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COVID-19 impact on liver: inter-organ cross-talk in an acute inflammation

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Abstract

Since coronavirus disease 2019 (COVID-19) has been a new disease, very less is known about the disease, and guidance for the treatment are often being made on the basis of an experiences or expert opinions. Now it is known that COVID-19 is caused by a new Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus which elicit infection to the cells by binding of the spike protein to angiotensin converting enzyme 2 (ACE2). Given the high transmissibility rate of the SARS-Cov-2 virus and known to have cytokine dysregulation by inducing an immune-mediated systemic inflammation, patients with underlying liver disease might be at an increased risk of severe infection and death. Here we report different mechanisms based on the organ cross-talk and other causes that how COVID-19 patients are prone to have liver injury.

Keywords: Coronavirus, COVID-19, liver disease, liver failure, liver injury, SARS-CoV-2

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Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, possibly from the bat or pangolin as an intermediate host.[1] It has been found that the genome sequence of SARS-CoV-2 shows 82% similarity to that of the severe acute respiratory syndrome coronavirus (SARS-CoV) which is also a coronavirus that is profoundly pathogenic and infective to humans leading to the global health emergency in 2003.[2,3] Moreover, about 60% of the patients with SARS were reported to have a liver injury. Although SARS-CoV-2 shares the majority similarity in the genome sequence with SARS-CoV, the large number of the published studies on COVID-19 only features the disease severity and deaths based on respiratory complications. However, emerging evidence from new studies shows the impact of SARS-CoV-2 infection on the other organ systems like the heart, kidney, intestine, and liver. Taking this into consideration, some patients with underlying liver disease and liver transplantation (LT) recipients might be at an increased risk of severe infection and death. Therefore, understanding the impact caused by SARS-CoV-2 on the liver and the underlying mechanisms is of the greatest importance, so that management of the patients with liver disease and LT recipients can be done effectively within time; hence, reducing morbidity and mortality.

In this review, we will highlight the evidence of liver injury in COVID-19 and put forward the possible mechanism that could explain how SARS-CoV2 can lead to liver injury.

Method

Studies for this review were searched in-between December 2001 to 15 May 2021 in PubMed/MEDLINE, Embase, Cochrane Library databases, WHO database of COVID-19 publications, and COVID-19 resource center of different journals. The search was carried out with the use of the following Medical Subject Headings (MeSH) and non-MeSH terms: Coronavirus, novel Coronavirus, interorgan cross-talk, Coronavirus Disease 2019, COVID-19, severe acute respiratory syndrome coronavirus 2, and SARS-CoV-2.

Discussion

Clinical Manifestations and laboratory findings of COVID-19 patients

Patients with COVID-19 show a wide range of clinical manifestations, asymptomatic to septic shock and multiple organ dysfunction syndromes (MODS).[4] Most of the patients with COVID-19 presents with fever (99%), fatigue (70%), dry cough (59%), sputum production (27%), and diarrhea (2–10%).[5, 6] Further, based on the severity of the presentation, patients with COVID-19 have been classified into mild, moderate, severe, and critical cases.[5] The majority of COVID-19 cases (81%) are mild to moderate in severity with symptoms like fever, fatigue, dry cough, and diarrhea.[7] Additionally, patients with severe disease (14%) present with severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, or septic shock.[7] Furthermore, about 5% of the patients are found to develop a critical disease with respiratory failure, detectable serum SARS-CoV-2 viral load (RNAaemia), acute cardiac injury, acute kidney injury, liver injury, shock, or MODS.[7-9] According to the Chinese Centers for Disease Control and Prevention (China, CDC) the fatality rate is 49% in critical patients, and the high fatality rate is associated with prior comorbidities like diabetes, respiratory disease, cardiovascular disease, hypertension, and oncological complications.[7] In contrast, the low fatality rate i.e. 0.9% is seen in the patients without comorbidities.[5]

Laboratory findings in COVID-19 according to most of the published studies include prolonged prothrombin time and elevated D-dimer, creatine kinase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), and C-reactive protein (CRP).[8-10]

