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Liver dysfunction during COVID-19 pandemic: Contributing role of associated factors in disease progression and severity

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Abstract

In December 2019, a new strain of coronavirus was discovered in China, and the World Health Organization declared it a pandemic in March 2020. The majority of people with coronavirus disease 19 (COVID-19) exhibit no or only mild symptoms such as fever, cough, anosmia, and headache. Meanwhile, approximately 15% develop a severe lung infection over the course of 10 d, resulting in respiratory failure, which can lead to multi-organ failure, coagulopathy, and death. Since the beginning of the pandemic, it appears that there has been consideration that pre-existing chronic liver disease may predispose to deprived consequences in conjunction with COVID-19. Furthermore, extensive liver damage has been linked to immune dysfunction and coagulopathy, which leads to a more severe COVID-19 outcome. Besides that, people with COVID-19 frequently have abnormal liver function, with more significant elevations in alanine aminotransferase and aspartate aminotransferase in patients with severe COVID-19 compared to those with mild/moderate disease. This review focuses on the pathogenesis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in the liver, as well as the use of liver chemistry as a prognostic tool during COVID-19. We also evaluate the findings for viral infection of hepatocytes, and look into the potential mechanisms behind SARS-CoV-2-related liver damage.

Key Words: SARS-CoV-2; COVID-19; Liver function; Hepatic injury; Viral infection

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Core Tip: Understanding the hepatic consequences of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, as well as its molecular mechanism, has advanced significantly. Since the start of the pandemic, it appears that there has been thought that pre-existing chronic liver disease may predispose to deprived outcomes when combined with coronavirus disease 19 (COVID-19). Evidence suggests that COVID-19 patients have abnormal liver function more frequently, with more significant elevations in alanine aminotransferase and aspartate aminotransferase in severe COVID-19 patients than those with mild/moderate disease. In this review, we focus on the pathogenesis of SARS-CoV-2 infection in the liver, as well as the use of liver chemistry as a prognostic tool during COVID-19.

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INTRODUCTION

A new strain of coronavirus was discovered in China in December 2019 which was declared as a pandemic in March 2020 by the World Health Organization[1,2]. It was initially noted by the large number of pneumonia cases that suddenly appeared amongst local citizens of Wuhan region. The majority of those with coronavirus disease 19 (COVID-19) show no indications or just moderate manifestations which include fever, cough, anosmia, and headache. Meanwhile, about 15% develop severe lung infection over the course of 10 d, resulting in respiratory failure, that can result in multi-organ failure, coagulopathy, and ultimately death[3,4].

A systematic review and meta-analysis by Li *et al*[5] involving 281461 individuals with COVID-19 revealed that 23% of them developed severe lung infection, out of which 5.6% died. A similar study by Tan *et al*[6] with 16561 patients from 17 countries also reported that 15% developed severe lung infection and the mortality rate was between 23.4% and 33.0%. A recent population-based cohort study from England revealed that individuals with pre-existing respiratory diseases are more vulnerable to COVID-19 related admissions to intensive care unit (ICU) and death. A total of 8256161 individuals were screened for pre-existing lung disease like asthma, chronic obstructive pulmonary disease, and bronchiectasis, out of which 14479 (0.2%) were admitted in hospital with COVID-19 and among which 1542 were upgraded to ICU, while 5956 died from COVID-19[7]. Similar reports are also published from South Korea that 7669 individuals with pre-existing lung disease were admitted due to COVID-19 and 251 (3.2%) died[8].

Since the beginning of the pandemic, there seems to be consideration that pre-existing chronic liver disease (CLD) may dispose to deprived consequences along with COVID-19, especially because interconnecting possible causes for COVID-19 and CLD, such as old age, overweight, and diabetes. Furthermore, extensive liver damage is linked to immune dysfunction and coagulopathy, which leads to a more severe outcome of COVID-19[9,10]. In addition, individuals with COVID-19 often have abnormal liver function, with more substantial elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in severe COVID-19 than in mild/moderate COVID-19[11]. However, there are many unanswered questions that need to answer. In this context, this review deeply emphasizes on the pathogenesis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in the liver, as well as the application of liver chemistry as a prognostic tool during COVID-19. We also evaluate the findings for viral infection of hepatocytes and look into the potential mechanisms behind SARS-CoV-2-related liver damage. Lastly, we discuss the management of this disease and therapeutic strategies for liver damage due to COVID-19.

