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.

LETTERS TO THE EDITOR

Readers are encouraged to write letters to the editor concerning articles that have been published in Clinical Gastroenterology and Hepatology. Short, general comments are also considered, but use of the Letters to the Editor section for publication of original data in preliminary form is not encouraged. Letters should be typewritten and submitted electronically to http://www.editorialmanager.com/cgh.

Clinical Characteristics of COVID-19 in Patients With Liver Injury

Dear Editor:

Dr Fan et al[1] assessed the clinical characteristics of corona virus disease 2019 (COVID-19) in 148 patients with liver damage and found that more than one-third of patients admitted to the hospital with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had abnormal liver function, and 48.4% of patients with normal liver function had liver injury after admission, with a higher proportion in patients receiving lopinavir/ritonavir. Although the article by Fan et al provides valuable information for clinical treatment in COVID-19, we still have some concerns about it.

First, because patients were from a single, large city in China, these findings cannot be generalized to rural communities or other regions. Thus, selection bias cannot be entirely excluded. Furthermore, the data of other causes of liver injury in the patients progressing to liver injury, such as herbal medicines or other drugs used as self-medication before developing COVID-19 pneumonia, were not available for patients in current study. However, since the COVID-19 outbreak in China in December 2019, discussion about COVID-19 has spread rapidly on the Internet and has quickly become the focus of worldwide attention. Shanghai is one of the most developed cities in China, and access to the Internet is widespread, which means many in the population would have a high degree of awareness of the disease. Most patients (>70%) went to the hospital within 5 days after the onset of disease symptoms and rarely used over-the-counter medicine to self-treat because medical insurance is widely available in Shanghai. Hence, although the data on herbs and other drugs used as self-medication before developing COVID-19 pneumonia were not available in this study, their influence on the results cannot be ignored.

Second, high levels of positive end-expiratory pressure might contribute to liver injury in patients with COVID-19. Previous studies have shown that high levels of positive end-expiratory pressure can contribute to hepatic congestion by increasing right atrial pressure and impeding venous return.[2] However, whether the COVID-19 patients admitted to hospital with liver blood test abnormalities received mechanical ventilation remained unclear in current study. Furthermore, lymphocytes are important for inhibiting overactive innate immune responses during viral infection. Typical lymphopenia during SARS-CoV-2 infection may result in increases in interleukin 6, interleukin 10, and interferon-γ levels and aggravated inflammatory responses, leading not only to pulmonary injury but also the injury of non-pulmonary organs including the liver.[3] A study by Lu et al[4] investigated the risk factors involved with hepatic injury in patients with COVID-19 and found that lymphopenia and C-reactive protein level were independently associated with liver injury. However, there was no statistical difference between abnormal and normal groups in lymphopenia; the cause of these results that contradicted the data of Lu et al is also still unknown in this study.

Another issue is that the COVID-19 patients have been confirmed to tend to have underlying liver diseases, including nonalcoholic fatty liver disease, alcoholic liver disease, and chronic hepatitis B, and had cough as an initial symptom; however, the specific ratio of COVID-19 patients with liver comorbidities was unknown in this study. Preliminary data reported by Zhang et al[5] indicate that 2%–11% of patients with COVID-19 had liver comorbidities, and whether the results in this study contradict the data of Zhang et al was unclear in this study. In addition, remdesivir treatment during COVID-19 can also induce liver impairment. In an article describing the first 12 patients with COVID-19 in the United States, the 3 hospitalized patients, who received remdesivir at the time of clinical worsening, had elevated liver enzymes.[6] However, this issue has not been mentioned in the current study, and the authors should give some interpretation and explanation of these data.

Last, the authors did not apply the definition of drug-induced liver injury from the European Association for the Study of the Liver Clinical Practice Guidelines,[7] because currently there was no evidence indicating that the abnormal liver injury during hospitalization was fully induced by the drugs used.

PENG CHEN, MD
Department of Pharmacy
Renmin Hospital of Wuhan University
Wuhan, Hubei, P.R. China

BENHONG ZHOU, PhD
Department of Pharmacy
Renmin Hospital of Wuhan University
Wuhan, Hubei, P.R. China

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Cardiac and Muscle Injury Might Partially Contribute to Elevated Aminotransferases in COVID-19 Patients

Dear Editor:

Corona virus disease 2019 (COVID-19) patients can have elevated aminotransferases.[1–3] It seemed that increases of aspartate aminotransferase were more prominent than alanine aminotransferase in COVID-19 patients according to previous studies.[1–3] In the study by Fan et al,[1] the proportions of patients with elevated aspartate aminotransferase and alanine aminotransferase were 21.6% and 18.2%, respectively. Among severe COVID-19 patients, the proportion of patients with elevated levels of aspartate aminotransferase also seemed higher than the proportion with elevated levels of alanine aminotransferase (39.4% vs 28.1%) in the study by Guan et al.[2] In another study,[3] the absolute levels of aspartate aminotransferase were also higher than alanine aminotransferase (31 vs 24 U/L). Of note, the upper limits of normal for aspartate aminotransferase and alanine aminotransferase were different, which were 40 vs 50 U/L, respectively.[3]

But not all abnormal liver function test results mean liver damage. Guo et al[4] indicated that acute cardiac injury can occur in COVID-19 patients, which can be seen in up to 27.8% of patients (52/187). Patients with acute cardiac injury also had significantly higher levels of aspartate aminotransferase than those without cardiac injury (39.5 vs 29.0 U/L; $P < .001$). However, the difference in alanine aminotransferase did not reach statistical significance between patients with acute cardiac injury and without it (28.5 vs 23.0; $P = .11$).[4] Meanwhile, the heart may occasionally contain a high alanine aminotransferase activity,[5] so abnormal levels of alanine aminotransferase and aspartate aminotransferase might partly result from myocardial injury, especially when increases of aspartate aminotransferase are more prominent.

In addition, the viral infection can cause muscle injury. In the case of muscle injury, sarcoplasmic proteins including creatine kinase, alanine aminotransferase, and aspartate aminotransferase can be high. It has been reported that rhabdomyolysis can occasionally occur in COVID-19 patients.[2,6]

Hence, we think the incidence of liver damage might be overestimated in COVID-19 patients. We speculate that cardiac and muscle injury might partially contribute to elevated aminotransferases in COVID-19 patients. The largest study so far found that 13.7% of COVID-19 patients had elevated levels of creatine kinase, which may also indicate that muscle or cardiac injury occurred.[2]

Regarding the association between liver injury and overall prognosis in COVID-19 patients, Fan et al[1] indicated that baseline liver impairment was associated with a prolonged hospital stay, and abnormal liver function during admission had little effect on the length of hospital stay. However, the acute cardiac injury is significantly associated with fatal outcome in COVID-19 patients[4]; meanwhile, rhabdomyolysis is a potentially life-threatening condition. We suggest that patients with elevated aminotransferase be evaluated for the presence of acute cardiac injury or rhabdomyolysis.

YONGXING XU, MM
Department of Nephrology
PLA Strategic Support Force Characteristic Medical Center
Beijing, China

JIANWEN GU, MD, PhD
The Leading Group on COVID-19 Prevention and Control
PLA Strategic Support Force Characteristic Medical Center
Beijing, China

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