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LETTER TO THE EDITOR

Reply to: "COVID-19-associated liver injury (COVALI): role of hepatologists"

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Abbreviations

COVALI	COVID-19-associated liver injury
CLD	Chronic liver disease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
CAID	Cirrhosis-associated immune dysfunction
LT	Liver transplant

To the Editor

We read with great interest the letter by Yoshio Sumida et al. regarding our recent review [1], which systematically described the potential pathogenesis of COVID-19-associated liver injury (COVALI). The author summarized the recent advances in this field and emphasized that hepatologists must play a specific and important role in the management of COVALI, in collaboration with respiratory medicine and infectious disease specialists [2]. We thank Yoshio Sumida et al. for their interest in our manuscript and for their thoughtful comments. There is some additional valuable information worthy of attention and discussion.

Since the onset of the pandemic, two key questions have attracted much attention from hepatologists: whether patients with pre-existing chronic liver disease (CLD) are more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to their immunocompromised status, and whether CLD might predispose these patients to a poor prognosis after SARS-CoV-2 infection, especially due to the overlap of risk factors for severe COVID-19 and CLD, such as age, obesity, and diabetes. However, the currently available evidence does not suggest that patients with CLD are at a higher risk of infection. The aetiology of liver injury could influence the clinical outcome of COVID-19. Patients with cirrhosis suffer from high rates of hepatic decompensation and mortality following SARS-CoV-2 infection due to cirrhosis-associated immune dysfunction (CAID). There is also a stepwise increase in mortality with each higher Child–Pugh class, i.e., with increasing severity of cirrhosis [3].

There is keen interest in the effects of SARS-CoV-2 on liver transplant (LT) recipients, who are frequently exposed to health-care facilities and often experience medical complications or are in an immunosuppressive state. The incidence and outcomes of COVID-19 in LT recipients are still controversial. Current clinical data suggest that LT patients with chronic immunosuppression are more susceptible to SARS-CoV-2 infection, although this finding may be due in part to more intensive monitoring and a lower threshold for viral testing in LT patients [4, 5]. LT and the associated immunosuppression themselves do not

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seem to increase the risk of adverse outcomes following SARS-CoV-2 infection, whereas age and comorbidities seem to be key determinants of the severity of COVID-19 in LT patients. Therefore, major international guidelines currently still recommend against cessation or reduction of immunosuppressive therapy for asymptomatic LT patients in case of SARS-CoV-2 infection [6, 7]. In addition, LT recipients seem to develop substantially lower immunological responses to SARS-CoV-2 mRNA-based vaccines. Thus, vaccine regimens for LT recipients need to be carefully evaluated [8].

A consensus has not yet been reached for the optimal treatment regimen for COVID-19 patients with pre-existing CLD. Although there are some variations between international guidelines, it is basically agreed that patients with CLD are particularly vulnerable to severe complications. When evaluating COVID-19 patients with elevated liver biochemistry, aetiologies unrelated to COVID-19 should be considered, including other viruses, such as hepatitis A, B, and C, as well as myositis, cardiac injury, ischaemia, and cytokine release syndrome [7]. Patients with cirrhosis, those with autoimmune hepatitis, and post-transplant patients receiving immunosuppressant therapy should be prioritized for testing until further data become available. Notably, the majority of deaths in patients with COVALI are due to respiratory failure, although the exact mechanisms underlying this phenomenon remain unclear. However, considering that both cirrhosis and COVID-19 are related to coagulation dysfunction, the coexistence of these conditions might increase the cumulative risk of thrombotic complications [9]. However, it remains to be determined whether enhanced venous thromboembolism prevention will be beneficial to these patients.

Targeted therapy for COVID-19 is a rapidly developing field with considerable new or repurposed drugs continuing to emerge. Hepatologists must pay special attention to the potential secondary effects of these drugs on the liver and constantly assess the specific risks and benefits for patients with underlying liver diseases. Regardless of the baseline value, all hospitalized COVID-19 patients should be monitored regularly for liver biochemistry, particularly those receiving remdesivir or tocilizumab treatment. Theoretically, patients with CLD might respond poorly to SARS-CoV-2 vaccination due to both systemic inflammation and innate and adaptive immune dysfunction [10]. As vaccines continue to be licenced and deployed, more direct clinical data on COVID-19 vaccination in patients with advanced CLD and on different vaccine types are eagerly awaited.

In conclusion, the COVALI of SARS-CoV-2 infection is now considered an important component of COVID-19. While many aspects remain poorly understood, the recognition that patients with CLD, especially those with cirrhosis, are particularly vulnerable to the severe complications of COVID-19, and this fact must be kept in mind when caring for patients with COVID-19.

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Declarations

Competing interests The authors declare that they have no conflict of interest.

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