Journal of Medical Microbiology and Infectious Diseases

JoMMID
ISSN: 2345-5349
eISSN: 2345-5330

Correlation of SARS-CoV-2 Infection with Hepatitis and Liver Disorders

Kimia Kardani[1], Azam Bolhassani[1*], Mona Kardani[2], Elnaz Agi[2]

[1]Department of Hepatitis and AIDS, Pasteur Institute of Iran, Tehran, Iran; [2]Iranian Comprehensive Hemophilia Care Center, Tehran, Iran

ARTICLE INFO

Review Article

Keywords: SARS-CoV-2, COVID-19, Liver disorders, Hepatitis, Mechanism of action

Received: 12 Jun. 2020
Received in revised form: 06 Aug. 2021
Accepted: 11 Aug. 2021
DOI: 10.52547/JoMMID.9.3.122

***Correspondence**
Email: azam.bolhassani@yahoo.com; A_bolhasani@pasteur.ac.ir
Tel: +982166465132
Fax: +9866953311 Ext. 2240

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ABSTRACT

The coronavirus infectious disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a severe global health challenge. The primary target for this virus is the lung. However, SARS-CoV-2 can also attack other organs, including the kidney and liver. Some COVID-19 case reports demonstrated elevated liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. Indeed, higher levels of liver enzymes occur in severe cases compared with mild to moderate cases. The relationship between liver injury and COVID-19 might be due to various possible reasons such as reactivation of pre-existing liver disease, viral replication in hepatic cells causing direct cytotoxicity, liver ischemia and hypoxia, cytokine storm, and drug-induced liver injury (DILI). Thus, hepatitis prevention and care services are necessary during the COVID-19 pandemic. For instance, drugs that might reactivate hepatitis B should not be prescribed for treating COVID-19. Generally, the long-term effects of SARS-CoV-2 on human health and various organs are not well understood. This review briefly discusses the relationship between SARS-CoV-2 and liver injury (hepatitis), coinfection of hepatitis and COVID-19, and SARS-CoV-2 infection in autoimmune hepatitis.

INTRODUCTION

The coronavirus infectious disease-2019 (COVID-19) is caused by a new member of the *Coronaviridae* family, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This novel virus was primarily isolated from an infected individual in Wuhan city, China, in December 2019 [1]. Common symptoms associated with COVID-19 are fatigue, dry cough, fever, loss of smell, stuffy nose, loss of taste, and pharyngitis. Older patients, particularly with diabetes mellitus, coronary heart disease, and hypertension, are known as high risks of lethal disease progress with a mortality rate of more than 50%, while the mortality rate of the disease was about 2-5% in the general population [2, 3]. Although the primary target for SARS-CoV-2 is the lung, this virus can invade several other organs such as the kidneys, cardiovascular system, and liver [4].

Individuals suffering from COVID-19 may establish different degrees of liver dysfunction/injury. About 11% of subjects with COVID-19 infection had liver comorbidities [5]. In addition, COVID-19 could trigger liver injury with elevated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in 35% and 28% of patients, respectively. These changes predominantly occur in individuals admitted to the intensive care units (ICU) [6-8]. In another study, the ALT and AST ≥40U/L were observed in 22.2% and 21.3% of patients, respectively [9]. Enhanced liver enzymes were more frequent in males and severe disease conditions compared to mild cases. Also, low levels of albumin are a marker of severe infection and poor prognosis [10]. **Figure 1** indicates the possible causes of non-viral and viral hepatitis and SARS-CoV-2 effects on the liver.

World Health Organization (WHO) aims to eliminate viral hepatitis until 2030, which means the number of newly infected subjects, and related mortality should be reduced by 90% and 65%, respectively. This program covers various approaches, including diagnosis, treatment, vaccination against hepatitis B virus (HBV), preventing transmission from mother to child, and blood safety [11, 12]. Although scientists have recently focused on developing effective drugs and vaccines for COVID-19, other diseases and pathogens should be considered, as well [13]. Unfortunately, some agents such as social

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distancing may impact on diagnosis and treatment of other diseases. Enhancing public awareness plays a vital role in viral hepatitis elimination programs, resulting in more cases [14]. The long-term effects of COVID-19 are still unknown. As the number of infected people soars, more abnormalities in liver function are observed [15-17]. Indeed, SARS-CoV-2 uses the angiotensin-2 converting enzyme (ACE2) receptor to attack the host cells. *Ex vivo* studies indicated that SARS-CoV-2 could selectively target the liver, especially cholangiocytes, through ACE2, and thus hepatobiliary injury is probable [18]. Moreover, lymphopenia occur in 63%-70.3% of COVID-19 patients [19]. In severe cases of COVID-19, liver dysfunction was associated with significant activation of coagulative and fibrinolytic pathways and altered profiles of platelets, neutrophils, and lymphocytes [20].

