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Relationship Between Coronavirus Infection and Liver Disease

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Chan et al. [1] found that the novel coronavirus genome sequence had an 82% homology with human SARS-CoV and both SARS-CoV and SARS-CoV-2 infected cells via the angiotensin-converting enzyme 2 (ACE2) receptor [2]. It is reported that up to 60% of SARS patients have abnormal liver function [3]. The report by Xu et al. [4] on a pathological study of COVID-19 patients showed moderate microvascular steatosis and mild inflammation in the hepatic lobular portal region, and no direct killing effect of the virus on the liver was found in the autopsy results. One in two people in Mongolia are liver disease patients with chronic viral hepatitis, cirrhosis, fatty liver, alcoholic liver disease or other liver diseases [5]. Therefore, more attention should be focused on the liver function status of patients with COVID-19.

Liver injury in the setting of COVID-19–related illness poses a unique challenge to the clinician. First, there is often uncertainty about whether there is preexisting undiagnosed liver disease. Second, many of the medications used to treat moderate and severe disease have their own profiles of liver toxicity [6].

In a study by Wang et al. [7], Cai et al. [8], Zhang et al. [9], the liver function abnormalities in COVID-19 patients were mainly manifested as abnormal levels of Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST), with a slight increase in bilirubin levels. Another report found elevated gamma-glutamyl transferase (GGT) levels in nearly 50% of subjects. The pattern of abnormal liver biochemistries characterized by an AST level greater than ALT, with accompanying GGT elevation, is also commonly encountered in both alcoholic liver disease and ischemic or congestive liver injury [10].

ACE2 is a receptor on host cells that is the target of the SARS. Several studies [14-16] have also shown that SARS-CoV-2 can bind to the ACE2 receptor, enabling the virus to replicate in cells. Additionally, the expression level of ACE2 is very low in liver cells, accounting for 2.6% of the total number of cells, but is highly specific in bile duct cells (59.7%), which is similar to the expression in major targeted cells (type II alveolar cells) of SARS-CoV and SARS-CoV-2 in the lung [11, 12]. Therefore, the novel coronavirus does not necessarily directly infect liver cells but causes bile duct dysfunction by binding with bile duct cells, which play an important role in liver regeneration and immune response.

The largest published study to date encompassed 5700 hospitalized patients in New York. It examined admission serologies: AST and ALT were both frequently elevated (58.4% and 39.0% of subjects, respectively), and a separate large cohort found elevations to be more common in severe disease [13]. Two studies suggest that a higher proportion (44%-81%) of patients with underlying liver disease had abnormal liver biochemistries on admission [14-15].

There may be a direct viral cytopathic effect, given the known presence of the ACE2

receptor in the liver [16-17]. In SARS infection, viral RNA was detected in liver tissue [18-19]. Further, recently published data suggest that mitochondrial proteins may directly interact with the virus, providing a potential mechanistic explanation for the AST-dominant injury profile [20]. Alternatively, the robust inflammatory response seen in COVID-19 may play a central role. The immune response to SARS-CoV-2 is characterized by very high levels of IL-6 [21], which has been implicated in both the inflammatory and the repair responses in liver disease [22].

Additionally, the cytokine storm caused by excessive immune response induced by the virus may also be one of the pathways of liver damage [23, 24]. In most patients with severe COVID-19, there is an abnormal increase in serum proinflammatory cytokines. For example, Liu et al. [25] observed an inflammatory cytokine storm in 40 confirmed COVID-19 patients, of whom 13 with severe COVID-19 had a significant and continuous decrease in lymphocyte count and an increase in neutrophil count. In particular, interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-17, and interferon-γ levels in critically ill patients continued to increase in peripheral blood [26, 27]. Moreover, the T cell count and cytokine levels in patients with severe COVID-19 returned to the same level as those with mild symptoms with gradual improvement in the disease [28, 29]. Lu et al. [30] proposed that lymphocytopenia and C-reactive protein levels were independently correlated with liver injury in COVID-19 patients, which showed that the main mechanism might involve an inflammatory cytokine storm. Cao et al. [31] indicated that cytokine storms may cause shock and tissue damage in organs such as the heart, liver and kidney, and respiratory failure in severe cases. Additionally, pathological changes such as spleen atrophy and lymph node necrosis were found, which suggested immune-mediated injury.

ACE2 is a receptor of the coronavirus on host cells that causes SARS. Several studies [32-34] have shown that SARS-CoV-2 can also bind to the ACE2 receptor, enabling the virus to replicate in cells. Additionally, the expression level of ACE2 is very low in liver cells, accounting for 2.6% of the total number of cells, but highly specific in bile duct cells (59.7%), which is similar to the expression level in major targeted cells (type II alveolar cells) of SARS- CoV and SARS-CoV-2 in the lung [35, 36]. Therefore, the novel coronavirus does not necessarily directly infect liver cells, but causes bile duct dysfunction by binding with bile duct cells, which play an important role in liver regeneration and immune response. We, therefore, infer that liver injury may be induced by damage to bile duct cells caused by COVID-19.

In fact, antibiotics, antiviral drugs and steroids have been widely used to treat COVID-19, such as remdesivir, lopinavir, statin, azithromycin, acetaminophen have a hepatocellular and cholestatic effect. Importantly, abnormalities in liver function led to a longer hospital stay. Liver damage in COVID-19 patients may have been caused by the use of lopinavir/ritonavir as an antiviral treatment for SARS-CoV-2 infection.

There is a high prevalence of abnormal liver biochemistries on presentation in patients with COVID-19. In light of the risk for additional injury due to the complications and management of moderate-to-severe disease, it is important to monitor hepatic enzymes during the course of the disease [37]. If biochemistries worsen during disease progression, consideration must be given to possible contributors, including cardiac dysfunction, cytokine storm, ischemia, sepsis, and medication effect

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