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important issue because it may jeopardize the generalizeability of the conclusions from these studies. Although liver function abnormalities and clinically significant liver injury in COVID-19 should be investigated further, we suggest researchers pay extreme attention to the terminology and its definition to avoid ambiguity in future analysis and overtreatment in clinical practice.

ZHENG YE, PhD  
BIN SONG, MD  
Department of Radiology  
West China Hospital, Sichuan University  
Chengdu, Sichuan, China

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Reply. We thank Chen and Zhou, LV et al, and Ye and Song for the comments on our study. We did not apply the definition of drug-induced liver injury from the European Association for the Study of the Liver Clinical Practice Guidelines in our study because the exact mechanism of COVID-19-related liver damage is still unclear (eg, a drug, the virus itself, immune response, or a mixture). We defined COVID-19-related liver injury based on elevation in any 1 of the 5 (not 6) parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), and total bilirubin.3 This could also explain why our results contradicted the data from Li et al.5 In the study by Li et al,5 liver injury was defined as presence of elevated ALT (>1 × upper limit of normal [ULN]), so the differences in our definitions resulted in different conclusions. LV et al2 suggested that only 4 parameters (ALT, AST, ALP, total bilirubin) should be considered as markers of liver injury, based on the recommendations from the American College of Gastroenterology. However, these 4 parameters are recognized as indicators for currently known types of hepatobiliary diseases, not for the new emerging COVID-19-related injury. For example, COVID-19 patients are more likely to have abnormalities in GGT levels than that of ALP.4,6 Thus, we think it is necessary to take GGT into consideration while evaluating COVID-19-related liver function. We agree with Ye’s proposal7 that international consensus on the definition of COVID-19-associated liver injury is needed.

Xu and Gu7 proposed an important and interesting point of view and speculated that cardiac and muscle injury might partially contribute to elevated aminotransferases in COVID-19 patients. Indeed, routine serologic biochemical indicators (eg, ALT and AST) used to evaluate liver function can also reflect injury to other organs, including the heart and muscle. However, according to other studies, elevated aminotransferases seems to occur more commonly and easily in COVID-19 patients than expected based on cardiac and muscle injury.4,8,9 Also, no patient had obvious muscle injury in our study. Furthermore, transaminases were usually mildly elevated in most patients.4,9 In a COVID-19 case with rhabdomyolysis,10 for example, AST increased above 5 times the ULN. Moreover, there should be focal muscle pain and a sharp increase in the other indicators in patients with rhabdomyolysis. Xu and Gu7 indicated elevated AST may also reflect myocardial damage based on the phenomenon that elevated AST was more prominent than elevated ALT in COVID-19 patients and that elevated AST was more common in patients with severe symptoms. However, there was no statistically significant difference in the proportions of patients with abnormal AST and ALT. Also, there was no significant difference in the absolute values of these enzymes. Furthermore, another study6 reported that 10% and 6% of patients had increased levels of ALT and AST (more than 3 × ULN) during hospitalization, respectively. More importantly, the multivariable logistic regression showed elevated liver test values (≥3 × ULN) during hospitalization were independent predictors of severe illness. This seems to mean that elevated ALT is more frequent, and closely related with the severity in COVID-19. More importantly, recent study11 reported that AST highly correlated with ALT throughout the illness course, whereas correlations with markers of muscle injury and inflammation were weak. This suggests that hepatic injury is the predominant source of aminotransferase elevation. We appreciated the comment raised by Xu and Gu.7 After all, COVID-19 is a systemic disease that may involve many organs. Given the fact that rhabdomyolysis and acute cardiac injury can be potentially fatal, patients with highly elevated aminotransferase should be treated with more caution.

There were only 9 (6.1%) cases with underlying liver diseases in our study4 and we did not find any difference between patients with normal/abnormal liver function (P = .6409). It is noteworthy that none of the cases in our study received remdesivir. Therefore, we did not report the effect of remdesivir on liver function. We also did not study effect of positive end-expiratory pressure
on the liver. However, the focus of our study was on medications and prognosis. We also compared patients’ prehospital medications after symptom onset, and found no obvious difference, but we recognize that information on self-medication before developing COVID-19 pneumonia was not available in our retrospective study.

We selected procalcitonin, C-reactive protein, CD4⁺ T-cell counts, CD8⁺ T-cell counts, and CD3⁺ T-cell counts in our study because they could represent potential pathogenic mechanism of SARS-CoV-2. Liver damage may rise from dysregulated immunoinflammatory responses caused by SARS-CoV-2. In addition, we described changes in liver function tests. The clinical and laboratory features of patients with and without normal liver tests at admission were shown in Table 1. Of 95 patients with normal baseline liver function, 48.4% developed abnormal liver function tests following admission. The baseline normal levels for each test was not given because of space limitation, and Supplementary Figure 1 described the trajectory of liver enzymes in patients with abnormal liver function after admission.

Lastly, as to the difference between our results and those from Cao et al., 1 main reason was the patients studied were different. The patients enrolled in our study had relatively mild symptoms, whereas the patients enrolled in Cao’s study were severely ill with higher proportion of elevated ALT (41%) at baseline. Of note, multivariable logistic regression from a recent study found an association between the use of lopinavir/ritonavir and liver injury, which is consistent with our data. However, these present data from the clinical trial with small sample and retrospective studies were not enough to clarify the true effect of lopinavir/ritonavir on the liver. We agree that large-scale prospective studies are needed to fully address this question. A trial with lopinavir/ritonavir is currently underway. We believe this question will have an answer in the near future.

LIPING CHEN
ZHENYU FAN
JILIN CHENG, MD, PhD
Department of Gastroenterology and Hepatology
Shanghai Public Health Clinical Center
Fudan University
Shanghai, China

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