HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease

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HCC risk stratification after cure of hepatitis C in patients with cACLD

One-time assessment 12-48 weeks after end of treatment

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Proportion of patients</th>
<th>HCC incidence at 5 years (%)</th>
<th>BCLC (stages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (0-3)</td>
<td>70.8%</td>
<td>3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>High-risk (≥4)</td>
<td>29.2%</td>
<td>17.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

AFP/LSM/albumin-based
- AFP ≤ 6ng/mL → 3 points
- LSM >19kPa → 1 point
- Albumin <42g/L → 1 point
- Optionally: Alcohol consumption >30g/d / >20g/d, ≥ 2 points

LSM/albumin-based
- Age ≥50 years → 3 points
- LSM >19kPa → 2 points
- Albumin <42g/L → 2 points
- Optionally: Alcohol consumption >30g/d / >20g/d, ≥ 2 points

Notes:
- kPa: kilopascal
- BCLC: Barcelona Clinic Liver Cancer

Graphs show cumulative incidence of HCC over time.
HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease

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A.Z. has nothing to disclose.

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B.Si. received travel support from AbbVie and Gilead.

B.Sch. received travel support from AbbVie, Ipsen and Gilead.

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Ipsen, Eisai, Lilly, MSD, and Roche, and received travel support from Bayer and Bristol-Myers Squibb.

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ABSTRACT

Background&Aims: Hepatocellular carcinoma (HCC) is a main cause of morbidity and mortality in patients with advanced chronic liver disease (ACLD) due to chronic hepatitis C and who have achieved sustained virologic response (SVR).

We elaborated risk stratification algorithms for de-novo-HCC-development after SVR and validated them in an independent cohort.

Methods: Derivation cohort: 527 patients with pre-treatment ACLD and SVR to interferon-free therapy were evaluated for de-novo-HCC-development. Among others, alpha-fetoprotein (AFP) and non-invasive surrogates of portal hypertension including liver stiffness measurement (LSM) were assessed pre-/post-treatment. Validation cohort: 1500 patients with compensated ACLD (cACLD) from other European centers.

Results: During a median follow-up (FU) of 41 months, 22/475 cACLD (4.6%) (1.45/100 patient-years) vs. 12/52 decompensated patients (23.1%, 7.00/100 patient-years, p<0.001) developed de-novo-HCC. Since decompensated patients were at substantial HCC-risk, we focused on cACLD for all further analyses.

In cACLD, post-treatment-values showed a higher discriminative ability for patients with/without de-novo-HCC-development during FU than pre-treatment-values or absolute/relative changes. Models based on post-treatment AFP≥4.6ng/mL-1-3 points, alcohol consumption (males:>30g/d/females:>20g/d)-2 points (optional), age≥59years-2points, LSM≥19.0kPa-1point, and albumin<42gxL-1-1point, accurately predicted de-novo-HCC-development (bootstrapped Harrel’s C with and without considering alcohol:0.893 and 0.836). Importantly, these parameters also provided independent prognostic information in competing risk analysis and accurately stratified patients into low-(0-3points; ≈2/3 of patients) and high-risk (≥4points; ≈1/3) groups in the derivation (algorithm with alcohol consumption; 4-year HCC-risk:0%vs.16.5%) and validation
(3.3%/17.5%) cohorts. An alternative approach based on age/alcohol (optional)/FU-LSM/FU-albumin (i.e., without FU-AFP) also showed a robust performance.

**Conclusions:** Simple algorithms based on post-treatment age/albumin/LSM, and optionally, AFP and alcohol, accurately stratified *de-novo*-HCC-risk in cACLD patients with SVR. Approximately 2/3 were identified as having an HCC-risk <1%/y in both the derivation and validation cohort, thereby clearly falling below the cost-effectiveness threshold for HCC-surveillance.
LAY SUMMARY

Simple algorithms based on age, alcohol consumption, results of blood tests (albumin and α-fetoprotein), as well as liver stiffness measurement after the end of hepatitis C treatment identify a large proportion (approximately 2/3) of patients with advanced but still asymptomatic liver disease who are at very low risk (<1%/year) of liver cancer development, and thus, might not need to undergo 6-monthly liver ultrasound.
GRAPHICAL ABSTRACT

HCC risk stratification after cure of hepatitis C in patients with cACLD

One time assessment 12-48 weeks after end of treatment

AFPI/SM/albumin-based
AFPI > 6ng/mL → 3 points
Age ≥ 59 years → 2 points
LSM ≥ 15kPa → 1 point
Albumin < 42g/L → 1 point
Optionally: Alcohol consumption
>30g/day or >20g/day → 2 points

<table>
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<td>29.2%</td>
<td>17.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

LSM/albumin-based
Age ≥ 58 years → 3 points
LSM ≥ 15kPa → 2 points
Albumin < 42g/L → 2 points
Optionally: Alcohol consumption
>30g/day or >20g/day → 2 points

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<th>3-year HCC rate (median)</th>
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<tbody>
<tr>
<td>Low-risk (0.3)</td>
<td>66.1%</td>
<td>3.7</td>
<td>0.9</td>
</tr>
<tr>
<td>High-risk (0.4)</td>
<td>33.9%</td>
<td>11.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Note: α-fetoprotein; AFPI: AST/ALT ratio; SM: spleen to muscle ratio; LSM: liver stiffness measurement; pp: postpartum months; β: patients with a beta 1+ negative result; data shown are based on algorithms considering all patients recruited.
Introduction

Direct acting antiviral (DAA)-based interferon (IFN)-free therapies for chronic hepatitis C (CHC) are highly effective, achieving sustained virologic response (SVR; i.e., HCV-cure) in almost all patients with advanced chronic liver disease (ACLD) [1]. SVR following IFN-free treatment has not only been associated with improvements in surrogates of portal hypertension such as liver stiffness measurement (LSM) or von Willebrand factor (VWF) levels, but also with amelioration of portal hypertension as assessed by HVPG [2-6]. Decreases in portal hypertension severity translate into reductions in hepatic decompensation [5] and concordantly liver-related mortality [7-9]. Nevertheless, a considerable proportion of patients remains at risk of developing complications of ACLD. While the incidence of hepatic decompensation seems to be comparatively low [10] and non-invasive markers such as LSM and VWF/platelet count ratio (VITRO) facilitate risk stratification [11], de-novo HCC development remains a major concern. Specifically, the incidence of HCC ranged from 1.5-1.8 [10, 12] to 3.6/100 patient years [13, 14] in patients with ACLD/cirrhosis. Of note, clinically significant portal hypertension (CSPH, as defined by an HVPG ≥10mmHg) is accompanied by a 6-fold increased risk of HCC in compensated advanced chronic liver disease (cACLD), suggesting that the above-mentioned surrogates of portal hypertension may also indicate HCC risk [15]. While no data on VITRO is available, the occurrence of de-novo HCC has previously been associated with LSM as well as traditional HCC risk factors such as age, serum albumin, and AFP [8, 9, 16]. Several risk-prediction models have been proposed based on these and other factors; however, all of these previously published scores have yet to undergo external validation. Thus, no recommendation regarding the identification of a low-risk subgroup of ACLD patients in whom HCC surveillance is not cost-effective/warranted has been implemented in recent guidelines on the management and FU of CHC [17].
We investigated the incidence of de-novo HCC and its prediction in a comprehensively characterized cohort of ACLD patients from three tertiary centers and aimed to validate the elaborated prognostic algorithms in a large, independent validation cohort comprising cACLD patients from other European centers. In addition, we applied previously published risk prediction models to both cohorts to evaluate their prognostic accuracy.
Patients & methods

