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Prediction of hepatocellular carcinoma in Hepatitis C patients with advanced fibrosis after sustained virologic response

Short title: Prediction for HCC in HCV- SVR patients

Jessica Azzi¹; Céline Dorival¹; Carole Cagnot²; Hélène Fontaine³; Clovis Lusivika-Nzinga¹; Vincent Leroy⁴; Victor De Ledinghen⁵; Albert Tran^{6,7,8}; Fabien Zoulim⁹; Laurent Alric¹⁰; Jérôme Gournay¹¹; Jean-Pierre Bronowicki¹²; Thomas Decaens¹³; Ghassan Riachi¹⁴; Nabil Mikhaïl^{15,16}; Reham Soliman^{15,17}; Gamal Shiha^{15,18}; Stanislas Pol^{3,19}; Fabrice Carrat^{1,20}; Nathalie Ganne-Carrié^{21,22,23} for the ANRS-AFEF Hepather Study group.

¹Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France; ²ANRS (France Recherche Nord & Sud Sida-HIV Hépatites), Unit for Basic and Clinical Research on Viral Hepatitis, Paris, France; ³AP-HP, Hôpital Cochin, Unité d'Hépatologie, Paris, France; ⁴Department of Hepatology and Gastroenterology, Hôpital Henri Mondor, AP-HP, Université Paris-Est, INSERM U955, Créteil, France; ⁵Hepatology Unit Hôpital Haut-Lévêque, Pessac, INSERM U1053, Université Bordeaux Segalen, Bordeaux, France; ⁶Université Côte d'Azur, Nice, France; ⁷CHU de Nice, Digestive Center, Nice, France; ⁸INSERM, U1065, C3M, Team 8 « Chronic liver diseases associated with obesity and alcohol », Nice, France; ⁹Department of Hepatology, Hospices Civils de Lyon, INSERM U1052, Université de Lyon, Lyon, France; ¹⁰Department of Internal Medicine and Digestive Diseases, CHU Purpan, UMR 152 Pharma Dev, IRD Toulouse 3 University, France; ¹¹Gastroenterology and Hepatology Department, Institut des Maladies de l'Appareil Digestif, University Hospital of Nantes, Nantes, France; ¹²Inserm U1254 and Department of Hepato-Gastroenterology, University Hospital of Nancy Brabois, Université de Lorraine, Vandoeuvre-les-Nancy, France; ¹³Department of Hepatology and Gastroenterology, CHU Grenoble-Alpes; Université Grenoble-Alpes; Institute for

Advanced Biosciences INSERM U1209, Grenoble, France; ¹⁴Department of Hepatology and Gastroenterology, CHU Charles Nicolle, Rouen, France; ¹⁵Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt; ¹⁶Biostatistics and Cancer Epidemiology Department, South Egypt Cancer Institute, Assiut University, Assuit, Egypt; ¹⁷Tropical Medicine Department, Faculty of Medicine, Port Said University, Port Said, Egypt; ¹⁸Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt; ¹⁹Université de Paris, INSERM U1223 and USM-20, Institut Pasteur, Paris, France; ²⁰AP-HP, Sorbonne Université, Hôpital Saint-Antoine, Santé Publique, Paris, France; ²¹AP-HP, Hôpitaux Universitaires Paris Seine Saint-Denis, APHP, Liver Unit, Bobigny, France; ²²Université Sorbonne Paris Nord, Bobigny, France; ²³Inserm, UMR-1138 « Functional Genomics of solid tumors », Centre de Recherche des Cordeliers, Université de Paris, France.

Corresponding Author:

Pr Nathalie Ganne-Carrié

Service d'hépatologie, Hôpital Avicenne, 125 rue de Stalingrad, 93000 Bobigny, France

Tel : + 33 1 48 02 62 94 Fax : + 33 1 48 02 62 02 Mail : nathalie.ganne@aphp.fr

Declaration of interests:

J. Azzi, C. Dorival, C. Cagnot, N. Mikhal, R. Soliman and G. Shiha have nothing to disclose.

H. Fontaine reports personal fees and invitations for medical meeting from Gilead, Abbvie, BMS, MSD, Janssen, outside this work.

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Author's Contributions:

Study concept and design: Nathalie Ganne-Carrié, Fabrice Carrat.

Acquisition of data: Céline Dorival, Stanislas Pol, Hélène Fontaine, Nabil Mikhal, Reham Soliman, Gamal Shiha

Analysis and interpretation of data: Jessica Azzi, Fabrice Carrat, Nathalie Ganne-Carrié, Nabil Mikhal, Gamal Shiha

Drafting of the manuscript: Jessica Azzi, Fabrice Carrat, Nathalie Ganne-Carrié.

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Jessica Azzi, Clovis Lusivika-Nzinga, Fabrice Carrat, Nabil Mikhal, Reham Soliman

Administrative, technical and material support: Céline Dorival, Carole Cagnot, Fabrice Carrat

Study supervision: Nathalie Ganne-Carrié, Fabrice Carrat, Stanislas Pol, Hélène Fontaine

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Abbreviations: AFP: alfa-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; CI: confidence intervals; DAA: Direct Anti-viral agents; GGT: Gamma glutamyl-transferase; HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HR: hazard ratio; IDI: Integrated discrimination improvement; IQR: interquartile range; NRI: Net Reclassification Index; OS: overall survival; SVR: sustained virological response;

ANRS-AFEF Hepather Study group

Delphine Bonnet, Virginie Payssan-Sicart, Chloe Pomes (CHU Purpan, Toulouse, France), François Bailly, Marjolaine Beaudoin, Dominique Giboz, Kerstin Hartig-Lavie, Marianne Maynard (Hospices Civils de Lyon, Lyon, France), Eric Billaud, David Boutoille, Morane Cavellec, Caroline Chevalier (Hôpital Hôtel-Dieu, Nantes, France), Isabelle Hubert, Pierre Goepfert, Adrien Lannes, Françoise Lunel, Jérôme Boursier (CHU Angers, Angers, France), Nathalie Boyer, Nathalie Giuily, Corinne Castelnau, Giovanna Scoazec (Hôpital Beaujon, Clichy, France), Aziza Chibah, Sylvie Keser, Karim Bonardi, Anaïs Vallet-Pichard, Philippe Sogni (Hôpital Cochin, Paris, France), Juliette Foucher, Jean-Baptiste Hiriart, Amandine Legendre, Faiza Chermak, Marie Irlès-Depé (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Si Nafa Si Ahmed, Christelle Ansaldi, Nisserine Ben Amara, , Valérie Oules, Jacqueline Dunette (Hôpital Saint Joseph, Marseille, France), Rodolphe Anty, Eve Gelsi, Régine Truchi (CHU de Nice, Nice, France), Elena Luckina, Nadia Messaoudi, Joseph Moussali (Hôpital de la Pitié Salpêtrière, Paris, France), Barbara De Dieuleveult, Héloïse Goin,

Damien Labarrière, Pascal Potier, Si Nafa Si Ahmed (CHR La Source, Orléans, France),
Véronique Grando-Lemaire, Pierre Nahon, Séverine Brulé, Rym Monard (Hôpital Jean
Verdier, Bondy, France), Caroline Jezequel, Audrey Brener, Anne Laligant, Aline Rabot,
Isabelle Renard (CHU Rennes, Rennes, France), Thomas F. Baumert, Michel Dofföel,
Catherine Mutter, Pauline Simo-Noumbissie, Esma Razi (Hôpitaux Universitaires de
Strasbourg, Strasbourg, France), Hélène Barraud, Mouni Bensenane, Abdelbasset Nani, Sarah
Hassani-Nani, Marie-Albertine Bernard (CHU de Nancy, Nancy, France), Georges-Philippe
Pageaux, Michael Bismuth, Ludovic Caillo, Stéphanie Faure, Marie Pierre Ripault (Hôpital
Saint Eloi, Montpellier, France), Christophe Bureau, Sarah Launay, Jean Marie Peron, Marie
Angèle Robic, Léa Tarallo (CHU Purpan, Toulouse, France), Marine Faure, Bruno Froissart,
Marie-Noelle Hilleret, Jean-Pierre Zarski (CHU de Grenoble, Grenoble, France), Odile Gorla,
Victorien Grard, Hélène Montialoux (CHU Charles Nicolle, Rouen, France), Muriel François,
Christian Ouedraogo, Christelle Pauleau, Anne Varault (Hôpital Henri Mondor, Créteil,
France), Tony Andreani, Bénédicte Angoulevant, Azeline Chevance, Lawrence Serfaty
(Hôpital Saint-Antoine, Paris, France), Teresa Antonini, Audrey Coilly, Jean-Charles Duclos
Vallée, Mariagrazia Tateo (Hôpital Paul Brousse, Villejuif, France), Corinne Bonny,
Chanteranne Brigitte, Géraldine Lamblin, Léon Muti (Hôpital Estaing, Clermont-Ferrand,
France), Abdenour Babouri, Virginie Filipe (Centre Hospitalier Régional, Metz, France),
Camille Barrault, Laurent Costes, Hervé Hagège, Soraya Merbah (Centre Hospitalier
Intercommunal, Créteil, France), Paul Carrier, Maryline Debette-Gratien, Jérémie Jacques
(CHU Limoges, Limoges, France), Guillaume Lassailly, Florent Artu, Valérie Canva, Sébastien
Dharancy, Alexandre Louvet (CHRU Claude Huriez, Lille, France), Marianne Latournerie,
Marc Bardou, Thomas Mouillot (Dijon University Hospital, Dijon, France), Yannick Bacq,
Didier Barbereau, Charlotte Nicolas (CHU Trousseau, 37044 Tours, France), Caroline
Chevalier, Isabelle Archambeaud, Sarah Habes (CHU de Nantes, Nantes, France), Nisserine

Ben Amara, Danièle Botta-Fridlund, (CHU Timone, Marseille, France), Eric Saillard, Marie-Josée Lafrance, (CHU de la Guadeloupe, Pointe-à-Pitre Cedex, Guadeloupe).

