clinical events. Alanine aminotransferase (ALT) produced in the hepatocytes is a very specific marker of liver cell injury, with relatively lower concentrations in other organ tissues. The rise in ALT may occur with the use of specific drugs, such as antibiotics and glucocorticoids. AST, on the other hand, occurs in two isoforms, indistinguishable on standard assays. It is the mitochondrial isoenzyme, which is produced by the hepatocyte, that reacts to membrane damage similar to ALT, whereas the cytosolic isoenzyme is produced by cells of skeletal muscles, cardiac myocytes, and renal tissue. The use of AST in isolation is not recommended as a marker for hepatocellular injury.[2] The conclusion inculpating AST with COVID-19 liver injury is inaccurate and factually related to the evolving multiorgan dysfunction (MOD). This is underscored by the fact that most patients had already developed cardiac and renal injury before the development of proposed acute liver injury (ALI) at 10-15 days after admission, further exacerbated by antibiotics and glucocorticoids. AST and ALT levels were significantly high in those with lymphocytopenia, a marker of severe COVID-19.[3] Scoring systems for MOD were not used by the authors, adding to the confounding. The definition of ALI in the current study is flawed. An important criterion for diagnosing ALI in those without preexisting liver disease is an international normalized ratio >2.[4] The current study does not incorporate appropriate methods to clearly identify synthetic and metabolic hepatocellular dysfunction. The term "COVID-19-related liver injury" is perchance misleading, akin to the recently described COVID-19 involvement of the pancreas.[5]

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Potential conflict of interest: Dr. Philips advises Cipla.

REPLY:

We appreciate Philips and colleagues' interest in our report on the associations between liver injury markers and coronavirus disease 2019 (COVID-19) mortality.[1] They raised the question regarding the application of liver injury markers. However, several of their interpretations of our results are misleading or incorrect.

We understand that the use of aspartate aminotransferase (AST) in isolation cannot comprehensively characterize liver injury. To fully explore the associations of liver injury with COVID-19, we investigated the dynamic patterns of four respective and extensively applied markers of liver injury: alanine aminotransferase (ALT), AST, alkaline phosphatase, and total bilirubin. Their associations with COVID-19 mortality were clearly demonstrated. Importantly, we found that the increased levels of all four indicators are consistently associated with higher risk of COVID-19 death, with AST having the largest hazard ratio. Therefore, in our study, liver injury was characterized by four markers, rather than only AST as mentioned by Philips et al.

Until recently, the definition of acute liver injury (ALI) has been inconsistent in the literature.[2] In our study, ALI was defined by ALT, which has been extensively applied in more than 1,000 studies. However, the international normalized ratio (INR), proposed by Philips et al., is a marker of coagulopathy, which can occur in many pathological conditions.[3,4] Although prolonged prothrombin time/INR can occur in chronic liver disease, this condition is more likely to happen at

the advanced stage of liver injury because of diminished clotting factor production.[4] Remarkably, COVID-19 *per se* is often associated with a major blood hypercoagulability.[5] Thus, INR, as a measure of unspecific and synthetic coagulation, was not appropriate for specifically predicting liver injury in the setting of COVID-19 and would lead to confounding conclusions.

Based on our rational study design and rigorous statistical analyses, we insist that liver injury exists in the setting of COVID-19. These findings are further clinically meaningful that indicators of liver injury need to be timely monitored because of their strong association with COVID-19 mortality.

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Potential conflict of interest: Nothing to report.

Letter to the Editor: Relevance of Circulating Extracellular Vesicles Carrying Sphingolipid Cargo in Alcoholic Hepatitis: Need for More Validation!

TO THE EDITOR:

The study by Sehrawat et al. made an important observation that extracellular vesicles (EVs) and sphingolipid cargoes can distinguish alcoholic hepatitis from decompensated cirrhosis. The authors suggest that an EV value of 1.56×10^{11}/mL will help in differentiating alcoholic hepatitis and also predict 90-day survival, permitting risk profiling and thus having important clinical implications.[1]

The authors used the Model for End-Stage Liver Disease and Child-Turcotte-Pugh scores in the population of heavy drinkers; however, the question of whether these patients had underlying cirrhosis remains.

Although liver biopsies have been performed in 22 patients with alcoholic hepatitis, it would be