Version of Record: https://www.sciencedirect.com/science/article/pii/S0304380020304129
Manuscript_4cc229d22d8dfa8f0d4261dd9b928750

Personalized surveillance for hepatocellular carcinoma in cirrhosis – using machine learning adapted to HCV status

Short title: Liver cancer in HCV cirrhotic patients with SVR

Etienne Audureau[1], Fabrice Carrat[2], Richard Layese[1], Carole Cagnot[3], Tarik Asselah[4], Dominique Guyader[5], Dominique Larrey[6], Victor De Lédinghen[7], Denis Ouzan[8], Fabien Zoulim[9], Dominique Roulot[10], Albert Tran[11,12], Jean-Pierre Bronowicki[13], Jean-Pierre Zarski[14], Ghassan Riachi[15], Paul Calès[16], Jean-Marie Péron[17], Laurent Alric[18], Marc Bourlière[19], Philippe Mathurin[20], Jean-Frédéric Blanc[21], Armand Abergel[22], Olivier Chazouillères[23], Ariane Mallat[24], Jean-Didier Grangé[25], Pierre Attali[26], Louis d'Alteroche[27], Claire Wartelle[28], Thông Dao[29], Dominique Thabut[30], Christophe Pilette[31], Christine Silvain[32], Christos Christidis[33], Eric Nguyen-Khac[34], Brigitte Bernard-Chabert[35], David Zucman[36], Vincent Di Martino[37], Angela Sutton[38,39,40], Stanislas Pol[41,42], Pierre Nahon[43,44,45] for the ANRS CO12 CirVir group.

[1]AP-HP, Hôpital Henri Mondor, Département de Santé Publique, and Université Paris-Est, A-TVB DHU, CEpiA (Clinical Epidemiology and Ageing) Unit EA7376, UPEC, F-94000, Créteil; [2]Sorbonne Université, Inserm, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France; AP-HP, Hôpital Saint-Antoine, Unité de Santé Publique, Paris, France ; [3]Unit for Basic and Clinical research on Viral Hepatitis, ANRS (France REcherche Nord & sud Sida-HIV Hépatites-FRENSH), [4]AP-HP, Hôpital Beaujon, Service d'Hépatologie, Clichy; [5]CHU Pontchaillou, Service d'Hépatologie, Rennes; [6]Hôpital Saint Eloi, Service d'Hépatologie, Montpellier; [7]Hôpital Haut-Lévêque, Service d'Hépatologie, Bordeaux; [8]Institut Arnaud Tzanck, Service d'Hépatologie, St Laurent du Var; [9]Hospices Civils de Lyon, Service d'Hépatologie; INSERM U1052 - CRCL; Université de Lyon, Lyon; [10]AP-HP, Hôpital Avicenne, Service d'Hépatologie, Bobigny; [11]CHU de Nice, Service d'Hépatologie, F-06202, Cedex 3, Nice; [12]Inserm U1065, C3M, Team 8, "Hepatic Complications in Obesity", F-06204, Cedex 3, Nice; [13]Inserm 954, CHU de Nancy, Université de Lorraine,

© 2020 published by Elsevier. This manuscript is made available under the CC BY NC user license
https://creativecommons.org/licenses/by-nc/4.0/

Vandoeuvre-les-Nancy; [14]Hôpital Michallon, Service d'Hépatologie, Grenoble; [15]Hôpital Charles-Nicolle, Service d'Hépatologie, Rouen; [16]CHU d'Angers, Service d'Hépato-Gastroentérologie, Angers; [17]Hôpital Purpan, Service d'Hépatologie, Toulouse; [18]CHU Toulouse, Service de Médecine Interne-Pôle Digestif UMR 152, Toulouse; [19]Hôpital Saint Joseph, Service d'Hépatologie, Marseille; [20]Hôpital Claude Huriez, Service d'Hépatologie, Lille; [21]Hôpital St André, Service d'Hépatologie, Bordeaux et Hôpital Haut-Lévêque, CHU Bordeaux, 33604 Pessac; [22]Hôpital Hôtel Dieu, Service d'Hépatologie, Clermont-Ferrand; [23]AP-HP, Hôpital Saint-Antoine, Service d'Hépatologie, and Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine, Paris; [24]AP-HP, Hôpital Henri Mondor, Service d'Hépatologie, Créteil; [25]AP-HP, Hôpital Tenon, Service d'Hépatologie, Paris; [26]AP-HP, Hôpital Paul Brousse, Service d'Hépatologie, Villejuif; [27]Hôpital Trousseau, Unité d'Hépatologie, CHRU de Tours; [28]Hôpital d'Aix-En-Provence, Service d'Hépatologie, Aix-En-Provence; [29]Hôpital de la Côte de Nacre, Service d'Hépatologie, Caen; [30]AP-HP, Groupe Hospitalier de La Pitié-Salpêtrière, Service d'Hépatologie, Paris; [31]CHU Le Mans, Service d'Hépatologie, Le Mans; [32]CHU de Poitiers, Service d'Hépatologie, Poitiers; [33]Institut Mutualiste Montsouris, Service d'Hépatologie, Paris; [34]CHU Amiens Picardie Hôpital Sud, Service d'Hépatologie, Amiens; [35]Hôpital Robert Debré, Service d'Hépatologie, Reims; [36]Hôpital Foch, Service de Médecine Interne, Suresnes; [37]Hôpital Jean Minjoz, Service d'Hépatologie, Besançon, [38]CRB (liver disease biobank) Groupe Hospitalier Paris Seine-Saint-Denis BB-0033-00027 ; [39]AP-HP, Hôpital Jean Verdier, Service de Biochimie, Bondy; [40]Inserm U1148, Université Paris 13, Bobigny ; [41]AP-HP, Hôpital Cochin, Département d'Hépatologie; [42]Inserm UMS20 et U1223, Institut Pasteur, Université Paris Descartes, Paris ; [43]AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy; [44]Université Paris 13, Sorbonne Paris Cité, "Equipe labellisée Ligue Contre le Cancer", F-93206 Saint-Denis; [45]Inserm, UMR-1162, "Génomique fonctionnelle des tumeur solides", F-75000, Paris, FRANCE.

Correspondence: Pierre Nahon

Service d'Hépatologie, Hôpital Jean Verdier, 93140 Bondy, France

Email: pierre.nahon@aphp.fr

Tel: 33-1-48-02-62-80

Fax: 33-1-48-02-62-02

Keywords: cirrhosis; HCV clearance; liver cancer; screening; machine learning.

Abbreviations: DAA: direct antiviral agent; HCC: hepatocellular carcinoma; PLC: primary liver cancer; SVR: sustained virological response; US: ultrasound.

Electronic word count: 5985, **Tables:** 4**, Figures:** 3**, eTables:** 4, **eFigures:** 2, **References:** 36.

Grant Support: ANRS (France REcherche Nord & sud Sida-HIV Hépatites-FRENSH).

Disclosures: Dr. Nahon has received honoraria from and/or consults for Abbvie, AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Gilead, Ipsen, MSD, Roche. He received research grants from Abbvie and Bristol-Myers Squibb. Dr. Pol consults for and has received grants from Bristol-Myers Squibb, Gilead, Roche, and MSD. He consults for Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Abbvie, Roche and MSD. Dr. Guyader has received honoraria and/or grants from Abbvie, Gilead, Janssen and MSD.

