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.

mortality and in an analogous fashion to patterns seen in sepsis.[10] We still encourage clinicians to remain vigilant for drug-induced liver injury, and for liver damage in high-risk groups (*i.e.* drug/alcohol abusers, family history *etc.*), but not to get overly distracted by raised liver aminotransferases in this context.

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Authors' contributions
All authors contributed equally to the content and production of the letter, all authors checked and approved the final draft of the letter.

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Reply to: Correspondence relating to "SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19"

To the Editor:
We appreciate the thoughtful comments on our paper. Our study focused on coronavirus disease 2019 (COVID-19)-related liver enzyme abnormalities, rather than acute liver injury. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could infect the liver, it is not a hepatotropic virus that induces pronounced hepatitis. In keeping with this, abnormal liver function tests during the course of COVID-19 are common and primarily limited to aminotransferases, while clinically severe

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acute liver injury is rare.[1,2] This also explains the mild transaminase elevation and other well-preserved parameters, such as lactate, glucose and international normalized ratio, which most likely result from direct virus infection.

Regarding biochemical parameters, the median gamma glutamyltransferase (GGT) levels in both groups were in the normal range and there were no significant differences in levels of total or direct bilirubin and alkaline phosphatase, suggesting that cholangiocytes are unlikely the target sites. Aspartate aminotransferase was recently reported to highly correlate with alanine aminotransferase and reflect disease severity throughout the COVID-19 course, whereas the correlation with markers of muscle injury was weak.[3] Meanwhile, we noted that the median creatinine kinase (CK) was still in the normal range in the abnormal aminotransferases group, and the frequency of elevated CK was comparable between the 2 groups (17.86 % *vs.* 13.51%, p = 0.89), indicating that elevated CK and abnormal transaminases might not have a causal relationship. Leakage of albumin from blood vessels due to severe vasculitis was usually accompanied by hydrothorax or ascites. However, the albumin reduction in patients with COVID-19 was usually mild. Taken together, these aberrant blood variables appear to be predominantly the result of hepatic impairment.

We stated that SARS-CoV-2 directly contributed to cytopathy based on the ultrastructural findings of conspicuous mitochondria swelling, endoplasmic reticulum dilatation, glycogen granule decrease, and impaired cell membranes. Apoptotic and bi- or multi-nucleated syncytial hepatocytes were also signs of direct viral effects.[4,5] Previous studies demonstrated coronaviruses exerted extensive cytopathic effects through apoptosis, via a caspase-dependent pathway.[4,6–8] The 'corona-like' particles are characteristic of coronavirus particles, but not cholesterol crystals which are normally highly electron dense, structureless and inhomogeneous. Hepatocytes manifested no megamitochondria with linear crystalline inclusions, cristae loss, or increased matrix electrondensity, which would be expected in non-alcoholic fatty liver disease (NAFLD).[9–11] None of the reported autolytic microscopic modifications in the liver[12] were observed in our biopsies. Clathrins are generally located at the plasma membrane of synapses and play a role in synaptic vesicle reconstitution.[13] Clathrin possesses variable morphology, such as multiple coated buds which are formed on endosomes, distinctive from typical coronavirus.

In light of the low percentage of hepatocytes expressing ACE2, but not the absolute absence, it is not surprising that SARS-CoV-2 is capable of causing liver injury directly. On the other hand, there exist wide discrepancies between organ symptomatology and ACE2 expression levels.[14,15] For instance, ACE2 expression in the respiratory tract is only moderate compared with that in intestinal epithelia, but respiratory symptomatology is substantially more severe than intestinal.[14,15] It is therefore assumed that direct viral effects on the liver might not operate absolutely through ACE2 expression, and other receptors cannot be excluded. Alternatively, the finding of upregulated ACE2 expression in hepatocytes in cirrhotic liver inspired us to speculate that SARS-CoV-2 infection might induce compensatory hyperplasia of hepatocytes, which are possibly derived from cholangiocytes (with high ACE2 expression).[16] This procedure might result in a higher ACE2 expression in regenerative hepatocytes and facilitate viral infection in turn.

We acknowledge that fatty liver disease, drug-induced liver injury (DILI), sepsis and multiple organ dysfunction syndromes could be involved in liver damage in the setting of COVID-19, but our clinical and pathological findings do not favor these possibilities, as thoroughly described in our paper. Firstly, the prevalence of transaminase abnormalities was up to 23.5% even in the context of mild cases, precluding the role of COVID-19-related comorbidities. Secondly, despite steatosis, both biopsied cases had neither NAFLD nor other metabolic disorders. The pathological features of no obvious eosinophil infiltration, cholestasis, fibrin deposition, vasculitis, granuloma, massive central necrosis, or interface hepatitis did not comply with DILI. Thirdly, only 7 of 64 (10.9%) cases had sepsis and other severe comorbidities, which could not explain the apparently high rate (41.0%) of liver enzyme abnormality in our cohort. Additionally, the liver pathology in our septic case showed no pathological hallmark of sepsis, suggesting sepsis was not the main insult. All in all, our data fully support a direct role of SARS-CoV-2 in COVID-19-related hepatic impairment.

In conclusion, we believe SARS-CoV-2 is capable of infecting the liver and is a crucial factor in liver dysfunction, though other factors cannot be fully excluded.

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Conflict of interest

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Authors' contributions

JZ and FL contributed to study concept, critical revision of the manuscript; YW contributed to literature search and writing of the manuscript.

Supplementary data

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