MECHANISM OF LIVER INJURY DURING COVID-19

Mechanism of infection

Fan and colleagues[12] found that patients without a history of liver disease also had abnormal liver test parameters, indicating direct entry of the SARS-CoV-2 virus into the liver *via* interaction with angiotensin converting enzyme (ACE) 2 receptors. These receptors are also expressed in liver cells, lungs, intestines, and many other different tissues of the human body[13,14]. Evidence also demonstrates that SARS-CoV-2 spike proteins bind to ACE2 receptors in cholangiocytes rather than hepatocytes, which may cause liver damage[15]. However, Chai and colleagues found significantly low (0.31%) ACE2 expression in hepatocytes compared to 20 times higher expression in bile duct cells as per single-cell sequencing. Further, for transmission to the liver, the SARS-CoV-2 virus could use the gut-

liver route through the hepatic reticular system[16].

Systemic inflammatory response syndrome and cytokine storms

The inflammatory cytokine storms have been considered responsible for liver injury of COVID patients. There is increased levels of interleukins (ILs) like IL-2 and IL-6 in the serum of COVID-19 patients that have been linked with poor clinical outcomes (Figure 1). In addition to the secretion of tumor necrosis factor- α , IL-2, IL7, IL-18, IL-4, and IL-10 increased pro-inflammatory cells (CCR4+CCR6+ Th17), which was more prominent in ICU admitted patients compared to non-ICU admitted ones[17-19]. These inflammatory cytokine storms cause systemic inflammatory response syndrome, acute respiratory distress syndrome, ischemia, and ultimately cell destruction and necrosis of the liver and multiple organ damage[18].

Ischemia and hypoxia reperfusion injury

It is well known that most patients with severe symptoms of COVID-19 have hypoxia and severe cases require oxygen. The inefficient lung function and other multi-organ damage can cause hypoxia and ischemia along with shock. Ischemia and hypoxia promote lipid accumulation, glycogen consumption, and adenosine triphosphate depletion in hepatocytes, suppressing cell survival signal transduction, which leads to liver cell death. Also, respiratory distress syndrome accelerated reactive oxygen species (ROS) generation and oxidative stress. ROS and lipid peroxidation products can activate redox-sensitive transcription factors, causing the release of a variety of pro-inflammatory factors that harm the liver. These alterations can aggravate the ischemia of hepatocytes and affect the excretion of toxic metabolites that eventually induce liver injury[18,19].

