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# COVID-19 and hepatic injury: Diversity and risk assessment

COVID-19 and hepatic injury

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**Abstract**

The coronavirus disease (COVID-19) represents a global health and economic challenge. Hepatic injuries have been approved to be associated with severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection. The viral tropism pattern of SARS-CoV-2 can induce hepatic injuries either by itself or by worsening the conditions of patients with hepatic diseases. Besides, other factors have been reported to play a crucial role in the pathological forms of hepatic injuries induced by SARS-CoV-2, including cytokine storm, hypoxia, endothelial cells, and even some treatments for COVID-19. On the other hand, several groups of people could be at risk of hepatic COVID-19 complications, such as pregnant women and neonates. The present review outlines and discusses the interplay between SARS-CoV-2 infection and hepatic injury, hepatic illness comorbidity, and risk factors. Besides, it is focused on the vaccination process and the role of developed vaccines in preventing hepatic injuries due to SARS-CoV-2 infection.

**Key Words:** COVID-19; Hepatic injury; Viral tropism; COVID-19 comorbidity; Vaccination

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**Core Tip:** The association between COVID-19 and hepatic injury is demonstrated by determining the viral tropism and its different pathological implications. A better understanding of the diversity and risk factors of SARS-CoV-2-induced hepatic injury provides a fundamental approach to overcoming adverse effects. Moreover, vaccination can influence assessment and evaluation.

## INTRODUCTION

### Introduction

Coronavirus (CoV) is derived from the Latin word "corona," which means "crown"[1]. It can cause various human respiratory tract diseases, ranging from mild cold to severe respiratory distress syndrome (RDS)[2]. CoV has presented several challenges throughout its history, including viral isolation, detection, prevention, and vaccine development[3]. CoV is a member of the order *Nidovirales* and has the largest RNA genome[4]. Furthermore, it is recognized as arising from a zoonotic origin and frequently spreads by contact or respiratory droplets. The affected individual has non-specific clinical characteristics requiring virological diagnosis and molecular confirmation[5]. Seven coronaviruses have been recognized to infect humans, with SARS-CoV-2 being the most recent, and this might be due to frequent infections across different species and sporadic spillover episodes[4]. Two of these previously recognized coronaviruses are the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which originated in the Middle East in 2012, and the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), which originated in China from 2002 to 2003 and was responsible for significant epidemics in the previous two decades[6]. The recent CoV illness, also known as COVID-19 and the coronavirus disease of 2019, poses a risk to global health[7]. The COVID-19 pandemic began in the Chinese city of Wuhan near the end of December 2019 and spread rapidly in the following months to Thailand, Japan, South Korea, Singapore, and Iran[8]. This was followed by a viral outbreak worldwide, particularly in Spain, Italy, the USA, the United Arab Emirates (UAE), and the United Kingdom (UK). The COVID-19 disease is classified as a pandemic by the World Health Organization[9]. The three types of coronaviruses are zoonotic, can infect people, and cause severe and fatal diseases[10]. New coronaviruses are expected to emerge and cause sporadic seasonal outbreaks due to their great genetic diversity, frequent genome recombination, and rise in human-animal interface activities brought on by contemporary agricultural methods[11].

## VIRAL TROPISM

In COVID-19, viral tropism is responsible for spreading infection outside the respiratory tract and predisposing it to systemic symptoms, aggravating pre-existing disorders, and

multiorgan damage in the kidney, heart, nervous system, liver, and gastrointestinal tract[12,13]. However, the available data indicate the second multiorgan dysfunction inherent to the immune discrepancy or cytokine storm, developing hypoxic or ischemic injury and drug-induced injury[14,15]. Although viral tropism should be considered to understand the SARS-CoV-2 infection, the S protein of the virus mediates SARS-CoV-2 cell entrance, which represents a high affinity for cells expressing angiotensin-converting enzyme 2 receptors (ACE2)[16]. Furthermore, the affinity of the S protein to ACE2 receptors increases when SARS-CoV-2 is proteolytically activated[17]. In an *in vitro* study by Letko *et al*, the S protein of lineage B beta-coronaviruses such as SARS-CoV and the recent SARS-CoV-2 significantly improved its affinity for its receptor when it was pre-incubated with proteolytically activated trypsin[18]. Trypsin is expressed by liver epithelial cells[19]. Additionally, the protein of the SARS-CoV-2 contains a furin-like proteolytic site that has never been observed in other coronaviruses[20]. It is worth mentioning that furin is expressed in organs such as the salivary glands, liver, kidney, and pancreas involved in SARS-CoV-2 infection[21]. As a result, to determine tropism for a particular tissue, ACE2 should be present at the host cell surface[22]. Consequently, ACE2 expression is considered a mirror of viral load[23]. Controversially, the highest levels of ACE2 are detected in the small intestine, testis, heart, colon, and thyroid gland [24]. Nevertheless, respiratory system symptoms are dominant in COVID-19 because the nasal ciliated cells are the primary targets for SARS-CoV-2 replication in the early stages of infection[25]. Besides, ACE2 is abundantly expressed in more than 80% of alveolar lung cells, consequently affecting all respiratory functions[23].

## DIAGNOSIS

With increasing COVID-19 prevalence and mortality rates, as of 14 August 2022, the WHO reported that over 587 million people were infected with SARS-COV-2, including over 6 million deaths[26]. Therefore, the nation's healthcare systems face overwhelming psychological and economic burdens. Consequently, the most efficient method to prevent

infection is to separate symptomatic persons, quarantine others, and manage concomitants while increasing immunization rates.

The molecular test is the most practical method to confirm the diagnosis of COVID-19, using the reverse transcription polymerase chain reaction (RT-PCR) to detect viral genetic materials in different sample swabs from the nasal cavity, mouth, sputum, and feces[27,28]. This molecular test provides high sensitivity and specificity; however, it has several drawbacks, such as requiring trained technicians, being time-consuming, high cost, shortages in test kit supplies, and false negative thresholds[29]. Therefore, it is critical to develop new quick, reliable, and affordable diagnostic techniques.

Patients with fever, cough, and chest pain with breathing problems or pneumonia are usually diagnosed by imaging tests, such as chest X-ray or computed tomography (CT)[30]. Imaging tests are predominantly available worldwide, and the scanning process is relatively simple and rapid, enabling a large population's screening[31]. In a study based on chest X-ray findings and severity scores, a chest X-ray is a limited tool because it has an abnormality observed at a specific point[32]. In the same context, Borghesi A. and R. Maroldi mentioned that chest X-ray is an insensitive diagnostic tool for the early detection of lung abnormalities. In contrast, it is a valuable tool for monitoring (day after day) the rapid progression of lung abnormalities in infected patients, particularly in intensive care units[33]. Despite its limited sensitivity, the appearance of a local or bilateral patchy shadow infiltrating a chest X-ray is the most typical radiological presentation[34].

