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Liver dysfunction-related COVID-19: A narrative review

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Abstract

The coronavirus 2019 disease (COVID-19) is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was designated by the World Health Organization (WHO) as a pandemic on March 11, 2020, which is not seen before. There are no classical features among the cases of the disease owing to the involvement of nearly all body tissues by the virus. Hepatic involvement is one of the characteristics of the COVID-19 course. There are six possible mechanisms of such involvement; direct virus injury, drug-induced effect, inflammatory cytokine storm, hypoxia-ischemic destruction, abnormalities in liver function tests, and pre-exciting chronic liver diseases. Liver abnormalities are seen commonly in the severe or critical stage of COVID-19. Therefore, these abnormalities determine the COVID-19 severity as well as they carry a high rate of morbidity and mortality. The elderly and patients with comorbidities like diabetes mellitus and hypertension are more vulnerable to liver involvement. Another issue that needs to be disclosed is the liver manifestations following the COVID-19 vaccination, such as autoimmune hepatitis. Of note, complete vaccination with third and fourth booster doses is necessary for patients with previous chronic liver diseases or those who have been subjected to liver transplantation. Our minireview aimed to explore the various aspects of liver dysfunction during the COVID-19 course regarding the epidemiological features, predisposing factors, pathophysiological mechanisms, hepatic manifestation due to COVID-19 or following

vaccination, the role of the liver function tests in the assessment of COVID-19 severity, adverse effects of the therapeutic agents of the disease, and prognosis.

INTRODUCTION

The liver plays an essential role in the body. It deserves several physiological processes such as metabolism of the macronutrient, regulation of the blood volume, endocrine control of growth signaling pathways, support of body immunity, metabolism of cholesterol and lipid, and the destruction of xenobiotic materials like certain drugs[1].

Among various causes of liver dysfunction, many viruses might attack the liver directly or indirectly. These include, but are not limited to, hepatitis A (HAV), hepatitis B (HBV), and hepatitis C (HCV). There is approximately 60% of people in the previous pandemic in 2003, which was caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), affected by different involvements of the liver[2]. Hence, from the beginning of the current coronavirus disease-19 (COVID-19), scientists have paid great attention to liver involvement due to the novel coronavirus (SARS-CoV-2). As such, a prior investigation from China reported that around 50% of the individuals with COVID-19 had dysfunction of the liver at a certain point in their disease course[3].

Liver abnormalities associated with COVID-19 might be due to direct liver damage by the SARS-CoV-2, drugs used for the disease, unrecognized previous liver abnormality, cytokine storm, and as an indirect effect to the liver due to involvement of other body systems by the virus like the cardiopulmonary system [4].

Owing to the enormous research belonging to liver dysfunction-related COVID-19 [4-8], we design this narrative review to update and summarize the epidemiological features, predisposing factors, pathophysiological mechanisms, hepatic manifestation due to COVID-19 or following vaccination, the role of the liver function tests in the assessment of COVID-19 severity, adverse effects of the therapeutic agents of the disease, and prognosis.

EPIDEMIOLOGY

The source of SARS-CoV-2 is unknown and spreads quickly throughout the world. The WHO declared that COVID-19 is a pandemic on March 11, 2020 [9]. COVID-19 could be transmitted by two major methods; one of them is direct contact (close contact) from individual to individual through aerosol and respiratory droplets produced by talking, sneezing, and coughing. Another method is indirect noncontact through contaminated objects and surfaces. The incubation period ranges from 1 to 14 days, with a median of 5.5 days [10,11]. Based to the WHO dashboard on August 10, 2022, there were 584,065,952 confirmed cases of COVID-19 globally, with the vast majority from Europe at 243,772,549, the Americas at 172,407,904, and the Western Pacific at 76,247,604. While the total number of cases of deaths across the globe was 6,418,958, with the vast majority of death happening in the Americas (2,797,327) followed by Europe (2,058,965) and South-East Asia (793,446) [World Health Organization. WHO coronavirus disease (COVID-19) situation dashboard. 2022 [cited August 10, 2022]. Available from: https://www.who.int/]. The COVID-19 cases are still sharply increasing, with over three million cases weekly.

