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.

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Correspondence

Reply to: "Characteristics and in-hospital outcomes of COVID-19 patients with acute or subacute liver failure"

Dear Editor,

We read with great interest the Letter to the Editor by Xingshun Qi, M.D. et al. [1], which comments on our previously published paper, "COVID 19 and liver: An A–Z literature review" [2]. Although the true spectrum of COVID-induced liver injury is yet to be fully understood, acute liver failure is considered a rare complication. It is reasonable to consider that SARS-CoV2 can bind to the ACE2 receptors of cholangiocytes, inducing direct injury to bile ducts, acute liver injury, and even acute liver failure (ALF). Case reports of patients presented with severe COVID-related hepatitis which rapidly progressed to acute liver failure, have previously been described [3]. In your study, all patients who developed acute liver failure developed elevated serum transaminase levels with the highest level of AST and ALT exceeding 800 U/L and 1000 U/L, respectively. Viral causes for acute hepatitis including hepatitis A, B, C, E, EBV, CMV, HSV 1, HSV 2, and HIV, should have been excluded in those 6 patients.

Drug hepatotoxicity is an additional cause of liver impairment in patients with COVID-19, that should be considered. In the meantime, various antiviral (remdesivir, lopinavir/ritonavir, and favipiravir), and immunomodulating agents (corticosteroids, tocilizumab) drugs have been used in clinical studies, or in an off-label fashion. For most of these drugs, hepatotoxic potential has already been confirmed. Hence, detailed drug history for those patients with ALF should have been described to identify their culprit role [2].

A direct correlation between systemic inflammation (indicated by IL-6, CRP, and ferritin) and acute liver injury in COVID-19 also was recently reported, [4] thus, evaluation of these markers in those with liver failure in comparison to the rest of the patients is warranted . In the setting of acute and sub-acute liver failure, a trans-cutaneous liver biopsy could be difficult to perform due to coagulopathy, and given the rapidly progressive nature of the acute liver failure, transjugular liver biopsy may have been a better choice to reveal the patho-etiology of liver failure. Transjugular biopsy of COVID-19 presenting as a fulminant hepatic failure was performed by Melquist et al., and revealed panacinar hepatitis associated with focal giant cell transformation, zone 3 necrosis, mild fatty change, and focal hemophagocytosis, which is consistent with acute hepatitis. Moreover, tissue PCR may be helpful to confirm the direct hepatic cytopathic effect of the virus. Furthermore, secondary sclerosing cholangitis or hepatic vascular occlusion, might have contributed to liver dysfunction in COVID patients and should be excluded [5].

Addionaly, it was mentioned in your study that all patients who developed ALF were mechanically ventilated, in addition to developing myocardial failure, long-lasting hemodynamic, and/or respiratory failure. The established hypoxia results in hepatic cell death, histopathologically defined as centrilobular necrosis. Interestingly, transaminases were >5 times the upper reference limit in those 6 patients, which could fulfill the diagnostic criteria for hypoxic hepatitis. Invasive ventilation, high levels of positive end-expiratory pressure (PEEP), and vasoconstrictor use in those critically ill patients, may be accompanied by right ventricular dysfunction and congestive hepatopathy [6]. Liver failure secondary to multiorgan failure cannot be fully excluded in those patients.

A case report of COVID-induced hepatic encephalopathy was presented by Gamboa et al. SARS-COV 2 may access the CNS via blood circulation, neuronal pathway, or indirectly through hypoxemia, immune-mediated insult, or through multi-organ failure. ACE receptors are expressed on glial brain cells and neurons. SARS COV 2 has been detected in CSF of neurologically symptomatic infected patients, and this confirms the neuroinvasive nature of the virus. In COVID-related acute liver failure, the associated hyperinflammatory state can alter the permeability of the blood-brain barrier to ammonia [7]. Thus, in the setting of SARS-CoV-2 infection, encephalopathy is multi-factorial and should be evaluated cautiously, while serum arterial ammonia level may be helpful to distinguish those of a hepatic origin.

Finally, while elevated liver enzymes levels have been frequently seen during the course of COVID-19 infection, severe liver failure is a rare sequel. Additionally, close follow-up of liver chemistries, synthetic functions, and mental status is mandatory in those with SARS-COV-2. More research is needed to reveal the risk factors and pathophysiology for liver failure in patients without pre-existing liver disease.

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Walid Ibrahim Yousif
Alexandria University, Faculty of Medicine, Alexandria, Egypt