ABSTRACT

Background & Aims

Prediction of hepatocellular carcinoma (HCC) occurrence in patients with chronic hepatitis C (HCV) who achieved a sustained virological response (SVR) after direct acting antivirals (DAAs) remains challenging.

Methods

Among HCC-free HCV patients with advanced fibrosis enrolled in the ANRS CO22 HEPATHER cohort who achieved SVR 12 weeks after treatment with DAAs, HCC predictive models were developed using Cox multivariable regression. The derived score was externally validated in a large Egyptian cohort. Our main outcome was the HCC-free survival.

Results

During follow-up (median 3.05 years), 153 out of 3531 patients developed a HCC. Main variables associated with HCC occurrence were: male gender, HCV genotype 3, esophageal varices, albumin < 40 g/L, total bilirubin >11 μ mol/L and hypercholesterolemia before DAA initiation, together with age > 58 years, FIB-4 index ≥ 3.25 evaluated at SVR. A score was established allowing the stratification of patients by high (score $\geq 12/22$), intermediate ($7 \leq$ score <12) and low risk of HCC (score < 7/22) with 3-yrs HCC incidence of 18.96%, 5.50% and 1.65%, respectively. The integrated time-dependent area under the ROC curve (i-AUC) was 0.76 in our patients and 0.61 in the validation cohort.

Conclusion

The externally validated HEPATHER HCC score has good short-term predictive performance in HCV- patients who achieved SVR12 after DAAs allowing to identify high-risk patients in whom HCC screening may be cost-effective and low-risk patients in whom HCC screening may be superfluous in the first 3 years after SVR.

Keywords: Hepatitis C virus; HCC; risk factors; risk score.

The widespread implementation of anti-chronic C hepatitis (HCV) therapies has deeply modified the course of chronic viral liver diseases, especially of hepatocellular carcinoma (HCC) that has become the leading cause of death.

Sustained virological response (SVR) in patients with HCV are associated with a significant decrease in life-threatening complications such as HCC and liver-related mortality compared to untreated and non-SVR patients, especially in the presence of cofactors of liver morbidity.

However, although reduced following HCV eradication, HCC occurrence is not abolished especially in patients with advanced liver fibrosis. Thus, all international guidelines endorse lifelong HCC surveillance following SVR in patients with cirrhosis (1–3) while only European guidelines recommend also this practice in patients with bridging fibrosis (F3) (3).

Over the past decades, numerous HCC risk scoring systems for stratifying patients infected with HCV into various HCC risk classes have been proposed and validated. However, most of these risk scores are now outdated since they were designed either prior to the widespread use of antiviral therapies and they assigned heavy weighting to virological parameters, or based on studies conducted in the interferon treatment era.

Using direct-acting antivirals (DAAs), SVR rates rose over 90% in patients with HCV infection including those with advanced fibrosis and a short-term 34 to 71% decrease in HCC risk was reported in patients who achieved SVR with treatment compared to untreated patients (4–6). However, up to now, few risk prediction model were proposed after the achievement of HCV clearance with DAAs. Moreover, these models used most often routine clinical data assessed prior to SVR achievement and not at the time of SVR (7). Thus, longer follow-up of patients who received DAAs within large cohorts is crucial to clarify the pattern of temporal evolution of HCC incidence and to stratify the residual risk of HCC among patients with advanced fibrosis and cirrhosis in order to design and assess potential

personalized screening procedures and to avoid periodical surveillance in patients with low risk.

Based on the very large French cohort ANRS CO22 HEPATHER, our study aimed to develop a home-made predictive score of HCC risk in HCV patients following SVR achieved after DAAs, using routine clinical parameters assessed at the time of SVR enable to allocate patients into low-, moderate- or high-HCC risks, and to externally validate it in an Egyptian cohort.

Methods

Data source

Data for this study were extracted from the French ANRS CO22 HEPATHER cohort (6). We included HCV patients who achieved SVR 12 weeks after the end of DAAs before January 2019 without any evidence of HCC before or at SVR12. Patients with fibrosis < F3 and those with decompensated liver disease were excluded.

SVR was defined as a serum HCV RNA viral load below the lower limit of detection (< 10 IU/mL) at least 12 weeks after the end of DAAs. Fibrosis was assessed closest to the date of inclusion in the cohort, less than 1 year before and up to 3 months after inclusion, by either liver biopsy or non-invasive methods (6). Cutoffs for advanced fibrosis (F3 as defined by the METAVIR score and cirrhosis) by non-invasive methods were, respectively, 9.5 kPa and 12.5 kPa with Fibroscan, 0.59 and 0.75 with Fibrotest, 0.62 and 0.98 with Fibrometer, and 0.61 and 0.84 with the Hepascore. Screening for HCC was performed according to French national recommendations based on EASL guidelines (1) with liver ultrasonographic every 6 months, either before or after SVR. In the case of detected focal liver lesions, a recalled diagnostic procedure using contrast-enhanced imaging (computed tomography scan or MRI) and/or guided biopsy was performed according to the 2005 AASLD guidelines updated in 2011 (8, 9). A diagnosis of HCC was thus established by either histological examination or based on

probabilistic noninvasive criteria (mainly dynamic imaging revealing early arterial hyperenhancement and washout on portal venous or delayed phases) according to the different time periods (before and after 2011).

Written informed consent was obtained from each patient before enrolment. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the “Comité de Protection des Personnes Ile de France 3” Ethics Committee (Paris, France) and the French Regulatory Authority.

Predictable variables

Both baseline pretreatment and post-treatment variables at time of SVR that might contribute to HCC development were evaluated. Baseline factors included: gender, body mass index (BMI), past excessive alcohol use (defined as at least 15 alcoholic drinks (150g) per week for a woman or 22 alcoholic drinks (220g) per week for a man), smoking status, coffee consumption, comorbidities including diabetes, arterial hypertension, hypercholesterolemia, fibrosis score, past or current experience of ascites and esophageal varices. Characteristics of HCV were also considered including genotype, time since HCV infection diagnosis and past anti-HCV treatment. Serum alfa fetoprotein (AFP) and albumin levels were analyzed only at baseline. Post-treatment factors included: age and biological variables taken within a period of more or less 3 months from the date of SVR including: aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, FIB-4 index, and prothrombin time.

Statistical analysis

Selected patients were followed from time of SVR until occurrence of HCC or death or end of study period. Our main outcome was the HCC-free survival after SVR.

Baseline characteristics were compared using the Mann-Whitney test for quantitative variables or the Fisher’s exact test for categorical variables. Categorization of continuous covariates was based on their median value. Incidence of HCC was estimated during the follow-up per 100

person-years. Confidence intervals (CI) and trends in incidence were calculated based on the Poisson distribution.

Risk scores development

Different scores were developed using Cox proportional hazards models to estimate HCC risk after SVR, in all patients and according to cirrhosis at entry in the cohort, after adjusting for potential predictors of HCC. A backward elimination procedure was used to identify independent covariates associated with a HCC in multivariable analysis. The initial multivariable model included all factors associated with HCC in univariable models (p -value<0.20). In multivariable analysis, elimination of covariates was based on the significance of the Wald chi-square test for parameter estimates at the 0.05 level. We developed a simple point system by multiplying each β -coefficient by a factor of 4 and rounding off to the nearest integer. A risk score was assigned to each participant by summing the points for each risk factor present (10). Patients were further stratified into three subgroups of risk according to the tertiles of the score distribution. The cumulative incidence of HCC among these groups was determined by Kaplan–Meier analysis and compared with the Log-rank test after Šidák multiple-comparison adjustment.

Performance measures

By Feb 1, 2019 we performed a literature search of the PubMed database with the combination of the following keywords: “hepatitis C” AND SVR AND “hepatocellular carcinoma” AND “models” AND “score” and DAAs. We selected all publications with HCC risk scores that can be calculated from our database.

To assess the performance of the published scores, two separated analyses were performed, first using the coefficients as reported in the original publication (external analysis); second re-fitting the coefficients for the different covariates included in each score (internal analysis), which allowed a fair comparison with our home-made score.

To evaluate the discriminative performance of the different scores, we used the cumulative sensitivity and dynamic specificity with Inverse probability of censoring weighting (IPCW) as described in (11) to handle different survival times and censoring. Whereas C-statistics provide overall measures of predictive accuracy, time-dependent ROC curves and AUC functions summarize the predictive accuracy at specific times. For each event time, the AUC taking into account all event prior or up to time t is calculated. The integrated AUC is computed as a weighted average of the AUC values at all the event times. Event observations are weighted according to their probabilities of being censored to take into account a non-uniform distribution of censoring (assumed independent of the failure time distribution).

To validate the scores internally, we used the five-fold cross-validated i-AUC (12).

Calibration and model fit were assessed graphically by plotting model-derived against raw probabilities, and analytically by the Hosmer-Lemeshow (HL) χ^2 statistic.

To overcome the limitations of usual discrimination and calibration measures, we calculated the two relative metrics according to Pencina et al. (13), the Net Reclassification Index (NRI) and the Integrated Discrimination Improvement (IDI) which assess the significance of novel markers compared to former ones.

External validation

The external validation was done using an Egyptian cohort of 3075 consecutive patients, with advanced fibrosis ($\geq F3$) who achieved SVR with a 12 or 24-weeks course of one of several DAAs regimens in accordance with Egyptian national treatment protocol, AASLD 2014 and 2014 WHO guidelines for the treatment of genotype 4 HCV infection. Patients were recruited according to the same criteria than ours, between January 2014 and July 2019. Clinical and laboratory data were collected before the initiation of DAAs until the last visit at 6-monthly intervals of follow-up, according to a standardized protocol. All patients had virological,

hematological, and biochemical laboratory testing, abdominal ultrasound examination, FibroScan, and tomodensitometry or MRI if indicated.

