COVID-19: an emergent cause of liver injury?

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In December 2019, and at the beginning of 2020, multiple cases of new coronavirus infection [1] started in Wuhan, China. The virus was named after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a serious threat to global public health worldwide. Although the virus appears to be only partially similar to SARS-CoV and Middle East respiratory syndrome coronavirus, all of these viral infections are responsible for severe and potentially lethal acute respiratory syndromes in human beings with a mortality rate of around 3% [2,3]. In addition to the acute respiratory symptoms, patients suffering from COVID-19 also may develop varying degrees of liver damage/dysfunction [3]. Zhang *et al*. [3] reviewed recently the data concerning liver injury in COVID-19. They quoted that 2–11% of patients had liver comorbidities and 14–53% abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [3]. Usually present within patients with severe diseases hospitalized in ICU where many patients with multiorgan failure had frequently elevated levels of AST (up to 62%) [4], mild to moderate increase in aminotransferases are quoted in about 20% of patients [3]. However, most data concerning the prevalence of liver tests abnormalities are drawn from larger series which are not devoted to liver injury [3]. Moreover, the mechanisms of liver injury are probably related to many causes, that is, a direct infection of liver cells [1,5], a fatty liver, drug-induced liver diseases, hypoxic hepatitis within patients in intensive care, and elements of the inflammatory response [1,3–6]. In this issue of the *European Journal of Gastroenterology and Hepatology*, six papers are delivered: two are cases series coming from the USA [7,8], one is a case report of a child with autoimmune hepatitis [9], two are systematic reviews and meta-analyses [10,11] and the sixth one is an overview coming from Egypt [12]. In the New York series, five well documented reports are described [7]. Liver enzyme elevation had a hepatocellular pattern and persisted throughout the hospitalization [7]. In this series, viral B and C hepatitis were excluded and all patients underwent a liver ultrasonography showing hyperechoic features consistent with steatosis in one of them; the evolution was benign. In the Syracuse series [8], four out the seven patients had type 2 diabetes, which is common in patients with severe symptomatic SARS-Cov2-related disease [2–4]. In both cases series, patients presented with an increase in lactate dehydrogenase (LDH) activity and ferritine levels that were higher than expected according to the aminotransferase activities; a moderate increase in aminotransferase activity was noted, except in one patient in the Syracuse series who had a very high increase, probably related to hypoxic hepatitis. In the Syracuse series, however, results of viral serologies were not provided.

In the first meta-analysis of Wijarnpreecha *et al*. [10] from the USA, 64 studies with 11 245 patients with COVID-19 were included. Co-existing chronic liver disease was present in up to 37.6% of patients with COVID-19. A fourth of patients presented with liver test abnormalities. The pattern of abnormal liver enzymes was notable for higher AST than ALT levels. The overall global prevalence of elevated AST, ALT, total bilirubin, gamma-glutamyl transferase, and alkaline phosphatases was 23.2, 21.2, 9.7, 15.0, and 4.0%, respectively. The prevalence of elevated AST was higher among those with severe cases (45.5%) compared to nonsevere cases (15.0%). In the second meta-analysis of Labenz *et al*. [11] from Germany, 14 studies combining data from 2871 patients were retained for analysis, maybe due to the censoring of data earlier than in the US study. Results were very similar; in this study, they showed that elevated AST in patients in ICU was 2- to 2.5-fold higher compared to patients not in ICU [11]. These two well performed meta-analyses provide very important descriptive data in COVID-19 liver injury.

In the overview of Professor Amin from Cairo University [12], the possible mechanisms of liver injury are fairly discussed. Prof. Amin pointed also the fact that many patients presented with diabetes and other signs of metabolic syndrome well known to be associated with NAFLD/NASH. Prof. Amin questionned about the possible impact of COVID-19 in patients with cancer and/or liver transplant patients (out of the scope of this editorial).

Where do we stand then with COVID-19 liver injury?