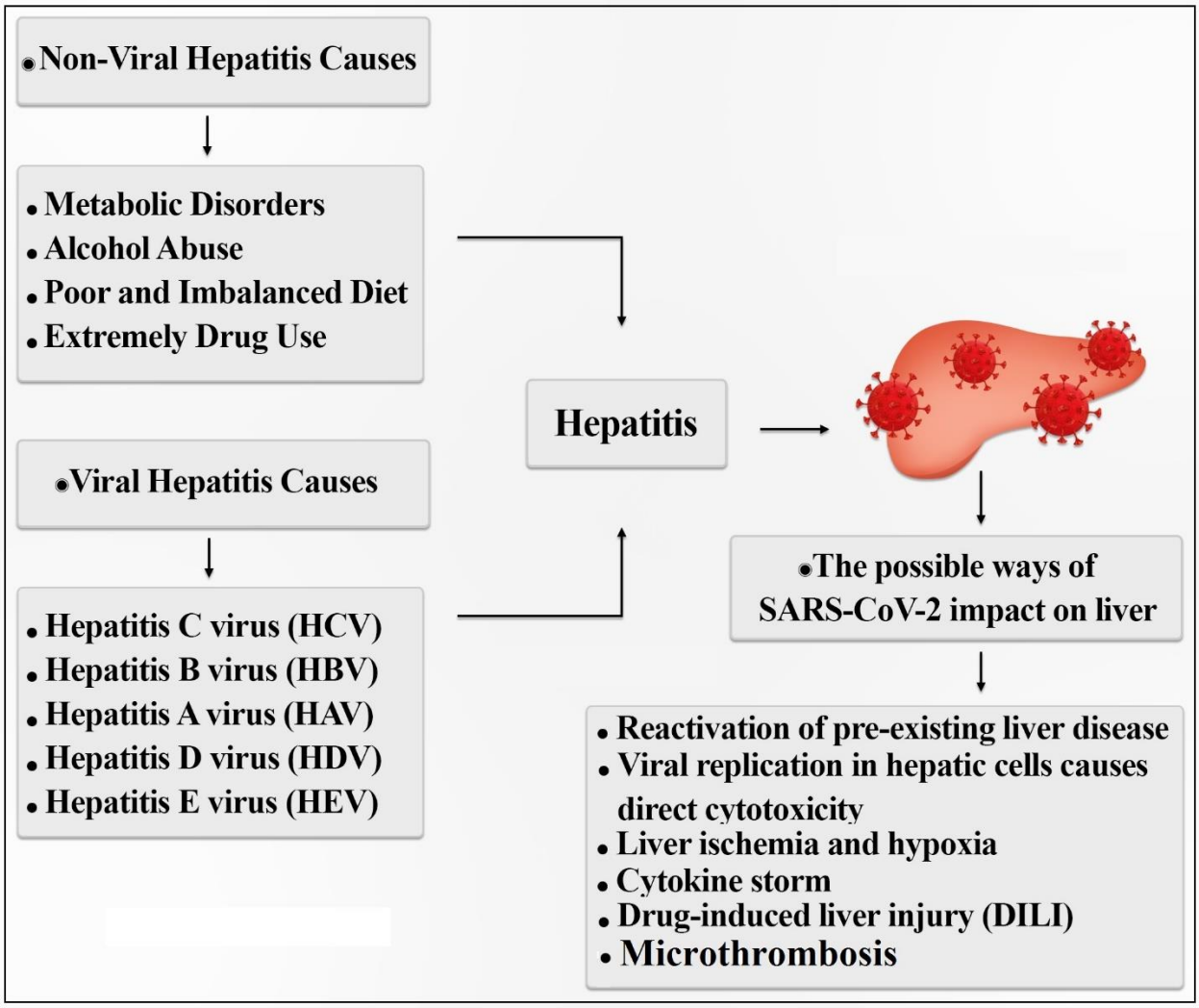

Fig. 1. The possible causes of non-viral and viral hepatitis, and the proposed approaches of SARS-CoV-2 effects on liver

