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Acute-On-Chronic Liver Failure in Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Abstract

The Coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a significant impact on the lives of millions of people, including those with other concomitant diseases, such as chronic liver diseases. To date, seven coronaviruses have been identified to infect humans. The main site of pathological action of the virus is lung tissue. However, a substantial number of studies have proven that SARS-CoV-2 shows affinity towards several organs, including those of the gastrointestinal tract and the liver. The current state of evidence points to several proposed mechanisms of liver injury in patients with COVID-19 and their combination. Liver impairment is considered to be the result of the direct effect of the virus on the hepatic tissue cells, a systemic reaction consisting of inflammation, hypoxia and cytokine storm, drug induced liver injury, with the possible contribution of a perturbed gut-liver axis. Reactivation of chronic hepatic disease could be another factor for liver impairment in patients with SARS-CoV-2 infection. Acute-on-chronic liver failure (ACLF) is a relatively new syndrome that occurs in 10–30% of all hospitalized patients with chronic liver disease. It is crucial to recognize high-risk patients due to the increased morbidity and mortality in these cases. Several published scientific papers have reported virus infection as a trigger factor for ACLF. However, to date, the number of published relevant studies describing the presence of ACLF in patients with acute SARS-CoV-2 infection is scarce. In this minireview we summarize

the current state of knowledge regarding the relation between acute-on-chronic liver failure and acute SARS-CoV-2 infection.

INTRODUCTION

Introduction

The COVID-19 (Corona Virus Disease 2019) pandemic caused by the novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) has had a significant impact on the lives of millions of people, including those with other concomitant diseases such as chronic liver diseases.

This mini review is focused on acute-on-chronic liver failure (ACLF) in cases involving COVID-19. Acute-on-chronic liver failure (ACLF) is a relatively new syndrome that occurs in 10–30% of all hospitalized patients with chronic liver disease [1]. Patients with ACLF are considered to be high-risk patients when they become infected with SARS-CoV-2 because of the increased morbidity and mortality in these cases. The etiology of chronic liver diseases varies substantially (Table1). Even after more than two years of global pandemic, this is a rather underestimated topic with an uneven ratio of patients with chronic liver disease who have been infected with SARS-CoV-2.

Therefore, understanding the pathophysiology mechanisms of SARS-CoV-2 virus affecting the liver along with improved stratification of patients with chronic liver diseases can ultimately result in better management, with a significant reduction in mortality and morbidity in the case of COVID-19 infection.

MAIN TEXT

Pathophysiology

To date, seven coronaviruses have been identified to infect humans. While human coronaviruses HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1 cause a "common cold", the other three, severe acute respiratory syndrome-related coronavirus (SARS-CoV) (2002-2003), Middle East respiratory syndrome-related coronavirus

(MERS-CoV) (2012) and SARS-CoV-2 (from 2019), are highly pathogenic to humans and cause severe acute respiratory syndrome (SARS), with significant morbidity and mortality [2], [3]. The main site of pathological action of these viruses is lung tissue. It has been widely hypothesized that the SARS-CoV-2 virus uses the ACE2 receptor to enter the respiratory tract cells [4]. The ACE2 receptor is expressed not only in the lungs, but also in other organs, such as the heart, intestine (ileum), pancreas, kidneys and endothelium, which may explain the multi-organ effect of virus infection [5]. A huge number of studies have proved that SARS-Co-V-2 shows affinity towards several organs, including those of gastrointestinal tract, such as the liver [6]–[9].

Evidence that coronaviruses could damage liver cells through the induction of apoptosis by activation of caspase has been known for some time [10], [11]. Liver impartment was also confirmed in the case of SARS-CoV during the pandemic in the early years of new millennium, and several studies have shown the direct negative impact of SARS-CoV on the liver on the cellular level [12], [13] . Liver biopsies in these patients revealed common pathologic findings, such as the presence of acidophilic bodies, the ballooning of hepatocytes and mild to moderate lobular activities [12]. Studies based on autopsies of SARS-CoV victims showed that the virus was detectable in 41% of liver tissue samples with a relatively high viral load [14]. Hepatocellular necrosis, mitoses, cellular infiltration and fatty degeneration were all visible in these biopsies [14]. Interestingly there was no detection of viral particles in liver specimens from patients with MERS [15].