Conflicts of interest: none to declare

Author contributions: Drs. Nahon and Audureau had full access to all data in the study and take responsibility for data integrity and the accuracy of data analysis.
Study concept and design: Nahon, Audureau.
Acquisition of data: Nahon, Bourcier, Layese, Marcellin, Guyader, Pol, Larrey, De Lédinghen, Ouzan, Zoulim, Roulot, Tran, Bronowicki, Zarski, Riachi, Calès, Péron, Alric, Bourlière, Mathurin, Blanc, Abergel, Chazouillères, Mallat, Grangé, Attali, Bacq, Wartelle, Dao, Thabut, Pilette, Silvain, Christidis, Nguyen-Khac, Bernard-Chabert, Zucman, Di Martino, Roudot-Thoraval.
Analysis and interpretation of data: Nahon, Layese, Sutton, Audureau.
Drafting of the manuscript: Nahon, Audureau.
Critical revision of the manuscript for important intellectual content: Nahon, Marcellin, Guyader, Larrey, De Lédinghen, Ouzan, Zoulim, Audureau, Pol, Carrat.
Statistical analysis: Layese, Audureau.
Validation cohort: Pol, Carrat.
Obtained funding: Prof Jean-Claude Trinchet
Administrative, technical and material support: Nahon, Bourcier, Cagnot, Layese, Roudot-Thoraval, Audureau.
Study supervision: Nahon, Audureau.

ABSTRACT

Background and Aims: To develop algorithms based on machine learning predictive approaches to refine individualized predictions of hepatocellular carcinoma (HCC) risk according to HCV eradication in patients with cirrhosis included in the French ANRS CO12 CirVir cohort.

Methods: Patients with compensated biopsy-proven HCV-cirrhosis were included in 35 centers and followed a semi-annual HCC surveillance program. Three prognostic models for HCC occurrence

were built, using (1) Fine-Gray regression as a benchmark, (2) single decision tree (DT), and (3) random survival forest for competing risks survival (RSF). Model performance was evaluated from C-indexes validated externally in the ANRS CO22 Hepather cohort (N=668 enrolled between 08/2012-01/2014).

Results: 836 patients were analyzed, among whom 156 (19%) developed HCC and 434 (52%) achieved sustained virological response (SVR) (median follow-up: 63 months). Fine-Gray regression models identified six independent predictors of HCC occurrence in patients before SVR: past excessive alcohol intake, genotype 1, elevated alpha-fetoprotein and GGT, low platelet count and albuminemia; and three in patients after SVR: elevated AST and low platelet count and PT. DT analysis confirmed these associations but revealed more complex interactions, yielding eight patient groups with differentiated cancer risks and varying predictors involved depending on SVR achievement. RSF ranked platelet count GGT, AFP and albuminemia as the most important predictors of HCC in non-SVR patients, and prothrombin time, ALT, age and platelet count after SVR achievement. Externally-validated C-indexes before/after SVR were 0.64/0.64 [Fine-Gray], 0.60/62 [DT] and 0.71/0.70 [RSF].

Conclusions: Risk factors for hepatocarcinogenesis differ according to SVR status. Machine learning algorithms can prove useful to individually assess HCC risk by revealing complex interactions between cancer predictors. Such approaches could help developing more cost-effective tailored surveillance programs.

Electronic Word Count: 274

Lay Summary

Patients with HCV-related cirrhosis must be included in liver cancer surveillance programs using ultrasound examination every 6 months, even after viral eradication. However, hepatocellular carcinoma (HCC) screening is hampered by sensitivity issues leading to cancer diagnosis at advanced stages in a substantial number of patients. Refining surveillance periodicity and modality using more sophisticated imaging techniques such as MRI may only be cost-effective in patients with the highest HCC incidence. Using machine learning algorithms (i.e. data-driven mathematical models to make predictions or decisions), this study highlights how such methods can refine the individualized

prediction of HCC risk in patients with compensated HCV cirrhosis as a function of their virological status.

Highlights

- HCC surveillance programs must be refined and personalized according to liver cancer incidence.
- Machine learning algorithms can prove useful to individually assess HCC risk by revealing complex interactions between cancer predictors.
- Their application in patients with HCV cirrhosis enabled the identification of novel HCC risk classes.
- This stratification differs according to SVR status.
- These approaches could trigger personalized and cost-effective HCC surveillance programs in HCV cirrhosis.

INTRODUCTION

Monitoring for hepatocellular carcinoma (HCC) in cirrhotic patients based on bi-annual ultrasound examinations (US) [1] is cost-effective [2] and associated with increased survival [3]. However and due to patients heterogeneity, it remains difficult to assess the specific risk at the individual level [4]. Furthermore, substantial numbers of patients included in surveillance programs are still diagnosed with advanced HCC [5], particularly because of the poor sensitivity of US in detecting HCC at a very early stage (smaller than 2 cm) [6]. While contrast-enhanced imaging techniques such as magnetic resonance imaging (MRI) could markedly improve early HCC detection [7], implementing such costly surveillance programs may however not be cost-effective in certain subsets of cirrhotic patients because of their particularly low annual incidence of HCC [2].

This is notably the case in HCV-infected patients with cirrhosis who achieve a sustained virological response (SVR) in whom the risk of HCC is strikingly low [8] thanks to the wide use of direct-acting antiviral agents (DAAs) [9]. Thus, identifying patients with a particularly low risk of HCC while reinforcing screening programs in high-risk individuals is of paramount importance to defining what policy makers will consider as feasible, cost-effective and safe.

Until now, simple scoring systems have been developed from varying combinations of routine clinical features, yet taking no account of population heterogeneity and/or viral eradication [10]. In this instance, machine learning algorithms (i.e. data-driven mathematical models to make predictions or decisions) such as decision-tree based approaches can prove very effective in identifying high-order interactions between predictors that might have been overlooked by conventional statistical approaches [11] but still remain underused in biomedical research.

The aim of this study was therefore to develop new prognostic algorithms based on decision-tree-based survival analyses in order to refine the individualized prediction of the risk of HCC in patients with compensated HCV cirrhosis treated for a viral infection included in the prospective ANRS CO12 CirVir cohort [12] as a function of their virological status.

METHODS

This study was sponsored and funded by the French National Research Agency (ANRS). The protocol was approved by an Ethics Committee (Comité de Protection des Personnes, Aulnay-sous-Bois, France) and complied with the ethical guidelines of the 1975 Declaration of Helsinki. All patients gave their written informed consent to participate in the cohort. The full CirVir protocol is available via the ANRS website (http://anrs.fr). The CirVir cohort has been previously extensively described [3, 8, 12-17].

Patient selection

This work was an ancillary study derived from the CirVir cohort [12] with specific goals and objectives redefined according to the STROBE statement [18]. Patients were recruited in 35 French clinical centers between 2006 and 2012. The selection criteria were: a) age over 18 years; b) histologically proven cirrhosis, whatever the time of biopsy; c) active HCV replication; d) an absence of previous complications of cirrhosis (particularly ascites, gastrointestinal hemorrhage or HCC; e) patients belonging to Child-Pugh class A; f) absence of severe uncontrolled extrahepatic disease resulting in an estimated life expectancy of less than one year. For the present study, patients who achieved SVR prior to inclusion were excluded from the analyses to enable an accurate evaluation of the time-varying prognostic value of SVR. The pre-inclusion assessment included standard clinical and biological parameters, and when available liver stiffness measurement (LSM) by Fibroscan®; patients with metabolic features (MF) were defined by BMI≥25 kg/m^2 and/or diabetes and/or dyslipidemia at baseline. Missing biological data were assessed from frozen serum samples provided by the CRB (Liver Disease Biobank at the Groupe Hospitalier Paris Seine-Saint-Denis BB-0033-00027). A Doppler US examination was also performed to verify the inclusion and non-inclusion criteria. Patient information was recorded in a computerized database by clinical research associates specifically dedicated to the ANRS CO12 CirVir cohort in each center. For all patients, past and ongoing alcohol and tobacco consumption levels were quantified and recorded at inclusion. Their past medical history was also recorded.

