
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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.09.015.

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# Association of chronic liver disease with the prognosis of COVID-19 patients

*To the Editor:*

We read with interest the recent work in the *Journal of Hepatology* by Mallet *et al.*, who studied the outcomes, including mechanical ventilation and day-30 mortality, of all adult patients with COVID-19 discharged from acute and post-acute care and private and public hospitals in France in 2020 (N = 259,110).[1] Their results suggested that chronic liver disease increases the risk of COVID-19-related death. However, there are some issues that need to be addressed to ensure that the results of this study are more convincing and therefore contribute to further investigations exploring the risk of death after COVID-19 in patients with chronic liver disease.

First, in this study, there may be a bias in demographic and clinical data between patients without (n = 243,634) and with (n = 15,476) chronic liver disease.[1] Patients with chronic liver disease were more likely to be male. The age distribution was also different ($p$ <0.001). Patients with chronic liver disease had more frequent ($p$ <0.001) alcohol use disorders, current or past tobacco use, obesity, hypertension, and diabetes mellitus. The author only conducted a propensity-matched analysis in the primary liver cancer subgroup (n = 1,821) and did not conduct a propensity-matched analysis between patients without (n = 243,634) and with (n = 15,476) chronic liver disease. A study on predictors of outcomes of COVID-19 in patients with chronic liver disease across multi-center studies in the United States showed that the liver-specific factors associated with independent risk of higher overall mortality were alcohol-related liver disease, decompensated cirrhosis, and hepatocellular carcinoma.[2] Other factors include increasing age, diabetes, hypertension, chronic obstructive pulmonary disease, and current smoking.[2] A study on the impact of chronic liver disease on outcomes of hospitalized patients with COVID-19 across multi-center studies in the United States showed that in multivariable analyses controlling for age, sex, body mass index, cardiac disease, hypertension, diabetes, and pulmonary disorders, chronic liver disease remained an independent predictor of intensive care unit admission ($p$ = 0.04) and the need for mechanical ventilation ($p$ = 0.0092) but not death ($p$ = 0.07).[3] Furthermore, another study about risk factors and outcomes for acute-on-chronic liver failure in COVID-19 across multicenter studies in the United States also indicated that the presence of chronic liver disease or cirrhosis by itself is not associated with a difference in in-hospital mortality after comparison with an age-, sex-, and comorbidity-matched control using propensity control methods.[4] Therefore, mechanical ventilation and day-30 mortality should be fairly compared by balancing the baseline characteristics of patients with and without chronic liver disease.

Second, in this study, the strengths of associations with mechanical ventilation and day-30 mortality were estimated using multivariate binary logistic regression.[1] However, selection criteria were not provided by the authors to conduct multivariate analysis for the variables, such as age, sex, current or past tobacco use, obesity, and hypertension. In addition, the authors did not conduct a collinearity analysis of obesity, diabetes, and other variables associated with chronic liver disease. For


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example, previous studies have shown that obesity and diabetes were associated with chronic liver disease.[5] Tjur's $R^2$ varies between 0 and 1, with 1 indicating perfect predictive power.[6] In this study, Tjur's $R^2$ of the multivariate model for mechanical ventilation after COVID-19 was 0.067, and Tjur's $R^2$ of the multivariate model for day-30 mortality after COVID-19 was 0.137. The explanatory power of these 2 models is weak. Therefore, collinearity analyses should be performed to improve the goodness of fit of the 2 models for mechanical ventilation and for day-30 mortality. Then, the odds ratio based on non-collinearity variables in the new models can be estimated.

In summary, we agree with the authors and appreciate this important study, which indicated that chronic liver disease increased the risk of COVID-19-related death. However, baseline differences must be excluded to obtain a more reliable conclusion.

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## Conflict of interest
The authors declare no conflict of interest pertaining to this work.

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

## Authors' contributions
All authors were involved in the writing of this commentary and reviewed it prior to submission.

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Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.07.011.

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# Reply to: "Association of chronic liver disease with the prognosis of COVID-19 patients"

**Prognosis of COVID-19 patients with chronic liver disease in France in 2020**

*To the Editor*:

We thank Dr. Zhao and colleagues [1] for their interest in our study evaluating the outcome of inpatients with chronic liver disease (CLD) and COVID-19 in a nationwide study conducted over 2020 in France. However, we believe that they might have been caught up in some statistical details and missed the general health policy implications of our study. Compared with other inpatients with COVID-19, we found that patients with CLD were at higher risk of mechanical ventilation (adjusted odds ratio [aOR] 1.54; 95% CI 1.44–1.64; $p$ <0.001) and 30-day mortality (aOR 1.79; 95% CI 1.71–1.87; $p$ <0.001). The term 'chronic liver disease' comprises a spectrum of conditions and liver disease stages, and this heterogeneity may affect COVID-19 outcomes. In particular, we found that inpatients with a liver-related complication recorded before COVID-19 had less chance of receiving mechanical ventilation (aOR 0.69; 95% CI 0.57–0.84; $p$ <0.001), although they were at higher risk of COVID-19-related death (aOR 2.98; 95% CI 2.69–3.30; $p$ <0.001). These findings suggest that a limitation of therapeutic efforts in patients with CLD and liver-related complications contributed to the COVID-19 death toll in France, in 2020. To our knowledge, the role of the limitation of therapeutic efforts on COVID-19 prognosis in selected groups of patients, independently of age, was not uncovered in previous prognostic studies, including in patients with CLD.[2,3] Regarding statistical analyses, Dr. Zhao and colleagues claim that a propensity-matched analysis should have been performed rather than conventional multivariate regression analysis. Propensity-

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