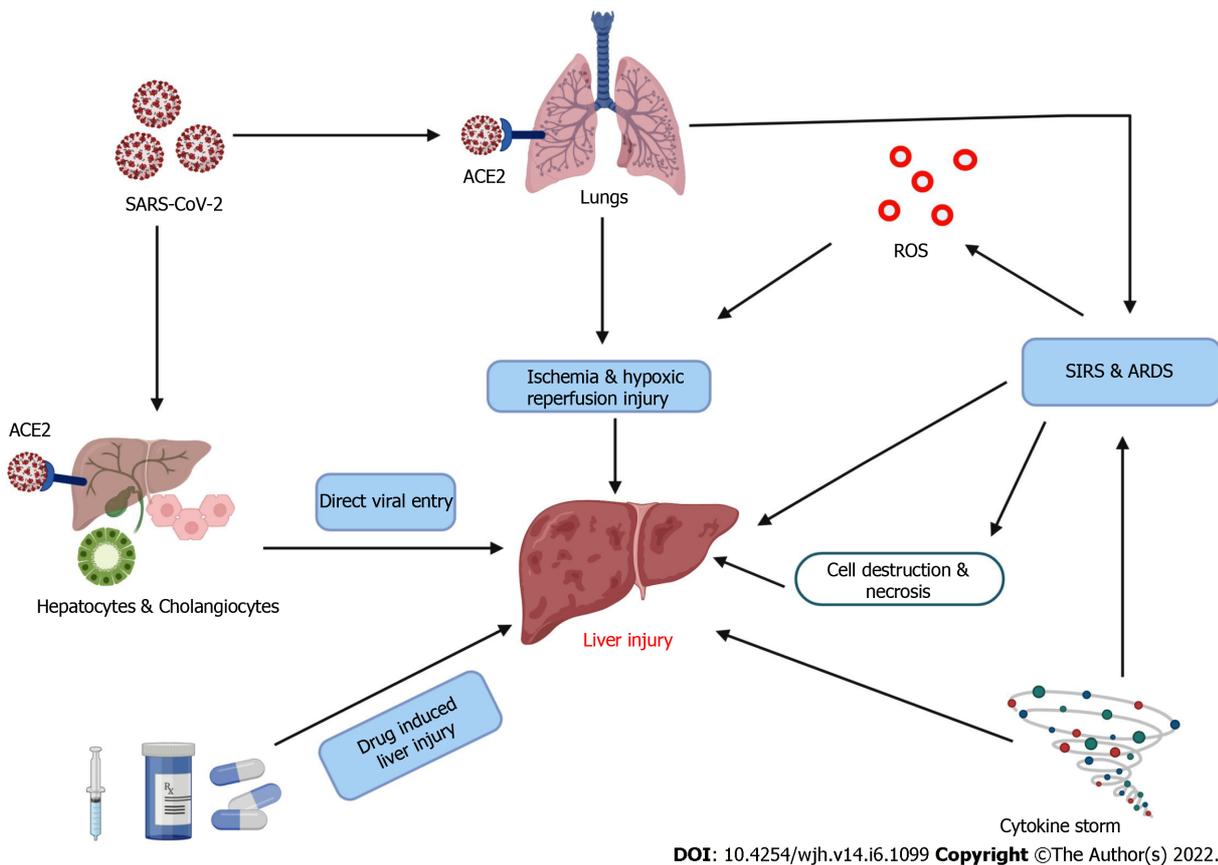
Antibody-dependent enhancement

To inhibit the viral infection, antibodies are used that specifically block the binding of viral protein and cell surface receptors. However, during certain viral infections, specifically viruses with many antigenic epitopes, there is enhanced affinity of binding of virus proteins to host cell receptors. This mechanism is known as antibody-dependent enhancement (ADE). Certain viruses like corona virus (SARS-CoV) through this pathway use the antiviral antibodies to enter into host cells like macrophages, granulocytes, and monocytes, and also for replication inside these cells through interaction with Fc and/or complement receptors[20,21]. This causes an increase in infection and disease progression with worsening outcomes. It has been suspected that SARS-CoV-2 may use ADE property to infect immune cells through a non-ACE2-dependent pathway, leading to liver injury[18]. However, further research is warranted to confirm the ADE mediated replication of the SARS-CoV-2 and the underlying mechanism. Further, ADE is considered an important aspect for the development and application of vaccines against SARS-CoV-2 since the virus may use ADE mechanism to amplify the infection and increase the severity of disease[22,23].

Hepatotropism of SARS-COV-2

Due to the challenges in obtaining tissue samples from COVID-19 persons and the need for research laboratory confinement facilities, the tissue repositories for SARS-CoV-2 replication have yet to be thoroughly understood. To obtain cell entrance, the viral protein binds ACE2, and TMPRSS2 and FURIN are also necessary for infection; hence, the activation of these receptors revealed initial signs for probable hepatic susceptible cells. According to RNA sequencing in healthy hepatocytes, cholangiocytes (alveolar type 2 cells) had the most significant gene expression levels for ACE2, followed by sinusoidal endothelial cells and liver cells[24,25]. TMPRSS2 and FURIN also have diverse gene expression patterns across various hepatic cells. Cell lines generated from hepatocellular carcinoma can sustain the whole viral life cycle[26], although replication in hepatic cells is still to be revealed. Zhao and colleagues created human liver ductal organoids that express ACE2 and TMPRSS2, which could mimic SARS-CoV-2 infection, indicating that the bile duct epithelium might facilitate pseudo-particle entrance[27].

The impact of liver damage and underlying liver disease on SARS-CoV-2 hepatotropism is unknown, and no research has mainly looked at the histological abnormalities seen in COVID-19 patients with pre-existing CLD. However, before COVID-19, studies indicated that in individuals with hepatitis C virus-related cirrhosis, ACE2 expression is 30 times higher than that in healthy people's livers[28]. Furthermore, hepatic mRNA expression of ACE2 and TMPRSS2 was elevated in non-infected individuals with obesity and non-alcoholic hepatic steatosis, but not with only steatosis[29]. SARS-CoV-2 hepatotropism might be exacerbated by liver damage and inflammation by altering viral receptor expression, with ACE2 being recognized as an interferon-inducible gene in human respiratory epithelial tissue[30]. Nevertheless, this discovery should be considered carefully since the upregulation might be due to the shortened isoform of ACE2, known as deltaACE2, instead of the viral receptor protein itself [31]. An *in vitro* study revealed that high-density lipoprotein scavenger receptor B type 1 (SR-B1) facilitates ACE2-dependent coronavirus adhesion[32], which is quite similar to hepatitis C virus infection[33].



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Figure 1 Schematic representation of possible causes of liver injury. ACE2: Angiotensin converting enzyme 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; ROS: Reactive oxygen species.

Clinical manifestations and pathological alterations in hepatic dysfunction and abnormality in COVID-19 patients

COVID patients suffer from respiratory problems as a primary consequence of SARS-CoV-2 infection. The last two years of extensive research has revealed different respiratory problems, including multi-organ damage due to COVID. Initial studies in COVID patients from China showed the prevalence of functional abnormality of the liver and liver damage in many hospitalized patients[34-37]. The liver dysfunction and damage have been observed at the biochemical and histological levels.

