Sohag University Faculty of Medicine Sohag Medical Journal

Liver Injuries in COVID-19 infected patients

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Abstract

Coronavirus outbreak in December 2019 was reported in the city of Wuhan, China firstly named 2019 novel coronavirus (2019-nCoV). Later on, the World Health Organization (WHO) declared another name for this disease which is Corona Virus Disease (COVID-19). On the eleventh of March, 2020, WHO considered the disease as a pandemic. Person-to-person transmission had been reported either through droplet transmission or direct contact. The affected individuals complain from mild symptoms to severe acute respiratory syndrome (ARDS).

With the increasing number of COVID-19 infected patients, several studies reported that the liver is the most frequently affected organ after lung damage. Elevation of transaminases was frequently reported in patients with severe disease and patients admitted to ICU. The mechanism of hepatic injury in COVID-19 not completely understood. Multiple factors have been accused including direct invasion of the hepatocyte by SARS-CoV-2, high level of inflammatory mediators, drug-induced hepatic injury, and or concomitant chronic liver diseases. So, evaluation of the mechanism of hepatic injuries in COVID-19 infection is needed.

Keywords: SARS-CoV-2, Transaminases, Mechanisms **of liver injury.**

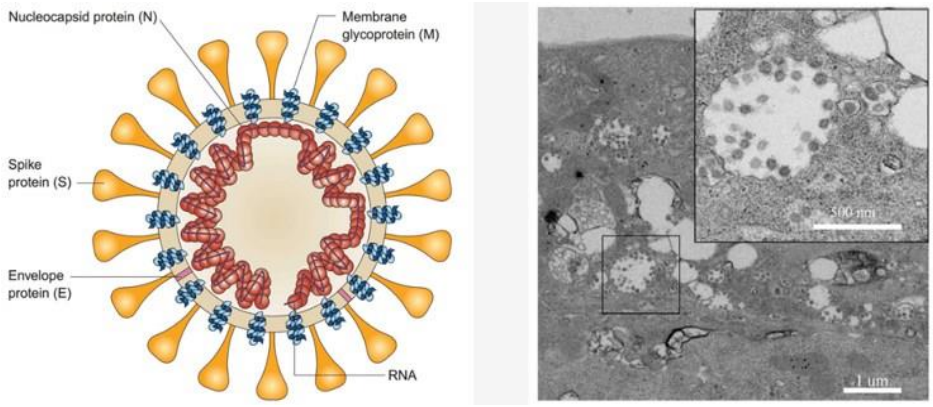
Introduction:

Another outbreak of coronavirus was reported in the city of Wuhan, China firstly named 2019 novel coronavirus (2019-nCoV). The diagnosis has been established using next-generation sequencing. Later on, the World Health Organization (WHO) declared another name for this disease which is Corona Virus Disease (COVID-19) [(1)]. On the eleventh of March, 2020, COVID-19 infection affects more than 118,000 cases in 114 countries. So, WHO considered the disease a pandemic [(2)].

Several coronaviruses affect humans. Mild clinical presentation is typical for this family, with two exceptions: severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), which was first recorded in Southern China, and coronavirus (MERS-CoV) in the Middle East which was first detected in Saudi Arabia [(3,4)].

Coronaviruses that affect the human-being were first discovered in the Mid-Sixties. They were positive-strand enveloped RNA viruses, 120 nm in diameter, they had large surface projections in a club-shaped form about 20 nm (Fig. 1) [(5)]. The 2019-nCoV is the 7th representative of enveloped RNA

coronavirus [12]. It is a new SARS-CoV-divergent and subsequently named SARS-CoV-2. There is a suggestion that bats are the primary viral host. However, an animal sold on the Wuhan seafood market could be an intermediate host that would allow the transfer of the virus to humans [6].



Figure(1): A) Structure diagram of SARS-CoV2 B) SARS-CoV2 under the electron microscope [7].

In a similar way to SARS-CoV, the 2019-nCoV enters the cell by attaching to the receptor Angiotensin-Converting Enzyme (ACE) [8]. After entering and replication of the virus, antigen presentation to the surface of the infected cell occurs leading to stimulation of the immune system. One of the main mechanisms for adult respiratory distress syndrome (ARDS) is the cytokine storm, which is triggered by an unregulated release of large quantities of pro-inflammatory cytokines and chemokines [9].

Most reported cases of COVID-19 infection are adults of middle age and old individuals [10]. Clinical manifestation among COVID-19 infected patients differs in severity from asymptomatic infection or mild disease to serious or fatal disease. Clinical deterioration occurs mostly during the second week of illness [11].

The most common presentations are fever and cough. Myalgia and fatigue are also common. Dyspnea, headache, hemoptysis, and chest pain had been reported. Upper respiratory tract symptoms and productive cough are less common [12, 13]. Gastrointestinal symptoms such as diarrhea and nausea may develop before the start of fever and lower airways affection [12].