The early stages of the disease are characterized by a noticeable reduction in CD4 and CD8 counts.[8] Additionally, patients with COVID-19 also have high amounts of Interleukin 6 (IL-6), Interleukin 1 beta (IL-1β), interferon-gamma (IFNγ), interferon gamma-induced protein 10 (IP10), and monocyte chemotactic protein 1 (MCP1).[9, 11] Furthermore, those patients requiring an ICU admission shows higher concentrations of granulocyte colony-stimulating factor (GCSF), IP10, MCP1, macrophage inflammatory protein-1 alpha (MIP-1α/CCL3), and tumor necrosis factor-α (TNFα) compared to those not requiring an ICU admission, suggesting that the disease severity is associated to the "cytokine storm", where patients have coagulation activation, cellular immune deficiency, myocardial injury, kidney injury, and liver injury.[8,9,12] Additionally, elevated D-dimer, ferritin, neutrophil counts, blood urea, and creatinine levels are associated with severe cases and bad prognosis.[8, 9] Further, elevated level of C-reactive protein shows the possibility of secondary infection.[13]

COVID-19 related liver injury should be characterized as any damage to the liver developed during disease progression or treatment with or without prior liver diseases. Over 50% of the COVID-19 patients are found to present with abnormal liver function at admission.[14] Overall, it is seen that there is primarily raised AST and ALT level, and slightly raised bilirubin level in 14% to 53% cases.[8, 9, 11, 12, 14] Moreover, in a recent study 54% of the patients hospitalized for COVID-19 had an elevated gamma-glutamyl transferase (GGT), which was considered as a possibility of cholangiocyte injury.[15] Additionally, most of the critical patients with severe infection are found to have low albumin.[11, 16] Apart from the SARS-CoV-2 RNA detection in blood, SARS-CoV-2 RNA has also been detected in stool of the COVID-19 patients and this should raise a concern about the transmission of SARS-CoV-2 through the fecal-oral route.[17, 18]

Angiotensin-Converting Enzyme 2 (ACE2) and COVID-19

From the recent studies, it is seen that both SARS-CoV and SARS-CoV-2 trigger infection to the host cells by binding the spike protein of the virus to the enzyme called Angiotensin-converting enzyme 2 (ACE2).[19, 20] ACE2 is a transmembrane protein attached to the cell membranes and is found to play an important protective role in cardiovascular diseases, immune systems, and liver fibrosis.[21-24] In addition, it is most copiously found in the type II alveolar cells of the lungs, heart, esophagus, ileum, colon, kidney, testes, and bladder.[25, 26] Nonetheless, high expression of ACE2 has also been identified in the liver and biliary epithelial cells.[14, 27] Thus, the expression and distribution of the ACE2 in the liver and biliary epithelial cells put liver as a potential target to SARS-CoV-2 infection, and this explains why most studies have frequently reported abnormal liver functions as an extrapulmonary clinical feature in the patients with COVID-19.[10] A study found that more than 50% of the COVID-19 patients presented with abnormal liver function at admission. Moreover, this study also analyzed the liver function according to the pre-hospital medication, where the study didn't find any significant difference between the groups, further suggesting that liver injury in the patients with COVID-19 might be a direct result from SARS-CoV-2 infection of the liver cells.[14] Additionally, this study further found the patient with abnormal liver function after admission prolonged the length of hospital stay.[14] The worsening liver function after the admission might be as a result of the dynamic nature of COVID-19, where the patients with mild illness can speedily worsen into a severe or critical case. In our recent meta-analysis, we found the patients with COVID-19 have a high prevalence of liver injury, and the patients with COVID-19 with liver injury are at an increased risk of severity and mortality.[10] The liver biopsy of COVID-19 patients revealed moderate microvesicular steatosis and mild lobular and portal activity, suggesting that the injury was either the result of direct SARS-CoV-2 infection or due to

