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Reply to: Correspondence on "Predicting portal thrombosis in cirrosis: A prospective study of clinical, ultrasonographic and hemostatic factors"

To the Editor:

We thank Li *et al.*[1] and Dai *et al.*[2] for their interest in our recent publication in the *Journal of Hepatology*.[3]

Li *et al.* reported the results of a thromboelastography assay in 58 patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt, 12 of whom had portal vein thrombosis (PVT). No differences in thromboelastography were found between the 12 patients with PVT and the 46 without. Despite this being a different scenario from ours, their results reinforced our finding that hemostatic alterations are not the main risk factors for PVT. In addition, the authors report decreased platelet responses and propose that antiplatelet therapy would likely be ineffective in prevention or treatment of PVT. It has to be noted, however, that platelet function tests in thrombocytopenic blood likely underestimate true platelet reactivity, and that normal to enhanced platelet responses in patients with cirrhosis have been reported using different methodology.[4] We agree that mechanisms underlying PVT development require further exploration. Of note, we have recently demonstrated that the portal vein thrombus frequently does not consist of typical thrombus components such as platelets and fibrin. Rather, we showed the thrombus to consist, at least partly, of collagenous thickening of the portal vein intima. These results also suggest that the role of coagulation activation in PVT is more minor than previously thought.[5]

Dai *et al.* highlighted the relevance of plasma levels of Factor X as an independent significant factor for PVT. However, we would like to point out that the higher risk of PVT was in patients with lower levels of pro-coagulant Factor X, suggesting that this is a further sign of severity of liver disfunction more than a reflection of increased hypercoagulability. That is why we did not consider it appropriate to further explore Factor X in stratified groups as they suggested. Additionally, patients undergoing surgical procedures, such as splenectomy or devascularization for the treatment of portal hypertension were excluded from our study because these are extremely rare procedures in the setting of cirrhosis in western countries; these special sub-populations fall beyond the objective our study. The occurrence of PVT in these surgical settings is also frequently acute, whereas the development of 'non-provoked' PVT is usually more chronic. The pathogenesis of surgery-associated PVT in patients with cirrhosis may therefore be different from that of non-provoked PVT. The role of anticoagulant therapy in prevention of surgery-associated PVT remains to be established. Importantly, it has been demonstrated that surgery-associated PVT in patients without cirrhosis is efficiently reduced by anticoagulant therapy.[6]

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Authors' contributions

All authors drafted and approved the final manuscript.

Supplementary data

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Author names in bold designate shared co-first authorship

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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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