Follow-up

Patients were seen by physicians every six months, and the usual clinical and biological data were recorded. Doppler US examinations were performed every six months. In a given patient, it was recommended that the US be performed at the same center by an experienced operator. A report was completed by each operator, mentioning the presence or not of focal liver lesions. If a focal liver lesion was detected, 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 [19] as updated in 2011 [20]. When the HCC diagnosis was established, treatment was determined using a multidisciplinary approach according to AASLD guidelines for HCC [19, 20]. All patients were followed-up uniformly according to these international recommendations, irrespective of their SVR status.

All events that occurred during follow-up (i.e. death, HCC occurrence, liver decompensation [21, 22], bacterial infections [17], extrahepatic malignancies [13] and cardiovascular diseases [14] were recorded using information obtained from the medical records of the patients held by each center.

Likely cause(s) of death were established. Patients who underwent liver transplantation were censored for analysis at the date of transplantation. All treatments, including antiviral therapies, were recorded at inclusion, and any modifications during follow-up were notified, particularly in the case of severe adverse events. All the information recorded during follow-up was secondarily monitored by the same panel of three clinical research associates located at institution 2 (AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy, Université Paris 13). All medical diagnoses of events occurring during follow-up were confirmed by two senior hepatologists (authors VB and PN). When a given event occurred during an interferon-based treatment, this was clearly described in the database. Data analysis was conducted using data available through December 31, 2016.

Antiviral therapies and viral replication

All patients included in the cohort received at least one antiviral therapy during follow-up. Before 2014, all antiviral therapies implemented were interferon-based [23]. Patients with HCV genotypes 1 or 4 infection received peg-interferon (Peg-IFN) plus a standard dose of ribavirin (RBV, 1,000 mg/day for a body weight <75 kg or 1,200 mg/day for a body weight >75 kg) for 48 weeks. Patients with HCV

genotypes 2 or 3 infection received Peg-IFN plus low-dose RBV (800 mg/day) for 16 or 24 weeks. After 2011, genotype 1 patients could also receive either 12 weeks of telaprevir (TVR, 750 mg every 8h) in combination with Peg-IFN and RBV and then 36 weeks of Peg-IFN/RBV, or 4 weeks (lead-in phase) of Peg-IFN and RBV and then 44 weeks of Peg-IFN/RBV and boceprevir (BOC, 800 mg every 8h) according to the European label. Since February 2014, interferon-free regimens have gradually become available for cirrhotic patients in France and are prescribed and reimbursed for all HCV genotypes. A sustained virological response (SVR) was defined as undetectable HCV RNA by a qualitative polymerase chain reaction (PCR) assay (<50 IU/mL) at the end of a 12-week untreated follow-up period [24].

Definition of endpoints

The primary endpoint was HCC occurrence measured from the date of enrollment to the date of HCC diagnosis or last follow-up. SVR achievement during follow-up was defined at the end of treatment that resulted in undetectable HCV RNA levels. An event was arbitrarily considered as occurring in a patient who achieved SVR if it was recorded at least one year after successful treatment completion. All analyses were conducted using a time dependent approach considering covariates at baseline for all patients and covariates updated at the time of SVR for those patients having ultimately achieved SVR (maximal two timepoints). All patients could possibly switch over time from non-SVR to SVR status and thus contribute to the estimates of the corresponding category. In addition to the SVR variable, other time-dependent covariates included clinical and biological features measured at baseline and updated at the time of SVR (namely, AST, ALT, GGT, AFP, prothrombin time, albumin, bilirubin, platelet count, BMI), while time-independent covariates (including demographics and genotype) were analyzed based on baseline values.

Validation cohort

A subset of patients from the national ANRS CO22 Hepather cohort served as external validation [25]. The ANRS CO22 Hepather cohort is a French national, multicentre, prospective, observational cohort study of patients with HBV or HCV infection, which started in August, 2012 among whom 3045 had active HCV-related cirrhosis at inclusion. Among the latter, a subset of 668 patients consecutively enrolled between 08/2012 and 01/2014 and who responded to similar inclusion criteria as those

included in the CirVir cohort were selected (except for histological diagnosis of cirrhosis). All cirrhotic patients from the Hepather cohort were included in HCC surveillance programs. Follow-up, antiviral treatment and definition of endpoint were identical as in the CirVir cohort.

Statistical analyses

Descriptive results were presented as median [interquartile range (IQR)] for continuous variables and as numbers (percentages) for categorical data.

Consistent with our objective, three modeling approaches to HCC prediction were implemented and compared for their predictive performance and clinical significance. First, Fine-Gray competing risks regression modeling was used to provide a benchmark for comparison with decision-tree based models because of its widespread use, ability to identify independent predictors while accounting for the competing risk of death or liver transplant, and generally good understanding by clinicians. A stepwise backward approach was applied for multivariate analysis based on the Akaike Information Criterion (AIC). Sub-hazard ratios (SHR) were reported along with their 95% confidence intervals, while regression coefficients (log(SHR)) were considered for use as weights to compute a predicted risk score estimated from the final model. All continuous predictors were both assessed as continuous variables and additionally categorized into binary variables, using univariate recursive partitioning analysis to identify the optimal threshold for each variable.

Second, a single decision tree was built by recursive partitioning analysis using the conditional inference tree methodology [26], because of its visual appeal to illustrate the main relationships at play, despite generally less robust predictions and a known tendency for overfitting. In a nutshell, decision trees automatically identify the optimal splits in data to partition the population into subgroups with differentiated HCC risks. Starting with all observations, the process is repeated recursively until a stopping criterion is met. We applied the conditional inference tree methodology which offers several advantages; these include unbiased variable selection (conventional methods are biased towards continuous variables with numerous possible splits), the non-necessity to prune the tree given the split selection process based on statistical tests, and the fact that the algorithm generates p-values that are helpful to quantify the level of confidence that can be achieved at each split.

Finally, we derived prognostic algorithms using a random survival forest approach for competing risks survival data, because of its generally higher predictive performance and lower proneness to overfit. Random forests combine the results obtained from a large ensemble of trees (1000 in the present analysis), thus avoiding the problem of selecting a single tree of appropriate size and often producing more powerful and stable predictive models [27]. Unlike Fine-Gray modeling or single decision trees, random forests do not produce regression coefficients or decision paths to enable direct interpretation of the complex underlying prognostic model, so they are sometimes viewed as "black-boxes". Variable importance measures (VIMP) were thus computed to help quantify the importance of each predictor within the random forest, by examining the increase in prediction error when a perturbation is added to the variable. VIMP was calculated by implementing the Breiman-Cutler permutation principle for a conditional RF approach [28].