A prior study has illustrated that the males are more likely to have abnormal liver biochemical tests related to higher concentrations of C-reactive protein (CRP) and procalcitonin and a longer period time of hospitalization, about 20 days during severe COVID-19 compared to the control group with the normal biochemical test (16 days)[12]. A meta-analysis by Xu *et al* has documented that males were more potential to have severe pneumonia than females[13]. In addition, obesity, older age, and comorbidities were dangerous factors for death among hospitalized SARS-CoV-2 patients[14].

COVID-19 has characterized by rapid transmission through the lack of herd immunity with increased mortality, and the infection is increased in elderly individuals and becomes a greater danger to those who have hypertension, diabetes mellitus, and cardiorespiratory diseases [15–17].

COVID-19 is not occurring in the elderly only but also occurs in the pediatric population with a range of ages between 0–18 years with only 3% involvement. Males

are a slight predominance of infection with 51%. In the same study, it has found that adolescents' ages predominated infection the ages of 15–18 years. It has been reported that COVID-19 gradually decreases with younger ages[18].

CHARACTERISTICS OF SARS-COV-2

SARS-CoV-2 is comprised of the positive sense single-stranded genomic RNA virus (ssRNA). SARS-CoV and MERS-CoV are the original gene viruses that lead to the SARS-CoV-2 pandemic. Other subgenres of Sarbecovirus have caused the infection combined with acute respiratory symptoms in human beings, such as 229E, NL63, OC43, and HKU1. They lead to mild to severe diseases in the infected people[10,19]. The sequence of SARS-CoV-2 spike glycoproteins is significantly similar to the sequence of SARS-CoV spike glycoproteins[20].

The receptor angiotensin-converting enzyme 2 (ACE-2) has accounted as the major viral receptor for SARS-CoV and SARS-CoV-2, and it facilitates into target cells *via* the spike protein of the virus. The mechanism includes the attachment of the surface of the host cell to COVID-19 by linking the surface to the ACE-2 receptor. SARS-CoV-2 gains access to the host *via* the ACE-2 receptor[21,22]. The expression of the ACE-2 receptor is widely shown on the surfaces of various types of human cells, systems, and organs. These include the muscular and nervous system, alveolar epithelial cells in the lungs, nasal and oral mucosa, adipose tissue, bronchial epithelial cells, nasopharynx, enterocytes of the small intestine, adipose tissues, pancreas, liver, brain, lungs, heart, kidney, *etc.*[10,23–25].

The expression of the ACE-2 receptor is mainly in the liver on cholangiocytes (bile duct) (60%) and less expression (3%) on hepatocytes, while there is no expression of ACE-2 in Kupffer cells [26]. COVID-19-related hepatic injury could be defined as any impairment in infected individuals to the liver which occurs during the infection course and treatment phase of COVID-19 with or without the presence of liver disease.

PATHOPHYSIOLOGY

The pathophysiology of liver injury induced by COVID-19 is complex and multifactorial. Other liver diseases should be considered, such as; chronic hepatic disease due to autoimmune or viral disease, metabolic dysfunction-correlated fatty liver disease, cirrhosis, or liver transplant. An autopsy study on tissue from the liver of the COVID-19 subject revealed a relatively low viral titer owing to the absence of a viral inclusion body in the hepatic tissue. However, the pathological evaluation reported two findings; mild active inflammation and moderate microvascular steatosis of the lobular portal part of the liver[27].

The mechanisms of liver injury related to COVID-19 are varied. Six probable mechanisms are proposed to clarify COVID-19 with liver disease, as shown in **Figure 1**:

The hypoxic-ischemic liver injury mechanism; the high level of AST in hepatitis could characterize ischemic hepatitis. The common outcome of COVID-19 is cardiomyopathy which happened in 33% of infected individuals in a series of critically ill US patients[28]. The hepatic ischemia, hypoxia as well as impaired tissue perfusion in the course of COVID-19 could develop as a result of circulatory failure, multiple organ failure, pneumonia-correlated hypoxemia, and respiratory distress syndrome[29]. In mechanically-ventilated patients, high positive end-respiratory pressure and hepatic congestion can also increase the hypoxic damage degree in hepatocytes[30,31].