Currently, computed tomography plays a pivotal role and is the main technique for diagnosing and following patients with COVID-19[35]. The CT finding is more sensitive than the chest x-ray, particularly in the initial assessment[32,36]. CT findings may be present early, even before the onset of the symptoms[36]. Additionally, Li Y. and L. Xia's comparative study reflected the low misdiagnosed rate of CT scans and detected positivity earlier than RT-PCR[37]. The most common chest CT findings included ground-glass opacity, ill-defined boundaries, smooth or uneven interlobular septal thickening, an air bronchogram, a crazy-paving pattern, and thickening of the nearby pleura[38]. Due to numerous drawbacks, chest CT has some restrictions; for instance, radiation exposure,

overuse of health care resources, hygiene, or inability to get a CT scan, as in critically ill patients, or clinically unstable, as in the case of ICU admission[39]. As a result, other methods are required to define and monitor patients rapidly.

Moreover, clinical pathologists have a significant role in monitoring inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cells (WBCs). The most significant markers during SARS-COV-2 infection and highly associated with COVID-19 progression were lymphocytopenia, elevated CRP, and alternation in the ESR levels[40-42]. Data obtained from 452 patients with COVID-19 revealed that lymphocytopenia, high WBCs, a high neutrophil-lymphocyte ratio (NLR), and lower percentages of monocytes, eosinophils, and basophils were mainly observed in severe cases[43]. Similar findings were demonstrated by Henry *et al* (2020) in their meta-analysis of 21 studies that included 3377 individuals who tested positive for COVID-19. They found that patients with severe and fatal diseases had more dramatic leukocytosis and lymphocytopenia and thrombocytopenia than mild to moderate diseased and survivor patients[44]. The study by Mardani R. *et al* (2022) attempted to explain the association between the inflammatory markers and COVID-19 progression and found that elevated CRP was correlated with the severity of COVID-19; furthermore, high ESR levels were observed in the severe cases only[41]. Additionally, interleukin (IL)-7, IL-8, IL-9, IL-10, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor A (VEGFA) were all found at high blood levels in COVID-19 patients[45].

In contrast, children show inconsistency and require further investigation. According to del Valle R *et al* (2022) children with SARS-CoV-2-associated community-acquired pneumonia have low CRP levels[46]. Additionally, a systematic review by Patel NA (2020) describes 2914 pediatric patients with COVID-19, the lab results for these children indicate stable WBC, lymphocyte count, and CRP levels[47]. Even though pneumonia causes an elevated CRP level, pneumonia with COVID-19 causes a drastic increase in CRP. This was revealed in a retrospective comparative study by analysis of the laboratory markers among children affected with pneumonia in the presence or absence of SARS-

CoV-2 infection[48]. A meta-analysis study covers 20 eligible studies to identify the laboratory abnormalities among 1810 pediatric patients including Leukopenia, lymphopenia and elevated CRP[49]. Furthermore, the major conclusion of a retrospective cohort study by Graff K *et al* (2021), which included 454 patients, was that elevated CRP is a predictor of severe COVID-19 in children[50]. All the previous studies show defects in the number of people involved in the studies. Hence, we recommend further investigation into many children.

Numerous investigations have demonstrated that liver damage occurred in SARS patients. This damage primarily took the form of mild to moderate elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in the early stages of the illness. Some individuals' blood albumin levels dropped as their bilirubin levels increased[51]. Compared to moderate cases, patients were more likely to have severe hepatic damage[52]. According to recent investigations into COVID-19, liver damage can occur in between 14.8 and 53% of cases, with aberrant ALT/AST values and slightly increased bilirubin levels serving as the significant indicators[53]. Severe cases reduced albumin (26.3-30.9 g/L)[54]. In recent research, including 1100 Chinese patients, Guan *et al* found that 56% of patients with a severe COVID-19 infection and about 18% of patients with a non-severe COVID-19 disease had increased blood AST levels. Additionally, it was shown that patients with a non-severe COVID-19 illness accounted for 20% of patients with increased blood levels of ALT. In contrast, patients with severe COVID disease constituted 28% of patients[34]. In COVID-19 fatality cases, liver damage occurred between 58.06% and 78% of the time[55]. A study showed that a patient with severe COVID-19 had blood ALT and AST values of 7590 and 1445 U/L, respectively[54].

## RISK FACTORS

Intriguingly, lifestyle characteristics such as smoking, a high body mass index (BMI), male gender, postmenopausal status, and higher age in females were cited as the most significant risk factors for SARS-CoV-2 infection, regardless of comorbidities[56-58]. According to some studies, the age for an elevated risk is > 64 or > 65 years old. With six

records, hypertension[59] and diabetes[60] are the most prevalent pre-existing comorbidities, followed by cardiovascular disease with three records. On rare occasions, associations were found between severity and TB, chronic renal illness, chronic obstructive pulmonary disease, or cerebrovascular disease. Significant effects on disease severity were reported for eight comorbidities that emerged because of COVID-19 infection[61]. Among them are organ failure, immune dysfunction, acute liver damage, hypoproteinemia, ARDS, severe pneumonia, an uncontrolled inflammatory response, and hypercoagulable conditions[58, 61].

Because their host defenses are compromised, patients with pre-existing liver diseases, such as cirrhosis of the liver and hepatocellular carcinoma, are more susceptible to infections and sepsis in general. Chronic liver diseases (CLDs) were present in 0.6% to 1.4% of hospitalized COVID-19 patients[62, 63]. These individuals were more likely to experience severe illness (up to 60%) and increased death (up to 18%)[64]. Additionally, SARS-CoV-2 infection worsened the clinical prognosis and exacerbated liver damage in persons with CLDs resulting in decompensation in 20% of cirrhotic patients and worsening the clinical outcomes of people who were unstable[65].

The relationship between metabolically associated fatty liver disease (NAFLD) and COVID-19, among instances of chronic liver disorders and COVID-19, has received full attention. According to two investigations by Qian *et al*[66] and Ji *et al*[67], Patients with NAFLD have a longer viral shedding period and are more likely to have abnormal liver functions from the time of admission until discharge. Moreover, other investigations reported the same findings, with more significant mortality in patients with NAFLD, obesity, and those over 60 years old[68].

Additionally, the chance of rapid SARS-CoV-2 infection and developing COVID-19 complications appear with immunomodulatory and immunosuppressive drugs mainly used in autoimmune liver diseases. Therefore, patients with autoimmune hepatitis receiving immunosuppressive therapy should be viewed as having a high risk of developing severe COVID-19[69]. In contrast, the incidence of SARS-CoV-2 infection in patients with autoimmune hepatitis was like the general population, and the prevalence

of severe COVID-19 was low[70]. Hence, we recommended further studies on patients with autoimmune hepatitis receiving immunosuppressive therapy.

