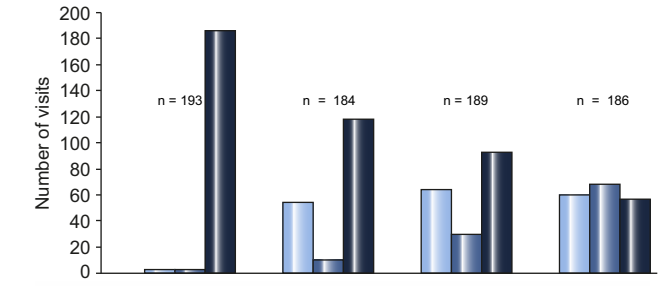

Fig. 1. Advanced liver disease and post-liver transplant visits from 2 March to 26 April, 2020 stratified by 2-week interval and visit modality (n = 752).

We do not yet have data on those with alcohol use disorders, relapse rates, or attendance in "virtual rehabilitation".

Notwithstanding the ongoing difficulties and uncertainty, we are learning valuable lessons about leveraging technology, being proactive in reaching out to patients, caregivers, and referring providers, and rapidly refining our processes to handle ongoing challenges. The most valuable lesson is how adaptable we can be in the face of adversity. While we do not believe that the COVID-19 disruption has led to apocalyptic consequences for our local patient population, we also cannot lose sight of the fact that well-resourced transplant and tertiary care centers are better-positioned in these challenging times. It is, therefore, incumbent upon us to continue to share detailed and contemporaneous outcome data as it becomes available and disseminate best practices that will last far beyond this crisis.

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

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Authors' contributions
All authors drafted and reviewed the letter for intellectual content. MS obtained and analyzed data.

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References
[1] Tapper EB, Asrani SK. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. J Hepatol 2020;73:441–445.
[2] Serper M, Cubell AW, Deleener ME, Casher TK, Rosenberg DJ, Whitebloom D, et al. Telemedicine in liver disease and beyond: can the COVID-19 crisis lead to action? Hepatology 2020. https://doi.org/10.1002/hep.31276.
[3] Penn Medicine Center for Health Care Innovation, Way to Health. Available at: https://healthcareinnovation.upenn.edu/projects/way-health. [Accessed 4 May 2020].
[4] AASLD's. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. Available at: https://www.aasld.org/about-aasld/covid-19-resources. [Accessed 5 May 2020].
[5] de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–752.
[6] Centers for Meedicare & Medicaid Services. Available at: https://www.cms.gov/files/document/cms-non-emergent-elective-medical-recommendations.pdf. [Accessed 5 May 2020].

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Lack of genetic evidence that fatty liver disease predisposes to COVID-19

To the Editor:
We read with interest the manuscript by Ji and coworkers, reporting that among 202 Chinese individuals with COVID-19,[1] those with likely metabolic-associated fatty liver disease (MAFLD) had a higher probability of abnormal liver function tests and disease progression than those without. Obesity and dysmetabolism are highly associated with severe COVID-19,[2] raising the possibility that fatty liver directly mediates inflammation and hypercoagulation leading to respiratory and systemic complications of COVID-19.[3] Alternatively, fatty liver may indirectly favor replication of the SARS-CoV-

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Table 1. Impact of genetic predisposition to MAFLD on the risk of developing COVID-19 in the UKBB (526 cases and 934 controls), and on the hepatic mRNA expression of cellular SARS-CoV-2 receptors in 125 obese individuals.

	UKBB association study			Gene expression		
Genetic instrument	***p* value***	**OR**	**95% CI**		**Estimate**	***p* value°**
GRS						
Unadjusted	0.46			*ACE2*	+37 ± 24	0.13
Model 1	0.70	0.90	0.51–1.56	*CTSL*	−130 ± 201	0.54
Model 2	0.69	0.89	0.51–1.56	*TMPRSS2*	+19 ± 89	0.83
Model 3	0.68	0.89	0.51–1.56	*PYKFYVE*	−49 ± 86	0.57
PNPLA3 p.I148M						
Unadjusted	0.06			*ACE2*	+13 ± 7	0.06
Model 1	0.12	0.86	0.71–1.04	*CTSL*	54 ± 61	0.80
Model 2	0.13	0.86	0.71–1.04	*TMPRSS2*	+13 ± 26	0.61
Model 3	0.13	0.86	0.71–1.04	*PYKFYVE*	2 ± 25	0.95
TM6SF2 p.E167K						
Unadjusted	0.46			*ACE2*	+5 ± 17	0.77
Model 1	0.48	1.10	0.85–1.42	*CTSL*	−17 ± 62	0.79
Model 2	0.52	1.09	0.84–1.41	*TMPRSS2*	−76 ± 146	0.60
Model 3	0.53	1.09	0.84–1.41	*PYKFYVE*	+29 ± 60	0.62
MBOAT7 rs738409 C>G						
Unadjusted	0.61			*ACE2*	−7 ± 6	0.23
Model 1	0.45	1.06	0.91–1.23	*CTSL*	+5 ± 50	0.91
Model 2	0.50	1.05	0.90–1.23	*TMPRSS2*	−10 ± 21	0.62
Model 3	0.50	1.05	0.90–1.23	*PYKFYVE*	−20 ± 21	0.34
GCKR p.P446L						
Unadjusted	0.34			*ACE2*	−1 ± 6	0.89
Model 1	0.32	1.08	0.93–1.26	*CTSL*	−11 ± 54	0.83
Model 2	0.28	1.09	0.93–1.28	*TMPRSS2*	−3 ± 23	0.90
Model 3	0.28	1.09	0.93–1.28	*PYKFYVE*	−18 ± 22	0.42

Model 1: adjusted for age, sex, BMI, PC1-10 (ethnicity), assessment center, array batch; Model 2: further adjusted for inpatient (origin of test sample, as coded in data-coding 1855); Model 3: further adjusted for diagnosis of diabetes.
BMI, body mass index; GRS, genetic risk score; MAFLD, metabolic-associated fatty liver disease; OR, odds ratio; UKBB, UK Biobank.
*At binary logistic regression analysis. GRS of MAFLD, based on the weighted impact of genetic risk variants on hepatic fat content.
°At generalized linear model adjusted for age, sex, BMI, and type 2 diabetes.