Direct viral injury: It has been assumed that COVID-19 might cause cytopathic effects. The expression of the ACE-2 receptor occurs during the pathogenesis of liver injury correlated with COVID-19. The reason for that when SARS-CoV-2 enters the liver on cholangiocytes, the spike proteins of SARS-CoV-2 binding to the ACE-2 receptor, and the viral replication will occur *via* interaction between the virus with ACE-2[32]. The expression of ACE-2 in cholangiocytes is considerably higher (about 60%) than in hepatocytes (about 3%)[31,33]. The direct viral injury to bile ductal epithelial cells could result from COVID-19-caused liver injury, which is recognized to have significantly diminished the immune response and liver regeneration[34]. Moreover, it could be clarified by the fact that cholangiocytes have a crucial function in inflammation, liver regeneration capacity, and immune response. The loss of cholangiocytes leads to

hepatocellular damage. The cytopathic effect of COVID-19 might not be the major reason for liver damage due to the previous discrepancy[34,35].

In liver biopsies from two infected individuals with COVID-19 who died, the particles of typical coronavirus were recognized in the cytoplasm of the hepatocytes; therefore, the cytopathic damage could be distinguished through endoplasmic reticulum dilatation, glycogen granule, and mitochondrial swelling[36].

Cholangiopathy is another mechanism to describe COVID-19-correlated liver injury. It is a broad domain of hepatic-biliary symptoms with COVID-19, including cholangiopathy's chronic and infrequent symptoms. It has illustrated that the bile duct structure mimics secondary sclerosing cholangitis (SSC). COVID-19 patients have failed in the ventilator, and circulatory system and then required prolonged support. It is ambiguous at this phase if they were an outcome of direct infection of COVID-19 of the biliary tract and liver or if these demonstrated alterations of biliary tree ischemia. The complete recovery in COVID-19 patients was not reported with the increased concentrations of serum ALP and bilirubin[37,38].

Drug-induced liver injury: COVID-19 requires drugs such as antiviral and antibodies agents (protease inhibitors, azithromycin, receptor antagonist, and monoclonal interleukin IL-6); such agents could cause hepatic injury. For example, Remdesivir is a drug confirmed by the US Food and Drug Administration (FDA) as a cause of liver injury[39]. The COVID-19-associated liver injury might also occur secondary to the effects of potentially hepatoxic of different drugs, such as antivirals, acetaminophen, corticosteroids, immune modulators, and antibiotics, among others. The presence of liver inflammation and microvesicular steatosis characterized by small intracytoplasmic fat vacuoles (liposomes) which accumulate within hepatocytes) in the liver biopsies of individuals infected with COVID-19 might also be drug-associated[27].

The interaction drug-cytochrome P-450 can demonstrate a few hepatic toxicities secondary to such medicines as acetaminophen, lopinavir/ritonavir, azithromycin, and droxychloroquine[26]. In the systematic review by Kulkarni *et al*, which included 20874

patients (107 articles), about a quarter of COVID-19 patients suffered drug-induced liver injury[40].

The histopathological analysis during autopsy for liver biopsy samples from COVID-19 patients recorded nominal lobular and portal activity, simple micro-vesicular steatosis, mitosis, as well as hepatocellular necrosis in the liver tissue, and no viral inclusion bodies. The abnormality of histopathological results may be due to COVID-19-caused liver damage or drug-induced liver injury[41].

Hyper-inflammatory cytokine storm: the concentrations of inflammatory cytokines, including TNF, IL-1, and IL-6, are observed to be increased in COVID-19 patients by around 20% resulting in a cytokine storm. The hepatocyte could be oversensitive to hypoxic hepatic injury during severe COVID-19; the further deterioration of hepatocytes occurs by the immune overreaction resulting in significantly abnormal liver biochemical tests[42]. COVID-19 patients with failure of multiorgan in the intensive care unit (ICU) might be associated with severe liver dysfunction[43]. In addition, the patients of SARS-CoV-2 with raised AST also have increased ferritin, IL-6, C-reactive protein, and lactate dehydrogenase compared to subjects with normal AST[44].

