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Covid-19 and Liver Injury: Mechanism Perspective

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1. Abstract

In this review, our understanding of covid-19 in people with liver disease is evolving. When making decisions related to covid-19 infections or prevention, having up-to-date information is critical. This review discusses the hepatotropism of SARS-CoV-2, including the differential expression of viral receptors on liver cell types, Covid-19 liver injury and the possible mechanism of liver injury in Covid-19. Lastly, we provide an overview of the pathogenesis and timeline of post-acute sequelae of SARS-CoV-2(PASC) colloquially as Long Covid on gastrointestinal system. SARS-CoV-2 might infect the liver and is a key factor in liver dysfunction, however, the direct toxic attack of SARS-CoV-2 on the liver is still questionable and needs more evidences.

2. Mechanism Perspective

Our understanding of covid-19 in people with liver cirrhosis is evolving. When making decisions related to covid-19 infections or prevention, having up-to-date information is critical (AASLD) [1]. Since the early days of the SARS-CoV-2 pandemic, there have been concerns that patients with advanced liver disease might be at increased risk of morbidity and mortality following SARS-CoV-2 infection. Prospective data from ongoing multicentre studies confirmed that patients with cirrhosis, particularly those who are decompensated, are at a higher risk of hospitalization, ventilation and death than those without chronic liver disease. Older age and cirrhosis severity as assessed by Chid-Push stage, are the most important predictors of mortality. Although most deaths in cirrhosis with severe COVID-19 are from respiratory failure, the pathophysiological mechanisms supporting this association remain unclear. One hypothesis is that prothrombotic alterations driven by COVID-19 tilt the fragile haemostatic balance of hospitalized patients with decompensated cirrhosis towards hypercoagulability, therefore leading to pulmonary venous micro thrombosis, parenchymal extinction and respiratory failure [2].

3. Hepatotropism of SARS-CoV-19

The virus spike protein binds ACE2 to gain cell entry and transmembrane serine protease 2 (TMPRSS2) and paired basic amino acid cleaving enzyme (FURIN) are also important for infection; therefore, the expression of these receptors provided early clues for putative hepatic permissive cells [3]. Single-cell RNA sequencing analyses in healthy livers have shown gene expression levels for ACE2 to be highest in cholangiocytes (comparable to alveolar type 2 cells), followed in turn by sinusoidal endothelial cells and hepatocytes [4,5]. However, in a combined analysis of three single-cell RNA sequencing datasets from liver tissue from healthy individuals, very few hepatocytes co-expressed ACE2 and TMPRSS2 [6]. Experimental cellular and organoid models have therefore been important in trying to decipher the permissibility of liver cell types to SARS-CoV-2 infection. Hepatocellular carcinoma-derived cell lines Huh-7 and HepG2 are able to support the complete viral life cycle [7]. However, replication in primary hepatocytes has not yet been confirmed. This discrepancy between cellular models could be related to the presence of cancer-associated mutations in hepatoma cell lines, such as the tumor suppressor p53, which, under normal conditions, serves to downregulate

intracellular SARS-CoV-2 replication [8]. Zhao et al. generated ACE2-expressing and TMPRSS2-expressing human liver ductal organoids that were able to recapitulate SARS-CoV-2 infection [9], suggesting that the bile duct epithelium could support pseudo particle entry. It is worth noting that the seemingly high SARS-CoV-2 entry receptor expression and viral permissibility of cholangiocytes is at odds with the non-cholestatic pattern of liver biochemistry typically found in COVID-19; the precise reasons for this aspect are currently unknown. However, it is possible that SARS-CoV-2 can undergo low level replication in cholangiocytes in vivo without triggering cell death. This process would be consistent with other reservoirs of long-term viral replication, such as in the small intestine, which can help shape memory B cell responses to the virus over time [10]. Human pluripotent stem cell-derived liver organoids comprising mostly albumin-expressing hepatocytes have also been shown to express ACE2 and permitted SARS-CoV-2 pseudo particle entry [11].

4. Liver Injury in Covid-19 Patients

An increasing number of studies have reported liver damage in patients with COVID-19 and several have reported COVID-19 patients to have an increased risk of liver dysfunction [12,13]. COVID-19 patients may incur different degrees of liver function damage with elevated aspartate amino transaminase (AST), glutamate moderately amino transaminase (ALT), and total bilirubin (TBil) [14,15] The risk of liver damage in severe and critically ill patients was higher than in mild patients in most studies. However, there was a subtle difference in the prevalence of lung injury and COVID-19 disease severity across studies, and the exact extent of liver involvement in the COVID-19 disease course remains uncertain [15,16]. In a meta-analysis of 12 studies comprised of 1267 patients, the pooled prevalence of liver injury was 19%, the prevalence of ALT elevation was 18%, the prevalence of AST elevation was 21%, and the prevalence of total bilirubin elevation was 6% [17. Jin et al reported that the incidence rate of elevated AST was significantly higher in patients with GI symptoms than in those without. Xu et al observed moderate micro vesicular steatosis and mild lobular and portal activity in the liver biopsy specimens of the patient with COVID-19, which provided evidence of liver injury [18]. It is worth noting that the elevated prothrombin time among COVID-19 patients with digestive symptoms is common, and several studies have reported thromboembolism as a presenting clinical feature of COVID-19 [19]. Therefore, liver function and the level of liver enzymes should be monitored early in COVID-19 patients with digestive symptoms.