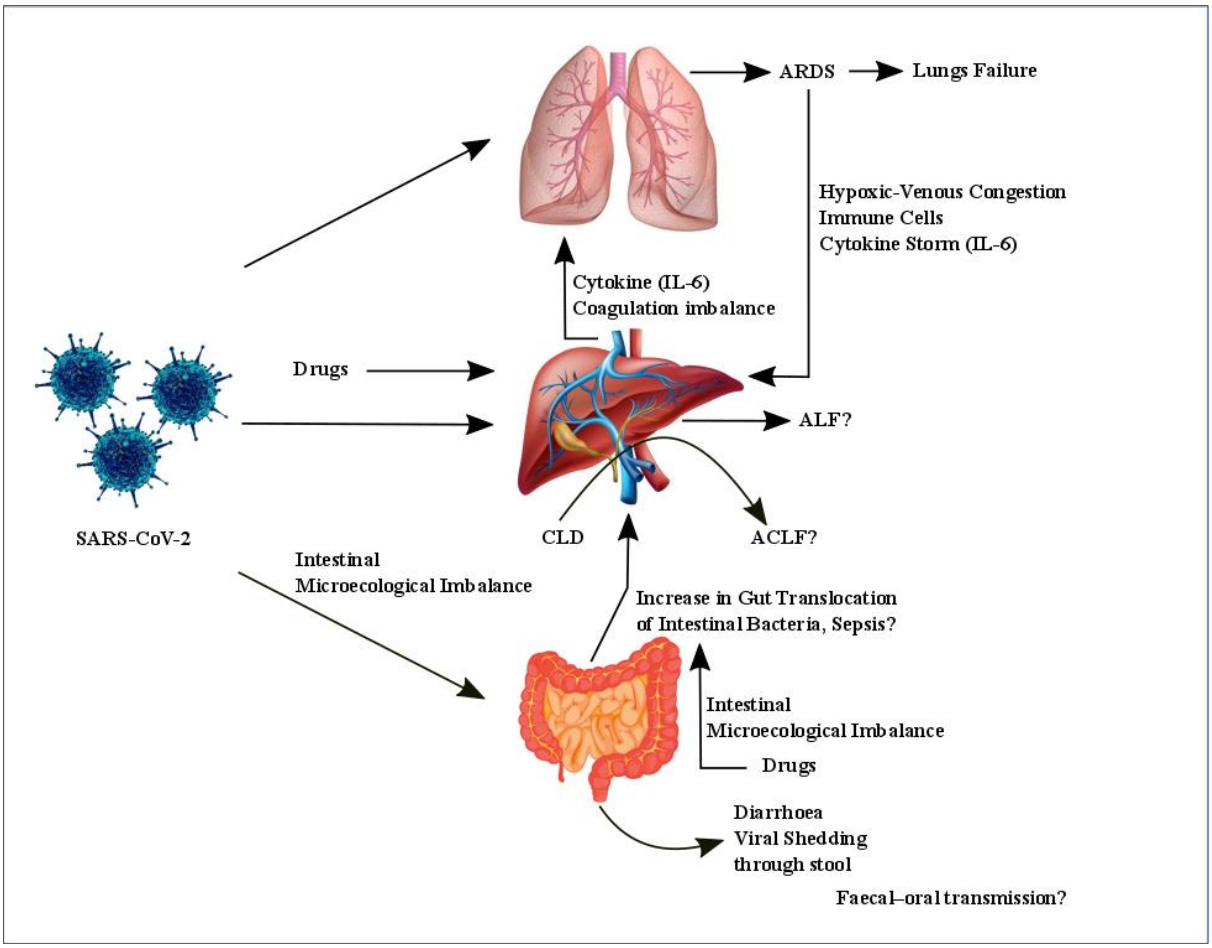

Figure 1. Possible mechanisms of the liver injury in COVID-19 patients.

ACLF: acute on chronic liver failure; ALF: acute liver failure; CLD: chronic liver disease; IL-6: interleukin 6; ARDS: acute respiratory distress syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

the drug used during the treatment.[28] Interestingly, RT-PCR of the liver biopsy showed direct evidence of the viral sequence in the liver.[29] However, it's still not clear that, if SARS-CoV-2 infects the liver cells or cholangiocytes directly and can shed an infective particle of SARS-CoV-2. More mechanistic studies are needed to address these questions.

