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Letter: liver disease and COVID-19—not the perfect storm. Authors' reply

Dear Editors,

We read with great interest the letter by Nathwani et al[1], commenting on our article on COVID-19 and liver disease[2]. They reported their experience in managing abnormal liver function tests during SARS-CoV-2 infection and the impact of COVID-19 in patients with underlying chronic liver disease. The authors concluded that mild serum elevations of aminotransferases were associated with more severe disease but not increased mortality. Additionally, they also reported that cirrhosis predisposes to increase in length of stay, although the overall mortality was similar to those without liver disease.

We agree that patients with cirrhosis would be of major concerns because of their immune dysfunction, resulting in a high risk of infection, prolonged hospitalisations and worse outcomes. However, in the series reported by Nathwani et al, liver cirrhosis did not predispose to increase in mortality, which is different from what has been reported in other recent publications. It should be noted that whether pharmacological therapy was used during hospitalisation was not reported; for example targeted anti-viral therapy, which is known to influence the outcomes of cirrhotic patients. In addition, the cause of death, whether liver related or not, was also not reported.

A recent systematic review and meta-analysis showed an increased risk of severity and mortality in COVID-19 patients with liver diseases[3]. Moreover, Moon et al analysed 152 cases of laboratory-confirmed SARS-CoV-2 infection in patients with chronic liver disease and reported that liver cirrhosis was strongly associated with COVID-19-related mortality[4]. Severe outcomes correlated strongly with baseline Child-Turcotte-Pugh (CTP) class and model for end-stage liver disease score. Indeed, CTP-B and CTP-C cirrhosis remained significant predictors of mortality in these patients. Finally, a multicentre study from the United States found that the relative risk (RR) of mortality was markedly higher not only in patients with pre-existing liver disease but especially in those with cirrhosis (RR 2.8 vs 4.6)[5].

The care of cirrhotic patients remains a challenge in the COVID-19 pandemic. The data reported by Nathwani et al are a valuable addition to the reported experience with COVID-19 in liver cirrhosis[1]. Protective measures aimed at preventing infection with SARS-CoV-2 and precautions to guarantee the best treatment to avoid hepatic decompensation are of utmost importance[6-7]. Patients with cirrhosis testing positive for SARS-CoV-2 must be admitted for inpatient care if another poor prognostic factor is present, such as cardiovascular diseases, CTP B/C, hepatocellular carcinoma or liver transplantation. It is also recommended to test for SARS-CoV-2 in patients with acute decompensation.

In conclusion, it is essential to make immediate contact after the appearance of signs or symptoms compatible with COVID-19 or decompensated cirrhosis for urgent referral and management. Additionally, more intensive surveillance and individually tailored therapeutic approaches are needed for cirrhotic patients with SARS-CoV-2 infection. Further research identifying interventions to reduce poor outcomes in these patients is required.

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LINKED CONTENT

This article is linked to Garrido et al and Nathwani et al papers. To view these articles, visit https://doi.org/10.1111/apt.15813 and https://doi.org/10.1111/apt.15872.

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Letter: moderate levels of serum hepatitis B virus DNA alone are not associated with increased risk of hepatocellular carcinoma in chronic hepatitis B patients

Dear Editors,

We read with great interest the study by Kim et al in which they described the nonlinear parabolic association between HBV DNA levels and hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) patients independent of age, serum aminotransferases (ALT), hepatitis B e Antigen (HBeAg) and other predictors. This study showed that HCC risk was highest in patients who had moderate serum HBV DNA levels (6-7 $\log_{10}$ IU/mL) as compared to those with high serum HBV DNA levels (above 7 $\log_{10}$ IU/mL).[1] We note that patients did not have cirrhosis (excluded by various criteria) at baseline. A large sample size and an adequate follow-up of patients were salient features of the study, but there are a few points which we would like to highlight.

Normal ALT in patient with CHB infection is not equivalent to the absence of significant fibrosis or inflammation on liver biopsy. In fact, 20%-40% of patients of CHB with persistently normal ALT may have significant inflammation or fibrosis histologically,[2,3] Hepatic fibrosis is a harbinger of development of HCC. So before attributing importance to HBV DNA levels in isolation the degree of fibrosis should be considered in those who develop HCC with respect to those who did not.

As far as pathogenesis of HCC in noncirrhotic CHB is concerned, insertional mutagenesis by HBV DNA integration in host chromosomes is an important event and is detected in about 80% of HCCs. Also, this HBV DNA integration is dependent on HBV DNA level and viral polymerase activity.[4]

There are several scoring systems like REACH-B and GAG-HCC to predict the risk of HCC in untreated CHB patients.[5] However, these scores were not determined which may lead to bias in results.

As suggested by the authors also, this being a single-centre retrospective study where most of the CHB patients were likely infected with genotype C (which is an independent risk factor for development of HCC); further studies in patients with a different ethnicity and HBV genotype are required before generalising the results.