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.

MR-PRESSO. Detailed MR Egger regression intercepts and MR-PRESSO global test results are presented in Table S1-S2.

There was no evidence derived from this work to support causal relationships between COVID-19 susceptibility/severity and NAFLD, which are consistent with results from previous genetic studies.[2,6] On the contrary, Innes *et al.* found that the rs738409 C>G variant in patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), which is well studied in the genetic regulation of NAFLD and liver injury, played a protective role in COVID-19 severity.[7] Previous observational studies revealed that COVID-19-infected patients had an increased risk of liver injury,[8,9] however, unmeasured/unmeasurable confounding cannot be ruled out in conventional multivariable regression analysis. In fact, our findings derived from the MR analysis could minimize confounding bias or reverse causation.[3] It is worthy of note that collider bias, which could distort the relationship between exposures and outcomes, existed in many observational studies and cannot be completely overcome by MR.[10] To investigate the potential impact of collider bias on the MR estimation, we replicated the bidirectional two-sample MR analysis using data from a previously published GWAS by Namjou *et al.*, where genetic associations might be biased due to adjusting for a collider variable (*e.g.*, BMI). Details on methods, results, and directed acyclic graph are included in the supplementary information. Future larger randomly sampled cohort studies on COVID-19 and NAFLD and rigorous statistical analysis might be helpful to minimize the impact of collider bias.

In conclusion, we found little evidence to support a causal relationship between COVID-19 susceptibility/severity and NAFLD.

Financial support
The authors received no financial support to produce this work.

Conflict of interest
The authors declare no conflicts of interest that relate to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
All authors drafted and reviewed this manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.11.014.

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Focus on the decisions to forego life-sustaining therapies during ICU stay of patients with cirrhosis and COVID-19: A case control study from the prospective COVID-ICU database

Received 30 July 2021; received in revised form 26 August 2021; accepted 17 September 2021; available online 30 September 2021
https://doi.org/10.1016/j.jhep.2021.09.018

To the Editor:
We read with interest the article by Mallet *et al.* evaluating prognosis of French COVID-19 patients with chronic liver

disease.[1] Based on the French National Hospital Discharge database, the outcomes of 259,110 adults with COVID-19 including 15,746 patients with chronic liver disease were analyzed. Results suggest that chronic liver disease *per se* is not a risk factor for COVID-19 mortality, but rather that limitations to therapeutic efforts, including reduced access to mechanical ventilation, may have accounted for the excess mortality of patients with cirrhosis. However, to date, no study has specifically analyzed the prognosis of patients with cirrhosis hospitalized in intensive care for COVID-19-related acute respiratory distress syndrome (ARDS) and, in particular, decisions to forego life-sustaining therapies (DFLST). Therefore, we took advantage of a COVID-related intensive care unit (ICU) study,[2] a multi-center prospective cohort study conducted in 149 ICUs across 3 countries (France, Switzerland and Belgium) from February to May 2020, describing outcomes of critically ill patients with COVID-19, to perform an ancillary analysis focusing on patients with cirrhosis. COVID-19 patients with a medical history of cirrhosis according to the physician in charge of the patient were compared with COVID-19 patients without cirrhosis. Matching 1:3 was performed according to sex, respiratory component of the sequential organ failure assessment (SOFA) score at admission, diabetes, immunosuppression, obesity and the closest case for age (±7 years). Morbidity, mortality and DFLST were analyzed in the 2 groups of patients.

