COVID-19 and liver disease: where are we now?

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Patients with end-stage liver disease and COVID-19 are at a higher risk of hospitalization, ventilation and death than those without chronic liver disease. Whether the aetiology of liver disease also affects the natural history of COVID-19 in cirrhosis is debated. Effective and universal vaccination is paramount to combat SARS-CoV-2 infection.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus first described in Wuhan, China, in December 2019. Since then, SARS-CoV-2 has spread globally, causing coronavirus disease 2019 (COVID-19), resulting in >458 million infections, with a death toll exceeding 6 million as of 15 March 2022 according to the World Health Organization COVID-19 dashboard.

SARS-CoV-2 has a tropism for cells expressing angiotensin-converting enzyme 2 (ACE2) receptors. In the liver, such receptors are expressed in the cholangiocytes and, to a lesser extent, in the hepatocytes[1]. However, current data suggest that liver injury in COVID-19 is mostly secondary to immune dysregulation and/or cytokine storm, development of endotheliopathy with hypoxic and/or ischaemic injury, drug-induced liver injury (DILI), or a combination thereof[1]. In fact, ischaemic, hypercoagulable and hyperinflammatory states — but not liver injury per se — are independent predictors of death in patients with COVID-19 (REF.[2]).

Since the early days of the SARS-CoV-2 pandemic, there have been concerns that patients with advanced liver disease might be at increased risk of morbidity and mortality following SARS-CoV-2 infection[3]. Prospective data from ongoing multicentre studies confirmed that patients with cirrhosis, particularly those who are decompensated, are at a higher risk of hospitalization, ventilation and death than those without chronic liver disease (CLD)[4]. Older age and cirrhosis severity, as assessed by Child–Pugh stage, are the most important predictors of mortality[4]. Although most deaths in cirrhosis with severe COVID-19 are from respiratory failure, the pathophysiological mechanisms supporting this association remain unclear. One hypothesis is that prothrombotic alterations driven by COVID-19 tilt the fragile haemostatic balance of hospitalized patients with decompensated cirrhosis towards hypercoagulability, therefore leading to pulmonary venous microthrombosis, parenchymal extinction and respiratory failure[3].

Whether the aetiology of liver disease also affects the natural history of COVID-19 in cirrhosis is unclear[3]. In an ongoing, international cohort including 745 patients with cirrhosis and SARS-CoV-2 infection, alcohol was the only aetiological factor independently associated with death[4]. Nonalcoholic fatty liver disease (NAFLD) and hepatic steatosis were initially associated with a purported increased risk of severe COVID-19 (REF.[3]). However, it might be that metabolic syndrome (rather than its hepatic expression) is the true driver for increased mortality in COVID-19. Individuals with autoimmune hepatitis and cholestatic liver diseases were considered at higher risk of severe COVID-19 owing to concomitant immunosuppression and were prioritized for vaccination (for example, see the EASL policy statement on vaccination). Interestingly, the outcome of patients with autoimmune hepatitis and SARS-CoV-2 infection seems to be equivalent to matched controls with CLD of other aetiologies[3]. Hence, in stable patients, reduction of immunosuppression seems not a strategy to reduce the risk of COVID-19 severity. Liver transplant recipients receive immunosuppression and would be similarly considered at increased risk of severe COVID-19. However, recent data demonstrate that their mortality risk is comparable with non-transplanted matched controls and is mostly influenced by comorbidities rather than liver transplantation status. Thus, current guidelines recommend against routine cessation and/or reduction of immunosuppression in liver transplant recipients[3].

Besides specific considerations regarding the management of immunosuppression, the approach to patients with COVID-19 and underlying liver disease is no different from patients without liver disease. Decompensating events such as worsening of ascites and encephalopathy are commonly observed in COVID-19 and should be managed according to clinical standards. Interestingly, patients with cirrhosis seem less likely to receive antiviral drugs, which probably reflects concerns about potential DILI in high-risk patients[4]. Specific trials investigating the safety and efficacy of monoclonal antibodies and new antivirals in patients with liver disease are therefore awaited.

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https://doi.org/10.1038/s41575-022-00607-9

The SARS-CoV-2 pandemic devastated routine clinical care of patients at risk of or with cancer, including hepatocellular carcinoma[5]. Modifications in screening, diagnostic and treatment algorithms led to a reduced rate of diagnosis and increased treatments delays[5]. Furthermore, it is likely that the COVID-19 pandemic will have a long-lasting effect on the clinical care for these patients owing to the risks from resource reallocation and potential exposure. The practice of liver transplantation has also been severely affected by the pandemic, with particularly detrimental effects on the countries that had a high burden of COVID-19 (REF.[6]). However, data from a joint effort by international liver societies (EASL, ESOT–ELITA and ILTS) demonstrated that the resilience of the transplant network enabled continued organ donation and transplantation despite ongoing emergencies, ultimately saving the lives of patients with end-stage liver disease[6].

Lastly, effective and universal vaccination is paramount to effectively managing SARS-CoV-2 infection. Unfortunately, data on patients with liver disease included in the original trials for vaccine approval are rather limited (few patients were included, the definition of liver disease was unclear and the proportion of those with advanced disease was low). The aetiology and severity of liver disease could have a role in conditioning the efficacy of vaccines. Preliminary data suggest that vaccination in patients with chronic hepatitis B virus infection[7] and NAFLD[8] without cirrhosis is safe and associated with good humoral response. Specific data regarding autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis are still lacking. Vaccination in patients at risk, such as those with cirrhosis and liver transplant recipients, seems safe and is associated with a marked reduction in the risk of hospitalization, admission to intensive care unit and/or need of ventilation and death[9]. However, ~25% of patients with CLD and ~60% of liver transplant recipients might have a non-optimal humoral response to vaccination with two doses of mRNA vaccines or a single dose of the Johnson & Johnson vaccine[10]. In fact, in most countries, these patients are now eligible or have received the 'third-booster' dose, and unpublished data from Israel suggest a further reduction of COVID-19 and severe illness after the fourth dose of vaccine. It could be that such a 'second booster' is beneficial in high-risk categories (and less needed in individuals without risk factors). In Italy, for instance, liver transplant candidates and recipients are considered at high risk and eligible for a fourth dose since 1 March 2022.

In conclusion, patients with liver disease have been severely affected by the SARS-CoV-2 pandemic. International collaborative studies helped clarify the course of COVID-19 in these patients, optimizing treatments and patient outcomes. However, the optimal approach to COVID-19 in those at higher risk is still largely unknown. A better understanding of COVID-19 in patients with liver diseases across different aetiologies and severities is expected and, together with updated results on safety and efficacy of vaccines and antiviral drugs, will further improve patient management. In the meantime, it is our responsibility to support vaccination independent of liver disease aetiology and severity. Vaccination has been instrumental in reducing the burden of COVID-19 and remains a pillar on which the future wellness of our liver community will be built. Experts advocate that a yearly vaccination might be needed to control SARS-CoV-2 infection, perhaps particularly in patients with pre-existing diseases. However, simply chasing an ever-increasing number of doses seems not the best solution in the long term, and we definitively need new vaccines that can effectively prevent infection with emerging variants.

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Competing interests
The authors declare no competing interests.

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