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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Reply to: Comments on "Association of liver abnormalities with in-hospital mortality in patients with COVID-19"

To the Editor:

We thank Singh *et al.*, Horvath *et al.*, and Luo *et al.* for their comments on our recent study.[1] In this study, we focused on investigating the association between abnormal liver chemistries at admission and in-hospital death, rather than the etiology of liver injury in COVID-19. We agree with comments from Singh *et al.* that liver injury in COVID-19 may not be attributable to COVID-19 infection alone, and associations of hypoxia, systemic inflammation, and hepatotoxic drugs with liver injury were explored in another study from our institute.[2] In our study, parameters of hypoxic injury (severity of COVID-19) and systemic inflammation (abnormal C-reactive protein or interleukin-6 levels) are listed in the predictive model for COVID-19-related fatal outcome, and we did not find the use of traditional Chinese medicine drugs (univariate OR 0.895; 95% CI 0.738–1.085; $p = 0.26$, logistic regression analysis) or antiviral drugs (univariate OR 0.922; 95% CI 0.775–1.096; $p = 0.357$) before admission are associated with liver injury at admission. High flow oxygen or invasive ventilation was not used before admission, thus these parameters were not included in the predict model of our study. In addition, only 41 patients had oral use of lopinavir/ritonavir before admission, and 13 patients had history of alcohol abuse in the cohort. We performed sensitivity analyses by excluding these patients; the associations of (at admission) liver injury (adjusted HR 1.88; 95% CI 1.22–2.89; $p = 0.004$), abnormal aspartate aminotransferase (adjusted HR 1.37; 95% CI 1.01–1.83; $p = 0.041$) and abnormal direct bilirubin (adjusted HR 1.61; 95% CI 1.18–2.21; $p = 0.003$) with in-hospital death of COVID-19 patients were similar.

Singh *et al.* mentioned that severity scoring systems of liver function were not described in our study. We and others have reported that serum levels of albumin, bilirubin, creatinine, prothrombin time, and international normalized ratio might be influenced by COVID-19 and result in deterioration of Child-Pugh, model for end-stage liver disease and Maddrey's discriminant function scores.[3] However, we were not able to retrieve prehospital status of liver function tests in these patients, thus we did not evaluate the baseline liver function of patients by using severity scores. Singh *et al.* also mention that the limited sample size of patients with chronic liver disease (CLD) in the cohort may account for the association of CLD and COVID-19-related mortality in our study. Notably, CLD constitutes a spectrum of diseases such as hepatitis B, MAFLD, cirrhosis, etc., and the prognosis of COVID-19 varies in patients with different CLD,[4] thus the association of CLD with COVID-19 mortality is always determined by the constitution of CLD in the investigated cohort, thus we suggested that the characteristics and outcome of COVID-19 patients with different CLD should be analyzed independently.

We appreciate the work done by Horvath *et al.* They validated the robustness of our predictive model for COVID-19 mortality and simplified it in an Austrian cohort of COVID-19 patients. We tested the robustness of the simplified model in our cohort and found that this simplified predictive model can still predict 28-day mortality (HR 1.31; 95% CI 1.26–1.37; $p < 0.001$). However, the simplified model showed reduced predictive accuracy in our cohort (AUC-difference -0.07; 95% CI -0.075 to -0.064; $p < 0.001$) (Fig. 1A) and provided less net benefit across the range of fatal risk compared with the full model in decision curve analysis (Fig. 1B). We are expecting these predictive models to be validated in more cohorts in the future.