Finally, according to preliminary findings on coinfection with SARS-CoV-2 and other viruses, it seems to cause severe progression, poor outcomes, or vial reactivation as in the case of the hepatitis C virus (HCV) and Hepatitis B virus (HBV) coinfection[71-73].

## CLINICAL CHARACTERISTICS OF LIVER INJURY IN COVID-19

Recent research shows that the frequent symptoms of fever and cough coincide with the beginning of COVID-19 infection. Other clinical characteristics, such as diarrhea, nausea, vomiting, and lack of appetite, represent at least a digestive system symptom[34]. Coronavirus infection has been linked to liver damage in SARS and Middle East respiratory disease patients[74]. In cases with COVID-19, abnormal liver function was observed, shown as isolated elevations in blood transaminase and LDH levels[75]. ALP, LDH, ALT, AST, and prothrombin time levels gradually increased during the hospitalization of the first COVID-19 case in the United States[76]. According to a study from Jin Yin-tan Hospital, out of the 99 patients with COVID-19, 43 had ALT or AST levels above the normal range, 75 had elevated LDH levels, and one had a severe disruption in liver function[54]. With 3.75% of all cases in Jiangsu province being imported and cases outside Wuhan, liver damage was said to be less common in these patients[77]. In an analysis of liver function among patients outside intensive care units, males were more likely to experience liver impairment than females[78]. In pediatric instances, liver damage was discovered in 22% of kids, most often between 2 and 18 days after admission[79]. In Wuhan, liver injury is a common factor among patients who are admitted to the ICU and non-survivors hospitalized patients. This reflects the relationship between liver injury and the severity of COVID-19[80]. Fifty-two patients who required mechanical breathing or had at least 60% inspired oxygen been included in a study of critically ill individuals. Twenty-nine percent of patients with critical conditions had liver damage. Fifteen percent had acute renal disease, and fifteen percent had cardiac injury [81]. In a multicenter study involving 1099 patients and 552 hospitals, abnormal

liver function was generally detected in critically ill participants, whereas jaundice was less frequently observed in COVID-19 patients. In harmony with the elevation of total bilirubin levels in 10% of patients, the percentage was increased in severe cases up to 20.5%[34]. Furthermore, a multicenter retrospective cohort study including 5771 patients in Hubei province suggested that upregulation in liver injury markers, particularly AST, is closely correlated with the probability of death during COVID-19[75]. Therefore, the dynamic patterns of liver injury markers and their putative risk variables may provide a significant explanation for the liver damage linked to COVID-19. Additionally, all studies indicated that liver injury parameters should be monitored during hospitalization.

**Possible mechanisms of COVID-19-associated liver injury (Figure 1)**

**SARS-CoV-2 tropism and liver injury**

ACE2 expression aroused the curiosity of researchers and scientists due to unusual ACE2 hepatic distribution and unexpected outcomes. Chai and colleagues assumed the hepatic abnormalities during COVID-19 were ascribed to cholangiocytes dysfunction, not due to hepatocytes damage. Their investigation using single-cell RNA-seq revealed that the primary target for SARS-CoV-2 in the liver was cholangiocytes. The ACE2 expression in hepatocytes is 20 times less than observed in cholangiocytes. Despite this, clinical data from COVID-19 patients showed rising ALT, AST, and LDH levels, while ALP and GGT, which describe bile duct injury, did not significantly increase[82]. At the same time, histological and immunohistochemistry assessments of Kupffer cells and T and B lymphocytes did not express ACE2[83], even though COVID-19-infected patients' livers frequently showed Kupffer cell activation and proliferation[84, 85]. Additionally, systemic inflammation typically results in Kupffer cell activation and proliferation[84]. Although Kupffer cells do not express, ACE2 may have a crucial role in the propagation of inflammation that results in SARS-CoV-2-mediated liver damage. It is noteworthy that prediction of SARS-CoV-2 consecutive signaling, and outcome is challenging because the expression of ACE2 Level is regulated by many factors and conditions, for example, liver

fibrosis, liver cirrhosis, hypertension, diabetes, chronic pulmonary diseases, hypoxia, old age, and smoking, which represent factors for COVID-19[17,86,87].

SARS-CoV-2 uses ACE2 receptors to invade host cells and utilizes other molecules to facilitate infection, such as furin, transmembrane serine protease 11A (TMPRSS11a), and neuropilin-1[88,89].

Neuropilin-1 is embedded in the liver, causing physiological and pathological conditions. Activation of the neuropilin-1 cascade triggers angiogenesis process via controlling cell proliferation, cell survival, and cell migration[90]. Regardless of the cause of hepatic injury and conditions resulting from a viral infection, the elevation of neuropilin-1 is the defense mechanism. Consequently, neuropilin-1 may influence liver damage induced by SARS-CoV-2[89]. Neuropilin-1 has been reported to be found and expressed in liver sinusoidal endothelial cells and hepatic stellate cells[91]. Meanwhile, hepatic stellate cells' activation is postulated to be the primary cause of liver disease and fibrosis[92,93]. In different conditions, the hepatic stellate increases proinflammatory and profibrotic cytokines[94]. One of those cytokines is IL-6, produced when SARS-CoV-2 activates the immune system in COVID-19 patients and is associated with altered liver enzyme levels[95]. Therefore, propagation of neuropilin-1 expression with activation of hepatic stellate cells promotes signaling transcription and stimulates the release of growth factors such as TGF-β and VEGF, elucidating their role in the progression of liver damage during SARA-CoV-2 infection[96].

All the data mentioned above are consistent with a detailed histological examination clarifying the possible mechanisms of hepatic injury. Wang Y. *et al* uncovered the presence of intact SARS-CoV-2 viral particles in the cytoplasm of hepatocyte samples obtained from 156 dead COVID-19 patients. Further observations revealed conspicuous mitochondrial swelling, endoplasmic reticulum dilatation, glycogen granule decrease, fibrin deposition, granulomas, massive central necrosis, and apoptosis[84]. Another study by Fiel M.I. *et al*, using in situ hybridization and electron microscopy, reported that SARS-CoV-2 directly invades liver cells and induces histological changes such as apoptosis, especially in cholangiocytes, abundant mitoses, mixed inflammatory infiltrates in portal

tracts, endothelins, and severe bile duct damage[97]. In a case study by Melquist S. *et al*, the direct SARS-CoV-2 cytopathic effect caused a rapid progression of acute hepatitis to fulminant liver failure with a mild increase in transaminase levels without developing respiratory symptoms[98]. Data from the international study involving 130 centers in 29 countries revealed that the stage of liver disease is closely correlated with COVID-19 mortality. The highest rates of hepatic decompensation and mortality were observed in patients with advanced liver cirrhosis and those with alcoholic liver disease[99].