Derivation cohort
All patients achieving SVR after DAA-based IFN-free treatment at the Medical University of Vienna, Padua University Hospital, and Ordensklinikum Linz Barmherzige Schwestern with pre-treatment ACLD (defined as baseline [BL]-LSM ≥10kPa, HVPG ≥6mmHg, or advanced fibrosis/cirrhosis on liver histology [F3/4]) were screened for eligibility for this retrospective study based on prospectively collected data [18]. After excluding all patients with Child-Turcotte-Pugh (CTP) stage C who were not candidates for liver transplantation (i.e., patients in whom surveillance is not recommended [19]), a history or a current diagnosis of HCC, porto-sinusoidal vascular disease, previous orthotopic liver transplantation (OLT), or an HCC diagnosis/OLT during treatment from the dataset, 527 patients were included. Notably, subgroups of these patients have been previously investigated with regard to changes in HVPG and their prognostic value [4, 5], the diagnostic/predictive ability of non-invasive markers for portal hypertension and hepatic decompensation [11], the predictive value of VITRO for hepatic decompensation [20], the influence of genetic variants on liver disease regression [21], as well as changes in coagulation after HCV-cure [22]. However, none of these studies focused on HCC.

Clinical and laboratory parameters and liver stiffness measurement
Clinical and laboratory parameters were evaluated by chart review. Alcohol consumption above the threshold for non-alcoholic fatty liver disease was defined by >30g/day and >20g/day for males and females, respectively [23]. Plasma VWF antigen levels were measured by a latex agglutination assay (STA LIATEST VWF, Diagnostica Stago, Asnieres, France). VITRO score was calculated by dividing VWF (%) over PLT (G × L⁻¹), as described previously [24]. Paired measurements of non-invasive markers
were performed prior to antiviral therapy, as well as after the end of treatment (EoT). Due to the retrospective design of this study (and also due to logistical reasons), the time points were not standardized. Vibration-controlled transient elastography (FibroScan; Echosens, Paris, France) was used for LSM. All measurements were performed after a minimum fasting period of 4 hours and in the absence of relevant amounts of ascites.

**HCV therapy**

All patients were treated with IFN-free therapies. The choice of the regimen was at the physicians’ discretion and depended on their availability, reimbursement policies, and national as well as international clinical practice guidelines at the time of treatment initiation [25-29]. Treatment duration ranged from 8 to 24 weeks.

**HCC surveillance**

All patients underwent HCC surveillance either by ultrasound, computed tomography, or magnetic resonance imaging on a 6-monthly basis. HCC was diagnosed based on EASL clinical practice guidelines at the time [19, 30].

**Validation cohort**

Data was collected from 1500 patients with cACLD and without a history of HCC/OLT treated at other European centers (Hospital General Universitario Gregorio Marañón and Hospital Universitario 12 De Octubre [Madrid, Spain], Hospital Universitari Vall d’Hebron and Hospital Clínic [Barcelona, Spain], and Klinikum Ottakring [Vienna, Austria]). All patients achieved SVR after DAA-based IFN-free treatments. For the Spanish cohorts, details regarding in- and exclusion criteria as well as study design are provided in the individual publications [10, 31], whereas for patients from the other
Viennese hospital (Klinikum Ottakring) contributing to the derivation cohort, criteria/design were similar to the validation cohort (Supplementary Table 1). Patients with missing data on FU-LSM and FU-albumin were not considered for our analyses.

**Statistical analyses**

Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., USA) and R 4.0.5. (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as mean ± standard deviation or median (interquartile range), while categorical variables were reported as proportion of patients with/without a certain characteristic. Student’s t-test was used for group comparisons of normally distributed variables and Mann-Whitney-U test for non-normally distributed variables, respectively. Group comparisons of categorical variables were performed using either Pearson’s Chi-squared or Fisher’s exact test. The areas under the curve (AUC) and respective 95% confidence intervals (95%CI) of receiver operating characteristic (ROC) analyses were calculated for continuous variables using the R-package ‘cutpointr’, applying Youden’s J-statistic to obtain the respective optimized cut-offs for classifying patients regarding HCC development. To increase the reliability of these cut-offs, we performed bootstrap resampling of our cohort for 5000 times. Univariable and multivariable Cox regression analyses were performed using the R ‘survival’ package to investigate the association of individual (continuous and binary) parameters with HCC development. For further model development, backward elimination excluding variables with p>0.100 was applied to identify variables that provide certain information for HCC prediction. For these analyses, the time to event was calculated from the end of treatment, and patients were censored at OLT, death, or end of FU. Harrel’s C-indices for the respective models were derived using the R package ‘dynpred’ with bootstrap resampling for 5000 times to increase generalizability.
of these models. Fine and Gray competing risks regression models were calculated with the R package ‘cmprsk’ to test whether variables included in the final model were still independently associated with HCC when considering OLT and death as competing risks [32]. Finally, a score was derived from respective adjusted subdistribution hazard ratios (aSHR). Moreover, published prediction models were tested in our cohort using Gray's test for subdistribution hazards. A p-value ≤0.05 was considered statistically significant. As p-values served only descriptive purposes, no multiplicity correction was applied.

Ethics
This study (derivation cohort) was approved by the institutional review boards (IRB) of the Medical University of Vienna (EK 1947/2019), Upper Austria (K-49-14), and Padua University Hospital (3103/A0/14). Written informed consent was obtained, if the requirement was not waived by the local IRB. For the validation cohort, approval of local IRB (City of Vienna for Klinik Ottakring; as described previously for Madrid [31] and Barcelona [10]) was obtained.
Results

Patient characteristics of the derivation cohort

Three hundred and twenty-eight patients (62.2%) were male with a mean age of 57.3±11.1 years (Supplementary Table 2). 475 (90.1%) had compensated ACLD (cACLD) while 52 (9.9%) had not previously experienced any hepatic decompensation (dACLD). Varices were prevalent in 122 (23.1%) and 44 patients (8.3%) had CTP stage B/C, while 483 (91.7%) had CTP stage A with a mean MELD score of 8.6±2.8 points. During a median FU of 41 (32) months, 34 (6.5%) developed HCC corresponding to an HCC incidence of 1.78/100 patient years. Of note, 22 cACLD patients (4.6%) developed HCC (1.45/100 patient years) vs. 12 dACLD patients (23.1%, p<0.001, 7.00/100 patient years). Since patients with dACLD were at very high risk for de-novo HCC development, we abstained from merging them with cACLD patients. Moreover, the limited number of patients precluded dedicated analyses on risk factors for HCC in dACLD patients. Accordingly, all other analyses focused on cACLD.

