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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.

with the highest sensitivity and one with the highest specificity. Consequently, between these two cutoff points there is a so-called grey zone of indeterminate results; for the FAST and MACK-3 scores, nearly 30% of test scores are in this zone. For the NIS4 score, with 0·36 as the lower cutoff point and 0·63 as the higher cutoff point, around 30% of patients in the training cohort and 27% of those in the validation cohort fell into the grey zone.[1] In the validation cohort, 56% of the patients in the grey zone had NASH confirmed by liver histology.[1] Thus, it is essential to find a more accurate test to identify patients who are at risk of NASH and who are in the grey zone of NIS4.

The sequential combination of non-invasive tests designed for liver fibrosis detection accurately classifies more than 90% of patients with advanced NAFLD fibrosis.[4] In a similar way, we propose that the sequential combination of NIS-4, MACK-3, and FAST scores might help to narrow the grey zone and further avoid unnecessary liver biopsies. The FAST score relies heavily on serum AST concentrations and thus it accurately classifies patients with advanced fibrosis, but could also place individuals with normal serum liver enzymes in the grey zone.[5] In such instances, we propose that additional testing with NIS4 or MACK-3 might better identify patients who are at risk of NASH, as these two blood-based diagnostic tests include in their equations other important parameters associated with NASH. Sequential combination of these three newly developed non-invasive tests to better identify patients who are at risk of developing NASH warrants further research.

We declare no competing interests.

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1   Harrison SA, Ratziu V, Boursier J, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. *Lancet Gastroentrol Hepatol* 2020; **5:** 970–85.

2   Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol* 2020; **5:** 362–73.

3   Boursier J, Anty R, Vonghia L, et al. Screening for therapeutic trials and treatment indication in clinical practice: MACK-3, a new blood test for the diagnosis of fibrotic NASH. *Aliment Pharmacol Ther* 2018; **47:** 1387–96.

4   Boursier J, Guillaume M, Leroy V, et al. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. *J Hepatol* 2019; **71:** 389–96.

5   Noureddin N, Alkhouri N, Brown KA, Noureddin M. Driving NASH forward using the FAST score but obey the traffic lights. *Hepatology* 2020; published online Aug 5. https://doi.org/10.1002/hep.31498.

COVID-19 and liver transplantation: the jury is still out

We read with interest the study by Gwilym Webb and colleagues[1] detailing outcomes of liver transplant recipients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from two international registries. We congratulate them for this contribution to the evidence base, being an exemplar of the global collaboration required in response to COVID-19. However, we believe that the study has generated questions that need to be answered before we can reassure the liver transplant community.

The authors developed a multiple logistic regression model for mortality among liver transplant recipients based on a limited number of variables. The liver transplant community is heterogeneous and practice varies between centres nationally and internationally (appendix). Compounding this variability are well documented differences in public health approaches to COVID-19 worldwide, which need to be considered in any analysis. We note that more than 50% of patients included within this study were from the UK or the USA.[1] Although this is probably due to these being the host nations of the registries, it is possible that practices adopted by these nations might increase the risk of hospitalisation of liver transplant recipients with SARS-CoV-2 infection. Further interrogation and risk adjustment in a suitably powered cohort of liver transplant recipients are required to truly understand their risk of mortality from COVID-19.

Comparing liver transplant recipients from multiple countries with patients admitted in Oxford (UK) is fraught with potential confounders. Although the authors have shown some similarities between both cohorts and have carried out a propensity-matched analysis for specific variables, we remain unconvinced that this cohort is a fair comparator. Mortality per population from COVID-19 was lower in Oxford than many areas where liver transplant centres are located in the UK.[2] Adverse outcomes from COVID-19 have been frequently associated with non-White ethnic groups and low socioeconomic status.[3] It is likely that there were differences between the Oxford cohort and non-liver transplant cohorts elsewhere in the world for

these variables, but these data are unavailable. The development of an internationally representative comparator cohort of individuals who have not received a liver transplant is required for fair comparison.

