Nomogram for individualized prediction of hepatocellular carcinoma occurrence in hepatitis C virus cirrhosis (ANRS CO12 CirVir)

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Short title: Predictive score for HCC in HCV-cirrhosis.

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ABSTRACT

*Background***:** To develop an individualized score for predicting hepatocellular carcinoma (HCC) in patients with hepatitis C (HCV)-compensated cirrhosis.

*Methods***:** Among 1,323 patients with HCV-cirrhosis enrolled in the French prospective ANRS CO12 CirVir cohort, 720 and 360 were randomly assigned to training and validation sets, respectively. Cox multivariate model was used to predict HCC, after which a nomogram was computed to assess individualized risk.

*Results***:** During follow-up (median: 51.0 months), 103 and 39 patients developed HCC in the training and validation sets, respectively. Five variables were independently associated with occurrence of HCC: age > 50 years (HR 1.94, 95%CI [1.16; 3.25], p=0.012); past excessive alcohol intake (HR 1.55, 95%CI [1.02; 2.36], p=0.041); low platelet count (< 100 Giga/ mm3: HR 2.70, 95% CI [1.62; 4.51], p < 0.001; [100; 150] Giga/ mm3: HR 1.87, 95%CI [1.10; 3.18], p=0.021); GGT above the upper limit of normal (HR 1.96, 95%CI [1.11; 3.47], p=0.021); and absence of a sustained virological response during follow-up (HR 3.02, 95%CI [1.67; 5.48], p<0.001). An 11-point risk score was derived from the training cohort and validated in the validation set. Based on this score, the population was stratified into three groups, in which HCC development gradually increased, from 0% to 30.1% % at 5 years for patients with the lowest (≤ 3) and highest (≥ 8) scores (p < 0.001). Using this score, a nomogram was built enabling individualized prediction of HCC occurrence at 1, 3 and 5 years.

*Conclusions***:** This HCC score can accurately predict HCC at an individual level in French patients with HCV-cirrhosis.

Approximately 80% of hepatocellular carcinomas (HCC) worldwide are related to chronic infection with hepatitis B (HBV) or hepatitis C virus (HCV).

In Western countries, spread of HCV infection has been partly responsible for a rise in the incidence of cirrhosis and HCC during recent decades (1). In those countries, historical cohort studies reported 5-year cumulative incidences of HCC of nearly 17% in patients with HCV-cirrhosis (2). More recently, large prospective Western cohorts confirmed the high incidence of HCC in HCV-cirrhosis: in the subgroup of 410 patients with HCV-cirrhosis enrolled in the HALT-C American cohort, and who did not respond to peg-interferon and ribavirin (3), and among 1,323 patients with histologically proven and uncomplicated HCV cirrhosis enrolled from 2006 to 2012 in the ANRS CO12 CirVir French multicenter cohort (4), cumulative HCC incidences were 7% at 5 years and 11.4% at 4 years, respectively. Since HCC screening is considered cost-effective if the incidence of HCC is over 1.5% per year (5, 6), patients with HCV-cirrhosis should thus undergo periodic surveillance for HCC. Moreover, in the ANRS CO12Cirvir French prospective cohort, this policy of periodic surveillance of cirrhosis was successful and resulted in detection of a high proportion of small HCC, fulfilling Milan criteria in 80% of cases and enabling curative treatment in 70% of cases (4).

However, while patients with cirrhosis, whatever its etiology, are at risk of HCC and should undergo periodic surveillance, experience shows that not all of them have the same risk of developing HCC, suggesting that HCC surveillance in certain subsets of cirrhotic patients may not be cost-effective. Several potential factors have been shown to be independently associated with higher risk of HCC occurrence in patients with HCV-cirrhosis: a) host factors, including male gender (7, 8), increasing age (3, 7, 8), black origins (3), diabetes and overweight (8); b) virological factors such as detectable serum HCV RNA (9) and HCV genotypes 1 (4) or 3 (10); c) disease factors, including liver failure assessed by albumin serum level (4) and portal hypertension assessed either by low platelet count (4) or by esophageal varices (3, 7); and d) environmental factors such as tobacco intake. Conversely, other factors were identified with lower risk of HCC and might be chemoprotective in patients with HCV-cirrhosis, such as coffee consumption (11) and metformin (12) or statin treatment (13).