The over-activation of the immune system, which is correlated with COVID-19, might be included in liver injury. A significant increase in serum inflammatory cytokine concentrations, including interferon-γ, IL-1β, IL-10, IL-6, tumor necrosis factor (TNF), and soluble IL-2 receptor, exist in subjects with SARS-CoV-2, particularly those patients with severe pneumonia[45,46]. The result of that is liver injury mediated by the immune system through the stimulation of intrahepatic CD4+ and CD8+ cells, kupffer cells, and T cells leading to dysregulated innate immune response[30,47]. This appearance has also been characterized in infections caused by other viruses such as SARS-CoV and herpes simplex virus, Epstein-Barr virus, cytomegalovirus (CMV), adenovirus, and parvovirus. These viruses target the upper respiratory tract[47].

Patients infected with SARS-CoV-2 might have chronic liver diseases, for example, non-alcoholic fatty liver disease (NAFLD), HBV or HCV, and cirrhosis. In patients with coexisting COVID-19 and previous history of HBV, HCV, and liver cirrhosis, there

might be a synergistic effect between the drugs used for these diseases with the drugs used for the COVID-19 treatment. As a consequence, acute hepatitis happens [48].

All previous findings contribute to the hypothesis of COVID-19-associated liver damage. Another study has reported from post-mortem liver histopathology that microvesicular steatosis could occur with the overactivation of T cells, assuming the liver injury is mediated through the immune system [49]. Endothelitites could be generated due to COVID-19, and damage the liver[50]. The involvement of endothelial cells in ischemia-reperfusion hepatic damage leads to the stimulation of oxidative stress *via* the reaction between the derivatives of nitric oxide (NO) and oxygen species[51].

SARS-CoV-2 RNA was discovered in feces. It appears sensible that the inflammatory mediators and virus are shown in the gut lumen, reaching the liver *via* portal circulation. The viral particles could remove by kupffer cells resulting in a rising inflammatory response[26,50]. The cholangiocyte-related enzymes are GGT and ALP. However, the abnormal concentration of GGT might contribute to acute inflammatory stress due to GTT being known as a delegate biomarker for raised inflammation and oxidative stress[52].

In the case of chronic hepatitis B or C and related to COVID-19, the count of the white blood cells and monocytes have significantly diminished in patients infected with COVID-19 with HBV compared to those in patients with COVID-19 alone, while CD8-T cells level has greatly increased, and HBV patients with COVID-19 infected had a greater danger of thrombocytopenia[53]. In addition, the viral HCV and active infection of HCV have a weak relationship with COVID-19. Mangia and his colleagues have reported that HCV patients have a lower effect of being infected with COVID-19. They suggested that antibodies of HCV act as a protection against COVID-19[54].

The metabolic syndrome nonalcoholic fatty liver disease (NAFLD) which is the most frequent CLD has a highly raised risk for severe COVID-19, it was estimated in a meta-analysis of epidemiological studies with 5.2 fold increased risk of severe COVID-19 [55]. A recent study by Jiling and his colleagues has reported that a significant association was recorded between NAFLD and severe COVID-19 with the risk factors (male sex

and old age) as well the casual risk factor obesity, while the other metabolic perturbations (diabetes Mellitus and hypertension) does not have an association with severe COVID-19[56]. CRP, D-dimer, and ferritin levels as well as lymphocyte and neutrophil count are similar for both NAFLD and non-NAFLD patients. The liver parameters such as serum albumin, ALP, and serum bilirubin levels are comparable across both groups. In contrast, increased concentrations of ALT, AST, and GGT have been observed in NAFLD patients compared to non-NAFLD patients. The mortality and hospitalization stays have not increased in COVID-19 patients with NAFLD based on increased liver parameters [57].