On the other hand, chronic liver disease patients with impaired immunity due to classical hepatitis viruses, other hepatotropic virus infections, and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis were more susceptible to COVID-19 [21]. There are different treatments for COVID-19; some might be associated with hepatotoxicity. Further studies should focus on the causes of liver injury in COVID-19 and the effect of existing liver-related comorbidities on the treatment of COVID-19 [22]. The reports showed that SARS-CoV-2 might induce apoptosis in liver cells and increase inflammatory mediators like IL-1, IL-6, and IL-10, resulting in damaging hepatocytes or hepatic steatosis. The fatty liver can influence the severity of COVID-19 [23]. Herein, we will summarize and discuss the relationship between hepatitis or liver injury and SARS-CoV-2 infection.

Characteristics and Pathogenesis of SARS-CoV-2

Coronaviruses (CoVs) are enveloped positive-sense single-stranded RNA viruses extensively distributed in mammals such as humans, leading to human respiratory tract or animal intestinal infections [24-26]. The CoVs are

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serologically and genotypically classified into four main subfamilies, i.e., α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus. The α-coronavirus and β-coronavirus can cause infection in humans [27, 28].

The SARS coronavirus (SARS-CoV), MERS coronavirus (MERS-CoV) and SARS-CoV-2 are members of β-coronavirus [29]. Furthermore, SARS-CoV and SARS-CoV-2 share ~79% genome sequence identity [30]. The SARS-CoV-2 has 5' (265 nucleotides) and 3' (229 nucleotides) terminal sequences common among β-coronaviruses. The genomic RNA of SARS-CoV-2 codes both structural and non-structural proteins that are responsible for diverse functions. The 5' terminal region of the genomic RNA contains accessory genes encoding the non-structural proteins that contribute to genome transcription and replication [31-33]. Moreover, the 3' terminal region of the genomic RNA encodes structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [34-36].

The S protein is responsible for identifying and binding to C-type lectin (L-SIGN or CD209L) and angiotensin I converting enzyme 2 (ACE2) receptor (10-fold greater affinity than SARS-CoV), and invades the host cell through clathrin-mediated endocytosis [37-39]. Subsequently, the virus internalization occurs, and the virus recruits the host cell's reproductive machinery to generate more viral copies, then infect other host cells. Additionally, the virus recruits protein cleaving enzymes, cofactors, furin, and transmembrane proteases serine 2 (TMPRSS2) to cleave viral S protein and facilitate the virus-cell interaction [40, 41]. **Figure 2** shows the schematic model of the SARS-CoV-2 life cycle in the host liver cells.

Liver dysfunction and Hepatitis

The liver is a master gland of the body that conducts critical functions in cell homeostasis [42-44]. The metabolism of lipids, carbohydrates, and amino acids happens in the liver. Also, this organ detoxifies xenobiotics and endogenous residues. The liver can also support the digestive and hematopoietic systems. On the other hand, the liver acts as an immune-vigilant element and generates acute-phase proteins in inflammatory responses [21, 44-47]. The rate of people suffering from liver dysfunction is increasing globally. Indeed, liver dysfunction is the 9th leading cause of death in high-middle and low-middle income countries [48]. Moreover, hepatitis is a general term involving the inflammation of the liver established by wide-range reasons comprising both non-communicable (*e.g.*, drugs, autoimmune diseases, alcohol, fatty liver, and metabolic diseases) and communicable (*e.g.*, bacterial, parasitic, fungal, and viral pathogens) diseases [49, 50]. Hepatitis with a non-viral origin is emerging as a significant threat to public health. Several etiologies such as metabolic disorders, alcohol abuse, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH), insufficient and imbalanced diet, and excessive drug use [51-54] contribute to the development of chronic cirrhosis and hepatocellular carcinoma (HCC) in certain patients [55-57]. Viral hepatitis is caused by hepatotropic viruses such as hepatitis C virus (HCV), hepatitis B virus (HBV), hepatitis A virus (HAV), hepatitis D virus (HDV), and hepatitis E virus (HEV). These viruses can increase liver disease with the sign of nausea, fatigue, abdominal pain, and malaise jaundice [49, 50]. In 2015, 1.34 million deaths occurred due to viral hepatitis. Most of the viral hepatitis deaths in 2015 were due to chronic liver diseases (~720,000 deaths for cirrhosis) and primary liver cancer (~470,000 deaths for hepatocellular carcinoma) [58].

