Liver Disease - A Concern in SARS-COV2 Infection

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease (COVID-19) that has resulted in a global pandemic. The clinical symptoms of the disease vary from mild illness to acute respiratory issues. Older age, diabetes, cardiac diseases predict poor prognosis in COVID-19 patients. Various reports mention the incidence of liver injury with transient elevations in the levels of aminotransferases (liver function enzymes). The clinical characteristics, etiology and underlying pathophysiological mechanisms associated with liver damage in SARS-CoV2 infected patients need to be explored. This review highlights the severity of the hepatic injury in COVID-19.

Keywords: COVID19; ACE2; diabetes; SARS-CoV2; liver injury

Introduction

China on 31st December 2019 reported a pneumonia of unknown cause, which was later named the new coronavirus disease: Severe acute respiratory syndrome-related coronavirus (COVID-19). The disease was announced pandemic by World Health Organisation (WHO) affecting more than three million people across the globe with two lakh deaths worldwide[1]. The severe acute respiratory syndrome coronavirus-2 spread in a few months and continued to grow across the continents and unfortunately the fatalities emerged because of the lack of specific antiviral therapy and vaccines[2].

A majority of the patients developed mild symptoms with the exception of elderly population and people with underlying health issues. The severity of the disease ends up in deaths due to damage in the alveoli and progressive respiratory failure[3,4]. The virus is highly contagious and is transmitted through respiratory droplets and close contacts, affecting the upper respiratory tracts and finally residing in the lungs[2]. The infected people may develop mild to moderate flu like symptoms. While some patients develop critical illness like respiratory failure, septic shock or multi-organ failure[5].

The data suggests the association and increased mortality in COVID-19 patients with comorbidities like diabetes, cardiovascular diseases, chronic liver diseases (CLD), etc. With the rise in the number of COVID patients, abnormally high liver function tests are an important consideration[6]. The complex interaction of chronic liver disease (CLD) with COVID-19 and the effects of treatments on liver is still being explored.

ACE2, liver and COVID-19

The virus accesses the host machinery by penetrating through the mucous membranes. The virus interacts with ACE2 receptor for entry into the host cells and uses the transmembrane serine protein 2 (TMPRSS2) for priming to the viral spike protein[7,8]. Various *in vitro* and *in vivo* studies identified the ACE2 receptor responsible for viral entry and its replication into host[9,10]. The ACE2 receptor is a membrane bound aminopeptidase significantly present in the epithelia of small intestine and testis, renal and cardiovascular tissue and vascular endothelia[11,12] ACE homolog ACE2 cleaves Ang_{1-7} from Ang II that acts via Mas receptor unlike Ang II. The ACE2/Mas receptor signalling axis plays protective effects in various diseases like diabetes, coronary heart disease, liver diseases, hypertension and metabolic syndrome[13,14,15]. Studies also reveal the abundant expression of this receptor protein in the apical surface

of the polarized epithelia of the airway[16] and type II alveolar epithelial cells[17] responsible for viral invasion into the lungs and causing injury.

However, besides the respiratory infection, the SARS-CoV2 patients showed signs of liver damage, the exact mechanism of which needs to be elucidated. The RNA-seq data revealed cholangiocyte specific expression of ACE2 with very low expression in the liver[18]. Both SARS-CoV and SARS-CoV2 utilize the same receptor for invasion into the target cells. SARS-CoV patients developed liver injury and the pathological findings showed the presence of virus in the liver tissue. The histology from the liver sections of SARS-CoV confirmed moderate lobular inflammation with hyperproliferative hepatocytes and activated Kupffer cells[19]. Thus, it can be postulated that the liver injury in SARS-CoV2 might be due to cholangiocyte dysfunction and not by direct hepatocyte invasion.

Chronic liver disease and susceptibility to COVID19

Since the burden of liver diseases has spread across the globe. Liver diseases like viral hepatitis, fatty liver and other alcohol related liver disease affect huge population across the globe[20]. Thus, it becomes extremely critical to evaluate the mechanism of liver injury in COVID-19 with these underlying liver ailments. The exact cause of SARS-CoV2 infection in pre-existing liver disease has not been anticipated and thus needs to studied meticulously.