The pattern of hepatic injuries in COVID-19 infection:

With the increasing number of COVID-19 infected patients, several studies reported that the liver is the most frequently affected organ after lung damage [14-16]. The percentage of infected patients who had abnormal levels of transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) was about 14.8-53.1%. The elevation in serum bilirubin was mostly mild [12, 15,17,18]. Zhang et al. [18] reported that gamma-glutamyl transferase (GGT) was elevated in 54% out of 56 COVID-19 infected patients who were hospitalized at Fifth Medical Center, whereas only one patient (1.8%) had elevated alkaline phosphatase levels.

This elevation in liver function tests is usually mild, transient, and self-limited [19]. However, Shen et al. [17] reported that out of 43 patients with elevated transaminases, severe hepatitis with serum ALT increased up to 7590 U/L was reported in one case with a serious

condition. Also, Wander et al. [20] recorded the first case with COVID-19 infection who presented with the picture of acute hepatitis (AST 1230IU, ALT 697IU) before the development of respiratory complaints.

Elevation of transaminases (ALT, AST) was frequently reported in patients with severe disease and patients admitted to ICU [12, 16, 21]. However, obvious intrahepatic cholestasis or liver failure wasn't reported [17].

Fan et al. [21] reported in their studies that about half of affected patients showed abnormal liver function tests including ALT, AST, and GGT. This abnormal increase was mainly reported in male patients and those having moderate to high-grade fever. They also noticed a significant decrease in the level of CD4and CD8 T cells in a patient with elevated transaminases. However, the direct relationship between the decrease of T cell count and liver damage remains unclear. They also found that the hospital stay was prolonged in COVID-19 infected patients who develop elevated tran-saminases after admission.

Li et al [22] concluded that lymphopenia and raised C-reactive protein (CRP) are risk factors of hepatic injury in COVID-19 infected patients.

Histopathological examination of the liver in COVID-19 infected patients:

Postmortem analysis of the affected liver was enlarged with hepatocyte degeneration and focal necrosis of the lobules. Also, there was an infiltration of the portal triad with inflammatory cells as neutrophils, lymphocytes, and monocytes. Hepatic sinuses obstruction with micro-thrombosis had been noticed. However, the histological signs of hepatic failure or bile duct damage had not been identified [23]. Microscopic analysis of liver biopsy from another infected patient demonstrated micro-vesicular steatosis and mild inflammation of the hepatic lobules. However, viral par-ticles hadn't been noticed in the liver [24].

Mechanisms of hepatic injury:

The mechanism of hepatic injury in COVID-19 not completely known. However, The injury may be caused directly by the invasion of the virus to the liver tissue or may be indirect (drug-induced or effect of inflammatory mediators) [21].

As the SARS virus was detected in the hepatocyte in low titer. SARS-CoV-2 can similarly affect the liver as SARS-CoV causing direct injury to the heaptocyte [18]. Despite this, until now SARS-CoV-2 has not been found in the liver [24].

The direct liver damage may be due to the invasion of SARS-CoV2 to the bile duct cells by attaching to ACE2 on its surface [27]. However, the little increase in the level of ALP hadn't been correlated with the suspected bile duct injury. Also, the increase in transaminase levels is more common than the increase in ALP [20]. Also, The experimental results of a mouse model with acute hepatic injury viewed that there was an increase in the expression of ACE2 in the liver. This up-regulation caused by the compensatory hepatocyte proliferation related to bile duct epithelial cells during acute hepatic injury [26].

The hepatic injury is more frequent in seriously ill patients that can be explained by a high level of inflammatory mediators during this stage of the disease (cytokine storm). However, this not explained the elevation of transaminases during the mild stage of the disease [27].

The presence of moderate micro-vesicular steatosis with hepatic inflammation in histopathological examination raises the attention for the possibility of drug-induced hepatic injury [28]. Also, a majority of patients

use medications to treat fever. Most of these medications contain acetaminophen that is well known to cause hepatic injury. Also, multiple antiviral drugs as oseltamivir and lopinavir/ritonavir have been suggested to treat COVID-19 infected patients. These antiviral drugs can induce hepatic injury [(19)].

Hepatic injury may be due to concomitant chronic liver diseases [(16)]. Chronic hepatic disorders such as chronic hepatitis B infections, non-alcoholic steatohepatitis, and hepatic cirrhosis may be the main alternative etiologies of hepatic injury in Chinese COVID-19 patients. However, in most COVID-19 studies, information on concomitant hepatic disorders has not been assessed and the relationship between established hepatic disorders and SARS-CoV-2 infection has still not been analyzed [(19)].

Conclusions:

Hepatic involvement in COVID-19 infected patients has been frequently reported reaching up to half of the infected cases. Hepatic injury is usually mild and transit with few exceptions. Acute hepatitis as the first presentation of COVID-19 infection has been reported in an American case report. Multiple factors have been attributed to hepatic injury in COVID-19 infection including direct invasion of the hepatocyte by SARS-CoV-2, high level of inflammatory mediators, drug-induced hepatic injury, and or concomitant chronic liver diseases.

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