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.

Supplementary data

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Guangtong Deng[1,4,5]
Furong Zeng[1,4,5,*]
Lijuan Zhang[2,*]
Hui Chen[3,*]
Xiang Chen[1,5,*]
Mingzhu Yin[1,5,*]

[1]*Hunan Engineering Research Center of Skin Heath and Disease and Hunan Engineering Research Center of Gynecological Disease, Department of Dermatology, Xiangya Hospital, Central South University, Changsha, Hunan, China*
[2]*Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Harbin Medical University, Harbin, China*
[3]*Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[4]*Obstetrics and gynecology department, Xiangya Hospital, Central South University, Changsha, Hunan, China*
[5]*COVID-19 Research Group in Hunan, China*

[*]Corresponding authors. Address: Hunan Engineering Research Center of Skin Heath and Disease and Hunan Engineering Research Center of Gynecological Disease, Department of Dermatology, Xiangya Hospital, Central South University, Changsha, China.
E-mail addresses: zengflorachn@hotmail.com (F. Zeng), zhanglijuan18sui@163.com (L. Zhang), chinachen67@hust.edu.cn (H. Chen), chenxiangck@126.com (X. Chen), yinmingzhu2008@126.com (M. Yin)

SARS-CoV-2 related liver impairment – perception may not be the reality

To the Editor:

The catastrophic emergence of COVID-19 has led to large volumes of research from epicentres of infection, with some focusing on COVID-19-related liver impairment. In this regard, the study by Wang *et al.* published in the *Journal* intrigued us.[1] The authors associate very minimal elevations in alanine (ALT) and aspartate aminotransferase (AST; ALT >AST) to disease severity and demonstrate 'specific' COVID-19-related cytopathic changes and virus-like particles on post-mortem liver histopathology (n = 2). They found that severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) caused massive apoptosis and binucleation of hepatocytes, resulting in liver enzyme abnormality and synthetic liver dysfunction, the latter in the form of hypoalbuminemia. Their painstaking work is commendable, but their assessment of clinical and investigational events may not reflect the reality. It is recommended that the ideal cut-off for diagnosing acute hepatic injury is 200 U/L and 300 U/L for AST and ALT, respectively.[2] The degree of elevation in AST and ALT in the current study can only be considered an 'altered' liver test, not akin to acute hepatic injury. In hepatic impairment, there must be very clear evidence for metabolic (hypoglycaemia, hyperammonemia), secretory (hyperbilirubinemia) and synthetic (hypoalbuminemia, raised prothrombin time) dysfunction. Except for a mild rise in ALT and hypoalbuminemia, significant liver dysfunction is elusive in the current study. Importantly, hypoalbuminemia, in the absence of other significant liver test abnormalities, virtually rules out the hepatic origin of this abnormality. Acute liver injury

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is best identified by international normalized ratio >2.0, which was conspicuously absent in the current study.[3] The liver biopsy findings of hepatocyte apoptosis, binuclear or occasional multinuclear syncytial hepatocytes, in the absence of viral inclusions and presence of moderate steatosis, with mild focal lobular or portal inflammation are non-specific findings that may not be related to viral cytopathy. These findings can undoubtfully be seen in sepsis and multi-organ dysfunction associated with critical illness (moderate to severe apoptosis, steatosis, lobular and portal inflammation), aging, drug-induced liver injury and fatty liver disease (binucleation or polyploidy–a feature of liver cell renewal and not injury).[4–6] The liver biopsy does not correlate with increased gamma-glutamyltransferase, which could have been secondary to the systemic illness or drug toxicity. CD68+ cellular infiltration of the hepatic sinusoids (a marker of macrophage activation) can be noted in any acute or chronic systemic inflammatory state affecting the liver, including non-alcoholic fatty liver disease (NAFLD).[7] Finally, the 'spiked' inclusions and their degenerate components may not be of viral origin since confirmatory PCR testing for viral nucleic acids was not performed. Such 'corona-like' particles could be intrahepatic cholesterol crystals, lamellations, or 'crown-like' structures seen in patients with NAFLD. In the latter, Kupffer cells surround and engulf remnant lipid droplets (themselves granular or spiky cytoplasmic inclusions) of apoptotic hepatocytes. Moreover, associating mitochondrial changes to SARS-CoV-2 infection of hepatocytes could be erroneous. Electron microscopic changes of liver mitochondria in the form of enlarged mitochondria, intramitochondrial crystalline inclusions, mitochondrial matrix granules, vesicles containing electron-dense material in peribiliary Golgi-zone and electron-dense material accumulation in the space of Disse are notable in steatotic livers and drug-induced liver injury.[8,9] In non-hepatotropic viral infection, such as cytomegalovirus-hepatitis, the liver involvement occurs as part of the disseminated systemic disease or secondary organ dysfunction that could be true for the SARS-CoV-2.[10] To conclude, even though intriguing, the study by Wang *et al.* might have arrived at unfounded conclusions regarding SARS-CoV-2-related liver injury. Hepatic impairment is not confirmed, and multiple viral cytopathic effects described on liver histology may be misleading in the presence of multiple comorbidities. 'COVID-19 induced liver injury' may be illusory. Current research has not confirmed direct SARS-CoV-2-related liver injury, and the features described may only indicate hepatic involvement in a severe systemic inflammatory disease.

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Conflict of interests

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Authors' contributions

CAP and RA designed the study; PA critically revised the manuscript; all authors approved the final version.

Supplementary data

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Cyriac Abby Philips*
Rizwan Ahamed
Philip Augustine
The Liver Unit and Monarch, Cochin Gastroenterology Group, Ernakulam Medical Center Hospital, Kochi, Kerala, India
*Corresponding author. Address: The Liver Unit and Monarch, Cochin Gastroenterology Group, Ernakulam Medical Center Hospital, Kochi, Kerala, India. Tel.: +919207745776, fax: 91 484 2535838.
E-mail address: abbyphilips@gmail.com (C.A. Philips)