The expression of ACE2 receptor is low in normal liver[21]. However, the gene and protein expression of this receptor is upregulated in human liver disease leading to increased circulating Ang_{1-7} levels and posing counterregulatory effects to Ang II. The expression of ACE2 is also increased in hypoxic conditions to inhibit and maintain oxygenation in the local tissues[22]. The chronic liver disease is associated with hepatocellular hypoxia and thus may ambient conditions for viral invasion and further lead to severe liver damage.

The impaired hepatic innate immunity can also be related to the susceptibility to SARS-CoV2. Kupffer cells- liver resident macrophages a dynamic cytokine producer may possess an inflammation suppressive phenotype (M2 macrophage type) that may lead to COVID-19 progression[23]. The liver diseases like chronic hepatitis in the immunotolerant phase and under long term viral suppression treatments may be more susceptible to SARS-CoV2 infection. However, a deeper understanding of the role of chronic liver disease in COVID-19 needs to be done for the development of therapeutic interventions.

Liver injury in SARS-COV2 infection

The number of COVID-19 patients are increasing at an alarming rate SARS-COV2 across the globe. The severity of the disease may range from non-specific and mild symptoms like dry cough, fever, vomiting, diarrhoea to acute respiratory distress syndrome, hypoxia, metabolic acidosis, septic shock and even death. The patients are also associated with elevated CRP levels and lymphocytopenia[24].

The upcoming reports highlight a close association of abnormal liver function with severity of COVID 19. The infection is also associated with high aminotransferases levels (AST and ALT). Also, few patients reported increased bilirubin levels[25]. A post mortem biopsy from an elderly showed

microvascular steatosis with mild portal and lobular activity, a possible indication of liver injury induced by drugs[26]. The host innate and adaptive immune response trigger systemic inflammatory processes to inhibit viral replication and ensure its clearance. It has been reported that in SARS-COV2 infected patients, CD4^{+} T cells activate the B cells to produce antibodies against the virus and the CD8^{+} T population assures the clearance of virus infected cells[27]. It is worth noting that abnormally high immune response is responsible for immunopathogenesis and may cause tissue injury.

Still, there is lack of evidence about the direct liver injury by the coronavirus itself. It is well established that the SARS-COV2 invades via the ACE2 receptor and the expression of this receptor is low in the liver. The ACE2 expression is observed in the cholangiocytes and low in the hepatocytes, endothelial cells and the Kupffer cells. There is abundant expression of ACE2 receptors in the small intestine[28] and also the patients complain of diarrhoea, it can be expected that the virus can reach the liver through the hepatic reticular system. Thus, the exact underlying mechanism of liver injury in COVID-19 patients needs to be fully examined and determined.

Conclusion

There has been massive outbreak of SARS-CoV2 infection in the past three months posing a major risk to human health. The infection can be fatal causing upper respiratory diseases and multiple organ failure. The liver injury has been one of the manifestations of SARS-CoV2 infection. Interestingly, the ACE2 expression has been shown to be high in biliary cells and the liver damage induced is hepatocellular with no signs of cholestatic injury. Also, the post-mortem analysis of the liver from COVID 19 patient revealed the existence of overactivated immune cells. Thus, the most probable explanation for the liver injury in the SARS-COV2 infected patients may be from virus induced cytotoxic T cells (T_c cells) and impaired innate immune response.

Due to the lack of sufficient reports for the incidence of hepatic injury in SARS-CoV2 infected patients, it is difficult to summarize the underlying mechanisms. Since liver is the most frequently affected organ apart from the respiratory system in COVID-19 infection, thus intense supervision is needed especially in patients with pre-existing liver diseases, for efficient management of therapeutics in such patients. The future research should focus on understanding the mechanism of liver damage in SARS-CoV2 infection.

DECLARATION OF INTERESTS:

No potential conflicts of interest relevant to this article were reported.

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