Compensated advanced chronic liver disease subgroup of the derivation cohort

Patient characteristics of cACLD patients with and without HCC during FU (median 41 [33] months) are presented in Supplementary Table 3. Also, time points of FU-measurements are shown in Supplementary Figure 1A which clustered around 12 weeks after EoT. Differences in patient characteristics were observed for age, presence of varices and non-invasive markers of portal hypertension (i.e., LSM, PLT, VWF, and VITRO), hepatic function (i.e., MELD and serum albumin), as well as AST, AFP, and composite scores (i.e., APRI and FIB-4) both at BL and FU. Of note, none of the patients who developed HCC during FU had uncharacterized nodules at BL. Following univariable ROC analyses, a similar moderate accuracy (AUC <0.800) to identify HCC patients was evident for several continuous variables (Table 2).
Specifically, FU-albumin, FU-LSM, BL-VWF, BL-/FU-VITRO, FU-APRI, BL-/FU-FIB-4, BL-/FU-AFP showed an AUC of 0.700-0.800 with FU-AFP having the numerically highest AUC (0.796 [95%CI: 0.726-0.866]). Of note, FU variables tended to be more informative than BL parameters. Again, absolute and relative changes were considerably less accurate (AUC <0.700) with relative Δ LSM showing the highest AUC (0.674 [95%CI: 0.570-0.778]). These analyses indicated that single parameters are incapable of accurately predicting HCC development in the post SVR setting.

We aimed at identifying cut-offs that denote a high vs. low risk for HCC for the most promising parameters. Applying Youden’s J-statistics and bootstrap resampling, the following cut-offs were identified: Age ≥59.27 years, FU-albumin <42g x L⁻¹, FU-LSM ≥19.0kPa, FU-PLT <190G x L⁻¹, FU-VWF ≥186%, FU-VITRO ≥1.02, FU-FIB-4 ≥1.93, and FU-AFP ≥4.6ng x mL⁻¹ (Table 3, Supplementary Figure 2). We abstained from further analyzing APRI, as it basically contains the same information as FIB-4, but FU-FIB-4 yielded a higher AUC.

*Cox regression analyses and model estimation in the derivation cohort*

Next, we performed Cox regression analyses including dichotomized FU-values of non-invasive parameters and age as a central risk-factor, since these values were superior or equally accurate as compared to BL-values, and the utilization of data obtained at a single time point may facilitate the clinical application of the resulting risk prediction model (Table 4). We also included alcohol consumption above the threshold, while we did not include metabolic factors, since no statistically significant associations with HCC-development were evident (Supplementary Table 4).

Following significant univariable associations with HCC development, seven different multivariable models were built based on combinations of these variables. All of them
accurately predicted HCC, however, FU-FIB-4, FU-VWF, and FU-VITRO were not independently associated with HCC development. Following backward elimination, the models comprising age ≥59 years, FU-AFP ≥4.6ng x mL⁻¹, FU-LSM ≥19kPa, and FU-albumin <42.0g x L⁻¹ with and without alcohol consumption above the threshold showed the highest predictive ability (Harrel’s C: 0.893 and 0.874), while the same models without FU-AFP ≥4.6ng x mL⁻¹ also showed a high discriminative ability (Harrel’s C: 0.836 and 0.815).

**Competing risk analysis and modelling of a score**

To test whether the parameters included in the final version of models 5 and 7 (including alcohol) provided independent information for the prediction of HCC, while accounting for OLT and death as competing risks, we performed a competing risk regression analysis (Table 5). Importantly, all parameters were independently associated with HCC development during FU.

A simple score was derived from adjusted (subdistribution) hazard ratios assigning 3 points for FU-AFP ≥4.6ng x mL⁻¹, 2 points for age ≥59 years, 2 points for alcohol consumption above the threshold, 1 point for FU-LSM ≥19kPa, and 1 point for FU-albumin <42g x L⁻¹ (0 points were assigned if the respective criterion was not met). Following this approach, the derivation cohort was stratified according to the number of assigned points (Supplementary Figure 3). The subdistribution hazard ratio (SHR) was 2.47 (95%CI: 1.91-3.19, p<0.001) per point. Patients were then grouped into low-risk (0-3 points, n=308 [65.8%]) and high-risk (4-9 points, n=160 [34.2%]). Of note, 61.4% of the low-risk group had a BL- or FU-LSM value ≥12.5kPa [33], and thus, showed evidence of cirrhosis. This dichotomization identified patients at very low and
substantial risk of HCC at 4 years: 0% vs. 16.5% (Figure 1A; HCC incidence rate per 100 patient years: 0 vs. 4.3).

Since AFP is not routinely assessed at many centers, we also tested whether a simple score derived from the adjusted (subdistribution) hazard ratios of model 6 (i.e., without AFP) was also able to stratify HCC risk. We assigned 3 points for age ≥59 years, 2 points for alcohol consumption above the threshold, 2 points for FU-albumin <42g x L$^{-1}$, and 2 points for FU-LSM ≥19kPa and stratified the patients into low-risk (0-3 points, n=322 [68.8%]) and high-risk (4-9 points, n=146 [31.2%]). The HCC risk at 4 years was 1.3% vs. 14.8% (SHR: 13.70 [95%CI: 4.02-46.40], p<0.001; Figure 1B; HCC incidence per 100 patient years: 0.3 vs. 3.9).

Finally, both approaches also yielded a high discriminative ability without including alcohol consumption above the threshold as a variable, thereby acknowledging uncertainties regarding the quantification of alcohol consumption (AFP-based algorithm at 4 years: 0.5% vs. 16.7% [SHR: 21.90 (95%CI: 5.10-94.00), p<0.001]; non-AFP-based algorithm: 1.8% vs. 15.0% [SHR: 10.90 (95%CI: 3.67-32.40), p<0.001]; Supplementary Figure 4AB).

**External validation of proposed risk scores**

In an attempt to externally validate these findings, we tested these four scores in an independent validation cohort comprising patients from Madrid, Barcelona, and another Viennese center (validation cohort). Overall, 691 patients were included in the validation cohort for the FU-AFP-based algorithm, while 1500 patients were included in the validation cohort for the algorithm without FU-AFP. Despite small differences existing for age and FU-LSM, disease severity, FU time and HCC incidence were
comparable (Table 1). In the validation cohort, FU-measurements clustered around 48 weeks after EoT (Supplementary Figure 1B).

