Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Conflicts of interest
The authors disclose no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2020.04.042

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.[1] 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[1] 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.[2] 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.[3]

Second, Fan et al[1] 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,[1] 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[1] 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,[4] 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,[5] we hope more studies with rigorous design are conducted in the near future.

XIU-HE LV, MD
JIN-LIN YANG, MD
Department of Gastroenterology & Hepatology
West China Hospital, Sichuan University
Chengdu, Sichuan, China

KAI DENG, MD
Department of Gastroenterology & Hepatology
COVID-19 Medical Team (Hubei)
West China Hospital, Sichuan University
Chengdu, Sichuan, China

COVID-19 Medical Team (Hubei)
West China Hospital, East Hospital of Renmin
Hospital of Wuhan University
Wuhan, Hubei, China

References

1. Fan Z, et al. Clin Gastroenterol Hepatol 2020;18:1561–1566.
2. Bangash M, et al. Lancet Gastroenterol Hepatol 2020; 5:529–530.
3. Kwo PY, et al. Am J Gastroenterol 2017;112:18–35.
4. Cao B, et al. N Engl J Med 2020;382:1787–1799.
5. Peyrin-Biroulet L. Clin Gastroenterol Hepatol 2020 Mar 30. pii: S1542-3565(20)30431-6. https://doi.org/10.1016/j.cgh.2020.03.054. Epub ahead of print.

Conflicts of interest
The authors disclose no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2020.04.073

COVID-19 Related Liver Injury: Call for International Consensus

Dear Editor:

We read with interest the article by Fan et al[1] 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.

Table 1. Summary of Published Studies Regarding the Definition of Liver Injury in COVID-19

Study	Article type	Definitions	Sample size	Male/ female	Mean age, *y*	Pre-existing liver disease	ALT, *U/L*	AST, *U/L*	TBIL, *μmol/L*	ALP, *U/L*	GGT, *U/L*	Main conclusion
Xie et al[5]	Original article	Increased levels of ALT, AST, or TBIL	79	44/35	60	No	34 (18–67)	30 (23–50)	13.6 (8.8–17.6)	79.0 (59.0–100.0)	31.5 (19.0–81.3)	Liver injury is common in non-ICU hospitalized COVID-19 patients and may relate to severe pulmonary imaging lesions
Zhang et al[7]	Original article	Abnormal liver function: initial test >ULN, including ALT, AST, TBIL, ALP, GGT, and ALB Liver injury: according to the criteria of iSAEC	115	49/66	49.5	NA	25.71 ± 21.08	28.30 ± 15.66	11.31 ± 5.18	73.72 ± 24.37	36.14 ± 45.02	Although abnormalities of liver function indexes are common in COVID-19 patients, the impairment of liver function is not a prominent feature of COVID-19, and also may not have serious clinical consequences
Ji et al[6]	Original article	Hepatocellular type: ALT >30 for males and ALT > 19 for females Ductular type: ALP >ULN accompanied by GGT >ULN Mixed type: both hepatocellular and ductular enzyme levels were >ULN	202	113/89	44.5	NAFLD	NA	NA	NA	NA	NA	Liver injury in COVID-19 patients was frequent but mild The pattern was mostly hepatocellular rather than cholestatic in COVID-19 patients with NAFLD
Cai et al[9]	Original article	Liver injury: ALT and/or AST >3 ULN; ALP, GGT, and/or TBIL >2 ULN Hepatocyte type: ALT and/or AST >3 ULN Cholangiocyte type: ALP or GGT >2 ULN Mixed type: an increased combination of both types	417	198/219	47.0	21 patients with NAFLD, ALD, or hepatitis B	21 (15–31)	26.5 (21–35)	10.9 (8.3–16.3)	61 (50.5–74.5)	33.45 (37.41)	Patients with abnormal liver tests, especially in hepatocyte type or mixed type, had significantly higher odds of developing severe pneumonia

Table 1. Continued

Study	Article type	Definitions	Sample size	Male/ female	Mean age, *y*	Pre-existing liver disease	ALT, *U/L*	AST, *U/L*	TBIL, *μmol/L*	ALP, *U/L*	GGT, *U/L*	Main conclusion
Fan et al[1]	Original article	Any parameter >ULN on admission, including ALT, AST, LDH, GGT, ALP, and TBIL	148	73/75	50	9 patients with CLD	NA	NA	NA	NA	NA	More than a third of patients admitted to the hospital have abnormal liver function, and this is associated with a longer hospital stay
Qi et al[4]	Letter to the editor	Any parameter >ULN on admission, including ALT, AST, and TBIL	70	39/31	NA	No	NA	NA	NA	NA	NA	Dynamic monitoring of the liver function of patients with liver injury are needed, especially those in the ICU
Sun et al[11]	Comment	COVID-19–associated liver injury is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver diseases										
Xu et al[3]	Review	Liver injury was indicated mainly by abnormal ALT/AST levels accompanied by slightly increased bilirubin levels										

ALB, albumin; ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; GGT, γ-glutamyl transpeptidase; ICU, intensive care unit; iSAEC, international Serious Adverse Event Consortium; LDH, lactate dehydrogenase; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; TBIL, total bilirubin; ULN, upper limit of normal.

