FRIGID ZONE **MEDICINE**
Special Review • DOI: 10.2478/fzm-2022-0026

Corona virus disease 2019-associated liver injury in cold regions

Shima Tang, Fen Zhang, Qiuhong Liu, Lanjuan Li*

Abstract

The corona virus disease 2019 (COVID-19) pandemic has created a global health and economic crisis. Our studies uncovered that in addition to respiratory symptoms, liver damage is also common in COVID-19 patients; however, the cause of liver damage has not been fully elucidated. In this article, we summarize the clinical manifestations and pathological features of COVID-19 reported in published relevant studies and delineate the etiology and pathogenesis of COVID-19-related liver injury. We speculate that cold stimulation may be associated with COVID-19-related liver injury, which should be considered in clinical decision-making and treatment of COVID-19 in cold regions.

Keywords

corona virus disease 2019; severe acute respiratory syndrome coronavirus 2; liver injury; cold

Received 25 May 2022, accepted 4 September 2022

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310006, China

**Corresponding author Lanjuan Li, E-mail: ljli@zju.edu.cn*

1 Introduction

Corona virus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept across the globe with a surge in infections, becoming a worldwide public health emergency and triggering a health and economic crisis[1]. As of April 29, 2022, the accumulated number of confirmed cases of the new coronary pneumonia epidemic has exceeded 515 660 000, and the death toll has exceeded 6 245 000, with a mortality rate of 1.2%[2]. Increasing number of research has shown that patients with COVID-19 often experience symptoms of liver damage in addition to the respiratory syndromes[3-6]. The possible mechanisms and causes of liver injury are worth exploring.

Additionally, we found that the majority of cases occur in countries with temperate climates with cold winters, with few cases on other continents (with hot seasons, tropical climates or monsoons)[7]. Studies have shown that temperature may affect the infectivity and virulence of SARS-CoV-2, and a cold environment is conducive to the duplication and spread of the virus[8]. Determining the possible mechanisms and causes of liver injury is critical for making clinical decisions for the therapeutic management of COVID-19 in cold regions. Here, we discuss the possible connection between liver injury and cold environment and propose some ideas relevant to clinical decision-making and treatment of COVID-19 in cold regions.

2 The mechanism of virus infection

SARS-CoV-2 is an enveloped positive-stranded single-stranded RNA virus[9]. Coronavirus virions comprise nucleocapsid protein, membrane protein, envelope protein and spike protein (Fig. 1). The initial step for SARS-CoV-2 infection is access to target cells. Coronaviruses use the homo-trimeric spike glycoprotein (S protein) on the envelope to combine with cell surface receptors. The S protein is segmented into the S1 subunit that binds to the cellular receptor and the S2 subunit that fuses with the cell membrane[9-10]. The receptor binding domain is a vital functional segment within the S1 subunit in charge of the binding of virus to host cells[10]. SARS-CoV-2 enters target cells through angiotensin-converting enzyme 2 (ACE2), identical to SARS-CoV[4]. The transmembrane protease serine 2 (TMPRSS2) activates the S protein by cleaving it at a certain site[11]. In addition, there may also be furin cleavage sites that could lead to broader protease-mediated S protein activation[12]. This binding forms the ACE2-virus complex, which allows the fusion of virus and cell membrane to enter the host cell. Then, the viral RNA is released into the host cell, where the viral polymerase protein is translated in ribosomes. Next, full-length antisense genomic RNA is produced by replication, which serves as a template for viral genomic RNA. The nucleocapsid of SARS-CoV-2 comprises RNA and nucleocapsid proteins. Other components of the virus, including spike, envelope, and membrane proteins, are transferred into the

endoplasmic reticulum (ER) of the host cell. Each of the above viral parts enters the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) for viral assembly and budding. Eventually, newly produced SARS-CoV-2 is released from the host cell by exocytosis (Fig. 1).

