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Commentary

COVID-19 and the Liver: Uncovering the Hidden Culprit behind Liver Injury

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Commentary

The effects of COVID-19 have been of increasing interest in all fields of medicine after the pandemic, especially considering the important impact and incidence of patients infected with coronavirus. Numerous studies have reported the vast clinical implications related to permanent organ and tissue damage after infection and long COVID. A recent study published in *World Journal of Virology* in 2022 by Grando et al. [1], dealt with important factors related to liver damage due to coronavirus infection. In our commentary, the main issues reported in this manuscript will be summarized, including the different forms of liver damage, incidence, complications, occurrence, mechanisms of cellular and tissue damage, clinical signs and symptoms of liver injury, related comorbidities, and possible treatment option in patients with infection of SARS-Cov2.

COVID-19-induced liver injury is a common complication in adult patients, with reported incidence rates ranging from 14% to 53% [2]. The incidence is higher in severe cases, with a prevalence of up to 76%. The elevation of liver enzymes, such as alanine transaminase (ALT) and aspartate transaminase (AST), is the most common manifestation of liver injury in COVID-19 patients [3,4]. However, severe liver injury can also occur, leading to liver failure and death. The incidence of liver injury in COVID-19 patients varies depending on the patient population, disease severity, and the methods used to detect liver injury.

Several factors contribute to the increased incidence of liver injury in COVID-19 patients. The manuscript discusses various mechanisms of liver injury induced by COVID-19 infection, which include:

- **Direct Viral Infection:** SARS-CoV-2, the virus responsible for COVID-19 infection, uses angiotensin-converting enzyme 2 (ACE2) receptors to enter human cells [5]. The liver expresses ACE2 receptors, making it a potential target for SARS-CoV-2 infection. These receptors are highly expressed in cholangiocytes [6,7]. Studies have shown that SARS-CoV-2 RNA can be detected in liver tissue, suggesting that the virus can directly infect the liver and cause liver injury [8].

- **Immune-Mediated Injury:** COVID-19 infection can lead to a cytokine storm, characterized by the overproduction of cytokines, such as IL-6, IL-1β, and TNF-α [9]. The cytokine storm can cause systemic inflammation and organ damage, including liver injury. Studies have shown that COVID-19 patients with severe liver injury have higher levels of cytokines compared to those with mild liver injury [10]. Liver injury in COVID-19 patients may be related to the severity of the disease, thus liver function tests should be monitored in patients with severe disease or underlying liver disease.

- **Hypoxia-Induced Injury:** COVID-19 infection can cause respiratory distress, leading to hypoxia and ischemia-reperfusion injury [11]. Hypoxia can cause mitochondrial dysfunction, oxidative stress, and inflammation, leading to liver injury. Patients with COVID-19 have varying degrees of hypoxaemia, those with severe hypoxia have higher levels of liver enzymes compared to

those with mild hypoxia. In addition, Hepatic Ischemia-Reperfusion Injury (HIRI) is a common pathophysiological process [12].

- **Drug-Induced Liver Injury:** COVID-19 patients may receive drugs, such as remdesivir, lopinavir/ritonavir, and chloroquine/hydroxychloroquine, as part of their treatment regimen. These drugs can cause drug-induced liver injury, leading to liver dysfunction and other complications. Studies have shown that drug-induced liver injury is a common complication in COVID-19 patients receiving these drugs [12,13].

- **Pre-Existing Liver Disease:** Patients with pre-existing liver disease, such as cirrhosis and non-alcoholic fatty liver disease, may be at higher risk for liver injury due to COVID-19 infection. Studies have shown that COVID-19 patients with pre-existing liver disease have a higher incidence of poor outcomes of COVID-19 compared to those without pre-existing liver disease due to acute-on chronic liver failure [14].