As depicted in Figure 2, both approaches including alcohol consumption as a risk factor efficiently stratified the risk of HCC during FU with a probability of 3.3% vs. 17.5% developing HCC within 4 years according to the AFP-based algorithm (SHR: 5.11 [95%CI: 2.54-10.30], p<0.001; HCC incidence per 100 patient years: 0.9 vs. 4.4) and 3.7% vs. 11.6% developing HCC within 4 years according to the algorithm solely based on age, alcohol consumption, FU-albumin, and FU-LSM (SHR: 3.46 [95%CI: 2.05-5.84], p<0.001; HCC incidence per 100 patient years: 0.9 vs. 3.0). Comparable results were achieved without considering alcohol consumption as a risk factor (Supplementary Table 4CD).

**Sensitivity analysis stratifying patients according to time between EoT and FU-LSM**

Both scores considering alcohol maintained an adequate discriminative ability when combining the derivation and validation cohort and stratifying patients into tertiles of the time between EoT and FU-LSM (Supplementary Figure 5).
Discussion

In the present study, we investigated predictive factors for HCC development in patients with cACLD who achieved SVR to IFN-free therapies. We focused on patients with ACLD, since HCC incidence has been reported to be significantly higher in patients with ACLD/advanced liver fibrosis or cirrhosis [8, 12, 34] (and this is also reflected by current European surveillance recommendations [35]). We provided an easily applicable score that facilitates risk stratification in clinical routine, as it identified patients in whom HCC surveillance may not be cost-effective (low-risk) or in whom surveillance is clearly warranted (high-risk; i.e., AFP ≥4.6ng x mL⁻¹ OR age ≥59 years WITH either FU-LSM ≥19kPa AND/OR FU-albumin <42g x L⁻¹) due to a considerable probability of de-novo HCC despite SVR. Importantly – and in contrast to most previous attempts – our proposed algorithms underwent extensive external validation, which is critical due to the profound implications of a delayed diagnosis of HCC that may result from an unwarranted termination of surveillance due to an underestimation of HCC risk. The analysis of the multicenter validation cohort confirmed that approximately two thirds of patients (i.e., those who do not meet the above-mentioned high-risk criteria) are classified as low-risk and that these patients exhibit an HCC risk <1%/year. Accordingly, the incidence of HCC in these patients clearly falls below the cost-effectiveness threshold (at 50.000 USD/quality-adjusted life year) for HCC surveillance, which has been estimated at 1.32/year [17, 36]. Of note, this low-risk group also included a large proportion (61.4%) of patients with evidence of cirrhosis, indicating that current recommendations to identify at-risk patients who should undergo US surveillance have very limited accuracy.

Our approach has important advantages that may promote its application in the clinic. First, a ‘one-time’ assessment after treatment (e.g., around 12 weeks after EoT or up 48 weeks after EoT) is easily applicable in clinical routine, since patients can be
stratified according to their individual risk of HCC while confirming SVR. In addition, HCC risk stratification can be combined with the evaluation of the probability of hepatic decompensation by additionally assessing FU-PLT and FU-VWF to calculate the FU-VITRO score [11]. In contrast, if approaches rely on BL values, they cannot be applied later in case of incomplete pre-treatment work-up or unavailable information (due to changes in treatment center), leaving these patients unclassified. Similarly, consideration of absolute/relative changes seems particularly problematic, as it doubles the number of required variables, and thus, with the chance of missing information.

Secondly, our approach combines indicators of liver fibrosis and portal hypertension (i.e., LSM [37]) and hepatic dysfunction (i.e., serum albumin) with age (a strong driver of carcinogenesis in general [38]) and AFP – a broadly available biomarker that is commonly applied for HCC surveillance in clinical routine [39] and obligatory according to Asian Pacific for The Study of Liver, optional according to American Association for the Study of Liver Disease, and not recommended due to concerns about cost-effectiveness by European Association for the Study of the Liver (EASL) clinical practice guidelines [19]. However, the latter clinical practice guidelines also emphasize that the use of AFP should be reevaluated in patients who achieved etiological cure, as it may perform better after the amelioration of hepatic inflammation [19]. Interestingly, AFP showed the highest individual AUC for HCC development during FU and was considered as a binary variable in our risk prediction model at a cut-off of ≥4.6ng x mL⁻¹. Interestingly, this AFP cut-off is considerably lower when compared to the cut-offs proposed for HCC surveillance that were either 20 or 200ng x mL⁻¹ [40]. However, AFP usually decreases with HCV-cure (e.g., -2.5ng x mL⁻¹ or -41.3% in our study) and the proposed application of AFP (i.e., for risk stratification) differs from its
common use as a biomarker for HCC surveillance (i.e., diagnosis of [very] early-stage HCC).

Considerable evidence supports the use of LSM for predicting HCC risk in patients who achieved SVR, and which was recently summarized by a meta-analysis [41]. However, specific cut-offs for identifying patients at relevantly increased risk varied substantially according to the studied population, ranging from ≥20kPa [42] and >21.5kPa [43] to >30kPa [44, 45] pre-treatment and ≥10kPa post-treatment [10, 42]. Although several studies proposed that absolute and relative changes in LSM are related to HCC development (e.g., [46]), they showed (if at all) modest prognostic value in our series of patients. Moreover, when compared to the non-invasive diagnosis of CSPH and prediction of hepatic decompensation, the predictive ability of LSM for HCC seems inferior [11], which argues for the consideration of additional variables in order to increase prognostic accuracy.

The combination of high LSM and AFP with the traditional risk factors such as old age and low serum albumin might optimize previous approaches: these were often established in studies that were based on less thoroughly characterized patient cohorts, and were therefore unable to establish synergistic effects between these variables [10, 31, 47, 48]. Importantly, we have also included alcohol consumption above the threshold as a (modifiable) risk factor. Alcohol consumption has previously been associated with the development of HCC after SVR [12, 49-51] and – according to the Baveno VII recommendations – prohibits the discharge of cACLD patients who achieved SVR from portal hypertension surveillance. The consideration of alcohol consumption highlights the importance of this co-factor for progressive liver disease after SVR [11] even resulting in an increased liver-related mortality [52] and this may raise awareness both for physicians and patients. Fully acknowledging uncertainties regarding the quantification of alcohol consumption, we have confirmed that our risk
scores perform appropriately and do not require any modifications, even if alcohol consumption is not considered. Although diabetes and metabolic comorbidities have been discussed as other potential risk factors for HCC in the post-SVR context, we did not observe such a significant association [49]. Of note, our score does not include composite variables such as VITRO (which had a higher AUC than its individual components, VWF and PLT) or FIB-4, since none of these scores was predictive of HCC, when also considering other variables. Currently, the EASL (2020) clinical practice guidelines for the treatment of hepatitis C do not recommend a personalized surveillance strategy [35], and thus, a 6-monthly ultrasound surveillance is recommended in all patients with pre-treatment advanced liver fibrosis (F3) or cirrhosis (F4). Importantly, this approach might not be cost-effective, especially not in patients who only have advanced liver fibrosis (F3) pre-treatment [17]. A recent analysis estimated that the number of HCC surveillance candidates with SVR will increase more than 6-fold from 2012 to 2030 [53]. Therefore, personalized surveillance strategies are urgently needed to optimize resource utilization and these surveillance strategies should be based on a comprehensive evaluation of de-novo HCC risk – such as our proposed algorithms – rather than the pre-treatment liver fibrosis stage [36].