3 Liver injury in COVID-19

The respiratory system is the main target of SARS-CoV-2 infection; some infected individuals become severely ill and may progress to ARDS and even die[13]. Fever, cough, and fatigue are the most frequent clinical characteristics associated with the infection, while sputum, headache, haemoptysis, diarrhoea, sore throat, chest pain, chills, nausea, and vomiting are relatively rare[1, 14-16]. Additionally, a decreased sense of smell and taste and symptoms of skin disease have been reported[17]. The median incubation time for infection is 4 days. SARS-CoV-2 can affect people of any age, whereas older men with underlying health problems are more likely to develop severe respiratory disease requiring admission to the ICU and even end up with death, while the majority of young adults and children have no symptoms or only mild symptoms[15]. Furthermore, comorbidity with underlying chronic diseases has been widely taken as a high risk factor for COVID-19 mortality[18].

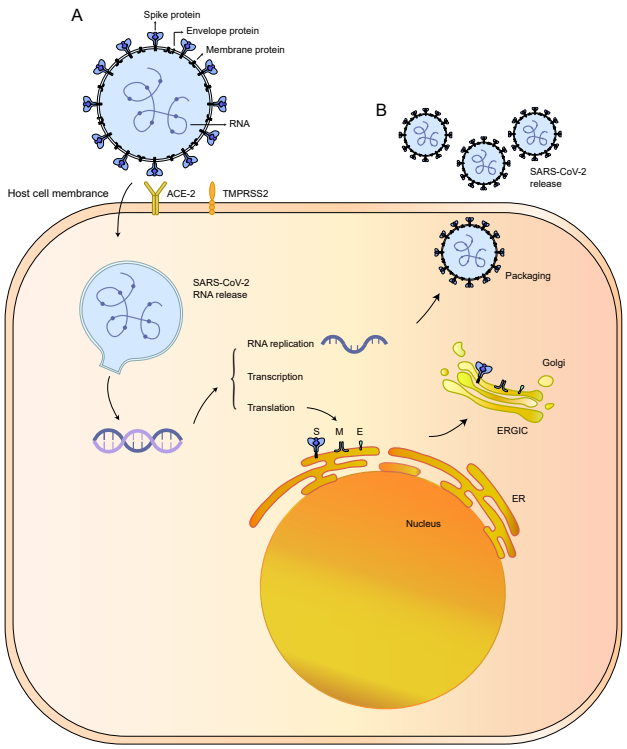

Fig. 1 Predicted structural model of SARS-CoV-2 and its life cycle in host cells

(A) Possible structural model of SARS-CoV-2; (B) The life cycle of SARS-CoV-2 in host cells:the S protein of SARS-CoV-2 forms a complex with the ACE2 receptor on the host cell membrane, with the help of proteases, the viral complex is then transported into the host cell, and the viral RNA is subsequently released into the cytoplasm. Spike (S), envelope (E), and membrane (M) proteins are translated in the ER of host cells. Viral RNA and S, M, and E proteins assemble in the ERGIC to generate a new SARS-CoV-2, which is then released from the host cell by exocytosis. ER, endoplasmic reticulum; ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine 2; ERGIC, endoplasmic reticulum-Golgi intermediate compartment.

It is worth noting that in addition to common respiratory symptoms, liver function indicators are also anomaly changed in a considerable proportion of COVID-19 patients[19]. COVID-19-related liver injury covers the whole spectrum of liver injuries that a patient develops after the onset of illness, regardless of any pre-existing liver disease[20-23]. Multiple studies have demonstrated that elevated serum liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are independent risk factors for adverse COVID-19 outcomes, including shock, ICU admission, and even death[24-28]. Moreover, the concentrations of ALT and AST in critically ill patients are significantly increased[29]. Nevertheless, some studies claimed that elevated liver enzyme levels do not significantly contribute to mortality[30-31]. The prognostic significance of abnormally elevated liver enzymes remains unclear. Our analysis on the relevant clinical data uncovered that the liver function abnormalities observed in COVID-19 cases are mainly manifested by elevated serum transaminase and lactate dehydrogenase (LDH) levels[1, 15-16, 31-36]. A multicentre retrospective cohort study of 5 771 COVID-19 pneumonia patients in Hubei Province revealed that elevated liver enzymes were strongly associated with poor prognosis. Of the liver enzymes listed in a study documented by Lei *et al.*, increased AST appears to be the risk factor with the best association with death[37]. In a cohort study of 5 700 confirmed patients in New York City, United States, elevated AST was observed in 58.4% and ALT in 39%[38]. COVID-19 patients with abnormally elevated liver enzymes are more likely to develop acute respiratory distress syndrome[24]. The peak level of liver function tests in patients is related to the severity or prognosis of COVID-19[27]. A study from Germany showed that elevated ALT and gamma-glutamyl transferase (GGT) and hypoalbuminemia were correlated with higher rates of ICU admission and mechanical ventilation. Hypoalbuminemia is a highly independent prognostic risk factor, especially when it is combined with elevated transaminases or transglutaminase. Albumin levels should be measured regularly and taken as an important reference for diseaseprognosis[26].

