LETTERS TO THE EDITORS

Letter: liver disease and COVID-19—not the perfect storm

EDITORS,

We read with great interest the article by Garrido et al on COVID-19 and liver disease.¹ We agree that COVID-19 is associated with elevated liver enzymes, but its significance needs to be further elucidated as well as the impact of underlying liver disease on COVID-19. From 535 patients SARS-CoV-2 patients admitted at Imperial College Healthcare NHS Trust, London, from 25 February to 5 of April 2020,² we found 27.7% (148/535) had elevated liver transaminases. Median ALT and AST levels were 48 IU/L (IQR 17–49) and 88 IU/L (52–172) respectively. Only 1.7% (9/535) had an ALT five times the upper limit of normal and no patients developed synthetic liver dysfunction nor acute liver failure suggesting COVID-19 is not associated with significant acute liver injury. Patients with elevated liver transaminases had similar mortality rates than patients with normal transaminases at admission (29.4% vs 23.3%, P = 0.462), although a greater proportion with abnormal liver transaminases were admitted to intensive care (29.8% vs 10.7%, P < 0.001), in line with previous findings.³ We also did not find a correlation between the degree of transaminilts and hypoxaemia on admission defined by a blood oxygen saturation level < 94% (r = 0.06, P = 0.42) suggesting no direct link between COVID-19-induced initial hypoxemia and liver damage.

In addition, we have explored the impact of pre-existing liver disease—including cirrhosis, on the outcomes of COVID-19, which we feel is of great importance. Immune dysfunction has been well described in cirrhotic patients resulting in a high risk of infection and cirrhotic patients have poor outcomes with acute respiratory distress syndrome (ARDS).⁴ In our cohort, 89/535 (16.6%) had suspected pre-existing liver disease based on radiological and laboratory results, including 21/535 (3.9%) with cirrhosis, supporting previously reported rates,³ and 13/21 (61.9%) had decompensated cirrhosis (Child-Pugh B/C) (Table 1). The main aetiology of cirrhosis was alcohol (47.6%). COVID-19 symptoms at admission, in cirrhotic patients, were mainly cough (71.4%), fever (57.1%) and shortness of breath (23.8%), rather than worsening features of hepatic decompensation. Following admission, 6/21 (28.6%) with compensated cirrhosis developed hepatic decompensation (ie new onset encephalopathy, ascites, variceal haemorrhage or jaundice). This hepatic decompensation rate was not higher than that observed in historical in-hospital pre-COVID cirrhosis data (28.6% vs 37%).⁵

The overall mortality of COVID-19 patients with cirrhosis was similar to those COVID-19 patients without liver disease (38.1% vs. 34.1%, P = 0.689). Median duration of admission was longer in cirrhotic patients compared to those without pre-existing liver disease (10 days vs. 7 days, P = 0.016), but development of ARDS requiring admission to ICU for intubation and ventilation was not statistically significant (5.3% vs. 13.7%, P = 0.280). At 14 days after diagnosis, hospital readmission rates for those with cirrhosis were comparable with those without liver disease (14.3% vs 11.8%, P = 0.78) and only one patient re-presented to hospital with bacterial superinfection.

To summarise, our findings suggest that: i. one third of COVID-19 patients have mild transaminitis, which may be associated with more severe disease but not increased mortality; ii. liver cirrhosis does not predispose to increase mortality but does increase length of stay. Further outcome data from large registries of COVID-19 patients with cirrhosis are awaited to confirm this.

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### TABLE 1  Baseline characteristics of the study population according to the pre-existing liver disease. Data are median (IQR) or n (%). Statistical test used for categorical data assessed using Chi-squared test. Statistical test used for continuous, nonparametric variable assessed using Kruskal-Wallis test