Because of the well-known benefits from SVR achievement, all modeling analyses were stratified on time-varying SVR status and were hence based either on predictors measured at baseline considering follow-up information until HCC occurrence, SVR or last follow-up (No SVR models), or on predictors measured at the time of SVR, if any (SVR models).

For all three modeling approaches, risk classes were generated based on tertiles of the predicted 5-year HCC risk. The discrimination performance of the prognostic models was assessed after external validation in the Hepather cohort by computing the Wolber's concordance index (C-index) for prognostic models with competing risks [29] which measures the probability of concordance between predicted and observed survival [30]. Calibration plots were generated to assess the agreement between observed outcomes and predicted survival probabilities. Cumulative incidence curves were plotted accounting for the competing risk of death or liver transplant.

Model development in the CirVir derivation cohort was based on patients with complete information for biological and key clinical variables, namely gender, age, past excessive alcohol intake, diabetes, dyslipidemia, hypertension and HCV genotype. Variables required for validation but with missing information in the Hepather cohort were imputed using the k-nearest neighbors (kNN) methodology.

Descriptive and Fine-Gray regression analyses were performed using Stata v15.1 (StataCorp, TX, USA), and decision tree and random forests with R v3.4.0 (R Foundation for Statistical Computing, Vienna, Austria; using randomForestSRC, party, partykit [26] and VIM packages).

RESULTS

Inclusion period and baseline characteristics of patients

A total of 1429 HCV-infected patients were included between 2006 and 2012 in the CirVir cohort (derivation cohort). Among them, 176 were subsequently excluded from our analysis after a revision of the individual data, either because of non-compliance with the inclusion criteria (n=69), the withdrawal of consent (n=6) or HBV/HIV-co-infection (N=101). Consequently, 1253 patients were considered, of whom 249 had achieved SVR before inclusion and 103 had a missing status or time of achievement for SVR, and 65 had missing information regarding key covariates as defined in the methods section. The remaining 836 patients constituted the study sample in which all prognostic models were developed (**Table 1**).

Virological response during follow-up

Median duration of follow-up was 63 months (interquartile range IQR: 36 – 89). During follow-up, a total of 434 patients (51.9%) achieved SVR (237 following an Interferon-based therapy). The median time period from inclusion to treatment was 0.5 months [range: 0 – 18.9]. The median duration of follow-up after SVR was 23 months (IQR: [15 – 46]; range: [0.3 – 114.3]).

Incidental cases of HCC and survival

Following a diagnostic procedure, a diagnosis of primary liver cancer (PLC) was established in 160 patients: HCC (n=156 [18.7%]; 5-yr cumulative incidence corrected for competing risks 19.3%) and intra-hepatic cholangiocarcinoma (n=4). The characteristics of HCC at diagnosis according to SVR status are shown in **eTable 1.** During follow-up, 172 patients (20.6%) presented with ≥1 episode of liver decompensation. A total of 1,247 extrahepatic events were recorded in 522 patients and included 111 cardiovascular events in 78 patients and 66 extrahepatic cancers.

Overall, 162 patients (19.4%) died during follow-up, which corresponded to a 5-year overall survival rate of 86.7%, and 38 patients (4.5%) were transplanted before any HCC occurred. Seventy-nine patients (48.8%) died of liver-related complications, while 58 extrahepatic events (35.8%) were responsible for the remaining deaths [missing data=25, 15.4%]. A progression of PLC was the most common liver-related cause of death (n=46; 28.4%).

Prognostic model using the Fine-Gray competing risks regression method

Tables 2 and 3 show the results of the unadjusted and multivariate Fine-Gray survival analyses according to SVR status. Under univariate analysis, factors significantly associated with an increased risk of HCC included in patients before SVR a past excessive alcohol intake, HCV genotype 1, elevated levels of AST, GGT, alkaline phosphatase and alpha-foetoprotein, and a lower platelet count, lower serum albumin and shorter prothrombin time. Stepwise multivariate analysis identified six variables independently associated with an increased risk of HCC, including a past excessive alcohol intake, HCV genotype 1, decreased serum albumin levels, increased serum AFP and GGT levels, a lower platelet count. No statistical difference was found between SVR achieved using DAA or DAA-free regimens. In patients who achieved SVR, three variables were ultimately kept in multivariable analysis, including elevated levels of AST, low platelet count (<70 x 10^3/mm3) and PT (≤85).

Prognostic model using single tree recursive partitioning

A recursive partitioning approach was then used to build the single decision trees shown in **Figure 1**. Five main predictors were identified by the algorithm, yielding eight groups (5 before SVR and 3 after SVR was achieved) from various combinations of these predictors and demonstrating markedly contrasted risks of HCC, as shown by the corresponding curves at each end node. Among non-SVR patients (**Figure 1A**), two groups had the highest risk of HCC: Group 1 defined by lower serum albumin levels (≤40 g/L) and a lower platelet count (≤180 10^3/mm^3), and Group 3 defined by unchanged serum albumin levels but a lower platelet count, though at an automatically detected lower threshold (≤170 10^3/mm^3). Two groups were at moderate HCC risk, either expressly defined by an impaired albuminemia (Group 2) or an elevated GGT level (>2.5xULN). It should be noted that Group 4, defined by a combination of preserved serum albumin, platelet count and GGT levels, was characterized by a very low risk of HCC, despite their failure to achieve SVR. In SVR patients

(**Figure 1B**), combinations of AST (≤2.5xN vs. 2.5) and PT (≤85% vs. >85%) defined two groups with a moderate risk of HCC (Groups 6 and 8), while Group 7 (characterized by preserved AST and PT levels) was associated with a very low risk of HCC.

The clinical and biological characteristics of the eight groups generated by decision tree analysis are depicted in **eTable 2** and summarized in radar plots (**eFigure 1)** with respect to liver features. In high HCC risk Groups 1 and 3, several other features were clearly impaired in addition to the criteria identified by decision tree analysis (i.e. platelet count, albuminemia), and included AST, ALT, AFP and PT (Group 1), and to a lesser extent AST and ALT (Group 3). By contrast, Group 4 was characterized by globally optimal liver parameters, and notably more favorable values at ultrasound elastography (**eTable 2**). In SVR patients, Group 7 with the lowest risk of HCC displayed globally preserved liver function but a moderately lowered platelet count, while Groups 6 and 8 with a moderate HCC risk showed worsened liver function, particularly in patients from Group 8 who had the worst liver phenotype with elevated AST, ALT and GGT levels. No statistically significant differences were found across the groups regarding past excessive alcohol intake and parameters relative to metabolic syndrome (diabetes, BMI, dyslipidemia) to the exception of arterial hypertension. **eFigure 2** shows overall survival in patients without or prior achievement of SVR (panel A) or after SVR achievement (panel B). Overall, patients belonging to the highest HCC risk groups had the lowest probability of survival.

Prognostic models using random survival forests

Finally, random forests were constructed by aggregating 1000 decision trees. **Figure 2** ranks the predictors in order of their relative importance in the random forest algorithm, with high importance values indicating the most influential variables predictive of HCC. Random forest approaches conducted separately in patients at baseline before SVR was achieved, if any (**panel A**), or at the time of SVR, if any (**panel B**), confirmed the results of the single decision tree analysis previously described, identifying platelet count, GGT, AFP and albuminemia as highly predictive in patients without SVR, and PT, ALT, age, platelet count and AST in patients with SVR. In addition, and as shown by the descriptive analyses of the eight groups from the decision tree, other variables were identified as having a potential but weaker influence, including GGT and AFP.

