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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Authors' contributions

G-J.H and M-S.L designed the letter; M-S.L wrote the letter; G-J.H revised the letter.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.04.023.

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Liver injury in COVID-19 – The culprit may not be COVID-19!

To the Editor:

We read the study by Ding *et al*[1] with great interest. We congratulate the authors on conducting this large, multicentric study. They have demonstrated that raised levels of aspartate aminotransaminase and direct bilirubin at admission can be used as independent predictors of mortality in patients with coronavirus disease 2019 (COVID-19). They developed a prognostic model with a nomogram that can be used to predict the overall survival probability in patients with COVID-19. Importantly, they have reported that chronic HBV infection is not associated with an increased risk of lethal outcomes in patients with COVID-19. Previous studies have revealed that liver abnormalities occur more frequently in patients with severe COVID-19 and this has been consequential in establishing the association between various liver function abnormalities and their effect on mortality in COVID-19.[2] This is due to the multiplier effect of multiple organ dysfunction, cytokine storm, drug effects and hypoxic liver injury, rather than the direct cytopathic effect of the SARS-CoV-2. Kulkarni *et al.*[3] performed a meta-analysis of 20,874 patients and reported that 3.6% of patients had chronic liver disease (CLD). The odds of developing severe COVID-19 in patients with CLD was 0.81 (95% CI 0.31–2.09; p = 0.67) compared to non-CLD patients. COVID-19 patients with elevated liver chemistries had higher risk of mortality (odds ratio [OR] 3.46 [2.42–4.95, p <0.001]) and severe disease (OR 2.87 [95% CI 2.29–3.6, p <0.001]) compared to patients without elevated liver chemistries. In this study,[1] around 61.8% patients had some abnormal liver chemistry during the course of hospitalization. However, there are some important issues that have not been addressed in the paper.

The study fails to identify underlying CLD as a predictor of worse outcome, possibly due to the small number of patients in the study. Also, the severity of liver disease in terms of various scoring systems has not been corelated with the outcomes. Only 11 individuals had compensated cirrhosis and 3 had decompensated cirrhosis. Standard severity scoring systems like Child-Pugh and model for end-stage liver disease for cirrhosis and Maddrey's discriminant function for alcoholic hepatitis have not been described and correlated with survival.[4,5]

Although most patients developed some transaminitis during admission, there were several confounding factors that blur the direct association of liver dysfunction attributable to COVID-19. Cai *et al.*[6] reported use of drugs, systemic inflammation, secondary sepsis, polypharmacy, shock and hypoxia as contributors to liver injury in COVID-19. The presence of hypoxic injury[7] is also a contributor to liver injury and has not been described in this study. It is evident from the description that the hospitalized patients in this cohort were sick, with most requiring high flow oxygen or invasive ventilation which could have contributed independently to liver injury. Also, the use of various medications during the hospital course should be included in the analysis. The use of hepatotoxic drugs like lopinavir and ritonavir have been shown to be associated with liver injury.[6] Alcohol abuse or use of Chinese herbal medication before admission should also be

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determined and adjusted for in multivariate analysis as that can be a potential contributor to liver injury.[8] The large number of drugs used in clinical trials and variable management of such patients based on evolving evidence also makes comparisons of cohorts difficult.[9]

In conclusion, we believe that Ding *et al.*[1] have meticulously analyzed various liver biochemistry abnormalities during COVID-19. However, the retrospective nature of the cohort, limitations of data, lack of external validation and other confounding factors described merit further investigation and research. It would be premature to attribute deranged liver function to COVID-19 infection alone with the available evidence.

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Authors' contributions
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Risk stratification in hospitalized COVID-19 patients

To the Editor:

Ding *et al.* recently published a retrospective analysis of potential predictors for mortality in 2,073 Chinese patients hospitalized with COVID-19.[1] As their main findings, they reported that increased liver parameters as well as liver injury were predictive for 28-day mortality, and proposed a nomogram that estimates the mortality risk of hospitalized patients with COVID-19 disease. However, as the understanding of COVID-19 disease improves, it becomes evident that the disease may present differently in different regions. Liver injury, as well as other gastrointestinal symptoms were associated with worse outcome in some, but not all studies.[2–7] Therefore, we set out to validate the main findings in an Austrian cohort of 405 hospitalized patients with COVID-19 disease.

We retrospectively collected demographic and laboratory data as well as in-hospital mortality from all patients with a positive SARS-Cov-2 PCR test hospitalized at either the University Hospital Graz or the State Hospital Graz II between February 28th, 2020 and May 30th, 2020. Due to availability, the nomogram parameters direct bilirubin and troponin I were substituted with total bilirubin and troponin T, respectively. Cox-Regression was used to estimate hazard ratios for 7-, 14-, 21- and 28-day in-hospital mortality; p values below 0.05 were considered significant. Monte-Carlo simulation were run to define cut-offs with the highest overall accuracy.

Firstly, we analysed whether elevated liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) or liver injury are predictive of 28-day mortality, as proposed in the original article. AST levels above the upper limit of normal were

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