The abnormal liver test results are essential biomarkers for evaluating liver abnormalities as a function of COVID severity[38]. The liver function abnormalities are confirmed through the increased concentrations of certain liver enzymes in serum such as ALT > 40 U/L, AST > 40 U/L, gamma-glutamyl transferase (GGT) > 49 U/L, alkaline phosphatase (ALP) > 135 U/L, and total bilirubin > 17.1 μmol/L[39,40]. Most of the studies showed increased concentrations of enzymes ALT and AST in SARS-CoV-2 infected patients[12,17,35]. Fan *et al*[12] in their retrospective, single-center study observed abnormal liver functions in one third which are characterized by abnormal liver tests like increased levels of enzymes, *i.e.*, the "cholangiocyte-related enzymes" such as gamma-glutamyl transferase & alkaline phosphatase, and total bilirubin in addition to alanine and aspartate aminotransferases (Table 1). In their multicentric study, Ding and colleagues found that the concentrations of AST and direct bilirubin both at the time of initial observation and peak were independently associated with COVID-19 patients' mortality[37]. Besides, LDH, prealbumin, albumin, ALP, GGT, and total and direct bilirubin in COVID patients have been suggested for diagnosis and progression of disease severity[41]. Liver damage in patients with COVID-19 has also been attributed to hypoxemia and reperfusion or passive congestion[42].

Xu and colleagues[43] reported liver damage through liver biopsy of a dead COVID patient manifested as moderate micro-vesicular steatosis and mild lobular and portal activity. This damage could be due to direct infection of SARS-CoV-2 or hepatotoxicity caused by drugs used to treat the patients[43]. Ji and colleagues also examined the postmortem liver biopsy showing microvascular steatosis over T cell activation. They suggested that COVID-19 associated liver injury may be immune-mediated rather than direct cytopathic damage[16]. Philips and colleagues' evidence regarding COVID-19-associated liver damage obtained through liver biopsy, such as hepatocyte apoptosis, binuclear or occasionally multinuclear syncytial hepatocytes, mild focal lobular or portal inflammation, and altered hepatocyte mitochondrial features, substantiated that SARS-CoV-2 may not be involved in liver damage

Table 1 Studies of abnormal liver biochemistries in patients with coronavirus disease 19

Ref.	Patients (n)	Findings	Conclusion
Wang <i>et al</i> [11], 2020	105	56.2% of the patients had abnormal ALT, AST, and total bilirubin throughout the course of the disease	Patients with COVID-19 often have abnormal liver function indices
Fan <i>et al</i> [12], 2020	148	37.2% had abnormal liver function at hospital admission; 14.5% out of these patients had high fever; patients with abnormal liver function had longer mean hospital stays (15.09 ± 4.79 d) than patients with normal liver function (12.76 ± 4.14 d)	More than one third of SARS-CoV-2 infected patients admitted to hospitals had elevated liver function parameters, which are linked to a prolonged hospital stay
Ding <i>et al</i> [37], 2021	2,073	Out of 2073 patients, 61.8% showed abnormal liver chemistries during hospitalization, and 14.3% had liver injury	COVID-19-related mortality is predicted by abnormal levels of AST and D-Bil during admission. Infection with HBV does not raise the risk of poor COVID-19-related outcomes in patients
Cai <i>et al</i> [38], 2020	417	76.3% had abnormal liver test results and 21.5% had liver injury during hospitalization. ALT, AST, total bilirubin, and gamma-glutamyl transferase levels rose to more than 3 × the upper limit of normal, respectively	The negative effects on liver damage are mostly due to certain drugs taken during hospitalization
Fan <i>et al</i> [41], 2021	288	Except for AST, the levels of total bilirubin and ALP in normal and severe patients varied within the normal range, with an increasing trend in critical patients	In critical patients, COVID-19 can induce significant hepatic dysfunction, necessitating early monitoring and management. Because of their connection with disease severity in COVID-19, LDH, ALP, GGT, total bilirubin, prealbumin, and albumin may be useful for assessing and predicting disease prognosis

COVID-19: Coronavirus disease 19; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; D-Bil: Direct bilirubin.

or impaired liver function, which indicated liver involvement in severe systemic inflammatory diseases, fatty liver disease, sepsis, or multi-organ dysfunction[44].

