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.

[5] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998–1004.
[6] Singh R, Domenico C, Rao SD, Urgo K, Prenner SB, Wald JW, et al. Novel coronavirus disease 2019 in a patient on durable left ventricular assist device support. J Card Fail 2020;26:438–439.
[7] **Bruni A**, **Garofalo E**, Zuccalà V, Currò G, Torti C, Navarra G, et al. Histopathological findings in a COVID-19 patient affected by ischemic gangrenous cholecystitis. World J Emerg Surg 2020;15:43.
[8] Ying M, Lu B, Pan J, Lu G, Zhou S, Wang D, et al. COVID-19 with acute cholecystitis: a case report. BMC Infect Dis 2020;20:437.
[9] Zong H, Yin B, Zhou H, Cai D, Ma B, Xiang Y. Loss of angiotensin-converting enzyme 2 promotes growth of gallbladder cancer. Tumour Biol 2015;36:5171–5177.
[10] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–773.

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The impact of COVID-19 on the clinical outcome of patients with cirrhosis deserves more attention and research

To the Editor:
We read with interest the paper "High rates of 30-day mortality in patients with cirrhosis and COVID-19" by Iavarone *et al.* in *Journal of Hepatology*.[1] In the article, the authors report that COVID-19 is associated with elevated 30-day mortality in cirrhotic patients. After carefully reading, we wish to put forth the following suggestions.

First, there were 4 predictor variables (MELD, delta-MELD, CLIF-OF, and moderate/severe respiratory failure) with 17 fatal outcome events in the multivariate Cox model. The rule of thumb is that logistic and Cox models should be used with a minimum of 10 events per predictor variable (EPV). Previous results showed increasing bias and variability, unreliable confidence interval coverage, and problems with model convergence as EPV declined below 10 and especially below 5.[2,3] Therefore, a larger sample size is needed to validate the results of this study. Second, it might be reasonable to use logistic regression, with the outcome being a dichotomous status (alive or dead) since the relative granularity of time is low (a short-term follow-up: 30 days). Third, the authors report that patients with cirrhosis had increased MELD and CLIF-OF scores at COVID-19 diagnosis. However, most patients (80%) with COVID-19 in the cohort received thromboprophylaxis, which would affect the results of prothrombin time (PT) and international normalized ratio (INR). Prolonged PT and high INR levels would result in higher MELD, Child-Pugh and CLIF-OF scores. Finial, previous studies found that ACE2 internalization by SARS-CoV-2 would potentially result in the loss of ACE2 activity at the cell surface and voids a key pathway of angiotensin (Ang)-II metabolism and Ang-(1-7) generation.[4,5] Experimentally, Ang-(1–7) inhibits liver fibrogenesis and exerts natriuretic and portal hypotensive effects.[6] The reduction in ACE2 by SARS-CoV-2-induced internalization would be predicted to aggravate liver fibrosis and portal hypertension, and exacerbate disease severity, especially in the long-term. Therefore, the impact of COVID-19 on the long-term liver-related outcomes in patients with cirrhosis deserves attention.

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Study concept and design: Feng Gao, Zhi-Ming Huang; Drafting of the manuscript: Feng Gao; Study supervision: Zhi-Ming Huang. All authors contributed to the manuscript for important intellectual contents and approved the submission.

Supplementary data
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References
[1] Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73:1063–1071.

[2] Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol 1995;48:1495–1501.
[3] Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503–1510.
[4] South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences 2020; 2020;318:H1084–H1090.
[5] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020.
[6] Sansoè G, Aragno M, Wong F. Pathways of hepatic and renal damage through non-classical activation of the renin-angiotensin system in chronic liver disease. Liver Int 2020;40:18–31.

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Letter regarding "High rates of 30-day mortality in patients with cirrhosis and COVID-19"

To the Editor:

We read with great interest the paper published in *Journal of Hepatology* by Iavarone *et al.*[1] This paper is very important for our daily practice as hepatologists, particularly in Egypt, which has the highest prevalence of HCV in the world and is currently experiencing a peak in reported COVID-19 cases.[2] The authors concluded that COVID-19 infection is associated with higher 30-day mortality rates in cirrhotic patients; however, we are not sure about the rationality of this generalization.

We think that the sample size is too small to evaluate the actual effect of COVID-19 infection on mortality rates in cirrhotic patients. Additionally, old age has been considered the most important prognostic factor for mortality in patients with COVID-19 since the onset of the pandemic. The median age of the study population is 67 years old (IQR 61–74), which is significantly older than the comparative group of cirrhotic patients with pneumonia (59, IQR 50–65), which may affect the mortality rate in the former group. A recently published meta-analysis on patients with COVID-19 reported mortality rates of 3%, 9.5%, and 22.5% for the following age groups, 50–59, 60–69, 70–79, respectively,[3] and the median age of patients who died was 70 (IQR 61–80). Moreover, 48% of the patients included had decompensated cirrhosis at the time of their last outpatient visit, which carries a 1-year probability of mortality of about 20%,[4] even in the absence of COVID-19 infection.

Multiple comorbidities other than cirrhosis were reported in the study group; so, high rates of mortality cannot be attributed to complications of cirrhosis alone. Regarding the group of cirrhotic patients with pneumonia, the number of patients with comorbidities was lower in this group relative to cirrhotic patients with COVID-19 infection, which may partly explain the lower mortality rate in patients without COVID-19.

The majority of deaths (12 out of 17) were due to respiratory failure, while only 5 were due to end-stage liver disease, which may indicate a modest effect of COVID-19 infection on mortality among cirrhotic patients. Furthermore, the authors did not document the occurrence of hepatopulmonary syndrome and/or porto-pulmonary hypertension in the recruited patients, which could affect the respiratory failure rate in this study. Chronic obstructive pulmonary disease was one of the reported comorbidities in this study; clarifying its relationship to the occurrence of respiratory failure in patients with acute-on-chronic liver failure is of great importance.

What was really interesting is that nosocomial SARS-CoV-2 infection was documented in 40% of the study patients, which emphasizes the importance of EASL[5] and AASLD[6] recommendations regarding the role of telemedicine in the management of cirrhotic patients during the COVID-19 pandemic, and the advice to postpone any in-hospital procedures for those patients whenever possible.

Finally, we thank Dr. Iavarone *et al.* for their important thoughts on the risks that face cirrhotic patients in the COVID-19 era, which pave the way for further studies to better evaluate this important issue. What's more, and with different observational studies merged into larger databases from various geographical areas, the issue of encountering specific impacts of COVID-19 on patients with chronic liver diseases may be much easier to ascertain.

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