Long-term outcome and risk stratification in compensated advanced chronic liver disease after HCV-cure

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FOOTNOTE PAGE

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ABSTRACT (275 words)

Background & Aims: World-wide, around 750.000 patients/year will be cured from hepatitis C-virus (HCV) infection until 2030. Those with compensated advanced chronic liver disease (cACLD) remain at risk for hepatic decompensation and *de-novo* hepatocellular carcinoma (HCC). Algorithms have been developed to stratify risk within the first post-treatment years, however, data on long-term outcome and the prognostic utility of these risk stratification algorithms at later timepoints are lacking.

Methods: We retrospectively analysed 2335 cACLD patients (LSM≥10kPa) who achieved HCV-cure by interferon-free therapies from 15 European centres. The incidence of first hepatic decompensation and HCC were studied during a median follow-up of 6years. Published risk stratification algorithms were evaluated by competing risk regression analyses.

Results: Median age before HCV-cure was 60.2±11.9years, 21.1% were obese, and 21.2% had diabetes. Hepatic decompensation occurred in 84 patients (3.6%,incidence rate [IR]:0.74%/year, cumulative incidence at 6 years:3.2%); 183(7.8%) patients developed *de-novo* HCC (IR:1.60%/year, cumulative incidence at 5 years:8.3%), with both risks being strictly linear over time.

Baveno VII criteria to exclude (FU-LSM<12kPa&FU-PLT>150G/L) or rule-in (FU-LSM≥25kPa) clinically significant portal hypertension (CSPH) accurately stratified the risk of hepatic decompensation with proportional hazards. Estimated probability of CSPH was the strongest individual factor associated with hepatic decompensation in the grey-zone (i.e., patients not meeting these criteria).

HCC risk stratification algorithms were capable of discriminating between high- and low-incidence groups, however, the size of the latter group varied substantially (9.9%-69.0%).

Conclusions: In patients with cACLD, the risks of hepatic decompensation and HCC remain constant after HCV-cure, even in the long-term (>3years). A one-time post-treatment risk stratification based on non-invasive criteria provides important prognostic information that is maintained during long-term follow-up, as the hazards remain proportional over time.

INTRODUCTION

The number of individuals treated for and cured of hepatitis C virus (HCV) infection worldwide is expected to be approximately 750,000 per year until 2030 [1]. In those with compensated advanced chronic liver disease (cACLD), the risks of hepatic decompensation and *de-novo* hepatocellular carcinoma (HCC) are reduced but not eliminated by HCV-cure [2, 3]. Thus, risk stratification is key to decrease resource utilization by individualizing post-treatment management. Previous studies have shown that portal hypertension is ameliorated after HCV-cure [4, 5] and that the presence or absence of post-treatment (FU) clinically significant portal hypertension (CSPH) is the decisive factor for the occurrence of hepatic decompensation [4, 6]. In the initial post-treatment phase, liver stiffness measurement (LSM) and platelet count (PLT) can be used to stratify the risk of hepatic decompensation by ruling-in CSPH (FU-LSM ≥25kPa; i.e., high-risk population) or excluding CSPH (FU-LSM <12kPa & FU-PLT ≥150G/L; i.e., negligible risk) [7]. However, the long-term impact of metabolic comorbidities, especially of ongoing alcohol consumption or diabetes is unclear. Similarly, numerous HCC risk stratification algorithms have been proposed [3, 8, 9], but their long-term prognostic accuracy remains to be evaluated.

Thus, we assembled a cohort of thoroughly characterized cACLD patients from 15 European centres to evaluate whether the incidences of hepatic decompensation and HCC decrease with time after HCV-cure and whether the discriminative ability of a one-time post-treatment assessment is maintained during long-term follow-up.