Hepatotropic viruses

Hepatitis C virus (HCV) belongs to the genus *hepacivirus* in the *Flaviviridae* family. HCV has an enveloped positive-sense single-stranded RNA genome containing about 0.6 kb nucleotides [59]. The RNA genome of HCV encodes ten viral proteins such as structural proteins (Core, E1, and E2) and non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7) [60, 61]. In addition to hepatocytes, the primary target cells, infection of dendritic cells (DCs) and B-cells have also been reported [62]. Various cellular factors such as CD81, scavenger receptor type B1 (SRB), and claudin-1 are required for virus entry into hepatocytes [63, 64]. Inflammatory immunity against viral core proteins and the antigens expressed on the surface of HCV-infected hepatocytes leads to hepatocyte injury [65]. Moreover, acute HCV (AHC) infections are commonly asymptomatic [66]. HCV infections progress to chronic in approximately 70%-80% of infected individuals. On the other hand, spontaneous viral clearance (SVC) occurs in 25%-40% of individuals within 12 months of infection [64, 67, 68]. The cases with cirrhosis and chronic hepatitis C (CHC) are at a high risk of hepatocellular carcinoma and liver failure [64].

Hepatitis B virus (HBV) belongs to the *Hepadnaviridae* family [69, 70], and its genome contains a partially double-stranded relaxed circular DNA (rcDNA) with approximately 3200 bp nucleotides. The rcDNA of HBV encodes four overlapping frame-shifted reading frames, including the surface (S) gene, core (C) gene, X (X) gene, and polymerase (P) gene [71, 72]. After virus entry, the rcDNA is delivered to the nucleus and changed into complete double-stranded DNA [73]. However, other genomic forms of DNA persist. Moreover, the mutated viral proteins are produced to contribute to hepatocarcinogenesis [74]. The probability of HBV infection relies on age. In most cases, perinatal infection results in chronicity, while the infection in adults in most cases is controllable. This difference is might be due to various immune maturities between young children and adults [75].

Hepatitis A virus (HAV) establishes only acute hepatitis and belongs to the *Hepatovirus* genus in the

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Picornaviridae family. HAV has a positive-sense single-stranded RNA genome containing about 7500 nucleotides and includes a single large open reading frame encoding a polyprotein. The RNA genome of HAV is packaged with icosahedral capsid composed of sixty copies of each VP1, VP2, and VP3 protein, which are major structural proteins of HAV [76].