Since a late diagnosis of HCC has serious implications for the outcome of an individual patient, extensive external validation is mandatory, before risk stratification approaches are applied in the clinic to identify low-risk patients in whom HCC surveillance can be deferred. Therefore, we also evaluated previously proposed approaches based on the cACLD subgroup of our derivation cohort and the validation cohort. In this context, several specific aspects of individual scoring/grading systems were notable, and these are extensively discussed in the Supplementary information. Of note, the international multicenter design increases the generalizability of our findings. Since we only included specialized centers, we were able to acquire a large,
comprehensively characterized derivation cohort that provided information on the vast majority of potential predictors of HCC development in ACLD patients who achieved SVR. However, presumably the most important strength of our study is the external validation of our algorithms in up to 1500 patients from different centers across Europe. Although there were statistically significant differences in patient characteristics, the differences between cohorts were very small (<10%) for variables considered in our prognostic models (age and FU-LSM). Moreover, slight variations between the derivation and validation dataset may even increase the generalizability of our models. The main limitation of our study is its retrospective design, which introduced considerable variability regarding the time point for the assessment of post-treatment data. These measurements were clustered around 12 weeks after EoT in our derivation cohort and around 48 weeks after EoT in the validation cohort. These differences are mainly due to the design of the contributing studies [10, 31] as well as limited patient compliance and capacity restrictions. However, the heterogeneity in the assessment time point may actually improve the robustness and generalizability of our risk stratification approach, as it showed an excellent discriminative ability both in the derivation and validation cohort, despite differences in the time point of assessment.

In addition, sensitivity analyses using time point-dependent stratification revealed that the discriminative ability of our risk stratification approach was maintained at all assessment time points. Accordingly, the lack of standardization may also be seen as a strength of our study, as some variation in the time point of assessment will be unavoidable in ‘real-world’ clinical practice, and thus, risk stratification systems should show a robust performance under rather unstandardized conditions to ascertain external validity.

Similar to the variability in the time point of post-treatment measurements, HCC surveillance prior to therapy and EoT was not standardized. However, all patients had
at least one unsuspicious imaging after EoT. Currently, it is recommended that HCC surveillance be pursued lifelong since a similar HCC-incidence over time after SVR to IFN-free [34] and IFN-based [13] therapies has been reported. However, our study cannot provide information on the long-term risk of HCC, and this is an unavoidable limitation of all studies available to date. Accordingly, long-term studies are warranted: these should also address the question of whether a re-evaluation of the laboratory/elastography parameters at a later time point may refine risk stratification regarding events occurring during long-term FU. Since the vast majority of included patients was of Caucasian ethnicity (>90%), it remains to be shown whether our findings can be extrapolated to other ethnicities. Especially data from Asia are needed to confirm the accuracy of the proposed algorithms.

In conclusion, based on our international multicenter study, we developed and externally validated simple algorithms for HCC prediction in cACLD patients who achieved SVR to IFN-free treatments, comprising a set of broadly available parameters, which were all evaluated at a single post-treatment time point. Approximately two thirds of patients were identified to have an HCC risk <1%/year, thereby clearly falling below the cost-effectiveness threshold for HCC surveillance.
Abbreviations:

ACLD advanced chronic liver disease
AFP alpha-fetoprotein
AUC area under the curve
BL baseline
cACLD compensated ACLD
CHC chronic hepatitis C
CSPH clinically significant portal hypertension
CTP Child-Turcotte-Pugh
dACLD decompensated ACLD
EoT end of treatment
FIB-4 fibrosis-4-index
FU follow-up
HCC hepatocellular carcinoma
HE hepatic encephalopathy
HVPG hepatic venous pressure gradient
IFN interferon
IQR interquartile range
LSM liver stiffness measurement
MELD model of end-stage liver disease
OLT liver transplantation
PLT platelet count
ROC receiver operating characteristic
SVR sustained virologic response
VITRO von Willebrand factor antigen/platelet count ratio
VWF von Willebrand factor
Acknowledgements: Not applicable.
REFERENCES


**FIGURE LEGEND**

**Figure 1.** (A) Cumulative incidence curves (using competing risk analysis) of *de-novo* hepatocellular carcinoma (HCC) development of the post-treatment (follow-up [FU]) alpha-fetoprotein (AFP)/age/alcohol/liver stiffness measurement (LSM)/albumin-derived strata (low-risk [0-3 points] vs. high-risk [4-9 points]) in compensated advanced chronic liver disease (cACLD) patients of the derivation cohort. 3 points are assigned for FU-AFP ≥4.6ng x mL⁻¹, 2 points for alcohol consumption above the threshold, 2 points for age ≥59 years, 1 point for FU-LSM ≥19kPa, and 1 point for FU-albumin <42g x L⁻¹ (0 points if the respective criterion is not met). (B) Similar analysis based on the age/alcohol/LSM/albumin-derived score (i.e., without FU-AFP). Cumulative incidences are displayed according to low risk (0-3 points) and high risk (4-9 points) assignment. 3 points are assigned for age ≥59 years, 2 points for alcohol consumption above the threshold, 2 points for FU-LSM ≥19kPa, and 2 points for FU-albumin <42g x L⁻¹ (0 points if the respective criterion is not met).