Liver function abnormality was frequent, but usually mild, in COVID-19 patients. In patients with COVID-19, abnormal liver function may result from direct viral damage, immune-mediated inflammation, drug hepatotoxicity, hypoxia-reperfusion dysfunction, or reactivation of pre-existing liver diseases.[2] It is worthwhile to explore the mechanisms and clinical outcomes of liver dysfunction for better understanding and treatment of COVID-19. However, as a new contagious disease, there is no consensus on the definition of COVID-19–associated liver injury, and its definition has varied in recent studies (Table 1).

First, the parameters for evaluating liver function were different among studies, although alanine aminotransferase, aspartate aminotransferase, and total bilirubin were mostly included.[3–5] Several studies also included alkaline phosphatase and γ-glutamyl transpeptidase for the assessment of liver function,[6,7] probably because the angiotensin converting enzyme 2, the severe acute respiratory syndrome coronavirus 2 receptor, was reported to be highly expressed in cholangiocytes.[8] Interestingly, the current study included lactate dehydrogenase as a parameter for liver damage in COVID-19 patients,[1] which normally was regarded as an indicator for heart, kidney, and liver dysfunction, and thus may be less specific in this regard. The difference on diagnostic parameters may affect the grouping of liver injury and non–liver injury patients, and thus compromise the results.

More importantly, because of the different criteria for increased liver enzyme levels, researchers and clinicians may overestimate the value of abnormal liver function both in a scientific aspect and in clinical practice. Several studies have reported the potential clinical outcome of COVID-19 patients with liver injury, including longer hospitalization,[1] severe pulmonary lesions,[5] and higher odds of developing severe pneumonia.[9] In contrast, Zhang et al[7] reported that although impairment of liver function did exist in COVID-19, it was not a prominent feature. Notably, in these studies, some researchers defined liver injury as any liver function test result that was higher then the upper limit of normal (ULN),[1,5] however, other investigators have defined it as liver enzyme levels higher than 2 or 3 times the ULN,[9] or according to the guideline of drug-induced liver injury,[7] which may be the reason for the mixed results. Together with the comment published by Bangash et al,[10] we think it may be inappropriate to consider mild increases and fluctuations of liver enzyme levels (ie, just slightly >ULN) as clinically significant liver injury, which may be predominantly a clinical distraction.

Furthermore, the diagnostic time point (ie, on admission or during disease progression) of liver injury,[1,11] and the standardized definition of liver injury patterns[6,9] (ie, hepatocellular type, cholangiocytes type, and mixed type) in COVID-19, also varies and remains open questions.

Overall, from a scientific point of view, the lack of standardization in the definition is undoubtedly an

important issue because it may jeopardize the generalizability 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

References

1. Fan Z, et al. Clin Gastroenterol Hepatol 2020;18:1561–1566.
2. Feng G, et al. J Clin Transl Hepatol 2020;8:18–24.
3. Xu L, et al. Liver Int 2020;40:998–1004.
4. Qi X, et al. J Hepatol 2020. Epub ahead of print.
5. Xie H, et al. Liver Int 2020;40:1321–1326.
6. Ji D, et al. J Hepatol 2020. Epub ahead of print.
7. Zhang Y, et al. Liver Int 2020. Epub ahead of print.
8. Chai X, et al. bioRxiv 2020. Epub ahead of print.
9. Cai Q, et al. J Hepatol 2020. Epub ahead of print.
10. Bangash M, et al. Lancet Gastroenterol Hepatol 2020;5:529–530.
11. Sun J, et al. Liver International 2020;40:1278–1281.

Conflicts of interest
The authors disclose no conflicts.

Most current article

https://doi.org/10.1016/j.cgh.2020.05.013

Reply. We thank Chen and Zhou,[1] Lv et al,[2] and Ye and Song[3] 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.[4] 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 al[2] 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 proposal[3] that international consensus on the definition of COVID-19-associated liver injury is needed.

Xu and Gu[7] 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 Gu[7] 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 study[6] 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 study[11] 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 study[4] 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