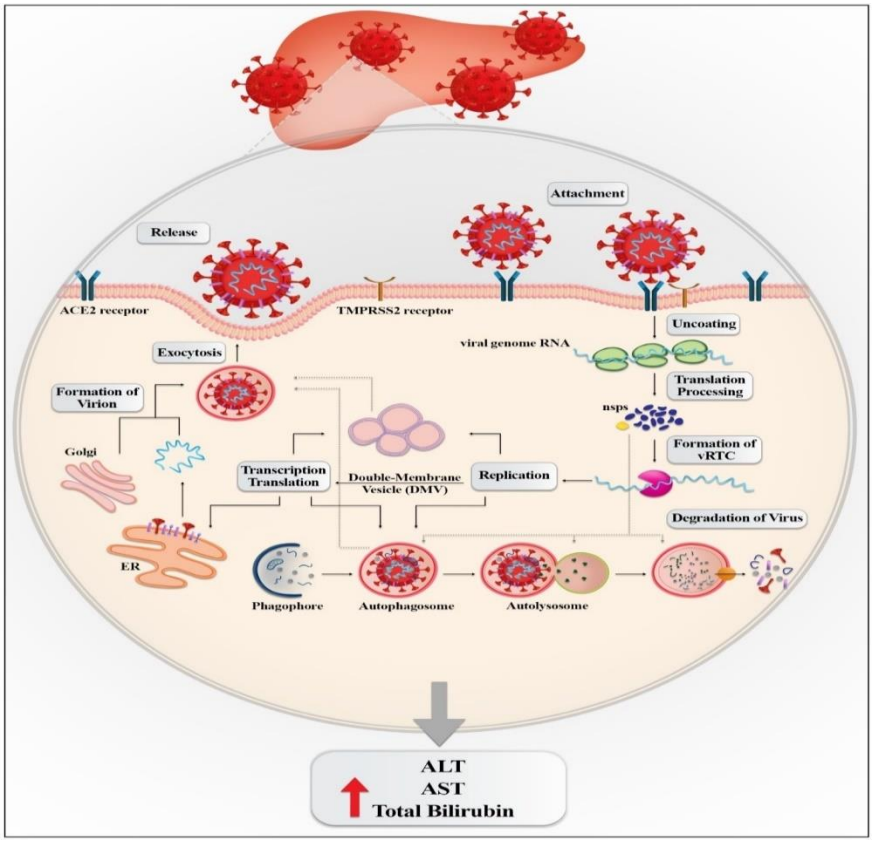

Fig.2. Schematic model of SARS-CoV-2 life cycle in the host liver cells: The spike (S) protein of SARS-CoV-2 is first attached to host liver cells (hepatocytes) through ACE2 receptor. Then, the transmembrane serine protease 2 (TMPRSS2) cleaves the S protein. Next, the entry of the virus occurs. After virus uncoating, the viral RNA genome (vgRNA) is released, and then the ribosome translates vgRNA into pp1a, and pp1ab which is cleaved into non-structural proteins (nsps). Subsequently, assembly of the replication/transcription complex (vRTC) of the virus, nsp6 (in yellow color), leads to the formation of autophagosome for providing a place for viral replication. In addition, replication of vgRNA can take place in double-membrane vesicles (DMV). Inhibition of autophagosome/lysosome expansion mediated by nsp6 can avoid degradation of the virus. Moreover, the synthesized structural and accessory proteins are assembled to form the nucleocapsid and envelope of the virus at the ER-Golgi compartment. Finally, the mature virions are released via the exploitation of the vesicular system of the host. Autophagosomes and DMV can be utilized by the virus for exocytosis and releasing the mature virions.

Hepatitis D virus (HDV) can only infect people who already are HBV-infected [77], but the proportion of deaths because of HBV in which HDV can be a cofactor has not yet been estimated by WHO. In 1980, HDV was shown to rely on envelope proteins of HBV for assembly of progeny virus and infection of susceptible cells [78]. HDV contains a circular genomic RNA of ~1700 bp size, a genome smaller than other infectious viruses. HDV exhibits similarities to non-coding RNAa recognized as viroids that are pathogenic for plants [79]. Circular genomic RNA of HDV encodes one protein (S-HDAg). During viral replication, S-HDAg is required to accumulate processed HDV RNA transcripts [80] and synthesize a longer form of S-HDAg (large HDAg or L-HDAg). The L-HDAg form contains 19 extra amino acids at its C-terminal and is required for the new virus assembly mediated by the envelope proteins of HBV [79, 81].

Hepatitis E virus (HEV) causes primarily acute hepatitis and belongs to the *Orthohepevirus* genus in the *Hepeviridae* family. The genus *Orthohepevirus* includes A, B, C, and D species, among which only the species A is transmitted to humans [82, 83]. The genome of HEV is a positive-sense single-stranded RNA of ~7.5 kb long containing a short 5'non-coding region capped with 7-methylguanosine, a short 3' non-coding region that ends in poly (A) tail, and three open reading frames [84]. As known, infection with HEV causes an acute, self-limiting

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form of liver inflammation. Acute hepatitis can be promoted to cirrhosis, chronic hepatitis, liver failure, and acute-on-chronic liver failure [85].

How can SARS-CoV-2 influence the liver?