| Variable                          | Patients with cirrhosis (n = 21) | Patients with pre-existing noncirrhotic liver disease (n = 68) | Patients without pre-existing liver disease (n = 446) | P   |
|----------------------------------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------|-----|
| Age – years                      | 71 (57-83)                       | 61 (53-76)                                                   | 67 (54-79)                                       | 0.115 |
| Gender – no (%), Male sex        | 14/21 (67.0%)                    | 40/68 (59.0%)                                                | 276/446 (61.9%)                                  | 0.976 |
| Ethnicity – no (%)               |                                  |                                                               |                                                  |     |
| Asian                            | 4/21 (19.0%)                     | 13/68 (19.1%)                                                | 51/446 (11.4%)                                   | 0.021 |
| Black                            | 2/21 (9.5%)                      | 16/68 (23.5%)                                                | 77/446 (17.3%)                                   |     |
| White                            | 10/21 (47.6%)                    | 25/68 (36.8%)                                                | 149/446 (33.4%)                                  |     |
| Other                            | 5/21 (23.8%)                     | 14/68 (20.6%)                                                | 169/446 (37.9%)                                  |     |
| Observations on admission        |                                  |                                                               |                                                  |     |
| BMI – kg/m²                       | 28.1 (21.8-31.3)                 | 30.3 (26.2-34.0)                                             | 274 (23.6-31.8)                                  | 0.023 |
| Systolic Blood Pressure (SBP) – mm Hg | 125 (121-154)                  | 129 (114-148)                                                | 131 (114-152)                                   | 0.869 |
| Diastolic Blood Pressure (DBP) – mm Hg | 73 (65-84)                  | 75 (69-87)                                                   | 75 (65-83)                                      | 0.750 |
| Heart Rate – beats per minute    | 82 (74-93)                       | 92 (68-151)                                                  | 91 (80-104)                                     | 0.026 |
| Respiratory Rate per minute       | 20 (16-24)                       | 20 (18-28)                                                  | 20 (18-26)                                      | 0.302 |
| Temperature – °C                  | 36.6 (36.0-37.7)                 | 37.5 (36.6-38.5)                                             | 37.2 (36.6-37.9)                                 | 0.108 |
| Overall in-hospital mortality – no (%) | 8/21 (38.1%)                  | 22/68 (32.4%)                                                | 151/446 (34.1%)                                 | 0.689 |
| Haemoglobin, g/L                  | 116 (103-150)                    | 130 (112-144)                                                | 134 (119-145)                                   | 0.008 |
| Platelet count, 10³/L             | 113 (74-209)                     | 205 (155-282)                                                | 199 (157-261)                                   | <0.001 |
| Lymphocyte count, 10⁹/L           | 0.9 (0.6-1.2)                    | 1.0 (0.7-1.5)                                                | 0.9 (0.6-1.3)                                   | 0.287 |
| Creatinine, µmol/L               | 94 (60-174)                      | 90 (69-127)                                                  | 91 (72-126)                                     | 0.944 |
| Urea, mmol/L                     | 6.6 (4.0-18.2)                   | 6.3 (4.2-11.0)                                               | 6.2 (4.1-10.4)                                  | 0.757 |
| Total bilirubin, µmol/L           | 31 (12-63)                       | 9 (8-16)                                                    | 11 (8-15)                                       | <0.001 |
| ALT, IU/L                        | 32 (14-50)                       | 30 (16-57)                                                   | 28 (17-49)                                      | 0.969 |
| AST, IU/L                        | 127 (83-170)                     | 71 (45-183)                                                  | 106 (71-193)                                    | 0.865 |
| ALP, IU/L                        | 152 (101-259)                    | 92 (61-127)                                                  | 79 (63-103)                                     | <0.001 |
| Albumin, g/L                     | 25 (20-30)                       | 31 (25-35)                                                   | 31 (27-34)                                      | 0.002 |
| Ferritin, µg/L                   | 437 (158-1104)                   | 889 (440-1916)                                               | 796 (430-1762)                                  | 0.092 |
| CRP, mg/L                        | 53.1 (27.8-161.1)                | 79.1 (27.0-183.5)                                            | 109.9 (52.6-189.2)                              | 0.037 |
| D-dimer, ng/ml                   | 2142 (1475-2484)                 | 1308 (764-2089)                                              | 1351 (714-2592)                                 | 0.476 |
| Prothrombin time, s              | 14.1 (13.1-25.1)                 | 14.3 (13.2-15.8)                                             | 13.8 (13.1-14.8)                                | 0.262 |
| Troponin, ng/L                   | 13 (9.5-32.5)                    | 16.5 (5.0-45.8)                                              | 13 (5-48)                                       | 0.967 |
| BNP, ng/L                        | 149 (58-421)                     | 23 (10-64)                                                   | 38 (13-114)                                     | 0.047 |

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**LINKED CONTENT**

This article is linked to Garrido et al papers. To view these articles, visit https://doi.org/10.1111/apt.15813 and https://doi.org/10.1111/apt.15886.

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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., commenting on our article on COVID-19 and liver disease. 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 concern 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. 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. 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).

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. 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. 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.