**Cytokine storm and liver injury**

SARS-CoV-2 induces immune dysregulation associated with the unspecified release of proinflammatory cytokines and coagulation enzymes. The massive release of cytokines is known as a cytokine storm or cytokine release syndrome and is characterized by the magnitude of the release of IFNs, TNFs, ILs, and chemokines[100]. Hence, uncontrolled systemic proinflammatory cytokine release represents unfavorable clinicopathological conditions in COVID-19 patients, for instance, progressive liver damage and liver failure. IL-6 is the most significant cytokine in liver hepatocytes and is a crucial inducer of the acute phase response and infection defense[101]. IL-6 stimulates hepatocytes during the initial phase of inflammation to upregulate CRP, fibrinogen, haptoglobin, alpha-antitrypsin, and serum amyloid-A which induce acute inflammatory phase[101]. Additionally, prolonged inflammation stimulates IL-6, targeting monocyte chemotaxis toward tissue-destructive injury[102]. Furthermore, IL-6 induces multiple effects during the storm *via* the activation of different transduction signaling pathways, *e.g.*, NF-κB, JAK/STAT, and the AKT/PI3K pathway[71,103].

Similarly, attention must be paid to the crucial roles of the ACE/Ang II/AT1R pathways. Ang II can directly activate the NF-κB pathway, increasing the secretion of IL-6, IL-1β, TNF-α, and IL-10[104]. Moreover, Ang II has been reported to induce mitogen-activated protein kinases activation, which in turn induce pro-inflammatory cytokines' release[105]. A case series study by Li et al., revealed elevated serum transaminase levels attributed to systemic inflammation, cytokine storm syndrome, and hepatocyte damage[106]. Effenberger M., *et al* reported that hepatic injury in patients with COVID-19 was

attributed to systemic inflammation[95]. Therefore, significant elevations in CRP, TNFα, and IL-6, concomitant with a significant elevation in aminotransaminase, describe hepatic injury associated with SARS-CoV-2 infection[107,108]. All these data confirm the relationship between inflammation during COVID-19 and hepatic injury.

**Hypoxia and liver injury**

18

One of the most common complications of COVID-19 is acute respiratory distress syndrome requiring a high level of management[81,109,110]. COVID-19 is associated with impaired respiration, an insult to blood flow, and hypotension, which are clues to hypoxic hepatitis, and might exacerbate liver damage or even lead to liver failure [11, 106]. Ischemia induces profoundly detrimental cellular effects and results in metabolic abnormalities, for example, disturbances in lipid metabolism as well as lack of oxygen supply initiate hepatocellular death[112]. Furthermore, rapid recovery of blood flow with reoxygenation of hepatocytes results in metabolic abnormalities, the generation of reactive oxygen species, an inflammatory response, and cellular death[113]. Hence, hepatic ischemia deteriorates hepatic status *via* destructive cellular reactions concomitant with immune stimulation[112-114]. Hypoxia has been determined as the primary pathway to regulating ACE2 expression in hepatic cells [110]. These phenomena rapidly progress with a conspicuous elevation of transaminase levels, accompanied by LDH elevation[116]. A retrospective study by Huang, H., *et al* revealed that hypoxic hepatitis is apparent in intensive care units and is often associated with a drastic elevation in ALT levels, multiorgan damage, and high mortality risk[117]. Additionally, patients with COVID-19 and hypoxic hepatitis are sometimes comorbid with respiratory failure, septic shock, or heart failure[53,80,118]. All these findings suggest an association between hepatic ischemia/hypoxia-reperfusion injury and liver injury during the SARS-CoV-2 infection.

**Endothelial cells and liver injury**

SARS-CoV-2 induces hypercoagulation, with the incidence of pulmonary embolism associated with complications aggravating heart failure and liver congestion [114]. Hypercoagulation and clotting disorders might occur through direct infection of platelets or a cytokine storm[120]. As mentioned above, patients with COVID-19 reported a change

in platelet count and prothrombin time with an elevation in D-dimer and fibrinogen concentrations[80,121-123]. A multicenter, retrospective cohort study found that patients who died from COVID-19 were more likely to have severe hematological (lymphopenia, ferritin, and elevated D-dimer) and cardiogenic factors (troponin and lactate dehydrogenase), providing support for this hypothesis[80]. Goshua G. *et al* reported that patients with COVID-19 showed a disturbance in epitheliopathy and platelet activation markers, particularly von Willebrand factor (vWF) antigen, P-selectin, and soluble thrombomodulin, anticipating a poor outcome or death[123]. Furthermore, a case report study by Antunes de Brito, C.A. *et al* observed hepatic artery thrombosis in a patient with COVID-19 who experienced acute abdominal pain in harmony with elevations in protein C and D-dimer[124]. Histological examination implied a severe disruption of the intrahepatic blood vessel network secondary to systemic changes induced by the virus that might also affect the cardiovascular system, coagulation cascade, and endothelial layer of blood vessels[125]. Additionally, a series of pathological examinations of liver autopsies obtained from deceased COVID-19 patients elucidated platelet aggregation in some portal veins as well as hepatic sinusoidal injury due to platelet-fibrin microthrombi[126]. However, ischemic-type damage in the liver has been observed in some cases[126]. Massive data indicate a relationship between hypercoagulation and liver injury in COVID-19 patients.

SARS-CoV-2 infection induces a pathological thromboinflammation response, including platelet hyperreactivity, hypercoagulability, and hypofibrinolysis[127]. SARS-CoV-2 binds to ACE2 receptors on the surface of endothelial cells and subsequently induces endothelial injury[127]. Additionally, SARS-CoV-2 invades megakaryocytes and platelets [123]. Endothelial cell activation and injury were confirmed by elevation of several blood hemostatic factors including Von Willebrand factor (vWF), thrombomodulin, and factor VIII [122,123]. Collectively, they trigger a platelet plug activation[129,130]. A procoagulant molecule and platelet tissue factor, produced by hepatocytes and endothelial cells, attach, and activate factor VII, a procoagulant molecule that circulates in the blood. Activated factor VII activates factor X, which subsequently resulted in thrombin formation.

Thrombin promotes a series of coagulation processes to produce fibrin which build a substantial fibrin mesh, in addition to platelet activation and aggregation[131,132]. Furthermore, Ang II increases PAI-1 expression in endothelial cells, which inhibits fibrinolysis and induces a hypercoagulable state[133].

Furthermore, hypoxia promotes coagulation through multiple pathways, such as hypercoagulation and inflammation. Hypoxia attenuates endothelial cells' anticoagulant function by suppressing thrombomodulin with increased PAI-1 upregulation. It promotes NF-κB and Toll-like receptor 4 (TLR4) signaling pathways in macrophages and neutrophils, stimulating the release of IL-6 and TNFα[134-136].