The liver biopsy specimens of people who died of severe COVID-19 infection indicated mild lobular and portal activity and moderate microvascular steatosis suggesting the injury by either drug-induced injury or SARS-CoV-2 [86]. The significant liver injury patterns of SARS-CoV-2 occur in chronic liver disease (CLD) patients, with or without cirrhosis. The CLD patients with diabetes and obesity were more susceptible and should be intensely monitored for COVID-19 infection [87]. Up to now, various mechanisms have been proposed: (A) reactivation of pre-existing liver disease; the patients with pre-existing chronic liver disease are more susceptible to liver injury caused by SARS-CoV-2 [88]. In addition, certain drugs such as tofacitinib, dexamethasone, baricitinib, and tocilizumab likely cause HBV reactivation and subsequent deterioration of liver function [89-91]. (B) Direct cytotoxicity via **v**iral replication in hepatic cells; SARS-CoV-2 binds to the target cells via angiotensin-converting enzyme-2 (ACE2) receptors, and this receptor is expressed in the liver, especially in biliary epithelial cells [92]. The elevation of ALT and AST levels has been observed in COVID-19 patients, indicating some degrees of liver damage caused by SARS-CoV-2 [93]. (C) Liver ischemia and hypoxia; the COVID-19 causes respiratory failure. Thus, anoxia leads to hypoxic hepatitis in severe cases. In detail, the liver is protected from ischemic damage via two routes of oxygenation, i.e., redundant blood flow from the hepatic artery and the portal vein. The hepatic artery and the portal vein contribute to 20%-25% and 75%-85% of liver blood supply, respectively [94]. The hepatic blood flow is reduced during systemic stress and is inadequate to provide the liver requirements. The inability of the liver to increase the oxygen extraction sufficiently results in hepatocellular hypoxia. Hypoxic liver damage remarkably elevates calcium overloading, aminotransferase, metabolic acidosis, and changes the mitochondrial membrane permeability [94, 95]. (D) Cytokine storm: extreme physiological stress may disrupt liver functions such as detoxification of the intestines-originated xenobiotics in portal blood. One of these solid physiological stresses is cytokine storm which led to a hyper-inflammatory situation followed by organ damage [96-98]. In this regard, an uncontrolled overproduction of inflammatory cytokines, *i.e.*, cytokine storm, results in acute respiratory distress syndrome (ARDS) and acute lung injury. The release of high levels of multiple cytokines, including IL-10, IL-7, IL-6, IL-2, GM-CSF, IP-10, TNF-α, MIP-1α, and MCP-1, occur in individuals with severe COVID-19 [96, 97]. Meanwhile, the immune system tries to suppress and eradicate the SARS-CoV-2 virus, and immunopathologic damage happens in organs and tissues [99]. The high levels of inflammatory cytokines result in more significant tissue and organ injury, and finally, death. Hence, a cytokine storm could potentially damage specific organs such as the lungs, gut, and liver resulting in death [95, 100]. In addition, the inflammation biomarkers such as serum ferritin, IL-2, IL-6, C-reactive protein (CRP), D-dimer, and lactate dehydrogenase (LDH) are significantly raised in severe COVID-19 cases [101, 102].

(E) Drug-induced liver injury (DILI): various medications, including antivirals, antibiotics, steroids, and antipyretics, are utilized to treat COVID-19 or alleviate the symptoms. Some of these medications for COVID-19 are potentially hepatotoxic in some instances. Histology demonstrated mild hepatic inflammation and moderate microvascular steatosis, likely due to drug-induced liver injury [100]. These drugs are paracetamol, remdesivir, oseltamivir, tocilizumab, arbidol (also known as Umifenovir), chloroquine, hydroxychloroquine, and lopinavir/ritonavir [5, 103, 104]. Moreover, while acetaminophen was confirmed as the most common cause of acute liver failure and toxicity, this medication is still a choice to treat fever and myalgia associated with COVID-19 [104, 105]. The Food and Drug Administration (FDA) approved remdesivir to treat individuals with COVID-19 on October 22, 2020 [106, 107]. Previously, remdesivir was deployed for the treatment of Ebola and hepatitis C (no appropriate success). Although no curative, it reduces the recovery time in hospitalized COVID-19 patients with low respiratory tract infections [108, 109]. Furthermore, the reports indicated elevated liver enzymes in COVID-19 patients receiving remdesivir [106, 107]. DILI was reported in 37.2% and 15.2% of cases treated with lopinavir/ritonavir and remdesivir, respectively [110].