Rather than relying on clinician reporting, we believe that data acquired through primary and secondary care coding would better capture accurate information for cohorts of interest and for comparison. Although there are well described limitations to this method, it will ensure not only more robust data capture but also that the studies are adequately powered to truly understand the risk of mortality from COVID-19 in liver transplant recipients. Until then, we believe the jury is still out on this risk.

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1   Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol* 2020; **5:** 1008–16.
2   Office for National Statistics. Deaths involving COVID-19 by local area and socioeconomic deprivation: deaths occurring between 1 March and 30 June 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingcovid19bylocalareasanddeprivation/deathsoccurringbetween1marchand30june2020 (accessed Aug 29, 2020).
3   Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.

Authors' reply

We thank Oliver Tavabie and colleagues for their interest in our work[1] and their comments. We also thank them for contributing patient data from their institution to our registries.

Tavabie and colleagues speculate as to the generalisability of our work.

However, the mortality following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in liver transplant recipients in our registries (19%) is similar to contemporaneous Spanish (18%), and UK national registries (20%), suggesting some consistency.[1–3] The Spanish liver transplant recipients also had no increased risk of severe disease compared with the general population.

A further point raised is that either the preponderance of patients from the UK and the USA in our study, or a focus on hospitalised patients, might have biased results. The rate of hospitalisation (70 [83%] of 84 vs 54 [81%] of 67; p=0·675) and death (14 [17%] of 84 vs 14 [21%] of 67; p=0·533) did not differ in patients from the UK and the USA versus those from elsewhere; furthermore, non-hospitalised patients were included in our analyses.

We recognise that mortality in our comparison cohort might have been lower than elsewhere. The Oxford area ranked 115th of 336 in UK COVID19 age-standardised mortality during the study period; slightly below average. Crucially, however, the lower the comparison cohort mortality, the greater the likelihood of recording excess mortality in the liver transplant cohort. Thus, when assessing for excess mortality among recipients of liver transplants, the key concern would in fact be high mortality in the comparison cohort increasing the risk of type II error. The relatively lower mortality in Oxford therefore provides reassurance that COVID-19 mortality is unlikely to be substantially higher in the liver transplant population. Using the same techniques, we have recently reported increased mortality from SARS-CoV-2 in patients with advanced cirrhosis.[4]

We agree with the final suggestion that coding data from primary and secondary care will provide additional valuable information, accepting that COVID-19 coding is not standardised. However, this approach will need

to compliment specifically reported work to allow accurate classifications. For example, primary aetiologies for patients who received liver transplants were discordant in more than 30% of liver transplant recipients between a secondary care dataset and a central clinician-reported registry, and ethnicity is absent in a third of UK primary care records.[5,6]

Although larger and more varied datasets will continue to improve our understanding of the risks from SARS-CoV-2 faced by liver transplant recipients, the urgency and changing nature of the pandemic mean that a variety of approaches are required to inform the risk stratification of specific patient groups in a timely manner.

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1   Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol* 2020; **5:** 1008–16.
2   Colmenero J, Rodríguez-Perálvarez M, Salcedo M, et al. Epidemiological pattern, incidence and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2020; published online Aug 1. https://doi.org/10.1016/j.jhep.2020.07.040.
3   Ravanan R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of wait-listed and solid organ transplant recipients in England: a national cohort study. *Am J Transplant* 2020; published online Aug 11. https://doi.org/10.1111/ajt.16247.
4   Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. *J Hepatol* 2020; published online Oct 1. https://doi.org/10.1016/j.jhep.2020.09.024.
5   Tovikkai C, Charman SC, Praseedom RK, et al. Linkage of a national clinical liver transplant database with administrative hospital data: methods and validation. *Transplantation* 2014; **98:** 341–47.
6   Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017; **357:** j2099.