METHODS

Patients

We included 2335 cACLD (as defined by LSM ≥10kPa [10, 11]) patients undergoing interferon-free therapy from 15 European centres: 9 from Spain (Hospital General Universitario Gregorio Marañón, Hospital Universitario 12 De Octubre, Hospital Universitario Fundación Alcorcón, Hospital Universitario Ramón y Cajal, Hospital Universitario Fundación Jiménez Díaz, Hospital Universitario Clínico San Carlos, and Hospital Universitario La Princesa Madrid [Madrid]; Vall d'Hebron University Hospital and Hospital Clínic [Barcelona]), 3 from Austria (Medical University of Vienna and Klinik Ottakring [Vienna]; Ordensklinikum Linz Barmherzige Schwestern [Linz]), 2 from Italy (University of Bologna [Bologna] and Padua University Hospital [Padua]), and 1 from Germany (Hannover Medical School [Hannover]). Specifically, only patients with paired LSM and platelet count (PLT) at baseline (BL), i.e., before, and at follow-up (FU), i.e., after HCV-cure were analysed. Patients with hepatic decompensation or HCC before or during therapy were excluded.

Collected parameters

Patients were characterized at BL by collecting data on body mass index (BMI), diabetes, arterial hypertension, statin use, and alcohol consumption as assessed from patient records, together with laboratory parameters regarding metabolic comorbidities (serum glucose, triglycerides, and total cholesterol). These data were complemented by data on LSM and laboratory parameters characterizing liver disease severity (PLT, model for end-stage liver disease score components, and serum albumin) and activity (AST, ALT, and GGT) assessed before and after HCV-cure. Due to the retrospective design of this study, the time points for FU-assessment

were not standardized. Vibration-controlled transient elastography (FibroScan; Echosens, Paris, France) was used for LSM and performed by experienced operators, as previously described [12]. Fibrosis-4 (FIB-4) score was calculated based on the previously published formula [13].

Risk stratification algorithms

To predict hepatic decompensation, patients were grouped as proposed by Semmler et al (2022)[7] into patients in whom CSPH could be ruled-in (FU-LSM ≥25kPa) or excluded (FU-LSM <12kPa & FU-PLT ≥150G/L) leaving the rest in the diagnostic 'grey-zone'. Also, the predicted probability of post-treatment CSPH was calculated based on the nomograms provided in Semmler et al (2022)[7] and Abraldes et al (2016)[14].

Since alpha-fetoprotein was available only in a subset of patients, the following algorithms for HCC risk stratification that have specifically been developed for the cACLD/post-SVR setting were evaluated:

- Pons et al (2020)[2]: Patients with FU-LSM ≥20kPa or FU-LSM 10-20 kPa + FU-albumin <44g/L were assigned to the high-risk group.
- Semmler et al (2022)[3]: 3 points were assigned for age ≥59years, 2 points for FU-LSM ≥19kPa, 2 points for FU-albumin <42g/L, and 2 points for alcohol abuse (>30g/d ♂ / >20g/d ♀). Patients with 0-3 and ≥4 points were assigned to the low-risk and high-risk group, respectively.
- Alonso et al (2020)[8] LSM score: 1 point for BL-LSM >17.3kPa, decrease <25.5%, or BL-albumin <42.0g/L; FIB-4 score: 1 point for BL-FIB-4 >3.7 or FU-FIB4 >3.3, 2 points for BL-albumin <42g/L or FU-GGT >42U/L. Patients with ≥1 point(s) were assigned to the high-risk group.

Additionally, the prognostic utility of the more universal aMAP score was evaluated:

- Fan et al (2020)[15]: 0.06 × age + 0.89 × sex (male sex =1) + 0.48 × [(log_{10} bilirubin × 0.66) + (albumin * [-0.085])] – 0.01 × PLT + 7.4)/ 14.77 × 100. The aMAP score was calculated based on BL- and FU-values of the respective parameters. Patients <50 points were assigned to the low-risk group, while those with >60 points were assigned to the high-risk group.

Clinical follow-up

Data on the clinical course during FU including occurrence of ascites, variceal bleeding, and hepatic encephalopathy as well as data on *de-novo* HCC development, transjugular intrahepatic portosystemic shunt (TIPS) placement, orthotopic liver transplantation (OLT), or death were assessed starting after end-of-treatment.