Excessive inflammatory cytokines, particularly IL- 6, facilitate SARS-CoV-2 and mediate coagulopathy[137]. IL-6 stimulates platelet formation and megakaryocytopoiesis generation, which could generate a hypercoagulability state[138]. A retrospective study by McConnell M.J. *et al* revealed that the IL-6/JAK/STAT pathway is responsible for coagulopathy and hepatic epitheliopathy associated with COVID-19 and could be the potential mechanism of liver injury in these patients[139].

**Drug-induced liver injury (DILI)**

Several medications can induce liver dysfunction and hepatocellular damage. Some are used as over-the-counter medications, for example, paracetamol, and others are used with precautions such as antibiotics, including azithromycin[140]. Although drug-induced liver damage is rare, it can immediately result in acute liver failure and require a liver transplant[141]. Drug metabolism is a possible cause of DILI development by generating chemically reactive drug metabolites. The failure to metabolize reactive drugs can result in mitochondrial damage and oxidative stress, activating different signaling pathways[142]. Furthermore, reactive metabolites can act as haptens and create neoantigens, which, when presented on human leukocyte antigen (HLA) molecules or attached to HLA molecules, can activate T cells, and trigger an adaptive immune response[143].

Several antiviral medications, supportive care, and trials of complementary therapies are among the therapeutic options being investigated against SARS-CoV-2. Hepatotoxicity

from nucleoside analogs and protease inhibitors, which are used to manage COVID-19, can occur because the liver is involved in the metabolism of many medications. In a case study from Wuhan, after receiving lopinavir and ritonavir, the patient developed liver damage[144]. A recent randomized controlled study compared the elevation of AST, ALT, and total bilirubin in COVID-19 patients associated with lopinavir and ritonavir[145]. In a retrospective analysis of COVID-19, Fan Z. *et al* found that significantly elevated liver enzymes and liver abnormalities were in harmony with receiving combination therapy. In this study, 47.3% of the released patients had increased liver function tests (LFTs) at baseline, and 23.7% experienced abnormalities during hospitalization, which might be due to treatments or the disease[146].

It was discovered that many COVID-19 patients had previously used antipyretics and analgesics, most frequently paracetamol, whose overdose is recognized as a cause of liver injury with a significant elevation of serum aminotransferases[147]. Additionally, hepatic injury worsens in critical illnesses and patients with preexisting CLDs[148]. Therefore, healthcare providers should be aware of over-the-counter medications used to control common COVID-19 symptoms such as fever and pain. Physicians play a role in monitoring abnormalities in LFTs as they can indicate unknown drug hepatotoxicity.

Hydroxychloroquine is one of the drugs suggested for COVID-19 therapy regimens, an anti-malarial medicine that relies on scant data in limited clinical settings[149]. Based on clinical data, hydroxychloroquine hepatotoxicity during COVID-19 is rare[150]. A few incidences of significant increases in aminotransferases brought on by hydroxychloroquine have never been documented[151]. Therefore, patients with liver disorders should use hydroxychloroquine cautiously since it can accumulate[152].

Azithromycin is an antibacterial drug belongs to macrolide antibiotic. It was used to treat bacterial infections before treating COVID-19 alone or in combination with hydroxychloroquine[153]. Hence, the hepatic injury should be considered due to the high use of these medications. Liver damage may rarely occur within the first two to three weeks of starting azithromycin. Most patients fully recover from it, and it is predominately a hepatocellular pattern[154].

Remdesivir belongs to an adenosine analog with antiviral action[155]. A multicenter, randomized, double-blind, placebo-controlled trial by Wang *et al* revealed that 10% of the remdesivir group had high blood bilirubin and 5% had increased aminotransferases[156]. Additionally, Remdesivir was used to treat COVID-19 in a case series ($n$ = 53), and 23% of the patients experienced elevated liver enzyme levels that required early treatment termination[157]. However, clinical data implied that the relation between remdesivir and hepatic injury during COVID-19 treatment needs more explanation[155].

To conclude, medications that reduce inflammation and preserve the liver should be given to individuals who are expected to experience liver damage, regardless of the drug, dosage, or dose[141].

## COVID-19 COMORBIDITY WITH DIFFERENT HEPATIC ILLNESSES

### COVID-19 and viral hepatitis

Hepatitis B virus (HBV) is a double-stranded DNA virus, a member of the *Hepadnaviridae* family. In contrast, HCV is a single-stranded RNA virus belonging to the Flaviviridae family[100]. Recently, several studies have indicated that the coinfection of COVID-19 and HCV is a predictor of acute-on-chronic liver failure and a high potential for ICU admission. A cohort study indicated that HCV patients with SARS-CoV-2 coinfection were more likely to be hospitalized. However, the mortality rate did not change[158].

In a retrospective cohort study that included 242 patients with hepatitis C cirrhosis, 46 patients were coinfected with SARS-CoV-2 and HCV and had high levels of ferritin, creatinine, blood urea nitrogen, prothrombin time, and HCV viral load, anticipating the development of acute-on-chronic liver failure and the potential for ICU admission[159]. An observational study by Toma L. *et al* among patients with SARS-CoV-2, active HCV, and cure HCV in a control group showed the highest serum concentrations of ALT, AST, CRP, and ferritin. Moreover, serum and fecal calprotectin were detected in a patient with SARS-CoV-2 infection[160]. In a serological study by León F.J.F. *et al*, patients with both HCV coinfection demonstrated a considerable elevation in IL-6 and IL-17, with lower TNF-α levels when compared with patients infected with HCV or SARS-CoV-2[161].

On the other hand, a nationwide population-based study has reported that patients infected with HBV were predisposed to have severe symptoms of SARS-CoV-2, a high probability of ICU admission, and more organ failures than patients without HBV infections, especially in older patients[162].

In addition, severe monocytopenia, lymphopenia, hypoalbuminemia, and lipid metabolism deficiency were observed in the liver of coinfected with SARS-CoV-2 and HBV[163, 164]. Besides the elevation of liver impairment markers, including ALT, AST, ALP, and total bilirubin, several novel risk factors have been identified, including elevated LDH, D-dimer, decreased albumin, and albumin/globulin ratio[165]. However, other studies have found that HBV is not related to the poor outcomes of COVID-19[166]. Furthermore, the reactivation of HBV may occur due to the COVID-19 vaccine, as observed in some cases[167-169].

**COVID-19 and viral hepatitis during pregnancy and its impacts on neonates**

Acute HBV infection during pregnancy is not a risk factor for fetal death or teratogenicity. However, many complications in HBV-infected pregnant women may be associated with an increased risk of gestational diabetes, postpartum hemorrhage, premature birth, and low birth weight[170]. Furthermore, in a prospective cohort study, Rajan M. *et al*[171] indicated that pregnant women with both HBV and SARS-CoV-2 coinfection had a high proportion of preterm deliveries and a low mean birth weight. In rare cases, the coinfection of both viruses has led to intrahepatic cholestasis in pregnancy and acute fatty liver disease of pregnancy (AFLP)[172]. Nevertheless, there is some indication that HBV and COVID-19 coinfection does not lead to worse results[171,173]. On the other hand, some studies have provided evidence that treatment regimens including antivirals, hepatoprotective, and low-dose dexamethasone drugs might be recommended in cases of pregnant women with HBV and COVID-19 coinfection, besides coagulation function monitoring as part of the management process[172,174].