The impact of COVID has been classified into mild or non-severe and severe according to the manifestation of symptoms. The mild symptoms are fever, cough, expectoration, shortness of breath, muscles ache, and other upper respiratory tract symptoms, and without abnormalities, or with mild changes on chest radiography, such as multiple small patchy shadows and interstitial changes, primarily in the outer zone of the lung and under the pleura. Severe COVID symptoms include significantly increased respiration rate (≥ 30 times/min) or hypoxia with oxygen saturation at resting state $\leq 93\%$; or partial pressure of oxygen/fraction of inspired oxygen (PaO_2 / FiO_2) ≤ 300 mmHg; or respiratory/another organ failure with emergency ICU monitoring and treatment, or shock[34,39].

CONTRIBUTING ROLE OF COVID ASSOCIATED FACTORS IN DISEASE PROGRESSION AND SEVERITY

Liver functional test abnormalities

Clinical evidence demonstrated that elevated serum levels of the liver enzymes ALT and AST were associated with adverse outcomes such as shock and ICU admission, and mechanical ventilation, as well as disease progression symptoms such as the development of severe pneumonia[39,45,46]. Fan and colleagues reported longer hospital stays of around average 15 d in COVID patients with abnormal liver functions. Increased levels of liver enzymes increased hospitalization compared to COVID patients with normal liver functions. The liver test abnormalities have been stated as a predictor of disease progression and severity of COVID symptoms[47]. According to Leo and colleagues, the underlying events for abnormal liver function test results are due to "cytokine storm, a sinusoidal thrombotic event associated to SARS-CoV-2 infection coagulopathy, liver damage induced by hypoxia or could be secondary to alterations of blood outflow and inflow that may occur when positive end-expiratory pressure is applied"[48]. Recently, in a retrospective study, Kalal and colleagues from India also documented elder age (median 50 years), longer hospital stays, and higher values for liver function tests in severe patients than in non-severe (mild and moderate) patients (median age 37 years)[49]. A large retrospective cohort study from China documented the abnormal AST and direct bilirubin levels in COVID patients at hospital admission were associated with COVID-19-related mortality[37]. Therefore, the liver function tests for monitoring AST and direct bilirubin have been suggested as imperative to halt the disease progression.

Drug hepatotoxicity

During the first phase of the COVID-19 pandemic, the primary therapeutic procedure was to treat patients with antibacterial drugs such as moxifloxacin, cephalosporins, antiviral drugs oseltamivir and acyclovir, and antipyretic drugs such as acetaminophen to alleviate COVID-19 symptoms[12]. The benefits like improved outcomes in decreasing diarrhea, fever, worsening of chest radiographs, and worsening of viral load by treating severe acute respiratory syndrome (SARS) patients with lopinavir/ritonavir for 3 wk were earlier validated[50]. However, the side effects of lopinavir and ritonavir administered during treatment of patients with SARS-CoV-2 viral infection have been noted[51], with even four times increased risk of liver damage, which can be attributed to a higher dose of this medication[12,39]. Yip and colleagues also recorded treatment with lopinavir-ritonavir, with or without ribavirin, interferon beta, or corticosteroids was independently linked with heightened ALT/AST serum concentrations[45].

It has been speculated that the overdose of a combination of lopinavir and ritonavir could trigger the hepatic endoplasmic reticulum stress cascade, stimulate inflammatory reactions, activate hepatocyte apoptosis through the caspase mechanism, suppress hepatocyte growth, and amplify the liver damage oxidative stress[18]. In a mouse model, the role of ritonavir in hepatotoxicity has been shown to occur through CYP3A4-dependent pathways, which are modulated by pregnane X receptor. This transcription factor is concerned with ritonavir bioactivation, oxidative stress, endoplasmic reticulum stress, destruction of membrane integrity, and interruption of the internal and external Ca²⁺ homeostasis of liver cells, and causes death[18,52]. It has been studied that SARS-CoV-2 replication can be inhibited by human immunodeficiency virus (HIV) protease inhibitors; however, progression of liver damage has been observed in patients undergoing hormones and HIV protease inhibitor therapy. In a retrospective study in China, Shen and colleagues also reported traditional Chinese medicines, herbal and dietary supplements, and antituberculosis drugs as the main causes of drug-induced liver injury[18,53]. Fan and colleagues also reported that administration with ACE inhibitors/angiotensin II receptor blockers (ARBs) did not produce any side effect in COVID-19 patients, even in those with hypertension as co-morbidities. Thus, the prolonged and higher dose of antibiotics, non-steroidal anti-inflammatory drugs, herbal medications, and interferon used to treat COVID-19 patients seems to link with the progression of disease with severe outcomes like liver failure.