Statistics

Statistical analyses were performed using R 4.3.0 (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. Group comparisons of categorical variables were performed using Chi-squared test. Missing data necessary for risk stratification algorithms (i.e., BL-AST, BL-ALT, BL-albumin, BL-bilirubin, FU-AST, FU-ALT, FU-GGT, FU-albumin, FU-bilirubin missing in <5%) were imputed by applying nearest neighbour matching based on age, sex, BL-/FU-LSM, BL-/FU-PLT, BL-/FU-albumin, BL-/FU-bilirubin, BL-/FU-AST, BL-/FU-ALT, BL-/FU-GGT, and BL-/FU-FIB-4.

Median survival was calculated by applying the reverse Kaplan-Meier method [16] and graphically illustrated as recommended by the STRATOS initiative [17].

Incidence rates in the overall cohort were calculated from end-of-treatment per 100 patient-years, respectively.

For all analyses on predictive/prognostic performance, time-to-event analyses started from the time of FU-LSM, and patients with hepatic decompensation or HCC before FU-LSM or no follow-up thereafter were excluded. Cumulative incidence functions were calculated with the 'cmprsk'-package to account for competing risks. Cumulative incidences were compared applying Fine & Gray competing risks regression models adjusted for clustering across centres as provided by the 'crrSC'-package. Landmark analyses were performed to test the predictive ability of proposed scores regarding events that occurred exclusively after >3 years after end-of-treatment. Cause-specific Cox proportional hazard regression analyses using the R 'survival' package were performed to study factors associated with hepatic decompensation in the overall cohort and the diagnostic 'grey-zone' adjusting for clustering across centers as random effect. Discrimination was assessed by applying Uno's C statistics to adjust for right-censored data by time-dependent weighting.

A p-value ≤0.05 was considered statistically significant.

Ethics

This study was approved by the institutional ethics committees of the individual centres. Written informed consent was obtained, if the local ethics committees did not waive its requirement.

RESULTS

Patient characteristics

Two thousand three hundred and thirty-three cACLD patients were included. The mean age was 60.2±11.9 years and 1388 (59.4%) were male (Table 1). Before treatment, median BL-LSM was 16.6 (12.4-25.0) kPa, including 585 (25.1%) with ≥25 kPa before treatment. At BL, median PLT was 144 (104-191) G/L including 1234 (52.8%) patients with <150 G/L. Median pre-treatment FIB-4 was 3.39 (2.02-5.77).

After treatment, median FU-LSM was 10.9 (7.8-17.1) kPa, with 1002 (42.9%) patients having a decrease to <10 kPa and 302 (12.9%) with FU-LSM ≥25 kPa. FU-PLT was 156 (114-204) G/L and FU-FIB4 2.14 (1.39-3.36).

Regarding metabolic comorbidities before aetiological cure, mean BMI was 26.8±4.5 kg/m² with 446 (21.1%) being obese (BMI ≥30 kg/m²); 494 (21.2%) and 321 (17.9%) had diabetes and prediabetes, respectively. Eight hundred fifty-four (39.9%) suffered from arterial hypertension and 318 (15.8%) from hypertriglyceridemia. one thousand seven hundred seventy-eight (84.3%) were abstinent, One hundred seventy-two (8.2%) reported regular consumption of small amounts of alcohol (i.e., compatible with the upper limit for metabolic dysfunction-associated steatotic liver disease (MASLD), while 158 (7.5%) reported significant alcohol consumption above the threshold for alcoholic liver disease (MetALD/ALD) (i.e., >30 g/day and >20 g/day for men and women)[18].

Constant long-term risk of hepatic decompensation and HCC

As detailed in Table 2 and Supplementary figure 1, patients were followed for a median of 6.0 (5.9-6.1) years. During this time, hepatic decompensation occurred in

84 (3.6%) corresponding to an incidence rate of 0.74/100 patient-years. Of note, 66 (2.8%) events of hepatic decompensation occurred prior to HCC.

One hundred eighty-three (7.8%) patients developed *de-novo* HCC, corresponding to an incidence rate of 1.60/100 patient-years. Of these, 173 (7.4%) developed HCC before hepatic decompensation.

Finally, 187 (8.0%) patients died, of which 57 (2.6%) were considered liver-related. This corresponds to incidence rates of 1.59/100 patient-years and 0.62/100 patient-years for any death and liver-related death, respectively. Importantly, the risks of hepatic decompensation and HCC were strictly linear over time (Figure 1), corresponding to a 6-year cumulative incidence of 3.2% for hepatic decompensation and 8.3% for HCC.