**Figure 2.** (A) Cumulative incidence curves (using competing risk analysis) of *de-novo* hepatocellular carcinoma (HCC) development of the post-treatment (follow-up [FU]) alpha-fetoprotein (AFP)/age/alcohol/liver stiffness measurement (LSM)/albumin-derived strata (low-risk [0-3 points] vs. high-risk [4-9 points]) in compensated advanced chronic liver disease (cACLD) patients of the validation cohort. 3 points are assigned for FU-AFP ≥4.6ng x mL⁻¹, 2 points for alcohol consumption above the threshold, 2 points for age ≥59 years, 1 point for FU-LSM ≥19kPa, and 1 point for FU-albumin <42g x L⁻¹ (0 points if the respective criterion is not met). (B) Similar analysis based on the age/alcohol/LSM/albumin-derived score (i.e., without FU-AFP). Cumulative incidences are displayed according to low risk (0-3 points) and high risk (4-9 points) assignment.
3 points are assigned for age ≥59 years, 2 points for alcohol consumption above the threshold, 2 points for FU-LSM ≥19kPa, and 2 points for FU-albumin < 42g x L⁻¹ (0 points if the respective criterion is not met).
**Table 1.** Comparison of patient characteristics at baseline (BL) and follow-up (FU), as well as duration of FU and incidence of hepatocellular carcinoma (HCC) between compensated advanced chronic liver disease (cACLD) patients in the derivation cohort.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Derivation cohort, cACLD, n=475</th>
<th>Validation cohort</th>
<th>Validation cohort</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.6±11.3</td>
<td>59.1±12.3</td>
<td>61.4±11.7</td>
<td>0.024</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>296 (62.3%)</td>
<td>435 (63.0%)</td>
<td>840 (56.0%)</td>
<td>0.825</td>
<td>0.015</td>
</tr>
<tr>
<td>Female</td>
<td>179 (37.7%)</td>
<td>256 (37.0%)</td>
<td>660 (44.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>438 (92.2%)</td>
<td>654 (94.9%)</td>
<td>1278 (96.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>30 (6.3%)</td>
<td>13 (1.9%)</td>
<td>15 (1.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7 (1.5%)</td>
<td>20 (2.9%)</td>
<td>22 (1.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin-American</td>
<td>0 (0%)</td>
<td>2 (0.3%)</td>
<td>6 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL-albumin, g x L⁻¹</td>
<td>41.5±4.2</td>
<td>41.3±4.5</td>
<td>41.3±4.4</td>
<td>0.452</td>
<td>0.343</td>
</tr>
<tr>
<td>BL-LSM, kPa</td>
<td>16.0 (14.3)</td>
<td>15.0 (13.1)</td>
<td>16.3 (12.5)</td>
<td>0.745</td>
<td>0.402</td>
</tr>
<tr>
<td>BL-PLT, G x L⁻¹</td>
<td>157±65</td>
<td>155±68</td>
<td>150±66</td>
<td>0.709</td>
<td>0.048</td>
</tr>
<tr>
<td>BL-AFP, ng x mL⁻¹</td>
<td>6.5 (10.7)</td>
<td>6.7 (9.0)</td>
<td>6.7 (9.0)</td>
<td>0.413</td>
<td>0.388</td>
</tr>
<tr>
<td>BMI, kg x m²</td>
<td>26.9±5.0 (n=470)</td>
<td>27.2±4.5 (n=503)</td>
<td>26.9±4.4 (n=1096)</td>
<td>0.305</td>
<td>0.942</td>
</tr>
<tr>
<td>≥30kg x m²</td>
<td>108 (23.0%)</td>
<td>115 (22.9%)</td>
<td>221 (20.2%)</td>
<td>0.966</td>
<td>0.210</td>
</tr>
<tr>
<td>Diabetes¹</td>
<td>79 (16.6%)</td>
<td>118 (17.1%)</td>
<td>274 (18.3%)</td>
<td>0.842</td>
<td>0.418</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below the threshold²</td>
<td>443 (93.3%)</td>
<td>605 (92.5%)</td>
<td>1206 (93.7%)</td>
<td>0.627</td>
<td>0.736</td>
</tr>
<tr>
<td>Above the threshold²</td>
<td>32 (6.7%)</td>
<td>49 (7.5%)</td>
<td>81 (6.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-albumin, g x L⁻¹</td>
<td>43.2±3.7</td>
<td>43.0±4.4</td>
<td>43.3±3.9</td>
<td>0.338</td>
<td>0.855</td>
</tr>
<tr>
<td>FU-LSM, kPa</td>
<td>11.8 (10.9)</td>
<td>10.4 (9.0)</td>
<td>10.4 (8.7)</td>
<td>0.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FU-PLT, G x L⁻¹</td>
<td>170±69</td>
<td>168±66</td>
<td>159±68</td>
<td>0.479</td>
<td>0.003</td>
</tr>
<tr>
<td>FU-AFP, ng x mL⁻¹</td>
<td>3.6 (3.3)</td>
<td>3.3 (2.8)</td>
<td>3.3 (2.8)</td>
<td>0.201</td>
<td>0.201</td>
</tr>
<tr>
<td>FU time³</td>
<td>42.4 (39.6-45.1)</td>
<td>44.4 (42.7-46.0)</td>
<td>40.4 (39.7-41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>22 (4.6%)</td>
<td>36 (5.2%)</td>
<td>65 (4.3%)</td>
<td>0.655</td>
<td>0.783</td>
</tr>
<tr>
<td>Incidence/100 patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>years</td>
<td>1.45</td>
<td>1.74</td>
<td>1.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Fasting blood glucose >125mg x dL⁻¹, HbA1c ≥6.5%, or antidiabetic medication.

² >30g/day and >20g/day for males and females, respectively (1).

³ According to the reverse Kaplan-Meier method.
(n=475), the alpha-fetoprotein (AFP)-based validation cohort (n=691) and the non-AFP-based validation cohort (n=1500).
Table 2