A study by Pan *et al* has illustrated liver injury for COVID-19 patients with NAFLD; it has found that liver injury happened in 50% and 75% of infected persons upon admission and during staying in the hospital, respectively. These findings are due to the increased expression of the ACE-2 receptor as well as chronic inflammation of the liver in NAFLD, which leads to liver injury[58]. In addition, the degree of liver fibrosis in NAFLD may affect the consequence of SARS-CoV-2; such the high or intermediate scores of FIB4 has associated with severe SARS-CoV-2 illness among patients with MAFLD[59].

THE USEFULNESS OF LIVER FUNCTION TESTS IN THE ASSESSMENT OF COVID-19 SEVERITY

The liver injury occurs during the changes in liver function tests above normal ranges; AST > 40 U/L, ALT > 40 U/L (higher than 3 times the upper limit unit of normal (ULN), ALP > 130 U/L (2 x ULN), bilirubin > 1.1 mg/dL, and GGT > 48 U/L (2 x ULN), they are monitoring in patients with asymptomatic-to-severe/critical COVID-19. Despite the accurate impact of SARS-CoV-2 on the liver being unclear, the biochemistries of liver enzymes with SARS-CoV-2 are occurring abnormalities around 15-65% in COVID-19 patients. Liver function is normally impaired in patients with COVID-19 due to abnormal liver biochemical markers, which lead to an increase in the danger of progressing to severe disease during staying in the hospital with cholestasis

hepatocellular injury[60,61]. A retrospective study by Lei and his colleagues documented the liver function tests regardless of COVID-19 severity, AST elevated, followed by an elevation in ALT with a variant concentration in bilirubin. The mortality risk is significantly related to the levels of AST[62].

In the Singhai study, among 600 COVID-19 patients, 416 have mild COVID-19, 23 have moderate COVID-19, and 161 have severe COVID-19. The severity of COVID-19 could be classified: as asymptomatic, mild, moderate, and severe/critical. Mild COVID-19 patients have no pneumonia and minor symptoms; moderate severity COVID-19 patients have respiratory tract symptoms, and fever, and show pneumonia without respiratory distress in imaging; the average hospitalization is 6.98 days. While severe COVID-19 has arterial blood partial pressure/O2 concentration of less than 300 mmHg, more than 50% of lung involvement showed in radiological imaging and lower than 93% of hypoxia and respiratory distress. Critical COVID-19 involved respiratory failure, shock, and multiorgan failure (5%) or death (2.3%); the average hospitalization is 11.41 days. The levels of AST and ALT are highest in moderate COVID-19, ALP is highest in mild COVID-19, and there are no different values in bilirubin between these groups[7,61,63].

The biomarker to diagnose the injury of cholangiocytes is GGT, but it is not raised in most patients. ALP is still at the normal level. While the indices of albumin and total protein (TP) are diminished at admission, indicating that COVID-19 may directly damage the liver. At the same time, the indices of total bilirubin, direct bilirubin, indirect bilirubin, ALT, and AST levels are increased during admission, during treatment as well as hospitalization, the observations have recorded that the aggravated liver dysfunction within increased levels of liver enzymes, AST, and ALT in the COVID-19 course which is associated with COVID-19 disease severity[12,64,65]. CRP level is greatly increased during admission in COVID-19 patients and returned to the normal range before discharge[64].

Liver injury in severe cases was higher than in patients with mild cases and non-severe COVID-19. Severe infection was more probably to have severe hepatic injury compared

to a mild infection. Patients with hypertension or diabetes are generally indicated through an increase in liver enzymes, bilirubin, and ALP and a decrease in albumin (2.6 – 3 g/dL). It could be detected for early severe COVID-19 through the abnormality of the liver test[66–68]. Liver injury with COVID-19 was more frequently found among severe patients compared to non-severe patients and mild COVID-10 (about 45% for severe patients, 15% for mild COVID-19, and 10% for non-severe COVID-19)[69,70]. Pneumonia developed by COVID-19 is associated with a high level of CRP, mildly elevated levels of bilirubin and AST, and a low level of serum albumin, which leads to COVID-19-induced liver dysfunction[64]. Liver abnormalities might occur by tissue hypoxemia and sepsis. The concentration of CRP is elevated in severe patients[71].