Risk stratification for hepatic decompensation and HCC by one-time assessments after HCV-cure

FU risk stratification was performed at a median of 7.2 (3.7-12.9) months after end of treatment.

Hepatic decompensation: Applying Baveno VII criteria to exclude (FU-LSM <12kPa & FU-PLT >150G/L) or rule-in (FU-LSM ≥25kPa) CSPH, we identified 884 (39.0%) patients (CSPH excluded) at negligible risk of future hepatic decompensation (at 6 years: 0.4%, Figure 2A). Conversely, FU-LSM ≥25kPa (CSPH ruled-in) identified 285 patients (12.6%) with a high risk of hepatic decompensation (at 6 years 14.3%, subdistribution hazard ratio [SHR] vs. CSPH excluded: 34.22 [95%CI: 13.80-84.90], p<0.001 In the remaining patients (n=1099, 48.5%) who remained in the diagnostic

grey-zone, the risk of hepatic decompensation was low (2.6%, SHR: 5.55 [95%CI: 2.60-11.80], p<0.001).

De-novo HCC: When patients were stratified according to Semmler et al (2022), 1564 (69.0%) patients were assigned to the low-risk group with a 6.2% cumulative incidence of HCC at 6 years (Figure 2B). In contrast, 704 (31.0%) patients in the high-risk group had a 6-year cumulative incidence of 15.6% and a significantly higher risk of HCC (SHR: 2.67 [95%CI: 1.81-3.93], p<0.001).

Notably, all published risk scoring systems were able to identify patient groups with a significantly higher/lower risk as compared to their counterparts (Supplementary table 1). However, there was substantial variation in the distribution of patients, ranging from 9.9% (Fan et al [2020] – BL) to 69.0% (Semmler et al [2022]) for the low-risk groups and from 31.0% (Semmler et al [2022]) to 79.1% (Alonso et al [2020] – LSM) for the high-risk groups. Consequently, the cumulative incidence at 6 years ranged from 1.6% to 6.2% in the low-risk groups and from 10.7% to 15.6% in the high-risk groups. Based on the discriminative ability, Alonso et al (2020) – FIB-4 (SHR: 3.96 [95%CI: 2.08-7.53], p<0.001) and Fan et al (2020) – FU (SHR: 11.53 [95%CI: 4.19-31.72], p<0.001) best discriminated the low-risk from the high-risk group, however, only 25.9% and 12.8% were included in the low-risk group, respectively, and 47.2% remained unclassified in the algorithm by Fan et al (2020).

Proportional hazards: For all risk assessment approaches, the hazards of hepatic decompensation or HCC were strictly proportional over the first 6 years after removal of the primary aetiological factor, indicating that a one-time risk assessment maintains its discriminative power even during long-term follow-up.

Landmark analyses: Limiting the prediction of hepatic decompensation or HCC to events after 2 years and patients with at least 2 years of follow-up (i.e., landmark

analysis), all algorithms could discriminate between low-risk vs. high-risk (Supplementary figure 3).

External validation: Applying the algorithm to exclude or rule-in CSPH only in patients that have not been used in Semmler et Lens et al (2022)[19] (i.e., patients from Madrid, Barcelona, Bologna, and Hannover; n=1514), results were comparable (Supplementary figure 4). Since only 300 patients have not been used for derivation or validation of the risk stratification algorithm for *de-novo* HCC by Semmler et al (2022)[3], there was no rationale for attempting external validation.