However, at an individual level, it remains difficult to assess the specific risk of HCC in a patient with HCV-cirrhosis, or to advise that person on the need for periodic screening for HCC. Personalized assessment of individual risk of HCC thus represents a challenge.

Therefore, the aims of this study were to build and validate a simple personalized scoring system using baseline independent variables for HCC occurrence, and to develop a nomogram for predicting HCC risk in patients with HCV-related compensated cirrhosis included in the large French prospective multicenter ANRS CO12 CirVir cohort (4).

METHODS

Patient selection

Among patients with biopsy-proven compensated (Child-Pugh A) and uncomplicated virus-related cirrhosis who were enrolled in the French multicenter ANRS CO12 CirVir cohort between March 2006 and July 2012 and prospectively followed up for development of HCC (4), those with chronic infection by HCV (positive HCV serology whatever the level of viral replication) and without HBV co-infection (negative serum HBsAg) were selected. If data on well known predictive factors for HCC occurrence in patients with cirrhosis were not available, patients were secondarily excluded.

Pre-inclusion assessment included usual clinical and biological parameters (gender, age, body mass index (BMI), diabetes, arterial hypertension, dyslipidemia, metabolic syndrome, prothrombin time, bilirubin serum level, albumin serum level, platelet count, liver enzymes (ASAT, ALAT, GGT), AFP serum level, esophageal varices, HCV genotype, HCV viral load, HIV co-infection), histological lesions of steato-hepatitis and a Doppler ultrasonography (US) to rule out complications at baseline, including HCC.

Patient information was recorded in a computerized database by a clinical research associate specifically dedicated to the ANRS CO12 CirVir cohort at each center. For all patients, past and ongoing alcohol or tobacco consumption was quantified and recorded at inclusion.

Excessive alcohol consumption was defined according to World Health Organization criteria (more than 2 glasses per day for females and more than 3 glasses per day for males); an overall minimal duration of 5 years was required.

Past medical history was also noted. In particular, the senior hepatologist in charge of a given patient at each center determined whether metabolic syndrome was present or not, based on clinical guidelines (14) and/or histological examination of liver biopsy (15).

Follow-up

Follow-up was scheduled according to French guidelines (Haute Autorité de Santé). Examination by Doppler US was performed every 6 months. For a given patient, it was recommended that US be formed at the same center by an experienced operator. A report was completed by each operator, mentioning the presence or not of focal liver lesions.

All events occurring during follow-up, liver-related or not, were recorded based on information obtained from medical files of patients at each center, and monitored by a panel of 3 dedicated clinical research associates. All treatments, including antiviral therapy, were recorded at inclusion, and any modification during follow-up was notified.

HCC diagnosis and treatment

In case of focal liver lesions detected by US, the following procedures were carried out: i) echogenicity, number and diameter of nodules (classified as <10 mm, 11-20 mm, 21-30 mm, 31-50 mm or >50 mm) and anatomic localization according to the Couinaud classification were reported; ii) portal vasculature (main trunk and branches), hepatic veins, and vena cava were systematically examined; and iii) a diagnostic procedure using contrast-enhanced imaging (CT-scan or MRI), serum alpha-fetoprotein (AFP) assay and/or guided biopsy was performed according to 2005 AASLD guidelines (6) updated in 2011 (16). HCC diagnosis was thus established either by histological examination by an experienced pathologist, or using probabilistic non-invasive criteria (mainly dynamic imaging showing early arterial hypervascularization and portal washout) according to the different periods of time (before and after 2011). When the HCC diagnosis was established, treatment was decided using a multidisciplinary approach according to AASLD or EASL guidelines for HCC (5, 6, 16). Reports of imaging techniques showing liver focal lesions were secondarily reviewed by the two senior hepatologists from institution 1 (authors VB and PN).