COVID-19-induced hepatitis (CIH), defined as "benign new transient hepatitis" in a SARS-CoV-2 patient, was characterized by different symptoms including gradual onset, elevated AST and ALT, dilated sinusoids with lymphocytic infiltration of liver parenchyma, non-obstructive jaundice, stable underlying liver disease, and no radiological new hepatobiliary changes [111]. On the other hand, due to existing metabolic abnormalities, nonalcoholic fatty liver disease (NAFLD) seems to contribute as a potential risk factor to severe SARS-CoV-2 infection. This is because of the interaction of chronically active inflammatory pathways in NAFLD- and COVID-19-associated acute cytokine storm. The relationship between NAFLD and severe COVID-19 was studied independent of obesity as a significant risk factor for both NAFLD and COVID-19. NAFLD showed to be a significant predictor of severe COVID-19 even after adjusting for the presence of obesity. The exact relationship between liver fat and COVID-19 should be further investigated [23].

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Atypical elevated liver enzymes in COVID-19 patients

Enhanced liver enzymes due to hepatic injury are common among COVID-19 cases with and without chronic liver diseases [112-116]. For the first time, Chen *et al*. (2020) reported abnormal elevation of liver enzymes. Among 99 COVID-19 patients, ~43.4% had enhanced serum levels of AST, ALT, and LDH. Most of the cases had a mildly elevated aminotransferase, and only one patient had high levels of ALT (7590 U/L) and AST (1445 U/L) [117]. In another report, among 12 COVID-19 severe cases, only one had an abnormal elevation of liver enzymes (AST: 62 U/L; ALT: 107 U/L) [118]. Moreover, in Wuhan, among 305 COVID-19 cases, 119 had enhanced ALT, AST, and bilirubin levels. Also, 19 and 24 cases had increased AST (80 U/L) and ALT (80 U/L) levels, respectively, whereas only six had an elevated bilirubin level [112]. Also, the first Chinese COVID-19 patient described in the USA with details of liver function tests exhibited enhanced AST, and ALT serum levels from 37 to 89 U/L and from 68 to 203 U/L, respectively [113].

Recently, several reports demonstrated the relationship of severity of COVID-19 infection with abnormal liver biochemistry. A report from 1099 COVID-19 patients in China showed that most of the abnormal levels of liver enzymes occurred in severe patients, i.e., 28.1% and 39.4% of cases had ALT>40 U/L and AST>40 U/L, respectively [9]. Also, among 265 patients in Shanghai, AST and ALT serum levels in severe cases were remarkably higher than those in mild to moderate patients [114]. The cases admitted to the ICU showed higher AST, ALT levels, and total bilirubin [6, 7]. The pathological characteristics of liver changes, *e.g.*, mild lobular and portal activity and moderate microvascular steatosis in the liver, were related to COVID-19 [86]. In fact, the potential liver damage was strongly associated with coronavirus infection [115, 116]. The HBV and HCV infections were described in COVID-19 cases; in 5700 hospitalized COVID-19 patients in the USA, HBV and HCV infections were found in 0.1% and <0.1% of cases, respectively [119]. Furthermore, among 1099 hospitalized patients (n=1099) in Wuhan, 2.1% of cases were HBV-infected, comprising ~2.4% of non-severe and~ 0.6% of severe subjects [9]. In another study in China, among 123 COVID-19 cases, 15 (12.2%) had HBV-infection [120]. In an observational study in two COVID-19-designated hospitals in Wuhu, Anhui province, China, two had HBV infection among 31 corticosteroid-treated COVID-19 cases. The data indicated a delayed clearance of SARS-CoV-2 in cases with HBV infection [121]. On the other hand, the COVID-19 pandemic has affected the programs and efforts to eliminate viral hepatitis globally. Mathematical models estimated excess mortality of 44,800 for HCC and 72,300 for liver-related deaths with a one-year delay of HCV treatment administration [122]. Patients with SARS-CoV-2 and HBV coinfection showed more severe monocytopenia and thrombocytopenia and had a more disturbing hepatic function in albumin production and lipid metabolism [123]. Generally, hepatic symptoms and fever, cough, and dyspnea are common among HBV and HCV patients infected with COVID-19, with a significant risk of mortality was among these individuals. Since about 290 million and 71 million people are affected with HBV and HCV worldwide, respectively, the number of patients with SARS-CoV-2 and HBV and/or HCV co-infections will likely increase [124].