Discrimination performance and calibration in the external validation cohort

Main characteristics of the validation cohort at baseline are detailed in **eTable 3** (88% males, 46% achieving SVR during follow-up, 22% HCC occurrence; median follow-up: 52 months (IQR 32-62) and median post-SVR follow-up: 36 months (IQR 21-44)).

Discrimination performance of all models were computed and compared in the validation cohort, yielding the following C-indexes: i) Before SVR: Fine-Gray model 0.645 (bootstrapped 95% confidence interval 0.592-0.699), single decision tree 0.598 (0.549-0.648), random survival forest 0.715 (0.670-0.760); ii) After SVR: Fine-Gray model 0.638 (0.533-0.770), single decision tree 0.623 (0.531-0.728), random survival forest 0.698 (0.620-0.776) (**Table 4**). To illustrate the clinical value of each model for discriminating between patients with differentiated risk, three risk categories (low, moderate, high) were determined based on tertiles of the predicted 5-year HCC risk yielded by the two main modeling approaches (i.e. Fine-Gray modeling and Random Survival Forest). **Figure 3** (1. before SVR and 2. after SVR) show the resulting 5-year cumulative incidence curves of HCC (left panels **A** and **C**). Consistent with the computed C-indexes, a clearly graded relation between predicted risk and observed HCC occurrence was apparent in patients before SVR for random forest, whereas discrimination was seemingly lower for Fine-Gray model (particularly in the low/moderate categories). Separation between risk categories was less clear in patients after SVR for both models, but random forests remarkedly discriminated the subgroup with the lowest 5-year HCC risk. Detailed predicted HCC risk and observed 5-year HCC incidence are given in **eTable 4**. Calibration plots **(Figure 3,** right panels **B** and **D**) indicated a general underestimation of the HCC risk predicted by Fine-Gray models, while random forests demonstrated a very good calibration in patients before SVR and overall good calibration in patients after SVR with a slight overestimation of HCC risk in the first HCC risk tertile.

DISCUSSION

These analyses, performed by applying machine learning techniques adapted to time-varying information, enabled the identification of novel associations between HCC risk factors in patients with compensated HCV-related cirrhosis, with notably differentiated results found as a function of achieving SVR. While previously developed predictive models mostly relied on standard regression modeling approaches using combinations of features independently and globally associated with liver cancer [31], we applied decision-tree based approaches in order to exploit their ability to model complexity and identify more specific combinations between prognostic factors. In addition, the development of models in the CirVir cohort (2006-2017) [12] and their validation in the Hepather cohort (2012-2019) [25] present several advantages as this approach covers different eras of antiviral therapy. Indeed, substantial numbers of patients have been cured in the last 15 years by interferon-based regimen and are still under surveillance worldwide: the latter therefore deserve full attention, in particular the generation of baby-boomers in the West and in the US. Indeed, this population is currently aging and has been recently highlighted by several epidemiological projections as the only generation who will not particularly benefit from global HCV eradication [32]. While waiting for larger cohorts of DAAs-treated cirrhotic patients with a longer follow-up, the present analyses, validated in the recent Hepather cohort which only comprised DAAs-treated patient, suggest that these observations will be transposable in such population.

One of the most clinically relevant applications of these analyses is the identification of subgroups of patients with a very low HCC risk. In particular, we were able to show that patients included in the CirVir cohort who achieved SVR and combined both low AST and high PT levels after viral eradication had a very low probability of developing liver cancer. While dropping the surveillance of low-risk groups is questionable, the intensification of screening programs in intermediate- or high-risk groups is a timely challenge as it would not only improve compliance with surveillance recommendations [3] but also to overcome the pitfalls related to the lack of sensitivity of US in patients with cirrhosis [33]; It has been shown that a liver-specific contrast MRI performed as routine

surveillance in cirrhotic patients with a yearly HCC incidence higher than 5% yielded a detection sensitivity of 84.8% for very early stage HCC, which was significantly better than the 27.3% achieved using US [7]; In this setting, using an expensive but highly sensitive imaging technique such as MRI to detect liver cancer might be justified in populations with the highest risk of HCC [34]; It was recently reported that using MRI for HCC surveillance was becoming increasingly cost-effective versus US in patients with an increasing annual incidence of HC .[35]; Indeed, contrast-enhanced MRI had a higher detection rate than US for very early stage HCC (BCLC stage 0; single lesion <2 cm) which affected the subsequent allocation of curative treatment options and survival. By using sophisticated statistical approaches to categorize patients into various HCC risk classes, our findings suggest that personalized surveillance could be implemented in patients with HCV-related cirrhosis. For example, the identification of low-risk groups (irrespective of SVR status) such as groups 4 and 7 in the decision tree or the low-risk categories identified through random forest suggests that their surveillance with contrast-enhanced techniques may not be cost-effective. The validity of this stratification is supported by the lowest reported LSM values in these two subgroups, although not available in all analyzed patients. Furthermore, reasons explaining this apparent protection from liver carcinogenesis process warrant further exploration, in particular through the potential identification of specific biological traits such as rare genetic variants. On the other hand, the intensification of screening in other subsets might improve the detection of early stage HCC and hence patient survival. This approach constitutes a clear step into precision medicine and deserves testing in the context of dedicated randomized trials that include cost-effectiveness analyses.

One of the strengths of this study was the derivation of prognostic models accounting for patients' SVR status, recorded in a protocol-driven framework during the lengthy follow-up of a prospective cohort monitored in the context of surveillance programs across different eras of antiviral therapy. From a statistical standpoint, the use of advanced statistical approaches based on decision trees to complement more conventional competing risks Fine-Gray regression modeling enabled the identification of prognostic subgroups based on complex combinations of predictors. We used both single tree and ensemble methods (random forests) in order to contrast their results and verify the robustness of our findings. Less prone to overfitting, random forests confirmed the results of the single

decision tree analysis regarding the main predictors in patients with/without SVR, but additionally achieved the best apparent discrimination performance among the three approaches. While the actual relevance of improving C-indexes of +0.06-0.07 (as was observed in the present study when comparing random forests to regression models) remains unclear in clinical practice, especially considering the somewhat large associated 95% confidence intervals, we believe these findings may further support the potential ability of random forests to capture patient's complexity for predicting subsequent outcomes. Despite a general underestimation of the actual HCC risk by all models, calibration was also excellent in the low risk category for random forests, a desirable property in clinical practice for detecting low-risk patients and tailoring optimized screening strategies. Conversely, while single decision trees provided visually attractive information potentially useful for improving our understanding of the relationships at play, their well-known tendency to overfitting was confirmed in our study where decision tree's C-index was the lowest after external validation.

Refining costly HCC screening programs is a timely challenge in view of the changing epidemiology of chronic liver diseases and HCC [36]. To that end, machine learning approaches may usefully optimize assessments of HCC risk and offer an accurate tool both for patient management and decision-making processes by policy makers. The adaptation of HCC screening modalities according to specific risk classes must now be scientifically assessed in the framework of randomized trials. Such efforts will optimize both cost-effectiveness and the allocation of limited medical resources and could ultimately make a substantial contribution to improving the prognosis of liver cancer.

ACKNOWLEDGMENTS

Role of the Sponsor: The funding sponsor had no role in the design and conduct of the study, the collection, management, analysis or interpretation of the data, and the preparation, review or approval of the manuscript.