All analyses were done with SAS 9.4. We followed the TRIPOD recommendations to report this study (14).

Results

Characteristics of the study population

Among 3531 selected subjects (62% male, mean age 60 yrs), 2445 (69%) were cirrhotic and 1086 (31%) had advanced fibrosis (Supplementary Figure 1, Table 1). The median follow-up was 3.05 years (IQR 1.94;3.88) after SVR, significantly ($P < 0.001$) higher among cirrhotics (3.16 years (IQR 1.99-4.01) than advanced fibrosis group (2.82 years (IQR 1.83-3.62) reflecting likely the prioritization policy in France from December 2013 to January 2017. 153 patients (4.4%) developed HCC, of whom 138 with cirrhosis (Supplementary Table 1); median time from date of SVR to HCC diagnosis was 17.65 (IQR 9.21-30.48) months. HCC incidence was 1.52 per 100 Person-years (PY) overall (95%CI 1.30; 1.78), 1.93 per 100 PY (95%CI 1.63; 2.28) and 0.52 per 100 PY (95%CI 0.31; 0.86) in cirrhotics and F3 patients, respectively. The incidence remained stable with time following SVR (1.54 per 100 PY (95%CI 1.17-2.02) and 1.51 (95%CI 1.24; 1.83) within and after the first year following SVR, respectively. Half of the patients (50.8%) had a US before SVR, with a median time from last US to SVR of 3.55 (IQR 1.81- 5.98) months. 112 (3.17%) patients died during the follow-up, and 115 (3.26%) were lost to follow-up.

Multivariable analysis and development of scores

Based on univariable analyses, (Supplementary table 2) clinical variables were included for multivariable analysis to predict the risk of HCC after SVR in total selected patients (Table 2). The final model retained eight independent factors: male gender (HR 1.91 CI95%: 1.26; 2.89), age at SVR > 58 years (HR 1.73 CI95%: 1.19; 2.51), genotype 3 (HR 1.88, CI95%: 1.22; 2.88), FIB-4 index at SVR ≥ 3.25 (HR 2.35, CI95%: 1.45; 3.82), baseline serum albumin < 40 g/L (HR 1.66, CI95%: 1.18; 2.34), baseline serum bilirubin > 11 $\mu\text{mol/L}$ (HR 1.52, CI95%: 1.03; 2.25), baseline hypercholesterolemia (HR 1.90 CI95%: 1.13; 3.20), baseline esophageal varices (HR 2.50, CI95%: 1.72; 3.63). A 22-point risk score was derived from the regression coefficients of

these 8 variables (Table 3). Patients were then stratified into three risk groups according to their scores: a low risk group (< 7 points, $n = 2043$, $n_{\text{HCC}} = 33$) with 3-year cumulative HCC incidence of 1.65% (95% CI 1.11- 2.38%), an intermediate risk (7–11 points, $n=1209$, $n_{\text{HCC}}=67$) with 3-year cumulative HCC incidence of 5.50% (95% CI 4.17- 7.07%), and a high-risk group (≥ 12 points, $n=279$, $n_{\text{HCC}}=53$) with 3-year cumulative incidence of 18.96% (95% CI 14.19- 24.26%), respectively (Figure 1). The score was applied to the cirrhotic group of patients. The cumulative incidence curves for the three groups of risk are shown in Supplementary figure 2.

Among cirrhotic patients, all identified predictors except hypercholesterolemia remained associated, thus generating a 18-point risk score. Conversely, no score was calculated for advanced fibrosis group giving the low number of events occurring ($n_{\text{HCC}}=15$)

Measures of discrimination

Three HCC risk prediction models for HCV patients who achieved SVR with DAAs were published in 2018 and 2019 (15–17) (Supplementary Table 3).

The published models exhibited better performances in the internal analysis (i-AUC ranging between 0.66 to 0.70 in all patients) than in the external analysis (i-AUC between 0.64 to 0.69- Supplementary Table 4). Our home-made scores showed higher i-AUC than published re-estimated scores in all selected patients with an i-AUC in validation sets of 0.76; and in cirrhotic patients with an i-AUC of 0.74 for our specific subgroup score. (Figure 2 and Supplementary Table 5). Overall, AUC decreased from first year to third year after SVR in all patients, cirrhosis, and severe fibrosis groups (Supplementary Table 6).

The predictive performance of our score was externally validated in an Egyptian cohort of 1037 F3 and 2038 F4 patients - whom characteristics are summarized in Supplementary Table 7 - followed during 24.32 ± 12.14 (range 6-72) months after the end of DAAs. 212 HCC cases were developed during the study period: 65 patients out of 1957 (3.3%), 117 out of 1023 (11.4%)

and 30 out of 95 (31.6%) in the low, intermediate and high risk groups, respectively. Incidence was 1.73 per 100 PY (95%CI 1.33; 2.20) in the low risk group, 5.45 per 100 PY (95%CI 4.51; 6.53) in the intermediate risk group and 9.40 per 100 PY (95%CI 6.33; 13.4) in the high risk group. However the overall performance was poor (AUC 0.61 ± 0.02) owing to a higher baseline risks of HCC in the Egyptian cohort compared with the French cohort (Supplementary table 8).

Measures of calibration

Calibration plots show a slight departure between observed and predicted probabilities with our models (Figure 3). The Hosmer-Lemeshow test was not significant neither when the general score was applied on all selected patients, nor with the cirrhosis score applied in the cirrhosis group ($p=0.46$) and ($p=0.88$), respectively; indicating a good calibration.

Both NRI and IDI significantly differed between our score compared to the previous published scores (Supplementary Table 9).

Discussion

Our simple home-made score outperforms all existing published scores for predicting residual HCC risks. This score could be simply calculated based on a limited number of data easily available in all HCV patients and according to a priori knowledge of pretherapeutic advanced liver fibrosis status.

The strengths of our study include the large cohort of patients treated with DAAs ensuring a high statistical power to identify an increased risk of events, the prospective design and the multicenter protocol with homogeneous systematic periodic surveillance by liver imaging for HCC screening according to international guidelines. We identified 8 independent predictors of HCC occurrence consistent with those already reported (18–20). As previously described, baseline comorbidities were frequent in our cirrhotics (diabetes 20%, hypertension 34%, past excessive alcohol intake 33%), the increased rates of diabetes and hypertension in cirrhotics compared to non-cirrhotics being probably linked to their older age and higher BMI. However, surprisingly these previous 3 comorbidities were not selected as HCC risk factors by multivariate Cox models; this was already the case for diabetes and hypertension in ANRS CO12 Cirvir cohort (20) but remains unexplained for alcohol and BMI in our cohort. Lastly, our home-made score was able to discriminate between low and intermediate or high risk of HCC occurrence in Egyptian HCV patients with advanced fibrosis who achieved SVR with DAAs. However, the poorer performance in the validation cohort may be partly due to a significantly higher baseline risk of HCC in all subgroups of Egyptian patients than in our cohort (supplementary table 8), and/or differential selection bias such as the exclusion of patients with non-malignant focal liver lesions (dysplastic nodules, cirrhotic nodules and haemangiomas) prior to DAA treatment.

Our study has several limitations. First, our sample might not be representative of all patients who achieved SVR. When DAAs were introduced in 2013, it was indicated mainly in patients with severe disease (prioritization policy for DAA access) who were at higher risk of HCC and therefore, since almost half of the patient in this study were included in 2014 (49%), the all-patients scoring system might exhibit different performances if applied to other people treated more recently, i.e. with a milder disease. Second, given that the follow-up started at SVR, some laboratory measurements were not available at this time in the cohort such as serum AFP and we used pre-treatment measurements. This point has been discussed in other studies which showed that post-treatment AFP better reflected the actual liver diseases status and risk of HCC development than pretreatment values (21,22). Similarly, the assessment of fibrosis and cirrhosis was based on patients' records at entry in the cohort, ascertained by different methods, and not updated during follow-up or when patients started DAA treatment. However, regarding fibrosis, misclassification is unlikely to occur unless patients' fibrosis strongly improved or worsened during the on-treatment period. Third, no formal statistical testing was performed to compare the i-AUC between the different scores, and it is likely that some published scores exhibited similar performances than our homemade score (15-17). Resampling or other bootstrap methods can be used to compute the 95% confidence interval (95% CI) of i-AUC or to estimate the differences between i-AUC (and the 95%CI). Fourth, incidence of HCC among cirrhosis patients depends on a range of epidemiological and clinical factors, including mechanisms for detection, schedule of HCC screening, and the timing and extent of follow-up. Because older age and more advanced cirrhosis are predictors of HCC development, some young patients with a mild liver disease might have undergone less regular screening for HCC than recommended, resulting in potentially missed diagnoses (in our study, approximately half of the patients had an US before SVR); hence, ending in a reverse causality question. Fifth, the risk of HCC did not appear to decrease rapidly, particularly in cirrhotics, and a longer

observation period is probably necessary to observe any beneficial effects. Although, reverse causality could be another possibility explaining the slow decrease if the residual risk over the first three years was related to undiagnosed cancers or HCC in the latent stage at treatment initiation. In other words, the score doesn't allow to distinguish between a risk of HCC in the latent stage and a risk of de novo HCC after SVR, therefore it might be irrelevant for longer follow-up.