A significant correlation between the elevation of AST, ALT, and bilirubin was observed in the critical illness of COVID-19, and they are higher concentrations compared to severe or mild COVID-19. Serum albumin decreased in the critical illness of COVID-19, and it is lower than those in severe COVID-19[72].

EFFECTS OF COVID-19 THERAPEUTIC AGENTS ON THE LIVER

Several therapeutic agents are utilized to treat patients with COVID-19 and correlated manifestations. There is no particular medication for COVID-19 at present, and antiviral drugs account for the significant treatment. These medications consist of antivirals (ritonavir, remdesivir, favipiravir, and lopinavir), antimalarials (chloroquine and hydroxychloroquine), some monoclonal antibody products, acetaminophen, steroids, antipyretics, immune-modulators, and corticosteroids. The liver metabolizes these drugs leading to hepatotoxicity[73]. Paracetamol and acetaminophen are medicines used to block some complications of COVID-19[74]. The use of acetaminophen used as an antipyretic drug causes sudden hepatic failure at high doses, and the treatment doses utilized to heal SARS-CoV-2 may cause abnormal levels of ALT and AST leading to mild liver injury[75].

The safety and effectiveness of ritonavir and lopinavir medicines were examined to treat COVID-19. They are accounted as HIV protease inhibitors to inhibit viral

replication *via* inhibiting the proteolytic cleavage of the polyprotein of virus polymerase[76]. Another study has demonstrated that ritonavir and lopinavir treatment caused increased concentrations of AST, ALT, and total bilirubin in a few infected persons[77].

Remdesivir inhibits viral replication through intracellular transformation to inhibit viral RNA polymerase[78]. The antiviral drug remdesivir antagonists RNA polymerase. It utilizes to heal patients with Marburg virus infection, Ebola virus disease, and hepatitis. Remdesivir has reported *in vitro* efficacy against COVID-19 and is partially metabolized through the cytochrome P450 enzymes[79]. A study by Lee *et al* reported that remdesivir has safety and efficacy properties in about 80 COVID-19 patients with severe disease; the clinical effectiveness has been reported on hospitalized patients with a mean duration of oxygen therapy was about 10 days, and the time for staying in hospital was 10 days[80]. A study by Van Laar and colleagues has demonstrated that remdesivir therapy causes hepatotoxic effects. In about a hundred SARS-CoV-2 patients, 25 individuals had elevated ALT, and 35 individuals had increased AST concentrations[81].

They controlled the anti-inflammatory and antimalarial properties, and with the appearance of the SARS-CoV-2 pandemic, they have a potential therapeutic indicator for patients infected with COVID-19[82]. The appropriate mechanism of impact of hydroxychloroquine on the resistance of COVID-19 is by inhibiting the attachment of the spike protein of COVID-19 to the receptor of ACE-2, leading to blocking the viral elements and the fusion of the cell membranes of the target cells. This might lead to reducing the key processes which result from COVID-19, including proteolytic activity, lysosome activity, and autophagy in the host cells; hydroxychloroquine has a role in the immunomodulatory effect by diminishing cytokine production[83]. A systematic review and randomized, parallel and clinical trial by Hernandez *et al* consisting of about 80 patients infected with COVID-19 demonstrated no relationship between abnormality of hepatic function test and hydroxychloroquine therapy[84].

The therapeutic agent, tocilizumab (IL-6 receptor monoclonal antibody), prevents the signal transduction of the cytokines pathway and blocks the pro-inflammatory actions[85]. Tocilizumab has many adverse effects, such as; dizziness, sore throats, fungal infection, hypertension, and headache[86]. In the case of utilizing tocilizumab to treat severe COVID-19 patients, IL-6 is significantly increased through the cytokine storm leading to develop the prognosis of severe SARS-CoV-2 patients[87]. The inflammatory markers, for example, D-dimer and CRP, have also diminished within utilizing tocilizumab in around 50 patients with severe COVID-19, although the reduction in these markers has not greatly influenced the outcome[88]. Tocilizumab administration damaged the liver after 2 wk *via* the development of liver injury induced by the drug in around 90 patients with COVID-19. However, close monitoring should be done during and after giving tocilizumab to COVID-19 patients[89].

