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**Conflicts of interest**

The authors disclose no conflicts.

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## The Topic of COVID-19–Related Liver Injury Needs More Rigorous Research



Dear Editor:

We read with great interest the study written by Fan et al.<sup>1</sup> The authors report the clinical features of COVID-19–related liver damage. Because liver injury in COVID-19 patients is common and occurs especially in severe cases, the results of this study therefore are important. However, we do have some concerns about it.

First, Fan et al.<sup>1</sup> defined liver injury as any one of 6 parameters more than the upper limit of normal value. We understand that guidance or consensus on classification of COVID-19–related liver injury is lacking. However, a mild abnormality of these parameters should be classified more accurately as a COVID-19–associated liver biochemistry abnormality, and be distinguished from COVID-19–related liver injury, because such exceptions can be observed in a variety of situations.<sup>2</sup> Furthermore, according to the recommendations from the American College of Gastroenterology, only 4 parameters including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin are markers of liver injury, and the increases in these parameters suggest hepatocellular injury.<sup>3</sup>

Second, Fan et al.<sup>1</sup> provided valuable comparisons between 2 groups. The results showed that significant differences were found for procalcitonin and C-reactive protein, but not for CD4+ T-cell counts, CD8+ T-cell counts, and CD3+ T-cell counts. However, why these markers were selected remains unclear. As mentioned by Fan et al.,<sup>1</sup> laboratory examination was conducted every 3 days. It is not clear whether the results were calculated using the data on the day of admission or from data collected throughout the hospitalization, which may lead to bias. In the meantime, the normal baseline levels for each parameter were not given, so the readers cannot understand the meaning of these changes between groups compared with their baseline.

Third, Fan et al.<sup>1</sup> concluded that a significantly higher proportion of patients with abnormal liver function had received lopinavir/ritonavir, recommending caution when using lopinavir/ritonavir. In a recently published randomized controlled trial,<sup>4</sup> there were no significant differences in alanine aminotransferase, aspartate aminotransferase, and bilirubin between the lopinavir/ritonavir group and the standard care group, showing its safety. We believe the problem may arise from a retrospective design of this study, and the fact that more patients used lopinavir/ritonavir in the abnormal liver function group may be owing to confounding resulting from age, sex, and the severity of illness.

We found that there were some studies published on the topic of COVID-19–related liver injury in recent weeks. However, current studies inevitably encounter the problem of bias owing to their retrospective design. They also have not yet addressed the causes and mechanisms of liver damage associated with COVID-19 clearly. As described in a correspondence,<sup>5</sup> we hope more studies with rigorous design are conducted in the near future.

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## COVID-19 Related Liver Injury: Call for International Consensus



Dear Editor:

We read with interest the article by Fan et al.<sup>1</sup> regarding the clinical characteristics of COVID-19 patients with liver damage. They defined abnormal liver damage in their study, and found that liver function abnormality was associated with a longer hospital stay and might have been related to the use of lopinavir/ritonavir during hospitalization. This study is interesting and provides the direction for future research, however, there is a need to address the importance of a standardized definition of COVID-19–related liver injury, which currently is unavailable; it also calls for an international consensus in this regard.