Finally, the study provides an easy single-time prediction score for risk stratification of HCC in a limited setting. Further multi-ethnic studies are warranted for HCC prediction with better generalizability.

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Conflict of interest
The authors declare no conflicts of interest.

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Authors' contributions
NB – Writing – original draft, NV – Conceptualization, Writing – review and editing, VS – Conceptualization, Writing – review and editing.

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Reply to: "HCC prediction post SVR: many tools yet limited generalizability!"

De novo HCC risk stratification after HCV cure: All roads lead to Rome?

To the Editor:

We would like to thank Dr. Bhagat and colleagues[1] for their interest in our study on *de novo* hepatocellular carcinoma (HCC) risk stratification in compensated advanced chronic liver disease (cACLD) patients who achieved sustained virologic response (SVR).[2] The authors provided a summary of 11 selected risk stratification approaches and highlighted 5 points related to our study but also HCC risk stratification/screening in general.

The multiplicity of available risk stratification tools underlines the high scientific interest in this clinically relevant issue. While some approaches follow beaten tracks (simple algorithms based on conventional statistical methods; *e.g.*, Pons *et al.*[3]), complex artificial intelligence-based methods discovered alternative routes that are less obvious. However, several factors/variables are shared between models, indicating their key role in regard to the outcome *de novo* HCC: age and alpha-fetoprotein, next to surrogates of hepatic dysfunction (serum albumin) and liver fibrosis/portal hypertension (*i.e.*, liver stiffness measurement [LSM] and platelet count as well as its derivatives, such as the fibrosis-4 score). It is important to note that variable selection is determined by their availability in retrospective datasets, indicating that their intersections – *i.e.*, broadly available parameters – are likely overrepresented throughout the different risk stratification tools. Importantly, our derivation cohort of comprehensively characterized patients allowed for the selection of the best, rather than the best available predictors.

As addressed by Bhagat *et al.*[1] in their first point, ACLD was diagnosed by either hepatic venous pressure gradient measurement, LSM, or histology in our derivation cohort. However, this does not induce selection bias, as liver disease severity was staged by one or more of these methods in all patients undergoing antiviral therapy, due to implications for reimbursement and regimen selection. Moreover, the generalizability of our risk stratification approach to other predominately Caucasian patient cohorts was confirmed by extensive validation – which is of paramount importance in the context of predictive modeling, but has often been omitted

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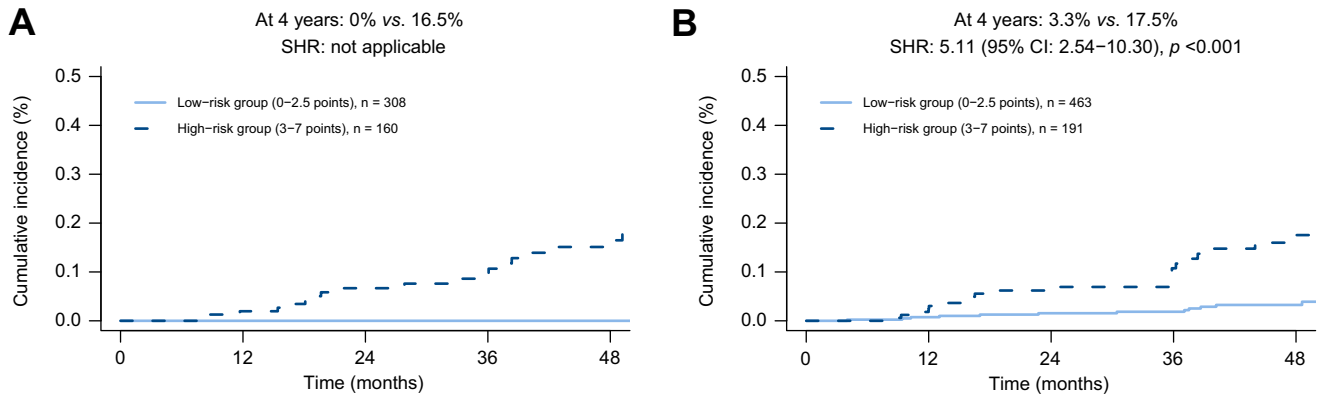