Scientific Committee
P. Nahon (principal investigator), R. Layese and E Audureau (data management), P. Bedossa, M. Bonjour, V. Bourcier, S. Dharancy, I. Durand-Zaleski, H.Fontaine, D. Guyader, A. Laurent, V. Leroy, P. Marche, D. Salmon, V. Thibault, V. Vilgrain, J. Zucman-Rossi, C. Cagnot (ANRS), V. Petrov-Sanchez (ANRS).
Clinical centers (Department/participating physicians)
CHU Jean Verdier, Bondy (P. Nahon, V. Bourcier); CHU Cochin, Paris (S. Pol, H. Fontaine); CHU Pitié-Salpétrière, Paris (D. Thabut); CHU Saint-Antoine, Paris (L. Serfaty); CHU Avicenne, Bobigny (D. Roulot); CHU Beaujon, Clichy (P. Marcellin); CHU Henri Mondor (A. Mallat); CHU Paul Brousse (P. Attali); CHU Tenon, Paris (J.D. Grangé); CHRU Hôpital Nord, Amiens (D. Capron); CHU Angers (P. Calès); Hôpital Saint-Joseph, Marseille (M. Bourlière); CHU Brabois, Nancy (J.P. Bronowicki); Hôpital Archet, Nice (A. Tran); Institut Mutualiste Montsouris, Paris (F. Mal, C. Christidis); CHU Poitiers (C. Silvain); CHU Pontchaillou, Rennes (D. Guyader); CH Pays d'Aix, Aix-en-Provence (C. Wartelle); CHU Jean Minjoz, Besancon (V. Di Martino); CHU Bordeaux - Hôpital Haut-Leveque, Pessac (V. de Ledinghen); CHU Bordeaux - Hôpital Saint-André, Bordeaux (JF. Blanc); CHU Hôtel Dieu, Lyon (C. Trepo, F. Zoulim); CHU Clermont-Ferrand (A. Abergel); Hôpital Foch, Suresnes (S. Hillaire); CHU Caen (T. Dao); CHU Lille (P. Mathurin); CH Le Mans (C. Pilette); CHU Michallon, Grenoble (JP. Zarski); CHU St Eloi, Montpellier (D. Larrey); CHU Reims (B. Bernard-Chabert); CHU Rouen (O. Goria, G. Riachi); Institut Arnaud Tzanck, St Laurent-du-Var (D. Ouzan); CHU Purpan, Toulouse (JM. Péron, L. Alric); CHU Tours (Y. Bacq).
Funding/Support: This study was sponsored by the ANRS (France REcherche Nord & sud SIDA-HIV Hépatites: FRENSH).

This work is dedicated to the memory of Professor Jean-Claude Trinchet.

ANRS CO12 Hepather group (validation cohort):
Funding
INSERM-ANRS (France REcherche Nord&sud Sida-vih Hepatites), ANR (Agence Nationale de la Recherche), DGS (Direction Générale de la Santé) and MSD, Janssen, Gilead, Abbvie, BMS, Roche.

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, Marjorie Cheraud-Carpentier (Hôpital Hôtel-Dieu, Nantes, France), Isabelle Hubert, Jaouad Benhida, Adrien Lannes, Françoise Lunel, Frédéric Oberti (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, Amy Wilson, Sarah Shili, Faiza Chermak (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Christelle Ansaldi, Nisserine Ben Amara, Laëtitia Chouquet, Emilie De Luca, Valérie Oules (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 Salptétrière, Paris, France), Barbara De Dieuleveult, Damien Labarriere, Pascal Poter, Si Nafa Si Ahmed (CHR La Source, Orléans, France), Véronique Grando-Lemaire, Pierre Nahon, Valérie Bourcier, Séverine Brulé, Thomas Stalhberger (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, 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 Goria, 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 Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe).

Scientific Committee:

- Voting members :

Marc Bourlière (Hôpital St Joseph, Marseille), Patrice Cacoub (Hôpital Pitié salpêtrière, Paris, France, Fabrice Carrat (Scientific Coordinator, Hôpital Saint-Antoine, Paris, France), Patrizia Carrieri (INSERM U912, Marseille, France), Elisabeth Delarocque-Astagneau (Inserm UMR1181, Paris), Victor De Ledinghen (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Céline Dorival (UPMC & INSERM U1136, Paris, France), Jean Dubuisson (Inserm U1019, Lille, France), Hélène Fontaine (Hôpital Cochin, Paris, France), Chantal Housset (Inserm UMR-S938 1 IFR65, Paris), Dominique Larrey (Hôpital Saint Eloi, Montpellier, France), Patrick Marcellin (Hôpital Beaujon, Clichy, France), Philippe Mathurin (CHRU Claude Huriez, Lille, France), Pierre Nahon (Hôpital Jean Verdier, Bondy, France), Georges-Philippe Pageaux (Hôpital Saint Eloi, Montpellier, France), Jean-Michel Pawlotsky (Hôpital Henri Mondor, Créteil, France), Ventzislava Petrov-Sanchez (ANRS, Paris, France), Stanislas Pol (Principal Investigator, Hôpital Cochin, Paris, France), Sophie Vaux (Agence Nationale de Santé Publique, Saint Maurice, France), Linda Wittkop (ISPED-INSERM U897, Bordeaux, France), Yazdan Yazdanpanah (Hôpital Bichat Claude Bernard, Paris, France), Jean-Pierre Zarski (CHU de Grenoble, Grenoble, France), Fabien Zoulim (Hospices Civils de Lyon, Lyon, France), Jessica Zucman-Rossi (Inserm U674/1162, Paris).

- Non voting members:

Marianne L'hennaff (ARCAT-TRT-5-CHV, France), Michèle Sizorn (SOS hépatites, France); one representative of INSERM-ANRS Pharmacovigilance team, Paris, France (Imane Amri, Alpha Diallo), Mélanie Simony, Carole Cagnot (INSERM-ANRS, Paris, France), one member of Inserm Transfert, Paris, France (Alice Bousselet, Mireille Caralp, Jean-Marc Lacombe), and one representative of each pharmaceutical company (MSD, Janssen, Gilead, Abbvie, BMS, Roche).

Sponsor: Imane Amri, Alpha Diallo, Carole Cagnot, Mélanie Simony (INSERM-ANRS, Paris, France), Ventzi Petrov-Sanchez (coordinator).

Methodology and Coordinating Centre: Loubna Ayour, Jaouad Benhida, Fabrice Carrat (coordinator), Frederic Chau, Céline Dorival, Audrey Gilibert, Isabelle Goderel, Victorien Grard, Warda Hadi, Georges Haour, Godwin Mawuvi, Léa Mba Mintsa, Grégory Pannetier, François Pinot, Muriel Sudres, François Téloulé (Sorbonne Université & INSERM U1136, Paris, France).

ANRS CO12 CirVir group

Pierre Nahon[1], Patrick Marcellin[2], Dominique Guyader[3], Stanislas Pol[4], Hélène Fontaine[4], Dominique Larrey[5], Victor De Lédinghen[6], Denis Ouzan[7], Fabien Zoulim[8], Dominique Roulot[9], Albert Tran[10], Jean-Pierre Bronowicki[11], Jean-Pierre Zarski[12], Vincent Leroy[12], Ghassan Riachi[13], Paul Calès[14], Jean-Marie Péron[15], Laurent Alric[16], Marc Bourlière[17], Philippe Mathurin[18], Sebastien Dharancy[18], Jean-Frédéric Blanc[19], Armand Abergel[20], Olivier Chazouillères[21], Ariane Mallat[22], Jean-Didier Grangé[23], Pierre Attali[24], Louis d'Alteroche[25], Claire Wartelle[26], Thông Dao[27], Dominique Thabut[28], Christophe Pilette[29], Christine Silvain[30], Christos Christidis[31], Eric Nguyen-Khac[32], Brigitte Bernard-Chabert[33], David Zucman[34], Vincent Di Martino[35].