2 virus.[4] However, several confounders, *e.g.* an independent role of insulin resistance, and reverse causation, *e.g.* the impact of SARS-CoV-2 and treatments on fatty liver, may complicate the interpretation of these initial retrospective observations.

Mendelian randomization is an epidemiological framework that bypasses confounding and reverse causation by using genetic variation as an instrument to establish the causal role of modifiable risk factors in disease pathogenesis.[5] We previously developed a genetic risk score (GRS) for MAFLD based on the weighted effect of risk variants in *PNPLA3-TM6SF2-MBOAT7-GCKR* on hepatic fat in the general population.[6] Exploiting this robust instrument, we showed that hepatic fat has a causal role in determining liver fibrosis and insulin resistance.[6]

Herein, we examined the impact of the MAFLD-GRS on the risk of COVID-19 in individual data of participants of the UK Biobank (UKBB) cohort. The UKBB comprises 502,640 individuals aged between 40 and 69 years.[7] Baseline assessment, medical history and biological samples are available, including also genetic data. We had access to these data with application #37142. UKBB started to release COVID-19 test results from March 16th 2020 (data-field 40100), and given that the tests were mainly restricted to hospitalized patients with symptoms, positive test results can be considered as a proxy of severe disease. As of May 2nd 2020, test results were available for 4,119 individuals (2,770 confirmed inpatients; data were only partially available for the rest). We restricted the analysis to the subset of white British ancestry. After applying quality control (supplementary data), the remaining number of individuals was 1,460, of whom 526 were positive (case) and 934 were negative (control) for SARS-CoV-2, respectively. Of these, 835 (57%) were confirmed inpatients. Results are shown in Table 1, left panel. The GRS was not associated with an increased risk of COVID-19, as also observed for carriage of each variant included in the score (all *p* values >0.1). These results suggest that genetic predisposition to hepatic fat accumulation does not increase *per se* the predisposition towards severe COVID-19, and that MAFLD does not play a causal role of in this condition.

These results should be interpreted with caution for several reasons: they were obtained in an initial set of cases without detailed characterization, and for a possible lack of power to detect the association. However, the current sample size clearly had the power to detect a >6-fold higher risk of severe COVID-19 conferred by MAFLD, as reported by Ji *et al.*[1] We actually detected a trend of protection against COVID-19 conferred by rs738409, encoding for the p.I148M *PNPLA3* variant, which is a major genetic determinant of hepatic inflammation.[5,8] Future larger studies are warranted to formally test this hypothesis. A

possible reason for differential susceptibility to severe COVID-19 is related to altered expression of SARS-CoV-2 cellular receptors.[9] We therefore looked at the impact of genetic risk variants on the hepatic mRNA expression of *ACE2*, *CTSL*, *TMPRSS2* and *PYKFYVE*[9] in a cohort of 125 obese individuals.[8] We found no significant impact of MAFLD-GRS and single variants on the expression of known viral receptors. However, we observed a trend towards higher *ACE2* expression associated with carriage of the p.I148M *PNPLA3* variant that was not statistically significant ($p = 0.06$).

In conclusion, the first available genetic data are not consistent with a strong predisposition conferred by MAFLD to the development of severe COVID-19. Larger prospective studies including the role of obesity, dyslipidemia and type 2 diabetes are warranted to understand the impact of genetic predisposition to MAFLD on COVID-19 susceptibility and severity, namely on the risk of hospitalization and mortality.

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Conflict of interest

Authors declare that they do not have any conflict of interest relevant to the present study. SR has served as a consultant for AstraZeneca, Celgene, Sanofi, Amgen, Akcea Therapeutics, Camp4, Medacorp, Pfizer in the last 5 years. SR has received research grants from AstraZeneca, Sanofi and Amgen. LV reports having received speaking fees from MSD, Gilead, AlfaSigma, AbbVie, having served as a consultant for: Gilead, Pfizer, Astra Zeneca, Novo Nordisk, Intercept, Diatech Pharmacogenetics, Ionis Pharmaceuticals, and received research grants from: Gilead.

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Authors' contributions

The study was conceived by LV and SR, OJ analysed the data, the final manuscript was approved by all Authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.05.015.

References

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[1] Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73:451–453.
[2] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052–2059.
[3] Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int 2020;40(6):1278–1281.
[4] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40(5):998–1004.
[5] **Trepo E**, **Valenti L**. Update on NAFLD genetics: from new variants to the clinic. J Hepatol 2020;72(6):1196–1209.
[6] **Dongiovanni P**, **Stender S**, Pietrelli A, Mancina RM, Cespiati A, Petta S, et al. Causal relationship of hepatic fat with liver damage and insulin resistance in nonalcoholic fatty liver. J Intern Med 2018;283:356–370.
[7] Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
[8] **Baselli GA**, **Dongiovanni P**, Rametta R, Meroni M, Pelusi S, Maggioni M, et al. Liver transcriptomics highlights interleukin-32 as novel NAFLD-related cytokine and candidate biomarker. Gut 2020. https://doi.org/10.1136/gutjnl-2019-319226 (In press).
[9] Biquard L, Valla D, Rautou P-E. No evidence for an increased liver uptake of SARS-CoV-2 in metabolic-associated fatty liver disease. J Hepatol 2020;73(3):717–718.

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