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Coronavirus Disease-19 and Liver Injury

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Abstract

Coronavirus Disease (COVID)-19 is a pandemic since March 11, 2020. The total case is more than a half million worldwide. Liver injury is quite common in COVID-19 patients. Direct viral infection is possible due to the presence of angiotensin converting enzyme 2 in cholangiocytes and hepatocytes. Other proposed mechanisms are virus-induced cytopathic effects, inflammation process, hypoxia and shock, increased apoptotic activity, increased positive end expiratory effect, and drug-induced. The manifestation of liver injury is mild and transient with elevated liver enzymes, bilirubin, and gamma-glutamyl transferase levels. Deterioration of liver function can occur in subjects with COVID-19 and underlying liver injury. The management is principally supportive. Hepatoprotective drugs may be administered in severe cases.

Introduction

Pneumonia due to unknown etiology was found in Wuhan, Hubei Province, China in December 2019 [1], [2], [3]. Huanan seafood market was suspected as the starting area of the spreading. A virus, namely, 2019 novel coronavirus (CoV) was identified as the etiology of the disease in January 7, 2020. In February 11, 2020, International Committee on Taxonomy of Viruses renamed 2019 nCoV as severe acute respiratory syndrome-CoV-2 (SARS-CoV-2). Later, World Health Association (WHO) announced the disease caused by SARS-CoV-2 infection as CoV disease-(COVID-19) [1], [4]. In March 11, 2020, the WHO announced COVID-19 as a pandemic [3], [5], [6], [7].

CoV is an enveloped, single-stranded positive-sense RNA virus [1], [7], [8]. Its Alpha and Beta generas commonly infect mammals while Gamma and Delta infect birds. SARS-CoV-2 itself is belonged to Beta-CoV genus and Coronaviridae family [1], [5], [7], [9]. Previously, two CoVs had caused epidemics. The first was SARS-CoV in Guangdong, China in November 2002 and the second was Middle East respiratory syndrome CoV (MERS-CoV) in Saudi Arabia in 2012 [1], [3], [10]. The first epidemic caused 774 deaths while the second caused 858 [1]. The mortality rate from SARS-CoV-2 is lower compared to SARS and MERS [9], [10].

Epidemiology

Median age of patients with COVID-19 is between 41 and 57 years. Male is dominant compared to female [1], [11]. Even though, there are several studies reporting comparable proportion of patients based on gender [2], [4]. About 25.2–50.5% patients have comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and malignancy [1]. About 10.8% patients have pre-existing liver disease [12]. The mortality of COVID-19 ranges from 0% to 14.6% [1]. The most common death-leading complication is acute respiratory distress syndrome [10]. Factors contributing to higher risk of mortality are older age, underlying comorbidities, and disease severity based on clinical findings and auxiliary examinations [11], [13]. At the time of writing, there are 5,491,678 cases of COVID-19 with total deaths of 349,190 cases. The most prevalent region is America, followed by Europe [14]. The incidence of

liver injury due to COVID-19 was varied between 14.8% and 78% [3], [9]. Other literatures stated that liver injury is observed in 60% patients with COVID-19 [8], [15]. Cai *et al*. found a similar rate of liver injury which was 76.3% of total patients with COVID-19 and 21.5% of all patients on admission [5].

Pathophysiology

Bats are the natural reservoir of SARS-CoV-2 and the virus spreads to human through pangolins as one of the intermediate hosts [1]. The virus may be isolated from pangolins, especially Malayan pangolins. However, genomic sequence of SARS-CoV-2 in human is different from the wild virus, suggesting that mutation may have been occurred which allows human-to-human transmission [13]. Human-to-human transmission occurs through respiratory droplets directly or indirectly [4]. Fecal-oral transmission must also be wary of since viable SARS-CoV-2 can be isolated from patient's fecal sample [16]. SARS-CoV-2 infection is initiated by binding of spike glycoprotein to angiotensin converting enzyme 2 (ACE2). This process is followed by cell membrane fusion [11], [15], [17]. Viral RNA then integrates into host cell DNA. This process initiates viral protein synthesis and assembly of new viruses which readily infect other cells and damaging the cell [15], [18]. The affinity of SARS-CoV-2 to ACE2 is stronger compared to SARS-CoV [12], [13].

