immunotherapy may bring. Over time, further information is expected to surface, which may contribute to the development of guidelines for selecting appropriate treatments during the post-COVID periods.

Conclusion

The hepatic implications of SARS-CoV-2 infection are now acknowledged as a significant element of the COVID-19 disease. This particular aspect holds significant clinical relevance in individuals with pre-existing cirrhosis, as they face a notably elevated risk of experiencing severe cases of COVID-19 and subsequent mortality. Additional research is necessary to gain a comprehensive understanding of the pathogenic mechanisms responsible for this clinical deterioration. It is probable that systemic inflammation, disordered coagulation, and immune dysfunction all play a role in contributing to this phenomenon. Various *in vitro* and *in vivo* models have been employed to elucidate the specific hepatotropic properties of SARS-CoV-2. However, the clinical implications of direct viral infection on different liver cell types have yet to be ascertained. The prognosis for individuals with cirrhosis who contract COVID-19 is notably more severe when compared to the population of individuals who have undergone liver transplantation, as the latter group tends to experience comparatively more favorable outcomes. Hence, it appears that the impact of cirrhosis-related immune dysfunction on the progression of COVID-19 is more deleterious compared to pharmacological immunosuppression. Given the availability of effective SARS-CoV-2 vaccines, it is imperative to prioritize immunization for patients with cirrhosis. Additionally, the hepatology community should be prepared to closely monitor the immune response in this specific subpopulation. Finally, it is imperative that we acknowledge the significant adverse impact of the pandemic on liver services and unhealthy patient behaviors, potentially leading to a rise in the worldwide prevalence of liver disease in the foreseeable future.

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