Pre-existing liver problem and other co-morbidities/factors

Most of the COVID-19 patients reported fever as a symptom of infection, for which they used antipyretic and analgesic drugs. Therefore, overdose or prolonged use of these drugs has been linked to liver damage. Due to their hepatotoxic properties, the use of drugs like lopinavir/ritonavir could be fatal to patients with pre-existing liver problems or weak immune systems like old age, children, and patients with co-morbidities[12,51].

Aged patients with co-morbidities such as hypertension, diabetes, cardiovascular disorders *etc.* showed severe outcomes compared to other age groups or those without co-morbidities[54]. In addition to age, clinical features like inflammation and hypoxia at the time of admission to hospital and drug treatment have been associated with COVID-19 related development and progression of liver damage [48]. COVID-19 patients with hypertension who received ACE inhibitors and ARBs at the time of hospitalization developed higher though insignificant liver abnormalities than patients without a history of hypertension[12]. Liver tissues of patients with chronic liver diseases such as existing cirrhosis, dysplasia, non-alcoholic steatohepatitis, and simple steatosis showed elevated levels of ACE2 than normal liver tissues[55]. Patients with alcohol-related liver disease have been suspected as a high-risk group for COVID-19 related severity because these patients, due to drinking habits, are less likely to maintain social isolation and follow regular therapy[56]. Ji and colleagues also noticed patients with non-alcoholic fatty liver disease with a high body mass index are at greater risk for progression and severity of COVID-19 outcomes and reported longer viral shedding time. The respective researchers hypothesized that in patients with non-alcoholic fatty liver disease, "the polarization status of hepatic macrophages might be skewed from inflammation-promoting M1 macrophages to inflammation-suppressing M2 macrophages, which results in progression of COVID-19"[16].

The virulence of SARS-CoV-2 has imposed challenges for organ transplants. Since the immune system of the recipient is already dwindling due to chronic illness, these patients are susceptible to infection. Both recipient and donor of liver transplant are at risk of SARS-CoV-2 infection before liver transplantation, increasing the hospital stay and treatment duration that further aggravating the infection in patients undergoing liver transplantation[57]. Thus, strict guidelines for the diagnosis of donor and maintenance of isolation and sterilized environment during operation and postoperative patient care should be assured.

DISEASE MANAGEMENT, PREVENTIVE MEASURES, AND TREATMENT

SARS-CoV-2 is a novel coronavirus that causes COVID-19. Retrospective studies and clinical trials that we mentioned in the previous section of this review demonstrated that the drug hepatocytotoxicity due

to inappropriate dose and long-term use causes aggravated immune response and systemic inflammatory reaction due to invading virus or viral reactivation of existing liver disease, and the adverse clinical outcome & disease progression and co-morbidities[16,46,47]. Therefore, frequent monitoring conditions of COVID-19 patients with pre-existing liver disease or who developed liver abnormalities during treatment is needed. Evaluating liver enzymes during in-hospital stay or post-COVID-19 duration at different time intervals in months could help track liver health and effective treatment. Still, there is a possibility of managing the disease with combined efforts among individual, societal, and health care sectors, the research community, and the government level. Detailed strategy is mentioned in [Figure 2](#).

Disease management of patients with liver disease

We confirmed from previous research that SARS-CoV-2 infection causes mainly liver damage and abnormal liver functions, which manifest as hypoxia, systemic inflammatory reactions, and medication; thus, regulating these associated factors, such as oxygen supplementation, mechanical ventilation, and renal replacement therapy for cytokine storm, could reduce liver injury[18,42]. If hepatotoxicity due to drug use is suspected, patients must be admitted to intensive care for any severe symptoms, and emergency precautionary measures must be taken. Patients with chronic liver diseases such as cirrhosis and non-alcoholic fatty liver disease treated with immunosuppressive drugs should be prioritized for COVID-19 testing and hospitalization. Patients showing signs of chronic viral hepatitis (HCV and HBV) should be treated according to prescribed guidelines. In case of urgent liver transplantation, the donor and recipient should be tested for COVID before operation and postoperative precautionary measures should be taken to prevent any infection. If post-transplant patients are detected with SARS-CoV-2 infection, they should be administered with a reduced dose of immunosuppressive agents according to a degree of severity along with vaccination[18,58].

Dietary management for health

Probiotics, vitamins, and minerals are essentially dietary supplements that are helpful to improve overall health condition and deficiency of proper nutrition weakens the immune system. Insufficient intake of vitamin A and serum retinol, vitamin C, and selenium have been linked with the severity of liver fibrosis in patients with non-alcoholic fatty liver disease[59]. As a result, it has been speculated that taking probiotics, vitamins such as fat-soluble vitamins A, D, and E and water-soluble vitamin C, and minerals such as zinc, magnesium, and copper during COVID-19 could boost and maintain liver health. Sivandzadeh and colleagues have highlighted the anti-inflammatory properties of probiotics and micronutrients, along with the antioxidant and immunomodulatory properties of vitamins that could reduce the TNF- α , oxidative stress, and apoptosis of hepatocytes[60].