Fig. 1. Cumulative incidence curves (using Fine & Gray competing risk analysis) of *de novo* HCC development. Cumulative incidence based on the post-treatment AFP/age/alcohol/LSM/albumin-derived strata (low-risk [0-2.5 points] *vs.* high-risk [3-7 points]) in patients with compensated advanced chronic liver disease in (A) the derivation cohort and (B) the validation cohort. Two points are assigned for FU-AFP ≥4.6 ngxml^{-1}, 1.5 points for alcohol consumption above the threshold, 1.5 points for age ≥59 years, 1 point for FU-LSM ≥19 kPa, and 1 point for FU-albumin <42 gxL^{-1} (0 points if the respective criterion is not met). AFP, alpha-fetoprotein; FU, follow-up; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement.

by the other studies listed by Bhagat and colleagues.[1] We fully agree about the underrepresentation of patients from Asia or Africa in our study and have repeatedly emphasized (see Discussion of our manuscript and correspondence[4]) the need for studies in other ethnicities/ethnically diverse populations.[2]

Second, we are well-aware of the dynamics of hepatic inflammation/portal hypertension[5,6] – and thus, LSM – after SVR. However, the clinical utility of risk stratification tools is critically dependent on their robustness in regard to variations in care/data availability, *e.g.* the time point of LSM. Accordingly, we do not consider the differences in LSM time points between the derivation and validation cohorts as a limitation – it is rather a strength of our study, as the consistent predictive performance underlines the generalizability/robustness of our algorithms.

Third, we want to emphasize that our score was intended to be an easy-to-use tool aiding clinical decision making and is as such not intended to be the basis for HCC surveillance policies. Similarly, while class imbalance is hard to avoid in the context of our research, we agree that advanced sampling methods applying balancing techniques and machine learning are promising options to increase the accuracy of classification[7] (at the cost of increased statistical complexity and clinical impracticability).

Fourth, we agree that cost-effectiveness requires a critical appraisal and should ideally be evaluated in the context of specific health care systems, as the cost of screening and treatment options may vary substantially. While an HCC incidence threshold of 1.32%/year[8] has been proposed to maintain an incremental cost-effectiveness ratio (ICER) below 50,000USD/quality-adjusted life year (QALY), the underlying model did not account for recent advances in HCC treatment.[9] Finally, the individual benefit of an early diagnosis of HCC critically depends on age and comorbidities – thus, a recent study[10] even proposed stopping HCC surveillance at the age of 70 in cirrhosis and 60 in advanced liver fibrosis, despite applying an ICER threshold as high as 150,000USD/QALY. However, the latter approach neglects profound variations in HCC risk within individual stages of liver fibrosis, as highlighted by the independent risk factors other than LSM that were identified in our study.[2]

Regarding the fifth and final point by Dr. Bhagat and colleagues,[1] we acknowledge that regression coefficients rather than adjusted subdistribution hazard ratios may have been the preferred indicator for weighting of individual risk factors. Nevertheless, using the regression coefficients for assignment (importance: 1-1.5-2 *vs.* 1-2-3) together with a cut-off of 2.5 (instead of 3), the resulting classification of patients into risk groups would have yielded the same results as with the previous weighting (Fig. 1).

All things considered, it appears that many roads lead to Rome (*i.e.*, personalized management after SVR). However, while we have already established a highway (*i.e.*, Baveno VII) for the individualization of portal hypertension surveillance, we fully acknowledge that the road to personalized HCC surveillance remains bumpy.

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Conflict of interest
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Authors' contributions
Analysis and interpretation of data (G.S., E.L.M., M.M.), drafting of the manuscript (G.S., E.L.M., M.M.), critical revision of the manuscript for important intellectual content (G.S., E.L.M., M.M.).

Supplementary data
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