Similarly, pregnant women with HCV infection are more likely to have infants born prematurely, stillborn infants, newborns with low birth weight, or infants with birth abnormalities[175,176]. Furthermore, from an epidemiological point of view, the worldwide

hepatitis elimination program has been affected due to COVID-19 spreading, and this may require new policies and strategies for hepatitis elimination[177-179].

Ahmed I. *et al*[180] reported a case-report study in which a 26-year-old Asian female pregnant patient was affected by a sudden onset of severe preeclampsia complicated by AFLP and acute kidney injury (AKI) following SARS-CoV-2 infection. Besides, the comorbidities of SARS-CoV-2 and preeclampsia in pregnancy can lead to AFLP and AKI. This comorbidity can cause calcifications of the bowel and gallbladder of the fetus[181,182], besides a liver parenchymal disease associated with liver rupture[183], liver coagulation, liver impairment, and preterm delivery[184]. Furthermore, a pregnant woman with SARS-CoV-2 infection at 28 weeks with a low-lying placenta was complicated by obstetric cholestasis (OC) and several episodes of minor antepartum hemorrhage (APH)[185]. Moreover, placental insufficiency and subsequent fetal hypoxia may occur[186].

**COVID-19 and pregnancy: several mechanisms for complications**

Recently, pregnant patients who were coinfected with SARS-CoV-2 showed a higher risk of developing complications than those who were not pregnant. Studies have shown that pregnant women with SARS-CoV-2 infection increased the probability of developing preeclampsia compared to individuals who did not have SARS-CoV-2 infection during pregnancy[187]. Nevertheless, symptomatic patients were more likely to have preeclampsia than asymptomatic ones[187,188].

On the other hand, several hypotheses may illustrate the high rate of preeclampsia associated with SARS-CoV-2 infection. A direct cytopathic effect with dysregulation of the RAAS system induces a change in the placenta's function[189-192] because it controls the proliferation of trophoblasts, angiogenesis, and placental blood supply. Thus, the interaction between SARS-CoV-2 and ACE2 receptors described in RAS system down-regulation and reduction of vasodilatory angiotensin 1 to 7 results in continuous vasoconstriction and pro-inflammatory effects of angiotensin II, which finally lead to a pathophysiological mechanism of preeclampsia[193-197]. A study conducted by Verma *et al*[198] suggested that the infected placenta had a reduction in ACE2 receptor expression, proangiogenic factors, and an increase in the production of soluble FMS-like tyrosine

kinase-1 (salt-1), which are biomarkers for preeclampsia. An in-silico study by Seethy *et al*[199] concluded that interactions between SARS-CoV-2 and the placenta are regulated through trophoblast invasion, migration, proliferation, and differentiation processes by the milk fat globule-EGF factor 8 protein (MFGE8), plasminogen activator (PLAT), and protease-activated receptor 2 (PAR2) proteins.

In parallel, pregnant women might be able to develop a pre-eclampsia-like syndrome (PE) characterized by proteinuria, hypertension, thrombocytopenia, the elevation of liver enzymes, an abnormal uterine artery pulsatility index (UtAPI), and increased soluble FMS-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF)[200], besides preeclampsia, coagulopathy, and the HELLP (hemolysis, elevated liver enzymes, low platelet count)[201].

**COVID-19 and liver fibrosis/cirrhosis**

Recently, it has been hypothesized that patients with a hepatic illness have a higher mortality rate after SARS-CoV-2 infection. Non-invasive indices, including the Fibrosis-4 index (FIB-4), the NAFLD fibrosis score (NFS), and the AST to platelet ratio index (APRI), have been developed to determine the severity of fibrosis, which plays a crucial role in assessing liver fibrosis[202]. In a multicenter observational study, Kim S.W. *et al*[203] reported that patients with diabetes mellitus (DM) showed a higher FIB-4 index, serious complications such as severe respiratory failure, venous thromboembolism, hepatic injury, and a high mortality rate compared to patients without DM. Meanwhile, the FIB-4 index might be used to assess the risk of progression to hepatic illness in middle-aged patients with COVID-19[204]. An association was observed between liver fibrosis scores and poor outcomes, and these findings were consistent with previous research that found worse outcomes in COVID-19 individuals with pre-existing chronic liver disorders, including a high proportion of ICU admission and the need for mechanical ventilation[205,206]. An explanation for liver injury could be the presence of high levels of lymphocytes and natural killer cells inside the hepatic tissue[207].

On the other hand, An Y. *et al*[208] conducted a STROBE observational study and reported that patients with liver cirrhosis and COVID-19 were frequently admitted to the hospital

more than those with liver cirrhosis only. Unlikely, in the same study, cirrhotic patients who lacked COVID-19 experienced more severe liver cirrhosis-related consequences and needed immediate treatment. In a multicenter cohort study, Bajaj J.S. *et al*[209] illustrated that those with cirrhosis alone or with COVID-19 had equal death rates, while patients with COVID-19 alone had a greater mortality rate.

**COVID-19 and liver fibrosis/cirrhosis during pregnancy**

As discussed above, having an infection makes pregnant women more susceptible to developing more severe symptoms. Biomarkers such as ALT, AST, ALP, elevated D-dimer levels, fibrin degradation, and prolonged prothrombin time lead to liver injury, liver fibrosis, and liver cirrhosis; hence, increasing the possibility of preeclampsia with HELLP syndrome[180].

**COVID-19 and hepatocellular carcinoma**

8

Hepatocellular carcinoma (HCC) is the third most important cause of cancer-related mortality and the sixth most frequent cancer in the world. SARS-CoV-2 virus infection has recently been considered a risk factor for cancer patients because SARS-CoV-2 might aggravate liver damage in HCC patients[210]. Furthermore, a US multi-center study by Kim D. *et al*[211] reported that having HCC indicates a greater mortality rate in individuals with HCC infected by SARS-CoV-2 than COVID-19 alone, especially in patients with obesity, diabetes mellitus, hypertension, hyperlipidemia, older patients (≥ 65 years), and Hispanic ethnicity. Also, in China, patients with HCC and COVID-19 were shown to be more susceptible to a higher risk of death and admission to the ICU[212]. In parallel, Leo M. *et al*[213] retrospectively analyzed 119 patients with HCC and COVID-19 infection. They found that about one-third of patients required hospital admission. Two-thirds had an elevation of transaminases, particularly ALP, which was independently linked to a high mortality rate, higher C-reactive protein levels, and more severe respiratory failure upon admission to the hospital.