Research in liver health

COVID-19 pandemic has arrived as a hurdle and interrupted research, clinical trials related to liver health, and drug development due to pandemic generated difficulties such as problem in the recruitment of patients, timely supply of research related aids, and maintenance of laboratories specifically during lockdown[61]. For example, liver cancer management has been affected due to COVID-19, and the more prominent among them is the cancellation of screening, diagnosis, and treatment[62]. The development of non-invasive tools, and proteomics, transcriptomics, lipidomics, and metabonomics based biomarkers for diagnosis and progression of liver disease could also helpful to lessen the COVID severity[63]. Research on development of software and algorithms for maintaining databases of patients' details for early diagnosis and treatment of liver disease such as liver fibrosis at the community level (<https://clinicaltrials.gov/ct2/show/NCT04666402>) could help to track patients with liver disease and their treatment & care at the time of COVID. Research and more clinical trials on regressing fibrosis and enhancing tissue regeneration using cell therapy could be the promising alternative to liver transplant that could increase the longevity of patients[64]. The clinical trials on role of vitamin C as an antioxidant to improve liver functions and the underlying mechanism on healing the non-alcoholic fatty liver disease suggest that it could be a compelling dietary supplement to reduce the COVID associated symptoms and the severity[65]. Drug development and clinical trials through nanotechnology for diseases like non-alcoholic fatty liver disease/metabolic-associated fatty liver disease[66], and other liver disease could ensure better health in patients with liver disease in this COVID pandemic era. Now, after global vaccination and following proper corona guidelines, the normal research activity has started, which could progress with the support of government and funding sources/sponsors.

Future directions

Still, there is a lack of safe drugs that can effectively treat COVID patients precisely because of its umbrella effect at the multi-organ level. In a meta-analysis from Morocco, around 20 medicinal plants belonging to 19 genera and 14 botanical families and their products have been reported to prevent and treat COVID 19. The extracts of these plant species are rich in bioactive compounds like flavonoids, alkaloids, saponins, essential oil, *etc.* which are effective as antiviral, antibacterial, antifungal, anti-

