Letter to the Editor: Additional Factors to Consider When Studying Liver Injury Indicators and Mortality in COVID-19 Patients

TO THE EDITOR:

In a recent issue of Hepatology, Lei et al.[1] conducted a multicenter retrospective cohort study that included 5,771 adult patients with coronavirus disease 2019 (COVID-19) pneumonia in Hubei Province. The purpose of the study was to evaluate the relationships between liver injury indicators (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and mortality in patients with COVID-19. The authors considered the possibility that elevated liver injury indicators, particularly AST, are strongly associated with mortality risk. However, the association between liver injury indicators and mortality in patients with COVID-19 should be interpreted cautiously in light of the following issues.

Hepatitis B virus (HBV) is a common epidemic virus in the Chinese population, especially in adults. HBV infection can cause severe liver damage, including elevated serum enzymes ALT and AST. HBV infection also has a strong correlation with the development of cirrhosis and hepatocellular carcinoma (HCC).[2] Similar to HBV, hepatitis C virus (HCV) infection is on the rise and is also associated with the development of HCC.[3] However, whether patients have HBV and/or HCV infection is not discussed in the article.

In addition, inspired by the AASLD Expert Panel Consensus Statement,[4] lactate dehydrogenase (LDH) is an important indicator in liver injury. Several studies have reported that LDH might be a risk factor for the progression of patients infected with COVID-19.[5] However, I did not find any data about LDH in this paper. It is my recommendation that LDH should be considered as an independent and/or joint indicator to assess the relationships between liver injury indicators and mortality in patients with COVID-19.

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Letter to the Editor: Perioperative Presentation of COVID-19 in a Liver Transplant Recipient

TO THE EDITOR:

In a recent issue of Hepatology, Qin et al.[1] report a case of a 37-year-old patient with COVID-19 after undergoing liver transplantation (LT) for hepatocellular carcinoma (HCC). While these are interesting data on the course of COVID-19 in an immunosuppressed patient, we would like to highlight some

particularly important issues related to management of liver disease and posttransplant care.

First, the exact staging of HCC, in particular levels of alpha-fetoprotein and intrahepatic tumor load, would be relevant to report. Because transarterial chemoembolization (TACE) was performed prior to LT, we assume that the HCC tumor load was extensive, requiring downstaging or bridging. However, because LT was "scheduled" for day 7, it seems that living donor LT was performed, which would suggest that TACE was applied for downstaging rather than bridging. Was the patient inside the Milan criteria or expanded criteria at the time of LT? How was the success of downstaging evaluated?

Second, there is no information on his underlying liver disease, i.e., hepatitis B virus (HBV) infection. Did the patient receive nucleos(t)ide analogues? What about hepatitis delta coinfection? Did the patient have cirrhosis based on noninvasive tests or explant histology? How did the authors perform prophylaxis for recurrent HBV infection posttransplant?

Third, it would be interesting to know the dosing of the immunosuppressive regimen that was implemented after LT and the corresponding tacrolimus levels. The potential use of antithymocyte globulin as induction therapy and associated leukopenia may put patients at risk for a severe or even fatal course of COVID-19 infection.[2]

The correct diagnosis of acute cellular rejection (ACR) after LT is particularly challenging in the context of COVID-19, which may itself lead to elevated transaminases.[3] Following an initial decline in transaminases after LT, aspartate and alanine aminotransferases increased again, and that was why the authors suspected ACR and raised the dose of tacrolimus. COVID-19 infection *per se* and drug-induced liver injury are alternative reasons why the transaminases were rising in this patient, and thus, we would strongly recommend relying on liver biopsy to prove ACR before increasing immunosuppression. The long course (or relapsing course by PCR) of severe acute respiratory syndrome coronavirus 2 infection may have been provoked by the therapy administered for the suspicion of ACR, and thus, it seems essential to use all available diagnostic means (i.e., liver biopsy to assess ACR by histology) prior to raising immunosuppression in a patient with confirmed COVID-19 infection.

Finally, we would like to congratulate the authors for the successful management of this patient despite the current restrictions in health care resources. Moreover, we thank the authors for their important contribution regarding the management of COVID-19 infection in the perioperative setting after LT.

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