Among the 4,244 patients from the COVID-ICU database, 33 (0.8%) had cirrhosis and were compared with 99 matched patients without cirrhosis. Patient's characteristics at admission are displayed in Fig. 1A. Median duration of ICU stay was 18 days [interquartile range 9-21] for patients with cirrhosis *vs.* 21 days [interquartile range 10-28] for patients without cirrhosis (p = 0.13). Life-sustaining therapies including mechanical ventilation, renal replacement therapy and extracorporeal membrane oxygenation tended to be less often introduced in patients with cirrhosis; their ICU and hospital mortality rates were slightly, but non significantly higher (Fig. 1B). Patients with cirrhosis were more frequently subject to a DFLST than patients without cirrhosis (27% *vs.* 4%, p <0.01). Moreover, while 71% of deaths were related to DFLST in patients with cirrhosis, only 25% were in patients without (p = 0.04). Among patients who had DFLST, the ICU and hospital mortality rates were 56% *vs.* 100% (p = 0.11) and 67% *vs.* 100% (p = 0.19) in patients with *vs.* without cirrhosis respectively. Among those who did not have DFLST, the ICU and hospital mortality rates were 13% *vs.* 19% (p = 0.46) and 15% *vs.* 21% (p = 0.54) in patients with *vs.* without cirrhosis, respectively**.** Median time to DFLST was not significantly different between the 2 groups (8 [3-21] days *vs.* 13 [7-19] days respectively, p = 0.48).

To explore the reasons for DFLST, we performed univariate analysis among patients with cirrhosis and identified SOFA score at admission, simplified acute physiology score 2 and model for end-stage liver disease score as associated with DFLST (all p <0.05). Patients with cirrhosis had higher SOFA score during the first days of ICU hospitalization than patients without (10 [7-14] *vs.* 7 [4-10], 12 [11-13] *vs.* 8 [5-11], 11 [9-13] *vs.* 8 [7-11], respectively, at day 1, 3 and 5, all p <0.05). These higher SOFA scores were mostly impacted by "liver" and "coagulation" sub-scores both strongly related to cirrhosis. "Hemodynamic", "respiratory", "renal" and "neurologic" components of the SOFA score at admission (Fig. 1A) and during the first 2 weeks of hospitalization (data not shown) did not differ between the 2 groups. Interestingly, DFLST also tended to be more frequent in patients with alcohol use disorders (50% *vs.* 18%, p = 0.06), confirming data already suggested by the study from Mallet *et al.*

As intensity of inflammatory response has been associated with both severity of COVID-19 and outcome of critically ill patients with cirrhosis,[3,4] we investigated the pattern of inflammatory response in our cohort. Apart from a lower C-reactive protein concentration on admission in patients with cirrhosis, daily measurements of leukocytes, neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio, C-reactive

A

	Patients with cirrhosis (n = 33)	Patients without cirrhosis (n = 99)	*p* value
Age (years)	59 [56-67]	60 [55-65]	0.88
Male sex	25 (75.8%)	74 (74.7%)	0.91
BMI (kg/m²)	27.5 [25-31]	28.1 [25.8-31.8]	0.38
Alcohol use disorders	10 (30.3%)	4 (4%)	<0.01
Current smoking	5 (15.2%)	4 (4%)	0.04
Chronic obstructive pulmonary disease	1 (3%)	3 (3%)	1.0
Asthma	1 (3%)	8 (8.1%)	0.22
Hypertension	16 (48.5%)	59 (59.6%)	0.44
Diabetes mellitus	15 (45.5%)	45 (45.5%)	0.68
Chronic kidney disease	3 (9.1%)	7 (7.1%)	0.82
MELD	13 [9-20]		
Etiologies of cirrhosis			
Non-alcoholic steatohepatitis	17 (51.5%)		
Alcohol use disorders	10 (30.3%)		
SAPS 2	35.5 [23-43]	34 [27-44]	0.77
SOFA score	10 [7-14]	7 [4-10]	<0.01
Respiratory component	3 [1-4]	3 [1-4]	0.44
Hemodynamic component	1 [0-4]	0 [0-3]	0.21
Renal component	0 [0-2]	0 [0-0.25]	0.18
Neurologic component	4 [0-4]	4[0-4]	0.37
Liver component	0 [0-1]	0 [0-0]	<0.01
Coagulation component	0 [0-2]	0 [0-0]	<0.01
Leukocytes (G/L)	7.3 [3.6-12.6]	8.5 [6.2-12.0]	0.19
Neutrophils (G/L)	6.6 [3.0-11.3]	7.2 [4.9-9.7]	0.76
Lymphocytes (G/L)	1.0 [0.6-1.4]	0.8 [0.6-1.2]	0.32
Neutrophil-to-lymphocyte ratio	6.6 [4.4-9.9]	8.1 [5.1-12.9]	0.19
C reactive protein (mg/L)	99.4 [39.2-173]	181 [121.5-253.8]	0.01
Procalcitonin (µg/L)	0.29 [0.22-0.47]	0.46 [0.15-1.03]	0.41