The diagnosis of COVID-19-induced liver injury is typically based on the elevation of liver enzymes, such as ALT and AST, in patients with COVID-19 [15]. Other liver function tests, such as bilirubin and albumin, may also be abnormal in patients with COVID-19-induced liver injury [16]. The diagnostic criteria for COVID-19-induced liver injury, however, are not well-defined, and there is no consensus on the optimal cut-off values for liver enzymes. Additionally, the elevation of liver enzymes can be caused by other conditions, such as pre-existing liver disease, drug-induced liver injury, and other viral infections, making the diagnosis of COVID-19-induced liver injury challenging [12]. Therefore, clinicians should consider the clinical context, such as the presence of COVID-19 symptoms, in the interpretation of liver enzyme levels. Imaging tests, such as abdominal ultrasound, may be used to assess the severity of liver injury and to rule out other causes of liver disease. Additionally, clinicians may perform tests for other viral infections, such as hepatitis B and C, to rule out co-infection.

The differential diagnosis of COVID-19-induced liver injury includes other causes of liver disease, such as drug-induced liver injury, alcoholic liver disease, viral hepatitis, and non-alcoholic fatty liver disease. Clinicians should also consider pre-existing liver disease and other comorbidities that may contribute to liver dysfunction in COVID-19 patients. Differential diagnosis is important in determining the appropriate treatment and management of liver injury in COVID-19 patients [17].

The management of COVID-19-induced liver injury depends on the severity of the liver injury and the overall clinical status of the patient. In mild cases, liver injury is usually self-limiting and does not require specific treatment [17]. However, in severe cases, liver injury may require supportive care, such as fluid and electrolyte management, nutritional support, and treatment of underlying liver disease. Additionally, clinicians should consider the potential impact of drugs used to treat COVID-19 on liver function, such as remdesivir, lopinavir/ritonavir, and chloroquine/hydroxychloroquine. These drugs can cause drug-induced liver injury, leading to liver dysfunction and other complications [18]. Therefore, close monitoring of liver function is essential in COVID-19 patients receiving these drugs.

COVID-19-induced liver injury is associated with worst outcomes and increased mortality [19,20]. Studies have shown that COVID-19 patients with pre-existing liver disease are at higher risk of developing severe disease and liver failure. Therefore, early detection and monitoring of liver injury in COVID-19 patients are crucial for appropriate management and better clinical outcomes [12]. Liver function tests, such as ALT and AST, should be routinely performed in COVID-19 patients, especially those with pre-existing liver disease.

The prognosis of COVID-19-induced liver injury depends on the severity of the liver injury [21] and the overall clinical status of the patient. Mild liver injury is usually self-limiting and does not affect long-term prognosis. However, severe liver injury can lead to liver failure and death. The overall prognosis of COVID-19-induced liver injury is also influenced by other factors, such as the presence of comorbidities and the severity of COVID-19 illness [3,17]. Therefore, close monitoring of liver function and early detection of liver injury are crucial for appropriate management and better clinical outcomes.

Despite the growing evidence of COVID-19-induced liver injury, many questions remain unanswered. Further research is needed to better understand the mechanisms underlying liver injury in COVID-19 patients, as well as the clinical implications and outcomes of liver injury. Additionally, more studies are needed to identify risk factors for liver injury in COVID-19 patients and to develop effective prevention and treatment strategies. Future research should also focus on the long-term effects of COVID-19-induced liver injury, including the potential for chronic liver disease and cirrhosis.

One limitation of the current manuscript is the lack of discussion on the potential long-term effects of COVID-19-induced liver injury. While the majority of liver injury in COVID-19 patients is mild and self-limiting, severe liver injury can lead to chronic liver disease and cirrhosis. Future research should focus on the long-term effects of COVID-19-induced liver injury and the potential for chronic liver disease and cirrhosis.

In conclusion, COVID-19-induced liver injury is a significant concern that warrants attention in clinical practice and research. As we continue to learn more about the SARS-CoV-2 virus and its effects on the body, it is crucial to develop effective strategies for the prevention, detection, and management of COVID-19-induced liver injury.

Conflict of Interest Statement

All the authors report no relevant conflicts of interest for this article or funding.

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