Literatures stated that ACE2 is highly expressed in cholangiocytes but only slightly in hepatocytes. As we know that bile duct epithelial cells play an important role in liver regeneration and immune response, it raises possibility that SARS-CoV-2 may directly invade those cells and cause liver function dysregulation [15], [16], [19], [20]. Furthermore, virus-induced cytopathic effects may directly cause liver damage [3]. Inflammation process, which is known as cytokine storm, also played an important role in damaging the liver of patients with critical condition due to COVID-19 [4], [6], [9], [11]. Lymphocytes are important in balancing immune response and preventing cytokine storm. Lymphopenia in COVID-19 patients leads to aggravation of inflammatory response. Lymphopenia and elevated C-reactive protein (CRP) level were associated with the severity of liver injury, confirming cytokine storm as one of the underlying mechanisms of liver injury [3], [11], [15]. Hypoxia and shock from COVID-19 may cause ischemia in body organs including liver. This is another hypothesized mechanism of liver injury in patients with COVID-19 [6], [11].

SARS-CoV-2 infection is also found to increase apoptotic activity of hepatocytes. The process is mediated by SARS-CoV-2-specific protein 7a through caspase-dependent pathway [9]. Increased positive end expiratory pressure may also cause hepatic congestion by increasing right atrial pressure and impending venous return [3], [15]. Drug-induced liver damage should also be put in mind since antiviruses and antibiotics may increase the workload of liver. Hydroxychloroquine is used as one of the treatment choices due to its effect in alleviating disease progression but, in the other hand, it may cause hepatic failure. In patients with underlying liver diseases, such as chronic hepatitis and non-alcoholic fatty liver, the above situation will surely even more impair the liver function [3], [4], [6], [9], [11], [15], [16], [17].

Clinical Manifestations

Clinical symptoms of COVID-19 range from mild to severe. A study reported that moderate clinical severity patients were dominant. Fever is the most common symptom, followed by cough, fatigue, myalgia, sputum production, and headache [1], [2], [3]. Gastrointestinal symptoms are quite common such as diarrheas, loss of appetite, nausea, and vomiting [1], [16]. Gastrointestinal symptoms are more frequent in SARS and MERS compared to COVID-19 [1].

Various degree of liver damage had been reported in COVID-19 patients marked by elevated total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels [19]. A study by Fan *et al*. showed that 37.2% patients with COVID-19 have abnormal liver function on admission and had higher fever compared to those with normal liver function [4]. Autopsy result of deceased patients showed that 58–78% of COVID-19 patients suffer from liver injury [16]. Higher prevalence of liver injury is observed in males, patients with more severe disease course, older age, and patient who received lopinavir/ritonavir [4], [16]. The use of lopinavir/ritonavir increases the risk of liver injury as high as 4 times compared to patients who do not receive those antivirals [5]. The severity of liver injury is associated with the severity of disease course [9], [15], [17]. Table 1 summarizes evidence regarding liver injury in patients with COVID-19.

Table 1: Evidences of liver injury in patients with COVID-19

Authors	Subjects	Findings
Fan *et al*. [4]	148	37.2% subjects had abnormal liver function on admission Patients with liver abnormality had higher fever, higher procalcitonin and CRP levels, and longer hospital stays
Cai *et al*. [5]	417	21.5% subjects had abnormal liver function during hospitalization ALT, AST, total bilirubin, and GGT levels were elevated more than 3 times the upper normal limit within 2 weeks of hospitalization
Huang *et al*. [10]	41	31% subjects had abnormal liver function Subjects admitted to ICU had higher AST level compared to non-ICU
Zhang *et al*. [21]	82	78% non-survivor subjects had hepatic injury
Huang *et al*. [22]	36	13.33% subjects had abnormal ALT, 58.06% had abnormal AST, and 12.9% had abnormal total bilirubin levels
Chen *et al*. [23]	99	28% subjects had elevated ALT, 35% had elevated AST, 18% had elevated total bilirubin, and 98% had low albumin levels

CRP: C-reactive protein. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, ICU: Intensive care unit. COVID: Coronavirus disease.