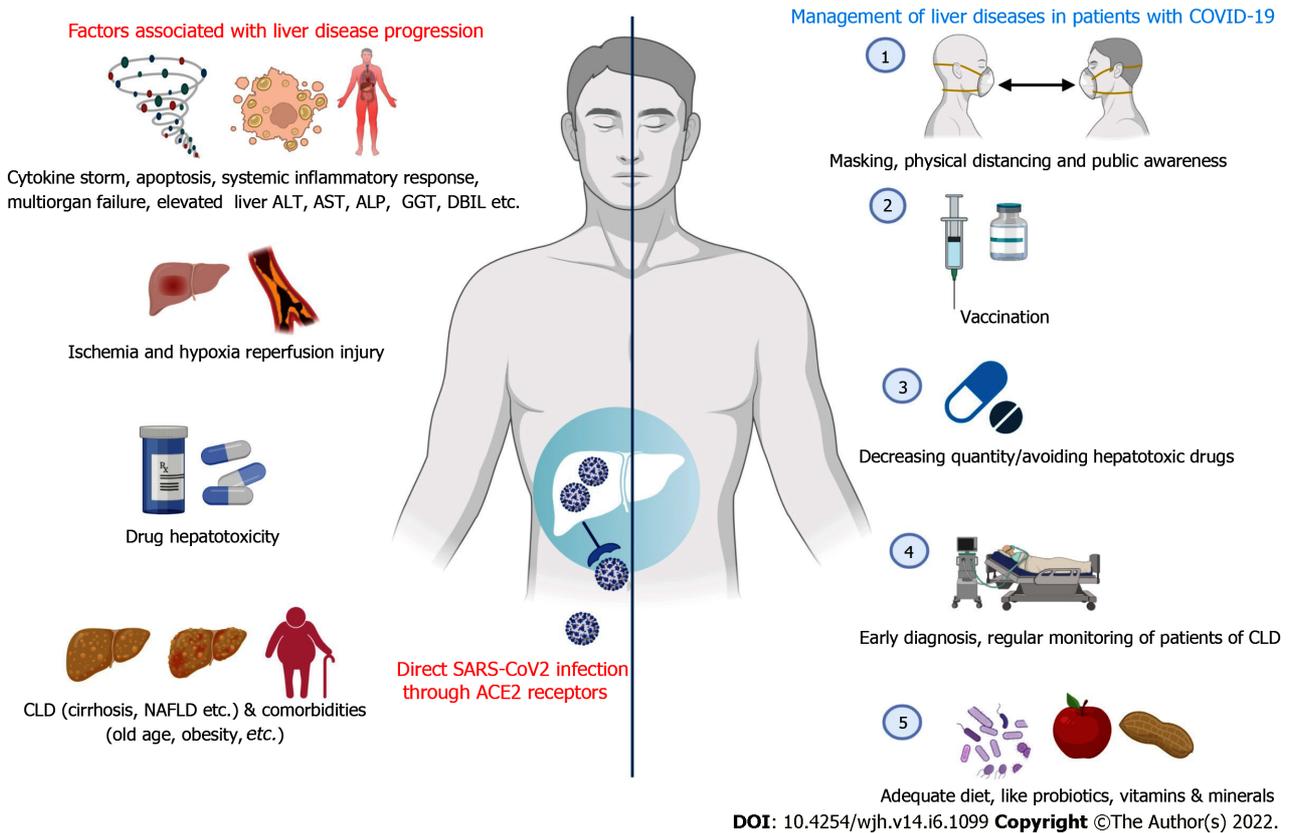


Figure 2 Associated factors for liver disease progression and its management strategies in patients with coronavirus disease 19. CLD: Chronic liver disease; NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; DBIL: Direct bilirubin. Created with BioRender.com.

inflammatory, antioxidant, antipyretic antiseptic, antibiotic, and analgesic agents[67]. Certain plants such as *Tinospora cordifolia*, *Andrographis paniculata*, *Cydonia oblonga*, *Zizyphus jujube*, and *Cordia myxa* are also beneficial for symptomatic management of COVID-19[68]. Through randomized controlled trials, the integrated therapy including treatment with both Western as well as herbal medicine has also been shown to promote faster recovery, and reduce symptoms and duration of treatment time in COVID-19 patients[69]. However, some traditional Chinese herbal medicines were suspected to impose side effects and increase the disease course[70]. The MACH-19 (Mushrooms and Chinese Herbs for COVID-19) trials are ongoing, and these herbs could be used as potential adjuvant to COVID-19 vaccines[71]. Thus, effective herbal medicines and more clinical trials to evaluate their potential to cure COVID-19 are required. The immunogenicity of vaccines developed against SARS-CoV-2 in patients still needs to explore. The vaccination of two doses has been widely carried out all over the world, so the post-vaccination symptoms are required to monitor in patients with liver diseases like chronic disease cirrhosis and non-fatty liver disease, and in liver transplant recipient whose immunity is compromised. Better pathogenesis knowledge helps to formulate specific therapy that may arrest viral replication. Therefore, the promotion of intensive research on liver health due to COVID-19 by the government and an approach for collaborative research among physicians, scientists, and academicians from different institutes is required. Public awareness regarding maintaining hygiene, the right lifestyle, self-care, following COVID-19 protocols, and vaccination could help to reduce community transmission and COVID-19 related casualties.

CONCLUSION

A large number of studies, including retrospective and clinical trials conducted around the world, have supported the existence of liver dysfunction in COVID-19 patients. The main factors contributing to disease severity and progression are drug-associated hepatotoxicity and immune-mediated liver injury due to the possibility of direct cell cyto-toxicity. Through ACE2 receptor mediated SARS-CoV-2 infection of liver cells, viral reactivation might occur in cases of pre-existing liver dysfunction. As predictors of disease progression and liver damage, biochemical indicators of the liver have been proposed. However, reports on liver damage by direct infection with SARS-CoV-2 and safer drug

rendering protection to the liver are insufficient. Therefore, further research on different aspects such as the mechanism of liver injury, drug-related toxicity, different stages of disease progression, link of liver dysfunction with co-morbidities, immune state of patients, along with effective drug (specifically exploiting the indigenous herbal medicine knowledge) and vaccine development is need of the time. Individuals, particularly patients with liver disease, may take preventive measures such as masking, physical distancing, avoiding self-medication without a physician's prescription, avoiding alcohol consumption, exercise, a balanced diet, adequate sleep, and a healthy lifestyle to reduce their chances of contracting SARS-CoV-2 infection.

FOOTNOTES

Author contributions: Verma HK designed the review; Sahu T, Manasa PL, and Pande B performed the literature search and collected and assembled the data; HKV and BP analyzed the obtained articles; Sahu T, Manasa PL, Pande B, and Verma HK wrote the manuscript and revised it critically; all authors have read and agreed to the published version of the manuscript.

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