COVID-19 and the Liver

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with global spread, currently characterized as a pandemic by World Health Organization (WHO). SARS-CoV-2 shares approximately 82% genome sequence homology to already known SARS-CoV responsible for the 2002-2004 SARS outbreak epidemic [1]. There is solid evidence that the new virus is not a laboratory construct or a purposefully manipulated virus but has evolved as a result of natural-selection [2]. Confirmed routes of transmission include respiratory droplets and close contact, but recent data reveal the fecal-oral as an alternative way, underlining the role of gastrointestinal system in the viral pathogenesis [3]. Common symptoms of COVID-19 include fever, dry cough, fatigue, myalgia and dyspnea. A subgroup of patients progresses into severe COVID-19 characterized by cytokine storm syndrome associated with acute respiratory distress syndrome (ARDS), multiple organ failure and increased mortality [4].

Abnormal liver function is a frequent extra pulmonary finding in hospitalized patients. It is documented that 14-53% of them present abnormal serum liver enzyme levels, mainly elevated aminotransferases, with mild bilirubin increase [4-12]. Decreased serum albumin on hospital admission appears to be an indicator of the disease's severity [7,10]. Whether laboratory test alterations are a sign of pre-existing occult or apparent well decompensated liver disease (alcoholic, viral, non-alcoholic steatohepatitis) remains unclear at this point due to a shortage of appropriate studies. Possibly, patients with advanced liver disease are more prone to developing a severe form of the illness due to cirrhosis associated immune dysfunction [5]. In a large multicenter cohort study including 1099 patients, critically ill subjects had higher rates of liver dysfunction when compared to non-severe cases [4]. Therefore, the incidence of liver impairment is speculated to be associated with the severity of the infection. In deceased patients liver injury is reported to be as high as 78% [12]. Acute liver failure has been described in one critically ill patient with serum ALT and AST levels rising to 7590 U/l and 1445 U/l respectively [9]. Nevertheless, in mild cases hepatic injury is temporary and no specific treatment is necessary. Lactate dehydrogenase (LDH) levels were found to be an independent risk factor for severe COVID-19 [7]. Nonetheless, increased serum LDH levels may be promoted by non-hepatic sources like muscles or red blood cells.

The pathophysiology of SARS-CoV-2 related hepatic damage has not been fully elucidated, albeit a variety of mechanisms is proposed. First, a direct virus-induced cytopathic effect in hepatocytes is possible [5]. In autopsies of SARS cases, virus particles were detected in hepatocytes and endothelial cells [6,13]. Postmortem liver biopsy in a COVID-19 patient showed microvesicular steatosis and mild lobular and portal activity [14]. Besides, SARS-CoV-2, in similarity to SARS-CoV, binds to the target cells via angiotensin converting enzyme 2 (ACE 2) [15]. Novel data reveal that, ACE-2 is expressed in hepatocytes and bile duct cells in a level comparable to that of alveolar type 2 cells in the lungs [16]. However, markers of cholangiocytes' injury, namely alkaline phosphatase (ALP) and gamma-glutamyl transferase (γ-GT), are not usually elevated in COVID-19 cases [7,16].

Second, liver injury may be induced indirectly through a cytokine-mediated mechanism [5,6]. Previ-

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Received: 02 April 2020; Accepted: 15 April 2020

Key words: *SARS-CoV-2; COVID-19; liver function*

ous studies have demonstrated elevated inflammatory biomarkers (C-Reactive Protein, procalcitonin, ferritin) and increased levels of inflammatory cytokines and chemokines (IL-1, IL-6, IL-8, IL-10) in severe COVID-19 patients [4,7,8,17]. In addition, activation of coagulation and fibrinolytic cascades with reduced platelet count and elevated D-dimers has been also shown [4,8]. Furthermore, lymphopenia with decreased CD4+ T cells and increased neutrophils-lymphocytes ratio (NLR) are described [7,8,17]. These findings suggest derangement in immunomodulation and a hyper-inflammatory response that may exert injurious effects in liver parenchyma possibly by oxidative stress-related mechanisms [18].

Patients with chronic liver diseases and cirrhosis constitute a potential high-risk group for liver injury from SARS-CoV-2. It is reported that 2-11% of COVID-19 patients have liver comorbidities, even though the dynamic evolvement of the pandemic does not allow accurate estimations [4,5,8,10]. Previous data on SARS-CoV patients with coexisting HBV and/or HCV infection showed increased susceptibility to hepatic impairment, possibly as a consequence of amplified replication of HBV/HCV viruses [6]. Given the homology between the two coronaviruses, clinicians should be more alert when a patient with chronic viral hepatitis is presented with COVID-19. Serologic testing for HBV and HCV is recommended in cases with laboratory findings of liver injury. Furthermore, given the abundant expression of ACE-2 in cholangiocytes, SARS-CoV-2 infection might aggravate cholestasis in patients with cholestatic disease [16]. Although data on this topic are scarce, patients with primary biliary cholangitis and primary sclerosing cholangitis should be closely monitored with meticulous evaluation of ALP and γ-GT measurements. Reasonably, patients with hepatocellular carcinoma or cirrhosis are at increased risk for severe infection by SARS CoV-2 due to immunosuppression. A concern has been raised regarding the manipulation of immunosuppressive treatments in patients with COVID-19. Discontinuation of immunosuppressive regimens could exacerbate autoimmune hepatitis or could trigger an acute rejection in a post-liver-transplant patient. American Association for the study of Liver Diseases (AASLD) does not advise preventive modification of therapy for chronic liver disease patients during this outbreak [19]. In case of infection, it is recommended to reduce the dosage of high-dose prednisone with caution to avoid adrenal insufficiency (at least 10mg/day is recommended). Similar adjustments are required for azathioprine, mycophenolate or calcineurin inhibitors [19]. Obviously, since our background knowledge on such cases is insufficient, individualized approach is necessary.

A series of therapeutic agents have already been used in hospitalized COVID-19 patients. Therefore, drug induced hepatotoxicity is a possible factor of liver damage [10,11]. A variety of antivirals (remdesivir, lopinavir/ritonavir), antimicrobials (macrolides, quinolones, beta-lactams, chloroquine), biological agents (tolicizumab) and antipyretics (paracetamol), used in SARS-2-CoV, have the potential to induce liver injury [4,6,7]. Up to now, such a causality has been demonstrated only for the anti-retroviral drug combination of lopinavir/ritonavir [7]. Abnormal liver function test results should not discourage the use of investigational or off-label therapeutics according to the AASLD [19]. Undoubtedly, all hospitalized SARS-CoV-2 patients should be submitted in regular testing of liver biochemistries, especially those under treatment with tolicizumab or remdesivir, regardless of baseline values. Finally, in critically ill COVID-19 cases liver dysfunction might be associated with mechanical ventilation. Application of positive end expiratory pressure (PEEP) results to high right atrial pressure with liver congestion. The absence of counterbalancing arterial vasodilation and the high surrounding tissue pressure lead to decreased arterial flow as well [20].

In conclusion, COVID-19 may induce a multifactorial liver injury with unresolved pathophysiology. Direct viral-induced hepatotoxicity or indirect mechanisms associated with hyperinflammation, have been hypothesized. Careful monitoring of serum hepatic enzymes is imperative, especially in hospitalized patient or those with liver comorbidities.

Conflict of interest disclosure: *None to declare*

Declaration of funding sources: *None to declare*

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