COVID-19 may promote deterioration of liver function in patients who had been diagnosed with chronic liver disease previously and predict an increased risk for severe illness. Several studies have demonstrated that baseline liver disease severity is strongly associated with COVID-19-related morbidity and mortality; additionally, decompensated cirrhosis, hepatocellular carcinoma, and alcohol-related liver disease are risk factors for adverse outcomes from COVID-19 [20,21]. A multi-center study involving 867 patients with chronic liver disease and COVID-19 reported that 14.0% of patients died, 60.4% were hospitalized, 23% were admitted to the ICU, and 7.7% developed hepatic decompensation [22]. Moon et al [23] found that 23.3% of patients with cirrhosis and COVID-19 were admitted to the ICU, 17.5% were treated with invasive ventilation, 18.6% were given non-invasive ventilatory support, 4.9% were given renal replacement therapy, and 39.8% died. Nowadays, accumulated data suggest that SARS-CoV-2 infection in patients with cirrhosis appears to be a particularly lethal combination. Compared to the patients without baseline liver disease, the patients with baseline liver disease are prone to unfavorable prognoses. The mechanisms of liver injury in COVID-19 patients are complex. The higher overall mortality among patients with CLD and COVID-19 may be due to cirrhosis-associated immune dysfunction and metabolic syndrome, while it needs more research to confirm and explore [24,25].

5. Possible Mechanism of Liver Injury in Covid-19

There are a number of potential contributors to elevated liver enzyme levels in COVID-19. Liver biopsy results in patients with SARS-CoV-2 have been characterized by non-specific findings, including steatosis, mild lobular and/or portal inflammation, and vascular pathology [26,27,28]. In most cases, abnormal biochemistries are likely multifactorial with potential contributions from immune-mediated inflammatory response, drug-induced liver injury, hepatic congestion and extrahepatic release of transaminases [29] as well as possible direct infection of hepatocytes. Among hospitalized patients with COVID-19, elevations of serum AST levels positively correlate with levels of ALT but not with markers of muscle breakdown (such as creatinine kinase) or systemic inflammation (such as C-reactive protein (CRP) and ferritin) [30]. These findings imply that elevated liver enzymes in COVID-19 result from direct hepatic injury, although COVID-19-associated rhabdomyolysis is rarely reported [31]. Lastly, AST is often found to exceed ALT during the course of COVID-19, which would be atypical for a classic hepatocellular pattern of liver injury outside of specific contexts such as alcohol-related liver disease, certain drug-induced liver injuries (for example, lamotrigine), ischemic hepatitis and cirrhosis [30]. The mechanisms responsible for an AST-predominant aminotransferase elevation remain incompletely defined but could include COVID-19-related mitochondrial dysfunction30, SARS-CoV-2-induced hepatic steatosis26and altered hepatic perfusion secondary to micro thrombotic disease [26,32]. As with many other infections, SARS-CoV-2 is associated with systemic inflammation that could contribute to elevations in liver biochemistries via cytokine release [33]. Patients with substantial elevations in serum ALT levels often have high levels of CRP (which is synthesized by the liver), D-dimer, ferritin and IL-6 [34,35,36,37]. IL-6, which is produced by monocytes,

macrophages and T cells in response to activation of the innate and adaptive immune system, is the key driver of CRP production and high IL-6 levels are associated with liver injury in COVID-19 [34, 36]. Notably, IL-6 increases during COVID-19 illness, declines as patients recover and correlates with severity of the disease course [38].

There are several other potential contributors to abnormal liver biochemistries in COVID-19, including ischemic hepatitis, hepatic congestion related to cardiomyopathy, and transaminase release due to the breakdown of skeletal and cardiac muscle [39]. Venous and arterial thromboses are now a well-recognized feature of COVID-19 [40,41] including in the liver [26, 28], which could contribute to elevations in liver biochemistries. Lastly, drug-induced liver injury is likely to contribute to elevated liver enzymes and might have been more common early in the pandemic due to the use of experimental therapies [42]. However, no study has yet comprehensively mapped the pattern of liver function tests found within studies over the course of the pandemic. Specific COVID-19 treatments implicated in cases of drug-induced liver injury include lopinavir–ritonavir [43,44] tocilizumab [45, 46] and remdesivir. The hepatotoxicity of remdesivir has been subject to debate. Although randomized trials in COVID-19 demonstrate equivalent liver enzyme elevations between treatment and control groups [46], screening of the WHO safety reports database still reveals a statistically significant odds ratio for liver injury with the use of remdesivir [47]. Fortunately, these considerations are likely to become less clinically relevant in light of the SOLIDARITY trial showing no benefit of remdesivir in hospitalized patients with COVID-19 [48] (Figure 1).