To conclude, we developed a practical, easy and reproducible tool that showed good performances to predict the risk of HCC in HCV patients after SVR achieved by DAAs. Beside male patients, older age and presence of advanced fibrosis and cirrhosis at the time of SVR are associated with a high enough risk to justify regular surveillance. Also, our prognostic score could be improved by further specific analyses of patients who were not adequately classified according to the score, particularly those who had a low-score but developed HCC.

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Legends to Figures

Figure 1. Kaplan-Meier curves for cumulative incidence of HCC in all selected patients after stratification into 3 risk strata according to their score: low (< 7 points, $n=2043$), medium (7-11 points, $n=1209$) and high (≥ 12 points, $n=279$) risk group. The 3-years cumulative incidences of HCC differed significantly between the 3 groups of risk (18.96% for the high risk group, 5.50% for the intermediate, and 1.65% for the low risk group. Log-rank test with Šidák multiple-comparison adjustment <0.001).

Figure 2. i-AUC estimates for the home-made score (black curve) and the previously published scores in total selected patients.

Figure 3. Calibration plots for home-made score showing no significant difference between observed and predicted probabilities of developing an HCC.

Supplementary Figure 1. Flow-chart for patients' selection according to the inclusion/exclusion criteria

Supplementary Figure 2. Kaplan-Meier curves for cumulative incidence of HCC in cirrhotic and advanced fibrosis patients after applying the general score.

Table 1. Patients Characteristics (Derivation cohort)

	Total patients (n=3531)	Cirrhosis (F4) (n=2445, 69%)	Advanced fibrosis (F3) (n=1086, 31%)
Age at SVR (years), mean (SD)	60.11 (10.46)	60.30 (10.46)	59.67 (10.45)
Male gender, n (%)	2192 (62.08%)	1578 (64.54%)	614 (56.54%)
BMI (kg/m²), mean (SD)	25.76 (4.59)	25.98 (4.70)	25.27 (4.29)
BMI class (kg/m²), n (%)			
<18.5	83 (2.36%)	52 (2.14%)	31 (2.87%)
[18.5-25[1641 (46.69%)	1105 (45.40%)	536 (49.58%)
[25-30[1238 (35.22%)	860 (35.33%)	378 (34.97%)
≥30	553 (15.73%)	417 (17.13%)	136 (12.58%)
Origin, n (%)			
French overseas department	61 (1.75%)	40 (1.65%)	21 (1.98%)
North Africa	437 (12.56%)	313 (12.94%)	124 (11.70%)
Sub Saharan Africa	192 (5.52%)	121 (5.00%)	71 (6.70%)
Asia	82 (2.36%)	62 (2.56%)	20 (1.89%)
Europe	2649 (76.16%)	1841 (76.14%)	808 (76.23%)
Other	57 (1.64%)	41 (1.70%)	16 (1.51%)
Comorbidities at baseline, n (%)			
Arterial hypertension	1186 (33.63%)	826 (33.78%)	360 (33.27%)
Diabetes	591 (16.74%)	484 (19.80%)	107 (9.85%)
Hypercholesterolemia	240 (6.80%)	156 (6.38%)	84 (7.73%)
Esophageal varices	369 (10.45%)	369 (15.21%)	
Past excessive alcohol intake	1130 (32.01%)	833 (34.07%)	297 (27.37%)
Tobacco consumption			
Current smoker	1276 (36.21%)	902 (36.92%)	374 (34.60%)
Past smoker	2296 (65.15%)	1619 (66.27%)	677 (62.63%)
Coffee consumption (cup/day), mean (SD)	1.91 (2.20)	1.81 (2.13)	2.14 (2.34)
Drug injection (IV)	1123 (31.80%)	785 (32.11%)	338 (31.12%)
Previous anti-HCV treatment, n (%)			
Naive to treatment	1227 (34.78%)	790 (32.31%)	437 (40.35%)
Interferon experience	1823 (51.67%)	1311 (53.62%)	512 (47.28%)
Unknown or other	478 (13.55%)	344 (14.07%)	134 (12.37%)
Laboratory results at baseline			
AFP (ng/mL), mean (SD)	14.39 (31.64)	17.26 (36.53)	7.14 (9.20)
Albumin (g/L), mean (SD)	40.88 (4.38)	40.38 (4.47)	42.10 (3.88)
Total bilirubin (μmol/L), mean (SD)	13.25 (8.13)	14.18 (8.65)	11.08 (6.29)
Fib4 index, mean (SD)	3.65 (3.41)	4.27 (3.81)	2.21 (1.50)
Laboratory results at SVR			
ALT, (UI/ L) mean (SD)	31.70 (110.36)	33.45 (101.37)	27.75 (128.35)
AST, (UI/ L) mean (SD)	29.72 (17.58)	31.74 (19.78)	25.15 (9.63)
Platelet count (G/mm3), mean (SD)	179.59 (66.12)	167.45 (66.27)	207.58 (56.62)
Prothrombin time (%), mean (SD)	88.74 (15.28)	86.76 (15.58)	93.32 (13.51)
FIB-4 index, mean (SD)	2.44 (2.19)	2.76 (2.49)	1.71 (0.88)
FIB-4 index groups, n (%)			

<1.45	1462 (41.40%)	866 (35.42%)	596 (54.88%)
[1.45-3.25 [1517 (42.96%)	1077 (44.05%)	440 (40.52%)
≥3.25	552 (15.63%)	502 (20.53%)	50 (4.60%)
HCV characteristics			
Genotype, n (%)			
1	2422 (68.87%)	1666 (68.39%)	756 (69.94%)
2	161 (4.58%)	107 (4.39%)	54 (5.00%)
3	442 (12.57%)	326 (13.38%)	116 (10.73%)
4	432 (12.28%)	293 (12.03%)	139 (12.86%)
5, 6 or 7	60 (1.71%)	44 (1.81%)	16 (1.48%)
HCV RNA viral load*10⁶, mean (SD)	2.33 (3.28) *10 ⁶	2.29 (3.32) *10 ⁶	2.42 (3.19) *10 ⁶
Age of infection (years), mean (SD)	14.13 (8.38)	14.08 (8.39)	14.23 (8.37)
Family history of HCC, n (%)	687 (19.64%)	470 (19.37%)	217 (20.26%)

Table 2. Multivariable analysis- Predictors of HCC in all patients, cirrhotics and non-cirrhotics.

Parameters	Estimate	Total patients (n=3531)		Estimate	Cirrhosis (F4) (n=2445, 69%)		Estimate	Advanced fibrosis (F3) (n=1086, 31%)	
		HR	CI 95		HR	CI 95		HR	CI 95
Age at SVR > 58 years	0.54737	1.729	1.19;2.51*	0.51141	1.668	1.12;2.48*	0.82419	2.280	0.71;7.32
Male gender	0.64646	1.909	1.26;2.89*	0.63161	1.881	1.21;2.91*	1.16178	3.196	0.85;12.01
BMI (kg/m²) (ref= 18.5-25)									
<18.5	-	-	-	-	-	-	1.98180	7.256	1.30;40.56*
25-30	-	-	-	-	-	-	-0.46151	0.630	0.19;2.15
>30	-	-	-	-	-	-	-0.70476	0.494	0.06;4.13
HCV Genotype (ref= G1)									
G2	-0.34412	0.709	0.26;1.94	-0.19650	0.822	0.30;2.26	-15.16591	0.000	0.000
G3	0.62925	1.876	1.22;2.88*	0.57359	1.775	1.12;2.82*	1.14811	3.152	0.91;10.96
G4	-0.02081	0.979	0.58;1.65	0.09001	1.094	0.65;1.86	-15.22468	0.000	0.000
G5-6-7	0.12412	1.132	0.36;3.59	-0.21038	0.810	0.20;3.31	1.99083	7.322	0.84;64.20
F4 (Metavir stage)	0.47696	1.611	0.91;2.85	-	-	-	-	-	-
Prothrombin time at SVR <70 %	0.35313	1.424	0.91;2.23	0.33923	1.404	0.89;2.22	-	-	-
Fib-4 index at SVR (ref = <1.45)									
1.45-3.25	0.27715	1.319	0.85;2.05	0.22704	1.255	0.78;2.02	-	-	-
≥ 3.25	0.85494	2.351	1.45;3.82*	0.80708	2.241	1.35;3.72*	-	-	-
AFP at baseline (ng/ml) >7	0.22168	1.248	0.89;1.74	0.22660	1.254	0.88;1.78	-	-	-
Albumin at baseline (g/L) <40	0.50797	1.662	1.18;2.34*	0.59158	1.807	1.25;2.60*	-	-	-
Total bilirubin at baseline (μmol/L) >11	0.42166	1.524	1.03;2.25*	0.45725	1.580	1.03;2.42*	-	-	-
Comorbidities at baseline									
Hypertension	-	-	-	-	-	-	0.74960	2.116	0.66;6.79

