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Reply to: "Failure to control variceal bleeding: Definition matters"

To the Editor:

We thank Baiges *et al.*[1] for their keen interest and observations regarding our study.[2] We completely agree that the definition of 'failure to control bleeding' is difficult to apply in individual clinical cases and in general its interpretation is dependent upon many factors including how sick the patients is, whether they have ongoing bleeding during an endoscopy session and the severity of bleeding. In our study,[2] we defined 'failure to control bleeding' strictly as failure to achieve haemostasis despite 2 endoscopies or need for adjuncts such as Sengstaken-Blakemore tube (SBT) or a stent within 5 days of the first bleed in combination with vasoactive drugs.

Baiges *et al.* raise several important questions.

1. What is the role of transjugular intrahepatic portosystemic shunt (TIPS) in patients without acute-on-chronic liver failure (ACLF) with 'failure to control bleeding'?

We believe that our paper is underpowered to make any new conclusions about the role of rescue TIPS in patients with failure to control bleeding but without ACLF. As is the current clinical practice, these patients should be offered TIPS.

2. How was 'failure to control of bleeding' controlled without TIPS?

As a large proportion of our patients were referred from other centres, we found that many still had endoscopic options. Out of 174 patients in our study, further therapeutic endoscopy was successful in achieving satisfactory haemostasis in 82 (47.1%).

3. Whether there is a sub-group in whom TIPS is futile?

As reported in the paper[2] and correctly observed by the Baiges[1] *et al.*, none of the patients who had grade 2-3 ACLF "prior to the acute episode of variceal bleeding" survived, irrespective of their TIPS status. Of the patients who developed ACLF following an episode of variceal bleeding, all the survivors had a CLIF-C ACLF score of 62 or below. This confirms the previous futility cut-off in patients with ACLF for whom liver transplantation is not an option. Patients with a CLIF-C ACLF score of >64 after 48 hours of intensive care unit care are at high risk of death and those with a score of >70 almost invariably die irrespective of the aetiology or precipitant.[3] Although these criteria provide a strong guide, futility of ongoing care needs to be decided on a case-by-case basis.

4. Would preemptive TIPS (pTIPS) have prevented the need for rescue TIPS?

The population studied was a highly selected patient group, most of whom were referred from other centres. It is extremely difficult to analyse this complex patient population in a retrospective study and come to any meaningful conclusion about whether pTIPS would have prevented the need for rescue TIPS. Despite high quality published data,[4,5] the role of pTIPS is still a matter of debate in the UK, which has been further fuelled by the recent negative trial from the Hayes group.[6] A large UK trial of pTIPS is in the process of being set up to definitively address this issue.

Received 18 February 2021; accepted 18 February 2021; available online 27 February 2021
https://doi.org/10.1016/j.jhep.2021.02.022

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Ltd, a spin out company from University College London. He is also a Founder of Thoeris Ltd.

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

Authors' contributions

RK drafted the letter, RJ did the critical review

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.02.022.

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Polygenic risk score: A promising predictor for hepatocellular carcinoma in the population with non-alcoholic fatty liver disease

To the Editor:

We were impressed by the promising results reported by Bianco and colleagues, who indicated that the polygenic risk score (PRS), which is based on *PNPLA3-TM6SF2-GCKR-MBOAT7* variants, may be useful for predicting the risk of hepatocellular carcinoma (HCC) in patients with non-alcoholic fatty liver disease (NAFLD) and dysmetabolism. In particular, positive PRS can be used to identify a subset of patients with dysmetabolism who are at high genetic risk of HCC.[1] Considering that all the variants included in the PRS can be assessed easily and non-invasively, the novelty of this result and its significant implications for clinical practice should be emphasized. However, we still have a few concerns regarding this study.

First, the AUC for HCC was 0.64 for hepatic fat PRS (PRS-HFC) and 0.65 for PRS-5 (PRS adjusted for HSD17B13) in the NAFLD cohort.[1] The assessment of performance for PRS is important; however, these AUC values are not stellar. In general, the traditional thresholds for AUC are defined as follows: 0.5, no discrimination; 0.5-0.7, poor discrimination; ≥0.7, acceptable discrimination; ≥ 0.8, excellent discrimination; and ≥0.9, outstanding discrimination.[2] An important question to address in future studies would be to investigate whether inherited or *de novo* genetic factors such as copy number variants, methylation marks, and rare but highly penetrant polymorphisms not captured in this analysis of common variants or other non-invasive assessments, such as ultrasound elastography,[3] can be integrated to generate a comprehensive risk score to enhance the predictive ability of PRS. In addition, this study used AUC to evaluate the predictive performance of PRS.[1] Although AUC can be used to evaluate the ability of PRS to distinguish between patients with and without HCC, it cannot quantify the contribution of PRS to the burden of HCC on a population level. Thus, the population attributable fraction (PAF) may be used to estimate the extent to which risk factors, including PRS, age, sex, body mass index, and type 2 diabetes (T2D), mostly contribute to the burden of HCC on a population level.[4]

Hepatic fat content has a strong genetic background.[5] To date, a vast amount of genome-wide association studies (GWAS) have been performed in individuals of European descent.[6] However, genetic structure differs between populations with different ethnic components.[7] Inter-ethnic differences in susceptibility to fatty liver disease have also been emphasized in multi-ethnic population studies, where for example, the susceptibility to fatty liver disease is shown to be lowest in individuals of African descent, intermediate in Europeans, and higher in Hispanics, independent of the confounders.[7] Notably, since PRS is derived from GWAS and is mostly determined in individuals of European ethnicity, it may not be meaningful for individuals of other ethnicities. Failure to include populations from different ethnicities will hinder the application of genetic discoveries (such as PRS) to multi-ethnic individuals in clinical practice. The participants included in this study, which consisted of the general population (UK Biobank [UKBB] cohort, n = 364,048; 202 individuals with HCC) and at-risk individuals (NAFLD cohort, n = 2,566; 226 individuals with HCC; and a replication cohort of 427 German patients with NAFLD), were of European descent.[1]

Keywords: polygenic risk score; hepatocellular carcinoma; non-alcoholic fatty liver disease.
Received 19 December 2020; received in revised form 31 December 2020; accepted 7 January 2021; available online 18 January 2021
https://doi.org/10.1016/j.jhep.2021.01.010