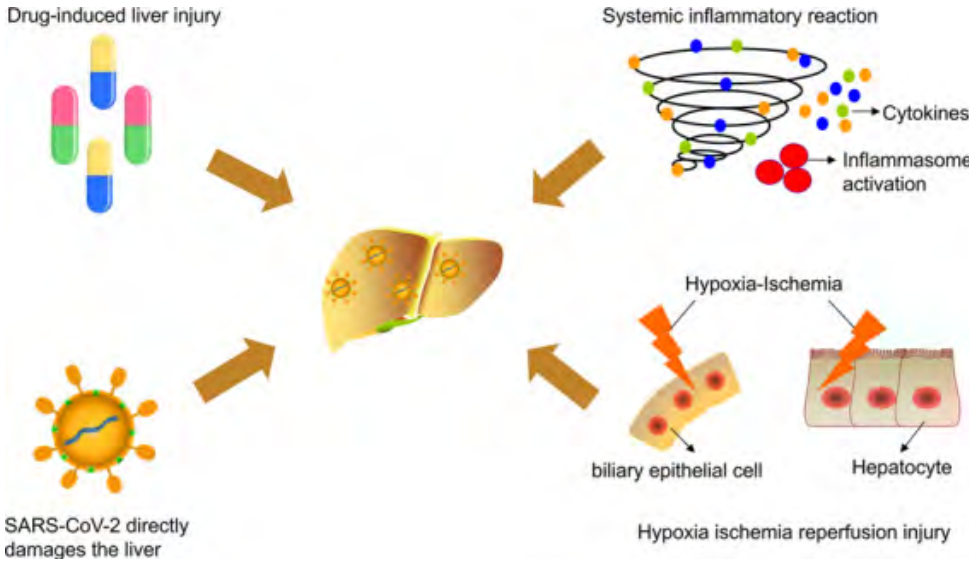

Figure 1: Mechanisms of COVID-19-associated liver injury: (1) drug-induced liver injury; (2) systemic inflammatory response (inflammatory cytokine storm); (3) hypoxic ischemia–reperfusion injury; (4) direct toxic effect of SARS-CoV-2 on the liver.

6. The Symptoms of Long Covid-19

Long COVID gastrointestinal symptoms include nausea, abdominal pain, loss of appetite, heartburn and constipation [49] The gut microbiota composition is significantly altered in patients with COVID-19 [50], and gut microbiota dysbiosis is also a key component of ME/CFS [51]. Higher levels of Ruminococcus gnavus and Bacteroides vulgatus and lower levels of Faecalibacterium prausnitzii have been found in people with long COVID compared with non-COVID-19 controls (from before the pandemic), with gut dysbiosis lasting at least 14 months; low levels of butyrate-producing bacteria are strongly correlated with long COVID at 6 months [52]. Persisting respiratory and neurological symptoms are each associated with specific gut pathogens [52]. Additionally, SARS-CoV-2 RNA is present in stool samples of patients with COVID-19 [53]. With one study indicating persistence in the feces of 12.7% of participants 4 months after diagnosis of COVID-19 and in 3.8% of participants at 7 months after diagnosis [54]. Most patients with long COVID symptoms and inflammatory bowel disease 7 months after infection had antigen persistence in the gut mucosa [55]. Higher levels of fungal translocation, from the gut and/or lung epithelium, have been found in the plasma of patients with long COVID compared with those without long COVID or SARS-CoV-2-negative controls, possibly inducing cytokine production [56]. Transferring gut bacteria from patients with long COVID to healthy mice resulted in lost cognitive functioning and impaired lung defenses in the mice, who were partially treated with the commensal probiotic bacterium Bifidobacterium longum [57].

7. Timeline

The onset and time course of symptoms differ across individuals and by symptom type. Neurological symptoms often have a delayed onset of weeks to months: among participants with cognitive symptoms, 43% reported a delayed onset of cognitive symptoms at least 1 month after COVID-19, with the delay associated with younger age [58]. Several neurocognitive symptoms worsen over

time and tend to persist longer, whereas gastrointestinal and respiratory symptoms are more likely to resolve [59,60,61]. Additionally, pain in joints, bones, ears, neck and back are more common at 1 year than at 2 months, as is paresthesia, hair loss, blurry vision and swelling of the legs, hands and feet [62].

8. Limitation and Questions Need Answering in Future Research

The tissue reservoirs for SARS-CoV-2 replication remain to be fully elucidated, partly due to difficulties in accessing biopsy samples from actively infected individuals and the requirement for high level laboratory containment facilities. Crucial questions remain open and need to be answered by future research: Which specific hepatic cells are infected by SARS-CoV-2? Which molecular processes are dysregulated by the infection? What is the real contribution of direct cytopathic effects, cytokine storm, DILI or hypoxia in hepatic dysfunction? By which means could liver injury promote respiratory failure and predispose to a severe course of COVID-19?

9. Conclusion

SARS-CoV-2 might infect the liver and is a key factor in liver dysfunction, however, the direct toxic attack of SARS-CoV-2 on the liver is still questionable and needs more evidences.

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