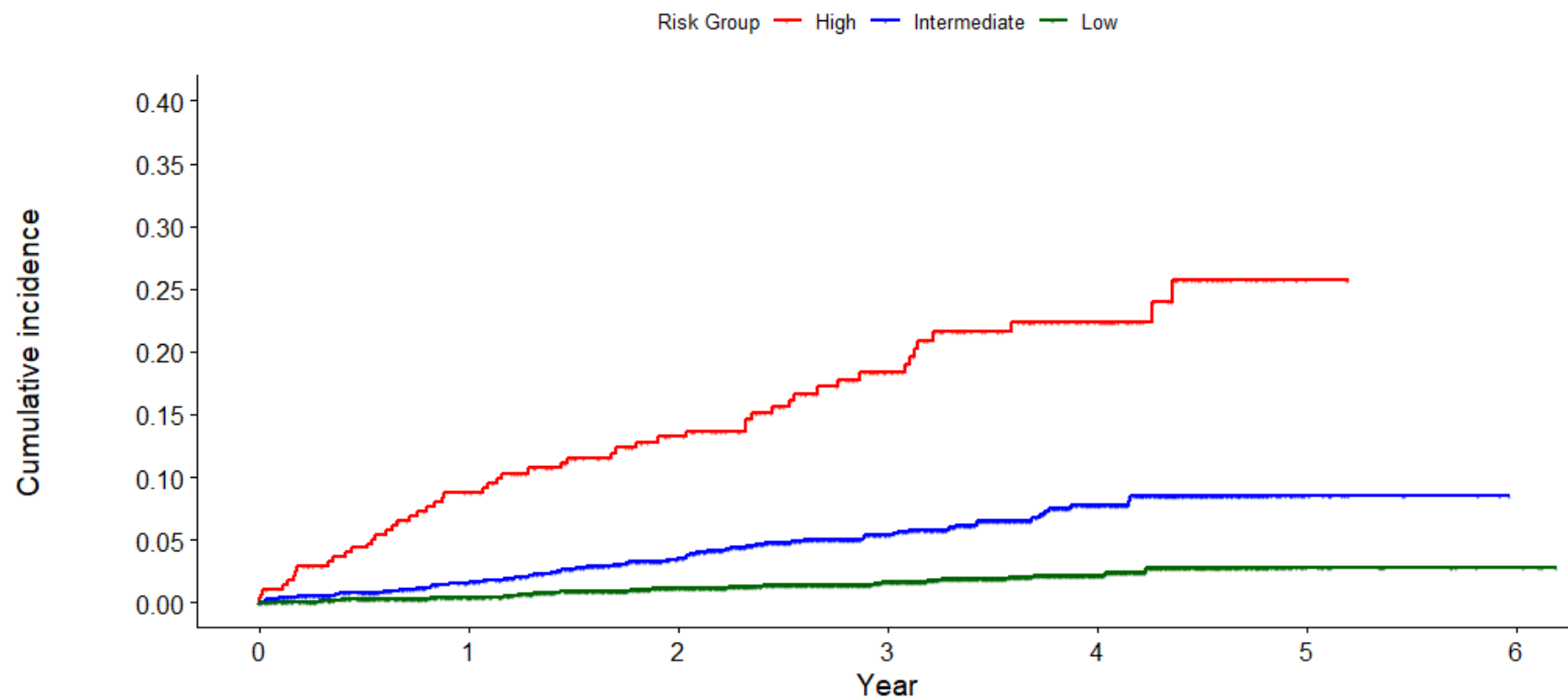
Hypercholesterolemia	0.64249	1.901	1.13;3.20*	0.46512	1.592	0.88;2.87	1.52512	4.596	1.29;16.39*
Esophageal varices	0.91611	2.500	1.72;3.63*	0.89430	2.446	1.68;3.55*	-	-	-
Past excessive alcohol intake	0.08174	1.085	0.76;1.56	0.08529	1.089	0.74;1.60	-	-	-
Current smoker	0.32234	1.380	0.93;2.06	0.27272	1.314	0.86;2.00	-	-	-
Past smoker	0.91611	2.500	0.88;2.17	0.30887	1.362	0.85;2.19	0.77616	2.173	0.55;8.63
Past anti-HCV treatment (ref = naive)									
Interferon experience	0.30851	1.361	0.91;2.03	0.26590	1.305	0.85;1.99	-	-	-
Unknown/other	0.04797	1.049	0.62;1.78	0.07284	1.076	0.62;1.87	-	-	-
Age of infection (years) >13 vs <13	-	-	-	-	-	-	2.19829	9.010	1.17;69.69*
Family history of HCC	-	-	-	-	-	-	0.18893	1.208	0.39;3.70

* P<0.05

Table 3. Scoring system overall and in cirrhotics only

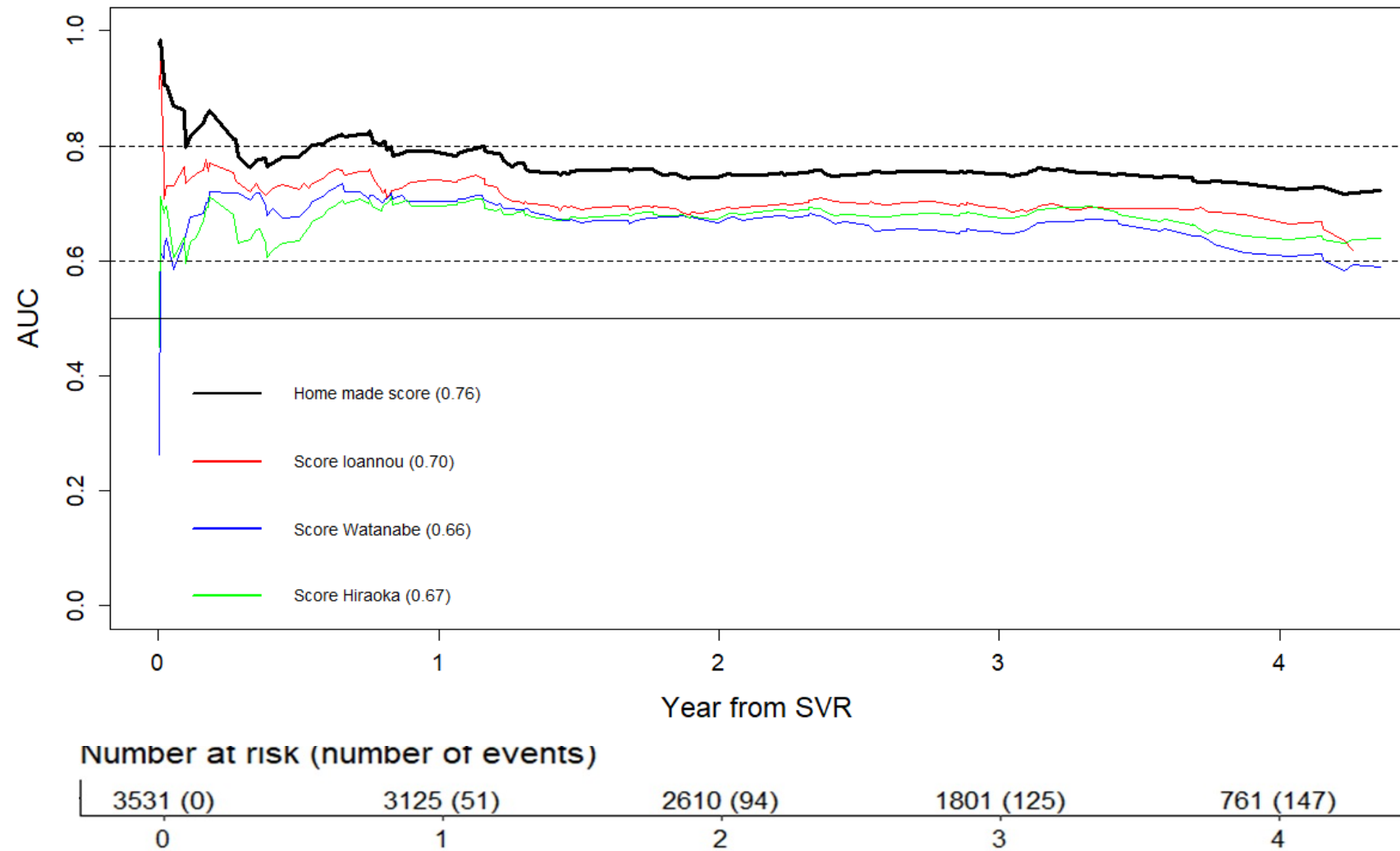
Factor	Total patients (n=3531)	Cirrhosis (F4) (n=2445, 69%)
Age> 58 years at SVR	2	1
Male gender	3	3
HCV genotype 3	3	2
Baseline hypercholesterolemia	3	-
Baseline albumin <40 g/L	2	3
Baseline total bilirubin >11 µmol/L	2	2
Esophageal varices	4	4
FIB-4 index ≥ 3.25 at SVR	3	3
Range	22	18
i-AUC	0.7637	0.7370