[1]AP-HP, Hôpital Jean Verdier, Service d'Hépatologie, Bondy, Université Paris 13, Bobigny et INSERM U1162, Université Paris 5, Paris; [2]AP-HP, Hôpital Beaujon, Service d'Hépatologie, Clichy; [3]CHU Pontchaillou, Service d'Hépatologie, Rennes; [4]AP-HP, Hôpital Cochin, Département d'Hépatologie et INSERM UMS20 et U1223, Institut Pasteur, Université Paris Descartes, Paris; [5]Hôpital Saint Eloi, Service d'Hépatologie, Montpellier; [6]Hôpital Haut-Lévêque, Service d'Hépatologie, Bordeaux; [7]Institut Arnaud Tzanck, Service d'Hépatologie, St Laurent du Var; [8]Hôpital Hôtel Dieu, Service d'Hépatologie, Lyon; [9]AP-HP, Hôpital Avicenne, Service d'Hépatologie, Bobigny; [10]CHU de Nice, Service d'Hépatologie, et INSERM U1065, Université de Nice-Sophia-Antipolis, Nice; [11]Hôpital Brabois, Service d'Hépatologie, Vandoeuvre-les-Nancy; [12]Hôpital Michallon, Service d'Hépatologie, Grenoble; [13]Hôpital Charles-Nicolle, Service d'Hépatologie, Rouen; [14]CHU d'Angers, Service d'Hépatologie, Angers; [15]Hôpital Purpan, Service d'Hépatologie, Toulouse; [16]CHU Toulouse, Service de Médecine Interne-Pôle Digestif UMR 152, Toulouse; [17]Hôpital Saint Joseph, Service d'Hépatologie, Marseille; [18]Hôpital Claude Huriez, Service d'Hépatologie, Lille; [19]Hôpital St André, Service d'Hépatologie, Bordeaux; [20]Hôpital Hôtel Dieu, Service d'Hépatologie, Clermont-Ferrand; [21]AP-HP, Hôpital Saint-Antoine, Service d'Hépatologie, Paris; [22]AP-HP, Hôpital Henri Mondor, Service d'Hépatologie, Créteil; [23]AP-HP, Hôpital Tenon, Service d'Hépatologie, Paris; [24]AP-HP, Hôpital Paul Brousse, Service d'Hépatologie, Villejuif; [25]Hôpital Trousseau, Unité d'Hépatologie, CHRU de Tours; [26]Hôpital d'Aix-En-Provence, Service d'Hépatologie, Aix-En-

Provence; [27]Hôpital de la Côte de Nacre, Service d'Hépatologie, Caen; [28]Paris Sorbonne Université, AP-HP, Groupe Hospitalier de La Pitié-Salpêtrière, Service d'Hépatologie, Paris; [29]CHU Le Mans, Service d'Hépatologie, Le Mans; [30]CHU de Poitiers, Service d'Hépatologie, Poitiers; [31]Institut Mutualiste Montsouris, Service d'Hépatologie, Paris; [32]Hôpital Amiens Nord, Service d'Hépatologie, Amiens; [33]Hôpital Robert Debré, Service d'Hépatologie, Reims; [34]Hôpital Foch, Service de Médecine Interne, Suresnes; [35]Hôpital Jean Minjoz, Service d'Hépatologie, Besançon. FRANCE.

REFERENCES

[1] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
[2] Cadier B, Bulsei J, Nahon P, Seror O, Laurent A, Rosa I, et al. Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States. Hepatology 2017;65:1237-1248.
[3] Costentin CE, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Compliance With Hepatocellular Carcinoma Surveillance Guidelines Associated With Increased Lead-Time Adjusted Survival of Patients With Compensated Viral Cirrhosis: A Multi-Center Cohort Study. Gastroenterology 2018;155:431-442 e410.
[4] Nahon P, Zucman-Rossi J. Single nucleotide polymorphisms and risk of hepatocellular carcinoma in cirrhosis. J Hepatol 2012;57:663-674.
[5] Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: A randomized trial comparing 3- and 6-month periodicities. Hepatology 2011;54:1987-1997.
[6] Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS medicine 2014;11:e1001624.
[7] Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, et al. MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma. JAMA oncology 2017;3:456-463.
[8] Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. Gastroenterology 2018;155:1436-1450 e1436.
[9] Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. Gastroenterology 2015;149:1471-1482 e1475; quiz e1417-1478.
[10] El-Serag HB, Kanwal F, Davila JA, Kramer J, Richardson P. A new laboratory-based algorithm to predict development of hepatocellular carcinoma in patients with hepatitis C and cirrhosis. Gastroenterology 2014;146:1249-1255 e1241.
[11] Zhou Y, McArdle JJ. Rationale and Applications of Survival Tree and Survival Ensemble Methods. Psychometrika 2015;80:811-833.
[12] Trinchet JC, Bourcier V, Chaffaut C, Ait Ahmed M, Allam S, Marcellin P, et al. Complications and competing risks of death in compensated viral cirrhosis (ANRS CO12 CirVir prospective cohort). Hepatology 2015;62:737-750.

[13] Allaire M, Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, et al. Extrahepatic cancers are the leading cause of death in patients achieving hepatitis B virus control or hepatitis C virus eradication. Hepatology 2018;68:1245-1259.
[14] Cacoub P, Nahon P, Layese R, Blaise L, Desbois AC, Bourcier V, et al. Prognostic value of viral eradication for major adverse cardiovascular events in hepatitis C cirrhotic patients. American heart journal 2018;198:4-17.
[15] Ganne-Carrie N, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Nomogram for individualized prediction of hepatocellular carcinoma occurrence in hepatitis C virus cirrhosis (ANRS CO12 CirVir). Hepatology 2016;64:1136-1147.
[16] Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology 2017;152:142-156 e142.
[17] Nahon P, Lescat M, Layese R, Bourcier V, Talmat N, Allam S, et al. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). Gut 2017;66:330-341.
[18] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-1457.
[19] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236.
[20] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
[21] European Association for the Study of the L. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397-417.
[22] de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762-768.
[23] Sarrazin C, Hezode C, Zeuzem S, Pawlotsky JM. Antiviral strategies in hepatitis C virus infection. J Hepatol 2012;56 Suppl 1:S88-100.
[24] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018;69:461-511.
[25] Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453-1464.
[26] Torsten Hothorn KH, and Achim Zeileis. Unbiased Recursive Partitioning: A Conditional Inference Framework. Journal of Computational and Graphical Statistics 2006;15:651-674.
[27] Ishwaran H, Kogalur UB. Consistency of Random Survival Forests. Statistics & probability letters 2010;80:1056-1064.
[28] Strobl C, Boulesteix AL, Kneib T, Augustin T, Zeileis A. Conditional variable importance for random forests. BMC bioinformatics 2008;9:307.
[29] Wolbers M, Blanche P, Koller MT, Witteman JC, Gerds TA. Concordance for prognostic models with competing risks. Biostatistics 2014;15:526-539.
[30] FE H. Regression modeling strategies: with applications to linear models. Logistic Regression, and Survival Analysis. . Springer: New York, NY 2001.
[31] Sherman M. HCC Risk Scores: Useful or Not? Seminars in liver disease 2017;37:287-295.