Almost three years after the COVID-19 pandemic broke out, there is undoubtedly a large amount of scientific and clinical evidence that COVID-19 is in many cases directly connected with abnormal liver function to a varying extent. Right from the beginning of the pandemic there were indications of a similar mechanism of influence of SARS-CoV and SARS-CoV-2 on hepatocytes [16], although the strains bear approximately 79% structural similarity [17] . It was pointed out that recipients of liver transplant could be at higher risk for virus transmission through the transplanted organ [18]. The fact that non-alcoholic fatty liver disease (NAFLD) presents with a

proinflammatory hypercoagulable state could be associated with a more severe course of the disease and thrombosis in these patients when infected with SARS-CoV-2 [19]. The structural hepatic abnormalities could persevere even after acute COVID-19, as was shown in a study using multiparametric ultrasound [20]. These changes include increased ultrasound image of liver stiffness and increased viscosity and attenuation, which could be indicative for various types of parenchymal impairment, including fibrosis, inflammation and steatosis [20].

The current state of evidence points to several proposed mechanisms of liver injury in patients with COVID-19 (Figure 1). Liver impairment is considered to be the result of the direct effect of the virus on hepatic tissue cells, a systemic reaction consisting of inflammation, hypoxia and cytokine storm, and drug induced liver injury [21], [22],[23]with the possible contribution of a perturbed gut-liver axis [24]. Reactivation of chronic hepatic disease could be another factor for liver impairment in patients with SARS-CoV-2 infection [25].

Moderate microvesicular steatosis and mild inflammation in the lobular and portal area was observed in the liver tissues obtained during autopsies of COVID-19 victims [26]. This is, however, not disease-specific, as it could also be detected in liver tissue samples in patients with sepsis or drug induced liver injury (DILI) [26].

Direct influence of the virus on the liver cells

There are several proposed mechanisms of SARS-CoV-2 influence on hepatocytes. One of the early histological and ultrastructural studies identified typical coronavirus particles in the hepatocytes' cytoplasm, with mitochondrial swelling, endoplasmic reticulum dilatation and glycogen granule decrease with a general histological picture of massive hepatocyte apoptosis and binuclear hepatocytes [27].

One possible explanation is based on the binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) receptors on the cholangiocytes, leading to their disfunction and induction of a local and systemic inflammatory response, ultimately resulting in liver injury [28]. Although the ACE2 receptor is present on the

biliary epithelial cells, it was repeatedly observed that the bilirubin level is normal in most of the cases [29], regardless of severity of the disease itself [30]. Although the effect of the virus is primary on the bile duct epithelial cells, some researchers proposed that the compensatory hyperplasia of hepatic parenchymal cells induce the up-regulation of ACE2 receptor expression in liver tissue [22]. This could be one of the pathways by which SARS-CoV-2 is responsible for direct liver parenchyma injury.

A study by Zhao *et al* showed a significant increase of viral loads in cholangiocytes 24-hours post-infection with a substantial decrease 48 h after infection [31]. Their data also indicated that the virus impairs the bile acid transporting function of cholangiocytes and impairs the luminal barrier by modulating the expression of genes involved in sustaining the tight junctions and transportation of bile acids [31]. The direct viral cytopathogenic effect is predominantly on target cells that express ACE2 and TMPRSS2 [31]. ACE2 expression is higher in cholangiocytes (59.7%) than in hepatocytes (2.6%) [32].

Stebbing *et al* reported massive induction of ACE2 expression in hepatocytes after 16 h of exposure to Interferone- α2 (IFN- α2) and Interferone- β [33]. Exposure to Interferone- γ, Tumor necrosis Factor- α and Interleukins (IL-1, IL-6, IL-10,Il-18) does not have the same effect. They further pointed out that the effect was strongest with Interferone- α2. Therefore, it has been proposed that the increased levels of predominantly IFN- α2 in patients with severe inflammatory response to SARS-CoV-2 infection could lead to significant ACE2 expression in parenchymal liver cells, contributing to virulence and further damage to the cells by the virus [33].

Another study focused on the expression of ACE2, TMPRSS2 and FURIN (paired basic amino acid-cleaving enzyme) levels in various cells within the liver tissue. It was shown that these receptors are expressed across various cell types. ACE2 is mostly expressed in cholangiocytes and hepatocytes, TMPRSS2 in cholangiocytes, hepatocytes, periportal liver sinusoidal endothelial cells, erythroid cells, non-inflammatory macrophages and T cells, and FURIN is expressed through all cell lines within liver tissue [23].