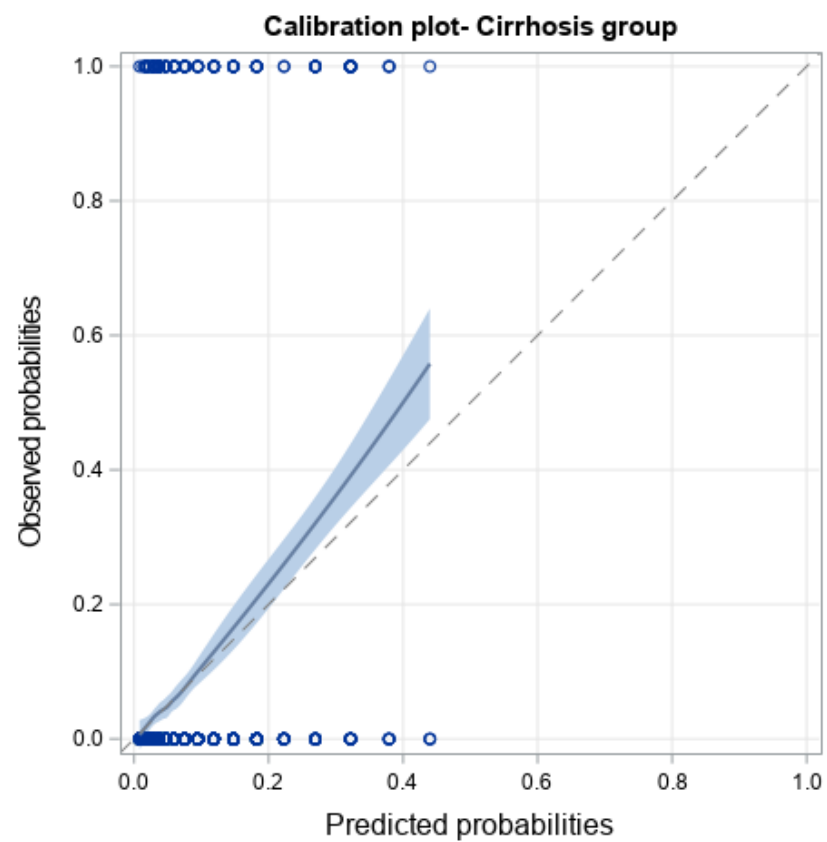
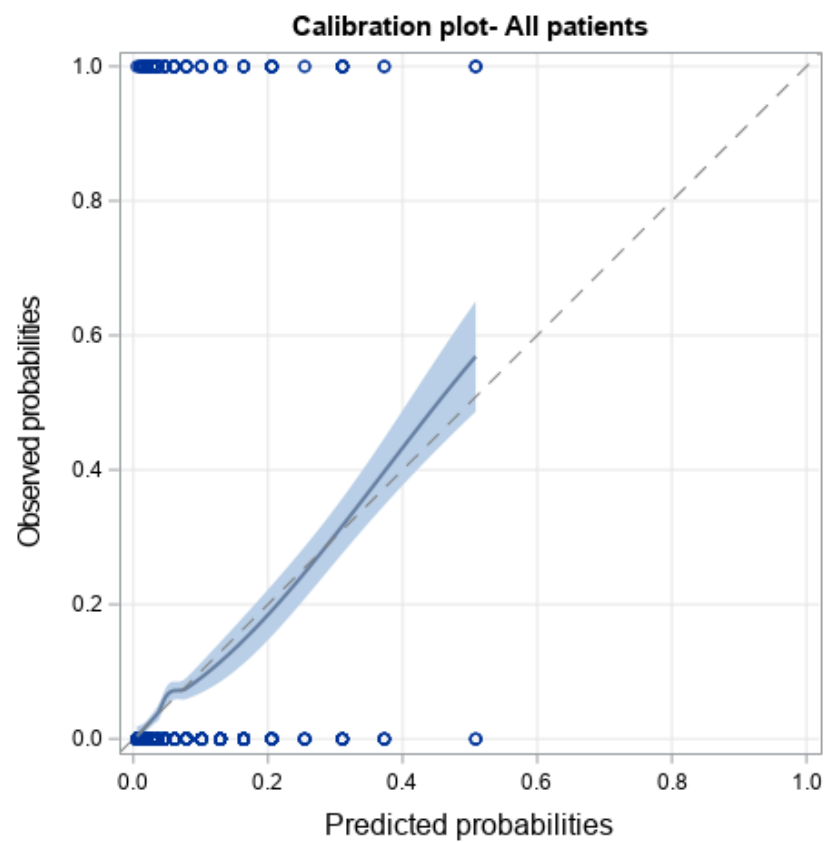
Cumulative incidence curves for all patients

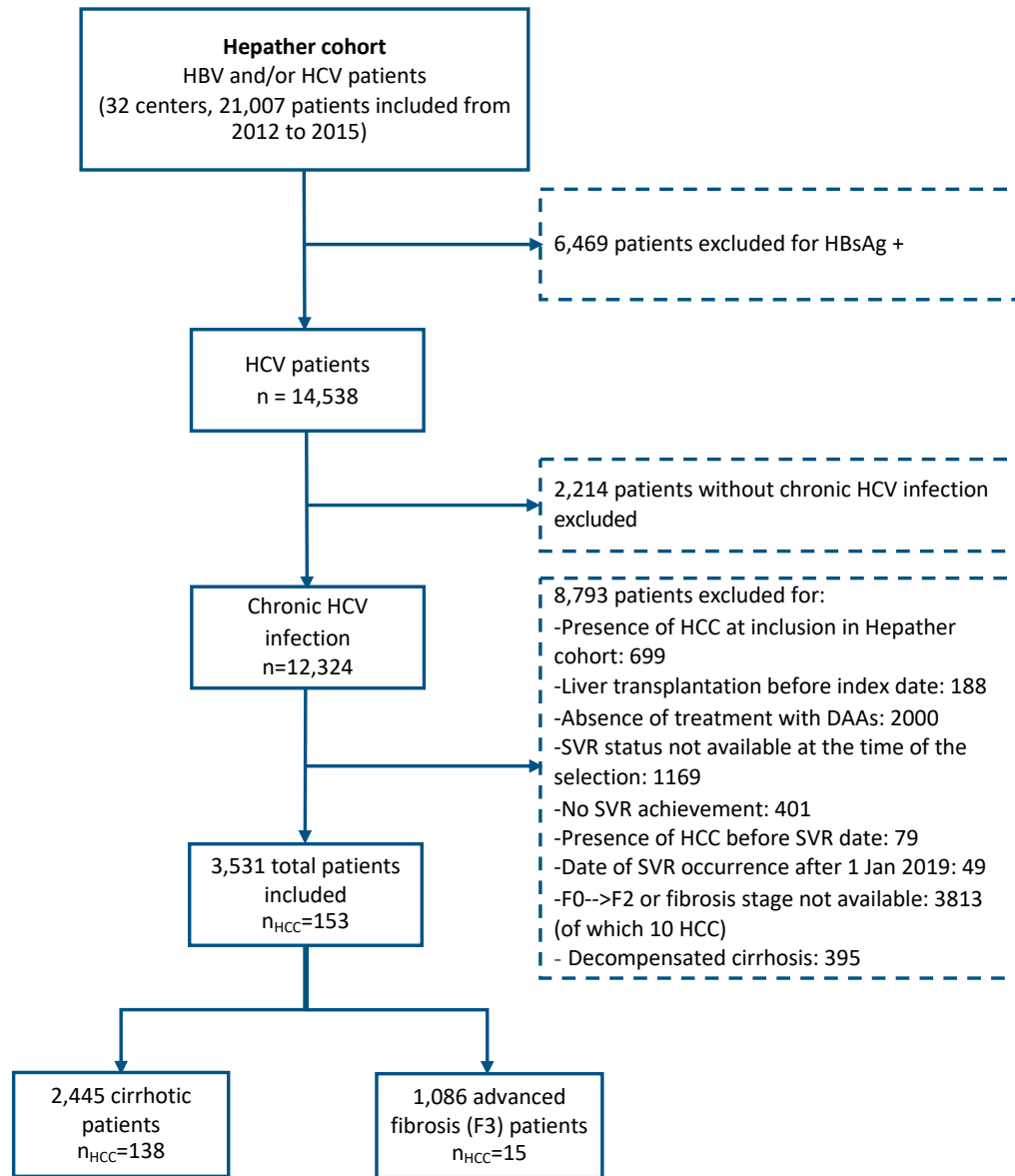


		Number at risk (number of events)						
Risk Group		Year						
		0	1	2	3	4	5	6
High		279 (0)	243 (24)	194 (35)	131 (45)	72 (51)	2 (53)	0 (53)
Intermediate		1209 (0)	1063 (19)	889 (38)	619 (53)	287 (65)	13 (67)	0 (67)
Low		2043 (0)	1819 (8)	1527 (21)	1051 (27)	402 (31)	18 (33)	4 (33)