Received 26 May 2021; accepted 28 May 2021; available online 6 June 2021
https://doi.org/10.1016/j.jhep.2021.05.027

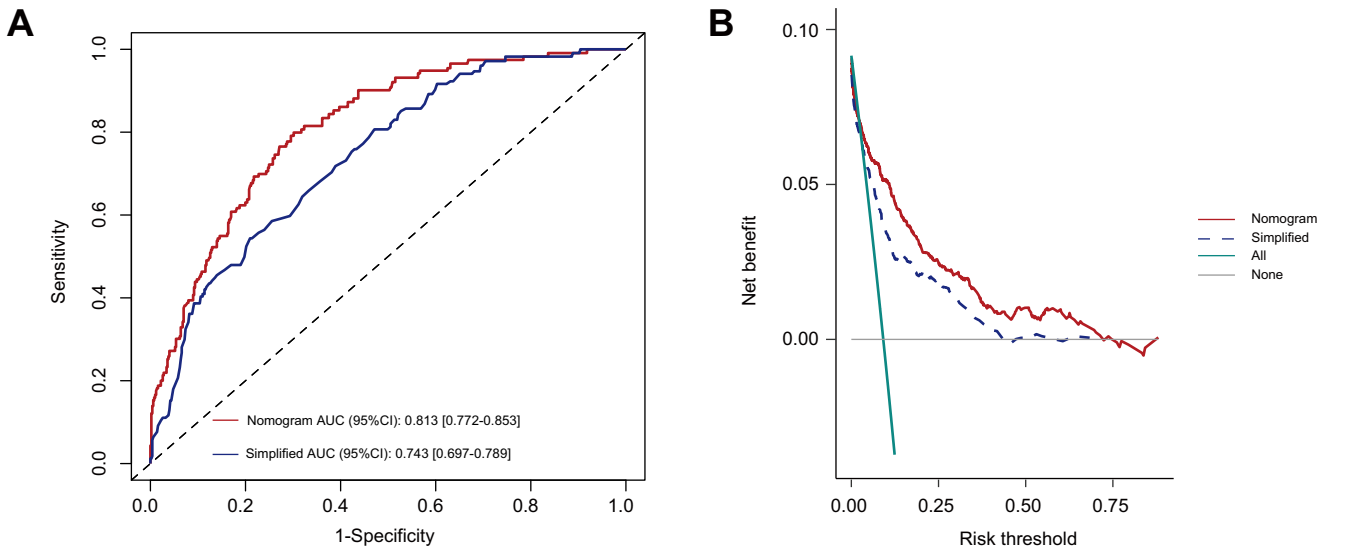

Fig. 1. Discriminative ability and clinical usefulness of the predict model for in-hospital mortality of COVID-19. (A) AUROC for the proposed nomogram and the simplified version. (B) Decision curve analysis for the nomogram and simplified risk prediction models. (This figure appears in color on the web.)

Luo *et al.* raised concerns regarding the statistical analyses and suggested that it is better to use disease-specific survival instead of overall survival to build the nomogram. This suggestion lacks feasibility, as COVID-19 is an emerging infectious disease whose pathophysiology is still being explored, and there is still no consensus on disease-specific death of COVID-19.[5] In addition, Luo *et al.* comments that based on the Riley's minimum sample size criteria,[6] a much larger sample size of 11,200 is required to establish a robust predictive model in our study. The predictive model in our study was used with an events per predictor parameter (EPP) of 20 (200 outcome events/10 parameters), which is compliant with the rule of thumb that a minimum of 10 EPPs is necessary for Cox models.[7] We noticed that when calculating sample size based on Riley's criteria, the short-term clinical course of COVID-19 leads to a very short anticipated mean follow-up (0.104 year), and results in the need for an impractically large sample size. Riley *et al.* only provide examples of investigating chronic diseases with anticipated mean follow-up of at least 2.07 years when introducing their methods of calculating sample size in prediction models for a time-to-event outcome.[6] Whether Riley's minimum sample size criteria are suitable for establishing predictive models of acute diseases needs to be confirmed and validated. In addition, the aim of the large sample size is to ensure the robustness of the predictive model, whereas this robustness has been internally validated by setting the bootstrap resampling cohort in our study and externally validated by Horvath *et al.* in an Austrian cohort.

