



# Abnormal liver blood tests among hospitalised patients with SARS-CoV2 (COVID-19)

doi:10.1136/flgastro-2020-101691

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The COVID-19 caused by the SARS-CoV-2 has rapidly spread throughout more than 200 countries, with more than 30 million confirmed cases to date. The disease is mainly represented by a respiratory tract illness with a wide severity spectrum. Nevertheless, other organs such as the liver are commonly affected. Since the very beginning of the pandemic, abnormalities in the liver blood tests (LBT) have been described in patients with COVID-19. These alterations have largely been reported as mild to moderate elevations in the serum transaminases.<sup>1-3</sup> In a minority of cases, hypertransaminasaemia may be severe or combined with increased levels of cholestatic parameters such as alkaline phosphatase or total bilirubin. The incidence of these LBT abnormalities is variable among studies but it can be present in up to half the hospitalised patients with SARS-CoV-2. The exact mechanisms whereby the virus causes damage in the liver parenchyma are still unknown. A direct cytotoxic injury against hepatocytes has been proposed, while an immune-mediated damage has also been suggested. These hypotheses have been raised since SARS-CoV-2 particles were found in the cytoplasm of hepatocytes of affected individuals.<sup>1</sup> In addition, lobular and portal inflammation have been described as the most frequent histopathological findings, apart from macrovesicular steatosis.<sup>4</sup> Another factor that should be considered is the potential role of drug induced liver injury given that several of the studied cohorts have been treated with potentially hepatotoxic substances. The impact of this infection on the liver does not seem to be relevant, although the scarce evidence about long-term course of these patients precludes a firm conclusion. On the other hand, the effect of the LBT abnormalities in the prognosis of COVID-19-affected individuals is uncertain. Several studies have reported a more severe clinical course and a more intense systemic inflammatory response in those patients with marked LBT abnormalities.<sup>1-3</sup> Unfortunately, the retrospective nature of most of these studies and the presence of other potential confounding factors prevent from drawing conclusions about the real

extent of the liver involvement in the COVID-19.

Yeoman *et al* recently shared their experience including 318 patients admitted at single centre with a positive test for SARS-CoV-2 and analysed the incidence of LBT abnormalities and their impact on prognosis.<sup>5</sup> As in previous studies, a 31% incidence of abnormal LBTs was reported, along with a higher proportion of males. The highlight is the predominant cholestatic pattern of LBT, expressed by the R factor described in the drug induced liver injury. The authors claim a higher presence of ACE2 receptor (known as the entrance of the SARS-CoV-2 to human cells) on the surface of the cholangiocytes as the potential explanation to this finding. In addition, an elevation of serum alkaline phosphatase and bilirubin were found to be associated with a poor prognosis in the univariate analysis. Although previous studies point the hepatocellular pattern as the most frequent LBT abnormality, both Cai *et al*<sup>2</sup> and Phipps *et al*<sup>3</sup> found an association between mixed or cholestatic forms and a more severe course of COVID-19. However, these cholestatic parameter elevations were mild. Major drawbacks in the present study are its retrospective nature and the potential confounding factors. As stated by the authors, the organ failures in critical ill patients may justify the alterations in the LBTs. Besides, the effect of the administered drugs may also play a role in the liver damage. Nevertheless, this is the first study describing a clearly predominant cholestatic pattern in COVID-19 patients. In addition, it provides an important sample size and a homogeneous follow-up of the patients from the admission to the end of the episode.

The evidence about the liver involvement in COVID-19 syndrome is in a constant growth, but there are still major gaps. First of all, as mentioned before, the pathogenesis of the liver damage by the SARS-CoV-2 is largely unknown. In this setting, the biochemical and histopathological findings reported are still insufficient to provide insight about the exact mechanisms of the hepatic injury. Moreover, there is an absence of prospective,

studies with pathological assessment at the diagnosis and after remission of the infection. These types of studies could provide more information about the long-term course and consequences of this infection on the liver. An imaging assessment may also rule out potential thrombotic complications in the liver vasculature as reported in other organs. Little is known about the LBTs in the outpatient and more importantly, the impact of the SARS-CoV-2 in individuals with previously diagnosed liver diseases. This is of utmost relevance not only to figure out the effect of the virus in this population (could it lead to decompensation or acute-on-chronic damage?), but also to find risk factors that may favour worse outcomes. A recent publication by Kim *et al* shows that in patients with chronic liver disease, the presence of alcohol-related liver disease, decompensated cirrhosis and hepatocellular carcinoma are independent factors of higher mortality.<sup>6</sup> Finally, the direction of the association between the liver damage and the COVID-19 prognosis is uncertain. Namely, there is still no evidence to support the liver injury as a consequence of the systemic inflammation develops in response to the SARS-CoV-2 or the source of a more severe clinical presentation. In any case, the published works point the liver as one of the most affected organs apart from the respiratory tract. Yeoman *et al* contribute to a deeper analysis of the LBT alterations in the COVID-19 and challenge the previous concept of a predominant hepatocellular pattern in the hepatic biochemistry. Further work should be done to assess the remaining questions about the liver involvement in the SARS-CoV2 infection.

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**Contributors** PR: interpreted the results, drafted and revised the manuscript. AC: interpreted the results, drafted, revised the manuscript and gave final approval.

**Funding** Andrés Cárdenas is funded by the Instituto de Salud Carlos III and Plan Estatal de Investigación Científica y Técnica y de Innovación-grant no PI19/00752 and has received funding for this work by 'Fundación Marta Balust'.

**Competing interests** AC is a consultant for Mallinckrodt Pharmaceuticals, Boston Scientific, Shionogi, has participated on Advisory Boards for Mallinckrodt Pharmaceuticals and has received grant support by Mallinckrodt and Boston Scientific.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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► <http://dx.doi.org/10.1136/flgastro-2020-101532>

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