Several hepatology national associations edicted proposals for the management of patients with chronic liver diseases and liver transplant; these recommandations are devoted to patients care according to local epidemiological data [13–15]. Indeed many patients treated for COVID-19 have underlying chronic liver disease in 2–11% of patients [2–5]. An increase in aminotransferases in 25–35% of patients, generally moderate with a higher rate, as high as 78% [5] in symptomatic and severe forms and in patients requiring hospitalization in an ICU [1–3,5].

The mechanism involved is uncertain to date. Indeed, the data suggesting the possibility of localization of the virus in the liver are preliminary. Expression of the SARS-CoV-2 receptor (angiotensin 2 converting enzyme receptor) by cholangiocytes and hepatocytes have been hypothesized [1]. Wander *et al*. [16] reported the first observation of COVID-19 infection in a 59-year-old female presenting as acute nonicteric hepatitis prior to the development of fever and respiratory symptoms. Apart from steatosis

being present in some patients, drug-induced liver injury, or hypoxemia mentioned by Kudaravalli *et al*. [17] in this journal, a special attention should be paid to the systemic inflammatory response associated with coronaviruses. Pulmonary and systemic inflammatory responses are triggered by the innate immune system when it recognizes the virus [17]. Some of the cases reported in the present series and in other papers may be related to the cytokine storm with different degrees of severity. High ferritin levels, high CRP, and elevation of lactate dehydrogenase may reflect the consequences of this cytokine release syndrome. Unfortunately, data concerning possible cytopenias, hypofibrinogenemia, and hypertriglyceridemia are missing. To our knowledge, secondary haemophagocytic lymphohistiocytosis related to COVID-19 has not yet been described. However, severe cases are associated with a hyperinflammatory condition. A massive release of interleukin-6 has been reported in patients with COVID-19 infection [18,19]. In a retrospective series in 150 patients in China, elevated IL6 and high-serum ferritin were associated with mortality [20]. Tocilizumab, an IL6-receptor blocker, has been approved with severe pneumonia and elevated IL6 in China [21].

Other causes of liver injury should be evoked in these patients such as hypoxic hepatitis when there is a sudden raise of aminotransferases in ICU patients. An increase in AST may be related to myocarditis for example.

Few pathological data are available. In a recent autopsy study [22] and in one case report in a patient with acute respiratory distress syndrome [23], microvesicular steatosis with mild inflammation was noted in the liver although it was unclear whether it was related to the virus or other underlying conditions [1].

In addition to these data, we are face with the fact that COVID-19 may aggravate chronic liver diseases and may have a deleterious effect in such patients. Large series involving complete screening for liver diseases (either viral or NAFLD related) are necessary to better assess the true impact of COVID-19 in these patients. National Hepatology and Gastroenterology societies are editing recommendations for the management of patients with chronic liver diseases and transplant recipients. Management of immunosuppressive treatment in autoimmune hepatitis patients is not well established, although American [14] and French [15] hepatology societies recommend the reduction in dosage of azathioprine. For the European Association for the Study of liver, reduction of immunosuppressive therapy should only be considered under special circumstances (e.g., lymphopenia, or bacterial/fungal superinfection in the case of severe COVID-19) [13]. Yuksel *et al*. [9] monitored the immune response in a 5-year-old boy with autoimmune hepatitis and type 1 diabetes infected with COVID-19 on the third month of immunosuppressive treatment. Azathioprine was discontinued and prednisolone was continued at a low dose (8 mg/day). According to their data, the authors hypothesized that continuing low dose of steroids in this patient abrogated Tregs, Bregs and consequently IL-6 production. It permitted the activation of CD8+ T cells to clear the virus. Additional data are needed to clarify the role of immune regulatory cells in COVID-19, and the management of immunosuppressive treatment in autoimmune hepatitis patients.

It is currently too early to assess the impact of COVID-19 in the outcome of chronic liver diseases and more data are needed to understand the mechanisms of liver injury in patients with COVID-19. The six papers presented in this issue of the Journal add pieces to the COVID puzzle which is far from being achieved.

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Conflicts of interest

There are no conflicts of interest.

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