**Liver transplantation (LT) and COVID-19**

According to the American Society of Transplantation, there has yet to be an agreement on the ideal timing of LT in patients infected with SARS-CoV-2. However, it is

recommended that before transplantation, recipients should have a negative SARS-CoV-2 test[214]. Nevertheless, Martinez-Reviejo *et al*[215] determined that, regardless of symptoms at the time of infection, using LT from SARS-CoV-2 positive donors appears to be a safe technique with a low risk of transmission. Furthermore, a multicenter network study by Mansoor E. *et al*[216] found that LT patients with COVID-19 had a substantially larger possibility of hospitalization but not mortality, thrombosis, or ICU admission when compared to those without LT and COVID-19. In contrast, a case-control study by Shafiq M. *et al*[217] stated that regarding death and hospitalization rates, there was no significant difference between the case and control groups in liver enzyme ratios, and both had a normalized value at the time of discharge. In addition, the only difference in the patient's pathological characteristics is the type of liver graft, alkaline phosphatase levels, and lymphovascular invasion[218]. A case-report study indicated that some LT could be successful in active SARS-CoV-2 patients without developing post-operative COVID-19 symptoms[214]. Furthermore, an Italian multicenter series by Romagnoli R.[219] found that liver transplantation from COVID-19-positive donors to informed recipients with SARS-CoV-2 immunity might help increase the safety of the donor pool. Rela M. *et al*[220] reported a successful LT in patients with severe liver failure due to cholestasis with good graft function and recovering function in the native liver remnant.

## VACCINES USED FOR COVID-19 PREVENTION

Recombinant DNA, mRNA, and adenovirus vector-based technologies were the three main methods of vaccine development that demonstrated immediate success. All have been shown to help prevent infections, especially in severe diseases, because breakthrough infections are typically asymptomatic or mild-to-moderate. BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) were emergently approved in the United States as the first mRNA vaccines[221]. Following that, an Emergency Use Authorization (EUA) license was granted for the two most effective adenovirus-based vaccinations in the United States (Ad26.COV2.S) (Janssen-Johnson & Johnson) and Europe (ChAdOx1.nCoV-19; Oxford-Astra Zeneca). Adenovirus-vectored vaccines have

demonstrated effectiveness in China (Ad5-vectored COVID-19 vaccine) and countries that produce traditional, inactivated viral vaccines. The most frequently used COVID-19 vaccinations are intramuscular injections, and a first dose is recommended to be followed by a second dose within three to four weeks. Currently, a booster dose is recommended administrated after six months of the initial immunization. Individuals 18 years of age and older may get a booster dose of the Johnson & Johnson COVID-19 vaccination 2 months following the initial single dose[222,223].

**Pfizer-BioNTech vaccine (BNT 162b2)**

An intramuscular mRNA vaccine called BNT 162b2 is administered in two doses (30 µg per dose) at 21-day intervals. The vaccine is accessible in multidose vials and must be refrigerated at a temperature between 60 and 80 °C[224], which might present a logistical challenge in developing nations. According to phase I/II/III, randomized, placebo-controlled trials published in December 2020, the FDA approved it for emergency use[225]. In the study, 43,448 volunteers were randomly assigned in a 1:1 ratio to the vaccination arm and the placebo arm. Compared to the placebo, the vaccination showed a 95% efficiency in preventing COVID-19, and this efficacy was maintained for subgroups based on age, sex, BMI, ethnicity, and comorbidities. Local site responses were the most prevalent adverse effects. Young patients were more likely to experience systemic symptoms such as fever, joint discomfort, and chills, which increased following the second dosage[226]. Just three individuals with moderate or severe liver disease were included in the trials, with 214 participants having mild liver disease. The virological status and disease severity of patients with HBV and HCV infections were included; however, it was unknown how severe their conditions were. Furthermore, immunosuppressive drug users were excluded. Hence, more information is required concerning people with liver illnesses[226,227].

**Moderna vaccine (mRNA-1273)**

The mRNA-1273 is another mRNA vaccination given in two doses of 100 µg each, separated by 28 days. Based on phase III randomized placebo-controlled trial published in December 2020, in which 30,420 participants were randomly allocated to the

immunization and placebo groups in a 1:1 ratio, the FDA approved the vaccine. The effectiveness of the vaccination in preventing COVID-19 was 94.1%. Only the placebo group experienced severe COVID-19, resulting in one participant's death. Serious, unanticipated adverse reactions to vaccinations were more frequent in the vaccine group, but none were fatal or forced to be completed until the research's end. After the second dose and in younger people, the unwanted local and systemic responses were more prevalent[228,229]. Although the liver condition was not specified, the study included 196 individuals with liver disease (divided equally between the vaccination and placebo groups). Participants in the experiment who were on systemic immunosuppressive medication were not allowed. For individuals with hepatic illness, no independent efficacy and safety data were available[228].

**ChAdOx1nCoV-19 vaccine (AZD1222)**

ChAdOx1 nCoV-19 vaccine (AZD1222) was created by the University of Oxford, which uses a replication-deficient chimpanzee adenovirus as a vector containing the gene encoding for the SARS-CoV-2 spike glycoprotein. Storage conditions may be kept between 2 and 8 °C and are less strict than mRNA vaccines. AstraZeneca and Serum Institute of India produce it (SII). In December 2020, the UK granted emergency use authorization for the vaccine produced by AstraZeneca. The vaccine, produced by SII under the brand name COVISHIELDTM, was approved for use in India by the Drug Controller General of India (DCGI)[230]. Two intramuscular vaccine doses, each containing 0.5 mL, were given over a 4–6 weeks interval. In patients who got a single dose, antibody responses peaked on day 28, and in individuals who received a booster dose four weeks later, they peaked on day 56[230,231]. A pooled intermediate analysis of four randomized controlled trials by Voysey *et al* conducted in Brazil, South Africa, and the UK, which included 23,848 people, was used to support the authorization. Of these, 11,636 patients were included in the interim study. The experiment showed total vaccination effectiveness of 70.1%. After 21 days following immunization, 10 COVID cases were recorded; all were in the control group and included two cases of severe COVID and one case of death. In addition, only three of the 175 cases with adverse effects

might have been caused by vaccination[232]. Individuals with hepatic disorders were mostly excluded from the 4 studies described above. Patients with severe liver diseases were not included in the trials in the UK and Brazil, although the severity standards were unclear. Furthermore, individuals using immunosuppressive drugs and those with alcohol dependence were excluded. Abnormal LFTs, Australian antigen-positive status, CLDs, and alcohol misuse were listed as exclusion criteria in a South African study. Only two individuals (one from each vaccination and control group) had abnormal liver function[232].