Table 2. Area under the curve (AUC) values of receiver operating characteristic (ROC) analyses of pre-treatment (baseline [BL]) and post-treatment (follow-up [FU]) parameters, as well as their absolute and relative changes, for predicting hepatocellular carcinoma (HCC) development during FU in patients with compensated advanced chronic liver disease (cACLD) in the derivation cohort.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC (95%CI)</th>
<th>Parameter</th>
<th>AUC (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.664 (0.546-0.782)</td>
<td>Absolute Δ albumin, g x L⁻¹</td>
<td>0.541 (0.423-0.658)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative Δ albumin, %</td>
<td>0.534 (0.414-0.654)</td>
</tr>
<tr>
<td>BL-albumin, g x L⁻¹</td>
<td>0.691 (0.586-0.796)</td>
<td>Absolute Δ LSM, kPa</td>
<td>0.610 (0.476-0.744)</td>
</tr>
<tr>
<td>FU-albumin, g x L⁻¹</td>
<td>0.714 (0.594-0.835)</td>
<td>Relative Δ LSM, %</td>
<td>0.674 (0.570-0.778)</td>
</tr>
<tr>
<td>BL-LSM, kPa</td>
<td>0.631 (0.522-0.741)</td>
<td>Absolute Δ Δ albumin, %</td>
<td>0.502 (0.381-0.622)</td>
</tr>
<tr>
<td>FU-LSM, kPa</td>
<td>0.713 (0.621-0.805)</td>
<td>Relative Δ PLT, %</td>
<td>0.526 (0.399-0.662)</td>
</tr>
<tr>
<td>BL-PLT, G x L⁻¹</td>
<td>0.687 (0.598-0.776)</td>
<td>Absolute Δ VWF, %</td>
<td>0.551 (0.427-0.675)</td>
</tr>
<tr>
<td>FU-PLT, G x L⁻¹</td>
<td>0.674 (0.580-0.768)</td>
<td>Relative Δ VWF, %</td>
<td>0.502 (0.380-0.625)</td>
</tr>
<tr>
<td>BL-VWF, %</td>
<td>0.723 (0.635-0.811)</td>
<td>Absolute Δ VITRO</td>
<td>0.601 (0.478-0.724)</td>
</tr>
<tr>
<td>FU-VWF, %</td>
<td>0.687 (0.577-0.798)</td>
<td>Relative Δ VITRO, %</td>
<td>0.503 (0.373-0.633)</td>
</tr>
<tr>
<td>BL-AST</td>
<td>0.567 (0.445-0.689)</td>
<td>Absolute Δ AST</td>
<td>0.516 (0.378-0.653)</td>
</tr>
<tr>
<td>FU-AST</td>
<td>0.631 (0.519-0.744)</td>
<td>Relative Δ AST, %</td>
<td>0.516 (0.387-0.645)</td>
</tr>
<tr>
<td>BL-ALT</td>
<td>0.501 (0.376-0.626)</td>
<td>Absolute Δ ALT</td>
<td>0.543 (0.409-0.676)</td>
</tr>
<tr>
<td>FU-ALT</td>
<td>0.598 (0.483-0.714)</td>
<td>Relative Δ ALT, %</td>
<td>0.586 (0.463-0.709)</td>
</tr>
<tr>
<td>BL-APRI</td>
<td>0.677 (0.560-0.794)</td>
<td>Absolute Δ APRI</td>
<td>0.600 (0.463-0.738)</td>
</tr>
<tr>
<td>FU-APRI</td>
<td>0.702 (0.594-0.809)</td>
<td>Relative Δ APRI, %</td>
<td>0.509 (0.376-0.642)</td>
</tr>
<tr>
<td>BL-FIB-4</td>
<td>0.730 (0.648-0.812)</td>
<td>Absolute Δ FIB-4</td>
<td>0.627 (0.517-0.737)</td>
</tr>
<tr>
<td>FU-FIB-4</td>
<td>0.720 (0.627-0.813)</td>
<td>Relative Δ FIB-4, %</td>
<td>0.543 (0.421-0.665)</td>
</tr>
<tr>
<td>BL-AFP</td>
<td>0.720 (0.655-0.785)</td>
<td>Absolute Δ AFP</td>
<td>0.631 (0.526-0.737)</td>
</tr>
<tr>
<td>FU-AFP</td>
<td>0.796 (0.726-0.866)</td>
<td>Relative Δ AFP, %</td>
<td>0.536 (0.421-0.652)</td>
</tr>
</tbody>
</table>
Table 3. Area under the curve (AUC) values following receiver operating characteristic (ROC) analyses of post-treatment (follow-up [FU]) parameters for predicting hepatocellular carcinoma (HCC) development during FU in patients with compensated advanced chronic liver disease (cACLD), and the respective Youden-optimized cut-offs, both without and after bootstrapping, in the derivation cohort.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC (95%CI)</th>
<th>Youden-optimized cut-off</th>
<th>Bootstrapped AUC</th>
<th>Bootstrapped Youden-optimized cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.664 (0.546-0.782)</td>
<td>59.27</td>
<td>0.67</td>
<td>59.24</td>
</tr>
<tr>
<td>FU-albumin, g x L^-1</td>
<td>0.714 (0.594-0.835)</td>
<td>42.0</td>
<td>0.71</td>
<td>42.0</td>
</tr>
<tr>
<td>FU-LSM, kPa</td>
<td>0.713 (0.621-0.805)</td>
<td>19.0</td>
<td>0.71</td>
<td>19.0</td>
</tr>
<tr>
<td>FU-PLT, G x L^-1</td>
<td>0.674 (0.580-0.768)</td>
<td>198.5</td>
<td>0.67</td>
<td>190</td>
</tr>
<tr>
<td>FU-VWF, %</td>
<td>0.687 (0.577-0.798)</td>
<td>186</td>
<td>0.69</td>
<td>186</td>
</tr>
<tr>
<td>FU-VITRO</td>
<td>0.713 (0.613-0.813)</td>
<td>0.95</td>
<td>0.71</td>
<td>1.02</td>
</tr>
<tr>
<td>FU-FIB-4</td>
<td>0.720 (0.627-0.813)</td>
<td>1.70</td>
<td>0.72</td>
<td>1.93</td>
</tr>
<tr>
<td>FU-AFP, ng x mL^-1</td>
<td>0.796 (0.726-0.866)</td>
<td>4.6</td>
<td>0.80</td>
<td>4.6</td>
</tr>
<tr>
<td>Parameter</td>
<td>Univariate analyses</td>
<td>Hazard ratio and 95% confidence interval</td>
<td>( P ) value</td>
<td>Backward elimination – First step</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
<td>----------------------------------------</td>
<td>-------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Age ≥59 years</td>
<td>5.454 (1.835-16.210)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-albumin ≥42 g x L&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>5.642 (2.067-15.400)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-PLT ≥1900 x L&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>9.619 (1.290-71.750)</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-VWF ≥186%</td>
<td>3.491 (1.354-9.005)</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-VITRO ≥1.02</td>
<td>3.704 (1.244-11.030)</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-AFP ≥4.6 ng x mL&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>17.130 (3.988-73.570)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-LSM ≥19.0 kPa</td>
<td>4.739 (1.964-11.440)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU-FIB-4 ≥1.93</td>
<td>4.535 (1.334-15.420)</td>
<td>0.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption above the threshold&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3.106 (1.044-9.244)</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 1

Parameter: FU-FIB-4 ≥1.93

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.341 (0.970-11.500)</td>
<td>0.059</td>
<td>3.341 (0.970-11.500)</td>
<td>0.059</td>
<td></td>
<td>0.720</td>
</tr>
<tr>
<td>4.639 (1.682-12.800)</td>
<td>0.003</td>
<td>4.639 (1.682-12.800)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 2

Parameter: FU-FIB-4 ≥1.93, FU-albumin <42.0

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.629 (0.455-5.832)</td>
<td>0.453</td>
<td>-</td>
<td>-</td>
<td></td>
<td>0.841</td>
</tr>
<tr>
<td>3.236 (1.140-9.188)</td>
<td>0.027</td>
<td>4.012 (1.463-11.000)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.721 (0.645-4.952)</td>
<td>0.278</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.575 (2.616-51.220)</td>
<td>0.001</td>
<td>13.797 (3.191-59.650)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 3