The antimicrobial therapeutic medicine Azithromycin is utilized to heal bacterial infections, which observed that have the ability to reduce severe lower respiratory tract infections [90]. Azithromycin binds to the ACE-2 receptor-COVD-19 spike protein complex leading to a reduction in the downstream signaling then the effect of the virus is deleted[91]. In COVID-19, azithromycin is used to prevent the first step of COVID-19 replication. The outcomes of clinical trials indicate to its administered alone and in combination with hydroxychloroquine[92]. The transaminase concentrations have significantly increased more than five times when using azithromycin in combination with ritonavir, hydroxychloroquine, and lopinavir to treat COVID-19 with no prior history of the hepatic disease[93].

COVID-19 VACCINES AND THE LIVER

SARS-CoV-2 patients could recover without specific medicines. So far, the impact of COVID-19 vaccination on CLD is still unknown. The early vaccination of COVID-19 is valuable for the proliferative responses of T lymphocyte and antibody production, resulting in diminished danger of COVID-19 severity. The COVID-19 vaccination is necessary for those with liver diseases such as liver cirrhosis and those with liver

transplants (LT). The immunogenicity of liver transplant patients was low for the vaccinated individuals. The neutralizing antibodies can be observed in approximately 48% of LT patients[94]. A study by Ruether *et al* illustrated that the rates of T-cell response and serum conversion in the second COVID-19 vaccination were 36.6% and 63%, respectively. The percentage of serum conversion for patients with hepatic cirrhosis could reach 100% after the second vaccination[95].

A study demonstrated that the infection of SARS-CoV-19 was diagnosed after a single dose of vaccine in 62% and after a couple of doses in 38%. It is reported that the COVID-19 vaccination reduced the infection by SARS-CoV-2, then the consequences of infection with CLD reduced, for example, respiratory symptoms, hospitalization, invasive ventilation, ICU admission, and death[96]. In the patient with prior LT as well as cirrhosis, it is recommended to fully vaccinate to reduce the cases of severe infection. The immunity of COVID-19 proceeds to progress after 2 wk of the first dose of the vaccine and elevates extra after the second dose[97].

To increase immunity and decrease COVID-19 cases, it is interesting to provide a booster dose of COVID-19 vaccination (3rd and 4th doses). The antibody titers were elevated after the third dose of COVID-19 vaccination in liver transplant recipients who had negative antibody titers[98,99].

It is well-known that COVID-19 vaccines have local (like local injection site pain) or systemic adverse effects (like smell and taste abnormalities). Local side effects are more common in occurrence than systemic ones. Autoimmune hepatitis and HCV reactivation are examples of liver involvement following COVID-19 vaccination [100,101,102]. These conditions were reported on rare occasions as case reports. Even though they are identified as rare complications, one should consider them in determining the future safety of these vaccines.

PROGNOSIS

Despite COVID-19 principally causing respiratory manifestations, it also could lead to extrapulmonary diseases as comorbidities, such as hyperglycemia and ketosis,

thrombotic complications, cerebrovascular disease, acute kidney failure, neurologic illnesses, diabetes mellitus, gastrointestinal symptoms, hypertension, hepatocellular injury, and dermatologic manifestations. These symptoms could happen in infected subjects without the recognized preexisting organic disease[64,103].

