Invited review article

COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies

Short Title: COVID-19 and liver dysfunction

Authors: Gong Feng,[1] Kenneth I. Zheng,[2] Qin-Qin Yan,[1] Rafael S. Rios,[2] Giovanni Targher,[3] Christopher D. Byrne,[4] Sven Van Poucke,[5] Wen-Yue Liu,[6] Ming-Hua Zheng,[2,7,8*]

Affiliations:

[1]Xi'an Medical University, Xi'an, China;

[2]NAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

[3]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy;

[4]Southampton National Institute for Health Research Biomedical Research Center, University Hospital Southampton, Southampton General Hospital, Southampton, UK;

[5]Ziekenhuis Oost-Limburg, Department of Anesthesiology, Critical Care, Emergency Medicine and Pain Therapy, Genk, Belgium;

[6]Department of Endocrinology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

[7]Institute of Hepatology, Wenzhou Medical University, Wenzhou, China;

[8]Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China.

***Corresponding author:**

Ming-Hua Zheng, MD, PhD

NAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of

Wenzhou Medical University; No. 2 Fuxue Lane, Wenzhou 325000, China.

E-mail: zhengmh@wmu.edu.cn; fax: (86) 577-55578522; tel: (86) 577-55579622.

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Abbreviations

ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR, toll-like receptor.

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Conflicts of interest

The authors have no conflicts of interest related to this article.

ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has attracted increasing worldwide attention. Cases of liver damage or dysfunction (mainly characterized by moderately elevated serum aspartate aminotransferase levels) have been reported among patients with COVID-19. However, it is currently uncertain whether the COVID-19-related liver damage/dysfunction is mainly due to the viral infection *per se* or other coexisting conditions, such as the use of potentially hepatotoxic drugs and the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia and multiple organ dysfunction. Based on the current evidence from case reports and case series, this review article focuses on the demographic and clinical characteristics, potential-mechanisms, and treatment options for COVID-19-related liver dysfunction. This review also describes the geographical and demographic distribution of COVID-19-related liver dysfunction, as well as possible underlying mechanisms linking COVID-19 to liver dysfunction, in order to facilitate future drug development, prevention and control measures for COVID-19.

Keywords: COVID-19; liver dysfunction; SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a serious threat to global public health.[1,2] Although the virus appears to be only partially similar to Severe Acute Respiratory Syndrome Coronavirus (SARS) and Middle East Respiratory Syndrome Coronavirus (MERS), all of these viral infections are responsible for severe and potentially lethal acute respiratory syndromes in humans.[3] Unfortunately, to date, there are no specific/targeted drugs, or vaccines, and the number of SARS-CoV-2 positive patients is growing in many parts of the world. The world and China map to show the geographical distribution of coronavirus disease 2019 (COVID-19) is shown in Figure 1; the cut-off date for this data extraction was March 5, 2020.[4] Surprisingly, in addition to the acute respiratory symptoms, patients with COVID-19 also have varying degrees of liver damage/dysfunction. For example, Chen et al. showed that more than a third of COVID-19 patients have some liver function test abnormalities.[5] Most of these infected patients had mild-to-moderate elevations of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels; one patient had severely elevated serum aminotransferases (ALT 7590 U/L, AST 1445 U/L).[5] Since COVID-19-related liver dysfunction is now attracting widespread attention, this review discusses the epidemiological characteristics, the potential mechanisms, and the treatment options for liver dysfunction induced by COVID-19..

1. EPIDEMIOLOGICAL CHARACTERISTICS OF COVID-19-RELATED LIVER DYSFUNCTION

To better understand the distribution of COVID-19-related liver dysfunction in different regions of the world, we searched the available literature between December

11, 2019 and February 20, 2020. The literature search focused on initial case reports and case series covering COVID-19 patients with a clear description of liver function tests. All case reports without any data on patients' liver function tests were excluded. Finally, we included 14 eligible studies, including 5 case reports (**Table 1**)[6-10] and 9 case series (**Table 2**)[5,11-18]. By reviewing these 14 studies, we have described geographical and demographic characteristics of COVID-19-related liver dysfunction (as summarized below).

1.1 Geographical distribution of COVID-19-related liver dysfunction

In two Chinese multi-center surveys, one of which was led by The First Affiliated Hospital of Guangzhou Medical University, including 552 hospitals in 31 provinces/provincial municipalities through January 29th, 2020, and the other was led by The First Hospital of Lanzhou University including seven hospitals, a considerable number of patients with COVID-19 had some abnormalities in liver function tests.[11,16] In particular, 6.2% to 22.2% of patients had increased serum aspartate aminotransferase (AST) levels (Figure 2) and 21.3% to 28.1% of patients had increased serum alanine aminotransferase (ALT) levels, respectively.[11,16] Of the six studies performed in Wuhan, China,[5,13-15,17,18] only four studies included data on the proportion of patients with abnormal liver function tests. Specifically, in these four studies the proportion of infected patients with increased serum AST levels ranged from 24.1% to 36.6% (Figure 2).[5,13,17,18] In a survey from Zhejiang Province, China, the proportion of patients with increased serum AST levels was only 16.1%, whereas the proportion of those with increased serum ALT levels was not specified.[12] It seems likely that the proportion of infected patients with increased serum AST levels in Wuhan (i.e. the area in which the epidemic of COVID-19 started) is much greater

than cases reported outside Wuhan. It is plausible to speculate that there may have been a higher viral load of COVID-19 in exposed patients in Wuhan where the infection began and was concentrated in a greater proportion of the population.