Factors associated with hepatic decompensation

Investigating metabolic factors associated with hepatic decompensation in the overall cohort, only BMI and significant alcohol consumption were linked to hepatic decompensation in cause-specific Cox proportional hazard regression models, while age, sex, diabetes, arterial hypertension, and hypertriglyceridemia were not associated (Supplementary table 2). As expected, FU-LSM, FU-PLT, FU-albumin, FU-GGT, FU-MELD, and FU-FIB-4 were significantly associated with hepatic decompensation. On multivariable analyses, however, only FU-LSM, FU-PLT, FU-albumin and FU-GGT remained independent predictors. Combining these four parameters achieved a high discriminative ability to identify patients with future hepatic decompensation (Uno's C: 0.873 [standard error (SE): 0.026], Supplementary table 3). Further adjusting for metabolic comorbidities (BMI, alcohol consumption) did not increase discriminative ability. Noteworthy, however, using the LSM/PLT-based nomogram to predict the probability of post-treatment CSPH according to Semmler and Lens et al (2022)[19] and Abraldes et al (2016)[20] achieved a similarly high

discriminative accuracy alone (Uno's C: 0.873 [SE: 0.022] and 0.875 [SE: 0.022], respectively).

Factors associated with hepatic decompensation in the 'grey-zone'

As a substantial proportion (48.5%) of patients remained in the 'grey-zone' regarding CSPH, predictors of the occurrence of hepatic decompensation were investigated in this specific subgroup (n=1099). As the number of events was generally low in this group (n=22), we abstained from performing multivariable regression models. Similar to hepatic decompensation in the overall cohort, FU-LSM, FU-PLT, FU-albumin, and CSPH-probability were identified as factors predictive of hepatic decompensation in these patients, with the latter estimated according to Semmler and Lens et al (2022) (Uno's C: 0.684 [SE: 0.087]) and Abraldes et al (2016) (Uno's C: 0.663 [SE: 0.104]) (Supplementary table 4).

Factors associated with elevated GGT

See supplementary materials.

DISCUSSION

In the present study, we evaluated 2335 cACLD patients cured of HCV who were thoroughly characterized by NIT before and after treatment from 15 European centers and 5 countries, respectively, representing the largest cohort of its kind to date. We specifically focused on patients with pre-treatment cACLD, as this is the target population for surveillance measures regarding hepatic decompensation and HCC. Patients were followed for a median of 6 years, being the longest follow-up period after aetiological cure to interferon-free treatment to date.

Hepatic decompensation was rare (overall incidence rate 0.76%/year), which is in line with previous studies reporting an annual incidence of 0.31-0.96% [2, 6]. Notably, the cumulative incidence of the competing event non-liver-related death exceeded the risk of hepatic decompensation only after ~3 years of post-treatment follow-up. The crossing curves are explained by a surge in non-liver-related death rather than a decrease in hepatic decompensation, with the prior being likely attributable to the aging of the patient population Importantly, HCC occurred more frequently (incidence rate 1.60%/year) than either of the aforementioned events, again within the range of previously published studies (e.g., 1.3-1.8%/year)[2, 3, 21-23].

Importantly, we observed a strikingly linear risk for both hepatic decompensation and HCC, in contrast to several previous reports. Two recent studies have raised hopes for a decrease in HCC incidence after HCV cure: The meta-analysis by Lockart and colleagues (2022)[23] showed a lower incidence rate of HCC in studies with longer follow-up suggesting a declining incidence in the long-term. In studies with a median follow-up <2 years, HCC incidence was 2.7/100 patient-years, while it was 1.9/100 patient-years in those with ≥2 years. However, these data have to be interpreted with caution due to general limitations of a meta-analytical approach in this context.

Ioannou et al (2019)[24] observed a decreasing yearly incidence after HCV-cure by interferon-free regimens in the short-term, i.e., up to 4 years after treatment initiation, although only half of patients were followed until this time point. Interestingly, this finding contrasts with long-term observations in patients undergoing interferon-based regimens that were reported in the same study, questioning the generalizability of the findings in the cohort of patients treated by interferon-free regimens. Unfortunately, our data paint a less encouraging picture, with a constant risk of HCC over time. Moreover, our study suggests that the observation of a constant long-term risk also applies to hepatic decompensation as the second major adverse liver-related outcome after HCV cure.