B

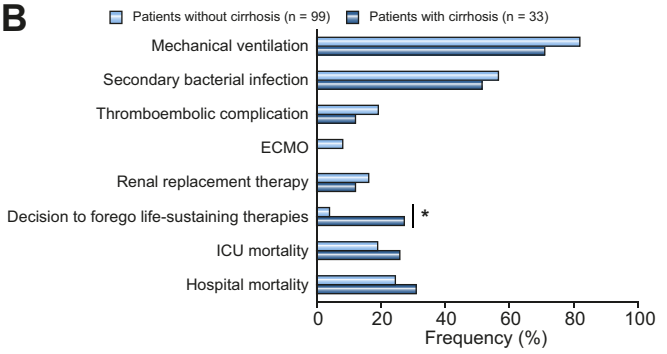

Fig. 1. Comparison of characteristics at ICU admission and outcomes of patients with and without cirrhosis. (A) Patient's characteristics at ICU admission. n (%); Median [IQR]; p values: Mann-Whitney test for continuous variables; Chi-squared test for qualitative variables. (B) Outcomes of patients with (dark blue) and without cirrhosis (light blue); p values: Chi-squared test for qualitative variables; univariable Cox regression for survival analyses. * p<0.05. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MELD, model for end-stage liver disease; SAPS 2, simplified acute physiology score 2; SOFA, sequential organ failure assessment.

protein and procalcitonin from day 1 to day 28 did not differ between the 2 groups (data not shown). Secondary bacterial infections and thromboembolic complications were not different either (Fig. 1B).

In conclusion, our data show that intensity of treatment of patients with cirrhosis admitted to ICU was more commonly limited compared to non-cirrhotic patients and suggest a significant impact of hepatic failure on these DFLST. Yet, patients with cirrhosis did not exhibit more pronounced inflammatory storm and did not more frequently develop secondary bacterial infections or thromboembolic complications. These results suggest that, such as in other critical illnesses affecting patients with chronic liver disease, cirrhosis should not *per se* justify DFLST in patients with COVID-19.

Financial support
The COVID-ICU study was funded by the Fondation APHP and its donators through the program "Alliance Tous Unis Contre le Virus", the Direction de la Recherche Clinique et du Développement, and the French Ministry of Health. The Reseau European de recherche en Ventilation Artificielle (REVA) network received a 75,000 € research grant from Air Liquide Healthcare. The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
MG: study concept, data acquisition, statistical analysis, interpretation of data, drafting of manuscript. ALM: study concept, data acquisition, interpretation of data. OR: interpretation of data, preparation and critical review of manuscript. PER: study concept, interpretation of data, preparation and critical review of manuscript. EW: study concept, interpretation of data, preparation and critical review of manuscript. All authors read and approved the final manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.09.018.

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Reply to: "Focus on the decisions to forego life-sustaining therapies during ICU stay of patients with cirrhosis and COVID-19: A case control study from the prospective COVID-ICU database"

To the Editor:
We thank Doctor Giabicani and colleagues for their comments [1] on our article published in the *Journal of Hepatology*.[2] Their investigations from a prospective, multicenter, international, cohort of more than 4,000 intensive care unit (ICU) patients with COVID-19 [3] confirm our results at the national level: despite similar COVID-19 severity, including initial non-hepatic organ failure, bacterial infections and thromboembolic complications, a decision to forego life-sustaining therapies was more frequently made for patients admitted to the ICU with cirrhosis.

Received 7 November 2021; accepted 16 November 2021; available online 25 November 2021
https://doi.org/10.1016/j.jhep.2021.11.020