Possible mechanisms of liver injury in COVID-19 patients

1. Liver injury due to the direct effect of viral replication in hepatic cells: As discussed earlier in this review because ACE2 is expressed in the liver and biliary epithelial cells; hence, SARS-CoV-2 can easily infect the liver cells.[14,27] Moreover, patients with comorbidities like hypertension and diabetes are found to present with a more severe form of COVID-19. Based on the data, patients taking drugs like ACE inhibitors and angiotensin II type I receptor blockers for hypertension may have overexpression of ACE2. Similarly, type 2 diabetes mellitus also induces ACE2 expression in the liver; therefore, these patients with upregulated ACE2 expression might be at a higher risk for developing COVID-19 and might have up to 10 times greater risk of death with COVID-19.[30, 31] Besides, levels of the ALT, AST, TB, LDH, and INR are shown to be significantly higher in the patients with severe COVID-19.[11] Thus, these abnormal liver function might be as a result of direct effects of viral replication in the hepatic cells.[29]

2. Liver Injury due to Cytokine: Cytokine dysregulation is crucial in the pathogenesis of

COVID-19. Additionally, it has been seen that serious and critical COVID-19 patients commonly present with a cytokine release syndrome (CRS), also known as "cytokine storm".[32, 33] In severe and critical COVID-19 patients, an acute liver injury might have occurred due to CRS. Additionally, a hyperinflammatory condition resembling that of the secondary haemophagocytic lymphohistiocytosis (sHLH) has been noticed in most of the COVID-19 patients admitted to ICU, with dramatically elevated IL-6, D-dimer, ferritin, an elevated liver function, low-level albumin, elevated C reactive protein, and neutrophil counts.[8, 9, 32, 34, 35] However, before reaching to the diagnosis of sHLH, this needs to be verified by careful studies. Extracorporeal membrane oxygenation (ECMO) and artificial liver support system (ALSS) have also been proposed as an approach to remove cytokines in COVID-19 patients to prevent CRS-induced organ damage.[13] Indeed, to mitigate the hyperinflammatory state a multicentre, randomized controlled trial of tocilizumab (IL-6 receptor blockade) has been approved for COVID-19 patients with elevated IL-6 in China.[32]

3. Lung-Liver Axis- Liver Injury due to Pneumonia-associated hypoxia: ARDS is seen as the hallmark of COVID-19. ARDS-induced hypoxic hepatitis also known as ischemic hepatitis or "Shock liver" due to anoxia and inadequate blood flow to the liver might also contribute to liver injury.[15] Additionally, ADRS also induces an immune-mediated inflammation and systemic inflammatory response, which may further cause an acute liver injury. Yet, it is unclear that if there is any prognostic aspect of liver injury on the prognosis of COVID-19 patients. This further requires critical consideration, which will have clinical outcomes for effective management of the COVID-19 patients.

4. Gut- Liver Axis- Liver Injury due to dysbiosis of Gut Microbiome: Perhaps, gastrointestinal manifestations are the most common non-respiratory symptom of COVID-19, and about 50% of the COVID-19 patients are found to present with gastrointestinal symptoms like diarrhea, vomiting, or abdominal pain.[36] Moreover, in a study viral RNA, was isolated in about 67% of the stool samples.[37] It is speculated that the presence of the gastrointestinal symptoms in COVID-19 patients must be the result of the SARS-CoV-2 virus infecting the human gut through ACE2 receptors present inside gastrointestinal cells.[25, 38] On the other hand, intestinal symptoms in the COVID-19 patients could also be as a result of the gut-lung axis, as both lung and gut are linked through the mucosal system.[39] Regardless of the different hypothesis behind how the gut is infected by SARS-CoV-2 virus, gastrointestinal symptoms in the COVID-19 patients indicates that there dysbiosis of the gut microbiome in these patients.[40] In recent years, there is growing evidence that dysbiosis of the gut microbiome plays an important role in the pathogenesis of liver injury and liver disease.[41, 42] As discussed above in this review, COVID-19 patients have a high level of cytokines and inflammatory mediators, which can lead to gut barrier dysfunction under stress and further leading to increased intestinal permeability of the gut microorganisms and pathogen-associated molecular patterns (PAMPs). In addition, these gut microorganisms and PAMPs can influx directly into the portal circulation and triggering a pro-inflammatory cascade that may cause liver injury or worsens hepatic function.