Treatment approaches of cases co-infected with COVID-19 and Hepatitis

Antiviral treatments are first given to COVID-19 cases with mild liver biochemical abnormalities to block viral replication, decrease inflammation, and improve immunity. The enzyme-lowering and liver-protecting drugs are not recommended [125]. In COVID-19 cases with the background of HCV infection, it is more reasonable to postpone HCV therapy until COVID-19 clearance. Moreover, there is a risk of HBV reactivation associated with medications including tocilizumab and corticosteroids, used in the context of COVID-19. Utilizing tocilizumab and prednisone reactivate HBV infection; hence, preventive measures should be adopted against this reactivation [126, 127]. The less toxic medications prescribed for treating COVID-19 patients with advanced liver disease including remdesivir, nitazoxanide+sofosbuvir, ivermectin, tocilizumab, convalescent plasma, and low molecular weight heparin in certain conditions. The advanced liver disease led to portal hypertension and splenomegaly, immune dysfunction, and impaired T cell function. Therefore, when a cytokine storm occurs due to an immune response to COVID-19, the mortality rate can increase in patients with advanced liver disease [98].

As known, several new direct-acting antiviral (DAAs) combinations, including elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir, have been approved for the HCV treatment. The newly approved DAA regimens may be prescribed alongside other medications simultaneously, increasing the potential of pharmacokinetic interactions. Therefore, managing drug-drug interactions (DDIs) with DAAs should be considered a vital issue in HCV therapy. Concerning DDIs, these newly approved DAA regimens were safe [128]. Sofosbuvir, ribavirin, and remdesivir were reported as potent drugs against COVID-19, which bind to COVID-19 RNA-dependent RNA polymerase (RdRp) [129]. Chen *et al.* [126] indicated that the Epclusa (velpatasvir/sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) drugs were very effective due to their dual inhibitory actions on two viral enzymes [126].

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COVID-19 and autoimmune hepatitis

The possible pathogenic mechanisms linking cirrhosis with severe COVID-19 include increased systemic inflammation, cirrhosis-associated immune dysfunction, coagulopathy, and intestinal dysbiosis. Abnormal liver biochemistry values are common in COVID-19 patients. However, liver transplant recipients showed no increased risk of mortality following SARS- CoV-2 infection [130]. Chronic immunosuppression was associated with increased viral infections. However, little was known of the association between immunosuppression and SARS-CoV-2 infection. Gerussi *et al*. (2020) studied the clinical course of patients with immunosuppressed autoimmune hepatitis (AIH) during COVID-19 infection in Italy. Patients under immunosuppressive therapy for AIH showed a disease course similar to that in the non-immunosuppressed population during COVID-19 infection [131]. The pilot clinical experiences demonstrated that immunosuppressed patients' morbidity and mortality rates did not differ significantly from the general population [132]. However, Marjot *et al.* [2021] showed that AIH patients were not at increased risk of adverse outcomes despite immunosuppressive treatment compared to other causes of chronic liver disease (CLD) and matched cases without the liver disease [133].

In conclusion, the reports showed that some COVID-19 patients experience various degrees of liver function abnormalities. Several mechanisms could affect the liver in cases with COVID-19, such as reactivation of pre-existing liver disease, viral replication in hepatic cells causing direct cytotoxicity, liver ischemia and hypoxia, cytokine storm, and drug-induced liver injury. Activation of the immune system and cytokine storm play a prominent role in an immune-mediated process of hepatic injury in COVID-19. The control of cytokine dysregulation at the first stages can be helpful to limit the disease progression. In COVID-19, the liver is the most affected organ apart from the respiratory system; thus, other therapeutic approaches are required for severe cases, particularly those with pre-existing liver disease. Hence, mechanistic understanding of the relationship of SARS-CoV-2 infection with liver injury is vital for the clinical practice of managing COVID-19 patients with hepatic injury. Hepatitis prevention and care services are necessary during the COVID-19 pandemic, such as vaccination of newborns and infants against hepatitis B. Further studies should concentrate on the mechanisms of liver injury in COVID-19 and the impact of liver diseases on COVID-19 treatment in the future.

ACKNOWLEDGMENT

We express our gratitude to Dr. Arash Nikyar for editing the manuscript.

CONFLICT OF INTEREST

We declare that there is no conflict of interest associated with this manuscript.

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Cite this article:
Kardani K, Bolhassani A, Kardani M, Agi E. Correlation of SARS-CoV-2 Infection with Hepatitis and Liver Disorders. J Med Microbiol Infect Dis, 2021; 9 (2): 122-132. DOI: 10.52547/JoMMID.9.3.122

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