[32] Shiels MS, O'Brien TR. Recent Decline in Hepatocellular Carcinoma Rates in the United States. Gastroenterology 2020;158:1503-1505 e1502.
[33] Del Poggio P, Olmi S, Ciccarese F, Di Marco M, Rapaccini GL, Benvegnu L, et al. Factors that affect efficacy of ultrasound surveillance for early stage hepatocellular carcinoma in patients with cirrhosis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2014;12:1927-1933 e1922.
[34] Goossens N, Singal AG, King LY, Andersson KL, Fuchs BC, Besa C, et al. Cost-Effectiveness of Risk Score-Stratified Hepatocellular Carcinoma Screening in Patients with Cirrhosis. Clinical and translational gastroenterology 2017;8:e101.
[35] Kim HL, An J, Park JA, Park SH, Lim YS, Lee EK. Magnetic Resonance Imaging Is Cost-Effective for Hepatocellular Carcinoma Surveillance in High Risk Patients with Cirrhosis. Hepatology 2018;doi: 10.1002/hep.30330.
[36] Valery PC, Laversanne M, Clark PJ, Petrick JL, McGlynn KA, Bray F. Projections of primary liver cancer to 2030 in 30 countries worldwide. Hepatology 2017;doi: 10.1002/hep.29498. .

Table 1. General characteristics of the study population at baseline (derivation cohort, N=836)

		N completed	Value
Gender, males		836	520 (62.2%)
Age, years		836	57.2 (±10.8)
Past excessive alcohol intake		836	258 (30.9%)
Tobacco consumption	Never	790	339 (42.9%)
	Past		177 (22.4%)
	Ongoing		274 (34.7%)
Body Mass Index, kg/m²	Continuous	743	26.6 (±4.9)
	Normal weight <25		294 (39.6%)
	Overweight [25-30[		302 (40.6%)
	Obesity ≥30		147 (19.8%)
Diabetes		836	172 (20.6%)
Dyslipidemia		836	45 (5.4%)
Hypertension		836	246 (29.4%)
Esophageal varices		688	220 (32.0%)
HCV Genotype	1	836	617 (73.8%)
	2		35 (4.2%)
	3		102 (12.2%)
	4		69 (8.3%)
	5		11 (1.3%)
	6		2 (0.2%)
Creatinine, µmol/L		836	70.7 (61.0;80.0)
eGFR (MDRD)		836	97.9 (83.1;114.0)
Serum ferritin, µg/L or ng/mL		836	382.0 (171.0;714.5)
Total bilirubin, µmol/L		836	12.0 (9.0;17.1)
AST	IU/L	836	68.0 (45.0;103.5)
	xN	836	1.9 (1.2;2.8)
ALT	IU/L	836	78.5 (47.0;122.5)
	xN	836	1.9 (1.1;3.0)
GGT	IU/L	836	99.0 (57.0;182.0)
	xN	836	2.1 (1.2;3.9)
Alkaline phosphatase	IU/L	836	96.0 (71.0;138.0)
	xN	836	0.8 (0.6;1.0)
Serum albumin, g/L		836	41.0 (37.7;44.1)
Alpha-fetoprotein, ng/mL		836	7.1 (4.0;14.0)
Platelet count, 10^3/mm3		836	129.0 (92.8;169.0)
Prothrombin time (%)		836	88.0 (78.5;97.0)

Table 2. Predictors of HCC occurrence before SVR: results of multivariate competing risk Fine-Gray regression model (derivation cohort, N=836 patients at baseline).

		Univariate analysis		*Multivariate analysis*		
		SHR (CI95%)	**p-value**	**SHRa (CI95%)**	**p-value**	**Regression coefficient**
Gender, males		1.04 (0.74;1.47)	0.81		-	
Age, years	Continuous	1.01 (0.99;1.02)	0.34		-	
	>60	1.13 (0.81;1.59)	0.47		-	
Past excessive alcohol intake		1.44 (1.02;2.04)	**0.037**	1.47 (1.04;2.08)	**0.028**	0.387
Tobacco consumption	Never	1(ref)			-	
	Past	1.38 (0.92;2.07)	0.12		-	
	Ongoing	0.97 (0.64;1.47)	0.88		-	
Body Mass Index, kg/m²	Continuous	0.97 (0.93;1.00)	0.082		-	
	Normal weight <25	1(ref)			-	
	Overweight [25-30]	0.82 (0.55;1.21)	0.31		-	
	Obesity ≥30	0.77 (0.47;1.26)	0.30		-	
Diabetes		0.88 (0.57;1.34)	0.55		-	
Dyslipidemia		0.70 (0.31;1.60)	0.40		-	
Hypertension		1.11 (0.78;1.60)	0.56		-	
Esophageal varices		1.41 (0.98;2.03)	0.061		-	
HCV Genotype 1		1.77 (1.11;2.81)	**0.016**	2.02 (1.27;3.22)	**0.003**	0.703
Creatinine, µmol/L		1.00 (1.00;1.00)	0.72		-	
eGFR (MDRD)		1.00 (0.99;1.00)	0.61		-	
Serum ferritin, µg/L or ng/mL		1.00 (1.00;1.00)	0.33		-	
Total bilirubin, µmol/L		1.00 (0.99;1.02)	0.56		-	
AST, xN	Continuous	1.05 (0.97;1.13)	0.24		-	
	≥1.5	1.67 (1.15;2.42)	**0.007**		-	
ALT, xN	Continuous	1.02 (0.95;1.10)	0.60		-	
	≥2.5	1.31 (0.94;1.84)	0.11		-	
GGT, xN	Continuous	1.04 (1.01;1.08)	**0.019**		-	
	>1	2.15 (1.24;3.71)	**0.006**	1.86 (1.06;3.26)	**0.03**	0.621
Alkaline phosphatase, xN	Continuous	1.49 (1.05;2.11)	**0.024**		-	
	>1	1.44 (1.01;2.05)	**0.042**		-	
Serum albumin, g/L	Continuous	0.94 (0.91;0.97)	**<0.0001**	0.96 (0.93;0.99)	**0.006**	-0.045
	≤40	1.80 (1.28;2.51)	**0.001**		-	
Alpha-fetoprotein, ng/mL	Continuous	1.01 (1.00;1.01)	**0.007**			
	≥6	1.91 (1.29;2.81)	**0.001**	1.40 (0.93;2.10)	0.11	0.334
Platelet count, 10^3/mm3	Continuous	0.99 (0.99;1.00)	**<0.0001**	0.99 (0.99;1.00)	**0.001**	-0.006
	>170	1(ref)	**<0.0001**		-	
	[70-170]	3.07 (1.76;5.37)	**<0.0001**		-	
	<70	4.10 (2.12;7.91)	**<0.0001**		-	
Prothrombin time (%)	Continuous	0.99 (0.98;1.00)	0.28		-	
	≤85	1.40 (1.00;1.95)	**0.048**		-	

SHR: sub-hazard ratio; SHRa: adjusted sub-hazard ratio; CI95%: 95% confidence interval