Antiviral treatment and viral replication

From 2006 to January 2014 (before the introduction of second-generation direct antiviral agents [DAAs] in France), all antiviral therapies conducted were interferon-based according to international guidelines. Since January 2014, patients could also receive second-generation DAAs with or without pegylated interferon and ribavirin for 12 to 24 weeks as part of early access programs, or after market approval according to national and/or international guidelines. The primary efficacy outcome was a SVR, defined as HCV RNA undetectable by qualitative polymerase chain reaction assay (< 50 IU/mL) at the end of either a 24-week untreated follow-up period for interferon-based antiviral therapies without second generation DAAs, or a 12-week untreated follow-up period for antiviral therapy, including second generation DAAs.

Statistical analyses

To internally validate the final adjusted HCC algorithm, we used a split-sample approach to assess discrimination, calibration and predictive ability of the model. We randomly divided the studied population of HCV-related Child-Pugh A cirrhosis into a development subset (2/3, on which model parameter estimates and the corresponding model-based HCC probabilities were derived) and a validation subset (1/3) to which model results were applied), and used our final model in these 2 samples.

Descriptive statistics are presented for the entire cohort and for the 2 subsets, as median [interquartile range (IQR)] for continuous variables and as numbers (percentages) for categorical data. Comparisons of patient subsets were performed using the Student t-test or Wilcoxon rank sum test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables.

The cumulative incidence of HCC was estimated in the training cohort in a competing risks framework, where deaths free of HCC were considered as competing events. Since no difference was observed with Kaplan-Meier estimates, univariate and multivariate Cox proportional hazards models were used in the training cohort to assess factors associated with occurrence of HCC. In particular, the effect of a SVR was assessed in Cox regression as a time-dependent co-variate, since patients without SVR at inclusion could be (re)treated and achieve SVR during follow-up. For these patients, end of treatment was defined as time T0, since patients with undetectable HCV RNA at that time were

considered as having a SVR. All variables tested in univariate Cox analysis with a p value less than 0.20 were tested in multivariate Cox regression.

A predictive score was then constructed as a weighted sum of all independent predictive factors for the occurrence of HCC, identified in Cox multivariate analysis. The weight of each factor was given by a linear transformation (multiplied by 3) of the estimated coefficient in Cox regression analysis and rounded off to the nearest integer. Baseline HCC-free probabilities were also estimated from Cox multivariate analysis at 1, 3 and 5 years. Predicted risks for HCC were estimated by the following equation: $1 - P_0^{\exp(\sum \tilde{\beta} \times score)}$, where P_0 was baseline HCC-free probability and $\tilde{\beta} = \frac{1}{3}$ was the inverse multiplicative coefficient used to build the HCC score. Predicted probabilities of HCC at 1, 3 and 5 years are presented for each level of the score as a nomogram.

Cumulative incidence curves according to the different risk groups of HCC determined from the score were built using a clock reset approach. Patients who switched from non-SVR to SVR status were censored at the time of SVR, which was the date of the end of treatment. The time of SVR was reset at time 0 for patients having SVR status during follow-up.

Comparison of cumulative incidence curves was assessed with univariate Cox regression analyses.

Discrimination was assessed by receiver operating curve (ROC) analysis. Overall predictive accuracy of the derived score for predicting the development of HCC at 1 and 3 years after inclusion was tested by estimating the area under the ROC curve (AUROC).

Calibration of the model was assessed by Harrell's C statistics and the correlation coefficient between predicted and observed probabilities of HCC.

The score was secondarily tested in the validation cohort.

Lastly, the score was reassessed after twelve months of follow-up.

All statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). A *P* value of 0.05 or less was considered statistically significant.

RESULTS

Among 1,671 patients consecutively enrolled between March 2006 and July 2012 in the French ANRS CO12 CirVir cohort, 1,323 patients had HCV-cirrhosis and were HBsAg-seronegative. Secondarily, 243 of them were excluded from analysis due to missing data regarding known predictive factors for HCC. Finally, 1,080 patients were analyzed and randomly assigned to training (n=720) and validation (n=360) sets (Figure 1).

Patient characteristics at inclusion were similar in the two groups, except for prothrombin time, which was slightly higher in the validation group. Patients were mainly male (64.0%), median age 55.6 years [48.9-64.0]. Median body mass index was 25.7 kg/m2. Co-morbidities were frequent, including overweight or obesity in 57.8%, diabetes in 18.9% and past excessive alcohol consumption in 31.3% of cases (median alcohol consumption 80 g/day (IQR 50-100) for 11.5 years (IQR 10-20)). Patients were mainly mono-infected (4.6% of patients with HIV co-infection) by genotype 1 (69.1%). Only 212 (19.6%) of them had SVR at baseline, confirmed at endpoint; overall, at endpoint, 427 of the 1,080 selected patients (39.5%) had SVR, including 215 who achieved SVR during follow-up (Table 1).

During a median follow-up of 51.0 months [32.3-71.9], a diagnosis of HCC was established for 142 of the 1,080 selected patients, i.e. 103 and 39 in the training and validation sets, respectively (Figure 1; Table 2).

Most HCCs were uni-nodular (n=87, 64.9%) and smaller than 30 mm (n=100, 80.0%). Portal obstruction and a serum AFP level >200 ng/mL at diagnosis were observed in 7.9% and 12.3%, respectively. Overall, 107 (75%) patients with HCC fell within Milan criteria, and curative treatment as first-line therapy was performed in 83 (66.4%). There were no significant differences in HCC characteristics between the two groups of patients (Table 2).

Training cohort

Based on multivariate Cox regression analysis, 5 out of 23 variables listed in Table 3 were independently associated with occurrence of HCC in the training cohort: age > 50 years (HR 1.94, 95% CI [1.16; 3.25], p=0.012); past excessive alcohol intake (HR 1.55, 95%CI [1.02; 2.36], p=0.041); low platelet count (< 100 Giga/mm3: HR 2.70, 95% CI [1.62; 4.51], p < 0.001; [100; 150] Giga/ mm3): HR 1.87, 95% CI [1.10; 3.18], p=0.021); GGT above the upper limit of normal (ULN): HR

1.96, 95% CI [1.11; 3.47], p=0.021); and no occurrence of SVR during the study period: HR 3.02, 95% CI [1.67; 5.48], p<0.001) (Table 3). An 11-point risk score was derived from the estimated β-regression coefficients of these 5 variables, by linear transformation (multiplied by 3) of the coefficients and rounding off (Table 4). The population was stratified into three groups according to this scoring system, with HCC occurrence gradually increasing from 2% to 30.1% at 5 years for patients with the lowest (≤ 3, n = 117, 13.8%) and highest (≥ 8, n = 349, 40.6%) HCC risk scores, respectively (p < 0.001, Figure 2A). AUROC for 1- and 3-year predictions after baseline was 0.678 [0.555-0.801] and 0.717 [0.661-0.773], respectively, in the training group. Implementation of this score after twelve months of follow-up, taking into account increasing age, new values of platelets and GGT and potential recent SVR, gave an AUROC for the 1 and 3-year predictions of 0.678 [0.574-0.783] and 0.727 [0.655- 0.800], respectively, in this subset of patients still at risk of HCC.

In order to develop an individualized prediction of HCC, a nomogram derived from this score was also built, given the 1-, 3-, and 5-year probabilities of HCC for each level of the score (Figure 3). The fit of the model was assessed by Harrell's C statistics at 0.72.