4 Possible causes of liver damage in COVID-19

The liver is the body's largest detoxification organ and plays a critical role in metabolism. Even a mild loss of liver function can alter the safety profile and therapeutic efficacy of antiviral drugs

metabolized by the liver. The liver can also generate coagulation factors, secrete bile, and metabolize toxic substances, to maintain the normal function of the human body. Therefore, impaired liver function can impose a huge impact on the health status of patients with COVID-19. Based on the data available to date, we came up with a few thoughts about the possible causes of COVID-19-related liver injury (Fig. 2), as outlined below.

4.1 Direct toxic effects of virus in the liver

Earlier studies discovered that in the autopsy of SARS patients, a crowd of virions appeared in the liver and other parenchymal organs and vascular endothelium in addition to in the lungs[39]. More recently, using in situ hybridization, Sonzogni *et al*. detected virus particles in liver specimens from COVID-19 patients, especially in sinusoidal and portal endothelial cells[40]. Other studies have found that complete virus particles exist in the cytoplasm of liver cells[41].

Through single-cell RNA sequencing, we found that ACE2 was expressed in human lung cells with an expression rate of 0.64%, of which 83% were alveolar type II cells[42]. In the gastrointestinal system, ACE2 is distributed in the intestinal epithelium, with the highest content in the duodenum and small intestine and a lower content in the stomach and large intestine. ACE2 receptors are also expressed in the nasal and oral mucosa, cardiovascular system, kidney, pancreas, and brain[43-44]. In the liver, ACE2 is highly expressed in arteriovenous endothelial cells but hardly found in cells such as sinus endothelial or Kupffer cells. Notably, ACE2 is expressed in 59.7% of cholangiocytes and 2.6% of hepatocytes, a 20-fold difference in mean expression levels[45]. Moreover, the distribution pattern of ACE2 in cholangiocytes even resembles that in alveolar type 2 cells. Therefore, we have reason to believe that the virus may be able to directly target ACE2-positive cholangiocytes to induce bile duct damage, thereby causing liver damage. A study demonstrated that some confirmed cases had significantly elevated GGT on admission, which was further increased to higher levels during hospitalization[24]. Weber *et al*. also identified GGT as a very significant independent risk factor for poor prognosis[26]. GGT is regarded as a "cholangiocyte-related enzyme", which may mediate the direct toxic effect of SARS-CoV-2 on cholangiocytes. Zhao *et al*.[46] constructed human liver ductal organoids coexpressing ACE2 and TMPRSS2 to study the relationship between *ex vivo* SARS-CoV-2 infection and liver tissue injury[46]. The tight junctions of cholangiocytes provide protection for parenchymal liver cells against toxic bile components. Upon viral infection, the barrier function and bile acid transport function of bile duct cells may be impaired due to deregulation of the formation of tight junctions and the expression of genes involved in bile acid transport. For example, viral infection reduces the mRNA expression of cholangiocyte tight junction proteins such as claudin 1[46], resulting in impairment of cholangiocyte barrier function. Toxic bile may leak into the pericellular space, diffuse into adjacent liver tissue and cause liver damage.

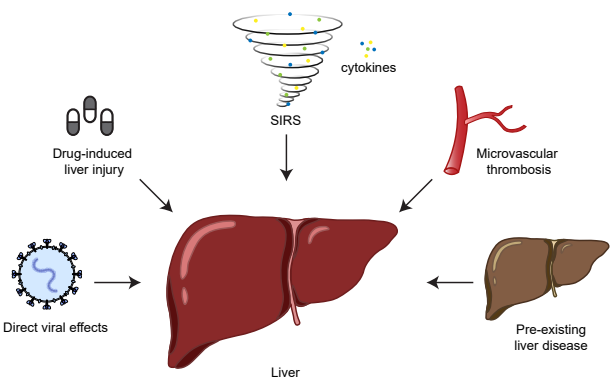

Fig. 2 Mechanisms of COVID-19-asscociated liver injury
SIRS, systemic inflammatory response syndrome.