5. Kidney-Liver Axis- Liver Injury due to AKI induced oxidative stress: According to the published report an incidence rate of acute kidney injury (AKI) was found to be about 15% in COVID-19 patients.[43] Furthermore, AKI is more common in severe and critical COVID-19 patients, and considered as a bad prognostic factor for survival of the patient.[43, 44] Of note, AKI in COVID-19 patients may be due to multiple factors related to the lung-kidney axis-in ARDS, like an immune-mediated inflammation, systemic inflammatory response, and CRS leading to the hypoperfusion-related injury of the renal tubules.[45, 46] Further, ACE2 is found to be highly expressed in the renal tubule epithelial cells, essential for SARS-CoV-2 infection to the host

cells.[47] Earlier studies have shown that AKI induces oxidative stress and stimulates inflammation, apoptosis, and tissue injury in the liver cells by a complex amalgamation of soluble inflammatory mediators and cellular immunity.[48]

6. Drugs induced liver injury (DILI): Most of the patients infected with SARS-CoV-2 were found to use antipyretic drugs like paracetamol for fever, which can cause liver injury. Moreover, antiviral drugs currently used (Oseltamivir, Lopinavir/Ritonavir, Ribavirin, and Chloroquine Phosphate or Hydroxy Chloroquine Sulfate) [8-10, 13] to treat the patients with COVID-19 metabolized in the liver and might induce hepatotoxicity; this was additionally confirmed by the pathological findings.[28] From the published studies, patients with prior comorbidities like diabetes, cardiovascular disease, and hypertension were more susceptible to develop severe COVID-19.[5] Besides, patients with these comorbidities commonly develop metabolic syndrome, which is a considerable risk factor non-alcoholic fatty liver disease (NAFLD).[49] Furthermore, patients with NAFLD are more prone to an acute liver injury due to the hepatotoxic drugs. Thus, it is recommended for careful consideration of drugs, along with the frequent and careful monitoring of the liver functions in COVID-19 patients during treatment to reduce the risk of drugs induced hepatotoxicity.

Concerns about COVID-19 patients with underlying Liver Disease

The COVID-19 patient with underlying liver diseases might to susceptible to develop acute on chronic liver failure (ACLF) as a “second hit” due to an immune-mediated inflammation and systemic inflammatory response induced by SARS-CoV-2 infection. However, ACLF has not been reported by any of the published studies on COVID-19 to date. It is still unknown, that how an underlying liver disease such as chronic viral hepatitis, autoimmune hepatitis, non-alcoholic fatty liver disease, and alcohol-related liver disease influence liver injury in the patients with COVID-19 should be carefully evaluated. For instance, patients with an immune tolerant chronic hepatitis B or under antiviral treatment are at a high risk to develop severe SARS-CoV-2 infection. Additionally, COVID-19 treatment may predispose to a flare-up of chronic hepatitis B due to immunosuppression. Then again, it is as yet obscure whether COVID-19 aggravates cholestasis in the patients with underlying cholestatic liver diseases, given that SARS-CoV-2 triggers infection via ACE2, and ACE2 is abundantly expressed in cholangiocytes, also needs to be explored.[27] Further, the prognosis and the effects of the glucocorticoids administration in the patient with autoimmune hepatitis and with SARS-CoV-2 infection is still unclear. Moreover, patients with liver cirrhosis or liver cancer are usually immunocompromised; thus, these patients are more susceptible to develop severe SARS-CoV-2 infection. Further, as most of the patients with a severe COVID-19 are found to have an elevated level of D-dimer,[8, 9] in some earlier studies it has been seen that an elevated D-dimer level was associated with an increased risk of 28-day mortality in a patient with decompensated cirrhosis.[50] Thus, special consideration should be given for the COVID-19 patients with an underlying disease throughout the time of treatment and in-depth studies are needed to address the above concerns.

Conclusion

The SARS-CoV-2 causes infection through ACE2, and ACE2 is abundantly expressed in the liver, while also may cause damage to the liver, although there are no published studies yet to prove it. Further, liver injury in COVID-19 patients can also be a result of DILI, cytokine storm, and interorgan cross-talk. In addition, patients with chronic liver disease and SARS-CoV-2 infection might have a poor prognosis. Therefore, special attention should be given to liver protection during the treatment for COVID-19. Additionally, multi-center clinical studies should be carried out to evaluate the impact of COVID-19 on the liver.

Conflict of Interest

None

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Author Contribution

DKY, BX, and TL were involved in the concept and design of this study; DKY, AS, RKY, and XH contributed to the acquisition and interpretation of the data; DKY, AS, RKY, and XH were involved in the drafting of the manuscript; DKY contributed to the figure concept and design; DKY, BX, and TL critically revised the manuscript; all authors approved the final manuscript.

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