Calibration was also assessed for predicted HCC risk and observed risk, and showed a good correlation (r=.0.91, p<0.001).

Validation set

The cumulative incidence of HCC risk was estimated by the Kaplan-Meier method according to the 3 groups of the score built from the training cohort. HCC occurrence gradually increased from 0% to 20.3% at 5 years, for patients with the lowest (≤ 3, n = 64, 14.7%) and highest (≥ 8, n = 165, 37.9%) HCC risk scores (p < 0.001, Figure 2B).

In this group, the AUROC for the 3-year prediction of HCC was 0.736 [0.639-0.833], similar to that of the training group (p=0.75 between AUCs). Correlation between observed and predicted HCC risk was estimated with a coefficient at 0.86 (p<0.001)

DISCUSSION

Our results show that personalized prediction of HCC using easily available variables is feasible in

patients with HCV-related cirrhosis. Indeed, a simple score combining 4 baseline variables and 1 time-dependent variable was accurate in predicting HCC at the individual level in a large prospective cohort of French patients with HCV-cirrhosis. Relevant baseline independent variables used in this score were in accordance with the literature; indeed, increasing age (3, 7, 8), low platelet counts (4) and detectable serum HCV RNA (9) are the usual predictive factors for occurrence of HCC in patients with cirrhosis.

Conversely, it takes in account an original variable - the serum level of GGT - that was less frequently reported as an independent predictive factor for HCC (17-19) and not previously used by another scoring system. This simple test mainly summarizes the weight of co-morbidities, as patients with GGT above ULN (76%) had a higher body mass index (25.9 [23.1 – 29.1] vs 25.4 [22.7 – 28.1], p = 0.038), more frequent dyslipidemia (6% vs 3.2%, p = 0.042) and more frequent histological evidence of steato-hepatitis (44.8% versus 25.5 %, p = 0.01). Conversely, patients with GGT above the upper limit of normal did not have an increased proportion of diabetes (20.1% vs 16.4%, p = 0.13), suggesting that increased serum GGT could be a very early surrogate marker of insulin resistance. Furthermore, an increased serum level GGT (> ULN) is usually associated with more severe liver disease.

This model, which can be easily applied to clinical practice, performed well in terms of discrimination (AUROC for 1- and 3-year predictions was 0.678 [0.555-0.801] and 0.717 [0.661-0.773], respectively, in the training group) in a split derivation sample of patients with HCV-related cirrhosis. Internal validation in the split sample confirmed the accuracy of this score in predicting HCC; the derived nomogram had good calibration, with an accurate correlation between predicted and observed HCC risk (r= 0.91). Moreover, updating of the score value 12 months after inclusion for patients still at risk of HCC was able to predict, with the same discriminatory accuracy, the risk of HCC, demonstrating the evolutive capacity of the score.

Numerous personalized risk-scoring systems constructed using baseline-independent variables for HCC occurrence had been previously developed and validated in patients with cirrhosis due to various causes (8, 20, 21), and more recent ones are targeting patients with hepatitis B (22-24). In the last few

years, Asian groups have derived and validated several HCC risk scores based on well-known risk factors such as cirrhosis, age, male sex and high HBV viral load (REACH-B, GAG-HCC, CU-HCC) (22-24). Overall, these recent scores have shown a high negative predictive value of over 95% for excluding HCC development in 3 to 10 years. These HCC risk scores were tested in several Western cohorts (25, 26), and appeared less effective in Caucasians.

In patients infected by HCV, a risk score for HCC was built whatever the stage of fibrosis (27, 28) and only one algorithm for HCC detection was developed and validated in American veterans with HCV-related cirrhosis (29), and in broader populations. While all risk scores for HCC in patients with HBV included viral load (22-24), no risk score for HCC in patients with HCV took into account a SVR.