1.2 Sex distribution of COVID-19-related liver dysfunction

A total of six case series reporting the percentage of abnormal liver function tests amongst COVID-19 patients suggested that the proportion of infected men with increased serum AST levels was higher than that observed in infected women. [5,11-13,16,17] In fact, in these case series the proportions of infected men with increased serum AST levels were, respectively, 68.7%, 58.2%, 58.1%, 72.4%, 62.8% and 73.2%, whereas the proportions of infected women were, respectively, 31.3%, 41.8%, 41.9%, 27.6%, 37.2% and 26.8%. It is possible to hypothesize that infected men are more predisposed to develop COVID-19-associated liver dysfunction than infected women, and we suggest that further research is required to better understand this sex-related difference.

1.3 Age distribution of COVID-19-related liver dysfunction

Of the five case reports, three were in children and two were in adults. The age of children ranged from three months to seven years, whereas the age of adult patients ranged from 35 to 56 years. None of these children had abnormal serum liver enzymes and, therefore, it is possible to hypothesize that older age is associated with a higher likelihood of liver damage/dysfunction. However, further studies are needed to confirm this finding. We look forward to more case reports/case series on COVID-19 related liver damage/dysfunction in different age groups in the future.

2. PUTATIVE MECHANISMS OF COVID-19-RELATED LIVER DYSFUNCTION

2.1 ACE2-mediated liver dysfunction

Whether SARS-CoV-2 has direct adverse effects on liver function is currently not known. Some studies have suggested that SARS-CoV-2 predominantly enters alveolar epithelial cells through the human angiotensin-converting enzyme-2 (ACE-2) receptor.[19,20] Therefore, the lung is considered the main target organ of SARS-CoV-2 infection. However, previous studies have found that bile duct epithelial cells may also express ACE-2 receptor at a concentration 20 times higher than in hepatocytes and these findings suggest that SARS-CoV-2 infection might also cause bile duct epithelial cell damage.[21,22] However, significant increases in circulating levels of serum alkaline phosphatase, bilirubin or gamma-glutamyltransferase (that may reflect bile duct injury) have been rarely reported in COVID-19 patients.[9] Liver histopathologic features from COVID-19 patients also did not show any significant damage in hepatocytes or bile duct cells[23]. For this reason, it is reasonable to assume that COVID-19-related liver dysfunction is more likely due to secondary liver damage than the use of hepatotoxic therapies or the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia, or multiple organ dysfunction.

2.2 Drugs

During the course of the COVID-19 epidemic, many infected patients have been treated with antipyretic agents. Most of these medications contain acetaminophen, which is a drug recognized as being able to cause significant liver damage or induce liver failure.[23] It is known that an acute ingestion of >7.5 to 10 g of acetaminophen in

adults or 150 to 200 mg/kg in children is likely to cause hepatotoxicity.[24] Although the US Food and Drug Administration Advisory Committee has proposed a decrease in the maximum daily dosage of acetaminophen from 4 to 3 g, and the maximum individual dosage from 1 to 0.65 g, (relegating 500-mg tablets to prescription status), these recommendations have not been implemented worldwide.[25] In addition, although there is currently no targeted antiviral treatment for COVID-19, many infected patients have been also treated with some antiviral drugs, such as oseltamivir, abidol or lopinavir, which may have some hepato-toxic effects.

2.3 Systemic inflammatory response syndrome

Although many COVID-19 patients were not too unwell, this infection in some patients resulted in sudden deterioration, ending in multiple organ failure. Most experts believe that the occurrence of multiple organ failure is mainly related to the sudden initiation of an inflammatory "*storm"* in the critically ill COVID-19 patients.[26] The so-called inflammatory "*storm*", or systemic inflammatory response syndrome (SIRS), is strongly related to activation of both natural and cellular immunity that is triggered by COVID-19 infection.[27] In fact, the virus is able to directly induce multiple proinflammatory signals via toll-like receptors (TLRs) and activation of killer T lymphocytes.[28] The activated T lymphocytes then attack the infected body cells, leading to their apoptosis and necrosis, until T lymphocytes are depleted. Damage-related pattern molecules released by dead infected cells can further amplify some inflammatory signals, such as TLRs. At the same time, T-lymphocyte depletion cannot control viral and bacterial infections, thereby activating multiple inflammatory signaling pathways, which lead to macrophage activation and secondary inflammatory reactions. Subsequently, when more inflammatory cytokines are released, more cell

damage and necrosis are observed (Figure 3). Such a vicious cycle is capable of causing multiple injuries, not only to the lungs but also to the liver, heart and kidneys.