A recent study by Wanner *et al* has provided multilevel evidence of SARS-CoV-2 human liver tropism by using a wide range of clinical, histopathological, virological, molecular and bioinformatic approaches [9]. Their data showed strong upregulation of JFN responses, JAK-STAT signaling and liver-specific metabolic modulation. Mismatch of the expression of the ACE2 protein and the location of the SARS-CoV-2 spike protein in Kupffer cells was also observed in this study [9]. Also, the main pro-inflammatory cytokines, such as IL-6, which is responsible for cytokine storm, is regulated by JAK-STAT signaling. Due to this known pathophysiological mechanism, JAK inhibitors such as baricitinib have been used for treatment and have shown improvement in clinical outcomes in patients infected with SARS-COV-2. On the other hand, considering the potential adverse effects of this drug on the liver, more studies are needed to establish the proper dosage and timing, so the risk/benefit ratio can be determined in patients with high vulnerability for drug induced liver injury [33], [34]. Although several medications were used for treating COVID-19 with different outcomes, the "perfect" compound is still missing. However, results of the studies mentioned herein could facilitate the push of research towards targeting signaling pathways, receptors or even the virus itself.

Another study proposed high-density lipoprotein scavenger receptor class B member 1 (SRB1) as a facilitator for cell entry for the SARS-CoV-2 because of its strong protein expression in human liver cells [35]. This is based on the observation that SRB1 plays a crucial role for hepatitis virus C (HCV) cell entry [36]. SARS-CoV-2 shares some molecular features with HCV in the means of liver tropism [9]. Therefore, it is possible to assume that SRB1 could facilitate SARS-CoV-2 entry into liver cells along the well described ACE2 pathway.

It is interesting to compare the mechanism of action of SARS-CoV-2 with other coronaviruses. An indirect mechanism that resulted in hepatic damage through a complex inflammatory cascade was proposed in case of the SARS-CoV virus [13], [37]. On the other hand, MERS-CoV requires dipeptidyl peptidase-4 (DPP-4) receptor for cell entry, which is different from SARS-CoV-1 and SARS-CoV-2 adherence mechanisms.

Thus, the pathophysiology of the disease is different to some extent. The liver damage observed in MERS-CoV cases was mostly mild. It is difficult to determine whether this is result of a direct action of the virus or the inflammation-mediated reaction due to a lack of sufficient data [37]. An interesting fact is the comparison with hepatitis viruses, which, from a phylogenetic point of view, have developed a natural affinity for the liver tissue and whose infections are of a stealthy nature. Despite the fact that the mechanism of infection is not fully understood, it is assumed that hepatitis viruses do not have a direct cytopathic effect on hepatocytes but rather to trigger immune mechanisms that result in liver damage [38]–[40].

Drug-induced liver injury

Lopinavir/ritonavir are widely used antiviral drugs that are predominantly metabolized by the liver. These drugs were shown to have a potentially damaging effect on the liver by inducing inflammation and lipid metabolism disorders using the endoplasmic reticulum stress pathway and also could cause apoptosis of hepatocytes *via* the caspase system [22].

Integration of drug cytochrome P-450 could contribute to the secondary toxicity of several drugs commonly and widely used in the treatment of COVID-19 such as paracetamol (acetaminophen), lopinavir/ritonavir or azithromycin [41]. The meta-analysis by Yadav *et al* pointed out that treatment by lopinavir/ritonavir is strongly correlated with liver injury, while other commonly used medications are not significantly connected with hepatic impairment [42].

Another commonly used drug in COVID-19 treatment is the antiviral drug favipiravir. It was reported that favipiravir used with interferon alpha resulted in liver injury in 2.9% of these patients [22].

Result of systemic inflammation response and general hypoxia

One of the factors contributing secondarily to the hypoxic damage of hepatocytes could be hepatic congestion due to high positive end respiratory pressure in critically ill, mechanically ventilated patients [32]. Platelet activation is well described in patients with a serious course of COVID-19, and it has been proposed that vascular dysfunction due to endotheliopathy and platelet activation in response to a systemic inflammatory response could contribute to impaired liver function, predominantly in patients with a pre-existing chronic liver disease [43].

Systemic inflammatory response generally leads to cellular ischemia and abnormal coagulation with micro thrombotic events. Inflammatory response in COVID-19 is characterized by high lymphocyte activation, neutrophilia with significantly elevated levels of serum interleukins, tumor necrosis factor, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon inducible protein 10, monocyte chemotactic protein 1 and macrophage inflammatory protein 1 alpha [44]. Accumulation of T cells in the post mortem liver histological findings further supports the theory of immune-mediated response related to liver damage [44].