The enhanced HCC risk assessment in our model would enable personalized screening practices. The algorithm could optimize HCC surveillance by reducing false-positives, thus having considerable impact upon subsequent testing, reducing surveillance costs and avoiding unnecessary patient/provider anxiety, while optimizing approximations of individualized patient risk. HCC risk assessments yielded by our model-based instrument can be used to create a binary decision rule for clinical action; for example, if HCC probability exceeds 20% at 5 years, then additional testing (e.g. cross-sectional imaging) could be performed. In contrast, in a very select group of patients (around 15%) with very low HCC risk (score $\leq$ 3, 5 years; HCC cumulative incidence around 2%), the need for HCC surveillance is questionable. However it is premature to adopt fixed cutoffs at this time.

The strengths of our study lie in the following: i) the homogeneity of patients selected using stringent criteria, particularly biopsy-proven cirrhosis; ii) its prospective design, conducted at 35 centers, with systematic periodic surveillance by liver imaging for HCC screening according to international guidelines; iii) stringent monitoring of all events during follow-up, in particular HCC; iv) internal validation of results in the split sample; and vi) the fact that SVR was taken into account. Conversely, our study had several limitations, mainly linked to the small number of patients with SVR at endpoint (39.5%), due to an inclusion period prior to introduction of second-generation DDAs in clinical practice. (30, 31). However, due to the high financial cost of these new antiviral treatments, only a

minority of patients with HCV-cirrhosis worldwide had received them, even in Western countries, mainly in Europe. In addition, this HCC score could be used in countries with limited resources. Finally, our score could be applied to SVR patients whose risk scores varied from 0 to 9, with a cumulative risk of HCC at five years ranging from 0 (for a score ≤ 3) to 30.1% (for a score ≥ 8). In addition, external validation outside of France is warranted. Interestingly, we showed that the score could be accurately updated with increasing age, but also with alterations in biochemical values and modification of viral status.

In conclusion, an HCC score constructed using 4 baseline variables (age, past excessive alcohol consumption, platelet count, GGT serum level) and SVR considered as a time-dependent covariate can accurately predict HCC occurrence at an individual level in a prospective French cohort of patients with HCV-cirrhosis. It can provide individualized estimation of HCC risk of occurrence in patients with HCV-cirrhosis whatever their viral status, and can be periodically reassessed in order to decide whether or not they should be included in a surveillance program. External validation in non-French populations is warranted.

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FIGURES LEGENDS

Figure 1: Flow chart for patient selection. Among 1,671 patients consecutively enrolled between March 2006 and July 2012 in the French ANRS CO12CirVir cohort, 1,323 had HCV-cirrhosis and were HBsAg-seronegative. Secondarily, 243 of them were excluded from analysis due to missing data of interest (well-known predictive factors for HCC occurrence). Finally, 1,080 patients were analyzed and randomly assigned to the training (n=720) or validation (n=360) set.

Figure 2: Incidence of HCC according to predictive score:

A. In the training set (n = 720): Three groups were selected, with HCC occurrence gradually increasing from 0% to 30.1% at 5 years, for patients with the lowest (≤ 3) and highest (≥ 8) HCC risk scores ($p < 0.001$);

B. In the validation set (n = 360): Three groups were selected, with HCC occurrence gradually increasing from 0% to 20.3% at 5 years, for patients with the lowest (≤ 3) and highest (≥ 8) HCC risk scores ($p < 0.001$).

**Since SVR is a time-dependent variable, the total number of patients at risk seems higher than expected: patients achieving SVR during follow-up were considered before SVR and after SVR for the corresponding time.*

Figure 3: Nomogram for individualized prediction of HCC occurrence at 1, 3 or 5 years. A nomogram derived from the score was also built, enabling individualized prediction of HCC occurrence at 1, 3 or 5 years for each level of the score. The fit of the model was assessed by Harrell's C statistics at 0.72. Calibration was also assessed for predicted HCC risk and the observed risk and showed a good correlation ($r=.0.91$, $p < 0.001$).

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