Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinics and Research in Hepatology and Gastroenterology (2020) 44, e84—e86

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LETTER TO THE EDITOR

Is SARS-CoV-2 associated with liver dysfunction in COVID-19 patients?

To the Editor,

The COVID-19 pandemic poses a big challenge to government and public healthcare sectors worldwide. Patients with increased age and pre-existing illnesses have been recognized as populations at risk of infection and severe course of COVID-19 [1]. It is speculated that SARS-CoV-2 is not only infectious but may also cause multi-organ dysfunctions in humans [2]. Up to now, there are limited reports on liver function abnormalities during COVID-19 infections. At this point it remains unclear to what extent hepatic diseases should be considered as potential risk factors of COVID-19 severity and mortality.

The available studies that have measured the liver function markers among COVID-19 patients are presented in the Table 1. A very recent study included 417 patients reported 76.3% of liver test abnormalities and 21.5% of liver injury among hospitalized COVID-19 patients [2]. In that study serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) were significantly higher in severe patients (ICU admitted) within 2 weeks of hospitalization. The authors observed that patients with elevated liver enzymes in the hepatocyte category had an increasing trend for progression to severe disease course. Serum GGT, a diagnostic biomarker of cholangiocyte injury, was a few folds higher in severe patients [2]. In another study, AST was elevated in 62% of patients in the intensive care unit (ICU) compared to 25% of patients who were not in the ICU [3]. The prevalence of ALT and AST abnormalities were observed at least two times higher among severe patients than non-severe patients with SARS-CoV-2 infection [4]. Moreover, in a study including 1099 patients, more severe patients had elevated ALT levels than non-severe patients with the disease [5]. Furthermore, in another study, the incidence of AST abnormalities was lower among patients before the onset of symptoms than the patients diagnosed after the onset of symptoms [6]. Therefore, liver dysfunctions are more prevalent in severe COVID-19 patients.

In the previous studies, pre-existing liver conditions have not been outlined, while increased ALT, decreased platelet counts and decreased albumin concentrations at the time of admission were associated with higher mortality [4], although not all these changes are independent risk factors. It remains unclear yet whether these alterations are an indicator of pre-existing liver disease with a more severe disease course, whether they rather reflect liver failure caused by the virus itself [1]. A high prevalence of liver test abnormalities in some studies, suggesting that liver injury in COVID-19 patients might be directly caused by the SARS-CoV-2 infection of liver cells [2,7]. Two new studies have shown that angiotensin-converting enzyme 2 (ACE2) is the key receptor for SARS-CoV-2 cell entry [8,9], which is mainly present in the heart and kidney and also expressed at a lower level in other tissues including colon and lung [10]. SARS-CoV-2 may bind to ACE2 positive cholangiocytes directly and causes hepatic injury [11], which may partially clarify the contribution of SARS-CoV-2 infection to the liver test abnormalities in COVID-19 patients [2]. It is also important to mention that other respiratory viruses cause similar elevation of liver test markers, which is thought to relate to hepatic damage from immune interactions involving intrahepatic Kupffer cells and cytotoxic T cells [7]. Therefore, further investigations would be worth to confirm the association between viral infection and liver failure in severe COVID-19 patients.

It is also possible that drugs used for the treatment are associated with liver damage in severe COVID-19 patients which could explain the large variations found across the various studies. Although, there is no evidence suggesting that liver test abnormalities are completely induced by the drugs used for the treatment of COVID-19 patients. However, it is considered that using of ACE-inhibitors and angiotensin II receptor blockers drugs may also interfere with liver function tests. In a recent study, a high prevalence of liver dysfunction was observed among patients who used ACE-Is/ARBs drugs at hospital admission, although the difference was not significant with those who did not use these drugs [2]. In the same study, the authors [2] observed that after admission, using drugs especially lopinavir and ritonavir contributed significantly to liver dysfunctions. These drugs increased the odds of liver injury (OR from 4.44 to 5.03, both $P < 0.01$) among patients. In their investigation, the liver biopsy of a patient who died from the disease had elevated liver enzymes that could be partly of the

https://doi.org/10.1016/j.clinre.2020.05.002

Table 1 Prevalence of elevated liver enzymes from different COVID-19 studies.

Reference	Group	Patients (*n*)	% of patients with abnormal liver test
[2]	Severe	85	ALT (82.3), AST (75.3), GGT (72.3), ALP (12.2)
	Non-severe	233	ALT (52.2), AST (26.9), GGT (39.1), ALP (10.5)
[12]	Hospitalized	99	ALT (28), AST (35)
[5]	Hospitalized	1099	ALT (21.3), AST (22.2)
[3]	Severe	13	62
	Non-severe	28	25
[6]	Hospitalized	81	53
[13]	Severe	36	Not known
	Non-severe	102	Not known
[14]	Hospitalized	62	16.1
[15]	Survivors	20	30
	Non-survivors	32	28
[4]	Severe	30	ALT (16.7), AST (26.7)
	Mild	61	ALT (8.2), AST (16.4)

Severe: patients admitted in the intensive care unit (ICU).

drugs used in treatment, and the observed liver dysfunction may be due to sepsis and shock [2]. Moreover, the use of antibiotics showed a significant association with liver injury in COVID-19 patients in the multivariate regression model; however, the association was not significant when the inverse probability weighting model was applied [2]. So, besides possible viral exposure and drug-induced toxicity, immune-mediated inflammation, such as cytokines storm and pneumonia-related hypoxia might be another mechanism of liver damage in COVID-19 patients; further studies should confirm these associations. To reduce the risk, it is important to evaluate the detrimental effects of certain drugs on liver injury during hospitalization of the COVID-19 patients. Patients with liver cirrhosis or liver cancer are at high risk of SARS-CoV-2 infection due to their systemic immunocompromised status. Therefore, it is suggested to care for COVID-19 patients with chronic liver disease with priorities even in the limited healthcare resources. Large-scale clinical studies are needed to identify the causes of liver injury in the severe disease course and the effects of pre-existing liver disease on treatment and clinical outcome of COVID-19.

Funding

None.

Disclosure of interest

The author declares that he has no competing interest.

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Available online 21 May 2020