Role of immunity

A well-functioning immune system is essential in the fight against infections. The liver is widely known to play an important role in the body's immune response to an infectious stimulus. Many factors are involved in the physiological immune response of the host, such as immune cells, antimicrobial peptides and so-called pattern recognition receptors (PRRs), which can detect dangerous microbial signals through molecular patterns [45]. The liver is the major source for the production of PRRs, which have two main functions: complement activation and opsonization, which is an important step of phagocytosis [46]. An important subgroup of PRRs is the toll-like receptors (TLRs), which play a crucial role in several liver disorders, such as alcoholic liver disease, non-alcoholic steatohepatitis, viral hepatitis, hepatic fibrosis, autoimmune hepatitis and liver cancer. Thus, the liver plays an important role in the adaptive immunity of the body, which is essential against infections and not only bacterial ones. Liver cirrhosis

interferes and damages the proper functioning of adaptive immunity by impairing the synthesis of PRRs and various proteins, which can result not only in immune dysfunction but also in immunodeficiency [47], [48]. The association between SARS-CoV-2 and the activation of the pro-inflammatory cascade results in excessive overproduction of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-alpha, and attenuation of the body's anti-inflammatory response, resulting in the development of the so-called cytokine storm, as it has been repeatedly described in the case of COVID-19 infection. The cytokine storm possibly reflects the severity of the disease [49]. Cirrhotic patients are at a higher risk of developing a systemic inflammatory response syndrome (SIRS) with overproduction of the above-mentioned cytokines, which, together with deregulation of the immune response and ongoing acute infection, may have fatal consequences. ACLF is a relatively novel umbrella term where acute and chronic liver insults exist along with an imbalance between systemic pro-inflammatory and anti-inflammatory responses. All the above-mentioned could then trigger an uncontrolled and complex sequence of events, which may result in ACLF with fatal consequences to patients with acute COVID-19 [47], [50].

SARS-CoV-2 infection in patients with known liver disease

A study considering histological finding from COVID-19 victim biopsies showed a 10-fold increase in the number of ACE-2 positive cells in the liver (predominantly in the form of activated hepatic stellar cells) in patients with preexisting alcohol use disorder compared to patients with normal liver function who died pre-pandemic [51]. As chronic alcohol abuse is related to chronic liver damage, these findings may have potential clinical implications. These are further supported by evidence of massive up-regulation of ACE2 (a 97-fold increase in a widespread parenchymal pattern) in cirrhotic liver and high-fat diet induced NASH [52]. The significant ACE2 upregulation in liver cells was also observed in animal models with high-fat diet induced non-alcoholic steatohepatitis, with concomitant treatment with pioglitazone [24]. Therefore, diabetic patients treated with PPARγ agonist and chronic liver impartment have a

higher susceptibility to SARS-CoV-2 infection, and possibly with more severe consequences. There is also evidence that the levels of hepatokines is disturbed in patients with COVID-19, and these are associated with disease severity and outcomes [53]. A relationship between hepatokines, liver steatosis and metabolic diseases, such as diabetes mellitus [54], has been suggested. ACE2, as a main receptor for viral entry and a modulator of inflammatory responses, is also considered a potential target for treatment strategies. There are only a few ACE2-related molecules (e.g. DIZE, Ang 1-7) that are tested in humans. Some of these molecules can, for example, reduce tissue ACE2 activity. Many of them have already been tested on animal models; however extensive research in humans is still needed [55].

In patients with viral hepatis B (HBsAg-positive and hepatitis B core antibody positive patients) a higher risk of HBV reactivation with liver injury and fatal course of the COVID-19 was observed [56]. This could be considered a secondary result of SARS-CoV-2 infection on the liver in patients with chronic hepatic disease.

Clinical aspects of ACLF and COVID-19

Acute-on-chronic liver failure (ACLF) is a relatively new syndrome that occurs in 10–30% of all hospitalized patients with chronic liver disease [1]. It is crucial to recognize high-risk patients due to the increased morbidity and mortality in these cases. The main hepatological societies (APASL, EASL and AASLD) have proposed their own definitions of ACLF, each of which differs from the others [57] (Table 2). However, despite several differences, the main criteria are roughly the same. These are dominantly the presence of liver disease, precipitant factors of ACLF and hepatic or extrahepatic failure [58]–[60]. One definition was proposed by the World Gastroenterology Organization in 2014 to unite and simplify the diagnosis. It defined ACLF as a syndrome with very high short-term mortality in patients with chronic liver disease with known or unknown cirrhosis characterized by acute hepatic decompensation, resulting in liver failure and at least one extrahepatic failure [61], [62].