Financial support
This work was funded by the research project for diagnosis and treatment of COVID-19 in Wuhan Tongji Hospital, China (XXGZBDYJ007 and XXGZBDYJ008), and the State Key Project on Infectious Diseases of China (2018ZX10723204-003).

Conflict of interests
All authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
ZD and BZ: writing, critical revision and obtain funding; GL, CS and PY: statistical analysis and writing reply to comments involving statistical analysis.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.05.027.

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Chronic fatigue should not be overlooked in primary biliary cholangitis

To the Editor:
We read with interest the paper by Corpechot *et al.*[1] on the long-term impact of preventive exposure to ursodeoxycholic acid (UDCA) treatment following liver transplantation (LT) for primary biliary cholangitis (PBC) in a multicentric international study. The authors reported during the interval-time 1983-2017 that 40% of graft failures (24/60 patients) were related to the recurrence of PBC (30%; 233/780 patients).[1] They observed that recurrence of PBC significantly decreased graft and patient survival, and that the preventive exposure to UDCA therapy was linked with a diminished chance of PBC recurrence, graft-loss, and death in the multivariable-adjusted Cox analysis.[1]

However, in this study,[1] the authors did not analyze the efficacy of such therapy on chronic fatigue (CF) symptoms that are commonly associated with PBC and progressively worsen during the disease course.[2–5]

Indeed, CF is a distinct, complex and disabling phenomenon afflicting – to different degrees – around 50–80% (despite a heterogeneous prevalence in some populations) of patients with PBC in many geographical areas, and particularly affecting young women.[2–7] The severity of CF symptoms in PBC predicts both liver-related fatality, and LT outcome.[3,4,6,7]

The pathogenesis of CF remains unclear and does not seem to be connected with the histological stage of liver disease, the degree of hepatic dysfunction, or the presence of definite serological markers of autoimmunity.[3–7] Besides, unlike PBC recurrence after LT, CF and cognitive impairment in PBC are unresponsive to any form of current treatment in many cases.[2–5] One possible explanation for the lack of benefit with standard treatments could be due to an early and slow-onset of disease processes, linked to a rather sneaky functional/organic injury in specific brain areas.[3,6–10]

On the other hand, CF in PBC, as well as PBC itself, may reappear frequently after LT (in approximately 37% and 10.9–42.3% of patients, respectively).[5,6] Specifically, LT is associated with improvement of fatigue in the short term.[5] Anyway, a large number of patients persistently suffer from CF at 2 years after LT,[6] which is not reversible over time,[5–7] and plausibly overlaps with the symptoms of minimal to manifest hepatic encephalopathy in advanced cirrhosis.[7] Moreover, the level of daily functioning and cardiorespiratory health have been strongly linked with the severity of PBC-related fatigue after LT,[6] thus impacting patient survival.[7]

Estimating the extrahepatic pathogenesis of CF and considering its clinical relevance,[7] raises a question: why Corpechot C and colleagues did not examine in their work pre-and post-transplant fatigue amongst the various variables? In our viewpoint, the diverse distribution of CF symptoms in both the non-preventive and preventive-UDCA groups may have influenced at least some results of the secondary objectives of their study (*i.e.*, graft loss, and/or all-cause mortalities).

Financial supports
The authors received no financial support to produce this manuscript.

Conflicts of interest
The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
ES, study concept/design, data acquisition, data analysis and interpretation, and writing manuscript; FA, data acquisition, critical revision.

Acknowledgements
We thank Mohamad Mouchli, MD (Department of Gastroenterology and Hepatology, Cleveland Clinic, Ohio, USA) and Erjon Shahini, Software engineer (Polytechnic University of Bari, Bari, Italy) for their valuable comments.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.02.020.

Keywords: PBC; cholestatic disease; liver transplantation; chronic fatigue; ursodeoxycholic acid.
Received 11 February 2021; received in revised form 16 February 2021; accepted 18 February 2021; available online 25 February 2021
https://doi.org/10.1016/j.jhep.2021.02.020