COVID-19 and the liver: little cause for concern

The largest study on COVID-19 to date[1] showed that the prevalence of elevated aminotransferases and bilirubin in people faring worst was at least double that of others. Although clinically significant liver dysfunction was not quantified, this and other studies have led some to suggest that this finding might present clinical challenges.[2] Close inspection of the available data supports a higher prevalence of abnormal aminotransferase levels in severe COVID-19 disease, but these studies actually suggest that clinically significant liver injury is uncommon, even when data for the most severely ill patients are selected (table).

Although high levels of positive end expiratory pressure can contribute to hepatic congestion by increasing right atrial pressure and impeding venous return, data suggest that many patients admitted to hospital with COVID-19 have liver blood test abnormalities without mechanical ventilation. Furthermore, the distribution of aminotransferase levels among patients with COVID-19 do not support hypoxic hepatitis being a common phenomenon, according to the published literature. Drug-induced liver injury is a possible contributing factor to the observed abnormal liver blood test abnormalities after therapeutics begin and should be considered by clinicians, but mild liver test derangement is present at baseline in many patients with COVID-19 before significant medication use. Several studies have reported elevated levels of creatinine kinase and lactate dehydrogenase or myoglobin in association with COVID-19 severity (table). It is therefore possible that aminotransferase elevations do not necessarily arise from the liver alone and that COVID-19 infection might induce a myositis similar to that observed in severe influenza infections.

It has been proposed that COVID-19 causes direct liver injury via a viral hepatitis, but we believe that there are alternative explanations. First, the derangement of liver function is clearly mild. Second, when liver function tests for patients with different durations of symptoms are examined, there is no evidence that later presentation is associated with greater liver function derangement.[3] The only post-mortem liver biopsy from a patient with COVID-19 showed only microvesicular steatosis, a common finding in sepsis.[4] Most importantly, other respiratory viruses produce similar elevations of liver function biomarkers, which is thought to relate to hepatic damage from immune interactions involving intrahepatic cytotoxic T cells and Kupffer cells.[5] This phenomenon waxes and wanes in parallel with respiratory viral disease and in the absence of hepatic viral replication, which might explain why worse outcomes were not seen in the 42 patients with chronic liver disease and COVID-19 who had outcome data (table).

Hepatic dysfunction in severe COVID-19 is accompanied by greater activation of coagulative and fibrinolytic pathways, relatively depressed platelet counts, climbing neutrophil counts and neutrophil to lymphocyte ratios, and high ferritin levels.[6] Although these markers are seen as non-specific markers of inflammation, we believe that they fit the paradigm of disease severity coinciding with a failure of innate immune regulation.[7] Such unbalanced immunity favours NETosis and coagulation activation and possibly also alters systemic iron metabolism secondary to macrophage activation.[8] Notably, this alteration of immune balance occurs with increased age, and older patients might therefore be expected to fare worse, with a greater reliance on this pathway.[9]

Clinicians cannot be complacent about the risks of COVID-19 in patients with chronic liver diseases and cirrhosis, because these patients have poor immune function and worse outcomes from acute respiratory distress syndrome than the rest of the critically ill

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See Online for appendix

	Group	Patients	Alanine aminotransferase (IU)	Aspartate aminotransferase (IU)	Prothrombin time (s)	Bilirubin (μmol/L)	Elevated lactate dehydrogenase, creatinine kinase, or myoglobin	Mortality (%)
Guan et al (2020)	ICU or death	67	Not known	Not known	Not known	Not known	Yes	22% (day 51)
Huang et al (2020)	ICU	13	49 (29–115)	44 (32–70)	12·2 (11·2–13·4)	14·0 (11·9–32·9)	Yes	38% (day 37)
Chen et al (2020)	Hospitalised	99	39 (22–53)	34 (26–48)	11·3 (1·9)	15·1 (7·3)	Yes	11% (day 24)
Wang et al (2020)	ICU	36	35 (19–57)	52 (30–70)	13·2 (12·3–14·5)	11·5 (9·6–18·6)	Yes	17% (day 34)
Shi et al (2020)	Hospitalised	81	46 (30)	41 (18)	10·7 (0·9)	11·9 (3·6)	Unclear	5% (day 50)
Xu et al (2020)	Hospitalised	62	22 (14–34)	26 (20–32)	Not known	Not known	Unclear	0% (day 34)
Yang et al (2020)	ICU	52	Not known	Not known	12·9 (2·9)*	19·5 (11·6)*	Not described	62% (day 28)
Extracted from all studies above	Chronic liver disease	42	Not known	Not known	Not known	Not known	Not known	0–2%†

Data is mean (SD) or median (IQR) depending on the original study. *Non-survivor intensive care unit (ICU) group. †One patient was either admitted to an intensive care unit or died. Details of references can be found in the appendix.

Table: **Liver test abnormalities from various COVID-19 studies, identifying the most severe disease categories where possible**

population.[10] However, we believe that collateral liver damage from virally induced cytotoxic T cells and the induction of a dysregulated innate immune response is a more probable explanation for the association between deranged liver markers and COVID-19 disease severity. Furthermore, we suspect that what is termed COVID-19-induced hepatic damage is predominantly a clinical distraction. We urge clinicians and the scientific community to focus attention towards viral control and modulating innate immune dysfunction in COVID-19.

We declare no competing interests.

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