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

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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 25th February to 5th 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 5 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), though 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 transaminitis and hypoxemia 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,[1] 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 (i.e. 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 % versus 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 versus 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 was comparable with those without liver disease (14.3% vs 11.8%, p=0.78) and only 1 patient re-presented to hospital with bacterial superinfection.

To summarize, 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 is awaited to confirm this.

References

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Table 1

Variable	Patients with cirrhosis (n=21)	Patients with pre-existing non-cirrhotic liver disease (n=68)	Patients without pre-existing liver disease (n=446)	p-value
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 Black White Other	 4/21 (19.0%) 2/21 (9.5%) 10/21 (47.6%) 5/21 (23.8%)	 13/68 (19.1%) 16/68 (23.5%) 25/68 (36.8%) 14/68 (20.6%)	 51/446 (11.4%) 77/446 (17.3%) 149/446 (33.4%) 169/446 (37.9%)	 0.021
Observations on admission BMI – kg/m^{2*} Systolic Blood Pressure (SBP) – mmHg Diastolic Blood Pressure (DBP) – mmHg Heart Rate – beats per minute Respiratory Rate per minute Temperature – ^0C	 28.1 (21.8 – 31.3) 125 (121 – 154) 73 (65 – 84) 82 (74 – 93) 20 (16 – 24) 36.6 (36.0 – 37.7)	 30.3 (26.2 – 34.0) 129 (114 – 148) 75 (69 – 87) 92 (68 – 151) 20 (18 – 28) 37.5 (36.6 – 38.5)	 27.4 (23.6 – 31.8) 131 (114 – 152) 75 (65 – 83) 91 (80 – 104) 20 (18 – 26) 37.2 (36.6 – 37.9)	 0.023 0.869 0.750 0.026 0.302 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, 10^9/L	113 (74 – 209)	205 (155 – 282)	199 (157 – 261)	< 0.001
Lymphocyte count, 10^9/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

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, non-parametric variable assessed using Kruskal-Wallis test.