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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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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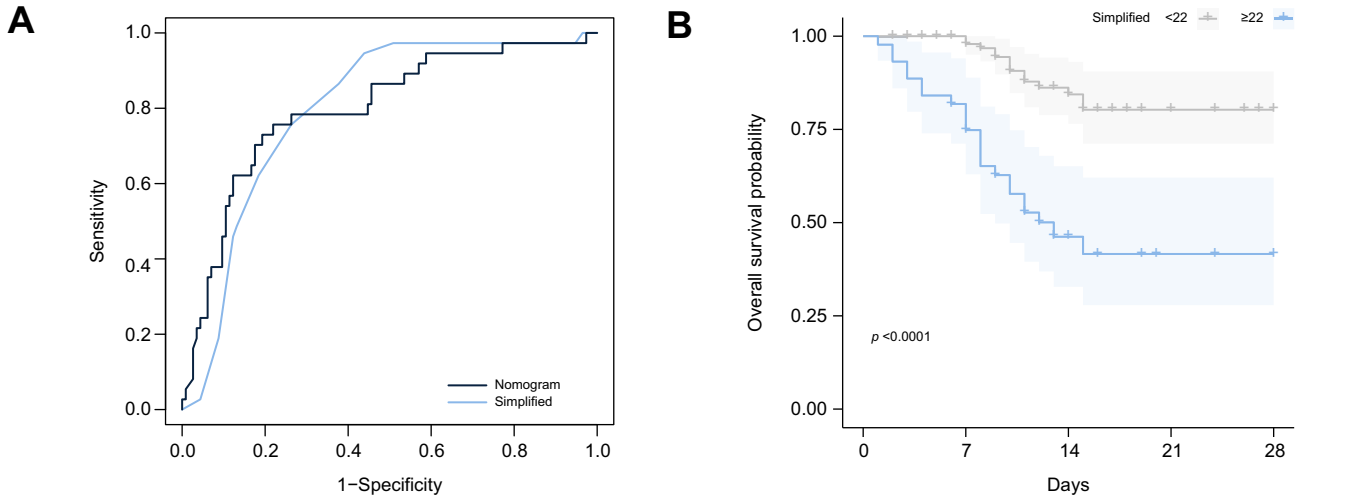

Fig. 1. Prediction of in-hospital mortality. (A) AUROC for the proposed nomogram and the simplified version. (B) Kaplan-Meier curves according to the simplified nomogram (p <0.0001, Log-rank test).

found in 189 of 305 (61,4%) patients, elevated ALT levels in 85 of 310 (27.4%) patients; 21 of 243 (8.6%) patients fulfilled the criteria for liver injury. We found that neither elevated AST (hazard ratio [HR] 1.23; 95% CI 0.77–1.96; p = 0.4), elevated ALT (HR 0.61; 95% CI 0.35–1.07; p = 0.09) nor liver injury (HR 0.74; 95% CI 0.27–2.05; p = 0.6) could predict hospital mortality in COVID-19 patients in Graz, Austria. Similar, non-predictive results were obtained for 7-, 14-, or 21-day mortality. GI symptoms in general, as well as diarrhoea in particular, were not associated with 28-day mortality (HR 0.58; 95% CI 0.15–2.16; p = 0.4 and HR 0.42; 95% CI 0.04–4.00; p = 0.5, respectively).

Secondly, we tested whether the proposed nomogram, including age, severe pneumonia, lymphocyte count, platelet count, C-reactive protein, D-dimer, creatinine, troponin, AST and bilirubin, could predict 28-day mortality in the Austrian cohort. A complete data set could be obtained from 151 patients, 37 (24.5%) of whom died within 28 days of hospitalization. The score derived from the nomogram was significantly associated with 28-day in-hospital mortality (HR 1.009; 95% CI 1.005–1.013; p <0.001) and showed a high predictive accuracy (AUROC 0.80; 95% CI 0.71–0.88; p <0.001). Similar results were obtained for 7-, 14-, or 21-day mortality. However, not all factors of the nomogram could predict in-hospital mortality individually. While age points (*i.e.* age*1.11-1.11), severe pneumonia, C-reactive protein over 10 mg/L, D-dimer over 1.3 mg/L (adjusted cut-off), creatinine over 84 μmol/L and troponin T over 15.6 ng/ml were predictive, lymphocyte count, platelet count, AST and bilirubin were not.

Although the proposed nomogram is performing well, it is rather complicated to calculate which could be a considerable disadvantage in well-frequented COVID-19 wards. We propose a simplified version based on the predictors that we could reliably reproduce in the Austrian cohort. The simplified score is composed of the sum of the following: age decade, 4 points for severe pneumonia, 8 points for C-reactive protein over 10 mg/L, 4 points for creatinine over 84 μmol/L. This simplified version can still predict 28-day mortality (HR 1.24; 95% CI 1.16–1.34; p <0.001) and shows comparable accuracy to the full version of the nomogram (AUC difference: -0.001; 95% CI -0.05 to 0.05; p = 0.9). A score of 22 or higher best identified patients at risk of 28-day in-hospital mortality (Fig. 1).

In conclusion, we validated and simplified the nomogram proposed by Ding *et al.*[1] although liver injury itself was not predictive in our cohort. The divergence in liver function-related findings is not unexpected. Several meta-analyses in the past 6 months showed that a certain fraction of individual studies indicated no association between liver function abnormalities and outcome, although, overall, they were associated with disease severity and outcome.[3,5,6] Our retrospective study design is not suited to address the source of this discrepancy. However, direct comparison of the 2 study populations showed that patients in our cohort were 74 (±14) years old and therefore 12 years older on average compared to Ding *et al.*, which might explain the considerably higher mortality rate as well as the higher prevalence of liver function abnormalities (74% *vs.* 61%, respectively) in our cohort. Our cohort is limited by the smaller sample size compared to Ding *et al.* and the unavailability of direct bilirubin which might also contribute to the observed discrepancies. Despite these limitations we could validate the nomogram proposed by Ding *et al.* and call for validation of the full[1] as well as our simplified version of the nomogram in other cohorts across the globe to improve the risk stratification of COVID-19 patients.

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Authors' contributions
TL, NF, HW collected data, AH, VS analysed the data and wrote the manuscript.

Supplementary data
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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.

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