2.4 Hypoxia-reperfusion dysfunction

Hypoxia and shock induced by COVID-19-related complications (such as respiratory distress syndrome, SIRS and multiple organ failure) may also cause hepatic ischemia and hypoxia-reperfusion dysfunction. Experimental data showed that hepatic cell death and inflammatory cell infiltration caused by hypoxia can be seen both *in vivo* and *in vitro* models of hepatic ischemia and hypoxia.[29] This suggests that oxygen reduction and lipid accumulation in hepatocytes during shock and hypoxic conditions may lead to cell death. The subsequent marked increase in reactive oxygen species and their peroxidation products can act as a second messenger, activating redox-sensitive transcription factors, and further amplifying the release of multiple pro-inflammatory factors causing liver damage.[30] All the aforementioned findings suggest that pneumonia-associated hypoxia is one of the most important factors causing secondary liver injury in COVID-19 patients.

In summary, the COVID-19-related liver dysfunction may be considered as the result of secondary liver damage mainly caused by several factors, such as the use of potentially hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia and multiple organ failure. In addition, critically ill COVID-19 patients with severe liver dysfunction are also more likely to have a poorer prognosis.

3. TREATMENT OPTIONS FOR COVID-19-RELATED LIVER

DYSFUNCTION

Presently, there is no specific treatment for COVID-19 infection.[31] Therefore, the cornerstone of COVID-19 management is patient isolation and supportive medical care where necessary, including also pulmonary ventilation and prevention of the underlying inflammatory "*storm*".[32]

From the findings discussed above, however, we believe that it is also reasonable to explore novel treatments for COVID-19 targeting of the ACE2 receptor. The ACE2 cellular receptor is highly expressed in human lung tissues, gastrointestinal tract, liver, vascular endothelial cells and arterial smooth muscle cells.[33] In addition, skin, nasal cavity, and oral mucosa basal cells also express ACE2 receptor.[27] All organs with high expression of ACE2 receptor may be targeted by SARS-CoV-2 infection.[34] Activation of the ACE2 / Ang (1-7) / Mas signaling pathway or inhibition of the ACE / Ang II / AT1R pathway could be potential pathways for the treatment of COVID-19. For SARS-CoV-2 infected patients, both ACE-inhibitors and angiotensin-II-receptor antagonists might be used not only for treating high blood pressure but also for reducing systemic inflammatory response and improving patient mortality.[35] Recently, Chen et al. reported that glycyrrhizic acid derivatives might also have antiviral activity against SARS-CoV-2.[36] Glycyrrhizic acid is one of the first-line drugs for anti-inflammatory protection in liver disease, and it has been used in clinical practice from many years.[37] In particular, glycyrrhizic acid is a triterpene glycoside isolated from the root of the licorice plant. ACE2 is a cellular type I membrane protein that is mostly expressed in the lungs, heart, kidneys and intestine. Full-length ACE-2 consists of an N-terminal peptidase domain and a C-terminal collectrin-like domain that ends with a single trans-membrane helix and a ~ 40-residue intracellular

segment.[38] Glycyrrhizin has the potential to bind to ACE2 receptor with an estimated ΔG (kcal/mol) - 9, with the binding cites ARG-559, GLN-388, ARG-393, and ASP-30.[39]

CONCLUSIONS

Our review shows that: (1) in highly epidemic areas of COVID-19 infection, such as Wuhan, China, the proportion of infected patients with abnormal liver function tests (mainly elevated serum AST levels) is greater than that observed in regions where a smaller proportion of cases of COVID-19 infection in the population have occurred. (2) The proportion of infected patients with elevated serum transaminase levels is higher in adults than in children and in men than in women, respectively. However, we suggest that further studies are needed to confirm these preliminary observations. In the meantime, we believe that the front-line medical staff should pay attention to liver function tests in patients infected with COVID-19. For those patients with a pre-existing history of liver diseases (especially older patients), special attention should be paid to monitoring hepatic changes caused by COVID-19 whilst carefully identifying the cause of the liver dysfunction.[40] We also recommend that front-line medical staff should assess the use of appropriate hepato-protective therapies, especially in patients with pre-existing liver disease, in order to attenuate the potentially deleterious impact of COVID-19-related liver damage/dysfunction.

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Table Legends

Table 1. Demographic and liver function characteristics of patients with COVID-19 based on the first case reports in three countries.

Table 2. Main characteristics related to liver disease in patients with COVID-19 infection in different Chinese regions based on a series of case reports.

Figure Legends

Figure 1. Geographical distribution of COVID-19 (The cut-off date for the data extraction was March 5, 2020).

Figure 2. Proportion of patients with liver dysfunction in Chinese regions (Wuhan and outside Wuhan).

Figure 3. Schematic diagram showing the systemic inflammatory response syndrome (SIRS) induced by SARS-CoV2. After the SARS-CoV-2 infection, pathogenic T cells are rapidly activated, producing granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6 and other proinflammatory factors. GM-CSF will further activate $CD14^{+}CD16^{+}$ inflammatory monocytes, produce a larger amount of IL-6 and other proinflammatory factors, thereby inducing an inflammatory "storm", leading to immune damage to other organs, such as the lungs and the liver. Both IL-6 and GM-CSF are two key proinflammatory factors that trigger the inflammatory "storm" in patients with COVID-19.