**Janssen vaccine/Ad26.COV2.S**

This full-length SARS-CoV-2 S protein-containing non-replicating human adenovirus type 26 triggers an immune response to the SARS-CoV-2 infection. The SARS-CoV-2 virus is prevented from invading type 2 alveolar cells in the lungs by an antibody directed against the S protein, lessening the severity and morbidity of the infection[233]. Adjuvant properties, scalability, and broad tissue tropism are benefits of adenoviral vectors[234]. Since these labs need biosafety level 2 certification, vaccine production will likely go more slowly during this pandemic. Additionally, a person with immunity to viral vectors would reduce the vaccine's efficacy. Employing the chimpanzee adenovirus (ChAdOx1), which serves as an alternative to the human Ad vector and does not confer any immunity on humans, Oxford/AstraZeneca could overcome this drawback[235,236].

Moreover, Sadoff *et al* revealed that a single-shot Janssen vaccination prevents severe SARS-CoV-2 infections. A total of 43783 seronegative volunteers participated in this study, and they were separated into two age groups: group 1 (18-59 years old) and group 2 (60≥ years old). These participants were randomly divided into two groups of like-minded individuals in a 1:1 ratio, one receiving the placebo and the other the vaccination[233]. The study group collected 468 confirmed cases after receiving the vaccination for 14 days. A total of 464 cases, including 116 from the vaccination group and 348 from the placebo group, were mild to moderate in severity, indicating an effectiveness of 66.9%. More than 66 moderates to severe-critical cases were confirmed to belong to the vaccine group after 28 days of follow-up, compared to 193 cases that

belonged to the placebo group. Moreover, less severe-critical cases were observed among older patients than younger patients, suggesting possible early protection from the vaccine, especially in the elderly. The effectiveness of the immunization was equal across all age groups after 28 days[233].

**Sinopharm COVID-19 vaccine (Sinovac)**

At least five distinct COVID-19 vaccines, including conventional inactivated viral vaccines and vaccines based on an adenovirus vector, have been created and given the go-ahead for use in China. The safety and efficacy of the majority have not been extensively reported. As part of its international COVID-19 immunization global project known as COVAX, the WHO has authorized two vaccines, the Sinopharm, Beijing, and Sinovac Corona Vac vaccines, both traditional inactivated viral vaccines, are essential to China's ambition to immunize most of its inhabitants by 2022[237]. After two dosages, the efficacy rates in clinical trials examining their safety and effectiveness from various regions of the world range from 50% to 91%. Other nations use these vaccinations, including Russia, Turkey, Brazil, Chile, Argentina, Peru, Mexico, Egypt, the UAE, Jordan, Morocco, Indonesia, and Pakistan. Although the range and incidence of adverse effects following the Sinopharm and Sinovac COVID-19 vaccinations are not documented, the methods of manufacture would imply that these vaccines are generally safe and unlikely to cause hepatocellular damage [222,238,239].

Patients with CLDs are particularly susceptible groups to increase the risk of death and more severe types of COVID-19. Many procedures or treatments for this demographic were postponed due to hospital overcrowding or to avoid putting patients at further risk. This population requires specific attention due to their underlying condition. Therefore, for these patients, immunization should also be a top priority. Interestingly, vaccination appears to be safe in stable CLDs[224]. Additionally, immunization priority was given to the high-risk liver disease such decompensated cirrhosis, liver cancer, and liver transplant recipients. They should receive the vaccination faster when their scores are higher. Indeed, the severity of the immune response induced by vaccine in these participants is unknown, and it is anticipated that it will be insufficient given their

underlying illnesses and treatments. The mRNA COVID-19 vaccines are especially remarkable since they are expected to have favorable, safe, and effective characteristics in these individuals[240]. Accordingly, to get COVID-19 vaccinations, patients with CLDs receiving medical care do not need to cease their medication. Besides, patients with HCC receiving systemic or locoregional therapy can get the vaccine without interrupting their medical care. Nevertheless, immunization should be postponed until the situation is stabilized in recent disease or fever cases. Intriguingly, immune-related adverse events are a potential outcome of vaccination interactions with immune checkpoint inhibitors (ICI), which raises concerns about their usage in patients with certain liver disorders (such as HCC) and calls for more research[241]. Influenza and pneumococcal vaccines are recommended for patients with advanced liver disorders to avoid lower immunogenicity in liver disease patients[242,243].

Despite the lack of long-term safety evidence about liver diseases patients vaccinated by SARS-CoV-2 vaccines, it is crucial to balance the potential benefits of vaccination against any possible risks, especially considering the catastrophic implications of SARS-CoV-2 infection in at-risk groups. When new vaccines are introduced, evaluation of safety and immunological response to immunization in individuals with liver disease should be conducted[244]. National and international perspective registries should start as quickly as possible, ideally without governmental obstacles. Individuals at risk should prioritize SARS-CoV-2 infection prevention by vaccination, given the promising short-term safety results of the recently approved vaccines[245].

## CONCLUSION

Hepatic injuries have been approved to be associated with SARS-CoV-2 infection. Indeed, several factors have been embedded in the pathological forms of SARS-CoV-2 hepatic injuries, including viral tropism, cytokine storm, hypoxia, endothelial cells, and even some drugs that treat COVID-19. In addition, previous studies have proved that pregnant women and neonates with hepatic illness are risky for COVID-19 complications. Due to the fast spread of new SARS-CoV-2 strains, vaccines were administered and developed

accordingly. In the present review, we believe that patients with CLDs especially those have severe cirrhosis, liver decompensation, and hepatobiliary cancer should be given a priority to get SARS-CoV-2 immunization. Since it is unknown whether vaccination gives sterilizing immunity and inhibits transmission from asymptomatic patients, preventative measures, such as wearing masks, proper hand washing, and social seclusion, remain of utmost relevance.

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|---|---|---|
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| 17 | Ladislav Štěpánek, Magdaléna Janošíková, Marie Nakládalová, Lubomír Štěpánek et al. "Relationship between Acute-Phase Symptoms and Immunoglobulin G Seropositivity up to Eight Months after COVID-19", Medicina, 2022<br>Crossref | 15 words — < 1% |
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| 23 | Fares E M Ali, Zuhair M Mohammedsaleh, Mahmoud M Ali, Osama M Ghogar. "Impact of cytokine storm and systemic inflammation on liver impairment patients infected by SARS-CoV-2: Prospective therapeutic challenges", World Journal of Gastroenterology, 2021<br>Crossref | 13 words — < 1% |

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|---|---|---|
| 24 | Mohamed Rela, Muthukumarassamy Rajakannu, Fadl H. Veerankutty, Mukul Vij, Ashwin Rammohan. " First report of auxiliary liver transplantation for severe cholangiopathy after ‐2 respiratory infection ", American Journal of Transplantation, 2022<br>Crossref | 13 words — < 1% |
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