Parameter: Age ≥59, FU-albumin <42.0, FU-VITRO ≥1.02, FU-AFP ≥4.6

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.164 (1.392-12.455)</td>
<td>0.011</td>
<td>4.107 (1.374-12.280)</td>
<td>0.011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.321 (1.172-9.409)</td>
<td>0.024</td>
<td>3.789 (1.379-10.410)</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.715 (0.549-5.358)</td>
<td>0.354</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.555 (2.389-46.625)</td>
<td>0.002</td>
<td>11.713 (2.694-50.930)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 4

Parameter: Age ≥59, FU-albumin <42.0, FU-VITRO ≥1.02, FU-AFP ≥4.6

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.500 (2.168-19.490)</td>
<td>&lt;0.001</td>
<td>6.500 (2.168-19.490)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.068 (1.464-11.300)</td>
<td>0.008</td>
<td>4.068 (1.464-11.300)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.644 (1.886-11.430)</td>
<td>&lt;0.001</td>
<td>4.644 (1.886-11.430)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 5

Parameter: Age ≥59, FU-albumin <42.0, FU-LSM ≥19.0, Alcohol consumption above the threshold<sup>1</sup>

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.203 (2.846-29.770)</td>
<td>&lt;0.001</td>
<td>9.203 (2.846-29.770)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.865 (1.394-10.720)</td>
<td>0.009</td>
<td>3.865 (1.394-10.720)</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.285 (2.103-13.280)</td>
<td>&lt;0.001</td>
<td>5.285 (2.103-13.280)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.252 (1.631-16.910)</td>
<td>0.005</td>
<td>5.252 (1.631-16.910)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 6

Parameter: Age ≥59, FU-albumin <42.0, FU-AFP ≥4.6

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.496 (1.781-16.959)</td>
<td>0.003</td>
<td>5.496 (1.781-16.959)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.229 (1.165-8.945)</td>
<td>0.025</td>
<td>3.229 (1.165-8.945)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.806 (2.161-44.502)</td>
<td>0.003</td>
<td>9.806 (2.161-44.502)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Model 7

Parameter: Age ≥59, FU-albumin <42.0, FU-AFP ≥4.6

<table>
<thead>
<tr>
<th>Hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adjusted hazard ratio and 95% confidence interval</th>
<th>( P ) value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.496 (1.781-16.959)</td>
<td>0.003</td>
<td>5.496 (1.781-16.959)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.229 (1.165-8.945)</td>
<td>0.025</td>
<td>3.229 (1.165-8.945)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.806 (2.161-44.502)</td>
<td>0.003</td>
<td>9.806 (2.161-44.502)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Hazard Ratio (95% CI)</td>
<td>P-value</td>
<td>Hazard Ratio (95% CI)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------</td>
<td>---------</td>
<td>-----------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>FU-LSM ≥19.0</td>
<td>3.150 (1.240-8.000)</td>
<td>0.016</td>
<td>3.150 (1.240-8.000)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption above the threshold</td>
<td>6.758 (2.152-21.227)</td>
<td>0.001</td>
<td>6.758 (2.152-21.227)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

1. >30g/day and >20g/day for males and females, respectively (1).
2. Calculated from Cox regression analyses.
3. Stepwise exclusion of variables with p>0.100.
4. Calculated from last step of backward elimination using bootstrapped Harrel's C-indices.

**Table 4.** Cox regression analyses on risk factors for hepatocellular carcinoma (HCC) development in patients with compensated advanced chronic liver disease (cACLD) in the derivation cohort. Parameters have been dichotomized according to the Youden’s index-optimized cut-offs (see Table 3).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted subdistribution hazard ratio</th>
<th>95% confidence interval</th>
<th>P value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥59 years</td>
<td>4.76</td>
<td>1.72-13.18</td>
<td>0.003</td>
</tr>
<tr>
<td>FU-albumin ≤42.0 g x L(^{-1})</td>
<td>3.12</td>
<td>1.08-8.98</td>
<td>0.035</td>
</tr>
<tr>
<td>FU-AFP ≥4.6 ng x mL(^{-1})</td>
<td>8.85</td>
<td>1.77-44.22</td>
<td>0.008</td>
</tr>
<tr>
<td>FU-LSM ≥19.0 kPa</td>
<td>2.64</td>
<td>1.04-6.71</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**Model 7**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted subdistribution hazard ratio</th>
<th>95% confidence interval</th>
<th>P value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥59 years</td>
<td>5.55</td>
<td>2.25-13.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FU-albumin ≤42.0 g x L(^{-1})</td>
<td>3.21</td>
<td>1.11-9.25</td>
<td>0.031</td>
</tr>
<tr>
<td>FU-AFP ≥4.6 ng x mL(^{-1})</td>
<td>9.94</td>
<td>2.45-40.40</td>
<td>0.001</td>
</tr>
<tr>
<td>FU-LSM ≥19.0 kPa</td>
<td>3.15</td>
<td>1.14-8.67</td>
<td>0.026</td>
</tr>
<tr>
<td>Alcohol consumption above the threshold</td>
<td>6.70</td>
<td>1.79-25.05</td>
<td>0.005</td>
</tr>
</tbody>
</table>

\(^1\) Calculated from Fine and Gray competing risks regression.

**Table 5.** Adjusted subdistribution hazard ratio of dichotomized risk factors for hepatocellular carcinoma (HCC) development during follow-up (FU) in compensated advanced chronic liver disease (cACLD) patients in the derivation cohort using competing risk analysis classifying liver transplantation and death as competing risks.
REFERENCES

A

at 4 years: 0.0% vs. 16.5%
SHR: NA

Cumulative incidence (%)

Time (months)

Low-risk group, n=308
High-risk group, n=160

B

at 4 years: 1.3% vs. 14.8%
SHR: 13.70 (95% CI: 4.02-46.40), p<0.001

Cumulative incidence (%)

Time (months)

Low-risk group, n=322
High-risk group, n=146
A

at 4 years: 3.3% vs. 17.5%
SHR: 5.11 (95% CI: 2.54-10.30), p<0.001

Cumulative incidence (%)

Time (months)

Low-risk group, n=463
High-risk group, n=191

B

at 4 years: 3.7% vs. 11.6%
SHR: 3.46 (95% CI: 2.05-5.84), p<0.001

Cumulative incidence (%)

Time (months)

Low-risk group, n=851
High-risk group, n=436
HIGHLIGHTS

- 475 and 1500 cACLID patients were studied for de-novo-HCC-development after SVR.
- Algorithms based on post-treatment age/albumin/LSM, and optionally, AFP and alcohol consumption, accurately stratified de-novo-HCC-risk.
- Approximately 2/3 of patients were identified as having an HCC-risk <1%/year.
- In these patients, HCC-surveillance might not be cost-effective.