Regarding the prediction of hepatic decompensation, the Baveno VII criteria to exclude (FU-LSM <12kPa & FU-PLT >150G/L) or rule-in (FU-LSM ≥25kPa) CSPH have been validated in the long-term and allocated ~10% of cACLD patients to the high-risk group, while >1/3 of patients were identified as having a negligible risk, which – in the absence of cofactors – warrants discontinuation of portal hypertension surveillance. In general, patients in the grey-zone had a very low risk of first hepatic decompensation (2.6% at 6 years). Importantly, although CSPH can neither excluded nor ruled-in in this specific subgroup of patients, the estimated probability of CSPH according to published nomograms (Semmler et al [2022][19] and Abraldes et al [2016][20]) was the main predictive factor for hepatic decompensation in this subgroup. This finding extends the notion that NIT reflect a continuum of risk to cACLD patients achieving HCV-cure.

In general, liver disease severity as assessed by FU-LSM, FU-PLT, and FU-albumin were the most relevant predictive factors of future hepatic decompensation. However, FU-GGT provided independent prognostic information. This is likely explained by FU-

GGT being a surrogate metabolic liver disease, as indicated by its associations with metabolic factors as well as alcohol consumption in our study – in line with this, an elevated GGT was associated with a less pronounced relative decrease in LSM. Interestingly, we found that metabolic comorbidities per se were of limited relevance in predicting the occurrence of hepatic decompensation when liver disease severity and FU-GGT were also considered. However, these findings do not undermine the importance of lifestyle intervention, which is downstream in the pathophysiological cascade, whereas the other factors are upstream surrogates of risk.

Given the steady incidence of *de-novo* HCC despite removal of the primary aetiological factor, risk stratification is of major clinical relevance. Although the incidence is lower than in active HCV infection, a recent study even found numerically higher incidence rates in patients with cirrhosis who achieved HCV-cure, as compared to patients with cirrhosis due to alcoholic liver disease or non-alcoholic fatty liver disease [21]. Therefore, cACLD patients cured from HCV will remain a key target group for HCC risk stratification. We show that all studied algorithms were able to stratify patients according to their HCC risk, but due to their comparatively low discriminatory power (compared to hepatic decompensation), all risk stratification criteria represent a trade-off between missing *de-novo* HCC (~1%/year when applying Semmler et al[3] or Pons et al[2]) and identifying an insignificant proportion of patients in whom screening may be avoided (Fan et al[15] and Alonso et al[8]). All things considered, in resource-rich settings, these algorithms are primarily useful for counselling patients who find HCC surveillance burdensome and consider discontinuing surveillance, while in resource-poor settings, they allow for the most effective use of limited resources by restricting HCC surveillance to the high-risk populations according to Semmler et al[3] or Pons et al[2].

Nevertheless, the limited discriminative ability of the investigated risk stratification algorithms based on broadly available data indicates the need to incorporate/investigate HCC-directed biomarkers (e.g., alpha-fetoprotein [3, 25], which however, would have only been available in a subgroup of patients).

The present study has several limitations. First, timepoints of follow-up assessment were not standardized due to the retrospective design and multicenter study. This was, however, mitigated by studying prognostication from the time point of FU-assessment (i.e., focusing on the prediction of future events rather than associations), and by adjusting for clustering as random effect. Second, follow-up data are right-censored, and therefore subject to survivorship bias. Third, only patients with paired NIT before and after HCV-cure were studied, as numerous data have shown that re-assessment after removal of the primary aetiological factor improves the prognostic value of respective NITs. However, this introduces a certain selection bias. Fourth, HCC risk score(s) did not include data on AFP, as they were not universally available. As the primary risk stratification algorithm proposed by Semmler et al[3] was derived based on a model that included AFP, the prognostic performance would likely have been improved. Finally, we have recently shown that dynamics in LSM increase the prognostic utility as compared to static values, and thus, repeating LSM (and other parameters) at a later time-point may have further refined prognostication[26]. However, recommendations to repeat LSM in cACLD at a yearly basis have only emerged very recently, i.e., with Baveno VII[10]. Nevertheless, a one-time post-treatment assessment of NIT maintained its prognostic value in a land-mark analysis restricted to a period starting after 2 years, indicating that even a single post-treatment assessment holds long-term prognostic information.

In conclusion, in patients with cACLD, the risks of hepatic decompensation and HCC remain constant after HCV-cure, even in the long-term. A one-time post-treatment risk stratification based on non-invasive criteria provides important prognostic information that is maintained during long-term follow-up, as the hazards remain proportional over time.

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