Another potential route of transmission is the liver-gut axis. Gastrointestinal symptoms, including diarrhoea, vomiting, nausea and inappetence, are common symptoms of COVID-19[15, 35, 47-48] and may even precede respiratory symptoms[49]. Numerous data suggest that the gastrointestinal tract may be the main site of SARS-CoV-2 infection[50]. ACE2 is widely distributed in various organs of the gastrointestinal system, with the highest expression in the colon, and studies have shown that ACE2 and TMPRSS2 are co-expressed in ileal and colon enterocytes[51]. Viral RNA and virions were found in the faeces and autopsies of confirmed patients. Viral infection of the gastrointestinal tract may damage the intestinal epithelium and vascular barrier, ultimately leading to viral entry into the liver through the portal vein[52]. Therefore, SARS-CoV-2 may infect hepatocytes through the liver-gut axis, leading to further liver damage.

4.2 Drug-induced liver injury

COVID-19-related liver injury may be drug-related. One of the primary clinical manifestations of COVID-19 is fever, and antipyretic drugs such as acetaminophen are often used to reduce fever during empirical treatment. In previous studies, acetaminophen has been shown to be a risk factor for liver failure, and higher doses are more likely to cause liver damage, leading to an increase in liver enzymes[53]. A combination of antibiotics and antiviral drugs, as well as systemic glucocorticoids, is often used to treat COVID-19[35, 54]. Antibiotics, antiviral drugs, and systemic glucocorticoids are positively associated with

abnormal liver enzyme levels in COVID-19 patients according to a multicentre retrospective cohort study[37].

The commonly used antiviral drugs lopinavir and ritonavir are mainly metabolized in the liver, and side effects of these agents, such as liver dysfunction, may occur. Patients receiving lopinavir/ritonavir combination therapy during hospitalization were more likely to develop liver dysfunction[55]. In addition, some hepatotoxic drugs, such as oseltamivir, remdesivir, tocilizumab, and interferon, have been used to fight COVID-19. Drugs should be selected carefully in the treatment of COVID-19, and liver function should be monitored during administration. Especially in patients with impaired liver function, hepatotoxic drugs should be avoided as much as possible, and the combined use of hepatotoxic drugs should be strictly prohibited.

4.3 System inflammatory response syndrome

Similar to SARS-CoV and MERS patients, COVID-19 patients have high levels of inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8, IL-10, interferon(IFN)-γ, monocyte chemoattractant protein (MCP)-1 and tumor necrosis factor (TNF)-α[1]. In addition, the levels of c-reactive protein (CRP), calcitonin and serum amyloid A increase significantly. A large number of immune cells release inflammatory cytokines, leading to acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS), which will cause respiratory system damage and liver injury as well. When the liver is infected with the virus, hepatocytic apoptosis may be induced and/or promoted. In the SIRS state, proinflammatory cytokines act on the liver to cause mitochondrial dysfunction and may also activate the inflammasome through damage-associated molecular patterns (DAMPs). These two processes can render a liver with low functional reserve extremely vulnerable to damage[56].

4.4 Microvascular thrombosis and hepatic ischaemia-reperfusion injury

COVID-19 can manifest as extensive vascular involvement accompanied by coagulation dysfunction and thrombosis. In addition to alveoli, ACE2 is also widely distributed in endothelial cells, and the virus likely infects these cells, leading to diffuse endotheliitis. Endothelial function is a major determinant of microvascular function, and endothelial dysfunction can cause vascular inflammation, hypercoagulability, tissue oedema, vasoconstriction, and even organ ischaemia[57-58]. Pathological examination of the liver also revealed microthrombi^{+} in a COVID-19 patient.Thrombotic complications are one of the critical factors of COVID-19 deaths[59]. During ischaemia-reperfusion, reactive oxygen species can cause a series of destructive cellular responses, inflammation, and cell damage, resulting in hepatic ischaemia-reperfusion injury. Patients with severe COVID-19-induced hypotensive shock or severe hypoxemia develop ischaemia-hypoxia-reperfusion liver injury. During reperfusion after ischaemia, reactive oxygen species can cause a series of destructive cell responses, inflammation, and cell damage, resulting in hepatic sinusoidal endothelial cell damage, and this microcirculation disorder further aggravates hepatic ischaemia and hypoxia, thereby aggravating liver damage and creating a vicious cycle. Notably, cold accelerates the constriction of blood vessels, especially microvessels, which exacerbates inflammatory responses by inducing hypoxia and stimulating aerobic glycolysis in cells[8].