Activated pathogen-associated molecular patterns (PAMPS) and damage-associated molecular patterns as drivers of systemic inflammation are proposed as the main etiopathological factors [63]. Activation of this systemic inflammatory response can be triggered by various conditions. Identification of precipitating factors can predict the course of the disease. The trigger of ACLF depends on the region. While in Asian populations this is usually reactivation of hepatitis B, in Western countries it is usually alcohol hepatitis, gastrointestinal bleeding or another infection [57], [62].

Several published studies have reported virus infection as a trigger factor for ACLF. Infection with Hepatitis B virus could lead to occurrence of a specific syndrome – hepatitis B virus-related ACLF with wide variety of disease course [64], [65]. Hepatitis A and hepatitis E viruses lead significantly less often to the development of ACLF [66], [67]. The ability of the SARS-CoV-2 virus to adhere to angiotensin-converting enzyme 2 (ACE2) on the hepatocyte and cholangiocyte membrane is known [68]. However, the data describing the prevalence of ACLF in patients with chronic liver diseases suffering SARS-CoV-2 infection are scarce. Iavarone *et al* published a retrospective study on a cohort of 50 cirrhotic patients infected with SARS-CoV-2 with an observed high mortality rate that exceeded 34% [69]. ACLF was present in 28% of patients, and death related to liver impairment was present in 29% of the cases. An independent factor for worse prognosis of COVID-19 in patients with concomitant chronic liver disease is the presence of an alcohol-related liver disease and ongoing drinking [69]. Reports of a predictive role of the CLIF and MELD scores in the setting of ACLF influenced by acute SARS-CoV-2 infection are emerging [70]. Sarin *et al* investigated a population of 228 patients with liver disease (185 patients with chronic liver disease and 43 patients with cirrhosis) and found that 43% of patients with chronic liver disease infected with SARS-CoV-2 also presented with acute liver injury. Almost 12 percent (11.9%) of cirrhotic patients in this patient group developed ACLF [71]. Complications related to liver function deterioration were present in half of the patients with decompensated cirrhosis, with higher mortality. Obesity was identified as a predictor of worse prognosis. In a multicentric study Bajaj *et al* reported the incidence of ACLF within a

group of cirrhotic patients infected with SARS-CoV-2 as high as 36%. Interestingly there was no significant difference in mortality rate compared to patients with cirrhosis and negative for acute SARS-CoV-2. Another study from Shalimar *et al* recorded the presence of ACLF in 9 of 28 patients from their study cohort [72]. Mortality in these patients reached 100% [72], and mechanical ventilation was associated with poor prognosis. Besides a scarce number of prospective or retrospective cohort studies, there are also several individual case reports describing the occurrence of ACLF in a patient with chronic liver disease [68].

CONCLUSION

Conclusion

SARS-CoV-2 is a virus with multiorgan affinity. A substantial percentage of patients with COVID-19 could be simultaneously diagnosed with a liver impairment to a varying degree, with different prognosis and duration. The virus affects the liver *via* different pathways (table 3). Patients with chronic liver disease are at a higher risk for poor disease outcome when infected with the novel coronavirus. One of the lesser reported and described subgroups of these patients are those with developed acute-on-chronic liver failure. Patients with chronic liver disease and cirrhosis simultaneously infected with SARS-CoV-2 are at a risk of developing ACLF, with poor prognosis for survival. Available published data are heterogenous, and the incidence of ACLF varies from 11.9% to 36%.

Although the clinical management of patients with liver diseases who contracted SARS-CoV-2 infection is still evolving, several consensus guidelines have been developed [73]–[75]. These guidelines were created based on multicenter and international studies, which can provide guidance for better clinical management. Several steps should be followed by clinicians to identify patients with higher risk of liver disease progression according to these recommendations. A thorough history and physical examination should be a cornerstone in the diagnosis process. It is also crucial to further investigate the possible presence of underlying chronic liver diseases. For doing this, a

serological test for hepatitis viruses, frequent monitoring of liver enzymes or implementation of widely available imaging examinations, such as ultrasound, could be used. Also important is to thoroughly review patients' chronic and currently administered medications due to the possibility of liver damage related to specific drugs (e.g. antivirals, antibiotics, anti-inflammatory medications *etc.*).

To summarize, it is important to consider patients with ACLF as a distinct patient population with a high risk for a severe course of SARS-CoV-2 infection and to manage them appropriately.

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