COVID-19 patients with CLD, particularly those with cirrhosis, have various methods of immune dysfunction which result in the raised capability to infection and abnormal inflammatory response during infection. The previous case calls cirrhosis-associated immune dysfunction (CAID). CAID consists of decreased macrophage activation, combinations of the complement system, upregulation of Toll-like receptors, intestinal dysbiosis, and impaired neutrophil and lymphocyte function[104]. The pre-exciting individuals with CLD and cirrhosis are more potential to infect with SARS-CoV-2. The etiology of hepatic disease could impact clinical outcomes in SARS-CoV-2. In general, advancing age, diabetes, and obesity are risk factors for SARS-CoV-2 mortality and morbidity[105]. Nevertheless, such patients are not diagnosed with NAFLD because liver steatosis was not reported or alcohol use was not determined. Many contradictions throughout the literature have been illustrated in the case of the impact of NAFLD on the SARS-CoV-2 course. The contradiction might be correlated to hard in distinguishing the influence of NAFLD from different metabolic comorbidities through the confusing influence of steatosis induced by viral or different diagnostic criteria. The retrospective study of 202 patients with COVID-19 infection recognized NAFLD as a dangerous aspect for longer viral shedding ties, abnormal concentrations of liver enzymes, and progressive COVID-19[49]. However, a study of 70 subjects with SARS-CoV-2 infection and autoimmune hepatitis revealed that there is an equivalent result to subjects with other causes of CLD and propensity score-matched controls despite the use of baseline immunosuppression in 86% of patients[106]. The major reason for death is CLD liver-correlated mortality preceded by SARS-CoV-2-induced pulmonary disease[107].

Of note, if the individuals are infected with COVID-19 and have preexisted CLD, the increase in mortality and morbidity has occurred with the rising severity of cirrhosis. An increase in mortality was found for the individuals who required intensive care, and

10% is the percent of survival who did the mechanical ventilation. However, a significant relationship has been illustrated between SARS-CoV-2-related mortality and preexisting severe liver cirrhosis resulting in a rise in the mortality percentage[107]. SARS-CoV-2, similar to influenza, could lead to acute-on-chronic liver failure (ACLF); ACLF could cause viral illness and bacterial infection, ACLF is noticed through increasing severity and liver decompensation as well as hepatic failure [108].

Gut microbiota composition has the function of regulating the severity of COVID-19 by modulating the responses of the host immune; cirrhosis is differentiated through the alterations to the gut microbiota composition and acts beside intestinal permeability. The changes in the axis of the gut-liver may participate in the course of severe SARS-CoV-2 noticed in the patient group[109].

It is worth mentioning that the main reason for deaths in individuals with COVID-19 and cirrhosis is respiratory failure, despite the accurate path of this observation still being unclear. It is reasonable that the hallmark of crucial SARS-CoV-2, pulmonary thromboembolic disease, has a participatory role in the hypercoagulable case related to cirrhosis. Thromboprophylaxis is recommended during the period that COVID-19 patients stay in the hospital[110]. Given together, the relationship and coexistence of coagulopathy with both COVID-19 and cirrhosis are leading to a cumulative danger of thrombotic complications[111]. Moreover, research has reported with 40 patients that the use of thromboprophylaxis in individuals with COVID-19 and cirrhosis yielded no risk of hemorrhagic complications[112].

CONCLUSION

Abnormal liver function tests are common at the presentation and increased during the COVID-19 course. There are six proposed pathophysiological mechanisms of liver involvement; hypoxia, direct viral effect, drug-induced liver injury, cytokine storm, elevated hepatic chemistry tests, and preexisting CLD. Various liver involvements occur, which include, but are not exclusive to, elevated AST and ALT, hyperbilirubinemia, prolonged prothrombin time, elevated alkaline phosphatase, GGT

elevation, and low serum albumin level. Hepatic involvements determine the severity of COVID-19. Abnormal liver function tests are more in non-survivors than survivors. Great care is highly recommended to avoid liver injury in COVID-19 patients with modulation of therapeutic agents and regular measurement of the liver function tests, particularly in patients with a history of CLD. COVID-19 vaccines have drawbacks on the liver, for example, autoimmune hepatitis. However, complete COVID-19 vaccination for patients with a history of CLD or those who were subjected to liver transplantation is highly recommended to avoid the occurrence of the disease and further hepatic destruction.

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