4.5 Pre-existing chronic liver disease

More than 122 million people live with chronic liver disease, of which more than 10 million have decompensated liver diseases, which is a huge global burden[60]. There are two blood supply systems in the liver: hepatic arterial system and portal venous system. However, despite its ability to compensate for hyperplasia, the liver may still be damaged by systemic inflammation. Therefore, if a patient with COVID-19 has pre-existing chronic liver disease and the liver lacks adequate functional reserves, liver failure can occur because of ARDS and SIRS. Since the onset of the pandemic, the risk factors for pre-existing chronic liver disease may have overlapped with COVID-19 to cause adverse outcomes[19]. A study including 202 patients analysed the impact of previous non-alcoholic fatty liver disease (NAFLD) on the development of liver damage in COVID-19 patients. The results indicate that NAFLD is highly correlated with COVID-19 progression and that patients with NAFLD are more likely to develop severe COVID-19[61]. After SARS-CoV-2 infection, the incidence of adverse outcomes in patients with chronic liver disease is distinctly higher than that in the general population, and vaccination of this population should be strengthened.

5 Possible link between liver injury in COVID-19 patients and cold environment

As early as in ancient Greece, humans have realized the close relationship between disease spread and seasons and temperatures[62]. Cold temperature is now widely recognized as a key factor in the spread of the winter flu[63]. A study reviewed SARS outbreaks in four affected cities in China and noted a significant correlation between temperature and viral transmission[64]. Some research models also suggest that cold climate is more favourable for viral transmission, relative to dry and tropical climate[65]. Wang *et al*. determined that temperature has a significant impact on the spread of COVID-19, with lower temperatures favoring the

growth and spread of viruses, and thus countries and regions with lower temperatures should implement more stringent and rigorous control measures[66].

In addition, cold stimulation is known to promote vasoconstriction and tachycardia[67]. Exposure to low-temperature environment may activate the sympathetic nervous system and renin-angiotensin system, cause blood pressure to rise, and aggravate hypertension, leading to cardiovascular and cerebrovascular complications, such as arrhythmia, myocardial ischemic infarction, and stroke[68-69]. The underlying diseases such as hypertension and cardiovascular disease are one of the highly related risk factors for COVID-19, and it is therefore rational and logical to infer that low temperature stimulation is a potential risk factor for COVID-19. On the other hand, the liver has dual blood-supply systems and its high-intensity metabolic activities require a large volume of blood supply. Low temperature stimulation causes vasoconstriction and other circulatory system disorders. In the case of systemic stress, the compensatory reduction of hepatic blood flow supply may induce hepatic ischemia and hypoxia, resulting in hepatic ischemia-reperfusion injury[70-71]. Active oxygen free radicals may damage liver cells and small blood vessels, thereby aggravating liver damage[72].

6 Conclusion

In addition to common respiratory symptoms, liver damage is also a common feature of COVID-19. We describe here the viral structure and life cycle of SARS-CoV-2 in host cells and summarize the clinical manifestations of COVID-19-associated liver injury. Of note, we proposed multiple causes as the possible etiology and mechanisms for COVID-19-associated liver injury: direct toxic effects of SARS-CoV-2 on the liver, drug-induced liver injury, systemic inflammatory response syndrome, microvascular thrombosis and hepatic ischemia-reperfusion injury, and/or exacerbation of previous chronic liver disease. Notably, COVID-19 occurs mostly in temperate countries with cold winters of low temperature which plays a key role in the transmission of SARS-CoV-2 and may as well promote the COVID-19-related liver injury. Yet, our understanding of the impact of cold stress on COVID-19-induced liver injury and the underlying mechanisms is still far from complete; therefore, the liver injury associated with COVID-19 in cold regions deserves more attention.

Conflicts of interests

All authors declare no competing interests.

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