Estimates of AUC (t) at all event times- All patients

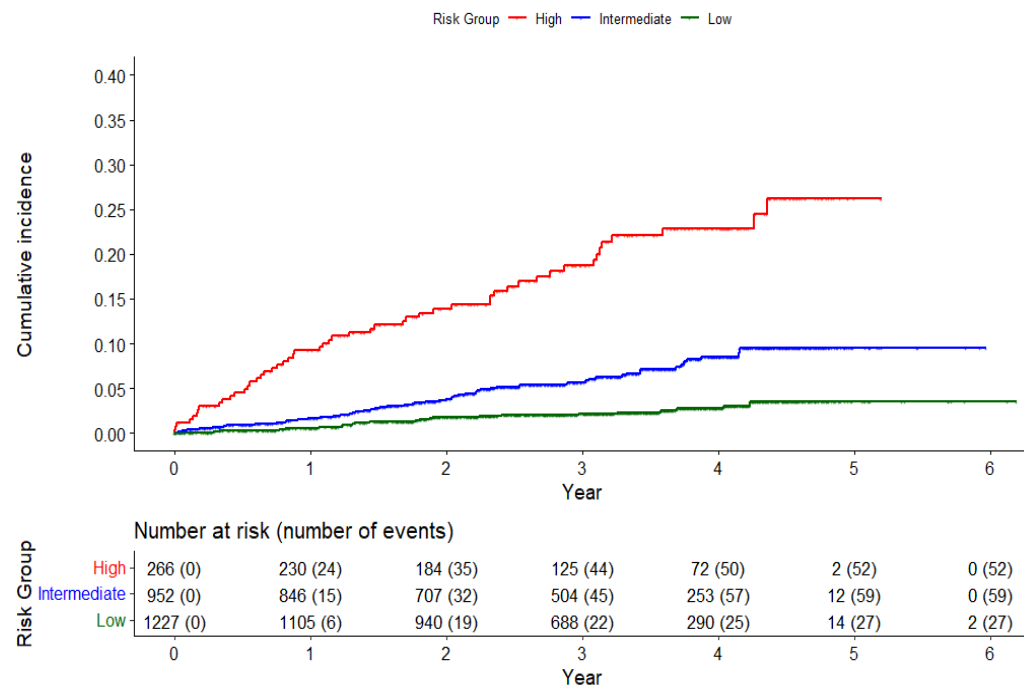




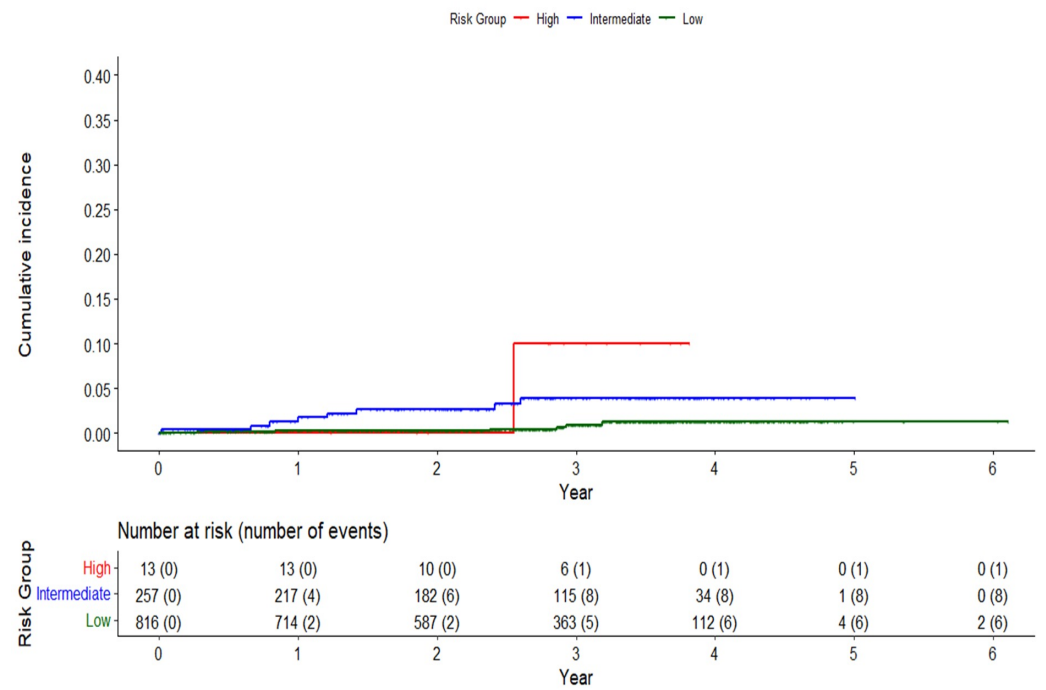


DAA: Direct acting antivirals, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HBsAg: Hepatitis B surface antigen, HCC: Hepatocellular carcinoma, SVR: Sustained virological response

Cumulative incidence curves for cirrhotic patients



Cumulative incidence curves for advanced fibrosis patients



Supplementary table 1 Characteristics of hepatocellular carcinoma according to the extent of baseline liver fibrosis

Number (%) of patients who developed HCC	Cirrhosis (n =138, 5.64%)	Advanced Fibrosis (F3) (n =15, 1.38%)	P-value
Age (years) , mean (SD)	61.93 (9.87)	64.07 (8.98)	0.4225
Male, n (%)	105 (73.33%)	11 (76.09%)	0.7590
BMI (kg/m2), mean (SD)	26.52 (4.58)	23.51 (3.61)	0.0150
Past excessive alcohol intake, n (%)	53 (38.41%)	5 (33.33%)	0.7856
Diabetes, n (%)	29 (21.01%)	2 (13.33%)	0.7369
FIB-4 at SVR	4.28 (3.21)	1.96 (1.00)	<0.0001
Time from SVR 12 to HCC in months, mean (SD)	20.60 (14.25)	20.11 (12.79)	0.8983
Diameter of the largest nodule, n (%)			0.0532
≤ 20 mm	59 (49.58%)	3 (25.00%)	
21-30 mm	32 (26.89%)	2 (16.67%)	
31-50 mm	17 (14.29%)	5 (41.66%)	
> 51 mm	11 (9.24%)	2 (16.67%)	
With Milan criteria, n (%)			0.6515
1 nodule ≤ 50 mm	75 (54.35%)	8 (53.33%)	
2 or 3 nodules ≤ 30 mm	21 (15.22%)	1 (6.67%)	
Outside Milan criteria, n (%)	42 (30.43%)	6 (40.00%)	
HCC treatment*, n			
Curative intent			**
Percutaneous radiofrequency	45	4	
Resection	27	2	
Radiotherapy	28	1	
Liver transplant	8	0	
Palliative intent			
Systemic treatment	23	8	
Chemoembolization	24	5	
Radio-embolization	6	2	
Portal vein embolization	1	0	

* Patients may have experienced several procedures

** No statistical test was performed as patients may have experienced several procedures

Supplementary table 2 Univariable analysis

Parameters	Total patients (n=3531)			Cirrhosis (F4) (n=2445, 69%)			Advanced fibrosis (F3) (n=1086, 31%)		
	Estimate	HR	p-value	Estimate	HR	p-value	Estimate	p-value	HR
Age at SVR >58 years	0.34359	1.410	0.0386	0.28121	1.325	0.1070	0.66838	0.2224	1.951
Male gender	0.67179	1.958	0.0004	0.57792	1.782	0.0038	0.79608	0.1728	2.217
BMI(kg/m²) (ref= 18.5-25)									
<18.5	0.01412	1.014	0.9809	-0.87259	0.418	0.3868	1.56111	0.0484	4.764
25-30	0.19433	1.215	0.3900	0.21401	1.239	0.3597	-0.85713	0.4192	0.424
>30	0.10962	1.116	0.5478	0.12921	1.138	0.5006	-0.34398	0.5744	0.709
HCV Genotype (ref= G1)									
G2	-0.43449	0.648	0.3944	-0.27505	0.760	0.5906	-15.79473	0.9961	0.000
G3	0.55893	1.749	0.0074	0.46932	1.599	0.0356	0.95999	0.1047	2.612
G4	0.04669	1.048	0.8555	0.19347	1.213	0.4546	-15.79527	0.9935	0.000
G5-6-7	0.13942	1.150	0.8120	-0.25679	0.774	0.7196	1.60413	0.1263	4.974
Biological factors									
AFP at baseline (ng/ml) >7	0.84208	2.321	<.0001	0.74114	2.098	0.0008	-0.02488	0.9712	0.975
Albumin at baseline (g/L) >40	0.90070	2.461	<.0001	0.89740	2.453	<.0001	-0.63630	0.4078	0.529
Total bilirubin at baseline (μmol/L) >11	0.98225	2.670	<.0001	0.98084	2.667	<.0001	0.14472	0.7798	1.156
Prothrombin time at SVR <70 %	1.22077	3.390	<.0001	1.06843	2.911	<.0001	1.18600	0.2675	3.274
F4 (Metavir stage) at baseline	1.31892	3.739	<.0001	-	-	-	-	-	-
Fib-4 index at SVR (ref = <1.45)									
1.45-3.25	0.49886	1.647	0.0235	0.40032	1.492	0.0978	0.51796	0.3378	1.679
≥ 3.25	1.62021	5.054	<.0001	1.41731	4.126	<.0001	0.66951	0.5355	1.953
Comorbidities at baseline									
Hypertension	0.19865	1.220	0.2317	0.14129	1.152	0.4231	0.77338	0.1352	2.167
Diabetes	0.21757	1.243	0.2794	0.07672	1.080	0.7135	0.33334	0.6608	1.396
Hypercholesterolemia	0.61060	1.842	0.0171	0.48236	1.620	0.0980	1.53737	0.0083	4.652
Esophageal varices	1.58510	4.880	<.0001	1.36049	3.898	<.0001	-	-	-
Past excessive alcohol intake	0.30033	1.350	0.0715	0.24283	1.275	0.1654	0.29168	0.5944	1.339
Current smoker	0.25650	1.292	0.1196	0.19593	1.216	0.2601	0.57397	0.2677	1.775
Past smoker	0.48185	1.619	0.0094	0.40244	1.495	0.0379	0.89841	0.1640	2.456
Coffee consumption (<2cups/day)	0.12344	1.131	0.4504	0.06130	1.063	0.7223	0.15272	0.7679	1.165
Past anti-HCV treatment (ref = naive)									
Interferon experience	0.46793	1.597	0.0184	0.37205	1.451	0.0775	0.65617	0.2675	1.927
Unknown/other	0.47574	1.609	0.0696	0.47230	1.604	0.0828	-0.38290	0.7321	0.682
Age of infection (years) >13 vs <13	0.13643	1.146	0.4120	-0.02359	0.977	0.8915	2.38448	0.0212	10.853
Family history of HCC	0.11233	1.119	0.5727	0.03626	1.037	0.8660	0.72473	0.1859	2.064

Supplementary table 3 Summary of published scores

Author (<i>Ref</i>)	Year	Area	Sample size	N _{HCC} (%)	AUROC/c-index
Ioannou (<i>15</i>)	2018	US	45810	1412 (3.08)	0.70-0.77
Watanabe (<i>16</i>)	2019	Japan	1174	33 (2.81)	0.71-0.74-0.79
Hiraoka (<i>17</i>)	2019	Japan	1069	22 (2.06)	0.84

Supplementary table 4. External validation of published scores

Scores (<i>Ref</i>)	Discrimination time-dependent AUC (external validation)	
	Total patients (n=3531)	Cirrhosis (F4) (n=2445, 69%)
Ioannou (<i>15</i>)	0.69	0.69
Watanabe (<i>16</i>)	0.64	0.63
Hiraoka (<i>17</i>)	0.64	0.63

Supplementary table 5. Discrimination time-dependent AUC (i-AUC) for the homemade and the published scores

Scores, year (<i>ref</i>)		i-AUC (internal validation)	
		Total patients (n=3531)	Cirrhosis (F4) (n=2445, 69%)
Home made	D	0.76	0.74
	V	0.76	0.74
Ioannou (<i>15</i>)	D	0.70	0.71
	V	0.70	0.70
Watanabe, 2019 (<i>16</i>)	D	0.66	0.66
	V	0.66	0.66
Hiraoka, 2019 (<i>17</i>)	D	0.67	0.66
	V	0.67	0.66