COVID-19 in Patients with Pre-existing Liver Disease

COVID-19 patients with liver injury tend to develop severe pneumonia and have longer hospital stay [4], [5], [24]. Literature stated that patients with hepatitis B or C viral infection are more prone to suffer from severe hepatitis due to enhanced viral replication during COVID-19 course. On the other hand, patients with pre-existing live diseases such as non-alcoholic fatty liver disease and liver cirrhosis had higher risk to develop severe form of COVID-19. Liver transplantation should be conducted prudently since the virus can be transmitted through transplanted organ [3]. Subjects with chronic liver disease coexisting with COVID-19 tended to suffer from deterioration of liver disease. The deterioration was in line with increasing stage of liver disease, resulting in higher mortality in subjects with liver diseases compared to those without (hazard ratio 19.2) [25]. This finding is confirmed by a study by Iavarone *et al*. They reported that the presence of COVID-19 deteriorates liver function and increases the mortality of subjects with underlying liver injury. The 30-day-mortality rate for subjects with COVID-19 and pre-existing liver cirrhosis was as high as 34%. The mortality was influenced by severity of liver disease [26].

Auxiliary Examinations

The most common laboratory findings are lymphopenia, thrombocytopenia, and leukopenia. Other inflammatory markers such as CRP and interleukin-6 are also elevated [1]. Liver enzymes elevation is also observed [1], [3], [5], [9], [15], [16], [17]. ALT level rose in 16–35% patients while elevated AST was observed in 21% patients [19]. Feng *et al*. reported the elevation of AST level in 6.2–36.6% patients with COVID-19 and elevation of AST level in 21.3–28.1% patients [11]. Ridruejo and Soza found a lower rate of AST and ALT elevation which is between 16% and 35% [6]. Other markers for liver injury are also detected including elevated bilirubin level and decreased albumin level. Gamma-glutamyl transferase (GGT) might also be elevated [3], [5], [9], [15], [16], [17]. In the other hand, alkaline phosphatase did not raise significantly [4], [5], [11], [16], [19]. Chest computed tomography showed ground glass opacity, bilateral patchy shadows, and consolidation in subsegmental areas [1], [10], [27]. Reverse-transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swab is considered as gold standard for diagnosing COVID-19 [1]. Other specimens also showed positive result with bronchoalveolar lavage fluid held the highest positive rate (93%), followed by sputum (72%), nasal swabs (63%), fibrobronchoscope brush biopsy (46%), pharyngeal swab (32%), feces (29%), and blood (1%) [28].

From percutaneous liver biopsy specimen of COVID-19 patients with elevated ALT, there was marked apoptosis activity in the liver tissue, ballooning of hepatocytes, and mild-to-moderate lobular infiltration of lymphocytes. RT-PCR showed evidence of SARS-CoV-2 genome in liver tissue but not in serum of patients [8], [9]. Viral particles could not been identified by electron microscopy or histopathology examination [3], [8], [15]. In contract, other literature reported that SARS-CoV-2 particles may be detected in liver tissue from autopsy of patients with COVID-19 [9]. Patients with underlying liver disease have higher risk of COVID-19 infection and poorer outcome [6]. Cirrhosis has higher risk of developing poorer outcome. As liver injury increases the risk of COVID-19 progression, the utilization of liver function tests may be used as predictor of disease outcome [5].

Management

The mainstay of COVID-19 management is supportive therapy. Antivirus (oseltamivir, lopinavir, remdesivir, and ritonavir), antibiotic, and antimalarial (chloroquine) are also administered but need further study regarding their efficacy [1]. Most liver damage in COVID-19 patients is mild and transient and may resolve without specific treatment. Supportive measures must be taken to fulfill pulmonary ventilation and prevent cytokine storm. Hepatoprotective drugs may be utilized in patients with pre-existing liver disease and in case of severely injured liver [11], [16], [17]. The development of vaccine is still under ongoing process and should be able in the next 12–18 months. Implementation of health protocol is important to contain the COVID-19 pandemic [24].

Conclusion

COVID-19 is an emerging pandemic which may cause liver injury. The presence of ACE2 in cholangiocytes and hepatocytes allows direct infection SARS-CoV-2 to liver. Other possible mechanisms are virus-induced cytopathic effects, inflammation process, hypoxia and shock, increased apoptotic activity, increased positive end expiratory effect, and drug-induced. Clinical manifestations are usually mild with elevated liver enzymes, bilirubin, and GGT levels. Albumin level may also decrease. Subjects with COVID-19 pre-existing liver injury tend to have deterioration of liver function and increased mortality. The management of liver injury in COVID-19 is supportive. Hepatoprotective drugs may be administered in severely injured liver.

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