D: derivation sets; V: Internal-Validation set

Supplementary table 6 AUC at 1st year and 3rd year after SVR for the homemade and published scores, overall and by fibrosis stage

Scores, (<i>ref</i>)	Total patients (n=3531)		Cirrhosis (F4) (n=2445, 69%)	
	AUC 1 year	AUC 3 year	AUC 1 year	AUC 3 year
Home made	0.79	0.75	0.78	0.73
Ioannou (<i>15</i>)	0.74	0.69	0.73	0.71
Watanabe (<i>16</i>)	0.70	0.66	0.71	0.66
Hiraoka (<i>17</i>)	0.70	0.68	0.70	0.67

Supplementary table 7 Baseline characteristics (External-validation cohort)

Variable	All patients	Non-HCC Patients	HCC patients	P-value*
Number	3075	2863	212	
Age (years)	56.0 (50.0-62.0)	56.0 (50.0-62.0)	59.0 (55.0-64.0)	<0.001
Sex	1628 (52.9%)	1467 (51.2%)	161 (75.9%)	<0.001
- Males	1447 (47.1%)	1396 (48.8%)	51 (24.1%)	
- Females				
ALT (U/L)	48.2 (34.0-75.8)	49.0 (34.0-75.0)	44.0 (30.0-76.0)	0.329
AST (U/L)	50.2 (35.0-76.0)	50.0 (35.0-75.0)	53.5 (36.3-90.5)	0.160
Total Bilirubin (mg/dL)	0.81 (0.60-1.10)	0.80 (0.60-1.10)	1.00 (0.80-1.50)	<0.001
Albumin (g/dL)	4.00 (3.60-4.30)	4.00 (3.60-4.30)	3.70 (3.11-4.10)	<0.001
Creatinine (mg/dL)	0.77 (0.63-0.90)	0.77 (0.63-0.90)	0.80 (0.68-0.96)	0.069
Platelets count (G/mm³)	135.0 (90.0-186.0)	137.0 (92.0-188.0)	93.0 (65.5-145.0)	<0.001
HgB (g/dL)	13.0 (12.3-14.8)	13.6 (12.3-14.8)	13.4 (11.7-14.6)	0.006
WBCs (/cmm³)	5.7 (4.3-7.2)	5.7 (4.4-7.2)	5.1 (3.6-6.6)	0.001
AFP (ng/ml)	6.51 (3.98-14.11)	6.20 (3.79-12.51)	14.50 (4.80-40.0)	<0.001
HCV RNA, log₁₀ IU/ml	5.55 (4.97-6.09)	5.56 (4.99-6.09)	5.44 (4.64-5.97)	0.072
Fibrosis stage				<0.001
- F3	1037 (33.7%)	1007 (35.2%)	30 (14.2%)	
- F4	2038 (66.3%)	1856 (64.8%)	182 (85.8%)	
CTP Classification^{##}				<0.001
- A	1520 (74.6%)	1406 (75.8%)	114 (62.6%)	
- B	518 (25.4%)	450 (24.2%)	68 (37.4%)	
Co-morbidities				
- DM	747 (24.3%)	704 (24.6%)	43 (20.3%)	0.079
- HTN	517 (16.8%)	481 (16.8%)	36 (17.0%)	0.489
- Over-weight [#]	1805 (58.7%)	1703 (59.5%)	102 (48.1%)	0.001

*p-value compared HCC and non-HCC patients

Data are presented as frequency (%) or median (IQR).

[#] Over-weight (BMI≥30 kg/m²)

^{##} For F4 patients only (1734 patients)

DM=Diabetes Mellitus, HTN=Hypertension, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, HgB=Hemoglobin, WBCs=White blood cells, AFP=Alpha Fetoprotein

Supplementary table 8 Validation cohort: Observed HCC and predicted HCC estimates using the derivation cohort.

	Risk group		
	Low	Intermediate	High
Person-Years (PY)	3765	2147	320
HCC Observed	65	117	30
Incidence /100 PY (derivation estimates)	0.57 (0.40; 0.80)	1.93 (1.52; 2.46)	6.83 (5.22;8.94)
HCC Predicted (using derivation estimates)	21.5 (15.1; 30.1)	41.4 (32.6; 52.8)	21.9 (16.7; 28.6)
HCC Observed/Predicted*	3.03 (2.33; 3.85)	2.83 (2.34; 3.39)	1.37 (0.92; 1.96)

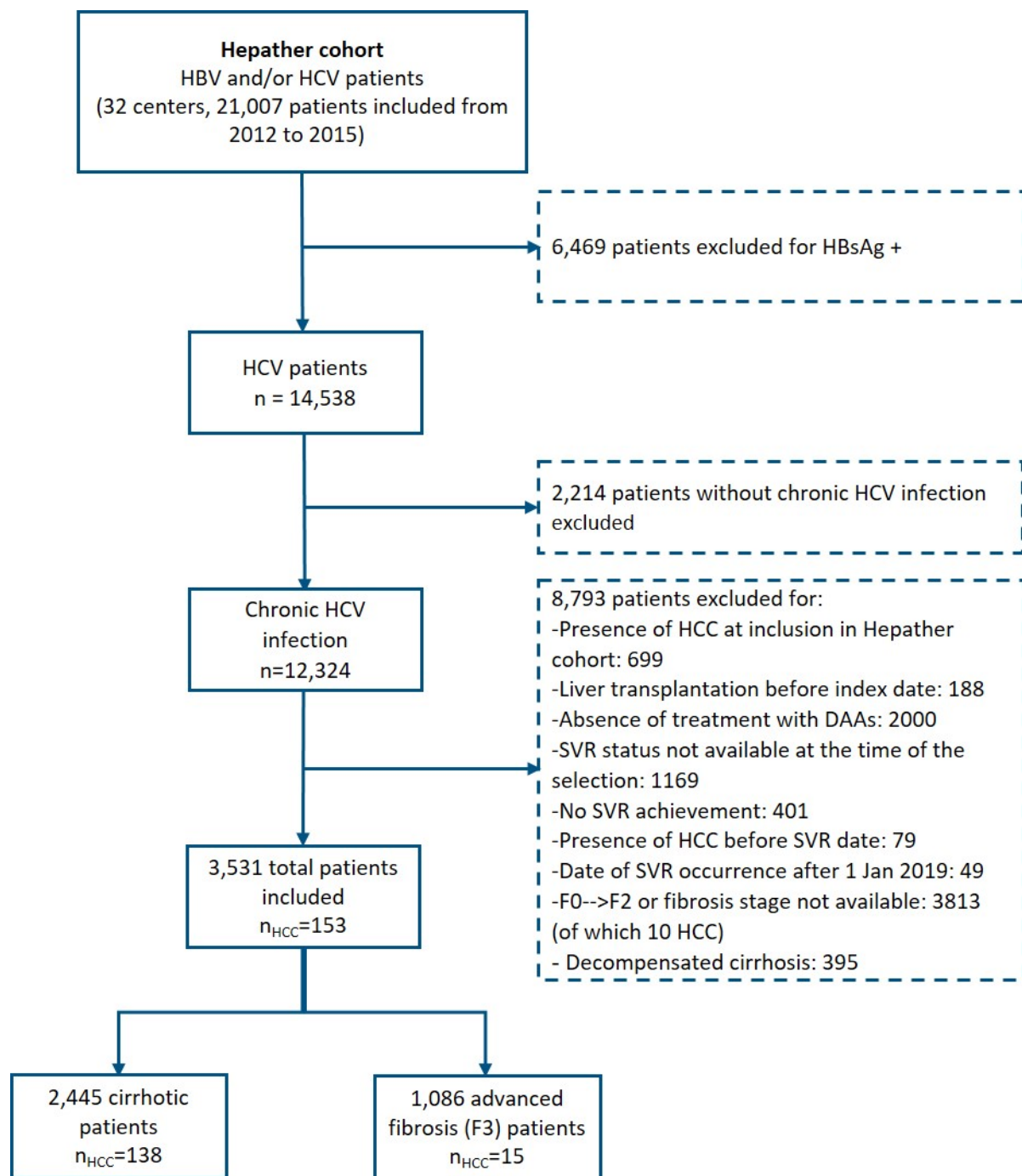
* Confidence limits were calculated using an exact method based on the Poisson distribution.

Supplementary table 9 Summary reclassification measures- comparison between home-made and published scores

Positive values of cNRI and IDI indicate that our homemade score has better discriminative ability than the compared score. No negative values of cNRI nor IDI were observed.

		Total patients (n=3531)		Cirrhosis (F4) (n=2445, 69%)		
Initial model	New model	Test [95% CI]	p-value	Test [95% CI]	p-value	
Ioannou (15)	Home-made score	cNRI	0.20 [0.140 - 0.266]	<0.0001	0.18 [0.110 - 0.240]	<0.0001
		IDI	0.02 [0.010 - 0.033]	<0.0001	0.02 [0.010 - 0.029]	<0.0001
Watanabe (16)		cNRI	0.22 [0.152 - 0.290]	<0.0001	0.19 [0.114 - 0.262]	<0.0001
		IDI	0.03 [0.014 - 0.036]	<0.0001	0.02 [0.015 - 0.034]	<0.0001
Hiraoka (17)		cNRI	0.11 [0.061 - 0.167]	<0.0001	0.12 [0.057 - 0.187]	0.00025
		IDI	0.02 [0.011 - 0.031]	<0.0001	0.02 [0.012 - 0.028]	<0.0001

Supplementary Figure 1



Supplementary Figure 2

